

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 Titulo 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 589 - Número de Publicación 1129
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3	OPOSICION PRESENTADA POR:
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OPOSITOR	Nombre: TECNOQUIMICAS S.A. Sociedad comercial organizada y existente a las leyes Colombianas, con domicilio y sede principal en la Ciudad de Cali Valle. Dirección: Calle 23 # 7-39 Cali Valle Teléfono: 882 5555 Fax: 883 8859 E-mail: Domicilio: Cali - Valle	IDENTIFICACION C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: 890 300 466-5
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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
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4	FUNDAMENTOS DE LA OPOSICION: Causa: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 488 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
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5	Comprobante de pago No. <u>07-42.778</u> (Oposición) Fecha <u>Mayo 29 de 2007</u> (Prórroga) Fecha _____
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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 WILLAMIZAR

FIRMA:

C.C No. 79.162.473 T.P. No. 44656

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 **TECNOQUIMICAS 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

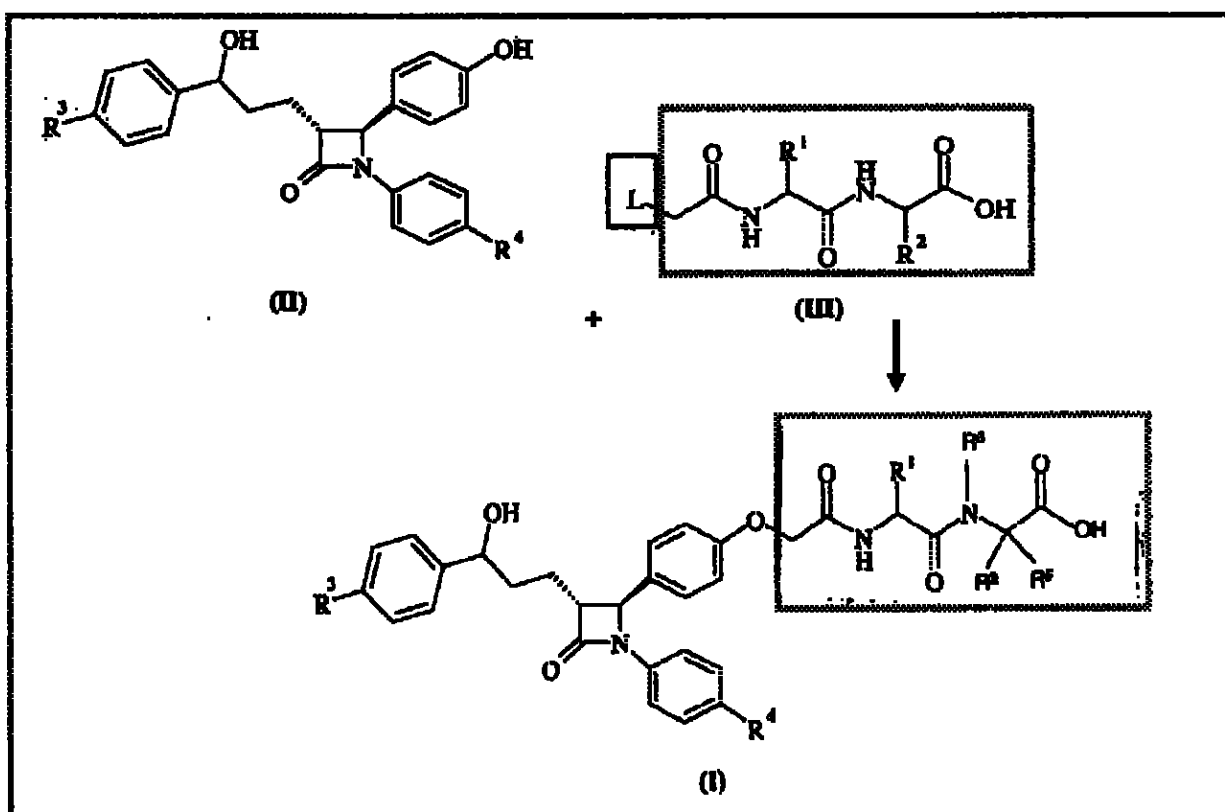
Asiste a **TECNOQUIMICAS S.A.**, en su calidad de industria farmacéutica nacional, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias y composiciones farmacéuticas carentes de nivel inventivo, en detrimento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

III. FUNDAMENTOS DE LA OPOSICIÓN

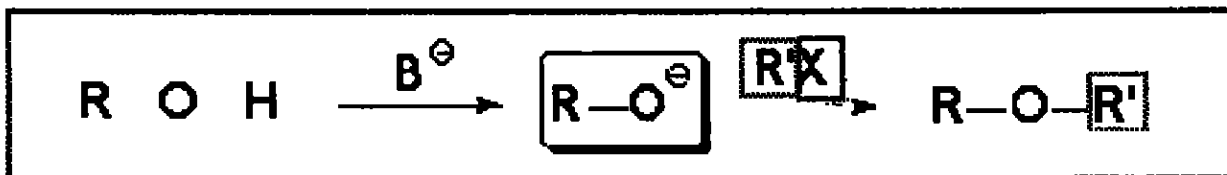
3.1. Los compuestos que reivindica la solicitud colombiana 06-060-216 que resultan ser derivados de ezetimibe, útiles como inhibidores de la absorción de colesterol en el tratamiento de hiperlipidemia, arteriosclerosis, alzheimer, tumores asociados con colesterol, sus formulaciones farmacéuticas, sus 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:

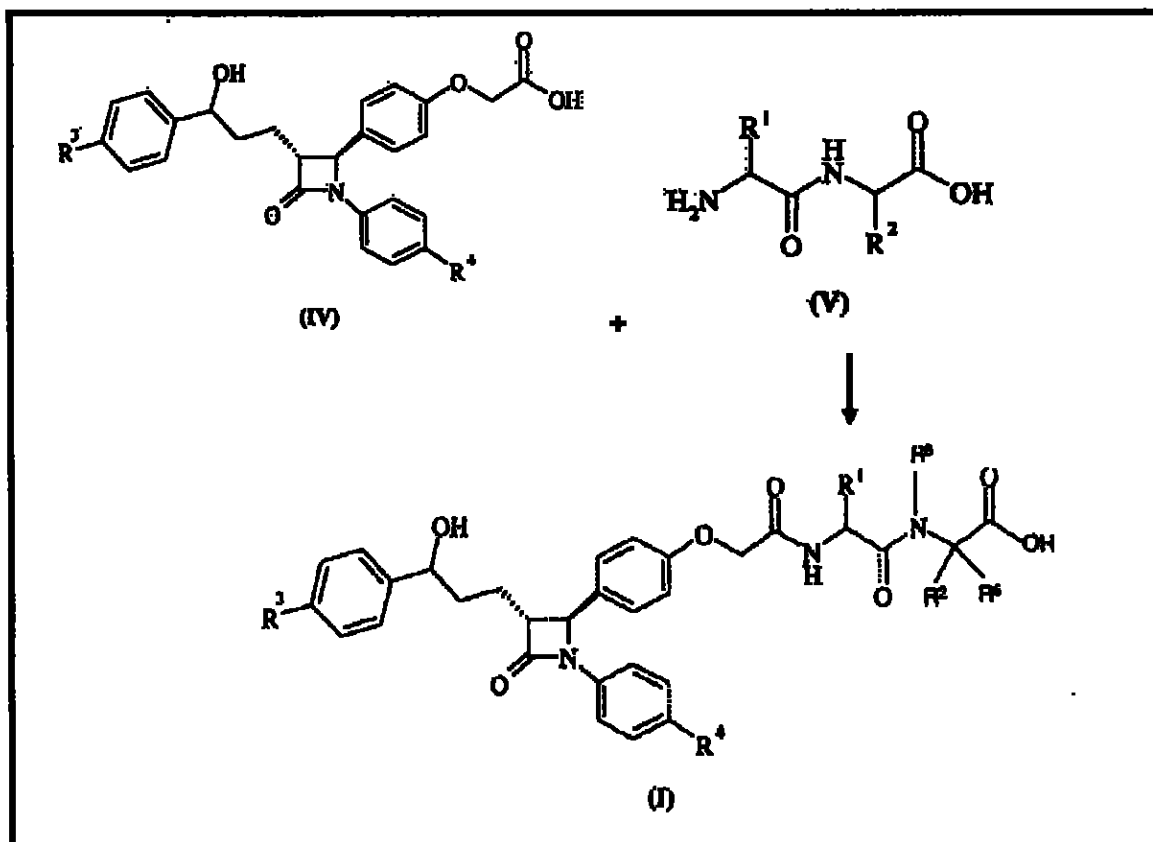


En la solicitud colombiana en trámite, el hidroxilo del grupo hidroxifenil que sustituye al núcleo de azetidinona en posición 4 reacciona con el compuesto de fórmula (III) (donde L es un grupo desplazable o saliente), donde al parecer por sustitución nucleofílica (SN2) permite obtener el compuesto de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

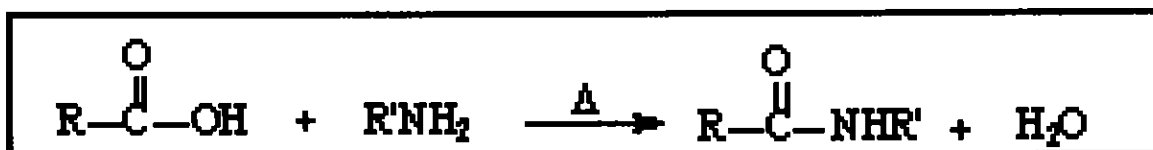


En síntesis orgánica, la manera más simple de preparar un éter es hacer reaccionar un alcóxido con un haluro o sulfonato de alquilo en una secuencia típica SN2.

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 hidroxí-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.

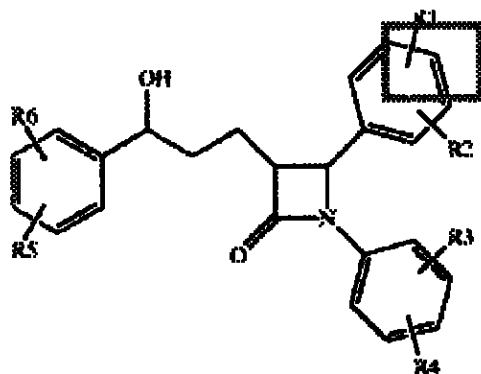
Se observa entonces, que la patente americana US 5,744,467 revela que el compuesto tipo azetidinona puede estar en combinación con un inhibidor de la biosíntesis de colesterol o como menciona en las reivindicaciones 2 y 3, que puede estar en combinación con un inhibidor de la HMG-CoA reductasa y, que 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, (C₃-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, C(O)-(C₁-C₆)-alkyl or CONH₂;

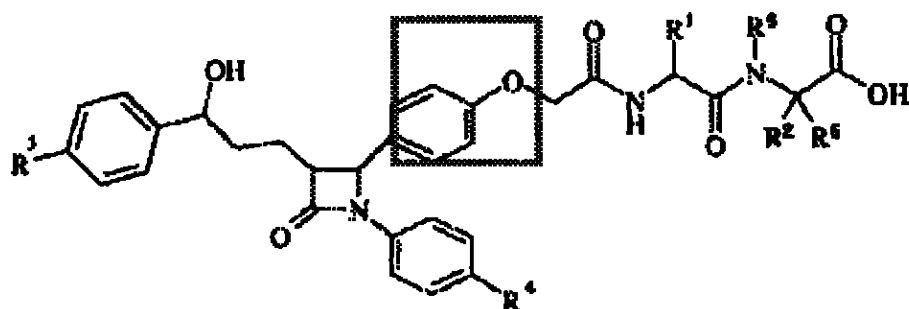
los cuales,

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:

(...)

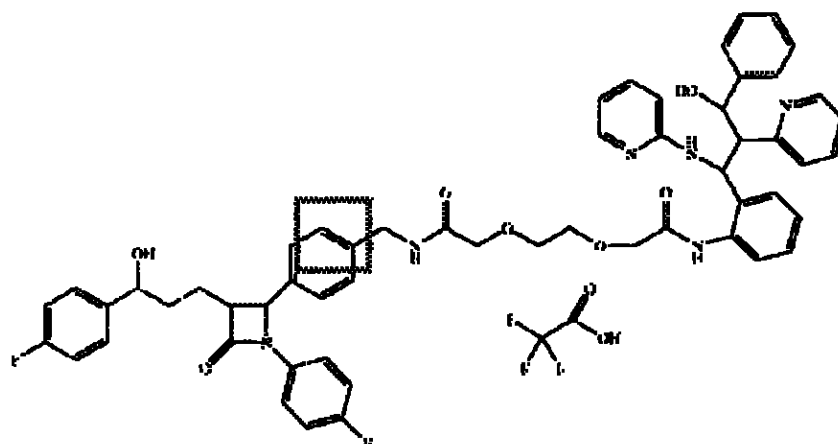
treatment of disease states associated with hyperlipidaemic conditions. The compounds of the present invention are not disclosed in any of the above applications and we have surprisingly found that the compounds of the present invention possess beneficial efficacious, metabolic and toxicological profiles 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:

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 hiperlipídicas, 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 1576, AVE 8042, 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:

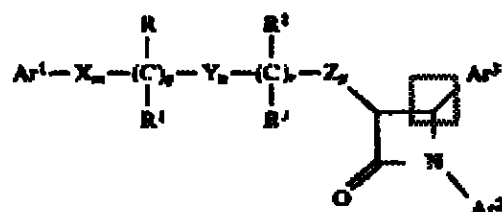
- * Derivados de azetidinona sustituidos en la misma posición y con sustituyentes de características químicas semejantes a los de la solicitud colombiana en trámite
- * Separación de los posibles enantiómeros
- * Derivados con características biofarmacéuticas modificadas útiles en el tratamiento de trastornos 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 R⁵-substituted aryl;

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)₁₋₁₀OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁶, —NR⁶(CO)NR⁷R⁸, —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 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

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 Tecnoquimicas S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.

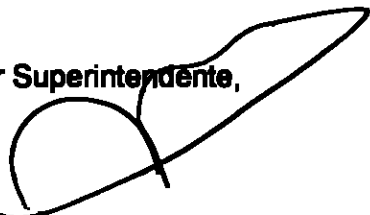
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222

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. Lafranco S.A., las recibirá en sus oficinas localizadas en la Calle 23 # 7-39 Cali – Valle.

Señor Superintendente,

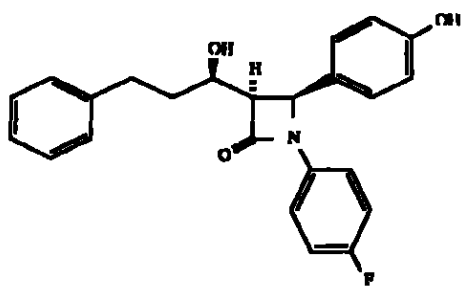


JOSE LUIS REYES VILLAMIZAR

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-*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 HIF (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 C₂₇H₃₂O₃FN: 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., 1/4", 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	113
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

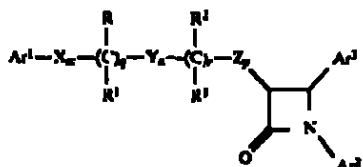
Method of Manufacture:
Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

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 ester) versus control, therefore, negative numbers indicate a positive lipid-lowering effect.

% Reduction			
Ex. #	Serum Cholest.	Cholest. Ester	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	-39	-77	10
3G	-16	-38	10
3H	41	-86	10
3I	0	-23	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	-54	-95	1
6A-1	-43	-93	1
6B	-40	-92	3
6C	0	-48	3
6D	-46	-95	10
8A	0	-44	3
8B	-90	95	3
8C	-14	-37	1
8D	40	08	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



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, —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(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁷, —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, —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)₁₋₁₀CONR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁷, —NR⁶(CO)NR⁶R⁷, —NR⁶SO₂R⁷, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₂R⁶, —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

R⁹ 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 1, 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 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 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-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;

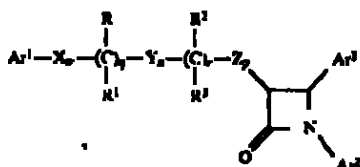
3(R)-[3(S)-acetyloxy]-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone; and

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 1

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 R⁵-substituted aryl;

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

R and R² are independently selected from the group consisting of —(R⁶), —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)₁₋₆OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁶, —NR⁶(CO)NR⁶R⁷, —NR⁶SO₂R⁷, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₂R⁶, —O(CH₂)₁₋₁₀OR⁶, —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)₁₋₆OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁶, —NR⁶(CO)NR⁶R⁷, —NR⁶SO₂R⁷, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₂R⁶, —O(CH₂)₁₋₁₀OR⁶, —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

R⁹ 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 —(R⁶), wherein R⁶ is lower alkyl or hydrogen; Ar³ is R⁵-substituted phenyl, wherein R⁵ is —(R⁶), 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 —(R⁶), 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.

