

TRASLADO

141

**FORMULARIO UNICO DE OPOSICION
2000-12**

1	OPOSICION A:
☒ Patente de Invención	☐ Marca Colectiva
☐ Patente de Modelo de Utilidad	☐ Marca de Certificación
☐ Diseño Industrial	☐ Lema Comercial
☐ Esquema de Trazado para Circuitos Integrados	
☐ Marcas de Productos o Servicios	

2	SOLICITUD PUBLICADA	Número del expediente: 06.060 216 Solicitante: ASTRAZENECA AB Apoderado: JUAN PABLO CADENA SARMIENTO Título de la nueva creación o denominación del signo "DERIVADOS DE DIFENILAZETIDINONA QUE POSEEN ACTIVIDAD INHIBIDORA DE LA ABSORCIÓN DE COLESTEROL" Gaceta: 573 de 28-02-2007, Página 599— Número de Publicación 1129
----------	----------------------------	--

3	OPOSICION PRESENTADA POR:	
OPOSITOR	Nombre: Lafranco S.A. Dirección: Carrera 1 No. 48-84 Teléfono: (092) 449.30.51 Fax: Domicilio: Cali - Valle	IDENTIFICACION C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: 890 301 463 -8
REPRESENTANTE O APODERADO (74)	Nombre: José Luis Reyes Villamizar Dirección: Cra. 17 No. 88-23, Of. 205 Teléfono: 621.26.31 E-mail: info@reyes-abogados.com Fax: 621.26.42 Domicilio: Bogotá, D.C.	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 79'152.473 de Usaquén TP 44655

4	FUNDAMENTOS DE LA OPOSICION:
	Causa: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, (las patentes de invención deben ser nuevas, tener nivel inventivo y ser susceptibles de aplicación industrial), 18 (una invención se considera nueva cuando no es obvia, ni se deriva de manera evidente del estado de la técnica), 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia) 20 (los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales). Justificación: VER ANEXO

5	Comprobante de pago No <u>07-42,777</u> (Oposición) Fecha <u>Mayo 29 de 2009</u> (Prórroga) Fecha _____
----------	--

6

Anexos:



Comprobante de pago de la tasa



Poderes, si fuere el caso



Pruebas de los fundamentos de la oposición



Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas



Documentos que acrediten el legítimo interés, si fuere el caso



Copia de la oposición para el traslado al solicitante.

142

7

NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA

C.C. No. 79.182.473 T.P. No. 44855

Señor**SUPERINTENDENTE DE INDUSTRIA Y COMERCIO****E.****S.****D.**

REF:**EXPEDIENTE 06-060-216**

TÍTULO SOLICITADO: "DERIVADOS DE DIFENILAZETIDINONA QUE POSEEN ACTIVIDAD INHIBIDORA DE LA ABSORCIÓN DE COLESTEROL".

PUBLICACIÓN: Gaceta 573 de 28 de febrero de 2007, número de publicación 1129

SOLICITANTE: ASTRAZENECA AB.

PRIORIDAD: GB 0329778.5 del 23 diciembre de 2003.

APODERADO: JUAN PABLO CADENA SARMIENTO.

TRÁMITE: PRESENTACIÓN DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO-COLOMBIANO LAFRANCOL S.A.**, en desarrollo de lo dispuesto por los artículos 42 y siguientes de la Decisión 486 de 2000 de la Comunidad Andina de Naciones, me permito solicitarle, muy respetuosamente, dar curso a la siguiente:

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente **06-060-216**, por no cumplir con los requisitos de patentabilidad a que se refieren los artículos 14, 16, 18 y 20 de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos de hecho y de derecho que me permito exponer a continuación.

II. LEGÍTIMO INTERÉS

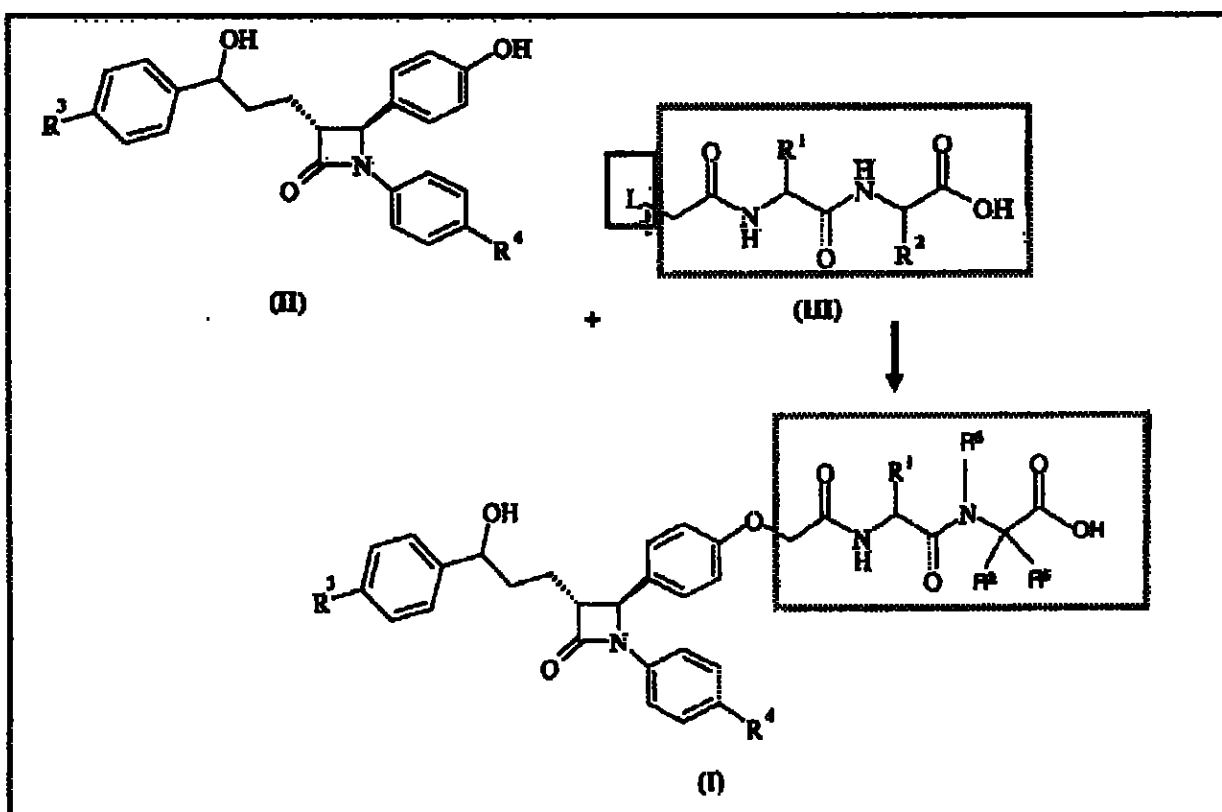
Asiste a **LAFRANCOL S.A.**, en su calidad de industria farmacéutica nacional, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias y composiciones farmacéuticas carentes de nivel inventivo, en detrimento de sus legítimos intereses comerciales y de la libre competencia.

III. FUNDAMENTOS DE LA OPOSICIÓN

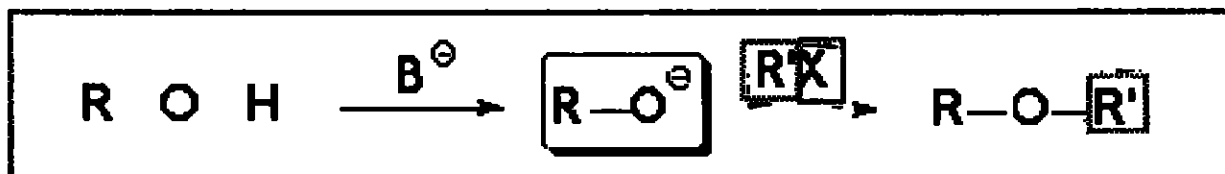
3.1. Los compuestos que reivindica la solicitud colombiana 06-060-216 que resultan ser derivados de ezetimibe, útiles como inhibidores de la absorción de colesterol en el tratamiento de hiperlipidemia, arteriosclerosis, alzheimer, tumores asociados con colesterol, sus formulaciones farmacéuticas, sus combinaciones con agonistas PPAR alfa y/o gamma o inhibidores de HMG Co-A reductasa y su proceso de obtención, resultan carentes de novedad y nivel inventivo como se argumenta a continuación:

- Los compuestos de la fórmula (XV) y (I) así como los procesos de obtención que se reivindican en la solicitud colombiana en trámite resultan ser simples derivados de ezetimibe (entre otros) y su enantiómero obtenidos por reacciones de síntesis muy comunes, veamos:

Proceso 1:

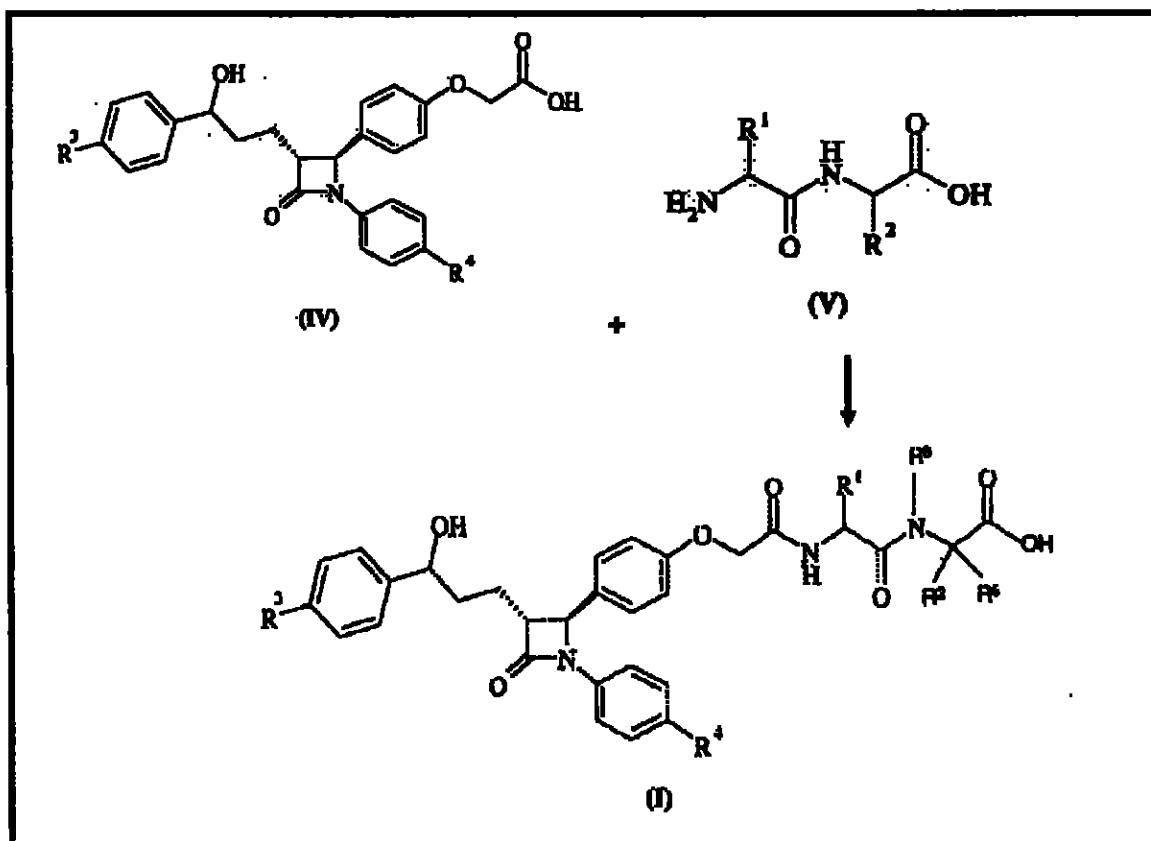


En la solicitud colombiana en trámite, el hidroxilo del grupo hidroxifenil que sustituye al núcleo de azetidiona en posición 4 reacciona con el compuesto de fórmula (III) (donde L es un grupo desplazable o saliente), donde al parecer por sustitución nucleofílica (SN2) permite obtener el compuesto de fórmula (I) (éter alquil sustituido arílico).

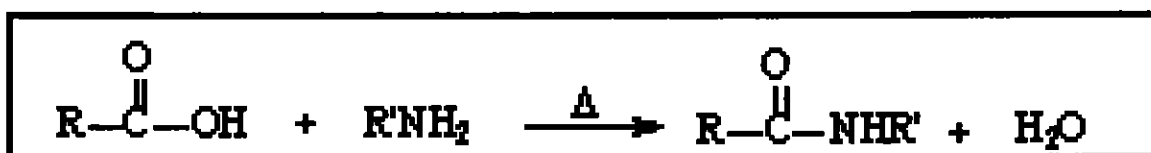


En síntesis orgánica, la manera más simple de preparar un éter es hacer reaccionar un alcóxido con un haluro o sulfonato de alquilo en una secuencia típica SN2.

Proceso 2:



En la solicitud colombiana en trámite, se hace reaccionar el ácido carboxílico de fórmula (IV) o su respectivo derivado éster con una amina de fórmula (V) para obtener el compuesto de fórmula (I) (amida).



En síntesis orgánica una amida puede ser preparada comúnmente haciendo reaccionar un ácido carboxílico o su respectivo éster con una amina.

Los compuestos obtenidos en estos procesos podrían describirse como profármacos de ezetimibe (u otro compuesto –dependiendo de los sustituyentes-) hidrolizables en el enlace formado por el grupo hidroxilo del sustituyente hidroxifenil de la posición 4 del núcleo de azetidinona de dichos compuestos.

Los profármacos, como toda persona versada en la materia sabe, son derivados terapéuticamente inactivos de un principio activo que mediante bioconversión, o sea, transformación química o enzimática en un medio biológico regeneran la sustancia activa; siendo el uso de los profármacos una forma de solución a eventualidades de una molécula activa tales como problemas de estabilidad y biofarmacéuticos entre otros, reconocidos y definidos por *Albert*¹ desde 1958 no puede entonces atribuírsele novedad y mucho menos nivel inventivo, a un proceso de obtención de profármacos de ezetimibe (u otro compuesto –dependiendo de los sustituyentes-) a través de reacciones sencillas de esterificación y formación de amidas.

- La patente americana US 5,846,966 publicada el 8 de diciembre de 1998 y titulada "COMBINATIONS OF HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS AND HMG-CoA REDUCTASE INHIBITORS", revela agentes hipocolesterolémicos azetidinona hidroxi-sustituidos (similares a los de la solicitud colombiana en trámite), así como un método de disminución del colesterol en suero por administración de dichos compuestos, solos o en combinación con un inhibidor de la biosíntesis de colesterol, composiciones farmacéuticas que los contienen y un proceso para obtenerlos.

Como se puede observar en su *abstract*, la patente americana US 5,846,966, revela que el compuesto tipo azetidinona puede estar en combinación con un inhibidor de la biosíntesis de colesterol o como menciona en las reivindicaciones 1 y 10, que puede estar en combinación con un inhibidor de la HMG-CoA reductasa como pravastatina, atorvastatina, lovastatina, entre otros, en un vehículo farmacéuticamente aceptable y, que según la reivindicación 6 y 10 son útiles en el tratamiento o prevención de la aterosclerosis o la reducción de los niveles de colesterol en plasma.

Al comparar lo descrito en el párrafo anterior con lo revelado en la solicitud colombiana en trámite es necesario concluir que, en ambos casos, el

¹ ALBERT A. Chemical aspects of selective toxicity. Nature 182. 421 (1958).

compuesto de tipo azetidinona puede estar en combinación de un inhibidor de la biosíntesis del colesterol como lo son los inhibidores de HMG-CoA reductasa, y que en ambos casos se revela la utilidad en el tratamiento de arteriosclerosis e hiperlipidemia, lo que claramente demuestra al menos la falta de nivel inventivo de las reivindicaciones 12, 13 y 20 de la solicitud colombiana en trámite.

- Por su parte, la patente americana US 5,744,467 publicada el 28 de abril de 1998 y titulada "SULFUR-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS", revela agentes hipocolesterolémicos derivados de azetidinona (similares a los de la solicitud colombiana en trámite) o sus sales farmacéuticamente aceptables, así como composiciones que los contienen y un método de disminución del colesterol en suero por administración de dichos compuestos, solos o en combinación con un inhibidor de la biosíntesis de colesterol.

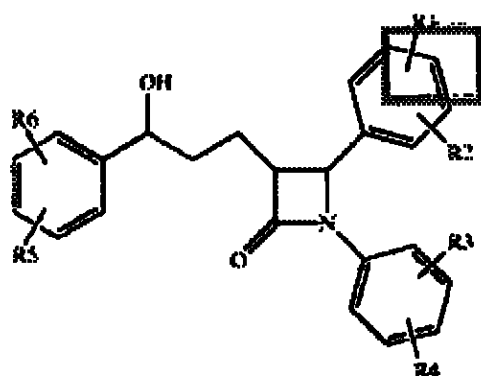
Se observa entonces, que la patente americana US 5,744,467 revela que el compuesto tipo azetidinona puede estar en combinación con un inhibidor de la biosíntesis de colesterol o como menciona en las reivindicaciones 2 y 3, que puede estar en combinación con un inhibidor de la HMG-CoA reductasa y, que según la reivindicación 1 y 4 son útiles en el tratamiento o prevención de la aterosclerosis o la reducción de los niveles de colesterol en plasma.

Si tenemos en cuenta lo descrito en el párrafo anterior con lo revelado en la solicitud colombiana en trámite podemos ver que en ambos documentos el compuesto de tipo azetidinona puede estar en combinación de un inhibidor de la biosíntesis del colesterol como lo son los inhibidores de HMG-CoA reductasa y que así mismo se revela la utilidad en el tratamiento de arteriosclerosis e hiperlipidemia, permite demostrar nuevamente la ausencia por lo menos de nivel inventivo de las reivindicaciones 12, 13 y 20 de la solicitud colombiana en trámite.

- La patente americana US 2002/0128253 publicada el 12 de septiembre de 2002 y titulada "DIPHENYL AZETIDINONE DERIVATIVES, PROCESS FOR THEIR PREPARATION, MEDICAMENTS COMPRISING THESE COMPOUNDS AND THEIR USE" revela compuestos de la fórmula:

(57) ABSTRACT

Compounds of the formula I.



in which R1, R2, R3, R4, R5, and R6 have the meanings given in the description, and their physiologically acceptable salts. The compounds are suitable for use, for example, as hypolipidemics.

En donde R1 a R6 pueden ser, entre otros:

[0008] H, F, Cl, Br, I, CF₃, NO₂, CN, COOH, COO(C₁-C₆)-alkyl, CONH₂, CONH(C₁-C₆)-alkyl, CONE(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl or O-(C₁-C₆)-alkyl, where one, more or all hydrogens in the alkyl radicals may be replaced by fluorine; or

[0010] NH₂, NH-(C₁-C₆)-alkyl, N(C₁-C₆)-alkyl, NH(C₁-C₆)-acyl, phenyl or O-(CH₂)_n-phenyl, where n=0-6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N(C₁-C₆)-alkyl, SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl or CONH₂

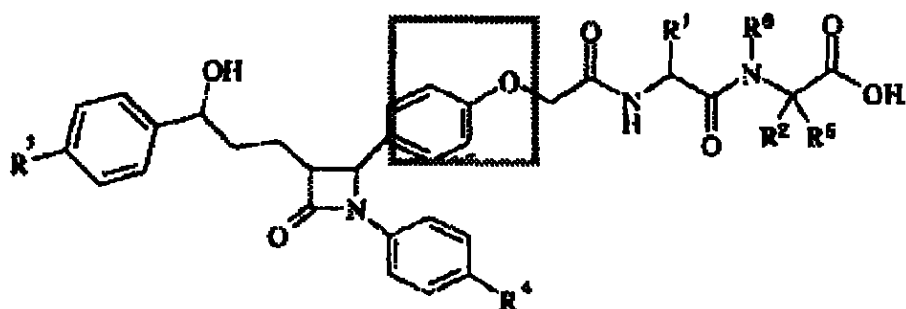
los cuales,

cuando se realizan las respectivas sustituciones en la posición encerrada en verde con los respectivos grupos resaltados en verde, resultan ser estructuras muy similares a las de la solicitud colombiana en trámite (derivados de ezetimibe —entre otros—) y que además tienen en común la funcionalidad u objetivo que se busca con dichas sustituciones:

(...)

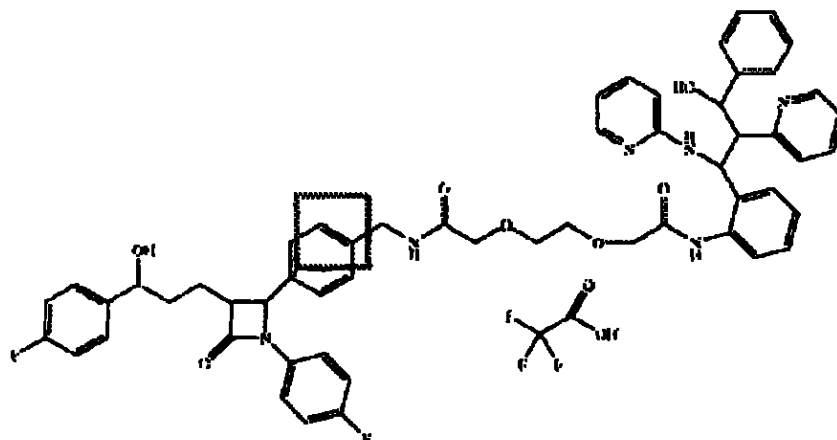
treatment of disease states associated with hyperlipidaemic conditions. The compounds of the present invention are not disclosed in any of the above applications and we have surprisingly found that the compounds of the present invention possess beneficial efficacious, metabolic and toxicological profiles that make them particularly suitable for *in vivo* administration to a warm blooded animal, such as man. In particular certain compounds of the present invention have a low degree of absorption compared to compounds of the prior art whilst retaining their ability to inhibit cholesterol absorption.

(...)



(RVO 05/081451 equivalente internacional de la solicitud colombiana en trámite)

[0004] It was an object of the invention to provide further compounds having a therapeutically utilizable hypolipidemic action. In particular, it was an object to find novel compounds which, compared to the compounds described in the prior art, are absorbed to a very low extent. Very low absorption is to be understood as meaning an intestinal absorption of less than 10%, preferably less than or equal to 5%. In particular, absorption of the novel compounds should be less than that of ezetimibe. Pharmaceutically active compounds which are absorbed to a very low extent generally have considerably fewer side-effects.



(Patente americana US 2002/0128253)

Lo anterior permite demostrar que en el estado del arte se encuentran compuestos derivados de azetidinona sustituidos con sustituyentes semejantes en características químicas a los de la solicitud colombiana en trámite y que se adicionan a la misma posición que estos, con el fin de mejorar características como la absorción de los mismos; de esta forma se ve afectado el nivel inventivo de la solicitud colombiana en trámite.

Así mismo, haciendo un paralelo entre lo reivindicado en la solicitud colombiana en trámite y la patente americana, podemos evidenciar muchas cosas en común, veamos:

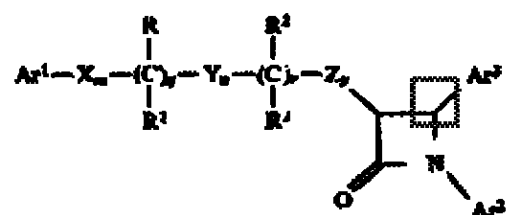
SOLICITUD COLOMBIANA EN TRAMITE	PATENTE AMERICANA US 2002/0128253
1. Un compuesto de la fórmula (...) o su sal farmacéuticamente aceptable, solvato, solvato de la sal o profármaco. 12. Un método de tratar o prevenir enfermedades hiperlipidémicas, que comprende la administración de una cantidad efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 11 a un mamífero necesitado de ello. 13. Un método de tratar o prevenir arteriosclerosis, que comprende la administración de una cantidad efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 11 a un mamífero necesitado de ello.	[0025] The compounds of the formula I and their pharmaceutically acceptable salts, esters, prodrugs and derivatives having physiological function are ideal medicaments for treating an impaired lipid metabolism, in particular hyperlipidemia. The compounds of the formula I are also suitable for modulating the serum cholesterol concentration and for treating arteriosclerotic manifestations. The compounds of the invention are also suitable for the treatment of insulin resistance. 12. A method as claimed in claim 11, wherein the host suffers from hyperlipidemia. 13. A method as claimed in claim 14, wherein the host suffers from an arteriosclerotic manifestation.
20. Una combinación de un compuesto de acuerdo con fórmula (I) o (XV) con un inhibidor de HMG Co-A.	[0035] In one embodiment of the invention, the compounds of the formula I are administered in combination with an HMG CoA reductase inhibitor such as simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin, rosuvastatin.
19. Una combinación de un compuesto de acuerdo con fórmula (I) o (XV) con un agonista PPAR alfa y/o gamma.	[0039] In one embodiment of the invention, the compounds of the formula I are administered in combination with a mixed PPAR alpha/gamma agonist, such as, for example, GW 1536, AVE 5042, AVE 5134, AVE 0847.
18. Un proceso para preparar un compuesto de fórmula (I) o su sal farmacéuticamente aceptable, solvato (...) y posteriormente, si es necesario o deseable (...) iv) separar dos o más enantiómeros (...)	[0070] The invention furthermore provides both stereoisomer mixtures of the formula I and the pure stereoisomers of the formula I, and diastereomer mixtures of the formula I and the pure diastereomers. The mixtures are separated by chromatographic means.

En conclusión, la patente americana nos permite demostrar la falta de nivel inventivo de la solicitud colombiana en trámite en tanto señala:

- * Derivados de azetidinona sustituidos en la misma posición y con sustituyentes de características químicas semejantes a los de la solicitud colombiana en trámite
- * Separación de los posibles enantiómeros
- * Derivados con características biofarmacéuticas modificadas útiles en el tratamiento de trastornos hiperlipidémicos y arterioscleróticos.

