



No. 06-060219- -00001-0000

Fecha 2007-05-30 14:50:08 Dep. 2020 NUECREACIONE
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FORMULARIO UNICO DE OPOSICION
2000-12

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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 | |

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**SOLICITUD
PUBLICADA**

Número del expediente: 06.060.219
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 598 - Número de Publicación 1128

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OPOSICION PRESENTADA POR:

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

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FUNDAMENTOS DE LA OPOSICION:

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

Justificación: VER ANEXO

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Comprobante de pago No. 07-42.781 (Oposición) Fecha Mayo 29 de 2007
(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.

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NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

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

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: EXPEDIENTE 06-060-219

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 1128

SOLICITANTE: ASTRAZENECA AB.

**PRIORIDAD: GB 0329780.1 del 23/12/2003
SE 0401907.1 del 21/07/2004
SE 0402785.0 del 15/11/2004**

APODERADO: JUAN PABLO CADENA SARMIENTO.

TRÁMITE: PRESENTACIÓN DE OPOSICIÓN

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

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente 06-060-219, por no cumplir con los requisitos de patentabilidad a que se refieren los artículos

14, 16, 18 y 20 de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos de hecho y de derecho que me permito exponer a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **LAFRANCOL S.A.**, en su condición de industria farmacéutica, 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.

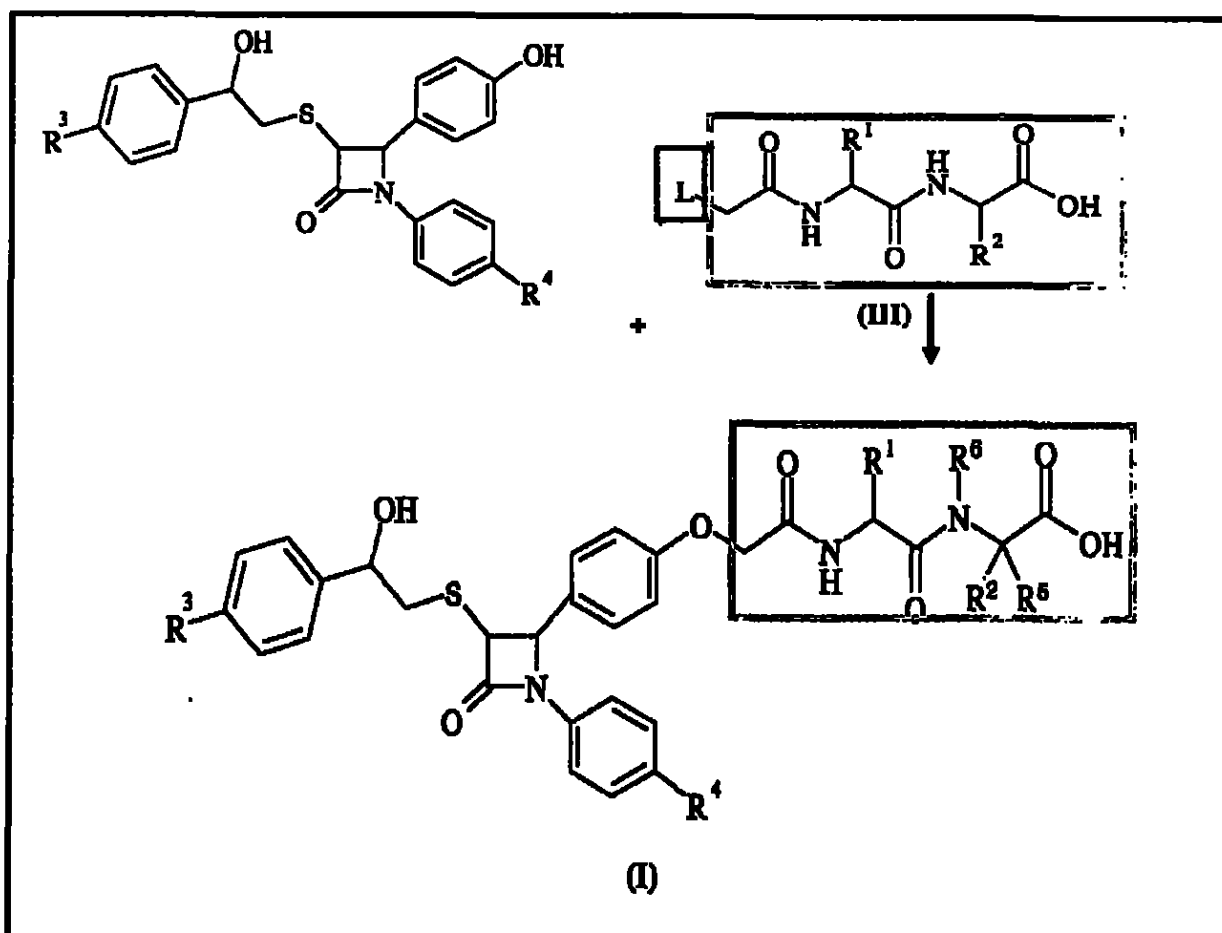
III. FUNDAMENTOS DE LA OPOSICIÓN

3.1. Los compuestos que reivindica la solicitud colombiana 06-060-219 que resultan ser análogos de ezetimibe (con un átomo de azufre en vez de un carbono en la posición 3 respecto al núcleo de azetidinona) 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, carecen de novedad y nivel inventivo como se argumenta a continuación:

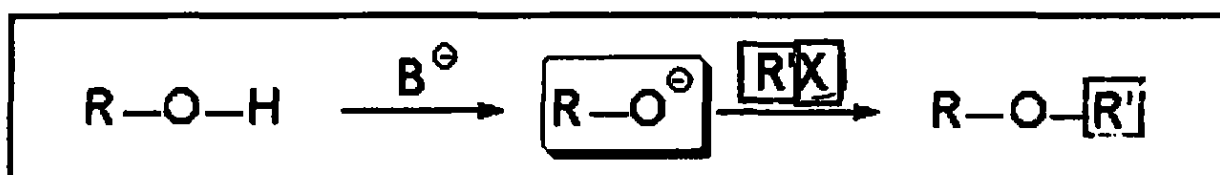
En primer término, los compuestos de la fórmula (12) y (I) así como los procesos de obtención que se reivindican en la solicitud en trámite resultan ser simples análogos de ezetimibe (entre otros) y su enantiómero obtenidos por reacciones de síntesis muy comunes, como se verá a continuación:

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Proceso 1:

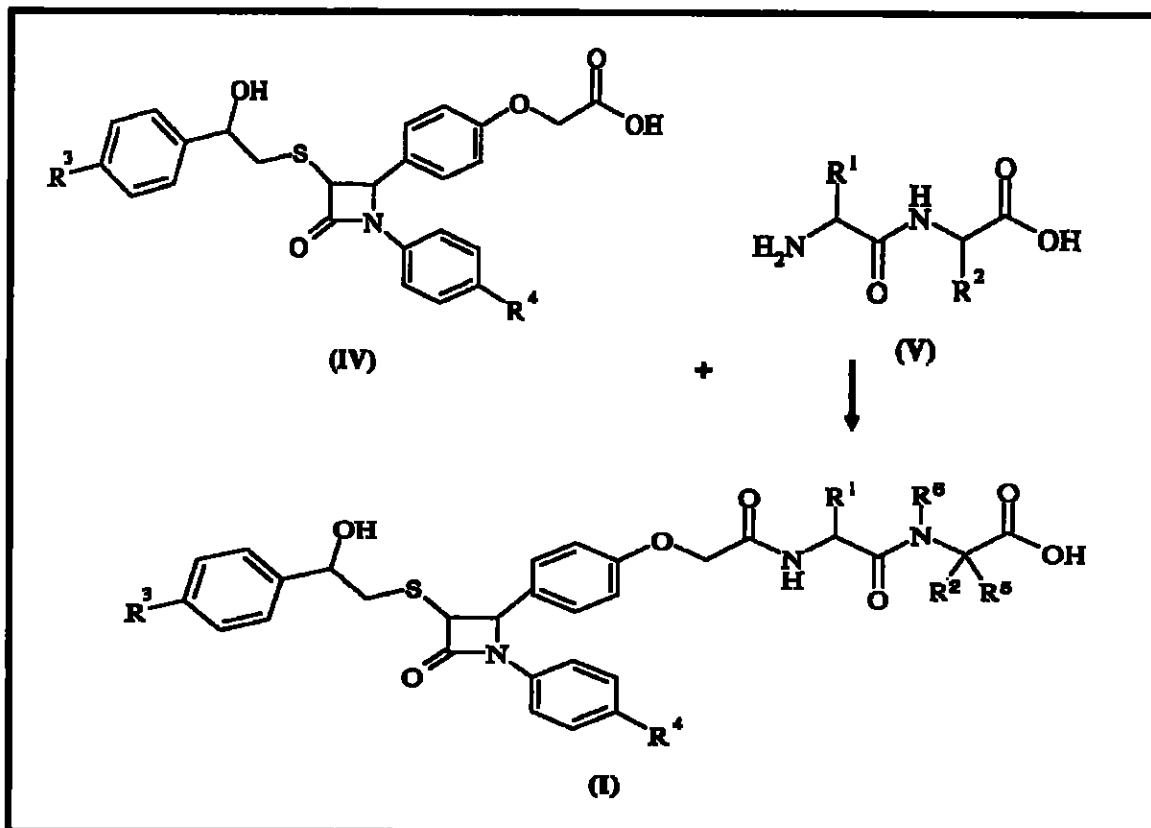


En la solicitud colombiana en trámite, el hidroxilo del grupo hidroxifenil que sustituye al núcleo de azetidinona en posición 4 reacciona con el compuesto de fórmula (III) (donde L es un grupo desplazable o saliente), donde al parecer por sustitución nucleofílica (SN2) permite obtener el compuesto de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

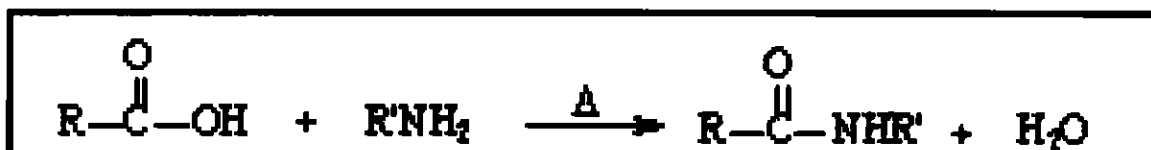


En síntesis orgánica, la manera más simple de preparar un éter es hacer reaccionar un alcóxido con un haluro o sulfonato de alquilo en una secuencia típica SN2.

Proceso 2:

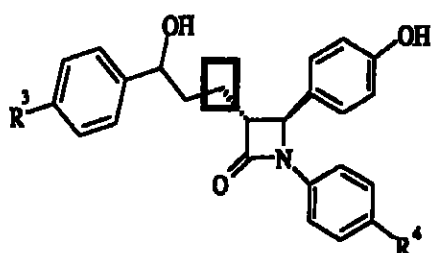


En la solicitud colombiana en trámite, se hace reaccionar el ácido carboxílico de fórmula (IV) o su respectivo derivado éster con una amina de fórmula (V) para obtener el compuesto de fórmula (I) (amida).

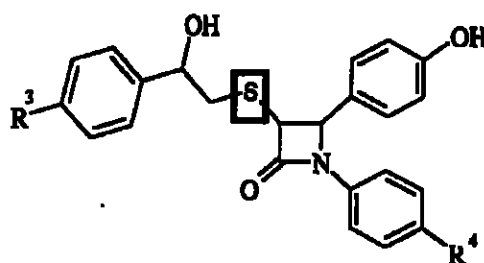


En síntesis orgánica una amida puede ser preparada comúnmente haciendo reaccionar un ácido carboxílico o su respectivo éster con una amina.

Adicional a lo anterior, es importante resaltar que la analogía de estos compuestos con ezetimibe (resaltada en rojo)



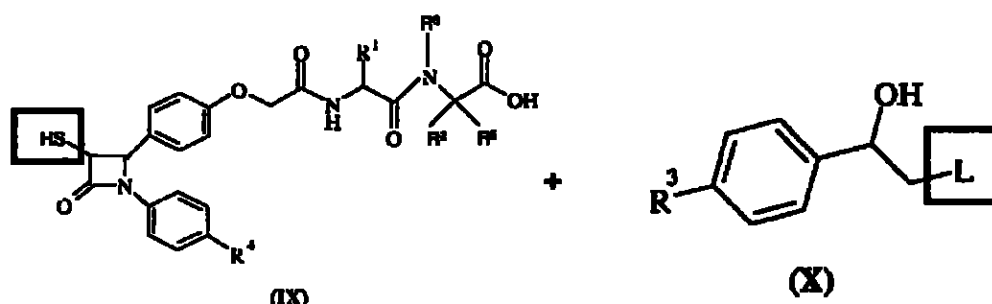
Ezetimibe con R3 y R4= Flúor.



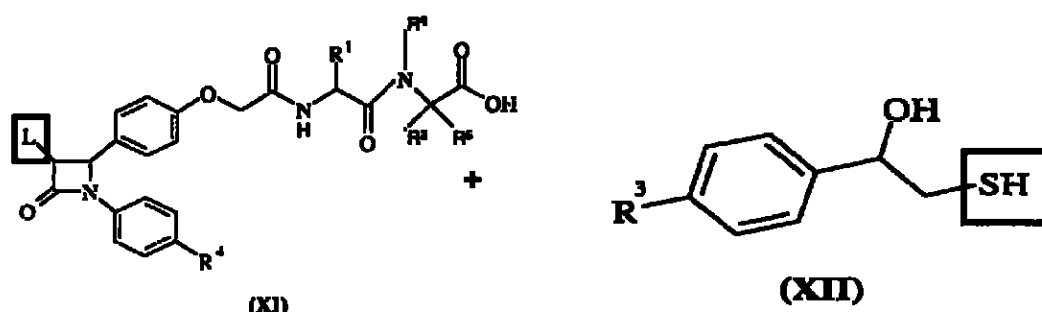
Análogos de Ezetimibe

que como toda persona versada en la materia reconoce, consiste en el cambio de átomos o grupos de átomos en un fármaco, que presentan propiedades fisicoquímicas y biológicas similares¹, a través de una reacción típica de sustitución nucleofílica de un grupo L por el átomo de azufre de un grupo SH, tal como se pretende hacer en el proceso 5 y 6 de la solicitud colombiana en trámite:

Proceso 5:



Proceso 6:



Del mismo modo se debe tener en cuenta que los isósteros más reconocidos son:

Isósteros clásicos

1. Átomos y grupos univalentes
 - a. CH₃, NH₂, OH, F, Cl
 - b. Cl, PH₂, SH
 - c. Br, *i*-Pr
 - d. I, *t*-Bu
2. Átomos y grupos bivalentes

a. $\text{—CH}_2\text{—}$	—NH—	—O—	—S—	—Se—
b. $\text{—COCH}_2\text{R}$	—CONHR	$\text{—CO}_2\text{R}$	—COSR	
3. Átomos y grupos trivalentes
 - a. —CH=
 - b. —P=
4. Átomos tetravalentes

a. —C—	—Si—
b. =C=	=N=
	=P=
5. Equivalentes de anillos

a. —CH=CH—	—S—	(ej. benceno, tiofeno)
b. —CH=	—N=	(ej. benceno, piridina)
c. —O—	—S—	(ej. tetrahidrofurano, tetrahidrotiofeno, ciclopentano, pirrolidina)

¹ http://www.qo.fcen.uba.ar/Cursos/quimed_files/QM5.pdf

Es así que, los compuestos obtenidos en estos procesos podrían describirse como profármacos de compuestos análogos 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 cambios isostéricos (*Langmuir 1919 y Erlenmeyer 1932*¹) y la formación de profármacos (reconocidos y definidos por *Albert*² desde 1958) herramientas ampliamente reconocidas para dar solución a diversas eventualidades de una molécula con actividad farmacológica, no puede entonces atribuírsele novedad y mucho menos nivel inventivo a un proceso de obtención de compuestos análogos de ezetimibe (u otro compuesto –dependiendo de los sustituyentes) o sus profármacos a través de reacciones sencillas de sustitución nucleofílica (por ejemplo en la obtención de los análogos con átomo de azufre en vez de CH₂) y esterificación y formación de amidas (en el caso de la formación de profármacos).