* * * * *

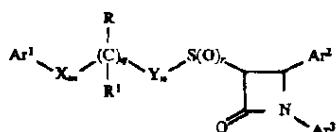
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Ex. #	% Reduction		Dose mg/kg
	Serum Cholest.	Cholest. Esters	
11	-55	-95	3
14	-20	-64	3
15	-27	-88	1
18	-27	-68	3

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, 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(dilower alkyl)-;

R is -OR⁶, -O(CO)R⁶, -O(CO)OR⁹ 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)OR⁹, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁹, -NR⁶(CO)NR⁷R⁸, -NR⁶SO₂R⁹, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₂R⁹, -O(CH₂)₁₋₁₀-COOR⁶, -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)OR⁹, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁹, -NR⁶(CO)NR⁷R⁸, -NR⁶SO₂R⁹, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₂R⁹, -O(CH₂)₁₋₁₀-COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -CF₃, -CN, -NO₂, halogen, -(lower alkylene)COOR⁶ and -CH=CH-COOR⁶;

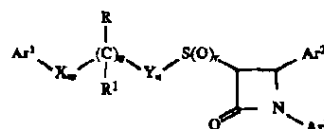
R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl; and R¹⁰ is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR⁶, -O(CO)R⁶, -O(CO)OR⁹, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁹, -NR⁶(CO)NR⁷R⁸, -NR⁶SO₂R⁹, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₂R⁹, -O(CH₂)₁₋₁₀-COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -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(dilower alkyl)-;

R is -OR⁶, -O(CO)R⁶, -O(CO)OR⁹ 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)OR⁹, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁹, -NR⁶(CO)NR⁷R⁸, -NR⁶SO₂R⁹, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₂R⁹, -O(CH₂)₁₋₁₀-COOR⁶, -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)OR⁹, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁹, -NR⁶(CO)NR⁷R⁸, -NR⁶SO₂R⁹, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₂R⁹, -O(CH₂)₁₋₁₀-COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -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

R¹⁰ is 1-5 substituents independently selected from the group consisting of lower alkyl, —OR⁶, —O(CO)R⁶, —O(CO)OR⁹, —O(CH₂)₁₋₁₀OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶(CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₂R⁹, —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)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; 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)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;

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;

(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.

* * * * *

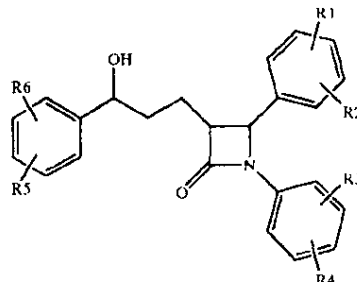
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MEDICAMENTS COMPRISING THESE
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Washington, DC 20005-3315 (US)(21) **Appl. No.: 10/021,044**(22) **Filed: Dec. 19, 2001**(30) **Foreign Application Priority Data**Dec. 21, 2000 (DE)..... 10064402.3
Nov. 7, 2001 (DE)..... 10154518.5**Publication Classification**(51) **Int. Cl.⁷** **A61K 31/397; C07D 25/08**
(52) **U.S. Cl.** **514/210.02; 540/200**(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**

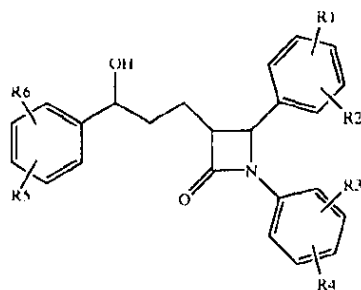
[0001] This application claims the benefit of priority under 35 U.S.C. §119(a) to German patent application no. 10064402.3, filed on Dec. 21, 2000, and German patent application no. 10154518.5, filed on Nov. 7, 2001. The contents of both priority documents are incorporated by reference herein.

[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-I., 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

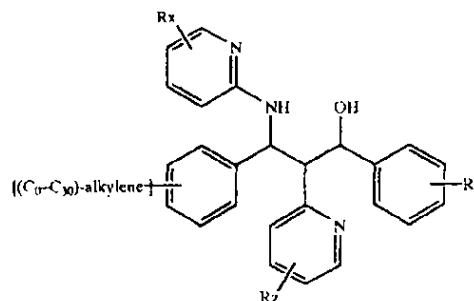
[0008] H, F, Cl, Br, I, CF₃, NO₂, CN, COOH, COO((C₁-C₆)-alkyl), CONH₂, CONH((C₁-C₆)-alkyl), CON((C₁-C₆)-alkyl)₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl or O—(C₁-C₆)-alkyl, where one, more or all hydrogens in the alkyl radicals may be replaced by fluorine; or

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

phenyl, 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, COO—(C₁-C₆)-alkyl or CONH₂;

[0011] L 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-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 (C₀-C₃₀)-alkylene-I., 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 (C₀-C₃₀)-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 (C₀-C₃₀)-alkylene-L, where one or more carbon atoms of the alkylene radicals 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 —(CH₂)_{C-1}—NH—(C=O)_{C-1}—(C₁-C_{C-1})-alkylene-(C=O)_{C-1}—NH—L, 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 L 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, sulfonic 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-azetidinone-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 Rote Liste 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, tiqeside, 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, JTI-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, BMS-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, colesolvam.

[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, 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, BMS-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, CJ-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. Reddy'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, doprexin), 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.

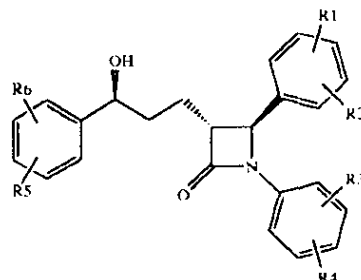
[0067] In one embodiment, the further active compound is mazindol or phentermine.

[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 muesli 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.

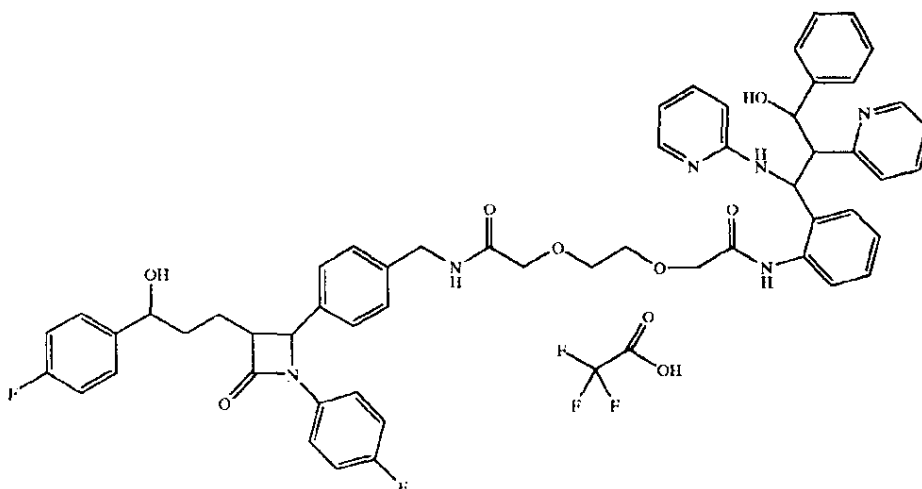
[0070] The invention furthermore provides both stereoisomer mixtures of the formula I and the pure stereoisomers of the formula I, and diastereomer mixtures of the formula I and the pure diastereomers. The mixtures are separated by chromatographic means.

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



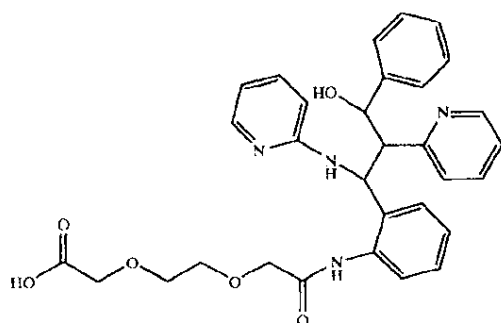
EXAMPLE XIX

[0098]

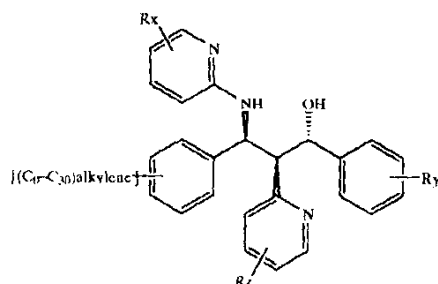


{1-[2-(2-{2-[(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxazetidin-2-yl}benzylcarbamoyl)methoxy]ethoxy}acetylaminophenyl)-3-hydroxy-3-phenyl-2-pyridin-2-ylpropyl}pyridin-2-ylammonium trifluoroacetate 36

[0099]

[0100] C₃₁H₃₂N₄O₆ (556.62) MS (ESI) 557 (M+H)

I. is shown connected to (C_0-C_{30}) -alkylene as follows:



Rx, Ry, Rz, independently of one another are H, F, Cl, Br, I, CF_3 , NO_2 , CN, COOH, $COO-(C_1-C_6)$ -alkyl, $CONH_2$, $CONH-(C_1-C_6)$ -alkyl, $CON-[(C_1-C_6)$ -alkyl] $_2$, (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_2-C_6) -alkynyl or $O-(C_1-C_6)$ -alkyl, where one, more or all hydrogens in the alkyl radicals may be replaced by fluorine; or

SO_2-NH_2 , $SO_2NH-(C_1-C_6)$ -alkyl, $SO_2N-[(C_1-C_6)$ -alkyl] $_2$, $S-(C_1-C_6)$ -alkyl, $S-(CH_2)_n$ -phenyl, $SO-(C_1-C_6)$ -alkyl, $SO-(CH_2)_n$ -phenyl, $SO_2-(C_1-C_6)$ -alkyl or $SO_2-(CH_2)_n$ -phenyl, where $n=0-6$ and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF_3 , NO_2 , CN, OCP_3 , $O-(C_1-C_6)$ -alkyl, (C_1-C_6) -alkyl or NH_2 ; or

NH_2 , $NH-(C_1-C_6)$ -alkyl, $N-[(C_1-C_6)$ -alkyl] $_2$, $NH-(C_1-C_7)$ -acyl, phenyl or $O-(CH_2)_n$ -phenyl, where $n=0-6$, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF_3 , NO_2 , CN, OCP_3 , $O-(C_1-C_6)$ -alkyl, (C_1-C_6) -alkyl, NH_2 , $NH-(C_1-C_6)$ -alkyl, $N-[(C_1-C_6)$ -alkyl] $_2$, SO_2-CH_3 , COOH, $COO-(C_1-C_6)$ -alkyl or $CONH_2$;

where one of the radicals R1 or R3 has the meaning $-(CH_2)_{0-1}-NH-(C=O)_{0-1}-(C_3-C_{25})$ -alkylene- $(C=O)_{0-1}-NH-I$, 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 BP antagonists, urocortin agonists, β_3 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.

* * * * *

United States Patent [19]

Rosenblum et al.

[11] Patent Number: 5,767,115

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

236

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

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[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, Jan. 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

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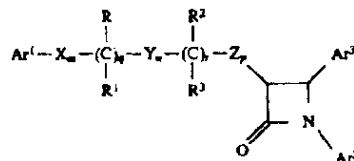
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Primary Examiner—Mark L. Berch
 Attorney, Agent, or Firm—Anita W. Magatti

[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(dilower alkyl)—;

R and R² are —OR⁶, —O(CO)R⁶, —O(CO)OR⁹ 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 R⁵ is selected from —OR⁶, —O(CO)R⁶, —O(CO)OR⁹, —O(CH₂)₁₋₅OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶(CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₂R⁹, —O(CH₂)₁₋₁₀—COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —(lower alkylene)COOR⁶ and —CH=CH—COOR⁶;

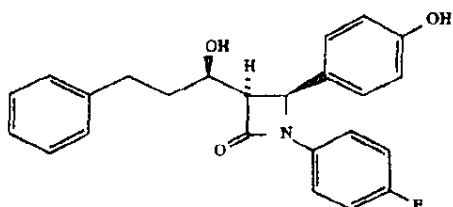
R⁶, R⁷ and R⁸ are H, lower alkyl, aryl or aryl-substituted

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.

9 Claims, No Drawings

37
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 C₂₄H₂₂O₃FN: 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., 1/4", 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.

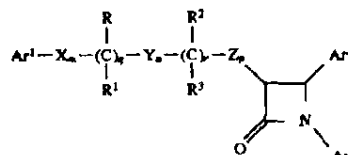
Using the test procedures described above, the following in vivo data were obtained for the exemplified compounds. Data is reported as percent change (i.e., percent reduction in cholesterol esters) versus control, therefore, negative numbers indicate a positive lipid-lowering effect.

% 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	-59	-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	-50	-95	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	-54	5	10	-26	-77	3
4B	-37	-89	8				

We claim:

1. A compound represented by the formula

55



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;

65

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

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

R⁵ is 1-5 substituents independently selected from the group consisting of $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^6$, $-\text{O}(\text{CH}_2)_{1-5}\text{OR}^6$, $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, $-\text{NR}^6\text{R}^7$, $-\text{NR}^6(\text{CO})\text{R}^7$, $-\text{NR}^6(\text{CO})\text{OR}^6$, $-\text{NR}^6(\text{CO})\text{NR}^7\text{R}^8$, $-\text{NR}^6\text{SO}_2\text{R}^9$, $-\text{COOR}^6$, $-\text{CONR}^6\text{R}^7$, $-\text{COR}^6$, $-\text{SO}_2\text{NR}^6\text{R}^7$, $\text{S}(\text{O})_{0-2}\text{R}^9$, $-\text{O}(\text{CH}_2)_{1-10}-\text{COOR}^6$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^6\text{R}^7$, $-(\text{lower alkylene})\text{COOR}^6$ and $-\text{CH}=\text{CH}-\text{COOR}^6$;

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 R⁶ 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(3S)-(4-methoxyphenyl)-1-phenyl-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.

* * * * *



239
AA 3286575
NOTARIA TERCERA
BOGOTÁ D.C.

ESCRITURA NUMERO CUATRO MIL QUINIENTOS -
TREINTA Y NUEVE (No.4.539) -----

En la ciudad de Cali, Capital del Depar-
tamento del Valle del Cauca, República de
Colombia, a los VEINTITRES (23) días -
del mes de OCTUBRE del año DOS MIL UNO --

(2.001), ante mi, JORGE ENRIQUE CAICEDO ZAMBRANO Notario

T E R C E R O (3o.) del Círculo de Cali -----

compareció JUAN MANUEL BARBERI OSPINA mayor de edad, vecino de Cali,
identificado con la cédula de ciudadanía número 14.949.561 de Cali, dijo: ----

PRIMERO.- Que obra en su carácter de Representante Legal de en nombre y
representación de TECNOQUIMICAS S.A. sociedad comercial organizada y existente
conforme a las leyes colombianas, con domicilio y sede principal en Cali constituida
mediante escritura pública número 2670 de la Notaría Segunda de Cali de fecha 12 de
junio de 1957, reformada en distintas oportunidades, según consta en el certificado
expedido por la Cámara de Comercio de Cali -----

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, identificado con C.C. # 79.152.473 de Isaquén, abogado en ejercicio, portador
de la T.P 44655 del C.S.de la J., domiciliado en Bogotá, D.C., República de Colombia
con dirección carrera 7 No. 88.23 oficina 205, de la misma ciudad, como su representante
con poder especial, amplio y suficiente, para obtener la protección de nuestra propiedad
industrial y contra la competencia desleal, a cuyo efecto lo autorizo, para que nos
represente ante cualesquiera entidad o persona, ejerzan o no jurisdicción, especialmente
ante las del 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 promovamos o se nos promuevan; y c) para

ESTE PAPEL NO TIENE COSTO ALGUNO PARA EL USUARIO

4539
0523

MERY CORDELL
BOGOTÁ D.C.
Notaría 3ª de Cali

11 ENE 2007
BOGOTÁ D.C., Colombia

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.