➤ La patente americana US 5, 767,115 publicada el 16 de Junio de 1998 y titulada "HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS" revela compuestos de la fórmula:

[57] ABSTRACT
Hydroxy-substituted azetidinone hypocholesterolemic agents of the formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ and Ar² are aryl or R⁴-substituted aryl;

Ar³ is aryl or R⁴-substituted aryl;

R⁴ is selected from lower alkyl, R⁵, —CF₃, —CN, —NO₂, and halogen R⁵ is selected from —OR⁶, —O(CO)R⁶, —O(CO)OR⁶, —O(CH₂)₁-₃OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁶, —NR⁶(CO)NR⁷R⁸, —NR⁶SO₂R⁶, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₁-₂R⁶, —O(CH₂)₁-₁₀—COOR⁶, —O(CH₂)₁-₁₀—CONR⁶R⁷, —(lower alkyl)nc—COOR⁶ and —CH=CH—COOR⁶;

R⁶, R⁷ and R⁸ are H, lower alkyl, aryl or aryl-substituted lc

R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl;

En donde los sustituyentes resaltados en verde, coinciden en buena parte con los sustituyentes correspondientes a la misma posición en los

derivados de la solicitud colombiana en trámite; así mismo, los derivados de la patente americana poseen la misma utilidad:

SOLICITUD COLOMBIANA EN TRAMITE	PATENTE AMERICANA
13. Un método de tratar o prevenir arteriosclerosis, que comprende la administración de una cantidad efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 11 a un mamífero necesitado de ello.	8. A pharmaceutical composition for the treatment prevention of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising an effective amount of a compound of claim 1 in a pharmaceutically acceptable carrier. 9. A method of treating or preventing atherosclerosis or reducing plasma cholesterol levels comprising administering to a mammal in need of such treatment an effective amount of a compound of claim 1.

➤ Por último, la solicitud colombiana en trámite en sus reivindicaciones 12, 13, 14 y 15 reivindican un método para tratar o prevenir enfermedades como las relacionadas a la hiperlipidemia, arteriosclerosis, alzheimer y tumores, lo cual va en contra de los dispuesto por el literal b del artículo 20 de la decisión 486 de la comunidad andina de naciones en donde claramente se expone que *"No serán patentables: los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnostico aplicados a los seres humanos o a animales."*

Por todo lo anterior reitero que la solicitud de la referencia, en todas sus reivindicaciones, incumple los requisitos materiales de patentabilidad establecidos por la Decisión 486 de 2000, razón por la cual no puede ser objeto de privilegio de patente de invención.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 16, 18 y 20, el artículo 30 (Reivindicaciones) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. PRUEBAS

153

Ruego que se tengan como tales, sin perjuicio de que el Despacho considere oficiosamente, en particular de las allegadas por el suscrito a los expedientes mencionados en este escrito, las siguientes:

- La patente americana US 5,846,966 publicada el 8 de diciembre de 1998 y titulada "COMBINATIONS OF HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS AND HMG-CoA REDUCTASE INHIBITORS" capítulo reivindicatorio.
- La patente americana US 5,744,467 publicada el 28 de abril de 1998 y titulada "SULFUR-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS" capítulo reivindicatorio.
- La patente americana US 2002/0128253 del 12 de septiembre de 2002 y titulada "DIPHENYL AZETIDINONE DERIVATIVES, PROCESS FOR THEIR PREPARATION, MEDICAMENTS COMPRISING THESE COMPOUNDS AND THEIR USE." Páginas 1, 2, 3, 4 12 y 17.
- La patente americana US 5, 767,115 del 16 de Junio de 1998 y titulada "HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS" página 21.

VI. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos:

1. Certificado de existencia y representación legal de Lafranco S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.

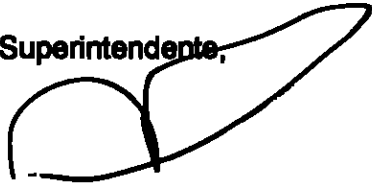
4. Copia para correr traslado al solicitante.
5. Las mencionadas en el acápite de pruebas

154

VII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Lafranco S.A., las recibirá en sus oficinas localizadas en la Carrera 1 N° 46-84 de Cali.

Señor Superintendente,

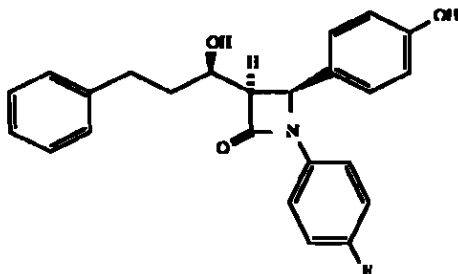


JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P.A 44.655 del C.S.J.

39
EXAMPLE 10



Step 1: Follow the procedure of Example 3, using 1-(4-fluorophenyl)-4-(4-1-butylidimethylsilyloxyphenyl)-2-azetidinone to obtain 1-(4-fluorophenyl)-3-(3-phenyl-1-hydroxypropyl)-4-(4-1-butylidimethylsilyloxyphenyl)-2-azetidinone.

Step 2: Treat a solution of the cis-azetidinone of Step 1 (0.25 g) in CH₃CN (21 ml) with 48% aqueous HF (2.5 ml). After 18 h, dilute the reaction mixture with cold H₂O and extract with Et₂O. Wash (2x H₂O, dilute NaHCO₃ and brine), dry (MgSO₄) and concentrate the Et₂O layer. Crystallize the residue from EtOAc:hexane (1:2) to obtain the title compound as colorless needles (123 mg, y=64%), mp 168°-171° C. Elemental analysis calc for C₂₄H₂₅O₄FN: C 73.64; H 5.66; N 3.58. found C 73.32; H 5.65; N 3.68.

The following formulations exemplify some of the dosage of this invention. In each the term "active compound" designates a compound of formula I.

EXAMPLE A

Tablets			
No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	122	113
3	Corn Starch, Food Grade, as a 10% paste in Purified Water	20	40
4	Corn Starch, Food Grade	45	40
5	Magnesium Stearate	3	7
Total		300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in suitable mixer for 10-15 minutes. Add the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/8", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

EXAMPLE B

Capsules			
No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	106	123
3	Corn Starch, Food Grade	40	70

40

-continued

Capsules			
No.	Ingredient	mg/tablet	mg/tablet
4	Magnesium Stearate NP	4	7
Total		250	700

Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

Representative formulations comprising a cholesterol biosynthesis inhibitor are well known in the art. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms disclosed above for substituted azetidinone compounds may readily be modified using the knowledge of one skilled in the art.

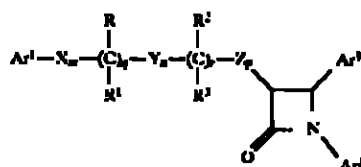
Using the test procedures described above, the following in vivo data were obtained for the exemplified compounds. Data is reported as percent change (i.e., percent reduction in cholesterol esters) versus control, therefore, negative numbers indicate a positive lipid-lowering effect.

% Reduction			
Ex. #	Serum Cholest.	Cholest. Esters	Dose mg/kg
1A	-25	0	50
1B	-15	-39	50
1C	14	0	50
2	0	0	50
3A	-31	-64	50
4C	-60	-92	50
3D	-17	-61	10
3E	0	0	10
3F	-39	-77	10
2G	-18	-38	10
3H	41	-86	10
3I	0	-22	10
3J	0	0	3
3K	0	0	10
3L	-15	-21	10
3M	0	-22	10
4A	0	-54	3
4B	-37	-89	3
4C	-12.5	0	3
4D	9	0	7
4E	0	-16	3
4F	-39	-95	3
5	0	-64	10
6A	-34	-75	1
6A-1	-43	-93	1
6B	-40	-92	3
6C	0	-48	3
6D	-46	-95	10
8A	0	-44	3
8B	-50	-95	3
8C	-14	-37	1
8D	-49	98	1
8E	-23	-66	3
8F	-43	-94	1
10	-26	-77	3

We claim:

1. A pharmaceutical composition for the treatment or prevention of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising an effective amount of a compound represented by the formula I

43



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ and Ar² are independently selected from the group consisting of aryl and R⁴-substituted aryl;

Ar³ is aryl or R⁴-substituted aryl;

X, Y and Z are independently selected from the group consisting of —CH₂—, —CH(lower alkyl)— and —C(lower alkyl)—;

R and R² are independently selected from the group consisting of —OR⁶, —O(CO)R⁶, —(XCO)OR⁶ and —(XCO)NR⁶R⁷;

R¹ and R² are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1; r is 0 or 1; m, n and p are independently 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R⁴ is 1-5 substituents independently selected from the group consisting of lower alkyl, —OR⁶, —O(CO)R⁶, —O(CO)OR⁶, —O(CH₂)₁₋₄OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁶, —NR⁶(CO)NR⁶R⁷, —NR⁶SO₂R⁷, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₂R⁶, —O(CH₂)₁₋₁₀—(CO)R⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —(lower alkylene)COOR⁶, —CH=CH—COOR⁶, —Cl₂, —CN, —NO₂ and halogen;

R⁵ is 1-5 substituents independently selected from the group consisting of —OR⁶, —O(CO)R⁶, —O(CO)OR⁶, —O(CH₂)₁₋₅OR⁶, —O(CH₂)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁶, —NR⁶(CO)NR⁶R⁷, —NR⁶SO₂R⁷, —(CO)OR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₂R⁶, —O(CH₂)₁₋₁₀—(CO)R⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —(lower alkylene)COOR⁶ and —CH=CH—COOR⁶;

R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R⁶ is lower alkyl, aryl or aryl-substituted lower alkyl; in combination with an effective amount of a cholesterol biosynthesis inhibitor selected from the group consisting of HMG CoA reductase inhibitors.

7. A method of claim 6 wherein, in the compound of formula I, Ar¹ is phenyl or R⁴-substituted phenyl, wherein R⁴ is halogen; Ar² is phenyl or R⁴-substituted phenyl, wherein R⁴ is halogen or —OR⁶, wherein R⁶ is lower alkyl or hydrogen; Ar³ is R⁴-substituted phenyl, wherein R⁴ is —OR⁶, wherein R⁶ is lower alkyl or hydrogen; X, Y, and Z are each —CH₂—; R¹ and R² are each hydrogen; R and R² are each —OR⁶, wherein R⁶ is hydrogen; and the sum of m, n, p, q and r is 2, 3 or 4.

8. A method of claim 6 wherein the HMG CoA reductase inhibitor is selected from the group consisting of lovastatin, pravastatin, fluvastatin, simvastatin and atorvastatin.

9. A method of claim 6 wherein the compound of formula I is selected from the group consisting of

44

rel 3(R)-(2(R)-hydroxy-2-phenylethyl)-4(R)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

rel 3(R)-(2(R)-hydroxy-2-phenylethyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(S)-(1(S)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(S)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(R)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(R)-(3(R)-hydroxy-3-phenylpropyl)-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

3(R)-(3(S)-hydroxy-3-phenylpropyl)-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

4(S)-(4-hydroxyphenyl)-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

4(S)-(4-hydroxyphenyl)-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

rel 3(R)-[3(RS)-hydroxy-3-[4-(methoxymethoxy)phenyl]propyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(R)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone;

4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone;

3(R)-[3(R)-acetyloxy]-3-phenylpropyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

3(R)-[3(S)-acetyloxy]-3-phenylpropyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

3(R)-[3(R)-acetyloxy]-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)-phenyl]-1-(4-fluorophenyl)-2-azetidinone;

3(R)-[3(S)-acetyloxy]-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)-phenyl]-1-(4-fluorophenyl)-2-azetidinone;

3(R)-[3(R)-acetyloxy]-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone;

3(R)-[3(S)-acetyloxy]-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone; and

rel 1-(4-fluorophenyl)-4(S)-(4-hydroxyphenyl)-3(R)-(1(R)-hydroxy-3-phenylpropyl)-2-azetidinone.

10. A method of claim 6 comprising administering a combination of 1-(4-fluorophenyl)-3(R)-[3(R)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone and lovastatin, pravastatin, fluvastatin, simvastatin or atorvastatin.

* * * * *

23

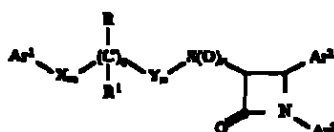
-continued

Ex. #	% Reduction		
	Serum Cholest.	Cholest. Esters	Dose mg/kg
11	-33	-85	3
14	-20	-64	3
15	-27	-88	1
18	-27	-68	3

For racemic compounds of formula I or active diastereomers or enantiomers of compounds of formula I, compounds administered at dosages of 0.1-25 mg/kg show a range of -21 to -97% reduction in cholesterol esters, and a -57 to 0% reduction in serum cholesterol. Compounds preferably show a range of -21 to -97% reduction in cholesterol esters at a dosage range of 0.1 to 3 mg/kg, more preferably a range of -21 to -97% reduction in cholesterol esters at a dosage range of 0.1 to 1 mg/kg.

We claim:

1. A pharmaceutical composition for the treatment or prevention of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising a compound represented by the structural formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ is aryl, R²⁰-substituted aryl or heteroaryl;

Ar² is aryl or R⁴-substituted aryl;

Ar³ is aryl or R⁵-substituted aryl;

X and Y are independently selected from the group consisting of -CH₂-, -CH(lower alkyl)- and -C(lower alkyl)-;

R is -OR⁶, -O(CO)R⁶, -O(CO)OR⁶ or -O(CO)NR⁷R⁸; R¹ is hydrogen, lower alkyl or aryl; or R and R¹ together are =O;

q is 0 or 1;

r is 0, 1 or 2;

m and n are independently 0, 1, 2, 3 or 4; provided that the sum of m, n and q is 2, 3 or 4;

R⁴ is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR⁶, -O(CO)R⁶, -O(CO)OR⁶, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁷R⁸, -NR⁷R⁸, -NR⁷(CO)R⁶, -NR⁷(CO)OR⁶, -NR⁷(CO)NR⁷R⁸, -NR⁷SO₂R⁶, -COOR⁶, -CONR⁷R⁸, -COR⁶, -SO₂NR⁷R⁸, S(O)₂R⁶, -O(CH₂)₁₋₁₀COOR⁶, -O(CH₂)₁₋₁₀CONR⁷R⁸, -(lower alkylene)COOR⁶ and -CH=CH-COOR⁶;

R⁵ is 1-5 substituents independently selected from the group consisting of -OR⁶, -O(CO)R⁶, -O(CO)OR⁶, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁷R⁸, -NR⁷R⁸, -NR⁷(CO)R⁶, -NR⁷(CO)OR⁶, -NR⁷(CO)NR⁷R⁸, -NR⁷SO₂R⁶, -COOR⁶, -CONR⁷R⁸, -COR⁶, -SO₂NR⁷R⁸, S(O)₂R⁶, -O(CH₂)₁₋₁₀COOR⁶, -O(CH₂)₁₋₁₀CONR⁷R⁸, -CF₃, -CN, -NO₂, halogen, -(lower alkylene)COOR⁶ and -CH=CH-COOR⁶;

R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

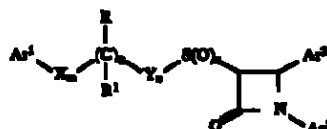
24

R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl; and R¹⁰ is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR⁶, -O(CO)R⁶, -O(CO)OR⁶, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁷R⁸, -NR⁷R⁸, -NR⁷(CO)R⁶, -NR⁷(CO)OR⁶, -NR⁷(CO)NR⁷R⁸, -NR⁷SO₂R⁶, -COOR⁶, -CONR⁷R⁸, -COR⁶, -SO₂NR⁷R⁸, S(O)₂R⁶, -O(CH₂)₁₋₁₀COOR⁶, -O(CH₂)₁₋₁₀CONR⁷R⁸, -CF₃, -CN, -NO₂ and halogen; a cholesterol biosynthesis inhibitor and a pharmaceutically acceptable carrier.

2. A pharmaceutical composition of claim 1 wherein the cholesterol biosynthesis inhibitor is selected from the group consisting of HMG CoA reductase inhibitors.

3. A pharmaceutical composition of claim 2 wherein the cholesterol biosynthesis inhibitor is selected from the group consisting of lovastatin, pravastatin, fluvastatin, atorvastatin and simvastatin.

4. A method of treating or preventing atherosclerosis or reducing plasma cholesterol levels comprising simultaneously or sequentially administering to a mammal in need of such treatment an effective amount of a cholesterol biosynthesis inhibitor and a compound represented by the structural formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ is aryl, R²⁰-substituted aryl or heteroaryl;

Ar² is aryl or R⁴-substituted aryl;

Ar³ is aryl or R⁵-substituted aryl;

X and Y are independently selected from the group consisting of -CH₂-, -CH(lower alkyl)- and -C(lower alkyl)-;

R is -OR⁶, -O(CO)R⁶, -O(CO)OR⁶ or -O(CO)NR⁷R⁸; R¹ is hydrogen, lower alkyl or aryl; or R and R¹ together are =O;

q is 0 or 1;

r is 0, 1 or 2;

m and n are independently 0, 1, 2, 3 or 4; provided that the sum of m, n and q is 2, 3 or 4;

R⁴ is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR⁶, -O(CO)R⁶, -O(CO)OR⁶, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁷R⁸, -NR⁷R⁸, -NR⁷(CO)R⁶, -NR⁷(CO)OR⁶, -NR⁷(CO)NR⁷R⁸, -NR⁷SO₂R⁶, -COOR⁶, -CONR⁷R⁸, -COR⁶, -SO₂NR⁷R⁸, S(O)₂R⁶, -O(CH₂)₁₋₁₀COOR⁶, -O(CH₂)₁₋₁₀CONR⁷R⁸, -(lower alkylene)COOR⁶ and -CH=CH-COOR⁶;

R⁵ is 1-5 substituents independently selected from the group consisting of -OR⁶, -O(CO)R⁶, -O(CO)OR⁶, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁷R⁸, -NR⁷R⁸, -NR⁷(CO)R⁶, -NR⁷(CO)OR⁶, -NR⁷(CO)NR⁷R⁸, -NR⁷SO₂R⁶, -COOR⁶, -CONR⁷R⁸, -COR⁶, -SO₂NR⁷R⁸, S(O)₂R⁶, -O(CH₂)₁₋₁₀COOR⁶, -O(CH₂)₁₋₁₀CONR⁷R⁸, -CF₃, -CN, -NO₂, halogen, -(lower alkylene)COOR⁶ and -CH=CH-COOR⁶;

R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl; and

25

R¹⁰ is 1-5 substituents independently selected from the group consisting of lower alkyl, —OR⁶, —O(CO)R⁶, —O(CO)OR⁶, —O(CH₂)₁₋₁₀OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁶, —NR⁶(CO)OR⁶, —NR⁶(CO)NR⁶R⁶, —NR⁶SO₂R⁶, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₂R⁶, —O(CH₂)₁₋₁₀COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —CF₃, —CN, —NO₂ and halogen.

5. A method as claimed in claim 4, wherein the cholesterol biosynthesis inhibitor is selected from the group consisting of HMG CoA reductase inhibitors.

6. A method as claimed in claim 5, wherein the cholesterol biosynthesis inhibitor is selected from the group consisting of lovastatin, pravastatin, fluvastatin, simvastatin and atorvastatin.

7. A composition of claim 3 comprising a compound of formula I wherein q is 0; Ar¹ is phenyl, R¹⁰-substituted phenyl or thienyl; Ar² is R⁴-substituted phenyl; Ar³ is phenyl or R⁵-substituted phenyl; X and Y are each —CH₂—; and the sum of m and n is 2, 3 or 4.

8. A composition of claim 3 comprising a compound of formula I wherein q is 1; Ar¹ is phenyl, R¹⁰-substituted phenyl or thienyl; Ar² is R⁴-substituted phenyl; Ar³ is phenyl or R⁵-substituted phenyl; X and Y are each —CH₂—; the sum of m and n is 1, 2 or 3; and R¹ is hydrogen and R is —OR⁶, wherein R⁶ is hydrogen, or wherein R and R¹ together form a =O group.

9. A composition of claim 3 wherein the compound of formula I is selected from the group consisting of

- trans-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-thio]-2-azetidinone;
trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-thio]-2-azetidinone;
cis-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-thio]-2-azetidinone;
trans-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
cis-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
cis-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
trans-4-[1-(4-fluorophenyl)-4-oxo-3-[(2-phenylethyl)-sulfinyl]-2-azetidinyl]-phenyl acetate;
cis-4-[1-(4-fluorophenyl)-4-oxo-3-[(2-phenylethyl)-sulfinyl]-2-azetidinyl]-phenyl acetate; and
(+/-)-trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
trans-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-oxoethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone;
trans-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-hydroxyethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone;
(3R,4R) 1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-oxoethyl]-sulfinyl]-4-(4-hydroxyphenyl)-2-azetidinone;
1-(4-fluorophenyl)-3(R)-[[2-(4-fluorophenyl)-2(R)-hydroxyethyl]-sulfinyl]-4(R)-(4-hydroxyphenyl)-2-azetidinone;
1-(4-fluorophenyl)-3(R)-[[2-(4-fluorophenyl)-2(S)-hydroxyethyl]-sulfinyl]-4(R)-(4-hydroxyphenyl)-2-azetidinone;
(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(2-thienyl)-2-oxoethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone;

26

(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(3-thienyl)-2-oxoethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone;

(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(3-pyridinyl)-2-oxoethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone;

(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(4-pyridinyl)-2-oxoethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone;

(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(2-pyridinyl)-2-oxoethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone;

(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-hydroxy-2-(3-thienyl)ethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone;

(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-hydroxy-2-(4-pyridinyl)ethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone;

(3S,4R) cis-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-oxoethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone; and

(3S,4R) cis-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-hydroxyethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone.

10. A method of claim 6 comprising a compound of formula I wherein q is 0; Ar¹ is phenyl, R¹⁰-substituted phenyl or thienyl; Ar² is R⁴-substituted phenyl; Ar³ is phenyl or R⁵-substituted phenyl; X and Y are each —CH₂—; and the sum of m and n is 2, 3 or 4.

11. A method of claim 6 comprising a compound of formula I wherein q is 1; Ar¹ is phenyl, R¹⁰-substituted phenyl or thienyl; Ar² is R⁴-substituted phenyl; Ar³ is phenyl or R⁵-substituted phenyl; X and Y are each —CH₂—; the sum of m and n is 1, 2 or 3; and R¹ is hydrogen and R is —OR⁶, wherein R⁶ is hydrogen, or wherein R and R¹ together form a =O group.

12. A method of claim 6 wherein the compound of formula I is selected from the group consisting of

- trans-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-thio]-2-azetidinone;
trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-thio]-2-azetidinone;
cis-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-thio]-2-azetidinone;
trans-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
cis-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
cis-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
trans-4-[1-(4-fluorophenyl)-4-oxo-3-[(2-phenylethyl)-sulfinyl]-2-azetidinyl]-phenyl acetate;
cis-4-[1-(4-fluorophenyl)-4-oxo-3-[(2-phenylethyl)-sulfinyl]-2-azetidinyl]-phenyl acetate; and
(+/-)-trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
trans-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-oxoethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone;
trans-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-hydroxyethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone;
(3R,4R) 1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-oxoethyl]-sulfinyl]-4-(4-hydroxyphenyl)-2-azetidinone;
1-(4-fluorophenyl)-3(R)-[[2-(4-fluorophenyl)-2(R)-hydroxyethyl]-sulfinyl]-4(R)-(4-hydroxyphenyl)-2-azetidinone;

27

1-(4-fluorophenyl)-3(R)-[[2-(4-fluorophenyl)-2(S)-hydroxyethyl]-sulfinyl]-4(R)-(4-hydroxyphenyl)-2-azetidinone;

(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(2-thienyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone; 5

(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(3-thienyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone;

(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(3-pyridinyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone; 10

(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(4-pyridinyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone;

(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(2-pyridinyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone;

28

(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-hydroxy-2-(3-thienyl)ethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone;

(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-hydroxy-2-(4-pyridinyl)ethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone;

(3S,4R) cis-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone; and

(3S,4R) cis-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-hydroxyethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone.

* * * * *



US 2002/0128253A1

(19) United States

(12) Patent Application Publication
Glombik et al.

(10) Pub. No.: US 2002/0128253 A1

(43) Pub. Date: Sep. 12, 2002

161

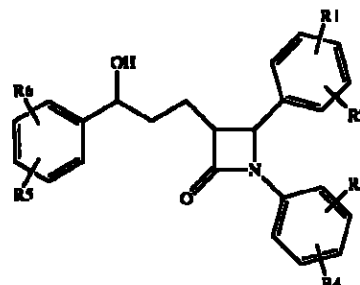
(54) DIPHENYLAZETIDINONE DERIVATIVES,
PROCESS FOR THEIR PREPARATION,
MEDICAMENTS COMPRISING THESE
COMPOUNDS AND THEIR USE

Publication Classification

(51) Int. Cl.⁷ A61K 31/397; C07D 25/18
(52) U.S. CL 514/210.02; 540/210(76) Inventors: Helner Glombik, Hofheim (DE);
Werner Krümer, Mainz-Laubenheim
(DE); Stefanie Flohr, Eppstein (DE);
Wendelin Frick, Hundstatten-Neurathach
(DE); Hubert Heuer, Schwabenheim
(DE); Gerhard Jaehne, Frankfurt am
Main (DE); Andreas Jodenschmidt,
Bad Soden (DE); Hans-Ludwig
Schaefer, Hofheim (DE)Correspondence Address:
Finnegan, Henderson, Farahow,
Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, DC 20005-3315 (US)

(57) ABSTRACT

Compounds of the formula I,



(21) Appl. No.: 10/021,044

(22) Filed: Dec. 19, 2001

(30) Foreign Application Priority Data

Dec. 21, 2000 (DE)..... 10064402.3
Nov. 7, 2001 (DE)..... 10154518.5in which R1, R2, R3, R4, R5, and R6 have the meanings
given in the description, and their physiologically acceptable
salts. The compounds are suitable for use, for example, as
hypolipidemics.