- La patente americana US 5,633,246 publicada el 27 de mayo de 1997 y titulada "SULFUR-SUBSTITUTED AZETIDINONE COMPOUND USEFUL AS HYPOCHOLERESTOLEMIC AGENTS" se refiere a compuestos de la fórmula:

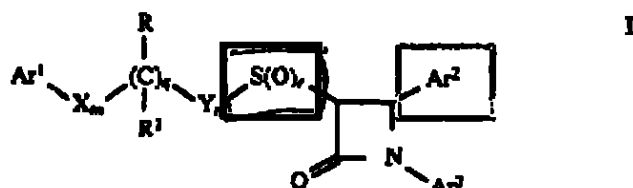
² ALBERT A. Chemical aspects of selective toxicity. Nature 182, 421 (1958).

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[57]

ABSTRACT

Sulfur-substituted azetidinone hypocholesterolemic agents of the formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ is aryl, R¹⁰-substituted aryl or heteroaryl;

Ar² is aryl or R⁴-substituted aryl;

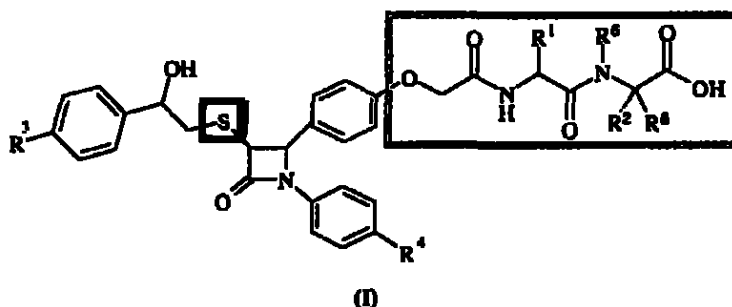
Ar³ is aryl or R⁵-substituted aryl;

q is 0 or 1; r is 0, 1 or 2; m and n are 0-5; provided that the sum of m, n and q is 1-5;

R⁴ is selected from 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)₀₋₃R⁹, -O(CH₂)₁₋₁₀-COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -(lower alkylene)-COOR⁶ and -CH=CH-COOR⁶;

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)₀₋₃R⁹, -O(CH₂)₁₋₁₀-COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -CF₃, -CN, -NO₂.

(Patente americana US 5,633,246)



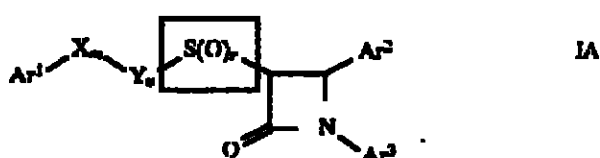
(Solicitud colombiana en trámite)

Como observamos, tanto la patente americana como la solicitud colombiana en trámite permiten la obtención de derivados de azetidinona sustituidos con un átomo de azufre en la posición 3 (rojo), así como de compuestos con

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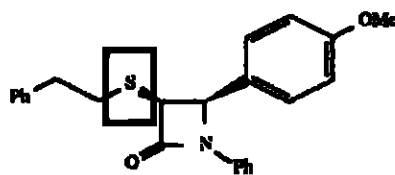
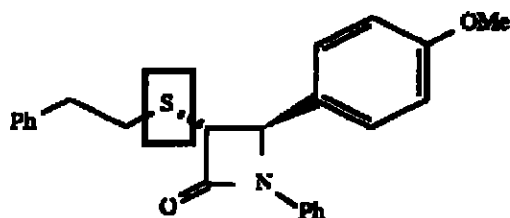
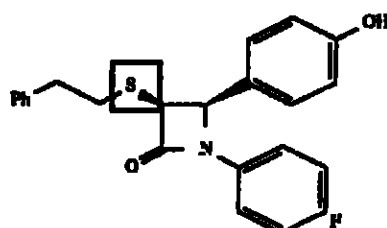
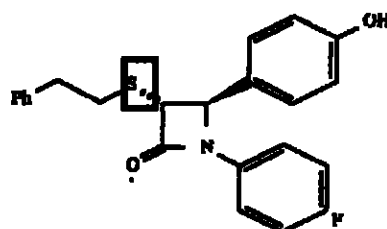
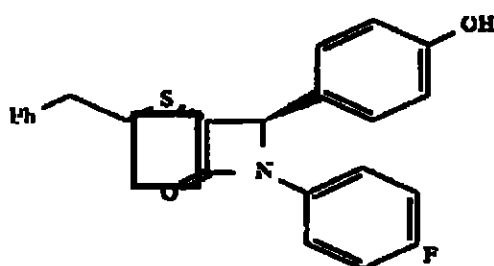
sustituyentes con características químicas similares en la misma posición 4 correspondiente al grupo hidroxifenil (verde).

De la misma manera, en el capítulo descriptivo de la anterioridad mencionada se hacen más evidentes las similitudes entre las características de los compuestos de la patente americana y de la solicitud colombiana, en especial en lo que respecta a que los compuestos poseen el mismo núcleo principal -el cual a su vez cuenta con la presencia del átomo de S-, y los demás sustituyentes en su gran mayoría son idénticos:



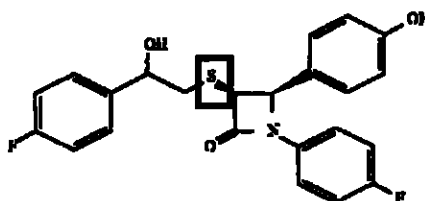
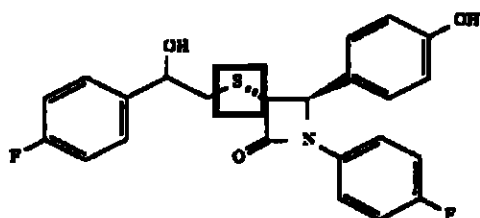
In compounds of formula IA, the sum of m and n is preferably 2, 3 or 4, more preferably 2. Also preferred are compounds wherein the sum of m and n is 2, and r is 0 or 1.

EXAMPLE 1



EXAMPLE 6

EXAMPLE 19



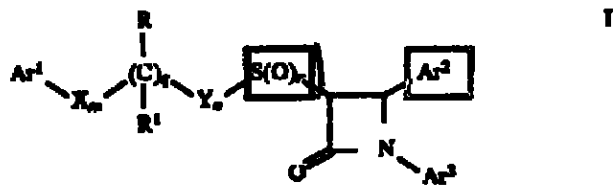
Así mismo, haciendo un paralelo entre lo reivindicado en la solicitud colombiana en trámite y la patente americana, podemos evidenciar muchas cosas en común, veamos:

SOLICITUD COLOMBIANA EN TRAMITE	PATENTE AMERICANA US 5,633,246
17. Una formulación farmacéutica que comprende un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 12 en mezcla con coadyuvantes, diluyentes y/o vehículos farmacéuticamente aceptables.	In still another aspect, the present invention relates to a pharmaceutical composition comprising a serum cholesterol-lowering effective amount of a compound of formula I is a pharmaceutically acceptable carrier.
14. 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 12 a un mamífero necesitado de ello.	The present invention also relates to a method of reducing plasma cholesterol levels, and to a method of treating or preventing atherosclerosis, comprising administering to a mammal in need of such treatment an effective amount of a combination of a sulfur-substituted azetidinone cholesterol
19. Una combinación de un compuesto de acuerdo con la formula (I) o (I2) con un inhibidor de HMG Co-A reductasa.	Cholesterol biosynthesis inhibitors for use in the combination of the present invention include HMG CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin, and CI-981; HMG CoA synthetase inhibitors.

➤ La patente americana US 5,744,467 del 28 de abril de 1998 y titulada "SULFUR-SUBSTITUTED AZETIDINONE COMPOUND USEFUL AS HYPOCHOLERESTOLEMIC AGENTS" revela compuestos de la formula:

[57] ABSTRACT

Sulfur-substituted azetidinone hypocholesterolemic agents of the formula



or a pharmaceutically acceptable salt thereof are disclosed, as well as pharmaceutical compositions containing them, and a method of lowering serum cholesterol by administering said compounds, alone or in combination with a cholesterol biosynthesis inhibitor.

Ar¹ is aryl, R¹⁰-substituted aryl or heteroaryl;

Ar² is aryl or R⁴-substituted aryl;

Ar³ is aryl or R⁵-substituted aryl;

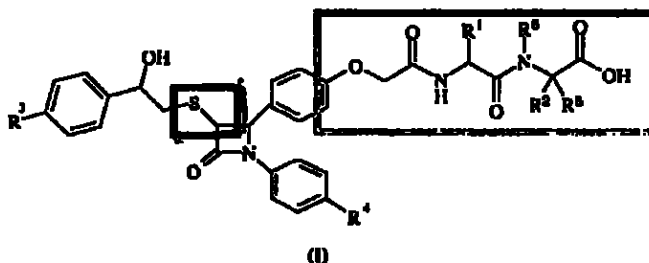
q is 0 or 1;

r is 0, 1 or 2;

R⁴ is 1-5 substituents independently selected from the group consisting of lower alkyl, —OR⁶, —O(CO)R⁶, —O(CO)OR⁶, —O(CH₂)₁₋₃OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁶, —NR⁶(CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₂R⁹, —O(CH₂)₁₋₁₀COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, (lower alkylene), COOR⁶ and —OH—OH—COOR⁶;

R⁵ is 1-5 substituents independently selected from the group consisting of —OR⁶, —O(CO)R⁶, —O(CO)OR⁶, —O(CH₂)₁₋₃OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁶, —NR⁶(CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷, —COR⁶, —SO₂NR⁶R⁷, S(O)₂R⁹, —O(CH₂)₁₋₁₀COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —CF₃, —CN, —NO₂, halogen, —(lower alkylene)COOR⁶ and —CH=CH—COOR⁶;

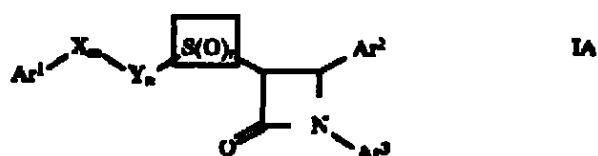
(Patente americana US 5,744,467)



(Solicitud colombiana en trámite)

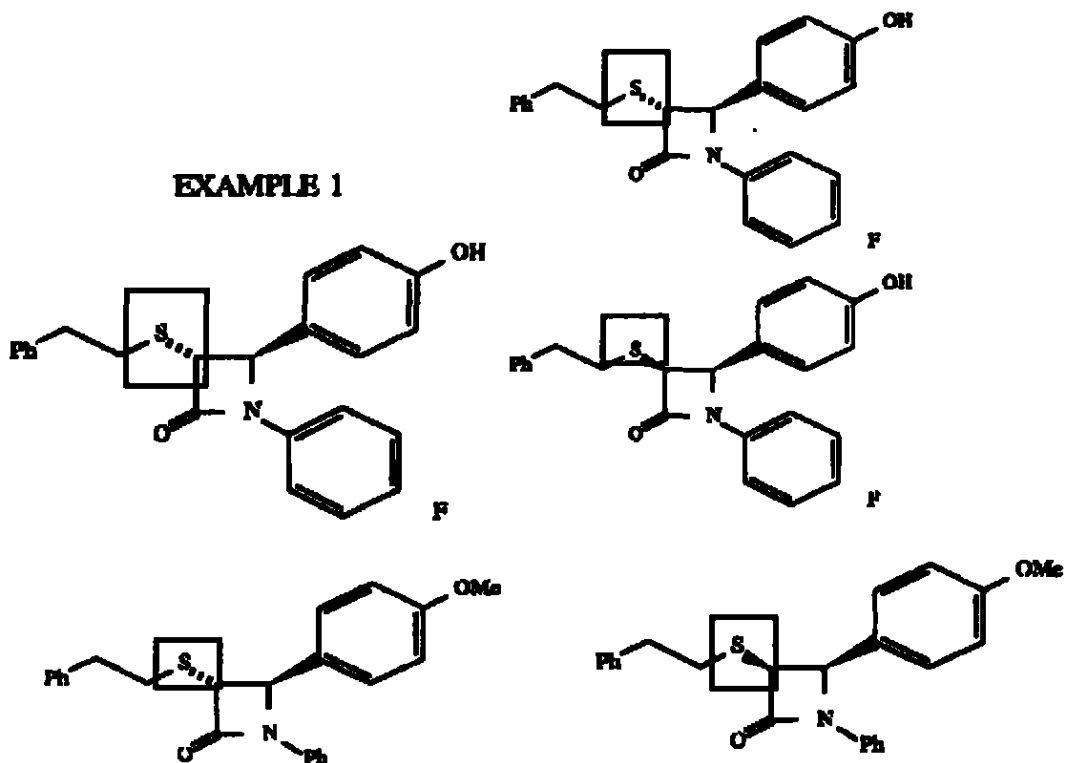
En donde los sustituyentes resaltados en verde, coinciden en buena parte con los sustituyentes correspondientes a la misma posición en los derivados de la solicitud colombiana en trámite, además, en ambos casos se pueden obtener derivados de azetidinona sustituidos con un átomo de azufre en la posición 3 (rojo).

De la misma manera, en el capítulo descriptivo de la anterioridad mencionada se hacen más evidentes las similitudes entre las características de los compuestos de la patente americana y de la solicitud colombiana, en especial en lo que respecta a que los compuestos poseen el mismo núcleo principal -el cual a su vez cuenta con la presencia del átomo de S-, y los demás sustituyentes en su gran mayoría son idénticos:



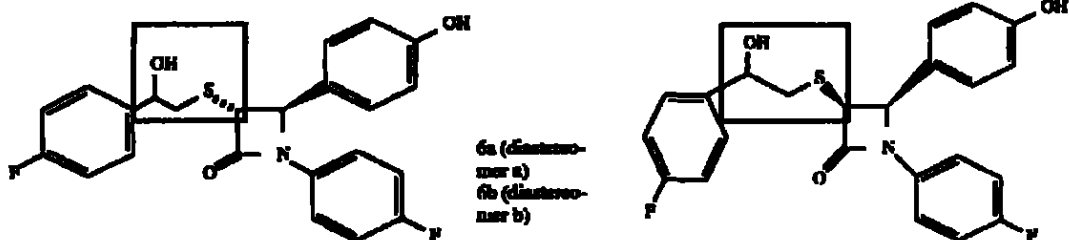
In compounds of formula IA, the sum of m and n is preferably 2, 3 or 4, more preferably 2. Also preferred are compounds wherein the sum of m and n is 2, and r is 0 or 1.