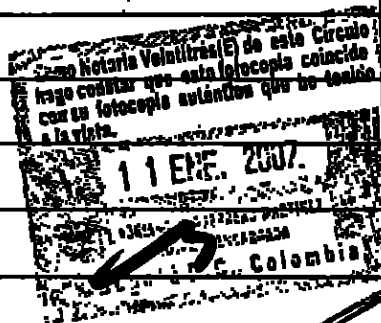
Leído el presente instrumento al otorgante, lo aprobó y en constancia firma conmigo el Notario de todo lo cual doy fe.

Se agregan comprobantes. Derechos \$30.000.00 Decreto 1681 de Septiembre 16 de 1996. Reformado mediante Resolución No.5839 de Diciembre 27 del año 2.000 y Decreto 1326 de Julio 06 del año 2.001. Se corrió en la hoja número AA 3286877. ENMENDADO "OCTUBRE" VALE.

Juan m. Barberi

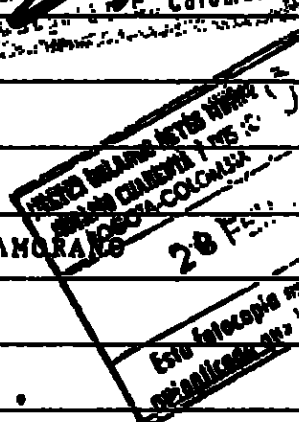
JUAN MANUEL BARBERI OSPINA

En rep. de TECNOQUIMICAS S.A.



El Notario Tercero de Cali

Dr. JORGE ENRIQUE CAICEDO ZAMORA



ccc11831951

FECHA: JUEVES 18 AGOSTO 2005 12:30:36

REPUBLICA DE COLOMBIA
CERTIFICADO DE EXISTENCIA Y REPRESENTACION

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE CALI

CERTIFICA

NOMBRE: TECNOQUIMICAS S A
DOMICILIO: CALI VALLE
DIRECCION COMERCIAL : --C 23 7 39
DIRECCION NOTIFICACION JUDICIAL: --C 23 7 39
CIUDAD: CALI
MATRICULA MERCANTIL NRO. 7049 - 4 FECHA MATRICULA : 01 DE JULIO DE 1957
AFILIADO

CERTIFICA

NIT : 890300466-5

CERTIFICA

QUE POR ESCRITURA NRO. 2670 DEL 12 DE JUNIO DE 1957 NOTARIA SEGUNDA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 01 DE JULIO DE 1957 BAJO EL NRO. 16627 DEL LIBRO IX, SE CONSTITUYO LA SOCIEDAD DENOMINADA COMPANIAS TECNOQUIMICAS LIMITADA

CERTIFICA

QUE POR ESCRITURA NRO. 8438 DEL 30 DE DICIEMBRE DE 1970 NOTARIA SEGUNDA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 07 DE ENERO DE 1971 BAJO EL NRO. 42260 DEL LIBRO IX, LA SOCIEDAD SE TRANSFORMO DE SOCIEDAD LIMITADA EN SOCIEDAD EN COMANDITA POR ACCIONES BAJO EL NOMBRE DE COMPANIAS TECNOQUIMICAS LIMITADA COMANDITA POR ACCIONES (SIC)

CERTIFICA

QUE POR ESCRITURA NRO. 2139 DEL 21 DE ABRIL DE 1972 NOTARIA SEGUNDA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 26 DE ABRIL DE 1972 BAJO EL NRO. 794 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE COMPANIAS TECNOQUIMICAS LIMITADA COMANDITA POR ACCIONES (SIC) POR EL DE TECNOQUIMICAS LIMITADA & CIA S.C.A.

CERTIFICA

QUE POR ESCRITURA NRO. 3255 DEL 30 DE AGOSTO DE 1983 NOTARIA DECIMA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 31 DE AGOSTO DE 1983 BAJO EL NRO. 62343 DEL LIBRO IX, LA SOCIEDAD SE TRANSFORMO DE SOCIEDAD EN COMANDITA POR ACCIONES EN SOCIEDAD ANÓNIMA BAJO EL NOMBRE DE TECNOQUIMICAS S A

CERTIFICA

REFORMAS

DOCUMENTO	FECHA.DOC	ORIGEN	FECHA.INS	NRO.INS	LIBRO
E.P. 4075	05/09/1957	NOTARIA SEGUNDA DE CALI	27/09/1957	16922	
E.P. 5718	28/11/1957	NOTARIA SEGUNDA DE CALI	30/12/1957	17242	
E.P. 5507	31/12/1957	NOTARIA PRIMERA DE CALI	13/03/1958	17529	
E.P. 3124	16/07/1958	NOTARIA PRIMERA DE CALI	17/10/1958	18365	
E.P. 3325	29/07/1958	NOTARIA PRIMERA DE CALI	17/10/1958	18366	
E.P. 5726	17/12/1958	NOTARIA PRIMERA DE CALI	12/05/1959	19258	

E.P. 2374	12/05/1959	NOTARIA PRIMERA DE CALI	03/06/1959	19368	
E.P. 2793	20/06/1961	NOTARIA PRIMERA DE CALI	07/07/1961	22616	
E.P. 2794	20/06/1961	NOTARIA PRIMERA DE CALI	07/07/1961	22617	
E.P. 6365	30/12/1961	NOTARIA PRIMERA DE CALI	23/01/1962	23489	
E.P. 1383	21/03/1962	NOTARIA PRIMERA DE CALI	28/03/1962	23850	
E.P. 3396	28/05/1963	NOTARIA PRIMERA DE CALI	11/06/1963	26016	
E.P. 8853	30/12/1963	NOTARIA PRIMERA DE CALI	23/01/1964	27107	
E.P. 5718	28/11/1957	NOTARIA SEGUNDA DE CALI	10/02/1964	27181	
E.P. 2743	29/04/1964	NOTARIA PRIMERA DE CALI	06/05/1964	27681	
E.P. 2744	29/04/1964	NOTARIA PRIMERA DE CALI	06/05/1964	27682	
E.P. 7057	21/10/1964	NOTARIA PRIMERA DE CALI	22/10/1964	28591	
E.P. 1693	26/04/1965	NOTARIA PRIMERA DE CALI	28/04/1965	29569	
E.P. 1799	10/05/1966	NOTARIA PRIMERA DE CALI	11/05/1966	31623	
E.P. 2498	18/11/1966	NOTARIA CUARTA DE CALI	25/11/1966	32757	
E.P. 2792	27/12/1966	NOTARIA CUARTA DE CALI	05/01/1967	33009	
E.P. 2209	25/09/1967	NOTARIA CUARTA DE CALI	04/10/1967	34591	
E.P. 6933	20/12/1967	NOTARIA SEGUNDA DE CALI	28/12/1967	35082	
E.P. 6363	14/11/1968	NOTARIA SEGUNDA DE CALI	26/11/1968	37141	
E.P. 7711	31/12/1968	NOTARIA SEGUNDA DE CALI	04/02/1969	37615	
E.P. 5597	30/09/1969	NOTARIA SEGUNDA DE CALI	18/10/1969	39341	
E.P. 5211	27/08/1970	NOTARIA SEGUNDA DE CALI	04/09/1970	41379	
E.P. 6576	07/10/1971	NOTARIA SEGUNDA DE CALI	14/10/1971	44154	
E.P. 7286	08/11/1971	NOTARIA SEGUNDA DE CALI	10/11/1971	44367	
E.P. 8042	03/12/1971	NOTARIA SEGUNDA DE CALI	21/12/1971	44716	
E.P. 6209	05/10/1973	NOTARIA SEGUNDA DE CALI	15/10/1973	5505	IX
E.P. 8741	31/12/1973	NOTARIA SEGUNDA DE CALI	08/03/1974	7636	IX
E.P. 9270	31/12/1974	NOTARIA SEGUNDA DE CALI	31/01/1975	11772	IX
E.P. 9504	31/12/1974	NOTARIA SEGUNDA DE CALI	04/04/1975	12441	IX
E.P. 7566	05/12/1975	NOTARIA SEGUNDA DE CALI	09/01/1976	15581	IX
E.P. 2671	09/05/1980	NOTARIA SEGUNDA DE CALI	22/10/1980	41529	IX
E.P. 779	10/03/1982	NOTARIA DECIMA DE CALI	03/08/1982	54655	IX
E.P. 4324	10/11/1982	NOTARIA DECIMA DE CALI	30/06/1983	61172	IX
E.P. 1269	18/03/1986	NOTARIA DECIMA DE CALI	01/04/1986	83730	IX
E.P. 5089	24/09/1986	NOTARIA DECIMA DE CALI	29/09/1986	87933	IX
E.P. 7064	04/11/1987	NOTARIA DECIMA DE CALI	19/11/1987	2552	IX
E.P. 7065	04/11/1987	NOTARIA DECIMA DE CALI	19/11/1987	2553	IX
E.P. 5929	14/07/1989	NOTARIA DECIMA DE CALI	26/07/1989	20225	IX
E.P. 8569	29/09/1989	NOTARIA DECIMA DE CALI	02/10/1989	22250	IX
E.P. 10571	04/12/1992	NOTARIA DECIMA DE CALI	15/12/1992	60929	IX
E.P. 10249	18/12/1995	NOTARIA DECIMA DE CALI	20/12/1995	10214	IX
E.P. 2359	22/05/1997	NOTARIA TERCERA DE CALI	27/05/1997	3813	IX
E.P. 2624	30/06/2000	NOTARIA TERCERA DE CALI	07/07/2000	4730	IX
E.P. 3814	15/09/2000	NOTARIA TERCERA DE CALI	18/09/2000	43815	IX
E.P. 3588	30/07/2004	NOTARIA TERCERA DE CALI	04/09/2004	8542	IX

CERTIFICA

VIGENCIA: 01 DE ENERO DEL AÑO 2057

CERTIFICA

OBJETO SOCIAL. LA SOCIEDAD TIENE POR OBJETO: A) LA FABRICACION, EL ENVASADO, LA IMPORTACION, LA EXPORTACION, LA VENTA Y DISTRIBUCION DE PRODUCTOS BIOLOGICOS Y QUIMICOS, MEDICAMENTOS O PRODUCTOS FARMACEUTICOS, PERFUMERIA O EFECTOS DE TOCADOR, PRODUCTOS VETERINARIOS, AGRICOLAS Y ALIMENTOS NATURALES Y/O PRODUCTOS DE CONSUMO POPULAR DE CUALQUIER NATURALEZA Y SERVICIOS EN GENERAL. B) INVERTIR EN SOCIEDADES O EMPRESAS DE CUALQUIER NATURALEZA O ESPECIE DE LA SOCIEDAD MERCANTIL, NACIONAL O EXTRANJERA, QUE TENGAN COMO ACTIVIDAD O NEGOCIO PROPIO DE SU OBJETO LA FABRICACION, DISTRIBUCION Y COMERCIO EN GENERAL DE PRODUCTOS BIOLOGICOS Y QUIMICOS, MEDICAMENTOS O PRODUCTOS FARMACEUTICOS, PERFUMERIA O EFECTOS DE TOCADOR, PRODUCTOS VETERINARIOS, AGRICOLAS, ALIMENTOS NATURALES Y/O PROCESADOS, PRODUCTOS DE CONSUMO POPULAR, SERVICIOS EN GENERAL O LA EXPLOTACION DE ESTABLECIMIENTOS DE COMERCIO DEDICADOS A DICHO GIRO. C) ADQUIRIR ACCIONES, CUOTAS SOCIALES, BONOS CEDULAS, TITULOS U OTROS VALORES EN COMPANIAS

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DE CUALQUIER NATURALEZA O TIPO LEGAL, DEDICADAS A LA EXPLOTACION DE CUALQUIER ACTIVIDAD ECONOMICA LICITA Y ENAJENARLAS. D) LA EXPLOTACION DEL NEGOCIO DE LA PUBLICIDAD Y EL ESTABLECIMIENTO DE OFICINAS DEDICADAS A ESTE NEGOCIO O A LA CREACION DE ORGANOS DE PUBLICIDAD HABLADOS O ESCRITOS. E) GARANTIZAR LAS OBLIGACIONES PROPIAS DE LOS ACCIONISTAS O DE TERCEROS. F) LA ADQUISICION DE BIENES MUEBLES, INMUEBLES Y DE TODA CLASE DE EQUIPO Y MAQUINARIA PARA SU ARRENDAMIENTO O PARA LA COMERCIALIZACION DE ELLOS. EN DESARROLLO DEL OBJETO SOCIAL PODRA OBTENER PRIVILEGIOS INDUSTRIALES, CONCESIONES, PATENTES DE INVENCION, DE MEJORAS O PROCEDIMIENTOS, MARCAS DE FABRICA O DE COMERCIO, YA SEA EN NOMBRE PROPIO O DE TERCEROS, OTORGAR A TERCEROS, DENTRO O FUERA DEL PAIS CONCESIONES O USOS DE EXPLOTACION SOBRE ESTOS DERECHOS, EJECUTAR TODA CLASE DE CONTRATOS DE COMPRAVENTA, DISTRIBUCION DE MATERIAS PRIMAS, DE PRODUCTOS SEMIELABORADOS O ELABORADOS EN EL MERCADO INTERNO O EN EL EXTERIOR Y EN GENERAL, LA CELEBRACION DE TODO ACTO O CONTRATO SOBRE BIENES MUEBLES O INMUEBLES DE COMERCIO INDUSTRIALES O DE OTRA INDOLE QUE SE REFIERAN DIRECTAMENTE A LAS ACTIVIDADES QUE PERSEGUE LA SOCIEDAD.

CERTIFICA

ORGANOS DE DIRECCION Y ADMINISTRACION. PARA LOS FINES DE SU DIRECCION, ADMINISTRACION Y REPRESENTACION, LA SOCIEDAD TIENE LOS SIGUIENTES ORGANOS: A) ASAMBLEA GENERAL DE ACCIONISTAS. B) JUNTA DIRECTIVA. C) PRESIDENTE EJECUTIVO. D) TRES VICEPRESIDENTES EJECUTIVOS. E) VICEPRESIDENCIAS ADMINISTRATIVAS.

LA DIRECCION DE LA SOCIEDAD CORRESPONDE, EN PRIMER TERMINO A LA ASAMBLEA GENERAL DE ACCIONISTAS Y EN SEGUNDO LUGAR, A LA JUNTA DIRECTIVA COMO DELEGADA DE AQUELLA.

LA REPRESENTACION LEGAL DE LA SOCIEDAD Y LA GESTION DE LOS NEGOCIOS SOCIALES, ESTARAN A CARGO DEL PRESIDENTE EJECUTIVO Y DE LOS TRES VICEPRESIDENTES EJECUTIVOS.

FUNCIONES DE LA ASAMBLEA DE ACCIONISTAS. ENTRE OTRAS LAS SIGUIENTES: 1) ACORDAR LA FUSION DE LA SOCIEDAD, SU TRANSFORMACION, LA ENAJENACION O EL ARRENDAMIENTO DE LA EMPRESA SOCIAL, LA DISOLUCION O LA PRORROGA Y CUALQUIER REFORMA, AMPLIACION MODIFICACION DEL CONTRATO SOCIAL. 9) AUTORIZAR LA ADQUISICION DE ACCIONES PROPIAS, CON SUJECCION A LOS REQUISITOS ESTABLECIDOS POR LA LEY. 10) ADOPTAR EN GENERAL, TODAS LAS MEDIDAS QUE RECLAMEN EL CUMPLIMIENTO DE LOS ESTATUTOS O EL INTERES DE LA SOCIEDAD.