DIPHENYLAZETIDINONE DERIVATIVES, PROCESS FOR THEIR PREPARATION, MEDICAMENTS COMPRISING THESE COMPOUNDS AND THEIR USE

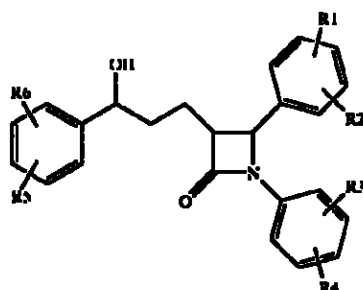
[0001] This application claims the benefit of priority under 35 U.S.C. §119(a) to German patent application no. 10064402.3, filed on Dec. 21, 2000, and German patent application no. 10154518.5, filed on Nov. 7, 2001. The contents of both priority documents are incorporated by reference herein.

[0002] The invention relates to substituted diphenylazetidinones, to their physiologically acceptable salts and to derivatives having physiological function.

[0003] Diphenylazetidinones (such as, for example, ezetimibe) and their use for treating hyperlipidemia and arteriosclerosis and hypercholesterolemia have already been described [cf. Drugs of the Future 2000, 25(7):679-685].

[0004] It was an object of the invention to provide further compounds having a therapeutically utilisable hypolipidemic action. In particular, it was an object to find novel compounds which, compared to the compounds described in the prior art, are absorbed to a very low extent. Very low absorption is to be understood as meaning an intestinal absorption of less than 10%, preferably less than or equal to 5%. In particular, absorption of the novel compounds should be less than that of ezetimibe. Pharmaceutically active compounds which are absorbed to a very low extent generally have considerably fewer side-effects.

[0005] Accordingly, an embodiment of the invention relates to compounds of the formula I,



[0006] in which

[0007] R1, R2, R3, R4, R5, R6 independently of one another are (C₁-C₃₀)-alkylene-1, where one or more carbon atoms of the alkylene radical may be replaced by -O-, -(C=O)-, -CH=CH-, -C≡C-, -N((C₁-C₆)-alkyl)- or -NH-; or

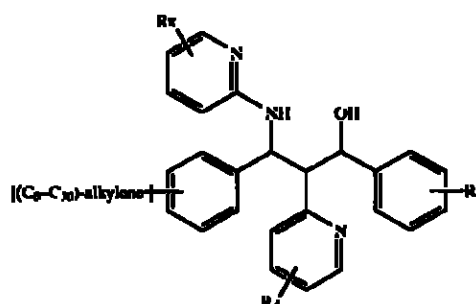
[0008] H, F, Cl, Br, I, CF₃, NO₂, CN, COOH, COO(C₁-C₆)-alkyl, CONH₂, CONH(C₁-C₆)-alkyl, CON((C₁-C₆)-alkyl)₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl or O-(C₁-C₆)-alkyl, where one, more or all hydrogens in the alkyl radicals may be replaced by fluorine; or

[0009] SO₂-NH₂, SO₂NH(C₁-C₆)-alkyl, SO₂N((C₁-C₆)-alkyl)₂, S-(C₁-C₆)-alkyl, S-(CH₂)_n-phenyl,

phenyl, SO-(C₁-C₆)-alkyl, SO-(CH₂)_n-phenyl, SO₂-(C₁-C₆)-alkyl or SO₂-(CH₂)_n-phenyl, where n=0-6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl or NH₂; or

[0010] NH₂, NH-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, NH(C₁-C₇)-acyl, phenyl or O-(CH₂)_n-phenyl, where n=0-6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, SO₂-CH₃, COOH, COX-(C₁-C₆)-alkyl or CONH₂;

[0011] I. is shown connected to (C₁-C₃₀)-alkylene as follows:



[0012] Rx, Ry, Rz independently of one another are H, F, Cl, Br, I, CF₃, NO₂, CN, COOH, COO-(C₁-C₆)-alkyl, CONH₂, CONH-(C₁-C₆)-alkyl, CON-((C₁-C₆)-alkyl)₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl or O-(C₁-C₆)-alkyl, where one, more or all hydrogens in the alkyl radicals may be replaced by fluorine; or

[0013] SO₂-NH₂, SO₂NH-(C₁-C₆)-alkyl, SO₂N-((C₁-C₆)-alkyl)₂, S-(C₁-C₆)-alkyl, S-(CH₂)_n-phenyl, SO-(C₁-C₆)-alkyl, SO-(CH₂)_n-phenyl, SO₂-(C₁-C₆)-alkyl or SO₂-(CH₂)_n-phenyl, where n=0-6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl or NH₂; or

[0014] NH₂, NH-(C₁-C₆)-alkyl, N-((C₁-C₆)-alkyl)₂, NH-(C₁-C₇)-acyl, phenyl or O-(CH₂)_n-phenyl, where n=0-6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, NH₂, NH-(C₁-C₆)-alkyl, N-((C₁-C₆)-alkyl)₂, SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl or CONH₂;

[0015] wherein at least one of the radicals R1 or R6 has the meaning (C₁-C₃₀)-alkylene-1, where one or more carbon atoms of the alkylene radical may be replaced by -O-, -(C=O)-, -CH=CH-, -C≡C-, -N((C₁-C₆)-alkyl)- or -NH-, and its pharmaceutically acceptable salts.

[0016] Another embodiment of the invention relates to compounds of the formula I, in which at least one of the radicals R1 to R6 has the meaning (C_6-C_{30}) -alkylene-1, where one or more carbon atoms of the alkylene radical may be replaced by $-O-$, $-(C=O)-$, or $-NH-$.

[0017] Another embodiment of the invention relates to compounds of the formula I, in which one of the radicals R1 or R3 has the meaning (C_6-C_{30}) -alkylene-1, where one or more carbon atoms of the alkylene radical may be replaced by $-O-$, $-(C=O)-$ or $-NH-$.

[0018] Another embodiment of the invention relates to compounds of the formula I, in which one of the radicals R1 or R3 has the meaning $-(CH_2)_{0-1}-NH-(C=O)_{0-1}-(C_3-C_{24})$ -alkylene- $(C=O)_{0-1}-NH-1$; where one or more carbon atoms of the alkylene radical may be replaced by oxygen atoms.

[0019] One of the radicals R1 to R6 may be linked, for example, to the L radical in the meta position of ring C of the I groups.

[0020] Owing to their increased solubility in water, compared to the parent compounds, pharmaceutically acceptable salts are particularly suitable for medical applications. These salts should have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds according to the invention are salts of inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, metaphosphoric acid, nitric acid, sulfuric acid and sulfuric acid, and of organic acids, such as acetic acid, benzenesulfonic acid, benzoic acid, citric acid, ethanesulfonic acid, fumaric acid, gluconic acid, glycolic acid, isothionic acid, lactic acid, lactobionic acid, maleic acid, malic acid, methanesulfonic acid, succinic acid, p-toluenesulfonic acid, tartaric acid and trifluoroacetic acid, for example. For medical purposes, very particular preference is given to using the chloride salt. Suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts).

[0021] The scope of the invention also includes salts having a pharmaceutically unacceptable anion, which salts may be useful intermediates for preparing or purifying pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.

[0022] Here, the term "derivative having physiological function" refers to any physiologically acceptable derivative of a compound according to the invention, for example an ester, capable of forming, upon administration to a mammal, for example man, to form such a compound or an active metabolite (directly or indirectly).

[0023] A further aspect of this invention are prodrugs of the compounds according to the invention. Such prodrugs can be metabolized in vivo to give a compound according to the invention. These prodrugs may or may not be active in their own right.

[0024] The compounds according to the invention can also be present in various polymorphic forms, for example as amorphous and crystalline polymorphic forms. The scope of the invention includes all polymorphic forms of the compounds according to the invention, which form a further

aspect of the invention. The compounds of the invention may also exist in the form of solvates.

[0025] The compounds of the formula I and their pharmaceutically acceptable salts, esters, prodrugs and derivatives having physiological function are ideal medicaments for treating an impaired lipid metabolism, in particular hyperlipidemia. The compounds of the formula I are also suitable for modulating the serum cholesterol concentration and for treating arteriosclerotic manifestations. The compounds of the invention are also suitable for the treatment of insulin resistance.

[0026] As used here, "treatment" or "therapy" of a condition and "treating" a condition can mean successfully eliminating the condition, reducing the effects associated with it, and/or reducing its severity. It also includes administering the relevant compounds to a patient to avoid recurrence of a condition. It also includes avoiding the onset of a condition by administering the relevant compounds to patients falling into a risk group or category for developing the particular condition. Those skilled in the art can routinely identify patients likely to present with a given condition, thereby qualifying as candidates for treatment.

[0027] The compound(s) of the formula (I) can also be administered in combination with other active compounds.

[0028] The amount of a compound of the formula (I) required to achieve the desired biological effect depends on a number of factors, for example on the specific compound chosen, on the intended use, on the mode of administration and on the clinical condition of the patient. In general, the daily dose is in the range from 0.1 mg to 100 mg (typically from 0.1 mg to 50 mg) per day per kilogram of bodyweight, for example 0.1-10 mg/kg/day. Tablets or capsules may contain, for example, from 0.01 to 100 mg, typically from 0.02 to 50 mg. In the case of pharmaceutically acceptable salts, the abovementioned weight data relate to the weight of the diphenyl-azetidione-ion derived from the salt. For the therapy of the abovementioned conditions, the compounds of the formula (I) can be used themselves as the compound, but preferably they are present in the form of a pharmaceutical composition with an acceptable carrier. The carrier must of course be acceptable in the sense that it is compatible with the other constituents of the composition and is not harmful to the health of the patient. The carrier can be a solid or a liquid or both and is preferably formulated with the compound as an individual dose, for example as a tablet, which can contain from 0.05% to 95% by weight of the active compound. Further pharmaceutically active substances can also be present, including further compounds of the formula (I). The pharmaceutical compositions according to the invention can be prepared by one of the known pharmaceutical methods, which essentially consist in mixing the constituents with pharmacologically acceptable carriers and/or auxiliaries.

[0029] Pharmaceutical compositions according to the invention are those which are suitable for oral or peroral (e.g. sublingual) administration, although the most suitable manner of administration is dependent in each individual case on the nature and severity of the condition to be treated and on the type of the compound of the formula (I) used in each case. Coated formulations and coated delayed-release formulations are also included in the scope of the invention. Acid-resistant and enteric formulations are preferred. Suit-

able enteric coatings include cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methylmethacrylate.

[0030] Suitable pharmaceutical compounds for oral administration can be present in separate units, such as, for example, capsules, cachets, lozenges or tablets, which in each case contain a specific amount of the compound of the formula (I); as a powder or granules; as a solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. As already mentioned, these compositions can be prepared according to any suitable pharmaceutical method which includes a step in which the active compound and the carrier (which can consist of one or more additional constituents) are brought into contact. In general, the compositions are prepared by uniform and homogeneous mixing of the active compound with a liquid and/or finely divided solid carrier, after which the product, if necessary, is shaped. For example, a tablet can thus be prepared by pressing or shaping a powder or granules of the compound, if appropriate with one or more additional constituents. Pressed tablets can be produced by tableting the compound in free-flowing form, such as, for example, a powder or granules, if appropriate mixed with a binder, lubricant, inert diluent and/or a (number of) surface-active/dispersing agent(s) in a suitable machine. Shaped tablets can be produced by shaping the pulverulent compound moistened with an inert liquid diluent in a suitable machine.

[0031] Pharmaceutical compositions which are suitable for peroral (sublingual) administration include lozenges which contain a compound of the formula (I) with a flavoring, customarily sucrose and gum arabic or tragacanth, and pastilles which include the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

[0032] Suitable other active compounds for the combination preparations include: all antidiabetics, mentioned in Rule Line 2001, Chapter 12, the disclosure of which is incorporated by reference herein. They can be combined with the compounds of the formula I according to the invention in particular to achieve a synergistically enhanced action. The active compound combination can be administered either by separate administration of the active compounds to the patient or in the form of combination preparations comprising a plurality of active compounds in a pharmaceutical preparation.

[0033] Antidiabetics include insulin and insulin derivatives, such as, for example, Lantus® or HMR 1964, GLP-1 derivatives, such as, for example, those disclosed by Novo Nordisk A/S in WO 98/08871, the disclosure of which is incorporated by reference herein, and oral hypoglycemic active compounds.

[0034] The oral hypoglycemic active compounds preferably include sulfonyl ureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, potassium channel openers, such as, for example, those disclosed by Novo Nordisk A/S in WO 97/26265 and WO 99/03861, the disclosures of which are incorporated by reference herein, insulin sensitizers, inhibitors of liver enzymes involved in stimulating gluconeogenesis and/or glycogenolysis, modulators of glucose uptake, compounds which modulate lipid

metabolism, such as antihyperlipidemic active compounds and antilipidemic active compounds, compounds which reduce food intake, PPAR and PXR agonists and active compounds which act on the ATP-dependent potassium channel of the beta cells.

[0035] In one embodiment of the invention, the compounds of the formula I are administered in combination with an HMGCoA reductase inhibitor such as simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin, rosuvastatin.

[0036] In one embodiment of the invention, the compounds of the formula I are administered in combination with a cholesterol absorption inhibitor, such as, for example, ezetimibe, liguexide, parnaquexide.

[0037] In one embodiment of the invention, the compounds of the formula I are administered in combination with a PPAR gamma agonist, such as, for example, rosiglitazone, pioglitazone, JTT-501, GI 262570.

[0038] In one embodiment of the invention, the compounds of the formula I are administered in combination with a PPAR alpha agonist, such as, for example, GW 9578, GW 7647.

[0039] In one embodiment of the invention, the compounds of the formula I are administered in combination with a mixed PPAR alpha/gamma agonist, such as, for example, GW 1536, AVE 8042, AVE 8134, AVE 0847.

[0040] In one embodiment of the invention, the compounds of the formula I are administered in combination with a fibrate, such as, for example, fenofibrate, clofibrate, bezafibrate.

[0041] In one embodiment of the invention, the compounds of the formula I are administered in combination with an MTP inhibitor, such as, for example, Bay 13-9552, RMS-201038, R-103757.

[0042] In one embodiment of the invention, the compounds of the formula I are administered in combination with a bile acid absorption inhibitor, such as, for example, HMR 1453.

[0043] In one embodiment of the invention, the compounds of the formula I are administered in combination with a CETP inhibitor, such as, for example, Bay 19-4789.

[0044] In one embodiment of the invention, the compounds of the formula I are administered in combination with a polymeric bile acid adsorber, such as, for example, cholestyramine, colestolvan.

[0045] In one embodiment of the invention, the compounds of the formula I are administered in combination with an LDL receptor inducer, such as, for example, HMR1171, HMR1586.

[0046] In one embodiment of the invention, the compounds of the formula I are administered in combination with an ACAT inhibitor, such as, for example, avasimibe.

[0047] In one embodiment of the invention, the compounds of the formula I are administered in combination with an antioxidant, such as, for example, OPC-14117.

[0048] In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein lipase inhibitor, such as, for example, NC-1886.

[0049] In one embodiment of the invention, the compounds of the formula I are administered in combination with an ATP citrate lyase inhibitor, such as, for example, SB-204990.

[0050] In one embodiment of the invention, the compounds of the formula I are administered in combination with a squalene synthetase inhibitor, such as, for example, HMS-188494.

[0051] In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein(a) antagonist, such as, for example, C1-1027 or nicotinic acid.

[0052] In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipase inhibitor, such as, for example, Orlistat.

[0053] In one embodiment of the invention, the compounds of the formula I are administered in combination with insulin.

[0054] In one embodiment, the compounds of the formula I are administered in combination with a sulfonyl urea, such as, for example, tolbutamide, glibenclamide, glipizide or glimepiride.

[0055] In one embodiment, the compounds of the formula I are administered in combination with a biguanide, such as, for example, metformin.

[0056] In another embodiment, the compounds of the formula I are administered in combination with a meglitinide, such as, for example, repaglinide.

[0057] In one embodiment, the compounds of the formula I are administered in combination with a thiazolidinedione, such as, for example, troglitazone, ciglitazone, pioglitazone, rosiglitazone, or the compounds disclosed by Dr. Reckly's Research Foundation in WO 97/41097, the disclosure of which is incorporated by reference herein, in particular 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinyl-methoxy)phenyl]methyl]-2,4-thiazolidinedione.

[0058] In one embodiment, the compounds of the formula I are administered in combination with an α -glucosidase inhibitor, such as, for example, miglitol or acarbose.

[0059] In one embodiment, the compounds of the formula I are administered in combination with an active compound which acts on the ATP-dependent potassium channel of beta cells, such as, for example, tolbutamide, glibenclamide, glipizide, glimepiride or repaglinide.

[0060] In one embodiment, the compounds of the formula I are administered in combination with more than one of the abovementioned compounds, for example in combination with a sulfonyl urea and metformin, a sulfonyl urea and acarbose, repaglinide and metformin, insulin and a sulfonyl urea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

[0061] In a further embodiment, the compounds of the formula I are administered in combination with CART agonists, NPY agonists, MC4 agonists, orexin agonists, H3 agonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists, β 3-agonists, MSH (melanocyte-stimulating hormone) agonists, CCK agonists, serotonin reuptake inhibitors, mixed serotonin and noradrenergic compounds,

5HT agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone-releasing compounds, TRH agonists, decoupling protein 2- or 3 modulators, leptin agonists, DA agonists (bromocriptin, dopamine), lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR- β agonists.

[0062] In one embodiment of the invention, the further active compound is leptin.

[0063] In one embodiment, the further active compound is dexamphetamine or amphetamine.

[0064] In one embodiment, the further active compound is fenfluramine or dexfenfluramine.

[0065] In another embodiment, the further active compound is sibutramine.

[0066] In one embodiment, the further active compound is Orlistat.

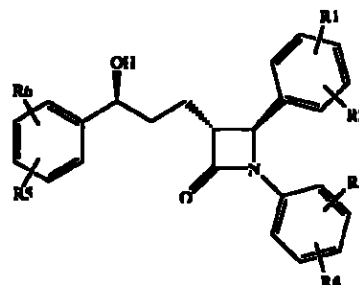
[0067] In one embodiment, the further active compound is mazindol or phentermine.

[0068] In one embodiment, the compounds of the formula I are administered in combination with fiber, preferably insoluble fiber, such as, for example, Caromax®. The combination with Caromax® can be given in one preparation or by separate administration of compounds of the formula I and Caromax®. Here, Caromax® can also be administered in the form of food, such as, for example, in bakery goods or muckli bars. Compared to the individual active compounds, the combination of compounds of the formula I with Caromax® is, in addition to an enhanced action, in particular with respect to the lowering of LDL cholesterol, also characterized by its improved tolerability.

[0069] It goes without saying that each suitable combination of the compounds according to the invention with one or more of the compounds mentioned above and optionally one or more further pharmacologically active substances is included in the scope of the present invention.

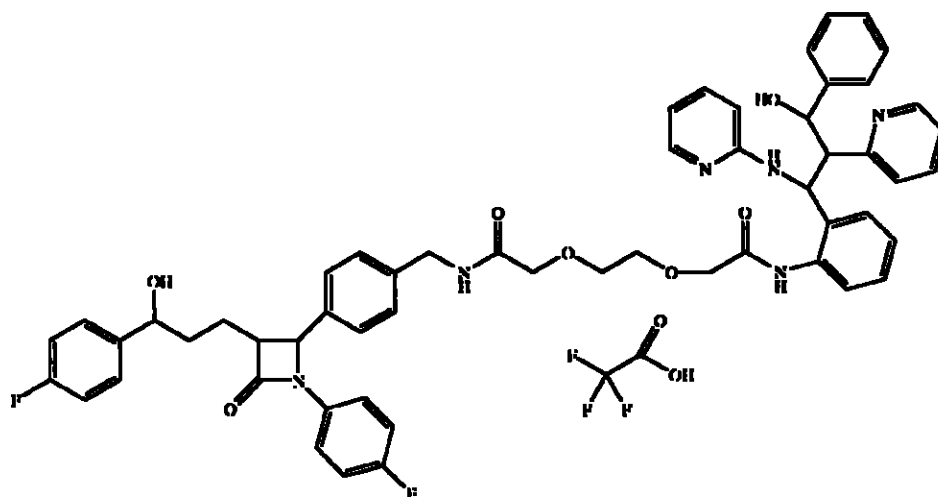
[0070] The invention furthermore provides both stereoisomer mixtures of the formula I and the pure stereoisomers of the formula I, and diastereomer mixtures of the formula I and the pure diastereomers. The mixtures are separated by chromatographic means.

[0071] Preference is given to both racemic and enantiomerically pure compounds of the formula I of the following structure:



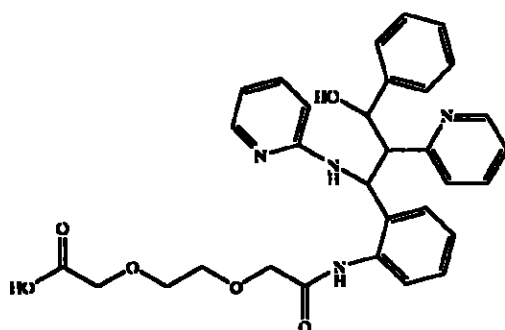
EXAMPLE XIX

[0098]



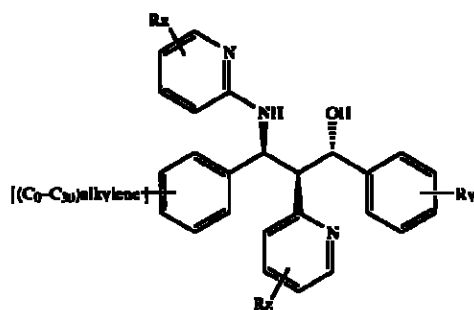
{1-[2-(2-{2-[(4-{1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxazetidin-2-yl}benzylcarbamoyl)methoxy]ethoxy}acetyl)amino)phenyl]-3-hydroxy-3-phenyl-2-pyridin-2-yl)propyl}pyridin-2-ylammonium trifluoroacetate 36

[0099]



[0100] $C_{31}H_{32}N_4O_6$ (556.62) MS (ESI) 557 (M+H)

1. is shown connected to (C₀-C₃₀)-alkylene as follows:



Rx, Ry, Rz independently of one another are H, F, Cl, Br, I, CF₃, NO₂, CN, COOH, COO-(C₁-C₆)-alkyl, CONH₂, CONH-(C₁-C₆)-alkyl, CON-[(C₁-C₆)-alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl or O-(C₁-C₆)-alkyl, where one, more or all hydrogens in the alkyl radicals may be replaced by fluorine; or

SO₂-NH₂, SO₂NH-(C₁-C₆)-alkyl, SO₂N-[(C₁-C₆)-alkyl]₂, S-(C₁-C₆)-alkyl, S-(CH₂)_n-phenyl, SO-(C₁-C₆)-alkyl, SO-(CH₂)_n-phenyl, SO₂-(C₁-C₆)-alkyl or SO₂-(CH₂)_n-phenyl, where n=0-6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl or NH₂; or

NH₂, NH-(C₁-C₆)-alkyl, N-[(C₁-C₆)-alkyl]₂, NH-(C₁-C₆)-acyl, phenyl or O-(CH₂)_n-phenyl, where n=0-6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, NH₂, NH-(C₁-C₆)-alkyl, N-[(C₁-C₆)-alkyl]₂, SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl or CONH₂;

where one of the radicals R1 or R3 has the meaning -(CH₂)_{n-1}-NH-(C=O)_{n-1}-(C₃-C₂₅)-alkylene-(C=O)_{n-1}-NH-L, where one or more carbon atoms of the alkylene radical may be replaced by oxygen atoms.

5. A pharmaceutical composition comprising one or more of the compounds as claimed in claim 1 and a pharmaceutically acceptable carrier.

6. A pharmaceutical composition comprising one or more compounds as claimed in claim 1 and at least one further active compound.

7. A pharmaceutical composition as claimed in claim 6, comprising, as a further active compound, one or more compounds that normalize lipid metabolism.

8. A pharmaceutical composition as claimed in claim 6, which comprises, as a further active compound, one or more

antidiabetics, hypoglycemically active compounds, HMG-CoA reductase inhibitors, cholesterol absorption inhibitors, PPAR gamma agonists, PPAR alpha agonists, PPAR alpha/gamma agonists, fibrates, MTP inhibitors, bile acid absorption inhibitors, CETP inhibitors, polymeric bile acid adsorbents, LDL receptor inducers, ACAT inhibitors, antioxidants, lipoprotein lipase inhibitors, ATP citrate lyase inhibitors, squalene synthetase inhibitors, lipoprotein(a) antagonists, lipase inhibitors, insulins, sulfonyl ureas, biguanides, meglitinides, thiazolidinediones, α-glucosidase inhibitors, active compounds which act on the ATP-dependent potassium channel of the beta cells, CART agonists, NPY agonists, MC4 agonists, orexin agonists, H3 agonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists, β3 agonists, MSH (melanocyte-stimulating hormone) agonists, CCK agonists, serotonin-reuptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT agonists, bombesin agonists, galanin antagonists, growth hormones, growth hormone-releasing compounds, TRH agonists, decoupling protein 2- or 3-modulators, leptin agonists, DA agonists, lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR-β agonists or amphetamines.

9. A method for the treatment of impaired lipid metabolism, which comprises administering to a host in need of the treatment an effective amount of at least one compound as claimed in claim 1.

10. A method as claimed in claim 9, wherein the host suffers from impaired lipid metabolism.

11. A method for the treatment of hyperlipidemia, which comprises administering to a host in need of the treatment an effective amount of at least one compound as claimed in claim 1.

12. A method as claimed in claim 11, wherein the host suffers from hyperlipidemia.

13. A method for controlling the serum cholesterol concentration in a host, which comprises administering to the host in need of the control of serum cholesterol concentration an effective amount of at least one compound as claimed in claim 1.

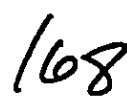
14. A method for the treatment of an arteriosclerotic manifestation, which comprises administering to a host in need of the treatment an effective amount of at least one compound as claimed in claim 1.

15. A method as claimed in claim 14, wherein the host suffers from an arteriosclerotic manifestation.

16. A method for the treatment of insulin resistance, which comprises administering to a host in need of the treatment an effective amount of at least one compound as claimed in claim 1.