EXAMPLE 1



EXAMPLE 6

EXAMPLE 19



6a (diastereomer a)
6b (diastereomer b)

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:

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SOLICITUD COLOMBIANA EN TRAMITE	PATENTE AMERICANA US 5,744,467
17. Una formulación farmacéutica que comprende un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 12 en mezcla con coadyuvantes, diluyentes y/o vehículos farmacéuticamente aceptables.	In still another aspect, the present invention relates to a pharmaceutical composition comprising a serum cholesterol-lowering effective amount of a compound of formula I in a pharmaceutically acceptable carrier. In yet another aspect, the invention relates to a pharmaceutical composition comprising an effective amount of a sulfur-substituted azetidinone cholesterol absorption inhibitor of formula I, a cholesterol biosynthesis inhibitor, and a pharmaceutically acceptable carrier. In a final aspect, the
14. 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 12 a un mamífero necesitado de ello.	preventing atherosclerosis, comprising administering to a mammal in need of such treatment an effective amount of a combination of a sulfur-substituted azetidinone cholesterol absorption inhibitor of formula I and a cholesterol biosynthesis inhibitor. That is, the present invention relates to the 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
20. Un proceso para preparar un compuesto de formula (I) que consta de (...) y posteriormente, si es necesario o deseable: (...) iv) separar dos o mas enantiómeros. (...)	Compounds of the invention have at least one asymmetric atom and therefore all isomers, including enantiomers and diastereomers are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture, including racemic mixtures. Isomers
19. Una combinación de un compuesto de acuerdo con la formula (I) o (I2) con un inhibidor de HMG Co-A reductasa.	Cholesterol biosynthesis inhibitors for use in the combination of the present invention include HMG CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin, and CI-981; HMG CoA synthetase inhibitors. 2. A pharmaceutical composition of claim 1 wherein the cholesterol biosynthesis inhibitor is selected from the group consisting of HMG CoA reductase inhibitors.
13. Un método de tratar o prevenir enfermedades hiperlipidémicas que comprende la administración de una cantidad efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 12 a un mamífero necesitado de ello.	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

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.
- Siendo la obtención de estos análogos de azetidinona, sustituidos con un átomo de azufre en la posición 3, al parecer el argumento central de novedad y nivel inventivo de esta solicitud colombiana en trámite, a continuación se demuestra con una publicación científica que estos compuestos derivados de azetidinona con un átomo de azufre son ampliamente reconocidos y caracterizados, y que por lo tanto no se puede adjudicar nivel inventivo en su obtención, tal y como pretende la solicitud colombiana en cuestión:

SYNTHESIS OF C3 HETEROATOM-SUBSTITUTED AZETIDINONES THAT DISPLAY POTENT CHOLESTEROL ABSORPTION INHIBITORY ACTIVITY³.

Abstract: The C3 phenylpropyl side chain of N-phenylazetidinones related to SCH 56524 was modified by replacing the hydroxymethylene with various isoelectronic or isosteric groups. Modifications at the 3' position led to less-active compounds; however, modifications at the 1' position provided compounds with improved cholesterol absorption inhibitory activity. An enantioselective route for the synthesis of C3 1'-sulfur-substituted azetidinones and the development of structure-activity relationships for this series of compounds are presented.

- 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 lo 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 diagnóstico aplicados a los seres humanos o a animales."*

³ **Synthesis of C3 heteroatom-substituted azetidinones that display potent cholesterol absorption inhibitory activity.** (eng; includes abstract) By McKittrick BA, Journal Of Medicinal Chemistry [J Med Chem], 1998 Feb 26; Vol. 41 (5), pp. 752-9; PMID: 9513603

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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 5,633,246 del 27 de Mayo de 1997 y titulada "SULFUR-SUBSTITUTED AZETIDINONE COMPOUND USEFUL AS HYPOCHOLERESTOLEMIC AGENTS" paginas 3, 4, 6, 7, 9 y 13.
- La patente americana US 5,744,467 del 28 de abril de 1998 y titulada "SULFUR-SUBSTITUTED AZETIDINONE COMPOUND USEFUL AS HYPOCHOLERESTOLEMIC AGENTS" paginas 2, 3, 4, 6, 7, 9, 12 y 13.
- La publicación científica SYNTHESIS OF C3 HETEROATOM-SUBSTITUTED AZETIDINONES THAT DISPLAY POTENT CHOLESTEROL ABSORPTION INHIBITORY ACTIVITY, abstract.

VI. ANEXOS

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

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

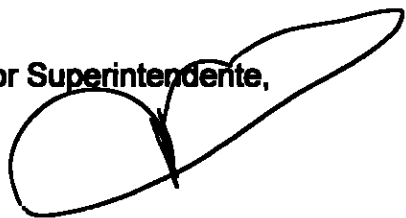
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4. Copia para correr traslado al solicitante.
5. Las mencionadas en el acápite de pruebas

VII. NOTIFICACIONES

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

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

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



US005633246A

United States Patent [19]
McKittrick et al.[11] Patent Number: 5,633,246
[45] Date of Patent: May 27, 1997

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[54] **SULFUR-SUBSTITUTED AZETIDINONE
COMPOUNDS USEFUL AS
HYPOCHOLESTEROLEMIC AGENTS**[75] Inventors: Brian A. McKittrick, Bloomfield;
Sandeep Dugar, Bridgewater; Duane
A. Burnett, Fairwood, all of N.J.[73] Assignee: Schering Corporation, Kenilworth,
N.J.

[21] Appl. No.: 463,619

[22] Filed: Jun. 5, 1995

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 342,197, Nov. 18, 1994.

[51] Int. Cl.⁶ C07D 205/08; C07D 401/12;
C07D 409/12; A61K 31/395

[52] U.S. Cl. 514/210; 540/360

[58] Field of Search 540/360; 514/210

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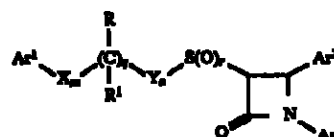
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Primary Examiner—Mark L. Berch*Attorney, Agent, or Firm*—Anita W. Magatti; Eric S. Dicker[57] **ABSTRACT**Sulfur-substituted azetidinone hypcholesterolemic agents
of the formula

or a pharmaceutically acceptable salt thereof, wherein:

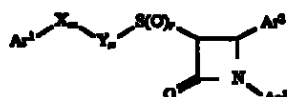
Ar¹ is aryl, R¹⁰-substituted aryl or heteroaryl;Ar² is aryl or R⁴-substituted aryl;Ar³ is aryl or R⁵-substituted aryl;X and Y are —CH₂—, —CH(lower alkyl)— or
—C(dilower alkyl)—;R is —OR⁶, —O(CO)R⁶, —O(CO)OR⁹ or —O(CO)
NR⁶R⁷; R¹ is hydrogen, lower alkyl or aryl; or R and
R¹ together are =O;q is 0 or 1; r is 0, 1 or 2; m and n are 0-5; provided that
the sum of m, n and q is 1-5;R⁴ is selected from lower alkyl, —OR⁶, —O(CO)R⁶,
—O(CO)OR⁹, —O(CH₂)₁₋₃OR⁶, —O(CO)NR⁶R⁷,
—NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶
(CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷,
—COR⁶, —SO₂NR⁶R⁷, S(O)₀₋₂R⁹, —O(CH₂)₁₋₁₀—
COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, (lower alkylene)
—COOR⁶ and —CH=CH—COOR⁶;R⁵ is selected from —OR⁶, —O(CO)R⁶, —O(CO)OR⁹,
—O(CH₂)₁₋₃OR⁶, —O(CO)NR⁶R⁷, —NR⁶R⁷, —NR⁶
(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶(CO)NR⁷R⁸,
—NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷, —COR⁶,
—SO₂NR⁶R⁷, S(O)₀₋₂R⁹, —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 H, lower alkyl, aryl or aryl-substituted
lower alkyl;R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl; andR¹⁰ is selected from lower alkyl, —OR⁶, —O(CO)R⁶,
—O(CO)OR⁹, —O(CH₂)₁₋₃OR⁶, —O(CO)NR⁶R⁷,
—NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁹, —NR⁶
(CO)NR⁷R⁸, —NR⁶SO₂R⁹, —COOR⁶, —CONR⁶R⁷,
—COR⁶, —SO₂NR⁶R⁷, S(O)₀₋₂R⁹, —O(CH₂)₁₋₁₀—
COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —CF₃, —CN,
—NO₂ and halogen;are disclosed, as well as pharmaceutical compositions
containing them, and a method of lowering serum
cholesterol by administering said compounds, alone or
in combination with a cholesterol biosynthesis inhibi-
tor.

15 Claims, No Drawings

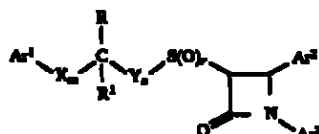
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—O(CO)OR⁶, —O(CH₂)₁₋₁₀OR⁶, —O(CO)NR⁶R⁷,
 —NR⁶R⁷, —NR⁶(CO)R⁷, —NR⁶(CO)OR⁶, —NR⁶
 (CO)NR⁶R⁷, —NR⁶SO₂R⁶, —COOR⁶, —CONR⁶R⁷,
 —COR⁶, —SO₂NR⁶R⁷, S(O)₂R⁶, —O(CH₂)₁₋₁₀
 COOR⁶, —O(CH₂)₁₋₁₀CONR⁶R⁷, —CF₃, —CN,
 —NO₂ and halogen.

Within the scope of formula I, there are two preferred structures. In formula IA, q is zero and the remaining variables are as defined above, and in formula IB, q is 1 and the remaining variables are as defined above:



IA



IB

R⁴, R⁵ and R¹⁰ are each preferably 1-3 independently selected substituents. Preferred are compounds of formula I wherein Ar¹ is phenyl, R¹⁰-substituted phenyl or thienyl, especially (4-R¹⁰)-substituted phenyl or thienyl, Ar² is preferably R⁴-substituted phenyl, especially (4-R⁴)-substituted phenyl, Ar³ is preferably phenyl or R⁵-substituted phenyl, especially (4-R⁵)-substituted phenyl. When Ar¹ is R¹⁰-substituted phenyl, R¹⁰ is preferably halogeno, especially fluoro. When Ar¹ is R⁴-substituted phenyl, R⁴ is preferably —OR⁶, especially wherein R⁶ is hydrogen or lower alkyl. When Ar¹ is R⁵-substituted phenyl, R⁵ is preferably halogeno, especially fluoro. Especially preferred are compounds of formula I wherein Ar¹ is phenyl, 4-fluorophenyl or thienyl, Ar² is 4-(alkoxy or hydroxy)phenyl, and Ar³ is phenyl or 4-fluorophenyl.

X and Y are each preferably —CH₂—. The sum of m, n and q is preferably 2, 3 or 4, more preferably 2. When q is 1, n is preferably 1 to 5.

Preferences for X, Y, Ar¹, Ar² and Ar³ are the same in each of formulae IA and IB.

In compounds of formula IA, the sum of m and n is preferably 2, 3 or 4, more preferably 2. Also preferred are compounds wherein the sum of m and n is 2, and r is 0 or 1.

In compounds of formula IB, the sum of m and n is preferably 1, 2 or 3, more preferably 1. Especially preferred are compounds wherein m is zero and n is 1. R¹ is preferably hydrogen and R is preferably —OR⁶ wherein R⁶ is hydrogen, or a group readily metabolizable to a hydroxyl (such as —O(CO)R⁶, —O(CO)OR⁶ and —O(CO)NR⁶R⁷, defined above), or R and R¹ together form a —O group.

This invention also relates to a method of lowering the serum cholesterol level in a mammal in need of such treatment comprising administering an effective amount of a compound of formula I. That is, the use of a compound of the present invention as an hypocholesterolemic agent is also claimed.

In still another aspect, the present invention relates to a pharmaceutical composition comprising a serum cholesterol-lowering effective amount of a compound of formula I in a pharmaceutically acceptable carrier.

The present invention also relates to a method of reducing plasma cholesterol levels, and to a method of treating or preventing atherosclerosis, comprising administering to a mammal in need of such treatment an effective amount of a combination of a sulfur-substituted azetidinone cholesterol

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absorption inhibitor of formula I and a cholesterol biosynthesis inhibitor. That is, the present invention relates to the use of a sulfur-substituted azetidinone cholesterol absorption inhibitor of formula I for combined use with a cholesterol biosynthesis inhibitor (and, similarly, use of a cholesterol biosynthesis inhibitor for combined use with a sulfur-substituted azetidinone cholesterol absorption inhibitor of formula I) to treat or prevent atherosclerosis or to reduce plasma cholesterol levels.

In yet another aspect, the invention relates to a pharmaceutical composition comprising an effective amount of a sulfur-substituted azetidinone cholesterol absorption inhibitor of formula I, a cholesterol biosynthesis inhibitor, and a pharmaceutically acceptable carrier. In a final aspect, the invention relates to a kit comprising in one container an effective amount of a sulfur-substituted azetidinone cholesterol absorption inhibitor of formula I in a pharmaceutically acceptable carrier, and in a separate container, an effective amount of a cholesterol biosynthesis inhibitor in a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION

As used herein, the term "lower alkyl" means straight or branched alkyl chains of 1 to 6 carbon atoms.

"Aryl" means phenyl, naphthyl, indenyl, tetrahydronaphthyl or indenyl.

"Heteroaryl" means pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl. All positional isomers wherein the heteroaryl ring is attached through a carbon atom are contemplated, e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl, and 2-thienyl and 3-thienyl. "Halogeno" means fluorine, chlorine, bromine or iodine atoms.

The above statement, wherein R⁶, R⁷ and R⁸ are said to be independently selected from a group of substituents, means that R⁶, R⁷ and R⁸ are independently selected, but also that where an R⁶, R⁷ or R⁸ variable occurs more than once in a molecule, those occurrences are independently selected (e.g., if R is —OR⁶ wherein R⁶ is hydrogen, R⁶ can be —OR⁶ wherein R⁶ is lower alkyl).

Compounds of the invention have at least one asymmetric atom and therefore all isomers, including enantiomers and diastereomers are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting chiral starting materials or by separating isomers of a compound of formula I. Isomers may also include geometric isomers, e.g., when a double bond is present. All such geometric isomers are contemplated for this invention.

Those skilled in the art will appreciate that for some compounds of formula I, one isomer will show greater pharmacological activity than another isomer.

Compounds of the invention with an amino group can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in

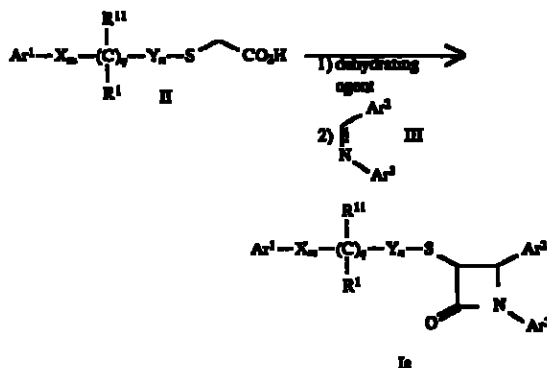
polar solvents, but the salt is otherwise equivalent to its respective free base form for purposes of the invention.