EN LA JUNTA DIRECTIVA SE ENTIENDE DELEGADO EL MAS AMPLIO MANDATO PARA ADMINISTRAR LA SOCIEDAD Y POR CONSIGUIENTE, TENDRA ATRIBUCIONES SUFICIENTES PARA ORDENAR QUE SE EJECUTE O CELEBRE CUALQUIER ACTO O CONTRATO COMPRENDIDO DENTRO DEL OBJETO SOCIAL Y PARA ADOPTAR LAS DETERMINACIONES NECESARIAS EN ORDEN A QUE LA SOCIEDAD CUMPLA SUS FINES Y DE MANERA ESPECIAL, TENDRA LAS SIGUIENTES FUNCIONES ENTRE OTRAS: C) NOMBRAR Y REMOVER LIBREMENTE AL PRESIDENTE EJECUTIVO, A LOS VICEPRESIDENTES EJECUTIVOS Y A LOS VICEPRESIDENTES ADMINISTRATIVOS. E) DISPONER EL ESTABLECIMIENTO O LA CLAUSURA DE SUCURSALES O AGENCIAS, DENTRO O FUERA DEL DOMICILIO SOCIAL. F) FIJAR LAS POLITICAS DE LA SOCIEDAD EN LOS DIFERENTES ORDENES DE SU ACTIVIDAD, ESPECIALMENTE EN MATERIA FINANCIERA, ECONOMICA Y LABORAL; APROBAR PLANES DE INVERSION Y DE PRODUCCION; DECIDIR SOBRE NUEVAS LINEAS DE PRODUCCION Y VENTA, ESTABLECER NORMAS GENERALES EN MATERIA DE PRECIOS Y DE VENTAS DE LOS PRODUCTOS ELABORADOS POR LA SOCIEDAD O DE LOS MATERIALES Y DEMAS ELEMENTOS EN QUE ELLA NEGOCIE Y DICTAR NORMAS Y REGLAMENTOS PARA LA ORGANIZACION Y EL FUNCIONAMIENTO DE TODAS LAS DEPENDENCIAS DE LA SOCIEDAD. G) DETERMINAR LA APLICACION QUE DEBA DARSE A LAS UTILIDADES QUE, CON EL CARACTER DE RESERVAS DE INVERSION, HAYAN SIDO APROPIADAS POR LA ASAMBLEA DE ACCIONISTAS. H) AUTORIZAR PREVIAMENTE LAS OPERACIONES QUE TENGAN POR OBJETO: 1) ADQUIRIR, HIPOTECAR Y EN CUALQUIER OTRA FORMA GRAVAR O LIMITAR EL DOMINIO DE BIENES RAICES CUYA CUANTIA SEA SUPERIOR A \$100.000.000.00 MONEDA CORRIENTE; 2) CONSTITUIR PRENDA SOBRE BIENES SOCIALES O DARLOS EN ANTICRESIS PARA ACTOS O CONTRATOS CUYA CUANTIA SEA SUPERIOR A \$100.000.000.00 MONEDA CORRIENTE; 3) HACER INVERSIONES EN BIENES DE CAPITAL O EFECTUAR REPARACIONES O MEJORAS DE LOS MISMOS, CUANDO UNAS U OTRAS IMPLIQUEN, EN CADA CASO, COSTOS O DESEMBOLSOS EN CUANTIA SUPERIOR A \$100.000.000.00 MONEDA LEGAL; 4) AUTORIZAR LOS CONTRATOS DE MUTUO QUE PUEDAN CELEBRAR LA SOCIEDAD LOS REPRESENTANTES LEGALES CUANDO SU CUANTIA SEA SUPERIOR A \$100.000.000.00 MONEDA LEGAL COLOMBIANA O A US\$300.000.00 L) AUTORIZAR AL REPRESENTANTE LEGAL PARA QUE SOLICITE, LLEGADO EL CASO, QUE SE ADMITA A LA COMPANIA A LA CELEBRACION DE CONCORDATO PREVENTIVO CON SUS ACREEDORES. M) SERVIR DE ORGANO CONSULTIVO Y ASESOR DE LOS REPRESENTANTES DE LA COMPANIA.

LA ADMINISTRACION INMEDIATA DE LA COMPANIA, SU REPRESENTACION LEGAL Y LA GESTION DE LOS NEGOCIOS SOCIALES ESTARAN A CARGO DEL PRESIDENTE EJECUTIVO Y DE LOS TRES VICEPRESIDENTES EJECUTIVOS, DESIGNADOS POR LA JUNTA DIRECTIVA PARA PERIODOS DE UN AÑO, REELEGIBLES INDEFINIDAMENTE Y REMOVIBLES LIBREMENTE POR ELLA EN CUALQUIER TIEMPO, QUIENES COMO REPRESENTANTES LEGALES PODRAN ACTUAR CONJUNTA O SEPARADAMENTE CON IGUALDAD DE FUNCIONES Y CALIDADES. TODOS LOS EMPLEADOS DE LA COMPANIA CON EXCEPCION DE LOS DESIGNADOS POR LA ASAMBLEA DE ACCIONISTAS Y LOS DEPENDIENTES DEL REVISOR FISCAL, SI LOS HUBIERE, ESTARAN SOMETIDOS EN EL DESEMPEÑO DE SUS CARGOS A LOS REPRESENTANTES LEGALES.

LOS REPRESENTANTES LEGALES SON MANDATARIOS CON REPRESENTACION INVESTIDOS DE FUNCIONES EJECUTIVAS Y ADMINISTRATIVAS Y COMO TALES TIENEN A SU CARGO LA REPRESENTACION LEGAL DE LA COMPANIA, LA GESTION COMERCIAL Y FINANCIERA, LA RESPONSABILIDAD DE LA ACCION ADMINISTRATIVA, LA COORDINACION Y LA SUPERVISION GENERAL DE LA EMPRESA, LAS CUALES CUMPLIRAN CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS Y A LAS DISPOSICIONES LEGALES Y CON SUJECION A LAS ORDENES E INSTRUCCIONES DE LA JUNTA DIRECTIVA.

COMO REPRESENTANTES LEGALES DE LA COMPANIA EN JUICIO Y FUERA DE JUICIO, LOS REPRESENTANTES TIENEN FACULTADES PARA EJECUTAR O CELEBRAR SIN OTRAS LIMITACIONES QUE LAS ESTABLECIDAS EN LOS ESTATUTOS EN CUANTO SE TRATE DE OPERACIONES QUE DEBAN SER PREVIAMENTE AUTORIZADAS POR LA JUNTA DIRECTIVA O POR LA ASAMBLEA DE ACCIONISTAS, TODOS LOS ACTOS O CONTRATOS COMPRENDIDOS DENTRO DEL OBJETO SOCIAL O QUE TENGAN CARACTER SIMPLEMENTE PREPARATORIO, ACCESORIO O COMPLEMENTARIO PARA LA REALIZACION DE LOS FINES QUE PERSIGUE LA SOCIEDAD Y LOS QUE SE RELACIONAN DIRECTAMENTE CON LA EXISTENCIA Y EL FUNCIONAMIENTO DE LA MISMA. LOS REPRESENTANTES QUEDAN INVESTIDOS DE PODERES ESPECIALES PARA TRANSIGIR, ARBITRAR Y COMPROMETER LOS NEGOCIOS SOCIALES; PROMOVER O COADYUVAR ACCIONES JUDICIALES, ADMINISTRATIVAS O CONTENCIOSAS ADMINISTRATIVAS EN QUE LA COMPANIA TENGA INTERES E INTERPONER TODOS LOS RECURSOS QUE SEAN PROCEDENTES CONFORME A LA LEY; DESISTIR DE LAS ACCIONES O RECURSOS QUE INTERPONGAN; NOVAR OBLIGACIONES O CREDITOS; DAR O RECIBIR BIENES EN PAGO; CONSTITUIR APODERADOS JUDICIALES O EXTRAJUDICIALES, DELEGARLES FACULTADES REVOCAR MANDATOS Y SUSTITUCIONES.

PARAGRAFO: LOS REPRESENTANTES LEGALES DE LA SOCIEDAD TIENEN AMPLIAS FACULTADES, SIN NINGUNA LIMITACION Y SIN REQUERIR AUTORIZACION PREVIA DE LA JUNTA DIRECTIVA, PARA ACTUAR EN NOMBRE DE LA SOCIEDAD EN LICITACIONES PUBLICAS, PRIVADAS O CUALQUIER OTRA MODALIDAD DE CONTRATACION, PRESENTAR PROPUESTAS, ACEPTAR ADJUDICACIONES Y CONTRATAR SIN LIMITACION DE CUANTIA ALGUNA ANTE LAS ENTIDADES PUBLICAS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA, BIEN SEAN ELLAS DEL ORDEN NACIONAL, DISTRITAL, DEPARTAMENTAL O MUNICIPAL.

CERTIFICA

DOCUMENTO: ACTA No. 393 DEL 20 DE ENERO DE 1993
ORIGEN: JUNTA DIRECTIVA
INSCRIPCION: 26 DE ENERO DE 1993 No. 62203 DEL LIBRO IX

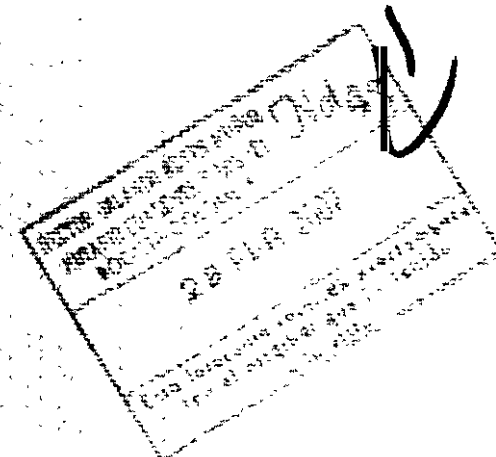
FUE(RON) NOMBRADO(S):

PRESIDENTE EJECUTIVO
FRANCISCO JOSE BARBERI OSPINA
C.C.14445880

VICEPRESIDENTE EJECUTIVO
JUAN MANUEL BARBERI OSPINA
C.C.14949561

VICEPRESIDENTE EJECUTIVO
JUAN BAUTISTA DE LOS RIOS GUTIERREZ
C.C.17108621

VICEPRESIDENTE EJECUTIVO
EMILIO SARDI APARICIO



CCC11831953

C.C.14434582

CERTIFICA

DOCUMENTO: ACTA No. 38 DEL 03 DE FEBRERO DE 1992
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 05 DE JUNIO DE 1992 No. 54016 DEL LIBRO IX

DOCUMENTO: ACTA No. 52 DEL 26 DE MARZO DE 1999
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 10 DE MAYO DE 1999 No. 3193 DEL LIBRO IX

DOCUMENTO: ACTA No. 54 DEL 31 DE MARZO DE 2000
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 24 DE MAYO DE 2000 No. 3622 DEL LIBRO IX

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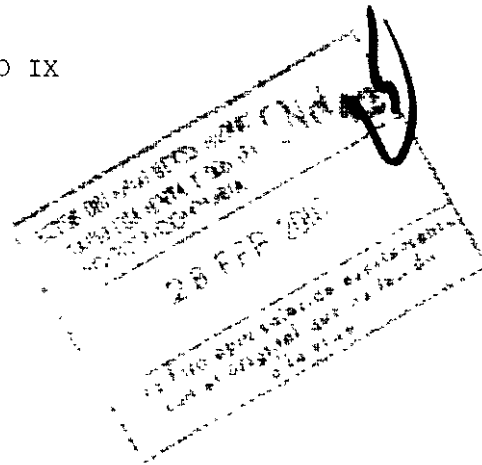
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CERTIFICA

DOCUMENTO: ACTA No. 59 DEL 31 DE MARZO DE 2003
 ORIGEN: ASAMBLEA DE ACCIONISTAS
 INSCRIPCION: 23 DE ABRIL DE 2003 No. 2845 DEL LIBRO IX

FUE (RON) NOMBRADO(S):

REVISOR FISCAL
 DELOITTE & TOUCHE LTDA D & T LTDA
 NIT.860005813

CERTIFICA

DOCUMENTO: DOCUMENTO PRIVADO DEL 26 DE AGOSTO DE 2004
 ORIGEN: DELOITTE & TOUCHE LTDA D & T LTDA
 INSCRIPCION: 30 DE AGOSTO DE 2004 No. 9417 DEL LIBRO IX

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 C.C.16789097

CERTIFICA

QUE POR ESCRITURA NRO. 5235 DEL 19 DE JULIO DE 1996 NOTARIA DECIMA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 25 DE JULIO DE 1996 BAJO EL NRO. 144 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A CARLOS ALBERTO QUINTERO, MAYOR DE EDAD, VECINO DE ESTA CIUDAD, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 14.440.778 DE CALI, PARA QUE EN NOMBRE Y REPRESENTACION DE LA SOCIEDAD CUYA PERSONERIA OSTENTA, EL REPRESENTANTE EN LOS SIGUIENTES ACTOS: A) PRESENTAR EN LA ADMINISTRACION DE IMPUESTOS Y ADUANAS NACIONALES O DEL ORGANISMO QUE HAGA SUS VECES Y FIRMAR EN REPRESENTACION DE LA SOCIEDAD, LAS DECLARACIONES DEL IMPUESTO SOBRE LA RENTA Y COMPLEMENTARIOS QUE CORRESPONDA A LA SOCIEDAD, Y TODAS LAS DEMAS DECLARACIONES QUE LA SOCIEDAD DEBA PRESENTAR ANTE DICHA ENTIDAD, TALES COMO LA DE VENTAS, RETENCION EN LA FUENTE, TIMBRE Y CUALESQUIER OTRA DECLARACION QUE POR LEY LA SOCIEDAD ESTE OBLIGADA A PRESENTAR.

B) PARA PRESENTAR Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE OBLIGUEN A TECNOQUIMICAS S.A., COMO DECLARANTE DEL IMPUESTO DE INDUSTRIA Y COMERCIO Y EL COMPLEMENTARIO DE AVISOS Y TABLEROS EN LOS MUNICIPIOS EN QUE LA SOCIEDAD ESTE OBLIGADA AL PAGO DE LOS CITADOS IMPUESTOS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE LOS MENCIONADOS TRIBUTOS. C) PARA PRESENTAR Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE OBLIGUEN A TECNOQUIMICAS S.A. COMO DECLARANTE DEL IMPUESTO PREDIAL Y COMPLEMENTARIOS EN LOS MUNICIPIOS DONDE TENGA BIENES INMUEBLES, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DEL CITADO IMPUESTO. D) PARA DAR RESPUESTA A LOS REQUERIMIENTOS ORDINARIOS Y A LAS SOLICITUDES DE INFORMACION EN RELACION CON LOS IMPUESTOS ADMINISTRADOS POR LA DIRECCION DE IMPUESTOS Y ADUANAS NACIONALES Y POR LAS DEPENDENCIAS MUNICIPALES QUE ADMINISTREN LOS IMPUESTOS DE CARACTER TERRITORIAL. E) Y EN GENERAL, PARA QUE ASUMA LA PERSONERIA EN NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO

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ÉSTIME CONVENIENTE, DE MANERA QUE EN NINGUN CASO LA SOCIEDAD QUEDE SIN REPRESENTACION EN LOS ASUNTOS RELACIONADOS CON LAS FACULTADES OTORGADAS.

CERTIFICA

QUE POR ESCRITURA NRO. 2719 DEL 15 DE JULIO DE 1999 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE AGOSTO DE 1999 BAJO EL NRO. 323 DEL LIBRO V MEDIANTE LA CUAL SE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE A SAMUEL GOMEZ UPEGUI, MAYOR DE EDAD, VECINO DE CALI, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 16.633.490, GERENTE DEL DISTRITO DE VENTAS DEL OCCIDENTE COLOMBIANO DE LA SOCIEDAD, CON SEDE EN CALI, UBICADO EN LA CALLE 23 NRO. 4-66, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO O POLICIVO, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES DE CARACTER LABORAL, CIVIL, COMERCIAL Y POLICIVO, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE. PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORGUE PODER Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESA FACULTAD PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRAPROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO. 4) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 5) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO: ES ENTENDIDO QUE EL APODERADO EN SU CONDICION DE GERENTE, ESTA FACULTADO PARA REALIZAR LA VENTA, SIN LIMITACION DE CUANTIA, DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA

QUE POR ESCRITURA NRO. 3703 DEL 17 DE SEPTIEMBRE DE 1999 NOTARIA TERCERA DE CALI INSCRITA EN LA CAMARA DE COMERCIO EL 05 DE OCTUBRE DE 1999 BAJO EL NRO. 356 DEL LIBRO MEDIANTE LA CUAL SE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE AL SENOR A PIO CLAUDIO GUTIERREZ BOTERO, MAYOR DE EDAD, VECINO DE MEDELLIN, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 8.238.529 DE MEDELLIN, GERENTE DEL DISTRITO DE VENTAS DE LA REGIONAL DE ANTIOQUIA DE LA SOCIEDAD, CON SEDE EN MEDELLIN, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES:

1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO O POLICIVO YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES DE CARACTER LABORAL, CIVIL, COMERCIAL Y POLICIVO, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE.

PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORGUE PODER Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y

PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRAPROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO. 4) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 5) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO: ES ENTENDIDO QUE EL APODERADO EN SU CONDICION DE GERENTE, ESTA FACULTADO PARA REALIZAR LA VENTA, SIN LIMITACION DE CUANTIA, DE LOS ARTICULO PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINE LOS MANUALES Y PROCEDIMIENTO INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA

QUE POR ESCRITURA NRO. 2873 DEL 10 DE JULIO DE 2001 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 06 DE SEPTIEMBRE DE 2001 BAJO EL NRO. 213 DEL LIBRO V MEDIANTE LA CUAL SE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A MARIA TERESA CANON DE GUZMAN, IDENTIFICADA CON LA CEDULA DE CIUDADANIA NRO. 31.238.104 DE CALI, CARLOS ARTURO PENA NIETO IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 19.483.439 DE BOGOTA Y ANGELA MARIA CORREA CARDONA IDENTIFICADA CON LA CEDULA DE CIUDADANIA No. 66.835.555 DE CALI, LA PRIMERA COMO PRINCIPAL Y EL SEGUNDO COMO PRIMER SUPLENTE Y LA TERCERA COMO SEGUNDA SUPLENTE, PARA QUE REPRESENTEN A LA SOCIEDAD EN TODOS LOS ASUNTOS CAMBIARIOS, CON FACULTAD PARA FIRMAR DECLARACIONES DE CAMBIOS SEA POR CREDITOS EN MONEDA EXTRANJERA, POR MOVIMIENTOS DE LAS CUENTAS CORRIENTES DE COMPENSACION, IMPORTACIONES DE BIENES Y SERVICIOS, TRANSFERENCIAS Y OTROS CONCEPTOS, REGISTRO DE PRESTAMO EN MONEDA EXTRANJERA OTORGADOS A LA EMPRESA EN SU CONDICION DE RESIDENTE Y TODOS AQUELLOS DOCUMENTOS O DECLARACIONES QUE DEBAN HACERSE ANTE EL BANCO DE LA REPUBLICA U OTRAS ENTIDADES GUBERNAMENTALES RESPECTO DE OPERACIONES EN EL MERCADO CAMBIARIO. LOS APODERADOS SUSCRIBIRAN TODOS LOS DOCUMENTOS Y REALIZAR TODOS LOS ACTOS QUE OBLIGUEN A TECNOQUIMICAS S.A. ANTE LAS AUTORIDADES CAMBIARIAS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS ADMINISTRATIVOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE DICHA ACTIVIDAD Y EN GENERAL PARA QUE ASUMA LA PERSONERIA A NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIMEN CONVENIENTE, DE MANERA QUE EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y CUMPLIMIENTO DE OBLIGACIONES DE CARACTER CAMBIARIO Y EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER. LOS APODERADOS SE CENTRAN RIGUROSAMENTE A LOS TERMINOS EXPRESADOS EN ESTE MANDATO QUE SE OTORGA POR TERMINO INDEFINIDO Y CUALQUIER NOTIFICACION O REVOCATORIA SE HARA EXPRESAMENTE POR ESCRITURA PUBLICA.

CERTIFICA

QUE POR ESCRITURA NRO. 307 DEL 31 DE ENERO DE 2002 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 13 DE FEBRERO DE 2002 BAJO EL NRO. 298 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A JORGE ROBERTO OBANDO RODRIGUEZ, MAYOR DE EDAD, VECINO DE ESTA CIUDAD, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 14.960.183 DE CALI, PARA QUE EN NOMBRE Y REPRESENTACION DE LA SOCIEDAD, CUYA PERSONERIA OSTENTA: lo.) PROMUEVA O DESISTA DE ACCIONES ANTE CORPORACIONES, ENTIDADES O FUNCIONARIOS DEL ORDEN JUDICIAL O GUBERNATIVO, YA SEA EN PROCESOS, ACTUACIONES O ACTOS SIMPLES, DILIGENCIAS O GESTIONES EN QUE TECNOQUIMICAS S.A. TENGA INTERES COMO ACTOR, DEMANDANDO O TERCERO INTERVINIENTE EN RELACION CON LOS ASUNTOS DE CARACTER LABORAL, POLICIVO, PENAL O DE FISCALIA, EN QUE LA EMPRESA SEA PARTE ACTIVA O PASIVA, CON CAPACIDAD PARA NOTIFICARSE Y CONTESTAR Y HACERSE PARTE DE ELLOS EN NOMBRE

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DE TECNOQUIMICAS S.A. 2o.) SUSCRIBA Y DE POR TERMINADO LOS CONTRATOS DE TRABAJO DEL PERSONAL VINCULADO A LA EMPRESA. 3o.) CONSTITUYA APODERADOS EN DESARROLLO DE ESTA REPRESENTACION LABORAL, REVOQUE Y SUSTITUYA DICHOS PODERES CUANDO LO ESTIME PROCEDENTE. 4o.) TRANSIGA, CONCILIE, DESISTA Y COMPROMETA A LA EMPRESA EN TODOS LOS TRAMITES ADMINISTRATIVOS Y PROCESOS JUDICIALES, DE CARACTER LABORAL, POLICIVO, PENAL O DE FISCALIA EN LOS QUE LA EMPRESA SEA PARTE DEMANDANTE, DEMANDADA O TERCERO INTERVINIENTE. PARAGRAFO. LA FACULTAD PARA TRANSIGIR O CONCILIAR SE LIMITA A LA SUMA DE QUINIENTOS (500) SALARIOS LEGALES MENSUALES. 5o.) OTORGUE PODERES Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES JUDICIALES DE CARACTER CIVIL, COMERCIAL Y PENAL TENDIENTES A LA RECUPERACION DE LOS CREDITOS A FAVOR DE LA SOCIEDAD, BIEN SEA REPRESENTADOS EN FACTURAS, CHEQUES, TITULOS VALORES O CUALQUIER OTRO DOCUMENTO REPRESENTATIVO DE CREDITO, HASTA POR SUMA EQUIVALENTE A QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE TECNOQUIMICAS S.A. A LAS AUDIENCIAS DE CONCILIACION QUE PROGRAMEN LOS JUZGADOS CIVILES MUNICIPALES Y DEL CIRCUITO, CON AUTORIZACION PARA TRANSIGIR, DESISTIR CONCILIAR O COMPROMETER A LA SOCIEDAD HASTA POR LA CUANTIA INDICADA. 6o. REPRESENTA A TECNOQUIMICAS S.A. DENTRO DE LOS TRAMITES DE CONCORDATOS, PROCESOS DE REESTRUCTURACION ECONOMICA PREVISTO EN LA LEY 550 DE 1999 Y LAS NORMAS QUE LA ADICIONEN O MODIFIQUEN Y LIQUIDACIONES OBLIGATORIAS QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE LAS ENTIDADES PERTINENTES CUANDO SE TRATE DE OTRA CLASE DE ACREEDORES O ANTE LOS JUZGADOS CIVILES, CON EXPRESAS FACULTADES PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER, NOMBRAR APODERADOS, PRESENTAR LOS CREDITOS, APORTAR LAS PRUEBAS QUE ESTIME NECESARIAS, ASISTIR A LAS AUDIENCIAS PRELIMINARES Y DEFINITIVAS, ACORDAR FORMULAS DE PAGO, RECIBIR Y EN GENERAL PARA EJERCER TODAS AQUELLAS GESTIONES NECESARIAS PARA OBTENER EL RECONOCIMIENTO Y PAGO DE LOS CREDITOS PRESENTADOS. LAS FACULTADES AQUI ESTABLECIDAS ESTAN LIMITADAS PARA LOS CREDITOS HASTA POR CUANTIA DE QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES. PARAGRAFO. IGUALMENTE QUEDA FACULTADO PARA ACEPTAR Y REPRESENTAR A TECNOQUIMICAS CUANDO LA EMPRESA SEA NOMBRADA EN JUNTA DE ACREEDORES O EN ORGANOS EQUIVALENTES O SIMILARES, EN LOS PROCESOS QUE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE LAS ENTIDADES PERTINENTES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES. 7o.) REPRESENTA A TECNOQUIMICAS S.A. EN LOS PROCEDIMIENTOS DE CONCILIACION QUE LOS DEUDORES DE LA SOCIEDAD CONVOQUEN ANTE LAS ENTIDADES FACULTADAS PARA ELLO CON EL FIN OBTENER UN ACUERDO EN EL PAGO DE LAS ACREENCIAS, CON EXPRESAS FACULTADES PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER Y RECIBIR, FACULTADES QUE SE LIMITAN HASTA POR LA SUMA DE QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES. 8o.) REVISE LOS EXPEDIENTES DE LOS PROCESOS JUDICIALES DE CARACTER EJECUTIVO EN QUE LA SOCIEDAD SEA PARTE DEMANDANTE, EN TODO EL TERRITORIO NACIONAL, PARA LA RECUPERACION DE SUS ACREENCIAS. 9o.) APRUEBE Y SUSCRIBA ACUERDOS PRIVADOS DE PAGO Y CONCILIACIONES DE OBLIGACIONES A FAVOR DE TECNOQUIMICAS POR LA VENTA DE SUS PRODUCTOS HASTA POR LA SUMA DE (500) SALARIOS MINIMOS LEGALES MENSUALES.

CERTIFICA

QUE POR ESCRITURA NRO. 309 DEL 31 DE ENERO DE 2002 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 13 DE FEBRERO DE 2002 BAJO EL NRO. 300 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE A DANIEL AMEZQUITA, MAYOR DE EDAD, VECINO DE BARRANQUILLA, IDENTIFICADO CON LA CÉDULA DE CIUDADANIA NRO. 8.681.962 DE BARRANQUILLA, GERENTE DEL DISTRITO DE VENTAS DE LA REGIONAL DE LA ZONA ATLANTICA DE LA SOCIEDAD, CON SEDE EN BARRANQUILLA, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS SE NOTIFIQUE Y PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO POLICIVO, PENAL O DE FISCALIA, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE. PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORGUE PODER Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON EL ESTABLECIMIENTO DE COMERCIO CON LAS LIMITACIONES

PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA HACERSE PARTE EN LOS PROCESOS CONCORDATARIOS, DE LIQUIDACION OBLIGATORIA, O REESTRUCTURACION ECONOMICA QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE OTRAS SUPERINTENDENCIAS O ENTIDADES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES, TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS DIVERSAS AUDIENCIAS CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL PRIMERO. 4) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VENTILE AL ESTABLECIMIENTO DE COMERCIO. 5) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 6) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO: ES ENTENDIDO QUE EL APODERADO, EN SU CONDICION DE GERENTE, ESTA FACULTADO PARA REALIZAR LA VENTA, SIN LIMITACION DE CUANTIA, DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA

QUE POR ESCRITURA NRO. 310 DEL 31 DE ENERO DE 2002 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 13 DE FEBRERO DE 2002 BAJO EL NRO. 301 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE A CARLOS ORLANDO MUTIS, MAYOR DE EDAD, VECINO DE BUCARAMANGA, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 91.200.418 DE BUCARAMANGA, GERENTE DEL DISTRITO DE VENTAS DE LA REGIONAL ORIENTE DE LA SOCIEDAD, CON SEDE EN BUCARAMANGA, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS SE NOTIFIQUE Y PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO POLICIVO, PENAL O DE FISCALIA, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO, Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE. PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON EL ESTABLECIMIENTO DE COMERCIO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA HACERSE PARTE EN LOS PROCESOS CONCORDATARIOS, DE LIQUIDACION OBLIGATORIA, O REESTRUCTURACION ECONOMICA QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE OTRAS SUPERINTENDENCIAS O ENTIDADES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES, TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS DIVERSAS AUDIENCIAS CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL PRIMERO. 4) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO. 5) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA

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REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 6) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO: ES ENTENDIDO QUE EL APODERADO, EN SU CONDICION DE GERENTE, ESTA FACULTADO PARA REALIZAR LA VENTA, SIN LIMITACION DE CUANTIA, DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA

QUE POR ESCRITURA NRO. 308 DEL 31 DE ENERO DE 2002 NOTARIA TERCERA DE CALI INSCRITA EN LA CAMARA DE COMERCIO EL 04 DE MARZO DE 2002 BAJO EL NRO. 318 DEL LIBRO V MEDIANTE LA CUAL SE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE A HERNANDEZ ANGULO MOYANO, MAYOR DE EDAD, VECINO DE BOGOTA, IDENTIFICADO CON LA CÉDULA DE CIUDADANIA NRO. 19.322.139 DE BOGOTA, GERENTE DEL DISTRITO DE VENTAS DE LA REGIONAL CUNDINAMARCA DE LA SOCIEDAD, CON SEDE EN BOGOTA, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS SE NOTIFIQUE Y PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO POLICIVO, PENAL O DE FISCALIA, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE.

PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON EL ESTABLECIMIENTO DE COMERCIO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA QUE OTORQUE PODER Y CONSTITUYA MANDATARIOS PARA HACERSE PARTE EN LOS PROCESOS CONCORDATARIOS, DE LIQUIDACION OBLIGATORIA, O REESTRUCTURACION ECONOMICA QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE OTRAS SUPERINTENDENCIAS O ENTIDADES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES, TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS DIVERSAS AUDIENCIAS CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL PRIMERO. 4) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO. 5) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 6) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO: ES ENTENDIDO QUE EL APODERADO, EN SU CONDICION DE GERENTE, ESTA FACULTADO PARA REALIZAR LA VENTA, SIN LIMITACION DE CUANTIA, DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR

A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA

QUE POR ESCRITURA NRO. 4.202 DEL 31 DE MAYO DE 1995 NOTARIA DECIMA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 24 DE SEPTIEMBRE DE 2003 BAJO EL NRO. 134 DEL LIBRO V SE CONFIERE PODER ESPECIAL A ANTONIO JAIRO RAMIREZ ECHAVE, ABOGADO TITULADO Y EN EJERCICIO, CON TARJETA PROFESIONAL No. 58.401 DEL MINISTERIO DE JUSTICIA, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NUMERO 16.741.040 DE CALI PARA QUE REPRESENTA A TECNOQUIMICAS S.A., EN LOS SIGUIENTES ACTOS: A) SOLICITAR Y ADELANTAR ANTE EL INSTITUTO COLOMBIANO AGROPECUARIO TODOS LOS TRAMITES ATINENTES A LA OBTENCION DE LICENCIAS DE VENTA Y LICENCIAS DE FUNCIONAMIENTO, RENOVACIONES, CERTIFICACIONES, AMPLIACIONES, INSCRIPCIONES Y MODIFICACIONES EN GENERAL; B) TODOS LOS TRAMITES ANTE EL INVIMA ATINENTES A LA OBTENCION DE REGISTRO SANITARIO, RENOVACION DEL MISMO, REFORMULACIONES, ADICIONES DE NUESTRA LINEA DE PRODUCTOS, CAMBIOS DE TITULAR Y DE FABRICANTE, CESIONES, CERTIFICACIONES DE FORMULA Y EXCLUSIVIDAD, MODIFICACIONES DE FABRICAR Y VENDER A IMPORTAR Y VENDER Y VICEVERSA, E IGUALMENTE CERTIFICACIONES SOBRE LA LINEA COMPLETA DE NUESTROS PRODUCTOS, A CUYO OBJETO LO FACULTO PARA DAR ANTE DICHAS AUTORIDADES TODOS LOS PASOS NECESARIOS, PRESENTAR SOLICITUDES, HACER DECLARACIONES, PAGAR DERECHOS, PROBAR EXPLOTACIONES, SOLICITAR TESTIMONIOS, RECIBIR DOCUMENTOS, FORMULAR APELACIONES Y RECLAMOS, DESISTIR Y PERCIBIR. ASI MISMO DICHO APODERADO ESTA AUTORIZADO PARA HACER CUANTO FUERE NECESARIO ANTE LAS AUTORIDADES ADMINISTRATIVAS PARA LOS FINES ARRIBA INDICADOS CON TODAS LAS DEMAS FACULTADES GENERALES Y ESPECIALES QUE FUEREN NECESARIAS INCLUIDAS LAS DE SUSTITUIR Y DELEGAR EL PRESENTE PODER SI LO ESTIMARE CONVENIENTE Y EN CASO NECESARIO REVOCAR DICHAS SUSTITUCIONES. PUDIENDO ATENDER ASI MISMO LAS NOTIFICACIONES QUE DIRECTA O INDIRECTAMENTE SE GENERE DE LOS ACTOS, ACTUACIONES, DILIGENCIAS O GESTIONES QUE TENGAN RELACION DE CAUSALIDAD POR LOS SUSODICHOS TRAMITES Y 3) EN GENERAL PARA QUE ASUMA LA PERSONERIA EN NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIME CONVENIENTE, DE MANERA QUE EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER. ANTONIO JAIRO RAMIREZ ECHAVE SE CENIRA RIGUROSAMENTE A LOS TERMINOS EXPRESADOS EN ESTE MANDATO QUE SE OTORGA POR TERMINO INDEFINIDO Y CUALQUIER MODIFICACION O SU REVOCATORIA SE HARA EXPRESAMENTE POR ESCRITURA PUBLICA.