17. A method as claimed in claim 16, wherein the host suffers from insulin resistance.

* * * * *



[11] Patent Number: 5,767,115

[45] **Date of Patent:** Jun. 16, 1998

[54] HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS

[75] Inventors: **Stuart B. Rosenblum, West Orange;**
Sandeep Dagar, Bridgewater; Denise
A. Burnett, Fanwood; John W. Clader,
Cranford; Brian A. McKittrick,
Bloomfield, all of N.J.

[73] Assignee: Schering-Plough Corporation,
Kenilworth, N.J.

[21] Appl. No.: 617,731

[22] Filed: May 18, 1996

Related U.S. Application Data

[63] Continuation-in-part of PCT/U894/10099, Sep. 14, 1994, continuation-in-part of Ser. No. 257,593, Jun. 9, 1994, Pat. No. 5,631,365, which is a continuation-in-part of Ser. No. 102,440, Sep. 21, 1993, abandoned.

[51] Int. Cl.⁶ _____ C07D 205/00; A61K 31/395

[52] U.S. Cl. _____ 514/210; 540/200

[58] **Field of Search** search other available sources **540/200; 514/210**

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,375,475	3/1983	Willard et al.	424/279
4,983,597	1/1991	Yang et al.	514/216
5,099,034	3/1992	Yoshida	562/579
5,350,868	9/1994	Yoshida	562/579

FOREIGN PATENT DOCUMENTS

199630	10/1986	European Pat. Off.
264231	4/1988	European Pat. Off.
337549	10/1989	European Pat. Off.
93/02048	2/1993	WIPO
WO94/17038	8/1994	WIPO

OTHER PUBLICATIONS

Ram et al, *Indian J. Chem., Sect A*, 29B, 12 (1990), pp. 1134-1137.

Hoekman et al. *J. Agric. Food Chem.*, 30 (1982), pp. 920-924.

Durst et al. *Can. J. Chem.*, 50 (1972), pp. 3196-3201.

Otto et al. *Liebigs Ann. Chem.*, (1983), pp. 1152-1161.

Panfil, et al. *Heterocycles*, 24, 6 (1986), pp. 1609–1617.

Schnitzer-Polokoff, et al. *Comp. Biochem. Physiol.*, 99A (1991), pp. 665-670.

Witzum, *Clavulonol*, 80, 5 (1989), pp. 1101-1114.

Hillgworth, *Drugs*, 36(Supp. 3) (1988), pp. 63-71.

Allain, et al. *Clin. Chem.*, 20, (1974), pp. 470-475.

Horie, et al. *Atherosclerosis*, 88 (1991), pp. 183-192.

Current Drugs: Anti-Atherosclerotic Agents-Summary

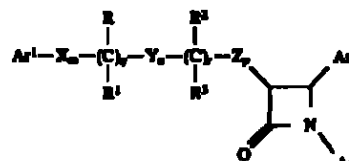
Georg et al. *Tet. Letters* 26, 33 (1985), pp. 3903-3906.

Hart et al. *Res. Letters*, 45 (1985), pp. 5493-5496.

Primary Examiner—Mark L. Berch
Attorney, Agent, or Firm—Anita W. Magatti

[57] ABSTRACT

Hydroxy-substituted azetidinone hypocholesterolemic agents of the formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ and Ar² are aryl or R⁴-substituted aryl:

Ar³ is aryl or R³-substituted aryl:

X, Y and Z are $-\text{CH}_2-$, $-\text{CH}(\text{lower alkyl})-$ or $-\text{C}(\text{dlower alkyl})-$:

R and R² are: —OR⁶, —O(CO)R⁶, —O(CO)OR⁹ or —O(CO)NR⁴R⁷;

R¹ and R² are H or lower alkyl:

q is 0 or 1; r is 0 or 1; m, n and p are 0-4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1-6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1-5;

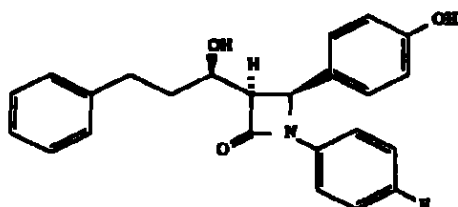
R^4 is selected from lower alkyl, R^5 —CF₃, —CN, —NO₂, and halogen R^3 is selected from —OR⁴, —O(CO)R⁵, —O(CO)OR⁶, —O(CH₂)₁₋₁₀OR⁶, —O(CO)NR⁷, —NR⁸, —NR⁸(CO)R⁵, —NR⁸(CO)OR⁶, —NR⁸(CO)NR⁷, —NR⁸(CO)NR⁷, —NR⁸SO₂R⁹, —COOR⁶, —CONR⁷, —CONR⁸, —SO₂NR⁷, S(O)₂R⁹, —O(CH₂)₁₋₁₀COOR⁶, —O(CH₂)₁₋₁₀CONR⁷, (lower alkylene)COOR⁶ and —CH=CH—COOR⁶.

R⁶, R⁷ and R⁸ are H, lower alkyl, aryl or aryl-substituted

R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl:

are disclosed, as well as a method of lowering serum cholesterol by administering said compounds, alone or in combination with a cholesterol biosynthesis inhibitor, pharmaceutical compositions containing them; and a process for preparing them.

3. Calcul. No Drawings

37
EXAMPLE 10

Step 1:

Follow the procedure of Example 3, using 1-(4-fluorophenyl)-4-(4-t-butyl-4-methoxyphenyl)-2-azetidinone to obtain 1-(4-fluorophenyl)-3-(3-phenyl-1-hydroxypropyl)-4-(4-t-butyl-4-methoxyphenyl)-2-azetidinone.

Step 2:

Treat a solution of the cis-azetidinone of Step 1 (0.25 g) in CH₃CN (21 ml) with 48% aqueous HF (2.5 ml). After 18 h, dilute the reaction mixture with cold H₂O and extract with Et₂O. Wash (2x) H₂O, dilute NaHCO₃ and brine, dry (MgSO₄) and concentrate the Et₂O layer. Crystallize the residue from EtOAc-hexane (1:2) to obtain the title compound as colorless needles (123 mg, y=64%), mp 168°-171° C. Elemental analysis calc for C₂₄H₂₇O₃FN: C 73.64; H 5.66; N 3.58. found C 73.32; H 5.63; N 3.68.

The following formulations exemplify some of the dosage of this invention. In each the term "active compound" designates a compound of formula I.

EXAMPLE A

Tablet				
No.	Ingredient	mg/tablet	mg/tablet	
1	Active Compound	100	500	
2	Lactose USP	122	113	
3	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40	
4	Corn Starch, Food Grade	45	40	
5	Magnesium Stearate	3	7	
Total		300	700	

Method of Manufacture

Mix Item Nos. 1 and 2 in suitable mixer for 10-15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 14', 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

38
EXAMPLE B

Capsule				
No.	Ingredient	mg/tablet	mg/tablet	
1	Active Compound	100	500	
2	Lactose USP	106	125	
3	Corn Starch, Food Grade	40	70	
4	Magnesium Stearate NF	4	7	
Total		250	700	

Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

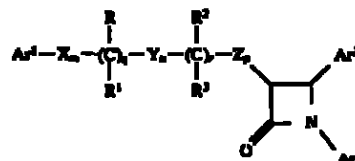
Representative formulations comprising a cholesterol biosynthesis inhibitor are well known in the art. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms disclosed above for substituted azetidinone compounds may readily be modified using the knowledge of one skilled in the art.

Using the test procedures described above, the following in vivo data were obtained for the exemplified compounds. Data is reported as percent change (i.e., percent reduction in cholesterol esters) versus control, therefore, negative numbers indicate a positive lipid-lowering effect.

% Reduction				% Reduction			
Ex. #	Serum Cholest.	Cholest. Esters	Dose mg/kg	Ex. #	Serum Cholest.	Cholest. Esters	Dose mg/kg
1A	-23	0	50	4C	-12.5	0	3
1B	-15	-39	50	4D	9	0	7
1C	14	0	50	4E	0	-46	3
2	0	0	50	4F	-29	-93	3
3A	-31	-49	50	5	0	-64	10
3C	-60	-92	50	6A	-39	-93	1
3D	-17	-41	10	6A-1	-45	-93	1
3E	0	0	10	6B	-40	-92	3
3F	-29	-77	10	6C	0	-48	3
3G	-16	-38	10	6D	-46	-93	10
3H	-41	-86	10	8A	0	-44	3
3I	0	-22	10	8B	-30	-93	3
3J	0	0	3	8C	-14	-37	1
3K	0	0	10	8D	-49	-98	1
3L	-15	-21	10	8E	-22	-66	3
3M	0	-22	10	8F	-43	-94	1
4A	0	-34	5				
4B	-37	-89	8				

We claim:

1. A compound represented by the formula



or a pharmaceutically acceptable salt thereof, wherein:
Ar¹ and Ar² are independently selected from the group consisting of aryl and R⁵-substituted aryl;
Ar³ is aryl or R⁵-substituted aryl;

39

X, Y and Z are independently selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{lower alkyl})-$ and $-\text{C}(\text{dlower alkyl})-$;

R and R^2 are independently selected from the group consisting of $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^6$ and $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1; r is 0 or 1; m, n and p are independently 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^4 is 1-5 substituents independently selected from consisting of lower alkyl, $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^6$, $-\text{O}(\text{CH}_2)_{1-5}\text{OR}^6$, $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{CO})\text{OR}^6$, $-\text{NR}^6(\text{CO})\text{NR}^7\text{R}^8$, $-\text{NR}^6\text{SO}_2\text{R}^9$, $-\text{COOR}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $\text{S}(\text{O})_{0-2}\text{R}^9$, $-\text{O}(\text{CH}_2)_{1-10}-\text{COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$, $-(\text{lower alkylene})\text{COOR}^6$, $-\text{CH}=\text{CH}-\text{COOR}^6$, $-\text{CF}_3$, $-\text{CN}$, $-\text{NO}_2$ and halogen;

R^5 is 1-5 substituents independently selected from the group consisting of $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^6$, $-\text{O}(\text{CH}_2)_{1-5}\text{OR}^6$, $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{CO})\text{OR}^6$, $-\text{NR}^6(\text{CO})\text{NR}^7\text{R}^8$, $-\text{NR}^6\text{SO}_2\text{R}^9$, $-\text{COOR}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $\text{S}(\text{O})_{0-2}\text{R}^9$, $-\text{O}(\text{CH}_2)_{1-10}-\text{COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$, $-(\text{lower alkylene})\text{COOR}^6$ and $-\text{CH}=\text{CH}-\text{COOR}^6$;

R^6 , R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl.

2. A compound of claim 1 wherein Ar^1 is phenyl or R^4 -substituted phenyl, Ar^2 is phenyl or R^4 -substituted phenyl and Ar^3 is R^5 -substituted phenyl.

3. A compound of claim 2 wherein Ar^1 is R^4 -substituted phenyl wherein R^4 is halogen; Ar^2 is R^4 -substituted phenyl wherein R^4 is halogen or $-\text{OR}^6$, wherein R^6 is lower alkyl or hydrogen; and Ar^3 is R^5 -substituted phenyl, wherein R^5 is $-\text{OR}^6$, wherein R^6 is lower alkyl or hydrogen.

4. A compound of claim 1 wherein X, Y, and Z are each $-\text{CH}_2-$; R^1 and R^3 are each hydrogen; R and R^2 are each $-\text{OR}^6$, wherein R^6 is hydrogen; and the sum of m, n, p, q and r is 2, 3 or 4.

5. A compound of claim 1 wherein m, n and r are each zero, q is 1 and p is 2.

6. A compound of claim 1 wherein p, q and n are each zero, r is 1 and m is 2 or 3.

7. A compound selected from the group consisting of
rel 3(R)-(2(R)-hydroxy-2-phenylethyl)-4(R)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

rel 3(R)-(2(R)-hydroxy-2-phenylethyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(S)-(1(S)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(S)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

40

3(R)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

rel 3(R)-(S)-hydroxy-(2-naphthalenyl)methyl-4(3S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

rel 3(R)-(R)-hydroxy-(2-naphthalenyl)methyl-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(R)-(3(R)-hydroxy-3-phenylpropyl)-1.4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

3(R)-(3(S)-hydroxy-3-phenylpropyl)-1.4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

4(S)-(4-hydroxyphenyl)-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

4(S)-(4-hydroxyphenyl)-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

rel 3(R)-[3(RS)-hydroxy-3-[4-(methoxymethoxy)phenyl]-1.4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(R)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone;

4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone;

3(R)-[3(R)-acetyloxy-3-phenylpropyl]-1.4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

3(R)-[3(S)-acetyloxy-3-phenylpropyl]-1.4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

3(R)-[3(R)-(acetyloxy)-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-fluorophenyl)-2-azetidinone;

3(R)-[3(S)-(acetyloxy)-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-fluorophenyl)-2-azetidinone;

3(R)-[3(R)-(acetyloxy)-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone;

3(R)-[3(S)-(acetyloxy)-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone; and

rel 1-(4-fluorophenyl)-4(S)-(4-hydroxyphenyl)-3(1R)-(1(R)-hydroxy-3-phenylpropyl)-2-azetidinone.

8. A pharmaceutical composition for the treatment prevention of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising an effective amount of a compound of claim 1 in a pharmaceutically acceptable carrier.

9. A method of treating or preventing atherosclerosis or reducing plasma cholesterol levels comprising administering to a mammal in need of such treatment an effective amount of a compound of claim 1.

* * * * *



No. 06-060216- -00001-0000

Fecha: 2007-05-30 14:48:59 Dep. 2020 NUECREACIONE
Tra 11 PATENTEIYII Eve 378 FASENACIONALI
Act 400 OPOSIOBSERVTER Folios 38

**FORMULARIO UNICO DE OPOSICION
2000-12**

1

OPOSICION A:

- | | |
|---|---|
| ☒ Patente de Invención | ☐ Marca Colectiva |
| ☐ Patente de Modelo de Utilidad | ☐ Marca de Certificación |
| ☐ Diseño Industrial | ☐ Lema Comercial |
| ☐ Esquema de Trazado para Circuitos Integrados | |
| ☐ Marcas de Productos o Servicios | |

2

**SOLICITUD
PUBLICADA**

Número del expediente: 06.060.216

Solicitante: ASTRAZENECA AB

Apoderado: JUAN PABLO CADENA SARMIENTO

Título de la nueva creación o denominación del signo:

**"DERIVADOS DE DIFENILAZETIDINONA QUE POSEEN ACTIVIDAD
INHIBIDORA DE LA ABSORCIÓN DE COLESTEROL"**

Gaceta: 573 de 28-02-2007, Página 599- Número de Publicación 1129

3

OPOSICION PRESENTADA POR:

OPOSITOR	Nombre: Lafranco S.A.	IDENTIFICACION	
	Dirección: Carrera 1 No. 46-84	C.C. ☐	NIT ☒
	Teléfono: (092) 449.30.51	C.E. ☐	Otro ☐
	Fax:	Número: 890 301 463 -8	
	Domicilio: Cali - Valle		
REPRESENTANTE O APODERADO (74)	Nombre: José Luis Reyes Villamizar	IDENTIFICACION	
	Dirección: Cra. 17 No. 88-23, Of. 205	C.C. ☒	NIT ☐
	Teléfono: 621.26.31	C.E. ☐	Otro ☐
	E-mail: info@reyes-abogados.com	Número: 79'152.473 de Usaquén	
	Fax: 621.25.42	TP 44655	
	Domicilio: Bogotá, D.C.		

4

FUNDAMENTOS DE LA OPOSICION:

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000) Se violan los artículos 14, (las patentes de invención deben ser nuevas, tener nivel inventivo y ser susceptibles de aplicación industrial), 16 (una invención se considera nueva cuando no es obvia, ni se deriva de manera evidente del estado de la técnica), 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia) 20 (los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales).

Justificación: VER ANEXO

5

Comprobante de pago No. 07-42,777 (Oposición) Fecha Mayo 29 de 2007
(Prórroga) Fecha _____

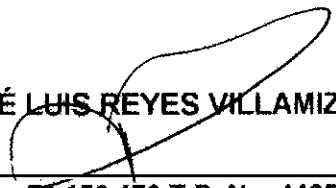
6

Anexos:

- ☒ Comprobante de pago de la tasa
- ☒ Poderes, si fuere el caso
- ☒ Pruebas de los fundamentos de la oposición
- ☒ Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso
- ☒ Copia de la oposición para el traslado al solicitante

7

NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA: 
C.C.No. 79.152.473 T.P. No. 44655

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF:

EXPEDIENTE 06-060-216

TÍTULO SOLICITADO: "DERIVADOS DE DIFENILAZETIDINONA QUE POSEEN ACTIVIDAD INHIBIDORA DE LA ABSORCIÓN DE COLESTEROL".

PUBLICACIÓN: Gaceta 573 de 28 de febrero de 2007, número de publicación 1129

SOLICITANTE: ASTRAZENECA AB.

PRIORIDAD: GB 0329778.5 del 23 diciembre de 2003.

APODERADO: JUAN PABLO CADENA SARMIENTO.

TRÁMITE: PRESENTACIÓN DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO-COLOMBIANO LAFRANCOL S.A.**, en desarrollo de lo dispuesto por los artículos 42 y siguientes de la Decisión 486 de 2000 de la Comunidad Andina de Naciones, me permito solicitarle, muy respetuosamente, dar curso a la siguiente:

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente **06-060-216**, por no cumplir con los requisitos de patentabilidad a que se refieren los artículos 14, 16, 18 y 20 de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos de hecho y de derecho que me permito exponer a continuación.

II. LEGÍTIMO INTERÉS

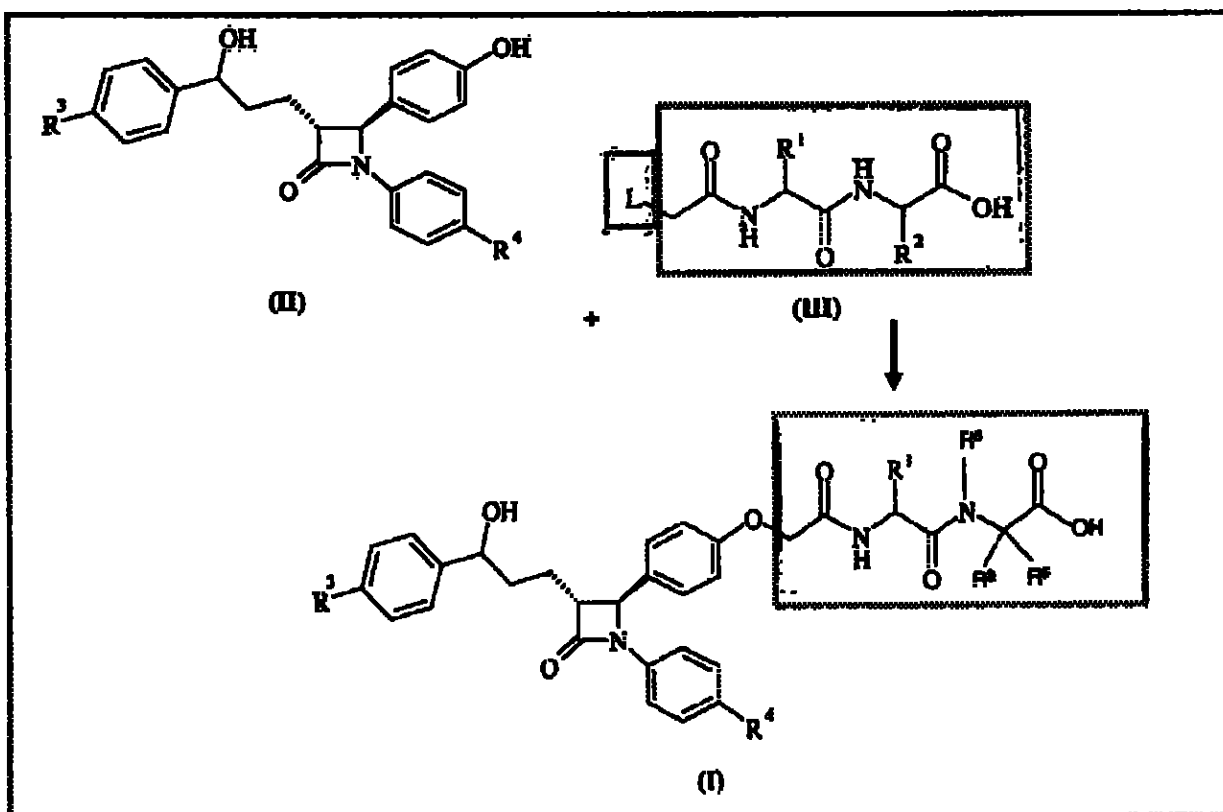
Asiste a **LAFRANCOL S.A.**, en su calidad de industria farmacéutica nacional, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias y composiciones farmacéuticas carentes de nivel inventivo, en detrimento de sus legítimos intereses comerciales y de la libre competencia.

III. FUNDAMENTOS DE LA OPOSICIÓN

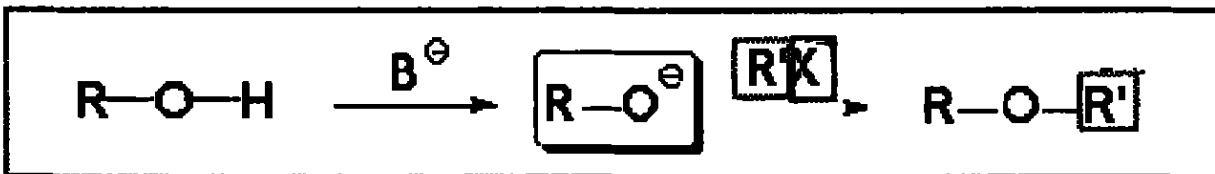
3.1. Los compuestos que reivindica la solicitud colombiana 06-060-216 que resultan ser derivados de ezetimibe, útiles como inhibidores de la absorción de colesterol en el tratamiento de hiperlipidemia, arteriosclerosis, alzheimer, tumores asociados con colesterol, sus formulaciones farmacéuticas, sus combinaciones con agonistas PPAR alfa y/o gamma o inhibidores de HMG Co-A reductasa y su proceso de obtención, resultan carentes de novedad y nivel inventivo como se argumenta a continuación:

- Los compuestos de la fórmula (XV) y (I) así como los procesos de obtención que se reivindican en la solicitud colombiana en trámite resultan ser simples derivados de ezetimibe (entre otros) y su enantiómero obtenidos por reacciones de síntesis muy comunes, veamos:

Proceso 1:

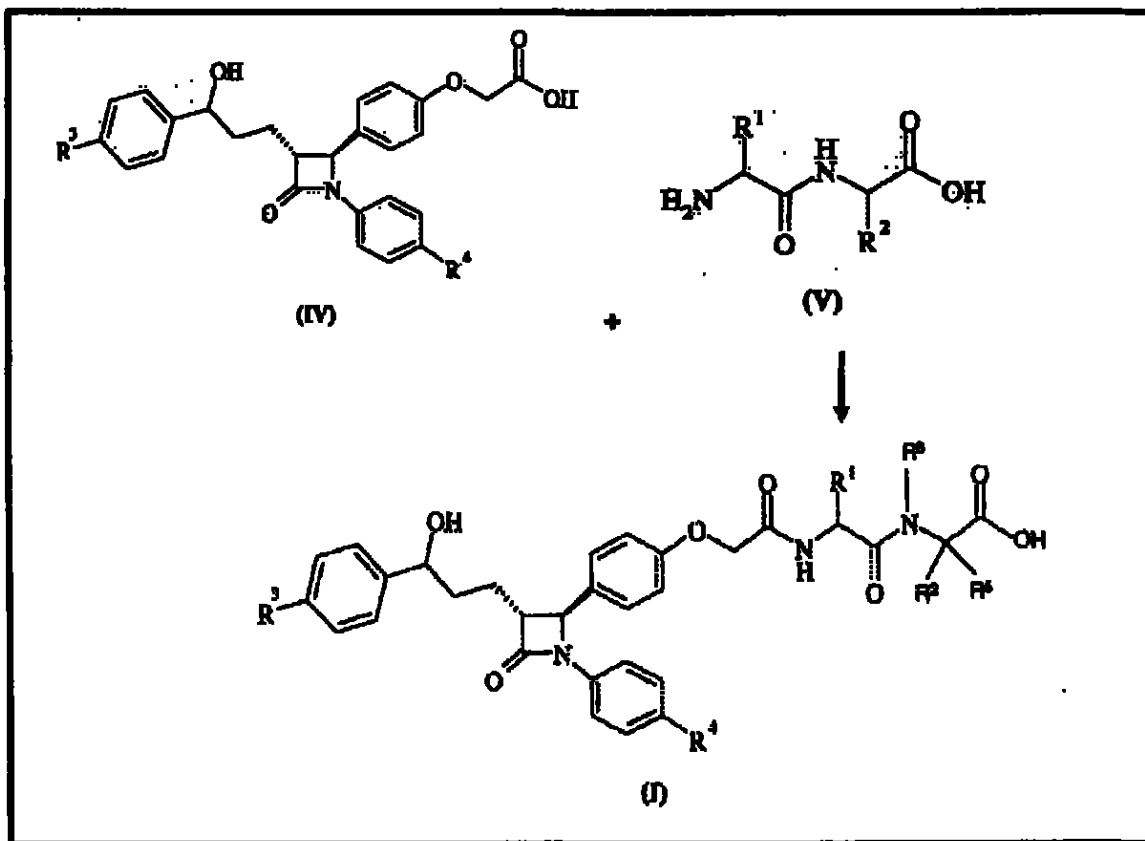


En la solicitud colombiana en trámite, el hidroxilo del grupo hidroxifenil que sustituye al núcleo de azetidinona en posición 4 reacciona con el compuesto de fórmula (III) (donde L es un grupo desplazable o saliente), donde al parecer por sustitución nucleofílica (SN2) permite obtener el compuesto de fórmula (I) (éter alquil sustituido arílico).