Certain compounds of the invention are acidic (e.g., those compounds which possess a carboxyl group). These compounds form pharmaceutically acceptable salts with inorganic and organic bases. Examples of such salts are the sodium, potassium, calcium, aluminum, gold and silver salts. Also included are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Cholesterol biosynthesis inhibitors for use in the combination of the present invention include HMG CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin, and CI-981; HMG CoA synthetase inhibitors, for example L-659,699 ((R,E)-11-[3R-(hydroxymethyl)-4-oxo-2R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid); squalene synthase inhibitors, for example squalenstatin I; and squalene epoxidase inhibitors, for example, NB598 ((R)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride) and other cholesterol biosynthesis inhibitors such as DMP-565. Preferred HMG CoA reductase inhibitors are lovastatin, pravastatin and simvastatin.

Compounds of formula I can be prepared by known methods, for example those described below.

Method A:



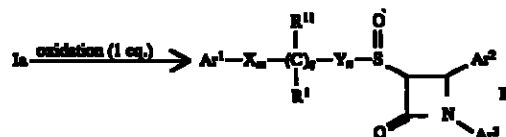
Compounds of formula I wherein r is zero, R^{11} is a protected hydroxy group, wherein the protecting groups are as defined below in Table 1, and the remaining variables are as defined above, i.e., compounds of formula Ia, can be prepared according to the above reaction scheme, wherein a carboxylic acid of formula II is reacted with an imine of formula III in the presence of a base such as triethylamine and a suitable dehydrating agent such as dimethylphosphorimidous dichloride. The resultant compound is treated with an acid such as hydrofluoric acid to obtain the thio compound of formula Ia. When the protected hydroxy group R^{11} is an alkoxy or benzyloxy group, such a protecting group need not be removed to obtain a compound of formula I, but other protecting groups can be removed using conventional techniques to obtain compounds of formula I wherein R is hydroxy.

Compounds wherein R is hydroxy can be converted by well known techniques to other compounds of formula I wherein R is functionalized, i.e., it is $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^9$, or $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, wherein R^6 , R^7 and R^9 are as defined above and R^6 is lower alkyl, aryl, or aryl-lower alkyl. For example, treatment of the alcohol with an alkyl halide in the presence of a suitable base such as NaH

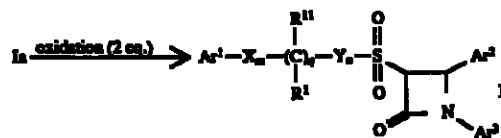
will afford alkoxy-substituted compounds (i.e., R or R^2 is OR^6 , wherein R^6 is lower alkyl); treatment of the alcohol with an acylating agent such as acetylchloride will result in compounds wherein R or R^2 is $-\text{O}(\text{CO})\text{R}^6$; treatment of the alcohol with phosgene followed by an alcohol of the formula HOR^9 affords compounds substituted with a $-\text{O}(\text{CO})\text{OR}^9$ group; and treatment of the alcohol with phosgene followed by an amine of the formula HNR^6R^7 affords compounds wherein R or R^2 is $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$.

Compounds of formula Ia wherein q is 1, and R and R^1 form an $=\text{O}$ group can be converted to the corresponding compounds wherein R^1 is hydrogen and R is OH by treatment with a reducing agent such as sodium borohydride.

To prepare the corresponding sulfinyl compounds, i.e., compounds of formula I wherein r is 1, and the remaining variables are as defined above (compounds of formula Ib), treat the hydroxy-protected thio compound of formula Ia with 1 equivalent of an oxidant such as a peracid, e.g., *m*-chloroperoxybenzoic acid, or sodium metaperiodate:

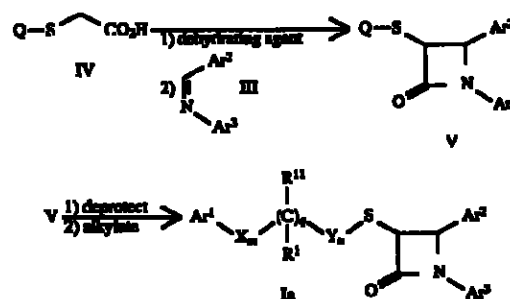


To prepare the corresponding sulfonyl compounds, i.e., compounds of formula I wherein r is 2, and the remaining variables are as defined above (compounds of formula Ic), treat the hydroxy-protected thio compound of formula Ia with 2 equivalents of an oxidant as described above:



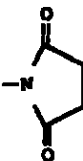
Compounds of formulae Ib and Ic can be deprotected at R^{11} as necessary to obtain compounds of formula I.

Method B:



Compounds of formula Ia, wherein the variables are as defined above, can be prepared by reacting a protected mercaptoacetic acid of formula IV, wherein Q is a sulfur-protecting group such as benzyl or substituted-benzyl, with an imine as described in Method A. The protecting group Q is then removed, and the mercapto group is alkylated with a compound of the formula

TABLE 1-continued

Group to be Protected	Group to be Protected and Protecting Group
-NH ₂	
-OH	$ \begin{array}{c} \text{CH}_3 \\ \\ -\text{OCH}_3, -\text{OCH}_2\text{OCH}_3, -\text{O}-\text{C}(\text{CH}_3)_2 \\ \\ \text{CH}_3 \end{array} $ -OSi(CH₃)₃, or -OCH₂phenyl

We have found that the compounds of this invention lower serum lipid levels, in particular serum cholesterol levels. Compounds of this invention have been found to inhibit the intestinal absorption of cholesterol and to significantly reduce the formation of liver cholesterol esters in animal models. Thus, compounds of this invention are hypocholesterolemic agents by virtue of their ability to inhibit the intestinal absorption and/or esterification of cholesterol; they are, therefore, useful in the treatment and prevention of atherosclerosis in mammals, in particular in humans.

The in vivo activity of the compounds of formula I can be determined by the following procedure:

In Vivo Assay of Hypolipidemic Agents Using the Hyperlipidemic Hamster

Hamsters are separated into groups of six and given a controlled cholesterol diet (Purina Chow #5001 containing 0.5% cholesterol) for seven days. Diet consumption is monitored to determine dietary cholesterol exposure in the face of test compounds. The animals are dosed with the test compound once daily beginning with the initiation of diet. Dosing is by oral gavage of 0.2 mL of corn oil alone (control group) or solution (or suspension) of test compound in corn oil. All animals moribund or in poor physical condition are euthanized. After seven days, the animals are anesthetized by intramuscular (IM) injection of ketamine and sacrificed by decapitation. Blood is collected into vacutainer tubes containing EDTA for plasma lipid analysis and the liver excised for tissue lipid analysis. Lipid analysis is conducted as per published procedures (Schnitzler-Polokoff, R., et al. *Comp. Biochem. Physiol.* 99A, 4 (1991), p. 665-670) and data is reported as percent reduction of lipid versus control.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier. The compounds of formula I can be administered in any conventional dosage form, preferably an oral dosage form such as a capsule, tablet, powder, cachet, suspension or solution. The formulations and pharmaceutical compositions can be prepared using conventional pharmaceutically acceptable excipients and additives and conventional techniques. Such pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.

The daily hypocholesterolemic dose of a compound of formula I is about 0.1 to about 30 mg/kg of body weight per day, preferably about 0.1 to about 15 mg/kg. For an average body weight of 70 kg, the dosage level is therefore from about 5 mg to about 1000 mg of drug per day, given in a

single dose or 2-4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

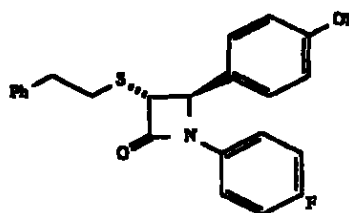
For the combinations of this invention wherein the sulfur-substituted azetidinone is administered in combination with a cholesterol biosynthesis inhibitor, the typical daily dose of the cholesterol biosynthesis inhibitor is 0.1 to 80 mg/kg of mammalian weight per day administered in single or divided dosages, usually once or twice a day; for example, for HMG CoA reductase inhibitors, about 10 to about 40 mg per dose is given 1 to 2 times a day, giving a total daily dose of about 10 to 80 mg per day, and for the other cholesterol biosynthesis inhibitors, about 1 to 1000 mg per dose is given 1 to 2 times a day, giving a total daily dose of about 1 mg to about 2000 mg per day. The exact dose of any component of the combination to be administered is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

Where the components of a combination are administered separately, the number of doses of each component given per day may not necessarily be the same, e.g. where one component may have a greater duration of activity, and will therefore need to be administered less frequently.

Since the present invention relates to the reduction of plasma cholesterol levels by treatment with a combination of active ingredients wherein said active ingredients may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. That is, a kit is contemplated wherein two separate units are combined: a cholesterol biosynthesis inhibitor pharmaceutical composition and a sulfur-substituted azetidinone cholesterol absorption inhibitor pharmaceutical composition. The kit will preferably include directions for the administration of the separate components. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g. oral and parenteral) or are administered at different dosage intervals.

Following are examples of preparing compounds of formula I. The terms cis and trans refer to the relative orientations at the azetidinone 3- and 4-positions unless otherwise indicated. The term "J" refers to the proton NMR coupling constant in hertz (Hz) between the 3- and 4-substituted protons of the azetidinone. CD spectra were obtained as solutions in methanol.

EXAMPLE 1

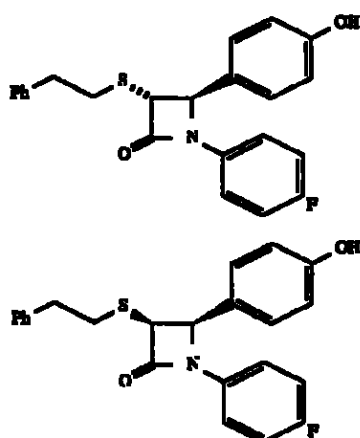


Step 1: Heat a mixture of 4-fluoroaniline (128 ml) and 4-*t*-butyldimethylsiloxy benzaldehyde (290 g) in toluene (1.2 L) to reflux under a Dean-Stark trap. After 24 h, concentrate in vacuo and dissolve the residue in warm hexane (0.2 L). Cool to -20° C. and collect the resultant imine (378 g, 94% yield) by filtration; mp 51.4°-52.2° C.

Step 2: To a mixture of phenethylmercapto acetic acid (0.55 g) [prepared in two steps by i) reaction of phenethyl mercaptan and ethyl bromoacetate and ii) saponification with ethanolic aqueous NaOH], the imine prepared in step

1 and triethylamine (TEA) (1.2 ml) in CH_2Cl_2 (20 ml), add dimethylaminophosphoryldichloride at 0°C . Stir overnight while allowing the reaction to warm to room temperature (rt). Partition the mixture between ethyl acetate (EtOAc) and 10% NaHCO_3 . Wash (H_2O), dry (MgSO_4) and concentrate the organic layer, then purify the residue by flash chromatography on silica using hexane/EtOAc (20:1) to obtain a yellow oil (0.48 g, 34%). Resolve this oil by HPLC with a Chiralcel OD column using hexane/isopropyl alcohol (66:1) and collect the second peak.

Step 3: Treat the product of step 2 (215 mg) in CH_3CN (21 ml) at 0°C with 48% HF (2.5 ml). Stir overnight while allowing the reaction to warm to rt. Partition the mixture between ether (Et_2O) and cold water and wash the organic layers with 10% NaHCO_3 and water. Dry (MgSO_4) and concentrate the organic layer and purify the residue by flash chromatography on silica using hexane/EtOAc (5:1) to collect the title compound (1) as a colorless solid (0.16 g, 96%). SIMS 394 (M+H), 256 (100%); Elemental analysis calculated for $\text{C}_{23}\text{H}_{20}\text{NO}_2\text{SF}_0.25\text{H}_2\text{O}$: C 69.41, H 5.19, N 3.52; found C 69.42, H 5.26, N 3.45; $[\alpha]_D^{25} = +44.8^\circ$ (1.25 mg/ml CH_3OH); $^1\text{H NMR}$ CDCl_3 : 2.95 (m, 4H), 3.93 (d, J=2.4 Hz, 1H), 4.67 (d, J=2.4 Hz, 1H), 5.06 (s, 1H), 6.85 (d, 1H), 6.92 (dd, 2H), 7.15–7.3 (9H). Method B:



Step 1: Add dropwise a solution of chloroacetyl chloride (9.76 ml) in CH_2Cl_2 (110 ml) to a 0°C solution of (S)-4-phenyl oxazolidinone (10.0 g), TEA (35 ml) and dimethylaminopyridine (DMAP) (0.5 g) in CH_2Cl_2 (150 ml). Gradually warm the reaction to rt, then add silica gel (approx. 50 g) and concentrate in vacuo. Purify the residue by flash chromatography on silica using EtOAc/hexane (1:4) to give a colorless solid (11.3 g, 77%).

Step 2: Add phenethyl mercaptan to a solution of the product of step 1 (6.0 g) and TEA (5.1 ml) in CH_2Cl_2 (0.1 l). Stir at rt for 16 h, then add silica gel (approx 50 gm) and concentrate in vacuo. Purify the residue by flash chromatography on silica using EtOAc/hexane (1:4) to give a colorless solid (7.81 g, 92%) which can be crystallized from EtOAc/hexane (1:4).

Step 3: Add titanium tetrakisopropoxide (7.5 ml) to a stirring solution of TiCl_4 (75 ml of 1N TiCl_4 in CH_2Cl_2) in CH_2Cl_2 (200 ml) at 0°C . After 15 min., add the product of step 2 (34.1 g), and 5 min. later add the imine from Method A, step 1 (66 g). Cool the reaction to -40°C , wait 20 min., and add diisopropyl ethylamine (35 ml). After 15 h at -40°C , cool the reaction to -70°C and add isopropyl alcohol (250 ml). Gradually warm to rt over 6

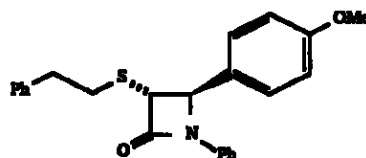
h, then add 0.1N HCl (500 ml) and partition the reaction mixture with Et_2O . Wash (H_2O) and dry (MgSO_4) the organic layer, concentrate, and purify the residue by crystallization from CH_3OH to give a colorless solid (30.9 g, 46%).

Step 4: Heat a solution of the product of step 3 (10 g) in toluene (0.5 l) to 90°C and add N,O-bis(trimethylsilyl)acetamide (BSA) (7.4 ml). After 1 h, cool the reaction to 45°C and add tetrabutylammonium fluoride (TBAF) (0.47 g). Periodically over the next 18 hr add additional BSA (a total of 3 molar equivalents) and continue stirring at 45°C . After a total time of 24 h, dilute the reaction with CH_3OH (150 ml) and stir at rt for 1 h. Concentrate the mixture in vacuo and purify by flash chromatography on silica using hexane/EtOAc (10:1) to elute the trans isomer. Continue to elute with hexane/EtOAc 5:1 to give the cis isomer.

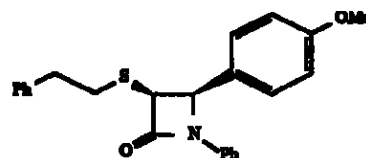
Step 5: Separately treat solutions of the trans and cis isomers from step 4 in CH_3CN with aqueous HF according to the procedure of Method A, step 3, to give the trans and cis anisidones 1 and 1a, respectively.

1a: SIMS 394(M+H) 100%; Elemental analysis calculated for $\text{C}_{23}\text{H}_{20}\text{NO}_2\text{SF}$: C 70.21, H 5.13, N 3.56, S 8.15; found C 70.33, H 5.43, N 3.71, S 8.20. $^1\text{H NMR}$ CDCl_3 : 2.78 (m, 4H), 4.52 (d, J=5 Hz, 1H), 5.23 (d, J=5 Hz, 1H), 6.82–7.3 (13H).