CERTIFICA

QUE POR ESCRITURA NRO. 6224 DEL 15 DE DICIEMBRE DE 2004 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 17 DE ENERO DE 2005 BAJO EL NRO. 3 DEL LIBRO V MEDIANTE LA CUAL CONCEDE PODER ESPECIAL PERO AMPLIO Y SUFICIENTE A DIEGO PEREZ MENDOZA MAYOR DE EDAD, VECINO DE BOGOTA, IDENTIFICADO CON CEDULA DE CIUDADANIA NUMERO 16.820.530 DE CALI, COMO SU REPRESENTANTE CON PODER ESPECIAL, AMPLIO Y SUFICIENTE, PARA REALIZAR TODOS LOS TRAMITES RELACIONADOS CON EL PROCEDIMIENTO DE OTORGAMIENTO DE LICENCIA DE VENTA DE LOS PRODUCTOS AGRICOLAS DE LA SOCIEDAD, CON FACULTAD PARA FIRMAR TODO TIPO DE DOCUMENTOS, SOLICITUDES, REQUERIMIENTOS, MEMORIALES RESPUESTAS, ACLARACIONES BIEN SEA ANTE EL INSTITUTO COLOMBIANO AGROPECUARIO ICA, MINISTERIO DEL MEDIO AMBIENTE, MINISTERIO DE PROTECCION SOCIAL O ANTE LAS AUTORIDADES GUBERNAMENTALES COMPETENTES EN LO RELACIONADO CON LOS TRAMITES QUE PERMITAN LA COMERCIALIZACION DE ESE TIPO DE PRODUCTOS. LA FACULTAD TAMBIEN COMPRENDERA LA DE NOTIFICARSE, RESPONDER E INTERPONER RECURSOS DE TODO TIPO DE ACTO ADMINISTRATIVO. EL APODERADO SUSCRIBIRA TODOS LOS DOCUMENTOS Y REALIZAR TODOS LOS ACTOS QUE OBLIGUEN A LA SOCIEDAD ANTE LAS AUTORIDADES MENCIONADAS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS ADMINISTRATIVOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE NUESTRA ACTIVIDAD Y EN GENERAL, PARA QUE ASUMA LA PERSONERIA A NOMBRE DE TECNOQUIMICAS S.A. SIEMPRE QUE LO ESTIME CONVENIENTE, DE MANERA QUE EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y CUMPLIMIENTO DE OBLIGACIONES EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER. EL APODERADO SE CENIRA RIGUROSAMENTE A LOS TERMINOS EXPRESADOS EN ESTE MANDATO QUE SE OTORGA POR TERMINO INDEFINIDO Y CUALQUIER MODIFICACION O REVOCATORIA SE HARA EXPRESAMENTE POR ESCRITURA PUBLICA.

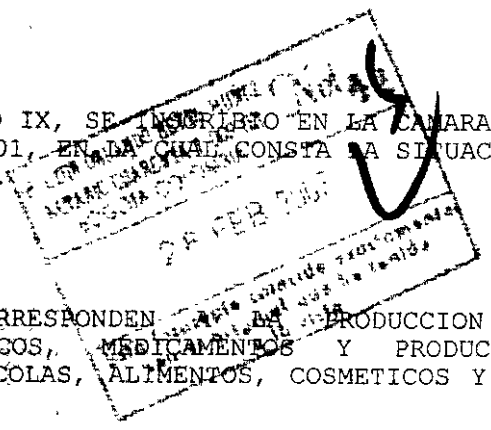
CERTIFICA

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CAPITAL AUTORIZADO: \$27,200,000,000
NUMERO DE ACCIONES: 54,400,000
VALOR NOMINAL: \$500
CAPITAL SUSCRITO: \$27,123,804,000
NUMERO DE ACCIONES: 54,247,608
VALOR NOMINAL: \$500
CAPITAL PAGADO: \$27,123,804,000
NUMERO DE ACCIONES: 54,247,608
VALOR NOMINAL: \$500

CERTIFICA

QUE EL 27 DE MARZO DE 2001 BAJO EL NRO.1979 DEL LIBRO IX, SE SUSCRIBIO EN LA CAMARA DE COMERCIO UN DOCUMENTO PRIVADO DE FECHA MARZO 21 DE 2001, EN LA CUAL CONSTA LA SITUACION DE CONTROL EJERCIDA POR LA SOCIEDAD TECNOQUIMICAS S.A.



MATRIZ: TECNOQUIMICAS S.A.
DOMICILIO: SANTIAGO DE CALI.
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: LAS ACTIVIDADES DE TECNOQUIMICAS CORRESPONDEN A LA PRODUCCION Y COMERCIALIZACION DE PRODUCTOS BIOLÓGICOS, QUÍMICOS, MEDICAMENTOS Y PRODUCTOS FARMACEUTICOS, PANALES, PRODUCTOS VETERINARIO Y AGRICOLAS, ALIMENTOS, COSMETICOS Y DE TOCADOR Y PRODUCTOS DE ASEO PARA EL HOGAR.

SUBORDINADA: ADHESIVOS INTERNACIONALES S.A.-ADHINTER S.A. DOMICILIO: PALMIRA. VALLE DEL CAUCA

NACIONALIDAD: COLOMBIANA
ACTIVIDAD: LAS ACTIVIDADES DE ADHINTER S.A. SE DESARROLLAN EXCLUSIVAMENTE EN LA ZONA FRANCA DEL PACIFICO CORRESPONDEN A LA PRODUCCION Y COMERCIALIZACION EN EL MERCADO NACIONAL E INTERNACIONAL DE ADHESIVOS MEDICINALES TALES COMO CURAS, VENDITAS, ESPARADRAPOS, PARCHES, VENDAS; ADHESIVOS PARA USO EN OFICINA TALES COMO CINTAS, PEGANTES, PAPELES ADHESIVOS Y CINTAS ADHESIVAS PARA USO INDUSTRIAL.

PRESUPUESTO DE CONTROL: TECNOQUIMICAS S.A., TIENE SUSCRITAS EN LA SOCIEDAD ADHESIVOS INTERNACIONALES S.A. ADHINTER S.A., LA CANTIDAD DE DOS MILLONES CUATROCIENTOS TREINTA MIL (2.430.000) ACCIONES ORDINARIAS DE VALOR NOMINAL DE CIENTO PESOS (\$100.00) SOBRE UN TOTAL DE TRES MILLONES (3.000.000) DE ACCIONES ORDINARIAS SUSCRITAS QUE REPRESENTA UNA PARTICIPACION DIRECTA DEL 81% SOBRE EL TOTAL DEL CAPITAL SUSCRITO Y PAGADO DE LA SOCIEDAD.

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.7050-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS
UBICADO EN: --C 23 7 39 DE CALI
RENOVO : POR EL AÑO 2005

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.311234-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS
UBICADO EN: --K 7 22 122 DE CALI
FECHA MATRICULA : 22 DE ABRIL DE 1992
RENOVO : POR EL AÑO 2005

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.311235-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS
UBICADO EN: --C 23 4 66 DE CALI

FECHA MATRICULA : 14 DE ABRIL DE 2003
 RENOV : POR EL AÑO 2005

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.606730-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS S.A JAMUNDI
 UBICADO EN: ---CARRETERA JAMUNDI KM. 23 DE JAMUNDI
 FECHA MATRICULA : 14 DE ABRIL DE 2003
 RENOV : POR EL AÑO 2005

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.606736-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS S.A YUMBO
 UBICADO EN: ---CL. 15 # 30 - 98 AUTOPISTA CALI-YUMBO KILOMETRO 4 DE YUMBO
 FECHA MATRICULA : 14 DE ABRIL DE 2003
 RENOV : POR EL AÑO 2005

CERTIFICA

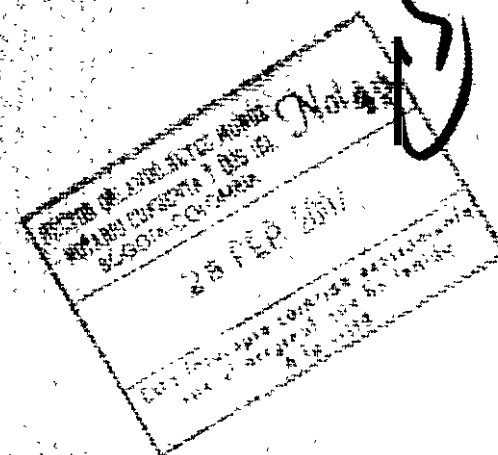
QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 31 DE MARZO DE 2005

CERTIFICA

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 PUBLICACION EN EL BOLETIN NOTICIAS DE INSCRIPCIONES, 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 18 DIAS DEL MES DE AGOSTO DEL AÑO 2005 HORA: 12:29:57

EL SECRETARIO

Claudia Urbina de Buitrago

247 29

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-060216-00002-0000

Fecha 2007-05-30 14:51:02 Dep. 2020 NUECREACIONE
Tra 11 PATENTEIYII Evs: 378 FASENACIONALI
Act 400 OPOSIOBSERVTER Folios: 39

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 000176089-2

RECIBO OFICIAL DE CAJA : 07 - 42,778
FECHA : MAYO 29 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ADOBADOS	CONSIGNACION	BANCO POPULAR	030-00110-6	54661331	28/05/2007	1,024.000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50003-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LENAS COMERCIALES	234,000.00
		TOTAL :	\$ 234,000.00

SON: DOSCIENTOS CINCUENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-060216-00002-0000
Fecha: 2007-05-30 14:51:02 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eje: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 38

FORMULARIO UNICO DE OPOSICION
2000-12

1 OPOSICION A: <table border="0"> <tr> <td>☐ Patente de Invención</td> <td>☐ Marca Colectiva</td> </tr> <tr> <td>☐ Patente de Modelo de Utilidad</td> <td>☐ Marca de Certificación</td> </tr> <tr> <td>☐ Diseño Industrial</td> <td>☐ Lenta Comercial</td> </tr> <tr> <td>☐ Esquema de Trazado para Circuitos Integrados</td> <td></td> </tr> <tr> <td>☐ Marcas de Productos o Servicios</td> <td></td> </tr> </table>			☐ Patente de Invención	☐ Marca Colectiva	☐ Patente de Modelo de Utilidad	☐ Marca de Certificación	☐ Diseño Industrial	☐ Lenta Comercial	☐ Esquema de Trazado para Circuitos Integrados		☐ Marcas de Productos o Servicios	
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☐ Patente de Modelo de Utilidad	☐ Marca de Certificación											
☐ Diseño Industrial	☐ Lenta 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: <table border="1"> <tr> <td rowspan="2"> OPOSITOR </td> <td> Nombre: TECNOQUIMICAS S.A. Sociedad comercial organizada y existente a las leyes Colombianas, con domicilio y sede principal en la Ciudad de Cali Valle. Dirección: Calle 23 # 7-39 Cali - Valle Teléfono: 882 5556 Fax: 883 8859 E-mail: Domicilio: Cali - Valle </td> <td> IDENTIFICACION C.G. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: 890.300.466-5 </td> </tr> <tr> <td> Nombre: José Luis Reyes Villamizar Dirección: Cra. 17 No. 84-23, Of. 206 Teléfono: 821.26.31 E-mail: info@reyes-abogados.com Fax: 821.25.42 Domicilio: Bogotá, D.C. </td> <td> IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 79'152.473 de Usaquén TP 44555 </td> </tr> </table>			OPOSITOR	Nombre: TECNOQUIMICAS S.A. Sociedad comercial organizada y existente a las leyes Colombianas, con domicilio y sede principal en la Ciudad de Cali Valle. Dirección: Calle 23 # 7-39 Cali - Valle Teléfono: 882 5556 Fax: 883 8859 E-mail: Domicilio: Cali - Valle	IDENTIFICACION C.G. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: 890.300.466-5	Nombre: José Luis Reyes Villamizar Dirección: Cra. 17 No. 84-23, Of. 206 Teléfono: 821.26.31 E-mail: info@reyes-abogados.com Fax: 821.25.42 Domicilio: Bogotá, D.C.	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 79'152.473 de Usaquén TP 44555					
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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), 19 (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>07-12.998</u> (Oposición) Fecha <u>Mayo 29 de 2007</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.

7

NOMBRE JOSÉ LUIS REYES VILLAMIZAR**FIRMA****C.C. No. 79 162.473 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 **TECNOQUIMICAS 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

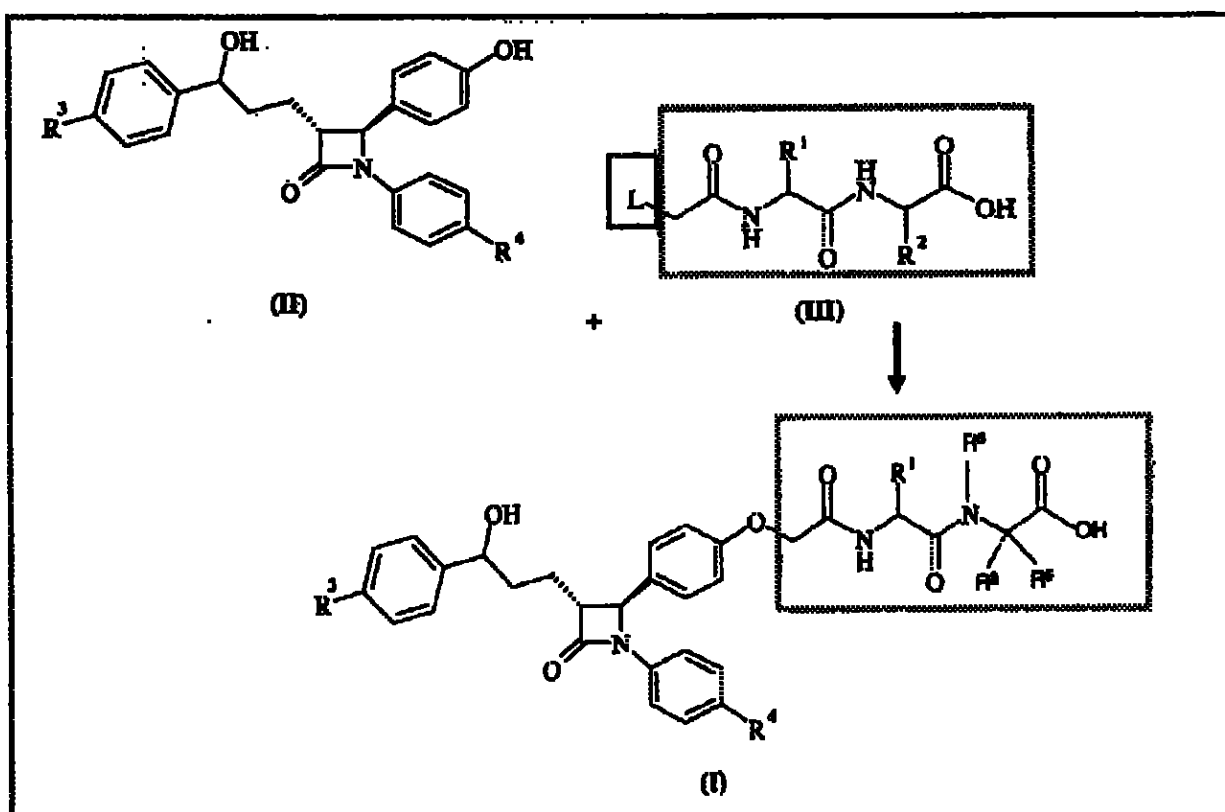
Asiste a **TECNOQUIMICAS S.A.**, en su calidad de industria farmacéutica nacional, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias y composiciones farmacéuticas carentes de nivel inventivo, en detrimento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