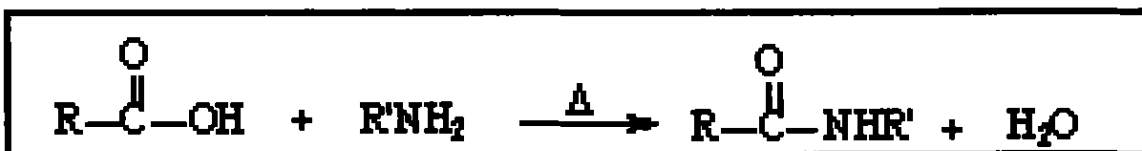


En síntesis orgánica, la manera más simple de preparar un éter es hacer reaccionar un alcóxido con un haluro o sulfonato de alquilo en una secuencia típica SN2.

Proceso 2:



En la solicitud colombiana en trámite, se hace reaccionar el ácido carboxílico de fórmula (IV) o su respectivo derivado éster con una amina de fórmula (V) para obtener el compuesto de fórmula (I) (amida).



En síntesis orgánica una amida puede ser preparada comúnmente haciendo reaccionar un ácido carboxílico o su respectivo éster con una amina.

Los compuestos obtenidos en estos procesos podrían describirse como profármacos de ezetimibe (u otro compuesto –dependiendo de los sustituyentes–) hidrolizables en el enlace formado por el grupo hidroxilo del sustituyente hidroxifenil de la posición 4 del núcleo de azetidinona de dichos compuestos.

Los profármacos, como toda persona versada en la materia sabe, son derivados terapéuticamente inactivos de un principio activo que mediante bioconversión, o sea, transformación química o enzimática en un medio biológico regeneran la sustancia activa; siendo el uso de los profármacos una forma de solución a eventualidades de una molécula activa tales como problemas de estabilidad y biofarmacéuticos entre otros, reconocidos y definidos por *Albert*¹ desde 1958 no puede entonces atribuírsele novedad y mucho menos nivel inventivo, a un proceso de obtención de profármacos de ezetimibe (u otro compuesto –dependiendo de los sustituyentes–) a través de reacciones sencillas de esterificación y formación de amidas.

- La patente americana US 5,846,966 publicada el 8 de diciembre de 1998 y titulada "COMBINATIONS OF HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS AND HMG-CoA REDUCTASE INHIBITORS", revela agentes hipocolesterolémicos azetidinona hidroxi-sustituídos (similares a los de la solicitud colombiana en trámite), así como un método de disminución del colesterol en suero por administración de dichos compuestos, solos o en combinación con un inhibidor de la biosíntesis de colesterol, composiciones farmacéuticas que los contienen y un proceso para obtenerlos.

Como se puede observar en su *abstract*, la patente americana US 5,846,966, revela que el compuesto tipo azetidinona puede estar en combinación con un inhibidor de la biosíntesis de colesterol o como menciona en las reivindicaciones 1 y 10, que puede estar en combinación con un inhibidor de la HMG-CoA reductasa como pravastatina, atorvastatina, lovastatina, entre otros, en un vehículo farmacéuticamente aceptable y, que según la reivindicación 6 y 10 son útiles en el tratamiento o prevención de la aterosclerosis o la reducción de los niveles de colesterol en plasma.

Al comparar lo descrito en el párrafo anterior con lo revelado en la solicitud colombiana en trámite es necesario concluir que, en ambos casos, el

¹ ALBERT A. Chemical aspects of selective toxicity. Nature 182, 421 (1958).

compuesto de tipo azetidinona puede estar en combinación de un inhibidor de la biosíntesis del colesterol como lo son los inhibidores de HMG-CoA reductasa, y que en ambos casos se revela la utilidad en el tratamiento de arteriosclerosis e hiperlipidemia, lo que claramente demuestra al menos la falta de nivel inventivo de las reivindicaciones 12, 13 y 20 de la solicitud colombiana en trámite.

- Por su parte, la patente americana US 5,744,467 publicada el 28 de abril de 1998 y titulada "SULFUR-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS", revela agentes hipocolesterolémicos derivados de azetidinona (similares a los de la solicitud colombiana en trámite) o sus sales farmacéuticamente aceptables, así como composiciones que los contienen y un método de disminución del colesterol en suero por administración de dichos compuestos, solos o en combinación con un inhibidor de la biosíntesis de colesterol.

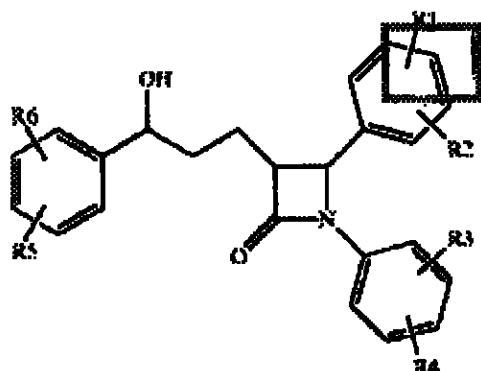
Se observa entonces, que la patente americana US 5,744,467 revela que el compuesto tipo azetidinona puede estar en combinación con un inhibidor de la biosíntesis de colesterol o como menciona en las reivindicaciones 2 y 3, que puede estar en combinación con un inhibidor de la HMG-CoA reductasa y, que según la reivindicación 1 y 4 son útiles en el tratamiento o prevención de la aterosclerosis o la reducción de los niveles de colesterol en plasma.

Si tenemos en cuenta lo descrito en el párrafo anterior con lo revelado en la solicitud colombiana en trámite podemos ver que en ambos documentos el compuesto de tipo azetidinona puede estar en combinación de un inhibidor de la biosíntesis del colesterol como lo son los inhibidores de HMG-CoA reductasa y que así mismo se revela la utilidad en el tratamiento de arteriosclerosis e hiperlipidemia, permite demostrar nuevamente la ausencia por lo menos de nivel inventivo de las reivindicaciones 12, 13 y 20 de la solicitud colombiana en trámite.

- La patente americana US 2002/0128253 publicada el 12 de septiembre de 2002 y titulada "DIPHENYL AZETIDINONE DERIVATIVES, PROCESS FOR THEIR PREPARATION, MEDICAMENTS COMPRISING THESE COMPOUNDS AND THEIR USE" revela compuestos de la fórmula:

(57) ABSTRACT

Compounds of the formula I.



in which R1, R2, R3, R4, R5, and R6 have the meanings given in the description, and their physiologically acceptable salts. The compounds are suitable for use, for example, as hypolipidemics.

En donde R1 a R6 pueden ser, entre otros:

[0008] H, F, Cl, Br, I, CF₃, NO₂, CN, COOH, COO(C₁-C₆)-alkyl, CONH₂, CONH(C₁-C₆)-alkyl, CON(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl or O-(C₁-C₆)-alkyl, where one, more or all hydrogens in the alkyl radicals may be replaced by fluorine; or

[0010] NH₂, NH-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, NH(C₁-C₆)-acyl, phenyl or O-(CH₂)_n-phenyl, where n=0-6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl or CONH₂

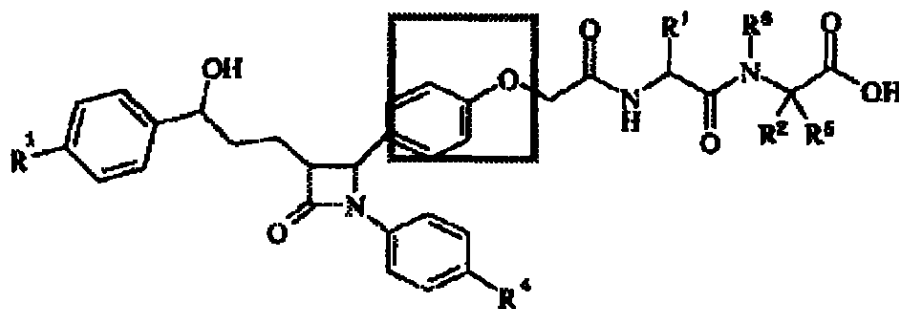
los cuales,

cuando se realizan las respectivas sustituciones en la posición encerrada en verde con los respectivos grupos resaltados en verde, resultan ser estructuras muy similares a las de la solicitud colombiana en trámite (derivados de ezetimibe –entre otros-) y que además tienen en común la funcionalidad u objetivo que se busca con dichas sustituciones:

(...)

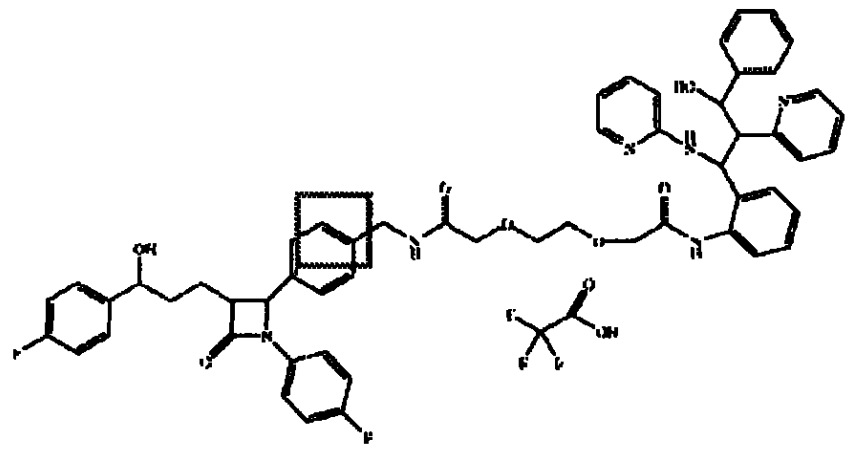
treatment of disease states associated with hyperlipidaemic conditions. The compounds of the present invention are not disclosed in any of the above applications and we have surprisingly found that the compounds of the present invention possess beneficial efficacious, metabolic and toxicological profiles that make them particularly suitable for *in vivo* administration to a warm blooded animal, such as man. In particular certain compounds of the present invention have a low degree of absorption compared to compounds of the prior art whilst retaining their ability to inhibit cholesterol absorption.

(...)



(WO 05/061451 equivalente internacional de la solicitud colombiana en trámite)

[0004] It was an object of the invention to provide further compounds having a therapeutically utilizable hypolipidemic action. In particular, it was an object to find novel compounds which, compared to the compounds described in the prior art, are absorbed to a very low extent. Very low absorption is to be understood as meaning an intestinal absorption of less than 10%, preferably less than or equal to 5%. In particular, absorption of the novel compounds should be less than that of ezetimibe. Pharmaceutically active compounds which are absorbed to a very low extent generally have considerably fewer side-effects.



(Patente americana US 2002/0128253)

Lo anterior permite demostrar que en el estado del arte se encuentran compuestos derivados de azetidinona sustituidos con sustituyentes semejantes en características químicas a los de la solicitud colombiana en trámite y que se adicionan a la misma posición que estos, con el fin de mejorar características como la absorción de los mismos; de esta forma se ve afectado el nivel inventivo de la solicitud colombiana en trámite.

Así mismo, haciendo un paralelo entre lo reivindicado en la solicitud colombiana en trámite y la patente americana, podemos evidenciar muchas cosas en común, veamos:

70
180

SOLICITUD COLOMBIANA EN TRAMITE	PATENTE AMERICANA US 2002/0128253
1. Un compuesto de la fórmula (...) o su sal farmacéuticamente aceptable, solvato, solvato de la sal o profármaco. 12. Un método de tratar o prevenir enfermedades hiperlipidémicas, que comprende la administración de una cantidad efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 11 a un mamífero necesitado de ello. 13. Un método de tratar o prevenir arteriosclerosis, que comprende la administración de una cantidad efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 11 a un mamífero necesitado de ello.	[0025] The compounds of the formula I and their pharmaceutically acceptable salts, esters, prodrugs and derivatives having physiological function are ideal medications for treating an impaired lipid metabolism, in particular hyperlipidemia. The compounds of the formula I are also suitable for modulating the serum cholesterol concentration and for treating arteriosclerotic manifestations. The compounds of the invention are also suitable for the treatment of insulin resistance. 12. A method as claimed in claim 11, wherein the host suffers from hyperlipidemia. 13. A method as claimed in claim 14, wherein the host suffers from an arteriosclerotic manifestation.
20. Una combinación de un compuesto de acuerdo con fórmula (I) o (XV) con un Inhibidor de HMG Co-A.	[0035] In one embodiment of the invention, the compounds of the formula I are administered in combination with an HMGCoA reductase inhibitor such as simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin, rosuvastatin.
19. Una combinación de un compuesto de acuerdo con fórmula (I) o (XV) con un agonista PPAR alfa y/o gamma.	[0039] In one embodiment of the invention, the compounds of the formula I are administered in combination with a mixed PPAR alpha/gamma agonist, such as, for example, GW 1536, AVE 5042, AVE 5134, AVE 0847.
18. Un proceso para preparar un compuesto de fórmula (I) o su sal farmacéuticamente aceptable, solvato (...) y posteriormente, si es necesario o deseable (...) iv) separar dos o más enantiómeros (...)	[0070] The invention furthermore provides both stereoisomer mixtures of the formula I and the pure stereoisomers of the formula I, and diastereomer mixtures of the formula I and the pure diastereomers. The mixtures are separated by chromatographic means.

En conclusión, la patente americana nos permite demostrar la falta de nivel inventivo de la solicitud colombiana en trámite en tanto señala:

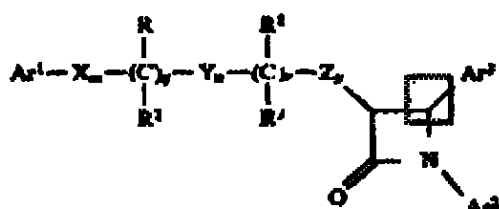
- * Derivados de azetidinona sustituidos en la misma posición y con sustituyentes de características químicas semejantes a los de la solicitud colombiana en trámite
- * Separación de los posibles enantiómeros
- * Derivados con características biofarmacéuticas modificadas útiles en el tratamiento de trastornos hiperlipídemicos y arterioscleróticos.

➤ La patente americana US 5, 767,115 publicada el 16 de Junio de 1998 y titulada "HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS" revela compuestos de la fórmula:

[57]

ABSTRACT

Hydroxy-substituted azetidinone hypocholesterolemic agents of the formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ and Ar² are aryl or R⁴-substituted aryl;

Ar¹ is aryl or R²-substituted aryl;

R^4 is selected from lower alkyl, R^5 , $-\text{CF}_3$, $-\text{CN}$, $-\text{NO}_2$ and halogen R^3 is selected from $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{OR}^6$, $-\text{O}(\text{CO})\text{NR}^7\text{R}^7$, $-\text{NR}^4\text{R}^7$, $-\text{NR}^4(\text{CO})\text{R}^7$, $-\text{NR}^4(\text{CO})\text{OR}^6$, $-\text{NR}^4(\text{CO})\text{NR}^7\text{R}^8$, $-\text{NR}^4\text{SO}_2\text{R}^8$, $-\text{COOR}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $\text{S}(\text{O})_2\text{R}^8$, $-\text{O}(\text{CH}_2)_{1-10}-\text{COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}-\text{CONR}^6\text{R}^7$, $-(\text{lower alkylene})\text{COOR}^6$ and $-\text{CH}=\text{CH}-\text{COOR}^6$.

R⁶, R⁷ and R⁸ are H, lower alkyl, aryl or aryl-substituted 1c.

R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl;

En donde los sustituyentes resaltados en verde, coinciden en buena parte con los sustituyentes correspondientes a la misma posición en los

derivados de la solicitud colombiana en trámite; así mismo, los derivados de la patente americana poseen la misma utilidad:

SOLICITUD COLOMBIANA EN TRAMITE	PATENTE AMERICANA
13. Un método de tratar o prevenir arteriosclerosis, que comprende la administración de una cantidad efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 11 a un mamífero necesitado de ello.	8. A pharmaceutical composition for the treatment prevention of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising an effective amount of a compound of claim 1 in a pharmaceutically acceptable carrier. 9. A method of treating or preventing atherosclerosis or reducing plasma cholesterol levels comprising administering to a mammal in need of such treatment an effective amount of a compound of claim 1.

➤ Por último, la solicitud colombiana en trámite en sus reivindicaciones 12, 13, 14 y 15 reivindican un método para tratar o prevenir enfermedades como las relacionadas a la hiperlipidemia, arteriosclerosis, alzheimer y tumores, lo cual va en contra de los dispuesto por el literal b del artículo 20 de la decisión 486 de la comunidad andina de naciones en donde claramente se expone que *“No serán patentables: los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnostico aplicados a los seres humanos o a animales.”*

Por todo lo anterior reitero que la solicitud de la referencia, en todas sus reivindicaciones, incumple los requisitos materiales de patentabilidad establecidos por la Decisión 486 de 2000, razón por la cual no puede ser objeto de privilegio de patente de invención.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 16, 18 y 20, el artículo 30 (Reivindicaciones) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de que el Despacho considere oficiosamente, en particular de las allegadas por el suscrito a los expedientes mencionados en este escrito, las siguientes:

- La patente americana US 5,846,966 publicada el 8 de diciembre de 1998 y titulada "COMBINATIONS OF HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS AND HMG-CoA REDUCTASE INHIBITORS" capítulo reivindicatorio.
- La patente americana US 5,744,467 publicada el 28 de abril de 1998 y titulada "SULFUR-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS" capítulo reivindicatorio.
- La patente americana US 2002/0128253 del 12 de septiembre de 2002 y titulada "DIPHENYL AZETIDINONE DERIVATIVES, PROCESS FOR THEIR PREPARATION, MEDICAMENTS COMPRISING THESE COMPOUNDS AND THEIR USE." Páginas 1, 2, 3, 4 12 y 17.
- La patente americana US 5, 767,115 del 16 de Junio de 1998 y titulada "HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS" página 21.

VI. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos:

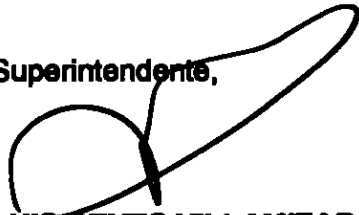
1. Certificado de existencia y representación legal de Lafranco S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.

4. Copia para correr traslado al solicitante.
5. Las mencionadas en el acápite de pruebas

VII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Lafrancol S.A., las recibirá en sus oficinas localizadas en la Carrera 1 N° 46-84 de Cali.

Señor Superintendente,

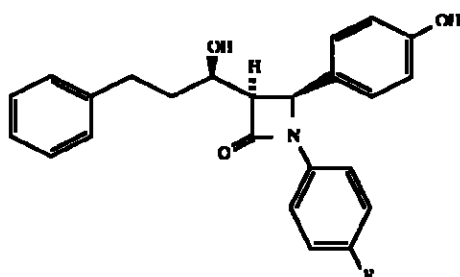


JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P.A 44.655 del C.S.J.

184

39
EXAMPLE 10

Step 1: Follow the procedure of Example 3, using 1-(4-fluorophenyl)-4-(4-t-butyldimethylsilyloxyphenyl)-2-azetidinone to obtain 1-(4-fluorophenyl)-3-(3-phenyl-1-hydroxypropyl)-4-(4-t-butyldimethylsilyloxyphenyl)-2-azetidinone.

Step 2: Treat a solution of the *cis*-azetidinone of Step 1 (0.25 g) in CH₃CN (21 ml) with 48% aqueous HF (2.5 ml). After 18 h, dilute the reaction mixture with cold H₂O and extract with Et₂O. Wash (2x H₂O, dilute NaHCO₃ and brine), dry (MgSO₄) and concentrate the Et₂O layer. Crystallize the residue from EtOAc:hexane (1:2) to obtain the title compound as colorless needles (123 mg, y=64%), mp 168°-171° C. Elemental analysis calc for C₂₄H₂₄O₃FN: C 73.64; H 5.66; N 3.58. found C 73.32; H 5.65; N 3.68.

The following formulations exemplify some of the dosage of this invention. In each the term "active compound" designates a compound of formula I.

EXAMPLE A

Tablets			
No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	122	113
3	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4	Corn Starch, Food Grade	45	40
5	Magnesium Stearate	3	7
Total		300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in suitable mixer for 10-15 minutes. Sate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., ¼", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

EXAMPLE B

Capsules			
No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	106	123
3	Corn Starch, Food Grade	40	70

40

-continued

Capsules			
No.	Ingredient	mg/tablet	mg/tablet
4	Magnesium Stearate NF	4	7
Total		250	700

10 Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

Representative formulations comprising a cholesterol biosynthesis inhibitor are well known in the art. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms disclosed above for substituted azetidinone compounds may readily be modified using the knowledge of one skilled in the art.

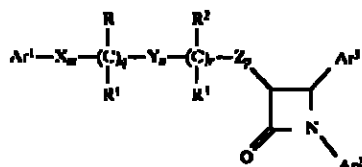
Using the test procedures described above, the following in vivo data were obtained for the exemplified compounds. Data is reported as percent change (i.e., percent reduction in cholesterol esters) versus control, therefore, negative numbers indicate a positive lipid-lowering effect.

2. Reduction			
Ex. #	Serum Cholest.	Cholest. Esters	Dose mg/kg
1A	-23	0	50
1B	-15	-39	50
1C	14	0	50
2	0	0	50
3A	-31	-69	50
3C	-60	-92	50
3D	-17	-61	10
3E	0	0	10
3F	-29	-77	10
3G	-16	-34	10
3H	-41	-86	10
3I	0	-22	10
3J	0	0	3
3K	0	0	10
3L	-15	-21	10
3M	0	-22	10
4A	0	-54	5
4B	-37	-89	8
4C	-12.5	0	3
4D	9	0	7
4E	0	-46	3
4F	-29	-95	3
5	0	-64	10
6A	-39	-95	1
6A-1	-41	-93	1
6B	-40	-92	3
6C	0	-48	3
6D	-46	-95	10
8A	0	-44	3
8B	-50	-95	3
8C	-14	-37	1
8D	-40	-98	1
8E	-22	-66	3
8F	-43	-94	1
10	-26	-77	3

We claim:

1. A pharmaceutical composition for the treatment or prevention of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising an effective amount of a compound represented by the formula I

185



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ and Ar² are independently selected from the group consisting of aryl and R⁴-substituted aryl;

Ar³ is aryl or R⁵-substituted aryl;

X, Y and Z are independently selected from the group consisting of —CH₂—, —CH(lower alkyl)— and —C(lower alkyl)—;

R and R² are independently selected from the group consisting of —OR⁶, —O(CO)R⁶, —O(CO)OR⁶ and —O(CO)NR⁶R⁷;

R¹ and R³ are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1; r is 0 or 1; m, n and p are independently 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R⁴ is 1-5 substituents independently selected from the group consisting of lower alkyl, —OR⁶, —O(CO)R⁶, —O(CO)OR⁶, —O(CH₂)₁₋₅OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁷, —NR⁶(CO)NR⁶R⁷, —NR⁶SO₂R⁷, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₂R⁶, —O(CH₂)₁₋₁₀COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —(lower alkylene)COOR⁶, —CH=CH—COOR⁶, —CF₃, —CN, —NO₂ and halogen;

R⁵ is 1-5 substituents independently selected from the group consisting of —OR⁶, —O(CO)R⁶, —O(CO)OR⁶, —O(CH₂)₁₋₅OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁷, —NR⁶(CO)NR⁶R⁷, —NR⁶SO₂R⁷, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₂R⁶, —O(CH₂)₁₋₁₀COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —(lower alkylene)COOR⁶ and —CH=CH—COOR⁶;

R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R⁸ is lower alkyl, aryl or aryl-substituted lower alkyl; in combination with an HMG CoA reductase inhibitor in a pharmaceutically acceptable carrier.

2. A pharmaceutical composition of claim 1 wherein, in the compound of formula I, Ar¹ is phenyl or R⁴-substituted phenyl, wherein R⁴ is halogen; Ar² is phenyl or R⁴-substituted phenyl, wherein R⁴ is halogen or —OR⁶, wherein R⁶ is lower alkyl or hydrogen; Ar³ is R⁵-substituted phenyl, wherein R⁵ is —OR⁶, wherein R⁶ is lower alkyl or hydrogen; X, Y, and Z are each —CH₂—; R¹ and R³ are each hydrogen; R and R² are each —OR⁶, wherein R⁶ is hydrogen; and the sum of m, n, p, q and r is 2, 3 or 4.

3. A composition of claim 1 wherein the HMG CoA reductase inhibitor is selected from the group consisting of lovastatin, pravastatin, fluvastatin, simvastatin and atorvastatin.

4. A composition of claim 1 wherein the compound of formula I is selected from the group consisting of

rel 3(R)-(2(R)-hydroxy-2-phenylethyl)-4(R)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

rel 3(R)-(2(R)-hydroxy-2-phenylethyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(S)-(1(S)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(S)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(R)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(R)-(3(R)-hydroxy-3-phenylpropyl)-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

3(R)-(3(S)-hydroxy-3-phenylpropyl)-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

4(S)-(4-hydroxyphenyl)-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

4(S)-(4-hydroxyphenyl)-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

rel 3(R)-[3(RS)-hydroxy-3-[4-(methoxymethoxy)phenyl]propyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(R)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone;

4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone;

3(R)-[3(R)-acetyloxy-3-phenylpropyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

3(R)-[3(S)-acetyloxy-3-phenylpropyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

3(R)-[3(R)-acetyloxy-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-fluorophenyl)-2-azetidinone;

3(R)-[3(S)-acetyloxy-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-fluorophenyl)-2-azetidinone;

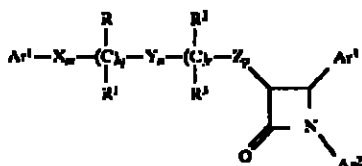
3(R)-[3(R)-acetyloxy-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone;

3(R)-[3(S)-acetyloxy-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone; and

rel 1-(4-fluorophenyl)-4(S)-(4-hydroxyphenyl)-3(R)-(1(R)-hydroxy-3-phenylpropyl)-2-azetidinone.

5. A composition of claim 1 comprising a combination of 1-(4-fluorophenyl)-3(R)-[3(R)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone and lovastatin, pravastatin, fluvastatin, simvastatin or atorvastatin.