Using the procedure described in Example 1, method B, steps 3 and 4, use 4-methoxybenzylidene anisidine to prepare the following compounds:

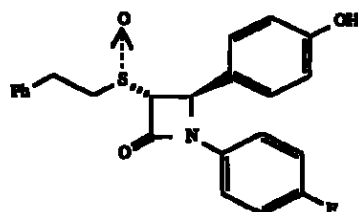


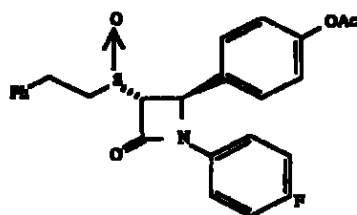
1b: Elemental analysis calculated for $\text{C}_{24}\text{H}_{22}\text{NO}_2\text{S}$: C 74.01, H 5.95, N 3.6, S 8.22; found C 74.19, H 6.0, N 3.73, S 8.03; $[\theta]_{232\text{nm}} = +3.4 \times 10^4$, $[\theta]_{248\text{nm}} = -3.07 \times 10^4$; $^1\text{H NMR}$ CDCl_3 : 2.95 (m, 4H), 3.82 (s, 3H), 3.95 (d, J=2.2 Hz, 1H), 4.72 (d, J=2.2 Hz, 1H), 6.9–7.3 (14H); SIMS 390(M+H), 252 (100%).



1c: $^1\text{H NMR}$ CDCl_3 : 2.78 (m, 4H), 3.8 (s, 3H), 4.53 (d, J=5.5 Hz, 1H), 5.27 (d, J=5.5 Hz, 1H), 6.9–7.3 (14H).

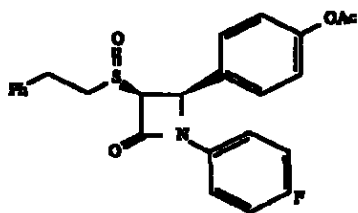
EXAMPLE 2



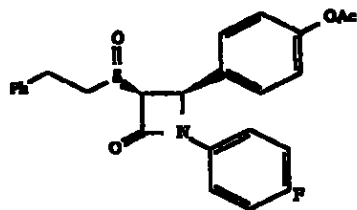
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EXAMPLE 4

Treat compound 2b (60 mg) in CH_2Cl_2 (5 ml) with TEA (0.025 ml) and acetic anhydride (0.017 ml). After 2 h, concentrate the reaction mixture and purify the residue by flash chromatography on silica using EtOAc/hexane (1:1), to give a white solid. Elemental analysis calculated for $\text{C}_{22}\text{H}_{22}\text{NO}_2\text{SF}$: C 66.5, H 4.91, N 3.1, S 7.1; found C 66.28, H 5.10, N 3.29, S 6.99.

Use the above procedure for preparing compound 4 with compounds 2c and 2d to obtain the following products 4a and 4b, respectively:

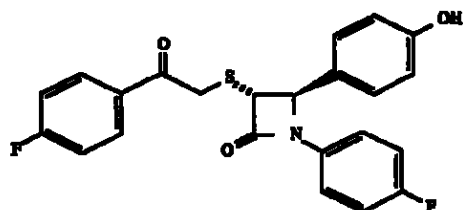


4a: Elemental analysis calculated for $\text{C}_{22}\text{H}_{22}\text{NO}_2\text{SF}$: C 66.5, H 4.91, N 3.1, S 7.1; found C 66.36, H 5.13, N 3.23, S 7.02; ^1H NMR CDCl_3 : 2.32 (s, 3H), 2.92 (m, 2H), 3.14 (m, 1H), 3.7 (m, 1H), 4.42 (d, $J=5.7$ Hz, 1H), 5.38 (d, $J=5.8$ Hz, 1H), 7.0 (m, 2H), 7.12–7.35 (9H), 7.44 (d, 2H).



4b: ^1H NMR CDCl_3 : 2.32 (s, 3H), 3.15 (m, 3H), 3.38 (m, 1H), 4.72 (d, $J=5.3$ Hz, 1H), 5.58 (d, $J=5.3$ Hz, 1H), 7.0 (m, 2H), 7.15–7.35 (9H), 7.40 (d, 2H).

EXAMPLE 5



Step 1: Add TEA (14 ml) to a mixture of 4-methoxybenzylchloride (13 ml) and ethyl-2-mercaptoacetate (10 ml) in CH_2Cl_2 (0.2 L) under N_2 . After 48 h, dilute the reaction with Et_2O (0.5 L) and sequentially wash the organic phase with 0.3N HCl (3x) and 10% NaHCO_3 . Dry and concentrate the organic layer to give an

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oil (22 g). Dissolve a portion of the oil (5 g) in THF (75 ml) and water (75 ml) and add LiOH (1 g). After stirring for 72 h, dilute the reaction with water (0.15 L) and extract with hexane (0.2 L). Acidify the aqueous phase with 1N HCl and extract with EtOAc. Wash (H_2O), and dry (MgSO_4) the organic layer and concentrate to give a yellow solid (4.25 g, 96%).

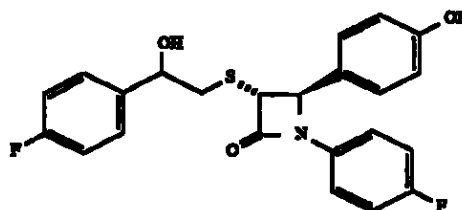
Step 2: Treat a mixture of the product of step 1 (1 g) and the imine from Example 1, Method A, step 1 (1.55 g) in CH_2Cl_2 (40 ml) with dimethylamino phosphorylchloride (0.56 ml) at 0°C . Warm to rt and stir for 16 h. Dilute the reaction with Et_2O (100 ml) and wash sequentially with 1N HCl, 10% NaHCO_3 , and brine. Dry (MgSO_4) and concentrate the organic phase and purify the resultant residue by flash chromatography on silica using hexane:EtOAc (20:1) to yield an oil (0.75 g, 30%).

Step 3: Add mercuric acetate (121 mg) to a solution of the product of step 2 (0.2 g) in trifluoroacetic acid (5 ml) at 0°C . After 15 min., partition the reaction mixture between H_2O and Et_2O . Wash, dry and concentrate the organic layer and purify the residue by flash chromatography on silica using hexane:EtOAc (10:1) to give an oil (0.15 g).

Step 4: Add 2-bromo-4'-fluoroacetophenone (86 mg) to a mixture of the product of step 3 (0.15 g) and TEA (0.06 ml) in CH_2Cl_2 (5 ml) at rt under N_2 . After 5 h, dilute the reaction with Et_2O and wash sequentially with 1N HCl, 10% NaHCO_3 , and brine. Dry and concentrate the organic layer and purify the residue by flash chromatography on silica using hexane:EtOAc (9:1) to give an oil. Resolve this by HPLC using a Chiralcel AS column with hexane:IPA (85:15) to elute enantiomer 5(1) ([α] 228 $\text{mM}=-3.77\times 10^3$, [6] 244 $\text{mM}=-3.34\times 10^3$) and then enantiomer 5(2) ([α] 228 $\text{mM}=-3.65\times 10^3$, [6] 244 $\text{mM}=-3.24\times 10^3$).

Step 5: Treat enantiomer 5(2) with HF according to the procedure of Example 1, Method A, step 3, to obtain compound 5. Elemental analysis calculated for $\text{C}_{22}\text{H}_{17}\text{NO}_2\text{SF}_2$: C 64.93, H 4.03, N 3.29, S 7.52; found C 64.87, H 4.39, N 3.31, S 7.25.

EXAMPLE 6



6a (diastereomer a)
6b (diastereomer b)

Step 1: Add NaBH_4 (28 mg) to a solution of enantiomer 5(2) from step 4 of Example 5 (0.4 g) in CH_3OH (20 ml). After 2 h, partition the reaction mixture between Et_2O and H_2O . Dry and concentrate the organic layers and purify the residue by flash chromatography using EtOAc:hexane (1:6) to give diastereomers 6(1) and 6(2).

Step 2: Individually treat diastereomers 6(1) and 6(2) from step 1 with HF according to the procedure of Example 1, Method A, step 3, to obtain 6a and 6b.

6a: ^1H NMR in CDCl_3 : 2.85 (dd, $J=6, 12$ Hz, 1H), 3.04 (dd, $J=3, 12$ Hz, 1H), 4.06 (d, $J=2.4$ Hz, 1H), 4.7 (d, $J=2.4$ Hz, 1H), 4.9 (d, $J=3, 9$ Hz, 1H), 6.85–7.35 (12H).

6b: ^1H NMR in CDCl_3 : 3.01 (m, 2H), 3.97 (d, $J=2.2$ Hz, 1H), 4.7 (d, $J=2.2$ Hz, 1H), 4.92 (d, $J=4, 8$ Hz, 1H), 6.85–7.36 (12 H).

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

R^6 , R^7 and R^9 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl; and

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

2. A compound of claim 1 wherein q is zero.

3. A compound of claim 1 wherein q is 1.

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

5. A compound of claim 2 wherein X and Y are each $-\text{CH}_2-$ and the sum of m and n is 2, 3 or 4.

6. A compound of claim 4 wherein X and Y are each $-\text{CH}_2-$, and the sum of m and n is 2, 3 or 4.

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

8. A compound of claim 3 wherein X and Y are each $-\text{CH}_2-$ and the sum of m and n is 1, 2 or 3.

9. A compound of claim 3 wherein R^1 is hydrogen and R is $-\text{OR}^6$, wherein R^6 is hydrogen, or wherein R and R^1 together form a $-\text{O}$ group.

10. A compound of claim 7 wherein X and Y are each $-\text{CH}_2-$; the sum of m and n is 1, 2 or 3; and R^1 is hydrogen

and R is $-\text{OR}^6$, wherein R^6 is hydrogen, or wherein R and R^1 together form a $-\text{O}$ group.

11. A compound of claim 10 wherein m is zero and n is 1.

12. A method of lowering serum cholesterol levels in a mammal in need of such treatment comprising administering an effective amount of a compound of claim 1.

13. A pharmaceutical composition comprising a cholesterol-lowering effective amount of a compound of claim 1 in a pharmaceutically acceptable carrier.

14. A compound of claim 3 selected from the group consisting of

(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; and

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

15. A compound selected from the group consisting of (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; and

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

* * * * *

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396.



US005744467A

United States Patent [19]

McKittrick et al.

[11] Patent Number: 5,744,467

[45] Date of Patent: Apr. 28, 1998

[54] SULFUR-SUBSTITUTED AZETIDINONE
COMPOUNDS USEFUL AS
HYPOCHOLESTEROLEMIC AGENTS[75] Inventors: Brian A. McKittrick, Bloomfield;
Sandeep Dagar, Bridgewater; Duane
A. Burnett, Fanwood, all of N.J.

[73] Assignee: Schering Corporation

[21] Appl. No.: 813,585

[22] Filed: Jan. 8, 1997

Related U.S. Application Data

[60] Division of Ser. No. 463,619, Jan. 5, 1995, Pat. No. 5,633,
246, which is a continuation-in-part of Ser. No. 342,197,
Nov. 18, 1994, Pat. No. 5,624,920.[51] Int. Cl.⁶ A61K 31/395; C07D 205/08

[52] U.S. Cl. 514/210; 540/359

[58] Field of Search 540/359; 514/210

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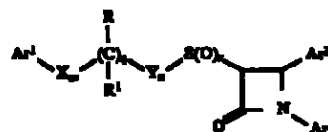
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Primary Examiner—C. Warren Ivy

Assistant Examiner—D. Margaret M. Mach

Attorney Agent, or Firm—Anita W. Magatti

[57] ABSTRACT

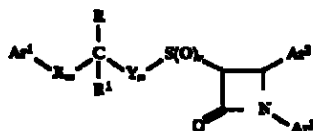
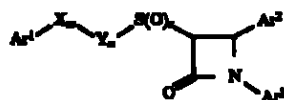
Sulfur-substituted azetidinone hypocholesterolemic agents
of the formulaor a pharmaceutically acceptable salt thereof are disclosed,
as well as pharmaceutical compositions containing them,
and a method of lowering serum cholesterol by administer-
ing said compounds, alone or in combination with a cho-
lesterol biosynthesis inhibitor.

12 Claims, No Drawings

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R^9 is lower alkyl, aryl or aryl-substituted lower alkyl; and R^{10} is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^6$, $-NR^6(CO)OR^6$, $-NR^6(CO)NR^6R^7$, $-NR^6SO_2R^6$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{1-2}R^6$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, $-CF_3$, $-CN$, $-NO_2$ and halogen.

Within the scope of formula I, there are two preferred structures. In formula IA, q is zero and the remaining variables are as defined above, and in formula IB, q is 1 and the remaining variables are as defined above:



R^4 , R^5 and R^{10} are each preferably 1-3 independently selected substituents. Preferred are compounds of formula I wherein Ar^1 is phenyl, R^{10} -substituted phenyl or thienyl, especially (4- R^{10})-substituted phenyl or thienyl. Ar^2 is preferably R^5 -substituted phenyl, especially (4- R^5)-substituted phenyl. Ar^3 is preferably phenyl or R^4 -substituted phenyl, especially (4- R^4)-substituted phenyl. When Ar^1 is R^{10} -substituted phenyl, R^{10} is preferably halogeno, especially fluoro. When Ar^2 is R^5 -substituted phenyl, R^5 is preferably $-OR^6$, especially wherein R^6 is hydrogen or lower alkyl. When Ar^3 is R^4 -substituted phenyl, R^4 is preferably halogeno, especially fluoro. Especially preferred are compounds of formula I wherein Ar^1 is phenyl, 4-fluorophenyl or thienyl, Ar^2 is 4-(alkoxy or hydroxy)phenyl, and Ar^3 is phenyl or 4-fluorophenyl.

X and Y are each preferably $-\text{CH}_2-$. The sum of m , n and q is preferably 2, 3 or 4, more preferably 2. When q is 1, n is preferably 1 to 5.

Preferences for X, Y, Ar^1 , Ar^2 and Ar^3 are the same in each of formulae IA and IB.

In compounds of formula IA, the sum of m and n is preferably 2, 3 or 4, more preferably 2. Also preferred are compounds wherein the sum of m and n is 2, and r is 0 or 1.

In compounds of formula IB, the sum of m and n is preferably 1, 2 or 3, more preferably 1. Especially preferred are compounds wherein m is zero and n is 1. R^1 is preferably hydrogen and R is preferably $-OR^6$ wherein R^6 is hydrogen, or a group readily metabolizable to a hydroxyl (such as $-O(CO)R^6$, $-O(CO)OR^6$ and $-O(CO)NR^6R^7$, defined above), or R and R^1 together form a $=O$ group.

This invention also relates to a method of lowering the serum cholesterol level in a mammal in need of such treatment comprising administering an effective amount of a compound of formula I. That is, the use of a compound of the present invention as an hypocholesterolemic agent is also claimed.

In still another aspect, the present invention relates to a pharmaceutical composition comprising a serum cholesterol-lowering effective amount of a compound of formula I in a pharmaceutically acceptable carrier.

The present invention also relates to a method of reducing plasma cholesterol levels, and to a method of treating or

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preventing atherosclerosis, comprising administering to a mammal in need of such treatment an effective amount of a combination of a sulfur-substituted azetidinone cholesterol absorption inhibitor of formula I and a cholesterol biosynthesis inhibitor. That is, the present invention relates to the use of a sulfur-substituted azetidinone cholesterol absorption inhibitor of formula I for combined use with a cholesterol biosynthesis inhibitor (and, similarly, use of a cholesterol biosynthesis inhibitor for combined use with a sulfur-substituted azetidinone cholesterol absorption inhibitor of formula I) to treat or prevent atherosclerosis or to reduce plasma cholesterol levels.