III. FUNDAMENTOS DE LA OPOSICIÓN

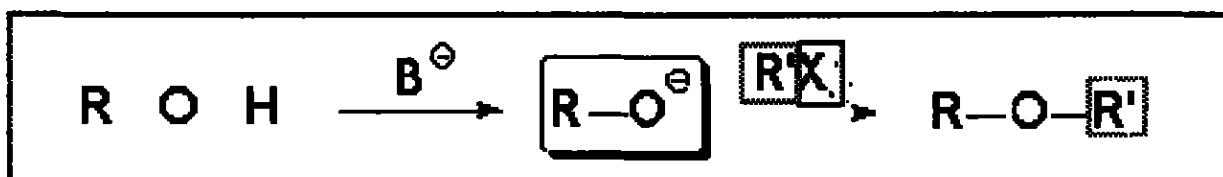
3.1. Los compuestos que reivindica la solicitud colombiana 06-060-216 que resultan ser derivados de ezetimibe, útiles como inhibidores de la absorción de colesterol en el tratamiento de hiperlipidemia, arteriosclerosis, alzheimer, tumores asociados con colesterol, sus formulaciones farmacéuticas, sus 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:

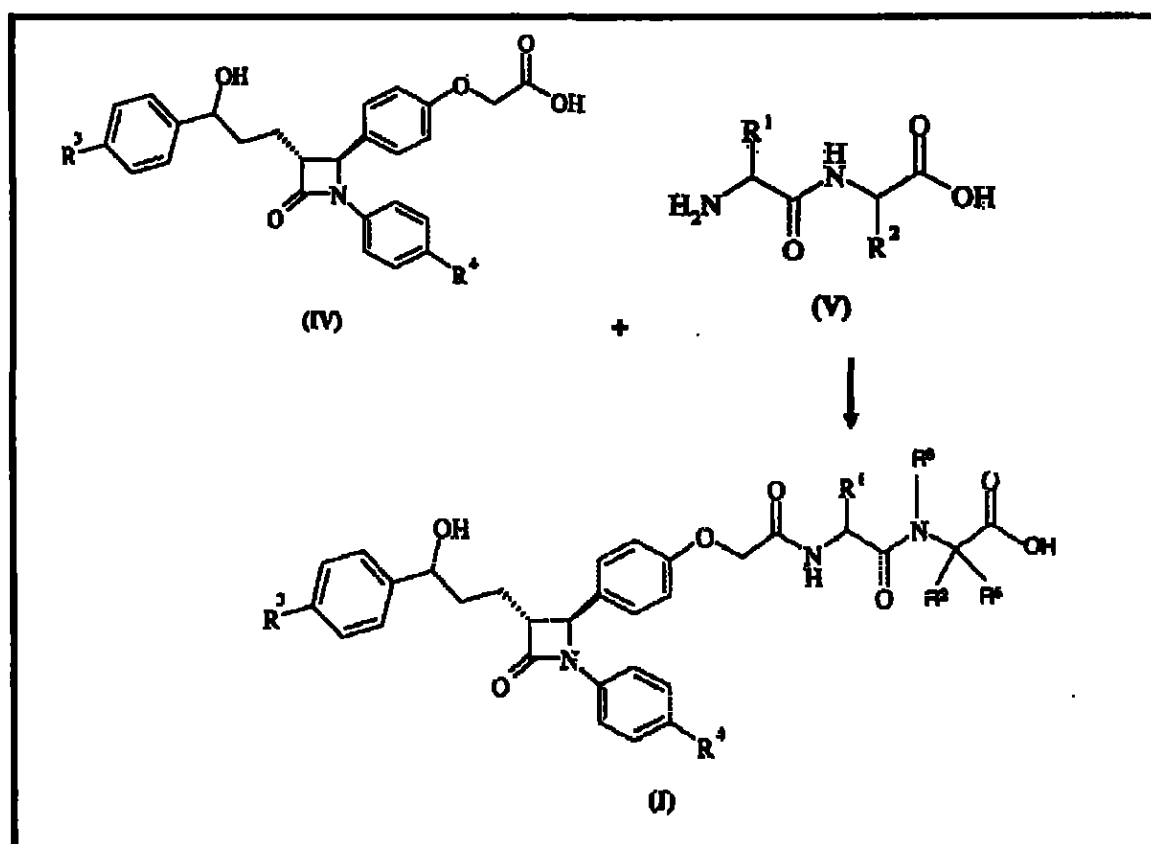


En la solicitud colombiana en trámite, el hidroxilo del grupo hidroxifenil que sustituye al núcleo de azetidinona en posición 4 reacciona con el compuesto de fórmula (III) (donde L es un grupo desplazable o saliente), donde al parecer por sustitución nucleofílica (SN2) permite obtener el compuesto de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

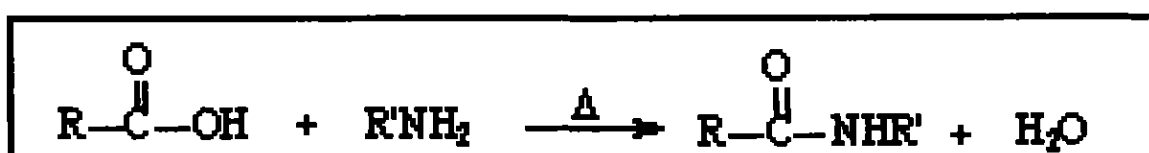


En síntesis orgánica, la manera más simple de preparar un éter es hacer reaccionar un alcóxido con un haluro o sulfonato de alquilo en una secuencia típica SN2.

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-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.

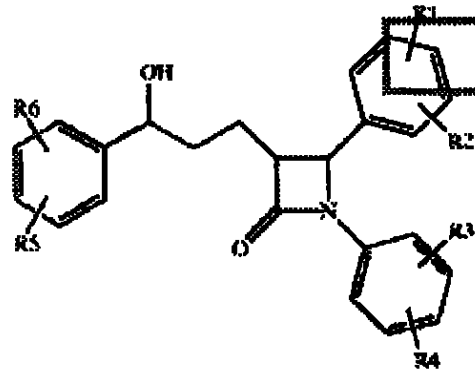
Si tenemos en cuenta lo descrito en el párrafo anterior con lo revelado en la solicitud colombiana en trámite podemos ver que en ambos documentos el compuesto de tipo azetidinona puede estar en combinación de un inhibidor de la biosíntesis del colesterol como lo son los inhibidores de HMG-CoA reductasa 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, CONH(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, NHC(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

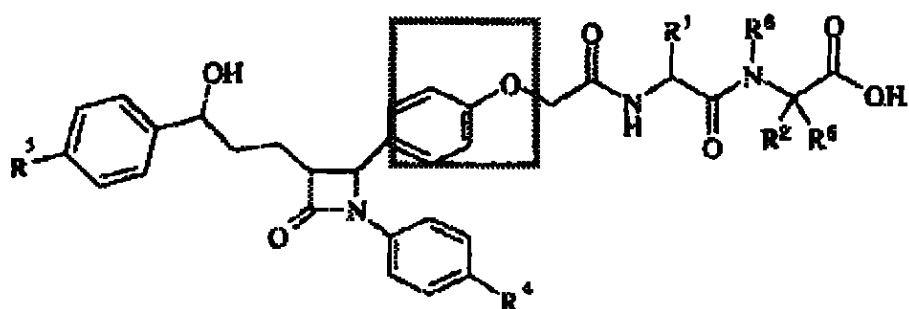
los cuales,

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:

(...)

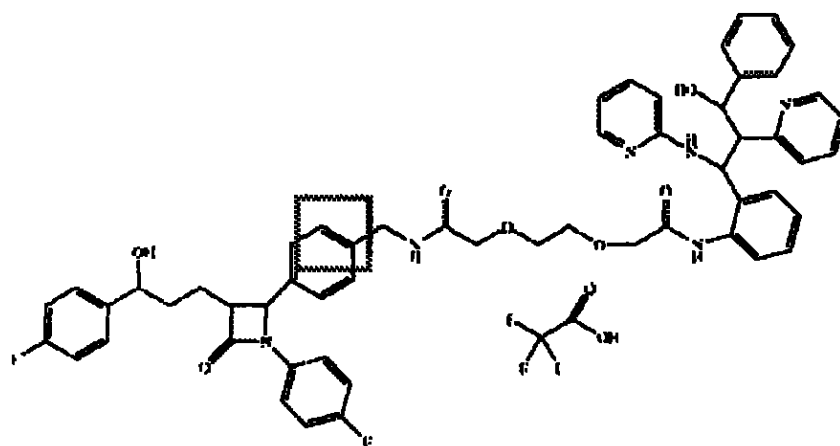
treatment of disease states associated with hyperlipidaemic conditions. The compounds of the present invention are not disclosed in any of the above applications and we have surprisingly found that the compounds of the present invention possess beneficial efficacious, metabolic and toxicological profiles 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.

(...)



(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:

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 1530, 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:

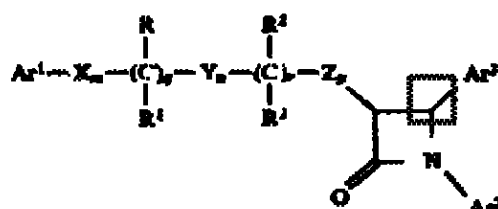
- * Derivados de azetidinona sustituidos en la misma posición y con sustituyentes de características químicas semejantes a los de la solicitud colombiana en trámite
- * Separación de los posibles enantiómeros
- * Derivados con características biofarmacéuticas modificadas útiles en el tratamiento de trastornos 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 R⁵-substituted aryl;

R⁴ is selected from lower alkyl, R⁵, —CF₃, —CN, —NO₂, and halogen R⁵ is selected from —OR⁶, —O(CO)R⁶, —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)₁-₃COOR⁶, —O(CH₂)₁-₃CONR⁶R⁷, —(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;

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 5,744,487 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 Tecnoquimicas S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.

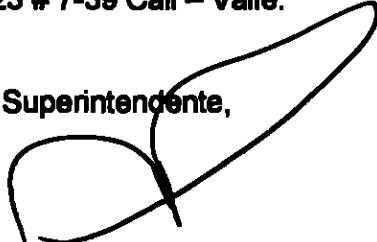
4. Copia para correr traslado al solicitante.
5. Las mencionadas en el acápite de pruebas

261

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 Calle 23 # 7-39 Cali – Valle.

Señor Superintendente,

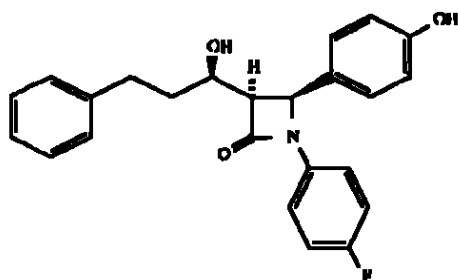


JOSÉ LUIS REYES VILLAMIZAR

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-*t*-butyldimethylsilyloxyphenyl)-2-azetidione to obtain 1-(4-fluorophenyl)-3-(3-phenyl-1-hydroxypropyl)-4-(4-*t*-butyldimethylsilyloxyphenyl)-2-azetidione.

Step 2: Treat a solution of the *cis*-azetidione 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 C₂₄H₂₁O₃FN: 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 1.

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. Introduce 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

Capsule			
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

Capsule			
No.	Ingredient	mg/tablet	mg/tablet
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 into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

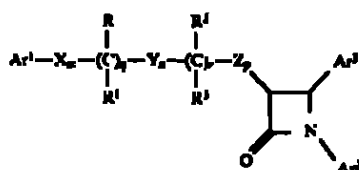
Representative formulations comprising a cholesterol biosynthesis inhibitor are well known in the art. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms disclosed above for substituted azetidione compounds may readily be modified using 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	-23	0	50
1B	-15	-39	50
1C	14	0	50
2	0	0	50
3A	-31	-69	50
3C	-80	-92	50
3D	-17	-61	10
3E	0	0	10
3F	-39	-77	10
3G	-16	-78	10
3H	-41	-86	10
3I	0	-23	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	-54	-95	1
6A-1	-43	-93	1
6B	-40	-92	3
6C	0	-48	3
6D	-46	-95	10
7A	0	-44	3
7B	-50	95	3
7C	14	-37	1
7D	-49	-98	1
7E	-22	-66	3
7F	-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 1

41



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)ₘ—, —CH(lower alkyl)— and —C(dilower alkyl)—;

R and R² are independently selected from the group consisting of —OR⁵, —O(CO)R⁵, —O(CO)OR⁵ and —O(CO)NR⁵R⁶;

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, —OR⁵, —O(CO)R⁵, —O(CO)OR⁵, —O(CH₂)₁-₅OR⁵, —O(CO)NR⁵R⁶, —NR⁵R⁶, —NR⁵(CO)R⁶, —NR⁵(CO)OR⁶, —NR⁵(CO)NR⁵R⁶, —NR⁵SO₂R⁶, —COOR⁵, —CONR⁵R⁶, —COR⁵, —SO₂NR⁵R⁶, S(O)ₐ₃R⁵, —O(CH₂)₁-₁₀—, —COOR⁵, —O(CH₂)₁-₁₀CONR⁵R⁶, —(lower alkylene)COOR⁵, —CH=CH—COOR⁵, —CF₃, —CN, —NO₂ and halogen;

R⁵ is 1-5 substituents independently selected from the group consisting of —OR⁵, —O(CO)R⁵, —O(CO)OR⁵, —O(CH₂)₁-₅OR⁵, —O(CO)NR⁵R⁶, —NR⁵R⁶, —NR⁵(CO)R⁶, —NR⁵(CO)OR⁶, —NR⁵(CO)NR⁵R⁶, —NR⁵SO₂R⁶, —COOR⁵, —CONR⁵R⁶, —COR⁵, —SO₂NR⁵R⁶, S(O)ₐ₃R⁵, —O(CH₂)₁-₁₀—, —COOR⁵, —O(CH₂)₁-₁₀CONR⁵R⁶, —(lower alkylene)COOR⁵ and —CH=CH—COOR⁵;

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; 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 1, Ar¹ is phenyl or R⁴-substituted phenyl, wherein R⁴ is halogen; Ar² is phenyl or R⁴-substituted phenyl, wherein R⁴ is halogen or —OR⁵, wherein R⁵ is lower alkyl or hydrogen; Ar³ is R⁴-substituted phenyl, wherein R⁴ is —OR⁵, wherein R⁵ is lower alkyl or hydrogen; X, Y, and Z are each —CH₂—; R¹ and R² are each hydrogen; R and R² are each —OR⁵, wherein R⁵ 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 1 is selected from the group consisting of

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

42

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;

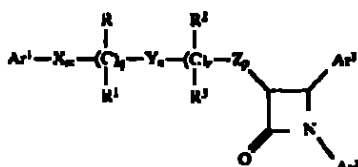
3(R)—[3(S)-acetyloxy]-3-(4-chlorophenyl)propyl]-4(S)—[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone; and

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 1

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, —O(CO)OR⁶ and —C(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)₁₋₁₀OR⁶, —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, —CH=CH—COOR⁶, —CF₃, —CN, —NO₂ and halogen;

R⁶ is 1-5 substituents independently selected from the group consisting of —OR⁶, —O(CO)R⁶, —O(CO)OR⁶, —O(CH₂)₁₋₁₀OR⁶, —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 —C(=O)—COOR⁶;

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; 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 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.