6. A method of treating or preventing atherosclerosis or reducing plasma cholesterol levels comprising administering to a mammal in need thereof an effective amount of a compound represented by the formula I



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ and Ar² are independently selected from the group consisting of aryl and R⁴-substituted aryl;

Ar^1 is aryl or R^1 -substituted aryl:

X, Y and Z are independently selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{lower alkyl})-$ and $-\text{C}(\text{dlower alkyl})-$:

R and R² are independently selected from the group consisting of —OR⁶, —C(X)OR⁶, —C(X)OR⁷ and —C(X)NR⁶R⁷;

R¹ and R² are independently selected from the group 20 consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1; r is 0 or 1; m, n and p are independently 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^1 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-\text{OR}^6$, $-(\text{XCO})\text{R}^6$, $\text{O}(\text{CO})\text{OR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{OR}^6$, $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{COOR}^6)$, $-\text{NR}^6(\text{CONR}^7)\text{R}^8$, $-\text{NR}^6(\text{SO}_2)\text{R}^8$, $-\text{XOOR}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $\text{S}(\text{O})_{1-2}\text{R}^8$, $-\text{O}(\text{CH}_2)_{1-10}\text{COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$, $-(\text{lower alkylene})\text{COOR}^6$, $\text{CH}=\text{CH}-\text{COOR}^6$, $-\text{CH}_3$, $-\text{CN}$, $-\text{NO}_2$ and halogen;

R^1 is 1-5 substituents independently selected from the group consisting of $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{X}(\text{CO})\text{OR}^6$, $-\text{O}(\text{CH}_2)_{1-3}\text{OR}^6$, $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{CO})\text{OR}^6$, $-\text{NR}^6(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{SO}_2\text{R}^6$, $-\text{COOR}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $\text{S}(\text{O})_{1-2}\text{R}^8$, $-\text{O}(\text{CH}_2)_{1-10}-\text{COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$, $-(\text{lower alkylene})\text{COOR}^6$ and $-\text{CH}=\text{CH}-\text{COOR}^6$.

Rⁿ, R⁷ and R^m are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^{*} is lower alkyl, aryl or aryl-substituted lower alkyl; in combination with an effective amount of a cholesterol biosynthesis inhibitor selected from the group consisting of HMG CoA reductase inhibitors.

7. A method of claim 6 wherein, in the compound of formula I, Ar¹ is phenyl or R⁴-substituted phenyl, wherein R⁴ is halogen; Ar² is phenyl or R⁴-substituted phenyl, wherein R⁴ is halogen or —OR⁴, wherein R⁴ is lower alkyl or hydrogen; Ar³ is R⁵-substituted phenyl, wherein R⁵ is —OR⁶, wherein R⁶ is lower alkyl or hydrogen; X, Y, and Z are each —CH₂—; R¹ and R³ are each hydrogen; R and R² are each —OR⁶, wherein R⁶ is hydrogen; and the sum of m, n, v, u and r is 2, 3 or 4.

8. A method of claim 6 wherein the HMG CoA reductase inhibitor is selected from the group consisting of lovastatin, pravastatin, fluvastatin, simvastatin and atorvastatin.

9. A method of claim 6 wherein the compound of formula 1 is selected from the group consisting of

rel 3(R)-(2(R)-hydroxy-2-phenylethyl)-4(R)-(4-methoxyphenyl)-1-phenyl-2-azetidinone:

rel 3(R)-(2(R)-hydroxy-2-phenylethyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(S)-(1(S)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidine:

3(S)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone:

3(R)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(R)-(3(R)-hydroxy-3-phenylpropyl)-1,4(S)-bis-(4-methoxyphenyl)-2-azolidinone;

3(R)-(3(S)-hydroxy-3-phenylpropyl)-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone:

4(S)-(4-hydroxyphenyl)-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

4(S)-(4-hydroxyphenyl)-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

rel 3(R)-[3(RS)-hydroxy-3-[4-(methoxymethoxy)-phenyl]propyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azepiklinone;

1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone:

1-(4-(fluorophenyl)-3(R)-[3(R)-(4-fluorophenyl)-3-hydroxypropyl])-4(S)-(4-hydroxyphenyl)-2-azetidinone:

4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

4(S)-[4-(acetoxy)phenyl]-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone;

3(R)-[3(R)-acetyloxy-3-phenylpropyl]-1,1(S)-bis-(4-methoxy-phenyl)-2-azetidinone:

3(R)-[3(S)-acetyloxy-3-phenylpropyl]-1,4(S)-bis-(4-methoxy-phenyl)-2-azetidinone:

3(R)-[3(R)-(acetyloxy)-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)-phenyl]-1-(4-fluorophenyl)-2-azetidinone;

3(R)-[3(S)-(acetyloxy)-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)-phenyl]-1-(4-fluorophenyl)-2-azotidinone;

3(R)-[3(R)-(acetyloxy)-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone;

3(R)-[3(S)-(acetyloxy)-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone; and

rel 1-(4-fluorophenyl)-4(S)-(4-hydroxyphenyl)-3(R)-(1(R)-hydroxy-3-phenylpropyl)-2-azetidinone.

10. A method of claim 6 comprising administering a combination of 1-(4-fluorophenyl)-3(R)-[3(R)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone and kwastatin, pravastatin, fluvastatin, simvastatin or atorvastatin.

◆ ◆ ◆ ◆ ◆

23

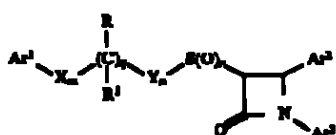
-continued

Ex. #	% Reduction		Dose mg/kg
	Serum Cholest.	Cholest. Esters	
11	-55	-95	3
14	-30	-64	3
15	-27	-88	1
18	-27	-68	3

For racemic compounds of formula I or active diastereomers or enantiomers of compounds of formula I, compounds administered at dosages of 0.1-25 mg/kg show a range of -21 to -97% reduction in cholesterol esters, and a -57 to 0% reduction in serum cholesterol. Compounds preferably show a range of -21 to -97% reduction in cholesterol esters at a dosage range of 0.1 to 3 mg/kg, more preferably a range of -21 to -97% reduction in cholesterol esters at a dosage range of 0.1 to 1 mg/kg.

We claim:

1. A pharmaceutical composition for the treatment or prevention of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising a compound represented by the structural formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ is aryl, R¹⁰-substituted aryl or heteroaryl;

Ar² is aryl or R⁴-substituted aryl;

Ar³ is aryl or R⁵-substituted aryl;

X and Y are independently selected from the group consisting of -CH₂-, -CH(lower alkyl)- and -C(lower alkyl)-;

R is -OR⁶, -O(CO)R⁶, -O(CO)OR⁶ or -O(CO)NR⁶R⁷; R¹ is hydrogen, lower alkyl or aryl; or R and R¹ together are =O;

q is 0 or 1;

r is 0, 1 or 2;

m and n are independently 0, 1, 2, 3 or 4; provided that the sum of m, n and q is 2, 3 or 4;

R⁴ is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR⁶, -O(CO)R⁶, -O(CO)OR⁶, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁶, -NR⁶(CO)NR⁶R⁷, -NR⁶SO₂R⁶, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₂R⁶, -O(CH₂)₁₋₁₀COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -(lower alkylene)COOR⁶ and -CH=CH-COOR⁶;

R⁵ is 1-5 substituents independently selected from the group consisting of -OR⁶, -O(CO)R⁶, -O(CO)OR⁶, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁶, -NR⁶(CO)NR⁶R⁷, -NR⁶SO₂R⁶, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₂R⁶, -O(CH₂)₁₋₁₀COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -(lower alkylene)COOR⁶ and -CH=CH-COOR⁶;

R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

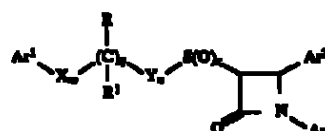
24

R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl; and R¹⁰ is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR⁶, -O(CO)R⁶, -O(CO)OR⁶, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁶, -NR⁶(CO)NR⁶R⁷, -NR⁶SO₂R⁶, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₂R⁶, -O(CH₂)₁₋₁₀COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -(lower alkylene)COOR⁶ and -CH=CH-COOR⁶; -CF₃, -CN, -NO₂ and halogen; a cholesterol biosynthesis inhibitor and a pharmaceutically acceptable carrier.

2. A pharmaceutical composition of claim 1 wherein the cholesterol biosynthesis inhibitor is selected from the group consisting of HMG CoA reductase inhibitors.

3. A pharmaceutical composition of claim 2 wherein the cholesterol biosynthesis inhibitor is selected from the group consisting of lovastatin, pravastatin, fluvastatin, simvastatin and atorvastatin.

4. A method of treating or preventing atherosclerosis or reducing plasma cholesterol levels comprising simultaneously or sequentially administering to a mammal in need of such treatment an effective amount of a cholesterol biosynthesis inhibitor and a compound represented by the structural formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ is aryl, R¹⁰-substituted aryl or heteroaryl;

Ar² is aryl or R⁴-substituted aryl;

Ar³ is aryl or R⁵-substituted aryl;

X and Y are independently selected from the group consisting of -CH₂-, -CH(lower alkyl)- and -C(lower alkyl)-;

R is -OR⁶, -O(CO)R⁶, -O(CO)OR⁶ or -O(CO)NR⁶R⁷; R¹ is hydrogen, lower alkyl or aryl; or R and R¹ together are =O;

q is 0 or 1;

r is 0, 1 or 2;

m and n are independently 0, 1, 2, 3 or 4; provided that the sum of m, n and q is 2, 3 or 4;

R⁴ is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR⁶, -O(CO)R⁶, -O(CO)OR⁶, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁶, -NR⁶(CO)NR⁶R⁷, -NR⁶SO₂R⁶, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₂R⁶, -O(CH₂)₁₋₁₀COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -(lower alkylene)COOR⁶ and -CH=CH-COOR⁶;

R⁵ is 1-5 substituents independently selected from the group consisting of -OR⁶, -O(CO)R⁶, -O(CO)OR⁶, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁶, -NR⁶(CO)NR⁶R⁷, -NR⁶SO₂R⁶, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₂R⁶, -O(CH₂)₁₋₁₀COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -(lower alkylene)COOR⁶ and -CH=CH-COOR⁶;

R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl; and

R^{10} is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^6$, $-O(CH_2)_{1-10}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^6$, $-NR^6(CO)NR^6R^7$, $-NR^6SO_2R^7$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_2R^6$, $-O(CH_2)_{1-10}-$, $-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, $-CF_3$, $-CN$, $-NO_2$ and halogen.

5. A method as claimed in claim 4, wherein the cholesterol biosynthesis inhibitor is selected from the group consisting of HMG CoA reductase inhibitors.

6. A method as claimed in claim 5, wherein the cholesterol biosynthesis inhibitor is selected from the group consisting of lovastatin, pravastatin, fluvastatin, simvastatin and atorvastatin.

7. A composition of claim 3 comprising a compound of formula I wherein q is 0; Ar^1 is phenyl, R^{10} -substituted phenyl or thienyl; Ar^2 is R^4 -substituted phenyl; Ar^3 is phenyl or R^5 -substituted phenyl; X and Y are each $-CH_2-$; and the sum of m and n is 2, 3 or 4.

8. A composition of claim 3 comprising a compound of formula I wherein q is 1; Ar^1 is phenyl, R^{10} -substituted phenyl or thienyl; Ar^2 is R^4 -substituted phenyl; Ar^3 is phenyl or R^5 -substituted phenyl; X and Y are each $-CH_2-$; the sum of m and n is 1, 2 or 3; and R^1 is hydrogen and R is $-OR^6$, wherein R^6 is hydrogen, or wherein R and R^1 together form a $=O$ group.

9. A composition of claim 3 wherein the compound of formula I is selected from the group consisting of

- trans-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-thio]-2-azetidinone;
- trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-thio]-2-azetidinone;
- cis-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-thio]-2-azetidinone;
- trans-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
- cis-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
- trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
- cis-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
- trans-4-[1-(4-fluorophenyl)-4-oxo-3-[(2-phenylethyl)-sulfinyl]-2-azetidinyl]-phenyl acetate;
- cis-4-[1-(4-fluorophenyl)-4-oxo-3-[(2-phenylethyl)-sulfinyl]-2-azetidinyl]-phenyl acetate; and
- (+/-)-trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-sulfonyl]-2-azetidinone;
- trans-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone;
- trans-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-hydroxyethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone;
- (3R,4R) 1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-oxoethyl]-sulfinyl]-4-(4-hydroxyphenyl)-2-azetidinone;
- 1-(4-fluorophenyl)-3(R)-[[2-(4-fluorophenyl)-2(R)-hydroxyethyl]-sulfinyl]-4(R)-(4-hydroxyphenyl)-2-azetidinone;
- 1-(4-fluorophenyl)-3(R)-[[2-(4-fluorophenyl)-2(S)-hydroxyethyl]-sulfinyl]-4(R)-(4-hydroxyphenyl)-2-azetidinone;
- (3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(2-thienyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone;

- (3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(3-thienyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone;
- (3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(3-pyridinyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone;
- (3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(4-pyridinyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone;
- (3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(2-pyridinyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone;
- (3R,4R) trans-1-(4-fluorophenyl)-3-[[2-hydroxy-2-(3-thienyl)ethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone;
- (3R,4R) trans-1-(4-fluorophenyl)-3-[[2-hydroxy-2-(4-pyridinyl)ethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone;
- (3S,4R) cis-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone; and
- (3S,4R) cis-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-hydroxyethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone.

10. A method of claim 6 comprising a compound of formula I wherein q is 0; Ar^1 is phenyl, R^{10} -substituted phenyl or thienyl; Ar^2 is R^4 -substituted phenyl; Ar^3 is phenyl or R^5 -substituted phenyl; X and Y are each $-CH_2-$; and the sum of m and n is 2, 3 or 4.

11. A method of claim 6 comprising a compound of formula I wherein q is 1; Ar^1 is phenyl, R^{10} -substituted phenyl or thienyl; Ar^2 is R^4 -substituted phenyl; Ar^3 is phenyl or R^5 -substituted phenyl; X and Y are each $-CH_2-$; the sum of m and n is 1, 2 or 3; and R^1 is hydrogen and R is $-OR^6$, wherein R^6 is hydrogen, or wherein R and R^1 together form a $=O$ group.

12. A method of claim 6 wherein the compound of formula I is selected from the group consisting of
- trans-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-thio]-2-azetidinone;
 - trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-thio]-2-azetidinone;
 - cis-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-thio]-2-azetidinone;
 - trans-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
 - cis-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
 - trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
 - cis-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;
 - trans-4-[1-(4-fluorophenyl)-4-oxo-3-[(2-phenylethyl)-sulfinyl]-2-azetidinyl]-phenyl acetate;
 - cis-4-[1-(4-fluorophenyl)-4-oxo-3-[(2-phenylethyl)-sulfinyl]-2-azetidinyl]-phenyl acetate; and
 - (+/-)-trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-sulfonyl]-2-azetidinone;
 - trans-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone;
 - trans-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-hydroxyethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone;
 - (3R,4R) 1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-oxoethyl]-sulfinyl]-4-(4-hydroxyphenyl)-2-azetidinone;
 - 1-(4-fluorophenyl)-3(R)-[[2-(4-fluorophenyl)-2(R)-hydroxyethyl]-sulfinyl]-4(R)-(4-hydroxyphenyl)-2-azetidinone;

20
190

27

1-(4-fluorophenyl)-3(R)-[[2-(4-fluorophenyl)-2(S)-hydroxyethyl]-sulfinyl]-4(R)-(4-hydroxyphenyl)-2-azetidinone;
(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(2-thienyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone; 5
(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(3-thienyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone;
(3R,4R) trans-1-(4-fluorophenyl)-3-[[2o(3-pyridinyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone;
(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(4-pyridinyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone; 10
(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-(2-pyridinyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone;

28

(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-hydroxy-2-(3-thienyl)ethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone;
(3R,4R) trans-1-(4-fluorophenyl)-3-[[2-hydroxy-2-(4-pyridinyl)ethyl]-thio]-4-(4-hydroxyphenyl)-2-azetidinone;
(3S,4R) cis-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-oxoethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone; and
(3S,4R) cis-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-hydroxyethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone.

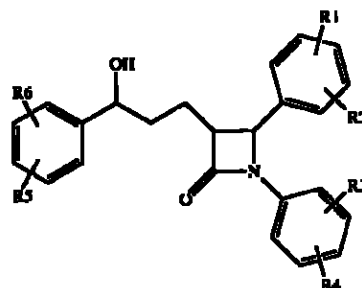
* * * * *



US 2002/0128253A1

(19) **United States**(12) **Patent Application Publication**
Gilombik et al.(10) **Pub. No.: US 2002/0128253 A1**(43) **Pub. Date: Sep. 12, 2002**(54) **DIPHENYLAZETIDINONE DERIVATIVES,
PROCESS FOR THEIR PREPARATION,
MEDICAMENTS COMPRISING THESE
COMPOUNDS AND THEIR USE****Publication Classification**(51) **Int. Cl.⁷** A61K 31/397; C07D 25/08(52) **U.S. CL** 514/210.02; 540/200(76) **Inventors:** Helner Gilombik, Hofheim (DE);
Werner Kramer, Mainz-Laubenheim
(DE); Stefanie Flohr, Eppstein (DE);
Wendelin Frick, Hunsletten-Neurathach
(DE); Hubert Heuer, Schwabenheim
(DE); Gerhard Jachne, Frankfurt am
Main (DE); Andreas Lindenschmidt,
Bad Soden (DE); Hans-Ludwig
Schaefer, Hofheim (DE)**Correspondence Address:**
Finnegan, Henderson, Farahow,
Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, DC 20005-3315 (US)(21) **Appl. No.: 10/021,044**(22) **Filed: Dec. 19, 2001**(30) **Foreign Application Priority Data**Dec. 21, 2000 (DE)..... 10064402.3
Nov. 7, 2001 (DE)..... 10154518.5(57) **ABSTRACT**

Compounds of the formula I,

in which R1, R2, R3, R4, R5, and R6 have the meanings
given in the description, and their physiologically acceptable
salts. The compounds are suitable for use, for example, as
hypolipidemics.

**DIPHENYLAZETIDINONE DERIVATIVES,
PROCESS FOR THEIR PREPARATION,
MEDICAMENTS COMPRISING THESE
COMPOUNDS AND THEIR USE**

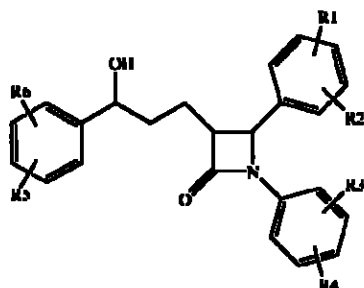
[0001] This application claims the benefit of priority under 35 U.S.C. §119(a) to German patent application no. 10064402.3, filed on Dec. 21, 2000, and German patent application no. 10154518.5, filed on Nov. 7, 2001. The contents of both priority documents are incorporated by reference herein.

[0002] The invention relates to substituted diphenylazetidinones, to their physiologically acceptable salts and to derivatives having physiological function.

[0003] Diphenylazetidinones (such as, for example, ezetimibe) and their use for treating hyperlipidemia and arteriosclerosis and hypercholesterolemia have already been described [cf. Drugs of the Future 2000, 25(7):679-685].

[0004] It was an object of the invention to provide further compounds having a therapeutically utilizable hypolipidemic action. In particular, it was an object to find novel compounds which, compared to the compounds described in the prior art, are absorbed to a very low extent. Very low absorption is to be understood as meaning an intestinal absorption of less than 10%, preferably less than or equal to 5%. In particular, absorption of the novel compounds should be less than that of ezetimibe. Pharmaceutically active compounds which are absorbed to a very low extent generally have considerably fewer side-effects.

[0005] Accordingly, an embodiment of the invention relates to compounds of the formula I,



[0006] in which

[0007] R1, R2, R3, R4, R5, R6 independently of one another are (C₀-C₃₀)-alkylene-1-, where one or more carbon atoms of the alkylene radical may be replaced by -O-, -(C=O)-, -CH=CH-, -C≡C-, -N((C₁-C₆)-alkyl)- or -NH-; or

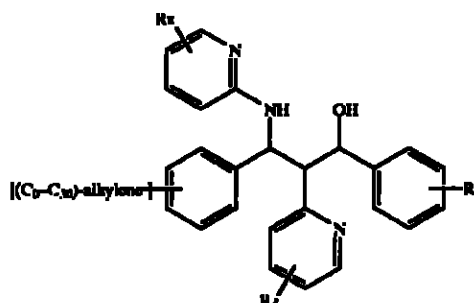
[0008] H, F, Cl, Br, I, CF₃, NO₂, CN, COOH, COO((C₁-C₆)-alkyl), CONH((C₁-C₆)-alkyl), CON((C₁-C₆)-alkyl)₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl or O-(C₁-C₆)-alkyl, where one, more or all hydrogens in the alkyl radicals may be replaced by fluorine; or

[0009] SO₂-NH₂, SO₂NH((C₁-C₆)-alkyl), SO₂N((C₁-C₆)-alkyl)₂, S-(C₁-C₆)-alkyl, S-(CH₂)_n-

phenyl, SO-(C₁-C₆)-alkyl, SO-(CH₂)_n-phenyl, SO₂-(C₁-C₆)-alkyl or SO₂-(CH₂)_n-phenyl, where n=0-6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl or NH₂; or

[0010] NH₂, NH-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, NH(C₁-C₆)-acyl, phenyl or O-(CH₂)_n-phenyl, where n=0-6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, NH₂, NH((C₁-C₆)-alkyl), N((C₁-C₆)-alkyl)₂, SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl or CONH₂;

[0011] I. is shown connected to (C₀-C₃₀)-alkylene as follows:



[0012] Rx, Ry, Rz independently of one another are H, F, Cl, Br, I, CF₃, NO₂, CN, COOH, COO-(C₁-C₆)-alkyl, CONH₂, CONH-(C₁-C₆)-alkyl, CON-((C₁-C₆)-alkyl)₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl or O-(C₁-C₆)-alkyl, where one, more or all hydrogens in the alkyl radicals may be replaced by fluorine; or

[0013] SO₂-NH₂, SO₂NH-(C₁-C₆)-alkyl, SO₂N-((C₁-C₆)-alkyl)₂, S-(C₁-C₆)-alkyl, S-(CH₂)_n-phenyl, SO-(C₁-C₆)-alkyl, SO-(CH₂)_n-phenyl, SO₂-(C₁-C₆)-alkyl or SO₂-(CH₂)_n-phenyl, where n=0-6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl or NH₂; or

[0014] NH₂, NH-(C₁-C₆)-alkyl, N-((C₁-C₆)-alkyl)₂, NH-(C₁-C₆)-acyl, phenyl or O-(CH₂)_n-phenyl, where n=0-6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, NH₂, NH-(C₁-C₆)-alkyl, N-((C₁-C₆)-alkyl)₂, SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl or CONH₂;

[0015] wherein at least one of the radicals R1 or R6 has the meaning (C₀-C₃₀)-alkylene-1-, where one or more carbon atoms of the alkylene radical may be replaced by -O-, -(C=O)-, -CH=CH-, -C≡C-, -N((C₁-C₆)-alkyl)- or -NH-, and its pharmaceutically acceptable salts.

[0016] Another embodiment of the invention relates to compounds of the formula I, in which at least one of the radicals R1 to R6 has the meaning (C_6-C_{30}) -alkylene-L, where one or more carbon atoms of the alkylene radical may be replaced by $-O-$, $-(C=O)-$, or $-NH-$.

[0017] Another embodiment of the invention relates to compounds of the formula I, in which one of the radicals R1 or R3 has the meaning (C_6-C_{30}) -alkylene-L, where one or more carbon atoms of the alkylene radical may be replaced by $-O-$, $-(C=O)-$ or $-NH-$.

[0018] Another embodiment of the invention relates to compounds of the formula I, in which one of the radicals R1 or R3 has the meaning $-(CH_2)_n-NH-(C=O)-C_6H_4-(C_2-C_6)$ -alkylene- $(C=O)-n_1-NH-I$; where one or more carbon atoms of the alkylene radical may be replaced by oxygen atoms.

[0019] One of the radicals R1 to R6 may be linked, for example, to the L radical in the meta position of ring C of the I groups.

[0020] Owing to their increased solubility in water, compared to the parent compounds, pharmaceutically acceptable salts are particularly suitable for medical applications. These salts should have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds according to the invention are salts of inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, metaphosphoric acid, nitric acid, sulfuric acid and sulfuric acid, and of organic acids, such as acetic acid, benzenesulfonic acid, benzoic acid, citric acid, ethanesulfonic acid, fumaric acid, gluconic acid, glycolic acid, isothionic acid, lactic acid, lactobionic acid, maleic acid, malic acid, methanesulfonic acid, succinic acid, p-toluenesulfonic acid, tartaric acid and trifluoroacetic acid, for example. For medical purposes, very particular preference is given to using the chloride salt. Suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts).

[0021] The scope of the invention also includes salts having a pharmaceutically unacceptable anion, which salts may be useful intermediates for preparing or purifying pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.

[0022] Here, the term "derivative having physiological function" refers to any physiologically acceptable derivative of a compound according to the invention, for example an ester, capable of forming, upon administration to a mammal, for example man, to form such a compound or an active metabolite (directly or indirectly).

[0023] A further aspect of this invention are prodrugs of the compounds according to the invention. Such prodrugs can be metabolized in vivo to give a compound according to the invention. These prodrugs may or may not be active in their own right.

[0024] The compounds according to the invention can also be present in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. The scope of the invention includes all polymorphous forms of the compounds according to the invention, which form a further

aspect of the invention. The compounds of the invention may also exist in the form of solvates.

[0025] The compounds of the formula I and their pharmaceutically acceptable salts, esters, prodrugs and derivatives having physiological function are ideal medicaments for treating an impaired lipid metabolism, in particular hyperlipidemia. The compounds of the formula I are also suitable for modulating the serum cholesterol concentration and for treating arteriosclerotic manifestations. The compounds of the invention are also suitable for the treatment of insulin resistance.

[0026] As used here, "treatment" or "therapy" of a condition and "treating" a condition can mean successfully eliminating the condition, reducing the effects associated with it, and/or reducing its severity. It also includes administering the relevant compounds to a patient to avoid recurrence of a condition. It also includes avoiding the onset of a condition by administering the relevant compounds to patients falling into a risk group or category for developing the particular condition. Those skilled in the art can routinely identify patients likely to present with a given condition, thereby qualifying as candidates for treatment.