In yet another aspect, the invention relates to a pharmaceutical composition comprising an effective amount of a sulfur-substituted azetidinone cholesterol absorption inhibitor of formula I, a cholesterol biosynthesis inhibitor, and a pharmaceutically acceptable carrier. In a final aspect, the invention relates to a kit comprising in one container an effective amount of a sulfur-substituted azetidinone cholesterol absorption inhibitor of formula I in a pharmaceutically acceptable carrier, and in a separate container, an effective amount of a cholesterol biosynthesis inhibitor in a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION

As used herein, the term "lower alkyl" means straight or branched alkyl chains of 1 to 6 carbon atoms.

"Aryl" means phenyl, naphthyl, indenyl, tetrahydronaphthyl or indenyl.

"Heteroaryl" means pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrimidinyl, pyrimidinyl or pyridazinyl. All positional isomers wherein the heteroaryl ring is attached through a carbon atom are contemplated, e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl, and 2-thienyl and 3-thienyl. "Halogeno" means fluorine, chlorine, bromine or iodine atoms.

The above statement, wherein R^6 , R^7 and R^8 are said to be independently selected from a group of substituents, means that R^6 , R^7 and R^8 are independently selected, but also that where an R^6 , R^7 or R^8 variable occurs more than once in a molecule, those occurrences are independently selected (e.g., if R is $-OR^6$ wherein R^6 is hydrogen, R^6 can be $-OR^6$ wherein R^6 is lower alkyl).

Compounds of the invention have at least one asymmetric atom and therefore all isomers, including enantiomers and diastereomers are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting chiral starting materials or by separating isomers of a compound of formula I. Isomers may also include geometric isomers, e.g. when a double bond is present. All such geometric isomers are contemplated for this invention.

Those skilled in the art will appreciate that for some compounds of formula I, one isomer will show greater pharmacological activity than another isomer.

Compounds of the invention with an amino group can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aque-

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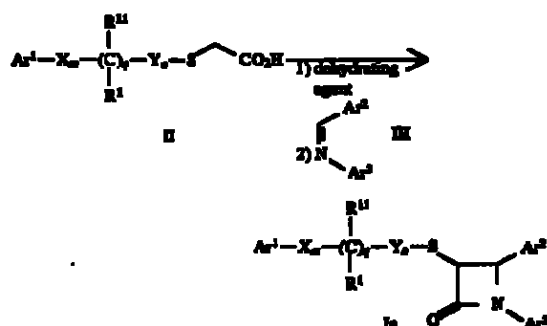
ous base solution such as dilute aqueous sodium bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in polar solvents, but the salt is otherwise equivalent to its respective free base form for purposes of the invention.

Certain compounds of the invention are acidic (e.g., those compounds which possess a carbonyl group). These compounds form pharmaceutically acceptable salts with inorganic and organic bases. Examples of such salts are the sodium, potassium, calcium, aluminum, gold and silver salts. Also included are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Cholesterol biosynthesis inhibitors for use in the combination of the present invention include HMG CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin, and CI-981; HMG CoA synthetase inhibitors, for example L-659,699 ((E,E)-11-[3'R-(hydroxy-methyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid); squalene synthesis inhibitors, for example squalostatins; and squalene epoxidase inhibitors, for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride) and other cholesterol biosynthesis inhibitors such as DMP-565. Preferred HMG CoA reductase inhibitors are lovastatin, pravastatin and simvastatin.

Compounds of formula I can be prepared by known methods, for example those described below.

Method A:



Compounds of formula I wherein r is zero, R^{11} is a protected hydroxy group, wherein the protecting groups are as defined below in Table 1, and the remaining variables are as defined above, i.e., compounds of formula Ia, can be prepared according to the above reaction scheme, wherein a carboxylic acid of formula II is reacted with an imine of formula III in the presence of a base such as triethylamine and a suitable dehydrating agent such as dimethylphosphorimidous dichloride. The resultant compound is treated with an acid such as hydrofluoric acid to obtain the thio compound of formula Ia. When the protected hydroxy group R^{11} is an alkoxy or benzyloxy group, such a protecting group need not be removed to obtain a compound of formula I, but other protecting groups can be removed using conventional techniques to obtain compounds of formula I wherein R is hydroxy.

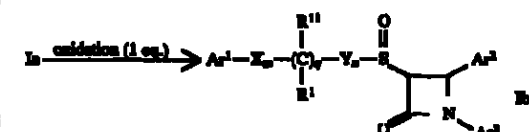
Compounds wherein R is hydroxy can be converted by well known techniques to other compounds of formula I wherein R is functionalized, i.e., it is $-\text{OR}^6$, $-\text{O}(\text{CO})\text{R}^6$, $-\text{O}(\text{CO})\text{OR}^6$, or $-\text{O}(\text{CO})\text{NR}^6\text{R}^7$, wherein R^6 , R^7 and R^8 are as defined above and R^6 is lower alkyl, aryl, or aryl-lower alkyl. For example, treatment of the alcohol with an alkyl halide in the presence of a suitable base such as NaH

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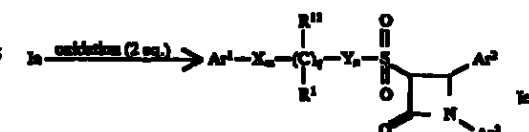
will afford alkoxy-substituted compounds (i.e., R or R^2 is OR^6 , wherein R^6 is lower alkyl); treatment of the alcohol with an acylating agent such as acetylchloride will result in compounds wherein R or R^2 is $-\text{OC}(\text{O})\text{R}^6$; treatment of the alcohol with phosgene followed by an alcohol of the formula HOR^6 affords compounds substituted with a $-\text{OC}(\text{O})\text{OR}^6$ group; and treatment of the alcohol with phosgene followed by an amine of the formula HNR^6R^7 affords compounds wherein R or R^2 is $-\text{OC}(\text{O})\text{NR}^6\text{R}^7$.

Compounds of formula Ia wherein q is 1, and R and R^1 form an $=\text{O}$ group can be converted to the corresponding compounds wherein R^1 is hydrogen and R is OH by treatment with a reducing agent such as sodium borohydride.

To prepare the corresponding sulfinyl compounds, i.e., compounds of formula I wherein r is 1, and the remaining variables are as defined above (compounds of formula Ib), treat the hydroxy-protected thio compound of formula Ia with 1 equivalent of an oxidant such as a peracid, e.g., m -chloroperoxybenzoic acid, or sodium metaperiodate:

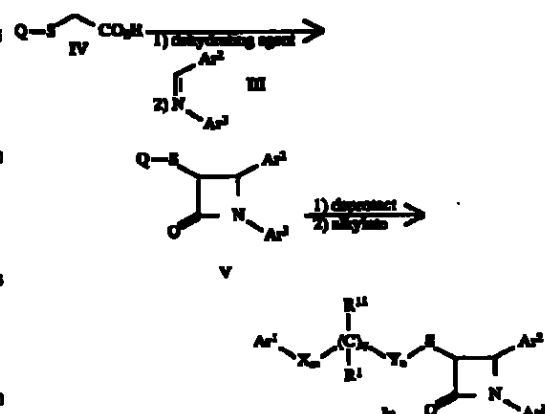


To prepare the corresponding sulfonyl compounds, i.e., compounds of formula I wherein r is 2, and the remaining variables are as defined above (compounds of formula Ic), treat the hydroxy-protected thio compound of formula Ia with 2 equivalents of an oxidant as described above:



Compounds of formulae Ib and Ic can be deprotected at R^{11} as necessary to obtain compounds of formula I.

Method B:



Compounds of formula Ia, wherein the variables are as defined above, can be prepared by reacting a protected mercaptocarboxylic acid of formula IV, wherein Q is a sulfur-protecting group such as benzyl or substituted-benzyl, with an imine as described in Method A. The protecting group Q

TABLE 1-continued

Group to be Protected	Group to be Protected and Protecting Group
-OH	$ \begin{array}{c} \text{CH}_3 \\ \\ -\text{OCH}_3, -\text{OCH}_2\text{OCH}_3, -\text{O}-\text{C}(\text{CH}_3)_2 \\ \\ \text{CH}_3 \end{array} $
	$-\text{OSi}(\text{CH}_3)_3$ or $-\text{OCH}_2\text{phenyl}$

We have found that the compounds of this invention lower serum lipid levels, in particular serum cholesterol levels. Compounds of this invention have been found to inhibit the intestinal absorption of cholesterol and to significantly reduce the formation of liver cholesterol esters in animal models. Thus, compounds of this invention are hypocholesterolemic agents by virtue of their ability to inhibit the intestinal absorption and/or esterification of cholesterol; they are, therefore, useful in the treatment and prevention of atherosclerosis in mammals, in particular in humans.

The in vivo activity of the compounds of formula I can be determined by the following procedure:

In Vivo Assay of Hypolipidemic Agents Using the Hyperlipidemic Hamster

Hamsters are separated into groups of six and given a controlled cholesterol diet (Purina Chow #5001 containing 0.5% cholesterol) for seven days. Diet consumption is monitored to determine dietary cholesterol exposure in the face of test compounds. The animals are dosed with the test compound once daily beginning with the initiation of diet. Dosing is by oral gavage of 0.2 mL of corn oil alone (control group) or solution (or suspension) of test compound in corn oil. All animals moribund or in poor physical condition are euthanized. After seven days, the animals are anesthetized by intramuscular (IM) injection of ketamine and sacrificed by decapitation. Blood is collected into vacutainer tubes containing EDTA for plasma lipid analysis and the liver excised for tissue lipid analysis. Lipid analysis is conducted as per published procedures (Schaffner-Polokoff, R., et al, *Comp. Biochem. Physiol.*, 99A, 4 (1991), p. 665-670) and data is reported as percent reduction of lipid versus control.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier. The compounds of formula I can be administered in any conventional dosage form, preferably an oral dosage form such as a capsule, tablet, powder, cachet, suspension or solution. The formulations and pharmaceutical compositions can be prepared using conventional pharmaceutically acceptable excipients and additives and conventional techniques. Such pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.

The daily hypocholesterolemic dose of a compound of formula I is about 0.1 to about 30 mg/kg of body weight per day, preferably about 0.1 to about 15 mg/kg. For an average body weight of 70 kg, the dosage level is therefore from about 5 mg to about 1000 mg of drug per day, given in a single dose or 2-4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

For the combinations of this invention wherein the sulfur-substituted azetidinone is administered in combination with

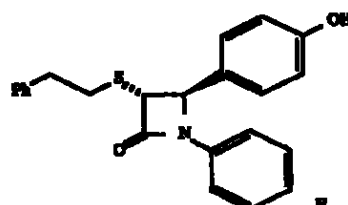
a cholesterol biosynthesis inhibitor, the typical daily dose of the cholesterol biosynthesis inhibitor is 0.1 to 80 mg/kg of mammalian weight per day administered in single or divided dosages, usually once or twice a day; for example, for HMG CoA reductase inhibitors, about 10 to about 40 mg per dose is given 1 to 2 times a day, giving a total daily dose of about 10 to 80 mg per day, and for the other cholesterol biosynthesis inhibitors, about 1 to 1000 mg per dose is given 1 to 2 times a day, giving a total daily dose of about 1 mg to about 2000 mg per day. The exact dose of any component of the combination to be administered is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

Where the components of a combination are administered separately, the number of doses of each component given per day may not necessarily be the same, e.g. where one component may have a greater duration of activity, and will therefore need to be administered less frequently.

Since the present invention relates to the reduction of plasma cholesterol levels by treatment with a combination of active ingredients wherein said active ingredients may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. That is, a kit is contemplated wherein two separate units are combined: a cholesterol biosynthesis inhibitor pharmaceutical composition and a sulfur-substituted azetidinone cholesterol absorption inhibitor pharmaceutical composition. The kit will preferably include directions for the administration of the separate components. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g. oral and parenteral) or are administered at different dosage intervals.

Following are examples of preparing compounds of formula I. The terms cis and trans refer to the relative orientations at the azetidinone 3- and 4-positions unless otherwise indicated. The term "J" refers to the proton NMR coupling constant in hertz (Hz) between the 3- and 4-substituted protons of the azetidinone. CD spectra were obtained as solutions in methanol.

EXAMPLE 1



Step 1:

Heat a mixture of 4-fluoroaniline (128 mL) and 4-tert-butylidimethyl-siloxy benzaldehyde (290 g) in toluene (1.2 L) to reflux under a Dean-Stark trap. After 24 h, concentrate in vacuo and dissolve the residue in warm hexane (0.2 L). Cool to -20° C. and collect the resultant imine (378 g, 94% yield) by filtration; mp 51.4°-52.2° C.

Step 2:

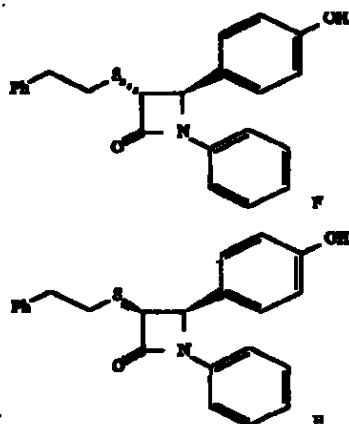
To a mixture of phenethylmercapto acetic acid (0.55 g) [prepared in two steps by i) reaction of phenethyl mercaptan and ethyl bromoacetate and ii) saponification with ethanolic aqueous NaOH], the imine prepared in step 1 and triethylamine (TEA) (1.2 mL) in CH₂Cl₂ (20 mL), add dimethylaminophosphoryldichloride at 0° C. Stir overnight while allowing the reaction to warm to room temperature (rt).

Partition the mixture between ethyl acetate (EtOAc) and 10% NaHCO₃. Wash (H₂O), dry (MgSO₄) and concentrate the organic layer, then purify the residue by flash chromatography on silica using hexane/EtOAc (20:1) to obtain a yellow oil (0.48 g, 34%). Resolve this oil by HPLC with a Chiralcel OD column using hexane/isopropyl alcohol (66:1) and collect the second peak.

Step 3:

Treat the product of step 2 (215 mg) in CH₃CN (21 ml) at 0° C. with 48% HF (2.5 ml). Stir overnight while allowing the reaction to warm to rt. Partition the mixture between ether (Et₂O) and cold water and wash the organic layers with 10% NaHCO₃ and water. Dry (MgSO₄) and concentrate the organic layer and purify the residue by flash chromatography on silica using hexane/EtOAc (5:1) to collect the title compound (1) as a colorless solid (0.16 g, 96%). SIMS 394 (M+H), 256 (100%); Elemental analysis calculated for C₂₀H₂₀NO₂SF_{0.25}H₂O: C 69.41, H 5.19, N 3.52; found C 69.42, H 5.26, N 3.45; [α]_D²⁵ = +44.8° (1.25 mg/ml CH₂OH); 1H NMR CDCl₃: 2.95 (m, 4H), 3.93 (d, J=2.4 Hz, 1H), 4.67 (d, J=2.4 Hz, 1H), 5.06 (s, 1H), 6.85 (d, 1H), 6.92 (dd, 2H), 7.15–7.3 (9H).