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

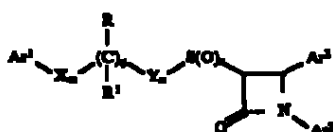
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Ex. #	% Reduction		Dose mg/kg
	Serum Cholest.	Cholest. Ester	
11	55	-95	3
14	30	-64	3
15	-27	-88	1
18	-27	-68	3

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, 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)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, -NR⁶SO₂R⁸, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₂R⁸, -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, -NR⁶SO₂R⁸, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₂R⁸, -O(CH₂)₁₋₁₀COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -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;

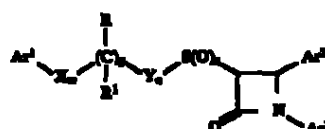
24

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)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁶, -NR⁶(CO)NR⁶R⁷, -NR⁶SO₂R⁸, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₂R⁸, -O(CH₂)₁₋₁₀COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -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, 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)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, -NR⁶SO₂R⁸, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₂R⁸, -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, -NR⁶SO₂R⁸, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₂R⁸, -O(CH₂)₁₋₁₀COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -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

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)NR⁶R⁷, —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 R⁶-substituted phenyl; Ar³ is phenyl or R⁷-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 R⁶-substituted phenyl; Ar³ is phenyl or R⁷-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)sulfonyl]-2-azetidinone;
cis-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)sulfonyl]-2-azetidinone;
trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)sulfonyl]-2-azetidinone;
cis-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)sulfonyl]-2-azetidinone;
trans-4-[1-(4-fluorophenyl)-4-oxo-3-[(2-phenylethyl)sulfonyl]-2-azetidinyl]-phenyl acetate;
cis-4-[1-(4-fluorophenyl)-4-oxo-3-[(2-phenylethyl)sulfonyl]-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]sulfonyl]-4-(4-hydroxyphenyl)-2-azetidinone;
1-(4-fluorophenyl)-3(R)-[[2-(4-fluorophenyl)-2(R)-hydroxyethyl]sulfonyl]-4(R)-(4-hydroxyphenyl)-2-azetidinone;
1-(4-fluorophenyl)-3(R)-[[2-(4-fluorophenyl)-2(S)-hydroxyethyl]sulfonyl]-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; Ar¹ is phenyl, R¹⁰-substituted phenyl or thienyl; Ar² is R⁶-substituted phenyl; Ar³ is phenyl or R⁷-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 R⁶-substituted phenyl; Ar³ is phenyl or R⁷-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)sulfonyl]-2-azetidinone;
cis-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)sulfonyl]-2-azetidinone;
trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)sulfonyl]-2-azetidinone;
cis-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)sulfonyl]-2-azetidinone;
trans-4-[1-(4-fluorophenyl)-4-oxo-3-[(2-phenylethyl)sulfonyl]-2-azetidinyl]-phenyl acetate;
cis-4-[1-(4-fluorophenyl)-4-oxo-3-[(2-phenylethyl)sulfonyl]-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]sulfonyl]-4-(4-hydroxyphenyl)-2-azetidinone;
1-(4-fluorophenyl)-3(R)-[[2-(4-fluorophenyl)-2(R)-hydroxyethyl]sulfonyl]-4(R)-(4-hydroxyphenyl)-2-azetidinone;

27

1-(4-fluorophenyl)-3(R)-[[2-(4-fluorophenyl)-2(5)-hydroxyethyl]-sulfanyl]-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.

* * * * *



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268

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

Publication Classification

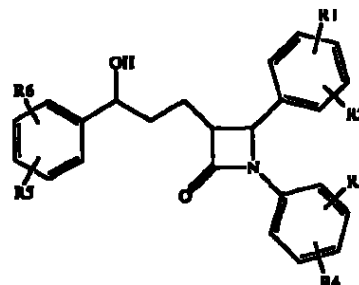
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(57) ABSTRACT

Compounds of the formula I,

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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**

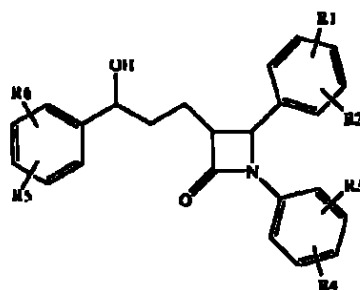
[0001] This application claims the benefit of priority under 35 U.S.C. §119(a) to German patent application no. 10064402.3, filed on Dec. 21, 2000, and German patent application no. 10154518.5, filed on Nov. 7, 2001. The contents of both priority documents are incorporated by reference herein.

[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. Pharmacologically 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 1,



[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-- or --C≡C--; --N((C₁-C₆)-alkyl)- or --NH--; or

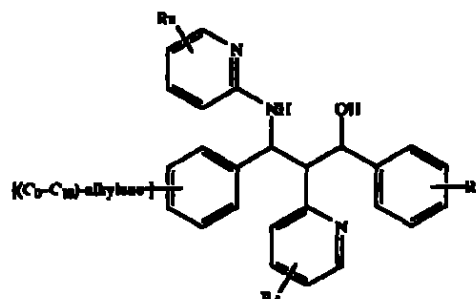
[0008] H, F, Cl, Br, I, CF₃, NO₂, CN, COOH, COO((C₁-C₆)-alkyl), CONH₂, CONH((C₁-C₆)-alkyl), CON((C₁-C₆)-alkyl)₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl or O--(C₁-C₆)-alkyl, where one, more or all hydrogens in the alkyl radicals may be replaced by fluorine; or

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

phenyl, 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] 1. 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-- or --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_0-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_0-C_{30}) -alkylene-L, where one or more carbon atoms of the alkylene radicals 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 $-(CH_2)_{0-1}-NH-(C=O)_{0-1}-(C_2-C_7)$ -alkylene- $-(C=O)_{0-1}-NH-I$; 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, sulfonic 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, in 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 mucrose 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 11ste 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, *Lanhus®* or IIMR 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, tiquemide, pamaquemide.

[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 13-9952, 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 CLTP 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, colesolvam.

[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, BMS-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, 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 gliazide.

[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, nateglitazone, or the compounds disclosed by Dr. Reddy'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, gliazide 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, IL3 agonists, TNF agonists, CRF agonists, CRF RP 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/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.

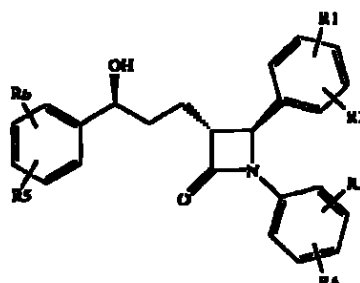
[0067] In one embodiment, the further active compound is mazindol or phentermine.

[0068] In one embodiment, the compounds of the formula I are administered in combination with fiber, preferably insoluble fiber, such as, for example, Carmax®. The combination with Carmax® can be given in one preparation or by separate administration of compounds of the formula I and Carmax®. Here, Carmax® can also be administered in the form of food, such as, for example, in bakery goods or muesli bars. Compared to the individual active compounds, the combination of compounds of the formula I with Carmax® 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.

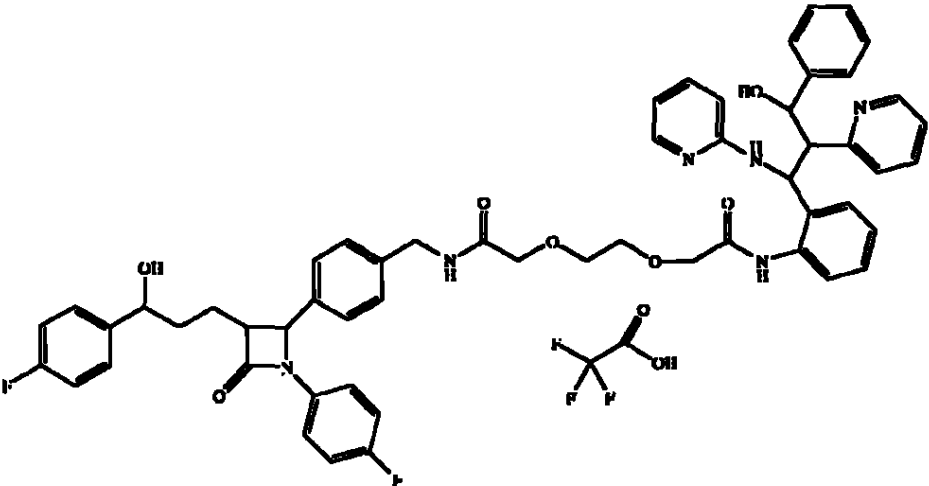
[0070] The invention furthermore provides both stereoisomer mixtures of the formula I and the pure stereoisomers of the formula I, and diastereomer mixtures of the formula I and the pure diastereomers. The mixtures are separated by chromatographic means.

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



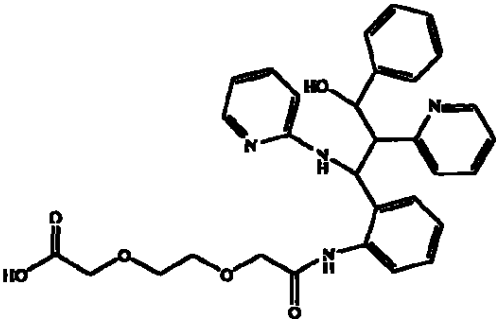
EXAMPLE XIX

[0098]



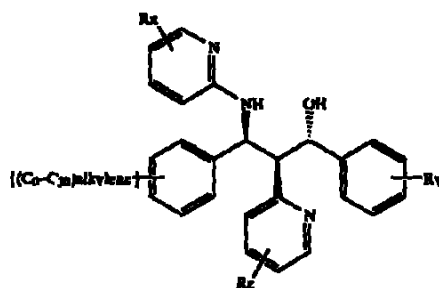
{1-[2-(2-{2-[(4-{1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxazetidin-2-yl)benzylcarbamoyl)methoxy]acetoxy}phenyl)-3-hydroxy-3-phenyl-2-pyridin-2-ylpropyl)pyridin-2-ylammonium trifluoroacetate 36

[0099]



[0100] C₃₁H₃₂N₄O₈ (556.62) MS (ESI) 557 (M+H)

1. is shown connected to (C_4-C_{20}) -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—NH—(C=O)—(C₃-C₂₃)-alkylene—(C=O)—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, insulin, 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, H3 agonists, MSH (melanocyte-stimulating hormone) agonists, CCK agonists, serotonergic compounds, mixed serotonergic 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/amyase 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.

* * * * *



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United States Patent [19]

[11] Patent Number: 5,767,115

Rosenblum et al.

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

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

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[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, Jan. 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 285/00; A61K 31/395

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

[58] Field of Search 340/200; 514/210

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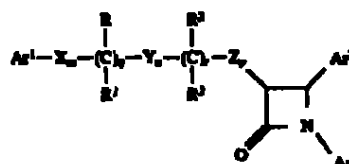
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Primary Examiner—Mark L. Borch
Attorney, Agent, or Firm—Anita W. Magatti

[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;

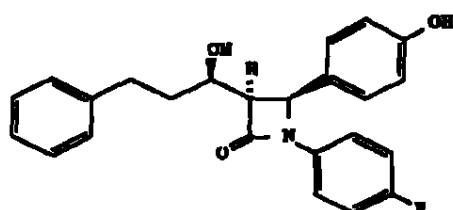
R⁴ is selected from lower alkyl, R⁴, —CF₃, —CN, —NO₂, and halogen R⁵ is selected from —OR⁶, —O(CO)R⁶, —O(CO)OR⁶, —O(CH₂)₁₋₁₀OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁶, —NR⁶(CO)OR⁶, —NR⁶(CO)NR⁶R⁷, —NR⁶SO₂R⁶, —COOR⁶, —CONR⁶R⁷, —CONR⁶, —SO₂NR⁶R⁷, Si(O)₂₋₄R⁶, —O(CH₂)₁₋₁₀COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —(lower alkylene)COOR⁶ and —CH=CH—COOR⁶;

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

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.

9 Claims, No Drawings

37
EXAMPLE 10

Step 1:

Follow the procedure of Example 3, using 1-(4-fluorophenyl)-4-(4-1-butyldimethylsilyloxyphenyl)-2-azetidinone to obtain 1-(4-fluorophenyl)-3-(3-phenyl-1-hydroxypropyl)-4-(4-1-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 C₃₄H₄₂O₃FN: 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

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., 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

Capsule			
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.

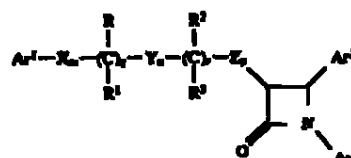
Representative formulations comprising a cholesterol biosynthesis inhibitor are well known in the art. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms disclosed above for substituted azetidinone compounds may readily be modified using 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. #	Series	Cholest.	Dose mg/kg	Ex. #	Series	Cholest.	Dose mg/kg
1A	-23	0	50	4C	-12.5	0	3
1B	-15	-39	50	4D	0	0	7
1C	14	0	50	4E	0	-46	3
2	0	0	50	4F	-29	-55	3
3A	-31	-49	50	5	0	-64	10
3C	-40	-92	50	6A	-39	-93	1
3D	-17	-41	10	6A-1	-43	-93	1
3E	0	0	10	6B	-40	-92	3
3F	-39	-77	10	6C	0	-48	3
3G	-16	-38	10	6D	-46	-95	10
3H	-41	-86	10	6A	0	-44	3
3I	0	-32	10	6B	-30	-98	3
3J	0	0	3	6C	-14	-57	1
3K	0	0	10	6D	-49	98	1
3L	-15	-21	10	6E	-22	-66	3
3M	0	-22	10	6F	-43	-94	1
4A	0	-34	3	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;

Ar³ is aryl or R²-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 R² are independently selected from the group consisting of $-\text{OR}^4$, $-\text{O}(\text{CO})\text{R}^4$, $-\text{O}(\text{CO})\text{OR}^4$ and $-\text{O}(\text{CO})\text{NR}^4\text{R}^7$;

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, $-\text{OR}^4$, $-\text{O}(\text{CO})\text{R}^4$, $-\text{O}(\text{CO})\text{OR}^4$, $-\text{O}(\text{CH}_2)_{1-10}\text{OR}^4$, $-\text{O}(\text{CO})\text{NR}^4\text{R}^7$, $-\text{NR}^4\text{R}^7$, $-\text{NR}^4(\text{CO})\text{R}^7$, $-\text{NR}^4(\text{CO})\text{OR}^4$, $-\text{NR}^4(\text{CO})\text{NR}^4\text{R}^7$, $-\text{NR}^4\text{SO}_2\text{R}^7$, $-\text{COOR}^4$, $-\text{CONR}^4\text{R}^7$, $-\text{COR}^4$, $-\text{SO}_2\text{NR}^4\text{R}^7$, $\text{S}(\text{O})_{2-3}\text{R}^7$, $-\text{O}(\text{CH}_2)_{1-10}\text{COOR}^4$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^4\text{R}^7$, $-(\text{lower alkylene})\text{COOR}^4$, $-\text{CH}=\text{CH}-\text{COOR}^4$, $-\text{CF}_3$, $-\text{CN}$, $-\text{NO}_2$ and halogen;

R⁵ is 1-5 substituents independently selected from the group consisting of $-\text{OR}^4$, $-\text{O}(\text{CO})\text{R}^4$, $-\text{O}(\text{CO})\text{OR}^4$, $-\text{O}(\text{CH}_2)_{1-10}\text{OR}^4$, $-\text{O}(\text{CO})\text{NR}^4\text{R}^7$, $-\text{NR}^4\text{R}^7$, $-\text{NR}^4(\text{CO})\text{R}^7$, $-\text{NR}^4(\text{CO})\text{OR}^4$, $-\text{NR}^4(\text{CO})\text{NR}^4\text{R}^7$, $-\text{NR}^4\text{SO}_2\text{R}^7$, $-\text{COOR}^4$, $-\text{CONR}^4\text{R}^7$, $-\text{COR}^4$, $-\text{SO}_2\text{NR}^4\text{R}^7$, $\text{S}(\text{O})_{2-3}\text{R}^7$, $-\text{O}(\text{CH}_2)_{1-10}\text{COOR}^4$, $-\text{O}(\text{CH}_2)_{1-10}\text{CONR}^4\text{R}^7$, $-(\text{lower alkylene})\text{COOR}^4$ and $-\text{CH}=\text{CH}-\text{COOR}^4$;

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 $-\text{OR}^4$, wherein R⁴ is lower alkyl or hydrogen; and Ar³ is R⁵-substituted phenyl, wherein R⁵ is $-\text{OR}^4$, 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 $-\text{OR}^4$, wherein R⁴ 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)-(3(S)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

rel 3(R)-(3(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]-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.

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