[0027] The compound(s) of the formula (I) can also be administered in combination with other active compounds.

[0028] The amount of a compound of the formula (I) required to achieve the desired biological effect depends on a number of factors, for example on the specific compound chosen, on the intended use, on the mode of administration and on the clinical condition of the patient. In general, the daily dose is in the range from 0.1 mg to 100 mg (typically from 0.1 mg to 50 mg) per day per kilogram of bodyweight, for example 0.1-10 mg/kg/day. Tablets or capsules may contain, for example, from 0.01 to 100 mg, typically from 0.02 to 50 mg. In the case of pharmaceutically acceptable salts, the abovementioned weight data relate to the weight of the diphenyl-azetidione-ion derived from the salt. For the therapy of the abovementioned conditions, the compounds of the formula (I) can be used themselves as the compound, but preferably they are present in the form of a pharmaceutical composition with an acceptable carrier. The carrier must of course be acceptable in the sense that it is compatible with the other constituents of the composition and is not harmful to the health of the patient. The carrier can be a solid or a liquid or both and is preferably formulated with the compound as an individual dose, for example as a tablet, which can contain from 0.05% to 95% by weight of the active compound. Further pharmaceutically active substances can also be present, including further compounds of the formula (I). The pharmaceutical compositions according to the invention can be prepared by one of the known pharmaceutical methods, which essentially consist in mixing the constituents with pharmacologically acceptable carriers and/or auxiliaries.

[0029] Pharmaceutical compositions according to the invention are those which are suitable for oral or peroral (e.g. sublingual) administration, although the most suitable manner of administration is dependent in each individual case on the nature and severity of the condition to be treated and on the type of the compound of the formula (I) used in each case. Coated formulations and coated delayed-release formulations are also included in the scope of the invention. Acid-resistant and enteric formulations are preferred. Suit-

able enteric coatings include cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methylmethacrylate.

[0030] Suitable pharmaceutical compounds for oral administration can be present in separate units, such as, for example, capsules, cachets, lozenges or tablets, which in each case contain a specific amount of the compound of the formula (I); as a powder or granules; as a solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. As already mentioned, these compositions can be prepared according to any suitable pharmaceutical method which includes a step in which the active compound and the carrier (which can consist of one or more additional constituents) are brought into contact. In general, the compositions are prepared by uniform and homogeneous mixing of the active compound with a liquid and/or finely divided solid carrier, after which the product, if necessary, is shaped. For example, a tablet can thus be prepared by pressing or shaping a powder or granules of the compound, if appropriate with one or more additional constituents. Pressed tablets can be produced by tableting the compound in free-flowing form, such as, for example, a powder or granules, if appropriate mixed with a binder, lubricant, inert diluent and/or a (number of) surface-active/dispersing agent(s) in a suitable machine. Shaped tablets can be produced by shaping the pulverulent compound moistened with an inert liquid diluent in a suitable machine.

[0031] Pharmaceutical compositions which are suitable for peroral (sublingual) administration include lozenges which contain a compound of the formula (I) with a flavoring, customarily sucrose and gum arabic or tragacanth, and pastilles which include the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

[0032] Suitable other active compounds for the combination preparations include: all antidiabetics mentioned in Rule 1201, Chapter 12, the disclosure of which is incorporated by reference herein. They can be combined with the compounds of the formula I according to the invention in particular to achieve a synergistically enhanced action. The active compound combination can be administered either by separate administration of the active compounds to the patient or in the form of combination preparations comprising a plurality of active compounds in a pharmaceutical preparation.

[0033] Antidiabetics include insulin and insulin derivatives, such as, for example, Lantus® or HMR 1964, GLP-1 derivatives, such as, for example, those disclosed by Novo Nordisk A/S in WO 98/08871, the disclosure of which is incorporated by reference herein, and oral hypoglycemic active compounds.

[0034] The oral hypoglycemic active compounds preferably include sulfonyl ureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, potassium channel openers, such as, for example, those disclosed by Novo Nordisk A/S in WO 97/26265 and WO 99/03861, the disclosures of which are incorporated by reference herein, insulin sensitizers, inhibitors of liver enzymes involved in stimulating gluconeogenesis and/or glycogenolysis, modulators of glucose uptake, compounds which modulate lipid

metabolism, such as antihyperlipidemic active compounds and antilipidemic active compounds, compounds which reduce food intake, PPAR and PXR agonists and active compounds which act on the ATP-dependent potassium channel of the beta cells.

[0035] In one embodiment of the invention, the compounds of the formula I are administered in combination with an HMGCoA reductase inhibitor such as simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin, rosuvastatin.

[0036] In one embodiment of the invention, the compounds of the formula I are administered in combination with a cholesterol absorption inhibitor, such as, for example, ezetimibe, tiqueside, pamaqueside.

[0037] In one embodiment of the invention, the compounds of the formula I are administered in combination with a PPAR gamma agonist, such as, for example, rosiglitazone, pioglitazone, J11-501, GI 262570.

[0038] In one embodiment of the invention, the compounds of the formula I are administered in combination with a PPAR alpha agonist, such as, for example, GW 9578, GW 7647.

[0039] In one embodiment of the invention, the compounds of the formula I are administered in combination with a mixed PPAR alpha/gamma agonist, such as, for example, GW 1536, AVE 8042, AVE 8134, AVE 0847.

[0040] In one embodiment of the invention, the compounds of the formula I are administered in combination with a fibrate, such as, for example, fenofibrate, clofibrate, bezafibrate.

[0041] In one embodiment of the invention, the compounds of the formula I are administered in combination with an MTP inhibitor, such as, for example, Bay 13-9952, RMS-201038, R-103757.

[0042] In one embodiment of the invention, the compounds of the formula I are administered in combination with a bile acid absorption inhibitor, such as, for example, HMR 1453.

[0043] In one embodiment of the invention, the compounds of the formula I are administered in combination with a CETP inhibitor, such as, for example, Bay 194789.

[0044] In one embodiment of the invention, the compounds of the formula I are administered in combination with a polymeric bile acid adsorber, such as, for example, cholestyramine, colestolvan.

[0045] In one embodiment of the invention, the compounds of the formula I are administered in combination with an LDL receptor inducer, such as, for example, HMR1171, HMR1586.

[0046] In one embodiment of the invention, the compounds of the formula I are administered in combination with an ACAT inhibitor, such as, for example, avasimibe.

[0047] In one embodiment of the invention, the compounds of the formula I are administered in combination with an antioxidant, such as, for example, OPC-14117.

[0048] In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein lipase inhibitor, such as, for example, NO-1886.

[0049] In one embodiment of the invention, the compounds of the formula I are administered in combination with an ATP citrate lyase inhibitor, such as, for example, SH-204990.

[0050] In one embodiment of the invention, the compounds of the formula I are administered in combination with a squalene synthetase inhibitor, such as, for example, HMS-18494.

[0051] In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein(a) antagonist, such as, for example, CI-1027 or nicotinic acid.

[0052] In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipase inhibitor, such as, for example, Orlistat.

[0053] In one embodiment of the invention, the compounds of the formula I are administered in combination with insulin.

[0054] In one embodiment, the compounds of the formula I are administered in combination with a sulfonyl urea, such as, for example, tolbutamide, glibenclamide, glipizide or glimepiride.

[0055] In one embodiment, the compounds of the formula I are administered in combination with a biguanide, such as, for example, metformin.

[0056] In another embodiment, the compounds of the formula I are administered in combination with a meglitinide, such as, for example, repaglinide.

[0057] In one embodiment, the compounds of the formula I are administered in combination with a thiazolidinedione, such as, for example, troglitazone, ciglitazone, pioglitazone, rosiglitazone, or the compounds disclosed by Dr. Rockly's Research Foundation in WO 97/41097, the disclosure of which is incorporated by reference herein, in particular 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinyl-methoxy)phenyl]methyl]-2,4-thiazolidinedione.

[0058] In one embodiment, the compounds of the formula I are administered in combination with an α -glucosidase inhibitor, such as, for example, miglitol or acarbose.

[0059] In one embodiment, the compounds of the formula I are administered in combination with an active compound which acts on the ATP-dependent potassium channel of beta cells, such as, for example, tolbutamide, glibenclamide, glipizide, glimepiride or repaglinide.

[0060] In one embodiment, the compounds of the formula I are administered in combination with more than one of the abovementioned compounds, for example in combination with a sulfonyl urea and metformin, a sulfonyl urea and acarbose, repaglinide and metformin, insulin and a sulfonyl urea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

[0061] In a further embodiment, the compounds of the formula I are administered in combination with CART agonists, NPY agonists, MC4 agonists, orexin agonists, H3 agonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists, β 3-agonists, MSH (melanocyte-stimulating hormone) agonists, CCK agonists, serotonin reuptake inhibitors, mixed serotonin and noradrenergic compounds,

5HT agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone-releasing compounds, TRH agonists, decoupling protein 2- or 3 modulators, leptin agonists, DA agonists (bromocriptin, doperxin), lipase/amy-lase inhibitors, PPAR modulators, RXR modulators or TR- β agonists.

[0062] In one embodiment of the invention, the further active compound is leptin.

[0063] In one embodiment, the further active compound is dexamphetamine or amphetamine.

[0064] In one embodiment, the further active compound is fenfluramine or dexfenfluramine.

[0065] In another embodiment, the further active compound is sibutramine.

[0066] In one embodiment, the further active compound is Orlistat.

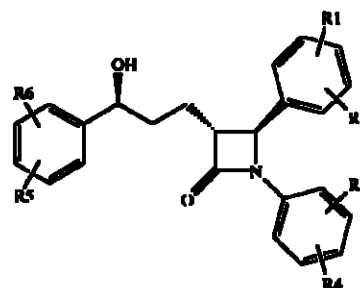
[0067] In one embodiment, the further active compound is mazindol or phentermine.

[0068] In one embodiment, the compounds of the formula I are administered in combination with fiber, preferably insoluble fiber, such as, for example, Carumax®. The combination with Carumax® can be given in one preparation or by separate administration of compounds of the formula I and Carumax®. Here, Carumax® can also be administered in the form of food, such as, for example, in bakery goods or mucali bars. Compared to the individual active compounds, the combination of compounds of the formula I with Carumax® is, in addition to an enhanced action, in particular with respect to the lowering of LDL cholesterol, also characterized by its improved tolerability.

[0069] It goes without saying that each suitable combination of the compounds according to the invention with one or more of the compounds mentioned above and optionally one or more further pharmacologically active substances is included in the scope of the present invention.

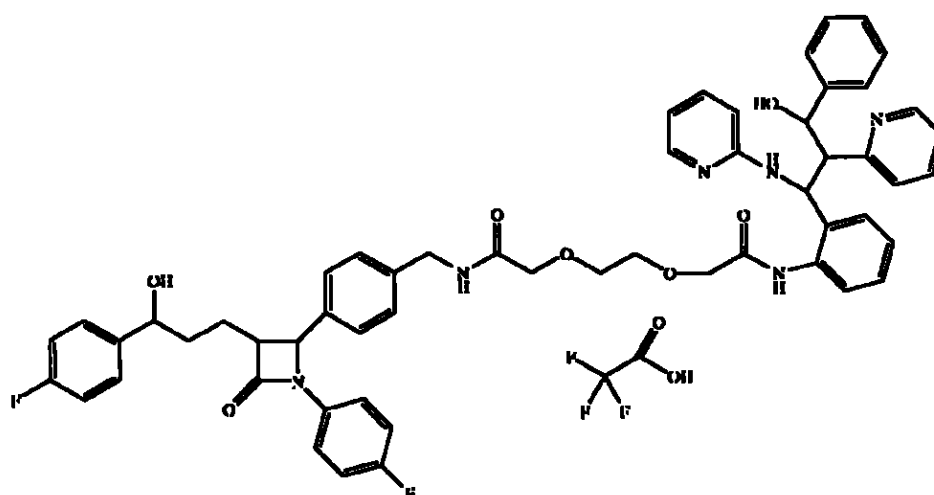
[0070] The invention furthermore provides both stereoisomer mixtures of the formula I and the pure stereoisomers of the formula I, and diastereomer mixtures of the formula I and the pure diastereomers. The mixtures are separated by chromatographic means.

[0071] Preference is given to both racemic and enantiomerically pure compounds of the formula I of the following structure:



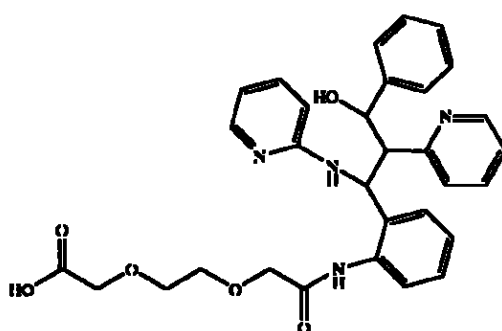
EXAMPLE XIX

[0098]



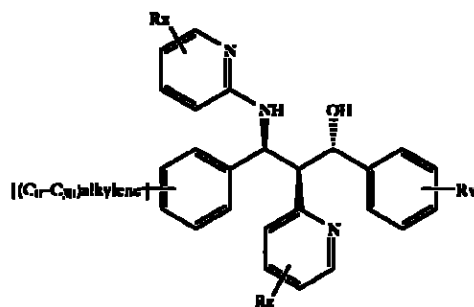
{ 1-[2-(2-{2-[(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxazolidin-2-yl]benzylcarbamoyl)methoxy]ethoxy}acetylaminophenyl)-3-hydroxy-3-phenyl-2-pyridin-2-ylpropyl]pyridin-2-ylammonium trifluoroacetate 36

[0099]



[0100] $C_{31}H_{32}N_4O_8$ (556.62) MS (ESI) 557 (M+H)

1. is shown connected to (C₆-C₂₀)-alkylene as follows:



Rx, Ry, Rz independently of one another are H, F, Cl, Br, I, CF₃, NO₂, CN, COOH, COO-(C₁-C₆)-alkyl, CONH₂, CONH-(C₁-C₆)-alkyl, CON-[(C₁-C₆)-alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl or O-(C₁-C₆)-alkyl, where one, more or all hydrogens in the alkyl radicals may be replaced by fluorine; or

SO₂-NH₂, SO₂NH-(C₁-C₆)-alkyl, SO₂N-[(C₁-C₆)-alkyl]₂, S-(C₁-C₆)-alkyl, S-(CH₂)_n-phenyl, SO-(C₁-C₆)-alkyl, SO-(CH₂)_n-phenyl, SO₂-(C₁-C₆)-alkyl or SO₂-(CH₂)_n-phenyl, where n=0-6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl or NH₂; or

NH₂, NH-(C₁-C₆)-alkyl, N-[(C₁-C₆)-alkyl]₂, NH-(C₁-C₆)-acyl, phenyl or O-(CH₂)_n-phenyl, where n=0-6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, NH₂, NH-(C₁-C₆)-alkyl, N-[(C₁-C₆)-alkyl]₂, SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl or CONH₂;

where one of the radicals R1 or R3 has the meaning -(CH₂)_{n-1}-NH-(C≡O)_{n-1}-(C₃-C₂₂)-alkylene-(C≡O)_{n-1}-NH-I, where one or more carbon atoms of the alkylene radical may be replaced by oxygen atoms.

5. A pharmaceutical composition comprising one or more of the compounds as claimed in claim 1 and a pharmaceutically acceptable carrier.

6. A pharmaceutical composition comprising one or more compounds as claimed in claim 1 and at least one further active compound.

7. A pharmaceutical composition as claimed in claim 6, comprising, as a further active compound, one or more compounds that normalize lipid metabolism.

8. A pharmaceutical composition as claimed in claim 6, which comprises, as a further active compound, one or more

antidiabetics, hypoglycemically active compounds, HMG-CoA reductase inhibitors, cholesterol absorption inhibitors, PPAR gamma agonists, PPAR alpha agonists, PPAR alpha/gamma agonists, fibrates, MTP inhibitors, bile acid absorption inhibitors, CETP inhibitors, polymeric bile acid adsorbents, LDL receptor inducers, ACAT inhibitors, antioxidants, lipoprotein lipase inhibitors, ATP citrate lyase inhibitors, squalene synthetase inhibitors, lipoprotein(a) antagonists, lipase inhibitors, insulins, sulfonyl ureas, biguanides, meglitinides, thiazolidinediones, α-glucosidase inhibitors, active compounds which act on the ATP-dependent potassium channel of the beta cells, CART agonists, NPY agonists, MC4 agonists, orexin agonists, H3 agonists, TNF agonists, CRF agonists, CRF-1R antagonists, urocortin agonists, β3 agonists, MSH (melanocortin-stimulating hormone) agonists, CCK agonists, serotonin-reuptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT agonists, bombesin agonists, galanin antagonists, growth hormones, growth hormone-releasing compounds, TRH agonists, decoupling protein 2- or 3-modulators, leptin agonists, DA agonists, lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR-β-agonists or amphetamines.

9. A method for the treatment of impaired lipid metabolism, which comprises administering to a host in need of the treatment an effective amount of at least one compound as claimed in claim 1.

10. A method as claimed in claim 9, wherein the host suffers from impaired lipid metabolism.

11. A method for the treatment of hyperlipidemia, which comprises administering to a host in need of the treatment an effective amount of at least one compound as claimed in claim 1.

12. A method as claimed in claim 11, wherein the host suffers from hyperlipidemia.

13. A method for controlling the serum cholesterol concentration in a host, which comprises administering to the host in need of the control of serum cholesterol concentration an effective amount of at least one compound as claimed in claim 1.

14. A method for the treatment of an arteriosclerotic manifestation, which comprises administering to a host in need of the treatment an effective amount of at least one compound as claimed in claim 1.

15. A method as claimed in claim 14, wherein the host suffers from an arteriosclerotic manifestation.

16. A method for the treatment of insulin resistance, which comprises administering to a host in need of the treatment an effective amount of at least one compound as claimed in claim 1.

17. A method as claimed in claim 16, wherein the host suffers from insulin resistance.

* * * * *



US005767115A

United States Patent [19]

Rosenblum et al.

[11] Patent Number: 5,767,115

[45] Date of Patent: Jun. 16, 1998

[54] HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS

[75] Inventors: Stuart B. Rosenblum, West Orange; Sundeeep Dugar, Bridgewater; Deanne A. Barnett, Farwood; John W. Clader, Cranford; Brian A. McKittrick, Bloomfield, all of N.J.

[73] Assignee: Schering-Plough Corporation, Kenilworth, N.J.

[21] Appl. No.: 617,751

[22] Filed: Mar. 18, 1996

Related U.S. Application Data

[63] Continuation-in-part of PCT/US94/10099, Sep. 14, 1994, continuation-in-part of Ser. No. 257,593, Jun. 9, 1994, Pat. No. 5,631,365, which is a continuation-in-part of Ser. No. 102,440, Sep. 21, 1993, abandoned.

[51] Int. Cl.⁶ C07D 205/08; A61K 31/395

[52] U.S. Cl. 514/210; 540/200

[58] Field of Search 540/200; 514/210

[56] References Cited

U.S. PATENT DOCUMENTS

4,375,475 3/1983 Willard et al. 434/279
4,983,597 1/1991 Yang et al. 514/216
5,099,034 3/1992 Yoshida 562/579
5,350,868 9/1994 Yoshida 562/579

FOREIGN PATENT DOCUMENTS

199630 10/1986 European Pat. Off.
264231 4/1988 European Pat. Off.
337549 10/1989 European Pat. Off.
9302048 2/1993 WIPO
WO94/17038 8/1994 WIPO

OTHER PUBLICATIONS

Ram et al. *Indian J. Chem., Sect. B*, 29B, 12 (1990), pp. 1134-1137.
Hockman et al. *J. Agric. Food Chem.*, 30 (1982), pp. 920-924.
Durst et al. *Can. J. Chem.*, 50 (1972), pp. 3196-3201.
Otto et al. *Liebigs Ann. Chem.*, (1983), pp. 1152-1161.
Paufl, et al. *Heterocycles*, 24, 6 (1986), pp. 1609-1617.
Schmitzer-Polokoff, et al. *Comp. Biochem. Physiol.*, 99A (1991), pp. 665-670.
Witzum, *Circulation*, 80, 5 (1989), pp. 1101-1114.
Bilgicworth, *Drugs*, 36(Supp. 3) (1988), pp. 63-71.
Allain, et al. *Clin. Chem.*, 20, (1974), pp. 470-475.
Horie, et al. *Atherosclerosis*, 88 (1991), pp. 183-192.
Baxter, et al. *J. Biological Chem.*, 267, 17 (1992), pp. 11705-11708.
Current Drugs: Anti-Atherosclerotic Agents—Summary Factfile, May, 1992.

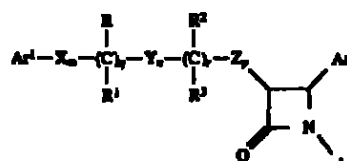
Georg et al. *Tet. Letters*, 26, 33 (1985), pp. 3903-3906.

Hart et al. *Tet. Letters*, 45 (1985), pp. 5493-5496.

Primary Examiner—Mark L. Berch
Attorney, Agent, or Firm—Anita W. Magatti

[57] ABSTRACT

Hydroxy-substituted azetidinone hypcholesterolemic agents of the formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ and Ar² are aryl or R⁴-substituted aryl;

Ar³ is aryl or R⁵-substituted aryl;

X, Y and Z are —CH₂—, —CH(lower alkyl)— or —C(lower alkyl)—;

R and R² are —OR⁶, —O(CO)R⁶, —O(CO)OR⁶ or —O(CO)NR⁶R⁷;

R¹ and R³ are H or lower alkyl;

q is 0 or 1; r is 0 or 1; m, n and p are 0-4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1-6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1-5;

R⁴ is selected from lower alkyl, R⁵, —CF₃, —CN, —NO₂ and halogen R⁶ is selected from —OR⁶, —O(CO)R⁶, —O(CO)OR⁶, —O(CH₂)₁₋₃OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁶, —NR⁶(CO)NR⁶R⁷, —NR⁶SO₂R⁶, —COOR⁶, —CONR⁶R⁷, —CONR⁶, —SO₂NR⁶R⁷, S(O)₂R⁶, —O(CH₂)₁₋₁₀COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —(lower alkylene)COOR⁶ and —CH=CH—COOR⁶;

R⁶, R⁷ and R⁸ are H, lower alkyl, aryl or aryl-substituted

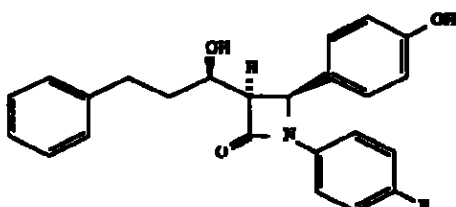
R⁸ is lower alkyl, aryl or aryl-substituted lower alkyl;

are disclosed, as well as a method of lowering serum cholesterol by administering said compounds, alone or in combination with a cholesterol biosynthesis inhibitor, pharmaceutical compositions containing them; and a process for preparing them.

9 Claims, No Drawings

5,767,115

37
EXAMPLE 10



Step 1:

Follow the procedure of Example 3, using 1-(4-fluorophenyl)-4-(4-t-butyldimethylsilyloxyphenyl)-2-azetidinone to obtain 1-(4-fluorophenyl)-3-(3-phenyl-1-hydroxypropyl)-4-(4-t-butyldimethylsilyloxyphenyl)-2-azetidinone.

Step 2:

Treat a solution of the cis-azetidinone of Step 1 (0.25 g) in CH₃CN (21 ml) with 48% aqueous HF (2.5 ml). After 18 h, dilute the reaction mixture with cold H₂O and extract with Et₂O. Wash (2x H₂O, dilute NaHCO₃ and brine), dry (MgSO₄) and concentrate the Et₂O layer. Crystallize the residue from EtOAc:hexane (1:2) to obtain the title compound as colorless needles (123 mg, y=64%), mp 168°-171° C. Elemental analysis calc for C₃₄H₃₇O₅FN: C 73.64; H 5.66; N 3.58. found C 73.32; H 5.65; N 3.68.

The following formulations exemplify some of the dosage of this invention. In each the term "active compound" designates a compound of formula I.

EXAMPLE A

Tablets			
No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	122	113
3	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4	Corn Starch, Food Grade	45	40
5	Magnesium Stearate	3	7
Total		300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in suitable mixer for 10-15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., W, 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

38
EXAMPLE B

Capsules			
No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	106	123
3	Corn Starch, Food Grade	40	70
4	Magnesium Stearate NF	4	7
Total		250	700

Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

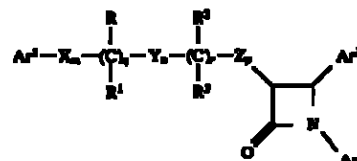
Representative formulations comprising a cholesterol biosynthesis inhibitor are well known in the art. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms disclosed above for substituted azetidinone compounds may readily be modified using the knowledge of one skilled in the art.

Using the test procedures described above, the following in vivo data were obtained for the exemplified compounds. Data is reported as percent change (i.e., percent reduction in cholesterol esters) versus control, therefore, negative numbers indicate a positive lipid-lowering effect.