Method B:



Step 1:

Add dropwise a solution of chloroacetyl chloride (9.76 ml) in CH₂Cl₂ (110 ml) to a 0° C. solution of (S)-4-phenyl oxazolidinone (10.0 g), TEA (35 ml) and dimethylaminopyridine (DMAP) (0.5 g) in CH₂Cl₂ (150 ml). Gradually warm the reaction to rt, then add silica gel (approx. 50 g) and concentrate in vacuo. Purify the residue by flash chromatography on silica using EtOAc/hexane (1:4) to give a colorless solid (11.3 g, 77%).

Step 2:

Add phenethyl mercaptan to a solution of the product of step 1 (6.0 g) and TEA (5.1 ml) in CH₂Cl₂ (0.1 L). Stir at rt for 16 h, then add silica gel (approx 50 gm) and concentrate in vacuo. Purify the residue by flash chromatography on silica using EtOAc/hexane (1:4) to give a colorless solid (7.81 g, 92%) which can be crystallized from EtOAc/hexane (1:4).

Step 3:

Add titanium tetrakisopropoxide (7.5 ml) to a stirring solution of TiCl₄ (75 ml of 1N TiCl₄ in CH₂Cl₂) in CH₂Cl₂ (200 ml) at 0° C. After 15 min., add the product of step 2 (34.1 g), and 5 min. later add the imine from Method A, step 1 (66 g). Cool the reaction to -40° C., wait 20 min. and add diisopropyl ethylamine (35 ml). After 15 h at -40° C., cool the reaction to -70° C. and add isopropyl alcohol (250 ml). Gradually warm to rt over 6 h, then add 0.1N HCl (500 ml)

and partition the reaction mixture with H₂O. Wash (H₂O) and dry (MgSO₄) the organic layer, concentrate, and purify the residue by crystallization from CH₂OH to give a colorless solid (30.9 g, 46%).

Step 4:

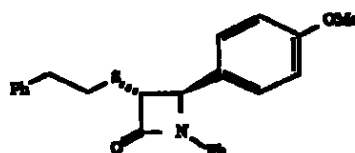
Heat a solution of the product of step 3 (10 g) in toluene (0.5 l) to 90° C. and add N,O-bis(trimethylsilyl)acetamide (BSA) (7.4 ml). After 1 h, cool the reaction to 45° C. and add tetrabutylammonium fluoride (TBAF) (0.47 g). Periodically over the next 18 hr add additional BSA (a total of 3 molar equivalents) and continue stirring at 45° C. After a total time of 24 h, dilute the reaction with CH₂OH (150 ml) and stir at rt for 1 h. Concentrate the mixture in vacuo and purify by flash chromatography on silica using hexane/EtOAc (10:1) to elute the trans isomer. Continue to elute with hexane/EtOAc 5:1 to give the cis isomer.

Step 5:

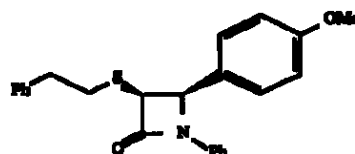
Separately treat solutions of the trans and cis isomers from step 4 in CH₃CN with aqueous HF according to the procedure of Method A, step 3, to give the trans and cis azetidinones 1 and 1a, respectively.

1a: CIMS 394(M+H) 100%; Elemental analysis calculated for C₂₀H₂₀NO₂SF: C 70.21, H 5.13, N 3.56, S 8.15; found C 70.33, H 5.43, N 3.71, S 8.20. 1H NMR CDCl₃: 2.78 (m, 4H), 4.52 (d, J=5 Hz, 1H), 5.23 (d, J=5 Hz, 1H), 6.82–7.3 (13H).

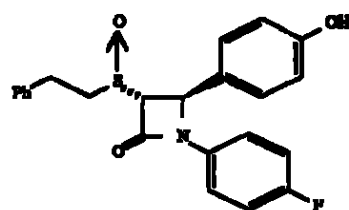
Using the procedure described in Example 1, method B, steps 3 and 4, use 4-methoxybenzylidene azetidine to prepare the following compounds:



1b: Elemental analysis calculated for C₂₀H₂₀NO₂S: C 74.01, H 5.95, N 3.6, S 8.22; found C 74.19, H 6.0, N 3.73, S 8.03; [θ] 232 nm = +3.4 × 10⁴, [θ] 248 nm = -3.07 × 10⁴; 1H NMR CDCl₃: 2.95 (m, 4H), 3.82 (s, 3H), 3.95 (d, J=2.2 Hz, 1H), 4.72 (d, J=2.2 Hz, 1H), 6.9–7.3 (14H); SIMS 390(M+H), 252 (100%).



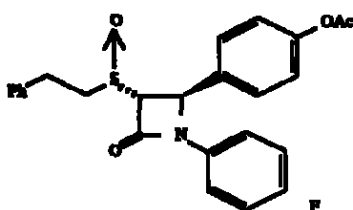
1c: 1H NMR CDCl₃: 2.78 (m, 4H), 3.8 (s, 3H), 4.53 (d, J=5.5 Hz, 1H), 5.27 (d, J=5.5 Hz, 1H), 6.9–7.3 (14H). Example 2



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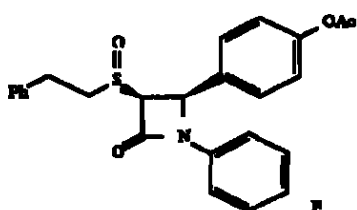
(s, 3H), 4.69 (d, J=5.2 Hz, 1H), 5.55 (d, J=5.2 Hz, 1H), 6.95-7.4 (14H); $[\alpha]_D^{25} = -136^\circ$ (CH₃OH).

EXAMPLE 4

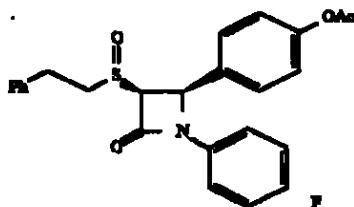


Treat compound 2b (60 mg) in CH₂Cl₂ (5 ml) with TEA (0.025 ml) and acetic anhydride (0.017 ml). After 2 h, concentrate the reaction mixture and purify the residue by flash chromatography on silica using EtOAc/hexane (1:1) to give a white solid. Elemental analysis calculated for C₂₂H₂₂NO₂SF: C 66.5, H 4.91, N 3.1, S 7.1; found C 66.28, H 5.10, N 3.29, S 6.99.

Use the above procedure for preparing compound 4 with compounds 2c and 2d to obtain the following products 4a and 4b, respectively:

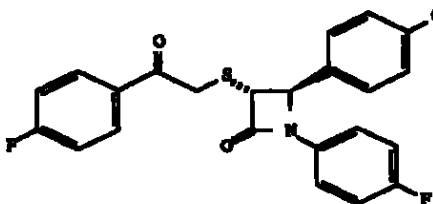


4a: Elemental analysis calculated for C₂₂H₂₂NO₂SF: C 66.5, H 4.91, N 3.1, S 7.1; found C 66.36, H 5.13, N 3.23, S 7.02; ¹H NMR CDCl₃: 2.32 (s, 3H), 2.92 (m, 2H), 3.14 (m, 1H), 3.7 (m, 1H), 4.42 (d, J=5.7 Hz, 1H), 5.38 (d, J=5.8 Hz, 1H), 7.0 (m, 2H), 7.12-7.35 (9H), 7.44 (d, 2H).



4b: ¹H NMR CDCl₃: 2.32 (s, 3H), 3.15 (m, 3H), 3.38 (m, 1H), 4.72 (d, J=5.3 Hz, 1H), 5.58 (d, J=5.2 Hz, 1H), 7.0 (m, 2H), 7.15-7.35 (9H), 7.40 (d, 2H).

EXAMPLE 5



Step 1:
Add TEA (14 ml) to a mixture of 4-methoxybenzylchloride (13 ml) and ethyl-2-

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mercaptoacetate (10 ml) in CH₂Cl₂ (0.2 L) under N₂. After 48 h, dilute the reaction with Et₂O (0.5 L) and sequentially wash the organic phase with 0.3N HCl (3x) and 10% NaHCO₃. Dry and concentrate the organic layer to give an oil (22 g). Dissolve a portion of the oil (5 g) in THF (75 ml) and water (75 ml) and add LiOH (1 g). After stirring for 72 h, dilute the reaction with water (0.15 L) and extract with hexane (0.2 L). Acidify the aqueous phase with 1N HCl and extract with EtOAc. Wash (H₂O), and dry (MgSO₄) the organic layer and concentrate to give a yellow solid (4.25 g, 96%).

Step 2:

Treat a mixture of the product of step 1 (1 g) and the imine from Example 1, Method A, step 1 (1.55 g) in CH₂Cl₂ (40 ml) with dimethylamino phosphoryldichloride (0.56 ml) at 0° C. Warm to rt and stir for 16 h. Dilute the reaction with Et₂O (100 ml) and wash sequentially with 1N HCl, 10% NaHCO₃, and brine. Dry (MgSO₄) and concentrate the organic phase and purify the resultant residue by flash chromatography on silica using hexane:EtOAc (20:1) to yield an oil (0.75 g, 30%).

Step 3:

Add mercuric acetate (121 mg) to a solution of the product of step 2 (0.2 g) in trifluoroacetic acid (5 ml) at 0° C. After 15 min., partition the reaction mixture between H₂O and Et₂O. Wash, dry and concentrate the organic layer and purify the residue by flash chromatography on silica using hexane:EtOAc (10:1) to give an oil (0.15 g).

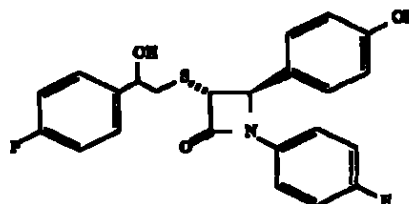
Step 4:

Add 2-bromo-4-fluorooctophenone (86 mg) to a mixture of the product of step 3 (0.15 g) and TEA (0.06 ml) in CH₂Cl₂ (5 ml) at rt under N₂. After 5 h, dilute the reaction with Et₂O and wash sequentially with 1 N HCl, 10% NaHCO₃, and brine. Dry and concentrate the organic layer and purify the residue by flash chromatography on silica using hexane:EtOAc (9:1) to give an oil. Resolve this by HPLC using a Chiralcel AS column with hexane:IPA (85:15) to elute enantiomer 5(1) ([θ] 228 mD=-3.77×10³, [θ] 244 mD=+3.34×10³) and then enantiomer 5(2) ([θ] 228 mD=+3.65×10³, [θ] 244 mD=-3.24×10³).

Step 5:

Treat enantiomer 5(2) with HF according to the procedure of Example 1, Method A, step 3, to obtain compound 5. Elemental analysis calculated for C₂₂H₂₂NO₂SF₂: C 64.93, H 4.03, N 3.29, S 7.52; found C 64.87, H 4.39, N 3.31, S 7.25.

EXAMPLE 6



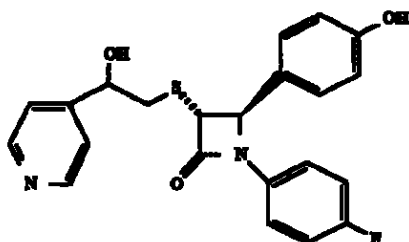
6a (diastereomer a)
6b (diastereomer b)

Step 1:
Add NaBH₄ (28 mg) to a solution of enantiomer 5(2) from step 4 of Example 5 (0.4 g) in CH₃OH (20 ml). After 2 h, partition the reaction mixture between Et₂O and H₂O. Dry and concentrate the organic layer and purify the residue by flash chromatography using EtOAc:hexane (1:6) to give diastereomers 6(1) and 6(2).

Step 2:

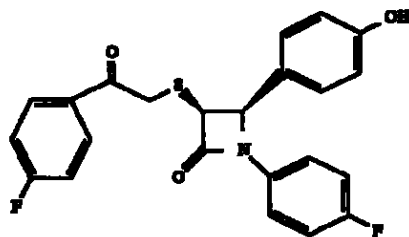
Individually treat diastereomers 6(1) and 6(2) from step 1 with HF according to the procedure of Example 1, Method A, step 3, to obtain 6a and 6b.

21
EXAMPLE 17



Using the procedure of Example 16, treat the compound of Example 13 to obtain the title compound, m.p. 95°-98° C. Elemental analysis calculated for $C_{22}H_{19}N_3O_2$, SP: C 64.38, H 4.67, N 6.82, S 7.81; found C 64.09, H 4.93, N 6.67, S 8.06.

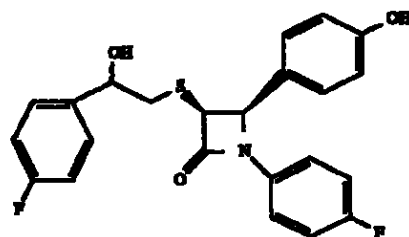
EXAMPLE 18



Step 1:
Treat the cis isomer prepared in Example 10, Step 1, according to the procedure of Example 10, Step 2, to obtain a solid.

Step 2:
React the product of Step 1 according to the procedure of Example 5, Steps 4 and 5, to obtain the title compound as a solid, m.p. 180°-185° C. Elemental analysis calculated for $C_{23}H_{17}NO_2S$: C 64.93, H 4.03, N 3.29, S 7.54; found C 65.13, H 4.16, N 3.43, S 7.70.

EXAMPLE 19



Treat the product of Example 18, Step 1, with $NaBH_4$, according to the procedure of Example 16, and treat the resultant product with HF according to the procedure of Example 1, Method A, Step 3, to obtain the title compound, m.p. 95°-105° C.

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

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EXAMPLE A

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

Method of Manufacture

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

EXAMPLE B

Capsules			
No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	300
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 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 ureidione 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 representative preferred compounds of formula I. 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
1	-27	-83	1
2a	-26	-82	1
3	-42	-97	1
4a	-43	-95	1
4b	-38	-95	1
7a	0	-48	0.1
7d	0	-42	0.1
9b	-34	-63	0.1

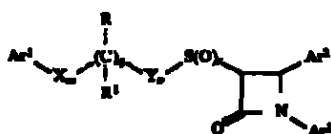
-continued

Ex. #	% Reduction		Dose mg/kg
	Serum Cholest.	Cholest. Esters	
11	-55	-95	3
14	-80	-64	3
15	-37	-88	1
18	-37	-68	3

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

We claim:

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



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ is aryl, R¹⁰-substituted aryl or heteroaryl;

Ar² is aryl or R⁴-substituted aryl;

Ar³ is aryl or R⁵-substituted aryl;

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

R is -OR⁶, -O(CO)R⁶, -O(CO)OR⁶ or -O(CO)NR⁶R⁷; R⁴ 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;

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

R⁷ is 1-5 substituents independently selected from the group consisting of -OR⁶, -O(CO)R⁶, -O(CO)OR⁶, -O(CH₂)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁶, -NR⁶(CO)NR⁶R⁷, -NR⁶SO₂R⁶, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₂R⁶, -O(CH₂)₁₋₁₀COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -CF₃, -CN, -NO₂, halogen, (lower alkylene)COOR⁶ and -CH=CH-COOR⁶;

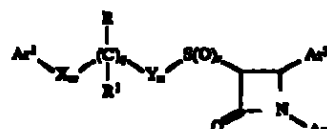
R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

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)₁₋₅OR⁶, -O(CO)NR⁶R⁷, -NR⁶R⁷, -NR⁶(CO)R⁷, -NR⁶(CO)OR⁶, -NR⁶(CO)NR⁶R⁷, -NR⁶SO₂R⁶, -COOR⁶, -CONR⁶R⁷, -COR⁶, -SO₂NR⁶R⁷, S(O)₂R⁶, -O(CH₂)₁₋₁₀COOR⁶, -O(CH₂)₁₋₁₀CONR⁶R⁷, -CF₃, -CN, -NO₂ and halogen; a cholesterol biosynthesis inhibitor and a pharmaceutically acceptable carrier.

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

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

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



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ is aryl, R¹⁰-substituted aryl or heteroaryl;

Ar² is aryl or R⁴-substituted aryl;

Ar³ is aryl or R⁵-substituted aryl;

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

R is -OR⁶, -O(CO)R⁶, -O(CO)OR⁶ or -O(CO)NR⁶R⁷; R⁴ 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;

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

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

735

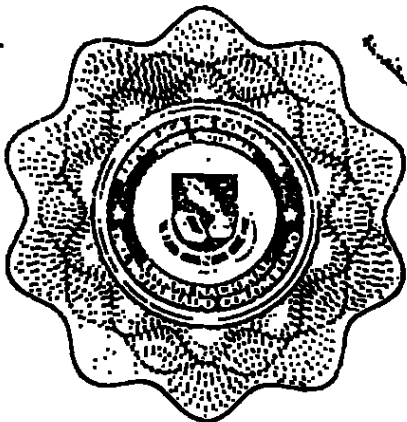
4/1/03

1 página o páginas que se imprimarán.

Registro: 1

Título: Synthesis of C3 heteroatom-substituted azetidinones that display potent cholesterol absorption inhibitory activity.
Autor(es): McKittrick BA; Ma K; Huie K; Yumibe N; Davis H Jr; Clader JW; Carmichael M; McPhail AT
Author's Address: Schering-Plough Research Institute, Kenilworth, New Jersey 07033, USA.
Fuente: Journal Of Medicinal Chemistry [J Med Chem] 1998 Feb 26; Vol. 41 (5), pp. 752-9.
Tipo de publicación: Journal Article
Idioma: English
Journal Information: Country of Publication: UNITED STATES NLM ID: 9716531 Publication Model: Print Cited Medium: Print ISSN: 0022-2623 (Print) NLM ISO Abbrev: Med. Chem. Subsets: MEDLINE
Términos MeSH: Anticholesteremic Agents/*chemical synthesis
Azetidines/*chemical synthesis
Animals; Anticholesteremic Agents/pharmacology; Azetidines/chemistry; Azetidines/pharmacokinetics; Azetidines/pharmacology; Bile/metabolism; Cholesterol/metabolism; Absorption/drug effects; Mececa fascicularis; Male; Molecular Structure; Stereoisomerism; Structure-Activity Relationship
Resumen: The C3 phenylpropyl side chain of N-phenylazetidinones related to SCH 56524 was modified by replacing the hydroxymethylene with various iso or leosteric groups. Modifications at the 3' position led to less-active compounds; however, modifications at the 1' position provided compounds with improved cholesterol absorption inhibitory activity. An enantioselective route for the synthesis of C3 1'-sulfur-substituted azetidinones and the development of structure-activity relationships for this series of compounds are presented.
CAS Registry Number: 0 (3-(2-phenethylsulfanyl)-4-(4-hydroxyphenyl)-N-(4-fluorophenyl)-2-azetidinone)
0 (3-(2-phenethylthio)-4-(4-hydroxyphenyl)-N-(4-fluorophenyl)-2-azetidinone)
0 (Anticholesteremic Agents)
0 (Azetidines)
148260-92-8 (1,4-bis(4-methoxyphenyl)-3-(3-phenylpropyl)-2-azetidinone)
57-88-5 (Cholesterol)
Fecha(s) de la entrada: Date Created: 19980414 Date Completed: 19980414 Latest Revision: 20031114
Código de actualización: 20061223
PMID: 9513603
URL: http://www.sinab.unal.edu.co:2337/login.aspx?direct=true&db=cmedm&AN=9513603&lang=es&site=ehost-live
Base de datos: MEDLINE

4/1/03



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AA 8567146

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REPUBLICA DE COLOMBIA

NOTARIA 33 DE BOGOTA D.C.

ESCRITURA PUBLICA NUMERO: 1 6 5 8

- - MIL SEISCIENTOS CINCUENTA Y OCHO - -

FECHA DE OTORGAMIENTO: CUATRO (4) DE

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Bogotá D.C. - Colombia.

DEL AÑO DOS MIL DOS (2002). -----

22 JUN 2006

ACTO: -----

1.- PODER ESPECIAL.-----

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VENTISER

OTORGADO POR: LAFRANCOL S.A., con Nit. No. - - -

890.301.463-8 - - -

a favor de: JOSE LUIS REYES VILLAMIZAR, con C.C.No.

79.152.473 de Usaquén - Bogotá.-----

DIANA BEATRIZ LOPEZ

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

EN LA CIUDAD DE BOGOTA, DISTRITO CAPITAL,

DEPARTAMENTO DE CUNDINAMARCA, REPUBLICA DE COLOMBIA,

ANTE MI, DIANA BEATRIZ LOPEZ, - - -

NOTARIA TREINTA Y TRES (33) - - -

DE ESTE CIRCULO SE OTORGA LA ESCRITURA PUBLICA QUE

SE CONSIGNA EN LOS SIGUIENTES TERMINOS:-----

COMPARECIO: JUAN MARIA RENDON, mayor de edad,

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

ciudadanía número 17.125.100 - - -

Expedida en Bogotá - - -

Y manifestó:-----

PRIMERO: Que obra en su carácter de Representante

Legal de en nombre y representación de LAFRANCOL

S.A, sociedad comercial organizada y existente

conforme a las leyes colombianas, con domicilio y

sede principal en Cali - Valle, constituida mediante

escritura pública número

ESTE PAPEL NO TIENE COSTO ALGUNO PARA EL USUARIO

De la Notaría

De fecha

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

SEGUNDO: Que en tal carácter, por este público instrumento, concede PODER ESPECIAL, ~~PERO~~ AMPLIO Y

SUFICIENTE a JOSE LUIS REYES VILLAMIZAR, mayor de

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

cédula de ciudadanía número 79.152.473 de Usaquén,

abogado en ejercicio, portador de la T.P.No. 446 55

del C.S. de la J., domiciliado en Bogotá, D.C,

República de Colombia, con dirección en la carrera

17 No. 88-23, Oficina 205, de la misma ciudad, como

su representante con poder especial, amplio y

suficiente, para obtener la protección los

derechos de propiedad industrial y de libre

competencia de Lafrancol S.A., a cuyo efecto lo

autorizo, par que nos represente ante cualesquiera

entidad o persona, ejerza o no jurisdicción,

especialmente ante las el orden administrativo,

contencioso, administrativo y judicial, en todo lo

concerniente a los siguientes asuntos:-----

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

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



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AA 8567152

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promueva Lafrancol S.A., o se
promuevan contra esta y.-----
c.- Para que en todos los asuntos
arriba determinados, tanto en
los términos señalados por los
artículos 42 y complementarios

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

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declaraciones del contenido y autenticidad de los
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Bogotá, hago constar que esta fotocopia
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Bogotá D.C. - Colombia.

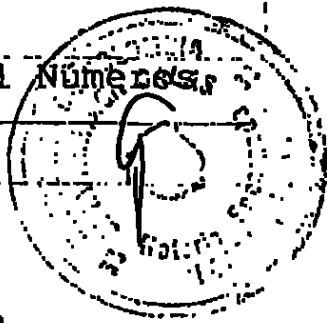
22 JUN 2006

HASTA AQUI LA MINUTA PRESENTADA

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VENTISEROS

OTORGAMIENTO Y AUTORIZACION: Leído el presente
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advertidos de la formalidad de su contenido, dentro
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lo autoriza. -----

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



DERECHOS NOTARIALES: \$ 49.600.00

RESOLUCION No. 4188 del 28 de Diciembre del 2001

JUAN MARIA RENDON

C.C. No. 17.125.100 de Bogotá

LAFRANCOL S.A.

Nit. No. 890.301.463-8

TEL: 622-04-66.

ACEPTO :

JOSE LUIS REYES VILLAMIZAR

C.C. No. 79.152.473

TEL: 621-2631

DIANA BEATRIZ LOPEZ

NOTARIA 33 DE BOGOTA D.C.

n.c.a.

Es segunda COPIA (FOTOCOPIA)

tomada de su original que se expide conforme al

Artículo 79 del Decreto 960 de 1970 en 06

hojas útiles con destino a Jose Luis Reyes

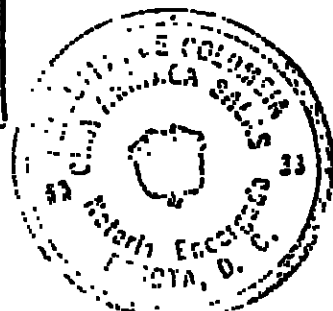
Villamizar

Santafé de

SEC. 100: Dcto. 1772/79

05 JUL. 2002

Qui





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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 1

null

CERTIFICA:

NOMBRE:LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.
DOMICILIO: CALI VALLE
DIRECCION COMERCIAL :---K 1 46 84
DIRECCION NOTIFICACION JUDICIAL:---K 1 46 84
CIUDAD:CALI
MATRICULA MERCANTIL NRO. 5233-4 FECHA MATRICULA : 02 DE OCTOBER DE 1958
DIRECCION ELECTRONICA : esperanzacortes@lafrancol.net
AFILIADO

CERTIFICA:

NIT : 890301463-8

CERTIFICA:

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

CERTIFICA:

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

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 2

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

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01



CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 3

625 IX

CERTIFICA:

VIGENCIA: 29 DE SEPTEMBER DEL A70 2057

CERTIFICA:

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

CERTIFICA:

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

ADMINISTRACION: LA ADMINISTRACION INMEDIATA DE LA SOCIEDAD, SU REPRESENTACION LEGAL Y LA GESTION DE LOS NEGOCIOS SOCIALES ESTARAN A CARGO DE UN GERENTE, DESIGNADO POR LA ASAMBLEA GENERAL DE ACCIONISTAS, PARA PERIODOS DE DE DOS (2) A7OS REELEGIBLE INDEFINIDAMENTE Y REMOVIBLE LIBREMENTE POR ELLA EN CUALQUIER TIEMPO.

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

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 4

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

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

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

CERTIFICA:

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

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

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

FUE(ON) NOMBRADO(S):

*** CONTINUA ***



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 5

VICEPRESIDENTE

ROBERTO S. VENTURA PAULY

C.C.16697614

GERENTE GENERAL Y REPRESENTANTE LEGAL

JUAN MARIA RENDON GUTIERREZ

C.C.17125100

PRIMER SUPLENTE DEL GERENTE

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

SEGUNDO SUPLENTE DEL GERENTE

ROBERTO M. VENTURA CRISPINO

C.C.9086003

PRESIDENTE

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

CERTIFICA:

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

ORIGEN: ASAMBLEA DE ACCIONISTAS

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

FUE(ON) NOMBRADO(S):

TERCER SUPLENTE DEL GERENTE

JUAN PABLO REYES VILLAMIZAR

C.C.80419709

CERTIFICA:

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529 Hora Certificado : 123616

Operacion: 02NA80529024 PAGINA No. 6

DOCUMENTO: ACTA No. 99 DEL 14 DE MARCH DE 2002
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 09 DE SEPTEMBER DE 2002 No. 14675 DEL LIBRO IX

DOCUMENTO: ACTA No. 105 DEL 09 DE NOVEMBER DE 2004
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 17 DE FEBRUARY DE 2005 No. 2031 DEL LIBRO IX

FUE (RON) _NOMBRADO (S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON
ESTHER ISABEL VENTURA DE RENDON
C.C.38979831

SEGUNDO RENGLON
ROSA VICTORIA VENTURA DE VISBAL
C.C.38992048

TERCER RENGLON
JUAN PABLO REYES VILLAMIZAR
C.C.80419709

SUPLENTES

PRIMER RENGLON
JUAN MARIA RENDON GUTIERREZ
C.C.17125100

SEGUNDO RENGLON
ROBERTO M. VENTURA CRISPINO
C.C.9086003

TERCER RENGLON
ROBERTO S. VENTURA PAULY
C.C.16697614

CERTIFICA:

***** CONTINUA *****



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 7

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

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

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

FUE(ON) NOMBRADO(S):

REVISOR FISCAL

ALFREDO LOPEZ & CIA. LTDA

NIT.800026893-5

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 20 DE OCTOBER DE 2006

ORIGEN: ALFREDO LOPEZ & CIA LTDA

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

FUE(ON) NOMBRADO(S):

REVISOR FISCAL PRINCIPAL

ALFREDO L?PEZ CAMPO

C.C.8241912

REVISOR FISCAL SUPLENTE

GEOVANA GONZALEZ GALINDO

C.C.66959852

CERTIFICA:

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

NUMERO DE ACCIONES: 750,000,000

VALOR NOMINAL: \$10

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

NUMERO DE ACCIONES: 600,000,000

VALOR NOMINAL: \$10

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

NUMERO DE ACCIONES: 600,000,000

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 8

VALOR NOMINAL: \$10

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.5234- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL
UBICADO EN: ---K 1 46 84 DE CALI
RENOVO : POR EL A?O 2007

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.369809- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S A
UBICADO EN: --K 1 46A 70 DE CALI
FECHA MATRICULA : 29 DE APRIL DE 1994
RENOVO : POR EL A?O 2007

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.369810- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S A
UBICADO EN: ---K 1A 46 A 32 DE CALI
FECHA MATRICULA : 29 DE APRIL DE 1994
RENOVO : POR EL A?O 2007

CERTIFICA:

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

CERTIFICA:

*** CONTINUA ***

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20070529

Hora Certificado : 123616

Operacion: 02NA80529024

PAGINA No. 9

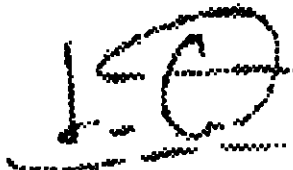
QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL PRESENTE CERTIFICADO.

LOS ACTOS Y DOCUMENTOS REGISTRADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO TERMINO NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

DE CONFORMIDAD CON EL DECRETO 2150 DE 1.995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.

DADO EN CALI A LOS 29 DIAS DEL MES DE MAY

DEL AÑO 2007 HORA: 12:28:45



41
363

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-060219-00001-0000

Fecha: 2007-05-30 14:50:08 Dep. 2020 NUECREACION
Tra 11 PATENTEIYII Eve: 379 FASENACIONALII
Act 400 OPOSIOBSERVTER Folios. 41

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 07 - 42.781
FECHA : MAYO 29 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	54661352	28/05/2007	1,024,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50003-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEMAS COMERCIALES	256,000.00
		TOTAL :	\$ 256,000.00

SOM: DOSCIENTOS CINCUENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

2020
Bogotá, D.C.,

Doctor:
Juan Pablo Cadena Sarmiento
Apoderado

Oficio N°: 7721

ASUNTO:	Radicación PCT N°	06-60219
	Trámite	011
	Evento	379
	Actuación	440
	Folios	034

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado del Laboratorio Franco Colombiano Lafranco S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


CLARA DE JAIMES
Jefe de la División de Nuevas Creaciones (E).

El anterior oficio fue notificado por fijación en lista de fecha, 29 JUN. 2007.

202021

Retire 6019
Tron lado box.
2a-5th Alex