% Reduction				% Reduction			
Ex. #	Serum Cholest.	Cholest. Esters	Dose mg/kg	Ex. #	Serum Cholest.	Cholest. Esters	Dose mg/kg
1A	-23	0	50	4C	-12.5	0	3
1B	-15	-39	50	4D	9	0	7
1C	14	0	50	4E	0	-46	3
2	0	0	50	4F	-29	-95	3
3A	-31	-69	50	5	0	-64	10
3C	-60	-92	50	6A	-39	-95	1
3D	-17	-61	10	6A-1	-43	-93	1
3E	0	0	10	6B	-40	-92	3
3F	-29	-77	10	6C	0	-48	3
3G	-16	-38	10	6D	-46	-95	10
3H	-41	-86	10	8A	0	-44	3
3I	0	-22	10	8B	-30	-83	3
3J	0	0	3	8C	-14	-37	1
3K	0	0	10	8D	-49	-98	1
3L	-15	-21	10	8E	-22	-64	3
3M	0	-22	10	8F	-43	-94	1
4A	0	-54	5	10	-26	-77	3
4B	-37	-89	8				

We claim:

1. A compound represented by the formula

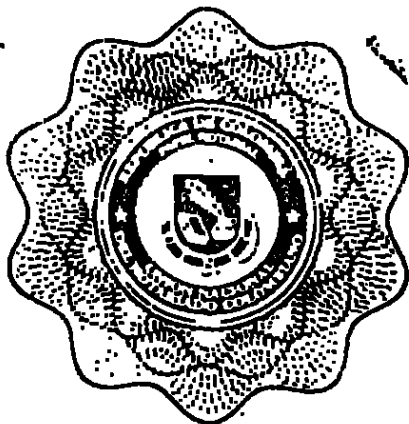


or a pharmaceutically acceptable salt thereof, wherein:
Ar¹ and Ar² are independently selected from the group consisting of aryl and R¹-substituted aryl;
Ar² is aryl or R²-substituted aryl;

- X, Y and Z are independently selected from the group consisting of $-\text{CH}_2-$, $-\text{CH}(\text{lower alkyl})-$ and $-\text{C}(\text{dlower alkyl})-$;
- R and R² are independently selected from the group consisting of $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^6$ and $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$;
- R¹ and R³ are independently selected from the group consisting of hydrogen, lower alkyl and aryl;
- q is 0 or 1; r is 0 or 1; m, n and p are independently 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;
- R⁴ is 1-5 substituents independently selected from consisting of lower alkyl, $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{OR}^6$, $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{CO})\text{OR}^6$, $-\text{NR}^6(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{SO}_2\text{R}^7$, $-\text{COOR}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $\text{S}(\text{O})_{2-3}\text{R}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$, $-(\text{lower alkylene})\text{COOR}^6$, $-\text{CH}=\text{CH}-\text{COOR}^6$, $-\text{CF}_3$, $-\text{CN}$, $-\text{NO}_2$ and halogen;
- R⁵ is 1-5 substituents independently selected from the group consisting of $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{OR}^6$, $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{CO})\text{OR}^6$, $-\text{NR}^6(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{SO}_2\text{R}^7$, $-\text{COOR}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $\text{S}(\text{O})_{2-3}\text{R}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$, $-(\text{lower alkylene})\text{COOR}^6$ and $-\text{CH}=\text{CH}-\text{COOR}^6$;
- R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and
- R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl.
2. A compound of claim 1 wherein Ar¹ is phenyl or R⁴-substituted phenyl, Ar² is phenyl or R⁴-substituted phenyl and Ar³ is R⁵-substituted phenyl.
 3. A compound of claim 2 wherein Ar¹ is R⁴-substituted phenyl wherein R⁴ is halogen; Ar² is R⁴-substituted phenyl wherein R⁴ is halogen or $-\text{OR}^6$, wherein R⁴ is lower alkyl or hydrogen; and Ar³ is R⁵-substituted phenyl, wherein R⁵ is $-\text{OR}^6$, wherein R⁶ is lower alkyl or hydrogen.
 4. A compound of claim 1 wherein X, Y, and Z are each $-\text{CH}_2-$; R¹ and R³ are each hydrogen; R and R² are each $-\text{OR}^6$, wherein R⁶ is hydrogen; and the sum of m, n, p, q and r is 2, 3 or 4.
 5. A compound of claim 1 wherein m, n and r are each zero, q is 1 and p is 2.
 6. A compound of claim 1 wherein p, q and n are each zero, r is 1 and m is 2 or 3.
 7. A compound selected from the group consisting of
rel 3(R)-(2(R)-hydroxy-2-phenylethyl)-4(R)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;
rel 3(R)-(2(R)-hydroxy-2-phenylethyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;
3(S)-(1(S)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;
3(S)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

- 3(R)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;
rel 3(R)-(S)-hydroxy-(2-naphthalenyl)methyl-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;
rel 3(R)-(R)-hydroxy-(2-naphthalenyl)methyl-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;
3(R)-(3(R)-hydroxy-3-phenylpropyl)-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;
3(R)-(3(S)-hydroxy-3-phenylpropyl)-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;
4(S)-(4-hydroxyphenyl)-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;
4(S)-(4-hydroxyphenyl)-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;
rel 3(R)-[3(RS)-hydroxy-3-(4-(methoxymethoxy)phenyl)-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone];
1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone;
1-(4-fluorophenyl)-3(R)-[3(R)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone;
4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;
4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;
1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone;
3(R)-[3(R)-acetyloxy]-3-phenylpropyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;
3(R)-[3(S)-acetyloxy]-3-phenylpropyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;
3(R)-[3(R)-(acetyloxy)-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-fluorophenyl)-2-azetidinone;
3(R)-[3(S)-(acetyloxy)-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-fluorophenyl)-2-azetidinone;
3(R)-[3(R)-(acetyloxy)-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone;
3(R)-[3(S)-(acetyloxy)-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone; and
rel 1-(4-fluorophenyl)-4(S)-(4-hydroxyphenyl)-3(R)-(1(R)-hydroxy-3-phenylpropyl)-2-azetidinone.
8. A pharmaceutical composition for the treatment prevention of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising an effective amount of a compound of claim 1 in a pharmaceutically acceptable carrier.
 9. A method of treating or preventing atherosclerosis or reducing plasma cholesterol levels comprising administering to a mammal in need of such treatment an effective amount of a compound of claim 1.

* * * * *



1658 B

AA 8567146

31
201

REPUBLICA DE COLOMBIA

NOTARIA 33 DE BOGOTA D.C.

ESCRITURA PUBLICA NUMERO: 1 6 5 8

- - MIL SEISCIENTOS CINCUENTA Y OCHO - -

FECHA DE OTORGAMIENTO: CUATRO (4) DE

JULIO - - -

DEL AÑO DOS MIL DOS (2002). - - -

ACTO: - - -

1.- PODER ESPECIAL. - - -

OTORGADO POR: LAFRANCOL S.A., con N.º

890.301.463-E - - -

a favor de: JOSE LUIS REYES VILLAMIZAR, con C.C.N .

79.152.473 de Usaquén - Bogotá. - - -

DIANA BEATRIZ LOPEZ

NOTARIA TREINTA Y TRES (33) DE BOGOTA D.C.

EN LA CIUDAD DE BOGOTA, DISTRITO CAPITAL,

DEPARTAMENTO DE CUNDINAMARCA, REPUBLICA DE COLOMBIA,

ANTE MI, DIANA BEATRIZ LOPEZ, - - -

NOTARIA TREINTA Y TRES (33) - - -

DE ESTE CIRCULO SE OTORGA LA ESCRITURA PUBLICA QUE

SE CONSIGNA EN LOS SIGUIENTES TERMINOS: - - -

COMPARECIO: JUAN MARIA RENDON, mayor de edad,

vecino de Bogotá, D.C, identificado con la cédula de

ciudadanía número 17.125.100 - - -

Expedida en Bogotá - - -

Y manifestó: - - -

PRIMERO: Que obra en su carácter de Representante

Legal de en nombre y representación de LAFRANCOL

S.A, sociedad comercial organizada y existente

conforme a las leyes colombianas, con domicilio y

sede principal en Cali - Valle, constituida mediante

escritura pública número

ESTE AFEL NO TIENE COSTO ALGUNO PARA EL USUARIO

Como Notario del Estado de Bogotá, he verificado que esta escritura es copia que se ha presentado en la Oficina de Registro de Bogotá D.C. - Colombia.

22 JUN 2006

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VENTIDOS

De la Notaría

De fecha

Reformada en distintas oportunidades, según consta en el certificado expedido por la Cámara de Comercio de Cali - Valle.-----

SEGUNDO: Que en tal carácter, por este público instrumento, concede PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE a JOSE LUIS REYES VILLAMIZAR, mayor de

edad, vecino de Bogotá, D.C, identificado con la cédula de ciudadanía número 79.152.473 de Usaqué, abogado en ejercicio, portador de la T.P.No. 446 55 del C.S. de la J., domiciliado en Bogotá, D.C,

República de Colombia, con dirección en la carrera 17 No. 88-23, Oficina 205, de la misma ciudad, como su representante con poder especial, amplio y

suficiente, para obtener la protección los derechos de propiedad industrial y de libre competencia de Lafrancol S.A., a cuyo efecto lo

autorizo, par que nos represente ante cualesquiera entidad o persona, ejerza o no jurisdicción, especialmente ante las el orden administrativo,

contencioso, administrativo y judicial, en todo lo concerniente a los siguientes asuntos:-----

a.- Obtención, formulación de observaciones y oposición a patentes de invención, modelos y dibujos industriales y el registro de licencias de uso de esos derechos.-----

b.- Las acciones de oposición, cancelación, nulidad, medidas cautelares, concesión de licencias y en general los procesos civiles, penales, administrativos o contencioso- administrativos relacionados con estos derechos u otros de diferente naturaleza, acciones y procesos que



16533

AA 8567152

202

promueva Lafrancol S.A., o se promuevan contra esta y.-----

c.- Para que en todos los asuntos arriba determinados, tanto en los términos señalados por los artículos 42 y complementarios

de la decisión 486 de la Comunidad Andina como del artículo 70 del C.P.C. pueda sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar y ratificar los actos de agentes oficiosos y ceder a título gratuito y/o oneroso, licenciar, inscribir contratos de cesión y de licencia, inscripción de prendas, levantamiento de prendas, inscribir derechos de retención y en general todos los asuntos que se deban tramitar ante la Superintendencia de Industria y Comercio.-----

Manifestamos que de la veracidad de las declaraciones del contenido y autenticidad de los documentos anexos en éste instrumento público sólo respondemos los comparecientes.-

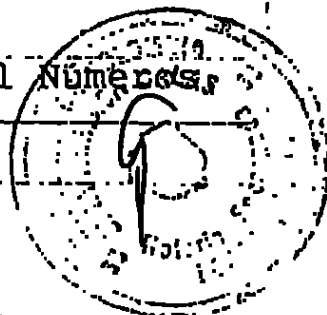
HASTA AQUI LA MINUTA PRESENTADA

Como Notario Valiente del Circuito de Bogotá, hago constar que esta fotocopia corresponde a copia que se ha presentado. Bogotá D.C. - Colombia.

22 JUN 2006

OTORGAMIENTO Y AUTORIZACION: Leído ~~NOTARIO VALIENTE~~ presente instrumento Público por los comparecientes y advertidos de la formalidad de su contenido, dentro del término legal, lo hallaron conforme con sus intenciones y lo aprobaron en todas sus partes y firmaron junto con la Suscrita Notaria quien da fe y lo autoriza. -----

Se utilizaron las hojas de papel Notarial Números AA 8567146, 8567152.



DERECHOS NOTARIALES: \$ 49.600.00

RESOLUCION No. 4188 del 28 de Diciembre del 2001

JUAN MARIA RENDON

C.C. No. 17.125.100 de Bogotá

LAFRANCOL S.A.

Nit. No. 890.301.463-8

TEL: 622-04-66.

ACEPTO :

JOSE LUIS REYES VILLAMIZAR

C.C. No. 79.152.473

TEL: 621-2631

DIANA BEATRIZ LOPEZ
DIANA BEATRIZ LOPEZ

NOTARIA 33 DE BOGOTA D.C.

n.c.a.

Es segunda COPIA (FOTOCOPIA)

tomada de su original que se expide conforme al

Artículo 79 del Decreto 960 de 1970 en 06

hojas útiles con destino a Jose Luis Reyes

Villamizar

Santafé de

SEP. 1999; Dcto. 1712/79

05 JUL. 2002

Qui





01



203 55

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 1

null

CERTIFICA:

NOMBRE: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

DOMICILIO: CALI VALLE

DIRECCION COMERCIAL : ---K 1 46 84

DIRECCION NOTIFICACION JUDICIAL: ---K 1 46 84

CIUDAD: CALI

MATRICULA MERCANTIL NRO. 5233-4 FECHA MATRICULA : 02 DE OCTOBER DE 1958

DIRECCION ELECTRONICA : esperanzacortes@lafrancol.net

AFILIADO

CERTIFICA:

NIT : 890301463-8

CERTIFICA:

QUE POR ESCRITURA NRO. 1434 DEL 29 DE SEPTIEMBRE DE 1958 NOTARIA CUARTA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE OCTOBER DE 1958 BAJO EL NRO. 18319 DEL LIBRO IX , SE CONSTITUYO LA SOCIEDAD DENOMINADA LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

CERTIFICA:

REFORMAS DOCUMENTO INS LIBRO	FECHA.DOC	ORIGEN	FECHA.INS	NRO.
E.P. 1104 19467	30/06/1959	NOTARIA CUARTA DE CALI	07/07/1959	
E.P. 2309 20089	26/12/1959	NOTARIA CUARTA DE CALI	29/12/1959	
E.P. 1725 24528	24/07/1962	NOTARIA CUARTA DE CALI	26/07/1962	
E.P. 1824	31/07/1963	NOTARIA CUARTA DE CALI	14/08/1963	

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 2

26360					
E.P. 2422	25/10/1963	NOTARIA CUARTA DE CALI		28/10/1963	
26717					
E.P. 1720	16/09/1964	NOTARIA CUARTA DE CALI		22/09/1964	
28406					
E.P. 101	31/01/1966	NOTARIA CUARTA DE CALI		01/02/1966	
31039					
E.P. 552	21/03/1968	NOTARIA CUARTA DE CALI		01/04/1968	
35711					
E.P. 4964	12/12/1972	NOTARIA CUARTA DE CALI		16/01/1973	
2975 IX					
E.P. 1956	30/05/1973	NOTARIA CUARTA DE CALI		13/06/1973	
4337 IX					
E.P. 4964	12/12/1972	NOTARIA CUARTA DE CALI		28/11/1973	
5994 IX					
E.P. 5579	12/11/1973	NOTARIA CUARTA DE CALI		28/11/1973	
5995 IX					
E.P. 4406	30/09/1974	NOTARIA CUARTA DE CALI		28/11/1974	
10887 IX					
E.P. 192	03/02/1978	NOTARIA CUARTA DE CALI		14/02/1978	
25355 IX					
E.P. 3479	07/09/1979	NOTARIA CUARTA DE CALI		19/09/1979	
34204 IX					
E.P. 4274	12/12/1984	NOTARIA NOVENA DE CALI		19/12/1984	
73088 IX					
E.P. 1155	21/05/1985	NOTARIA SEPTIMA DE CALI		03/06/1985	
76917 IX					
E.P. 1553	20/06/1986	NOTARIA SEPTIMA DE CALI		08/07/1986	
85997 IX					
E.P. 1458	09/06/1987	NOTARIA SEPTIMA DE CALI		24/12/1987	
3508 IX					
E.P. 7222	14/12/1988	NOTARIA TERCERA DE CALI		19/12/1988	
13847 IX					
E.P. 4530	04/09/1989	NOTARIA TERCERA DE CALI		07/09/1989	
21508 IX					
E.P. 3865	02/08/1990	NOTARIA TERCERA DE CALI		13/08/1990	
31708 IX					
E.P. 8305	13/12/1995	NOTARIA TERCERA DE CALI		23/01/1996	
557 IX					
E.P. 4559	16/11/1999	NOTARIA TERCERA DE CALI		26/11/1999	
7911 IX					
E.P. 6.004	02/12/2004	NOTARIA TERCERA DE CALI		14/12/2004	
13371 IX					
E.P. 6241	27/12/2006	NOTARIA TERCERA DE CALI		19/01/2007	

*** CONTINUA ***



01



204 24

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 3

625 IX

CERTIFICA:

VIGENCIA: 29 DE SEPTEMBER DEL A?O 2057

CERTIFICA:

OBJETO SOCIAL. SE OCUPA EN: A) FABRICACION, DISTRIBUCION Y VENTA EN EL TERRITORIO DE LA REPUBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUIMICOS, FARMACEUTICOS ALIMENTICIOS FUNCIONALES, COSMETICOS Y FISIOLOGICOS, REACTIVOS, ANTIBIOTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETETICOS, COLORANTES DE PERFUMERIA Y AFINES. B) LA REPRESENTACION DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. C) FABRICACION, IMPORTACION, DISTRIBUCION Y VENTA DE CUALESQUIERA TIPOS DE PRODUCTOS VETERINARIOS. D) LA REALIZACION DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. EN DESARROLLO DE SU OBJETO SOCIAL PODRA LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAICES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAICES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD; DAR Y RECIBIR A MUTUO COMERCIAL DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS.

CERTIFICA:

ORGANOS DE DIRECCION Y ADMINISTRACION: 1) ASAMBLEA GENERAL DE ACCIONISTAS; 2) JUNTA DIRECTIVA; 3) GERENCIA GENERAL. TAMBIEN TENDRA UN REVISOR FISCAL.

ADMINISTRACION: LA ADMINISTRACION INMEDIATA DE LA SOCIEDAD, SU REPRESENTACION LEGAL Y LA GESTION DE LOS NEGOCIOS SOCIALES ESTARAN A CARGO DE UN GERENTE, DESIGNADO POR LA ASAMBLEA GENERAL DE ACCIONISTAS, PARA PERIODOS DE DE DOS (2) A?OS REELEGIBLE INDEFINIDAMENTE Y REMOVIBLE LIBREMENTE POR ELLA EN CUALQUIER TIEMPO.

PARAGRAFO PRIMERO. SUPLENTES: EL GERENTE Y REPRESENTANTE LEGAL TENDRA LOS SIGUIENTES SUPLENTES: PRIMERO, SEGUNDO Y TERCERO QUE LO REEMPLAZARAN EN LOS CASOS DE AUSENCIAS ACCIDENTAL, TEMPORAL Y ABSOLUTA CON LAS LIMITACIONES QUE MAS ADELANTE SE ESTABLECEN.

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 4

PARAGRAFO SEGUNDO. EL TERCER SUPLENTE DEL GERENTE GENERAL Y REPRESENTANTE LEGAL ESTARA LIMITADO EN SUS FUNCIONES A: COMPROMETER LOS NEGOCIOS SOCIALES EN CUANTIA NO SUPERIOR A CUATRO MIL DOSCIENTOS SALARIOS MINIMOS MENSUALES LEGALES VIGENTES (4.200 SMLV); CELEBRAR CONTRATOS COMERCIALES DE COMPRAVENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS SOCIALES CIVILES Y COMERCIALES, CUALQUIERA QUE SEA SU NATURALEZA CON FACULTADES PARA EXIGIR O SUSCRIBIR LOS DOCUMENTOS Y GARANTIAS NECESARIOS HASTA LA CUANTIA ANTES MENCIONADA.

FUNCIONES DEL GERENTE: A) ... B) EJECUTAR Y HACER CUMPLIR LOS ACUERDOS Y DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS Y DE LA JUNTA DIRECTIVA Y HACER USO DE LA RAZON SOCIAL. C) REPRESENTAR LEGALMENTE A LA SOCIEDAD CONFORME A LA LEY ANTE TODAS LAS AUTORIDADES CIVILES, JUDICIALES, MILITARES, SANITARIAS, DE POLICIA, ADUANALES, POSTALES, ETC. G) LLEVAR A CABO LA GESTION COMERCIAL Y FINANCIERA. H) TENDRA LA PLENA RESPONSABILIDAD DE LA ACCION ADMINISTRATIVA, LA COORDINACION Y LA SUPERVISION GENERAL DE LA SOCIEDAD, LAS CUALES CUMPLIRA CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS.

EN EL EJERCICIO DE SUS FUNCIONES, EL GERENTE PUEDE: 1.- COMPARECER EN LOS JUICIOS, TRANSIGIR Y COMPROMETER LOS NEGOCIOS SOCIALES DE CUALQUIERA NATURALEZA QUE FUEREN, INTERPONER TODO GENERO DE RECURSOS Y CONSTITUIR APODERADOS QUE LO REPRESENTEN JUDICIAL O EXTRAJUDICIALMENTE. 2.- ENAJENAR A CUALQUIER TITULO Y COMPRAR BIENES MUEBLES, CELEBRAR CONTRATOS COMERCIALES DE COMPRA Y VENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS), EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS O SOCIEDADES CIVILES Y COMERCIALES CUALQUIERA QUE SEA SU NATURALEZA Y SU CUANTIA, CON AMPLIAS FACULTADES QUE EXIGIR O SUSCRIBIR LOS DOCUMENTOS, Y GARANTIAS NECESARIAS. CONTRATAR PRESTAMOS CUALQUIERA QUE SEA SU CUANTIA, CELEBRAR EL CONTRATO COMERCIAL DE MUTUO EN TODAS SUS MANIFESTACIONES Y SUSCRIBIR LOS DOCUMENTOS Y COMPROMISOS RESPECTIVOS. HACER DEPOSITOS EN BANCOS Y AGENCIAS BANCARIAS, FIRMAR CHEQUES, LETRAS, PAGARES, GIROS, LIBRANZAS Y CUALQUIER OTRO DOCUMENTO, ASI COMO NEGOCIAR ESTOS INSTRUMENTOS, TENERLOS, COBRARLOS, PAGARLOS, DESCARGARLOS, ETC.

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARCH DE 2002

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 09 DE SEPTEMBER DE 2002 No. 14675 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

*** CONTINUA ***



01



205 35

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 5

VICEPRESIDENTE

ROBERTO S. VENTURA PAULY

C.C.16697614

GERENTE GENERAL Y REPRESENTANTE LEGAL

JUAN MARIA RENDON GUTIERREZ

C.C.17125100

PRIMER SUPLENTE DEL GERENTE

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

SEGUNDO SUPLENTE DEL GERENTE

ROBERTO M. VENTURA CRISPINO

C.C.9086003

PRESIDENTE

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

CERTIFICA:

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVEMBER DE 2004

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 17 DE FEBRUARY DE 2005 No. 2032 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

TERCER SUPLENTE DEL GERENTE

JUAN PABLO REYES VILLAMIZAR

C.C.80419709

CERTIFICA:

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 6

DOCUMENTO: ACTA No. 99 DEL 14 DE MARCH DE 2002

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 09 DE SEPTEMBER DE 2002 No. 14675 DEL LIBRO IX

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVEMBER DE 2004

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 17 DE FEBRUARY DE 2005 No. 2031 DEL LIBRO IX

FUE (RON) _NOMBRADO (S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

SEGUNDO RENGLON

ROSA VICTORIA VENTURA DE VISBAL

C.C.38992048

TERCER RENGLON

JUAN PABLO REYES VILLAMIZAR

C.C.80419709

SUPLENTES

PRIMER RENGLON

JUAN MARIA RENDON GUTIERREZ

C.C.17125100

SEGUNDO RENGLON

ROBERTO M. VENTURA CRISPINO

C.C.9086003

TERCER RENGLON

ROBERTO S. VENTURA PAULY

C.C.16697614

CERTIFICA:

***** CONTINUA *****



01



206 35

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 7

DOCUMENTO: ACTA No. 99 DEL 14 DE MARCH DE 2002

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 09 DE SEPTEMBER DE 2002 No. 14675 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

REVISOR FISCAL

ALFREDO LOPEZ & CIA. LTDA

NIT.800026893-5

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 20 DE OCTOBER DE 2006

ORIGEN: ALFREDO LOPEZ & CIA LTDA

INSCRIPCION: 07 DE NOVEMBER DE 2006 No. 12672 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

REVISOR FISCAL PRINCIPAL

ALFREDO LOPEZ CAMPO

C.C.8241912

REVISOR FISCAL SUPLENTE

GEOVANA GONZALEZ GALINDO

C.C.66959852

CERTIFICA:

CAPITAL AUTORIZADO: \$7,500,000,000

NUMERO DE ACCIONES: 750,000,000

VALOR NOMINAL: \$10

CAPITAL SUSCRITO: \$6,000,000,000

NUMERO DE ACCIONES: 600,000,000

VALOR NOMINAL: \$10

CAPITAL PAGADO: \$6,000,000,000

NUMERO DE ACCIONES: 600,000,000

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529 Hora Certificado : 123616

Operacion: 02NA80529024 PAGINA No. 8

VALOR NOMINAL: \$10

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.5234- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL

UBICADO EN: ---K 1 46 84 DE CALI

RENOVO : POR EL A?O 2007

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.369809- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S A

UBICADO EN: --K 1 46A 70 DE CALI

FECHA MATRICULA : 29 DE ABRIL DE 1994

RENOVO : POR EL A?O 2007

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.369810- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S A

UBICADO EN: ---K 1A 46 A 32 DE CALI

FECHA MATRICULA : 29 DE ABRIL DE 1994

RENOVO : POR EL A?O 2007

CERTIFICA:

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 29 DE
MARCH DE 2007 .

CERTIFICA:

*** CONTINUA ***

207 28

CERTIFICADO NACIONAL

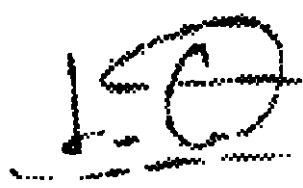
CAMARA DE COMERCIO DE CALI

Fecha : 20070529 Hora Certificado : 123616

Operacion: 02NA80529024 PAGINA No. 9

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL
PRESENTE CERTIFICADO.
LOS ACTOS Y DOCUMENTOS REGISTRADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES
DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO
TERMINO NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

DE CONFORMIDAD CON EL DECRETO 2150 DE 1.995 Y LA AUTORIZACION IMPARTIDA POR
LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A
CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.
DADO EN CALI A LOS 29 DIAS DEL MES DE MAY DEL AÑO 2007 HORA: 12:28:45

A handwritten signature or stamp, possibly reading "LE", is located below the text. It appears to be a stylized mark or initials.

38
208

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 06-060216-00001-0000
Fecha: 2007-05-30 14:48:59 Dep 2020 NUECREACION
Tra 11 PATENTEIYII Eve 378 FASENACIONALI
Act 400 OPOSIOBSERVTER Folios. 38

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 42.777
FECHA : MAYO 29 DE 2007

CONSIGNACION

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	54661331	28/05/2007	1.024.000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	30003-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LENAS COMERCIALES	236.000.00
		TOTAL :	\$ 236.000.00

MON: DOSCIENTOS CINCUENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____