REYES & REYES
A B O G A D O S

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

REF: **Expediente 08-033-464**

TÍTULO SOLICITADO: **COMPUESTOS ANTIHIPERCOLESTEROLÉMICOS.**

PUBLICACIÓN: **Gaceta 593 de 27/06/2008, Nº de publicación 524**

PRIORIDAD: **US 60/723,781 de 05/10/2005**

SOLICITANTE: **MERCK & CO., INC.**

APODERADO: **CARLOS OLARTE G.**

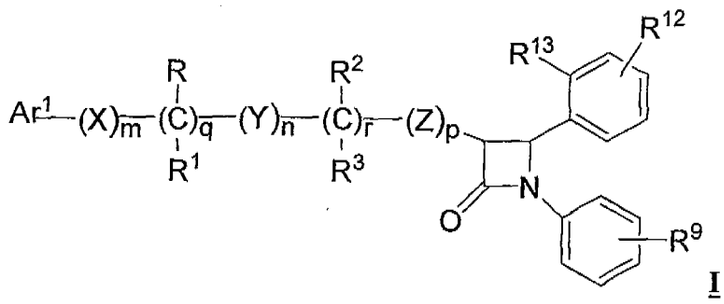
TRÁMITE: **SUSTENTACION DE OPOSICIÓN**

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.,** dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar la oposición presentada oportunamente ante ese Despacho, en los siguientes términos:

I. COMPLEMENTO DE INFORMACIÓN

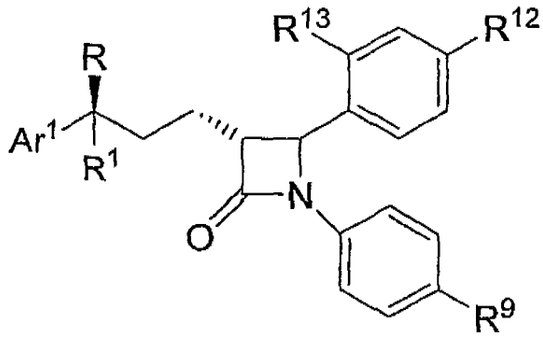
Comedidamente me permito presentar los argumentos que demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14, 16, 18 y 20 literal d) de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

La solicitud colombiana **08-033-464** que reivindica un compuesto de fórmula estructural I:



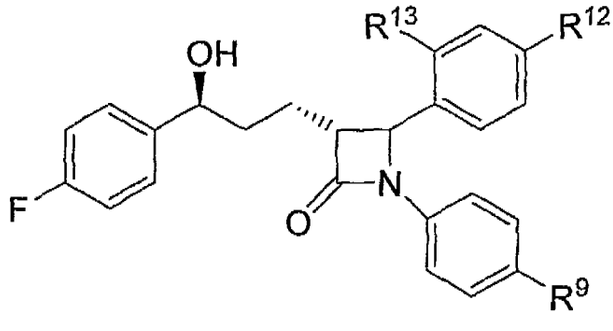
I

El compuesto de la reivindicación 1 que tiene la formula estructural Ia:



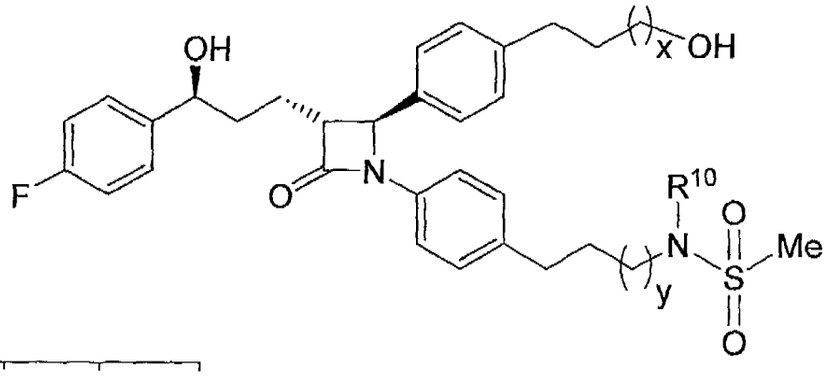
Ia.

El compuesto de la reivindicación 1 que tiene la formula estructural Ib:

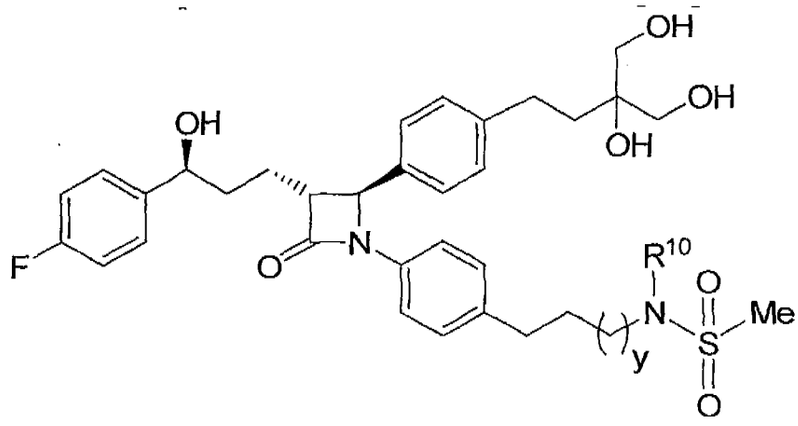


Ib.

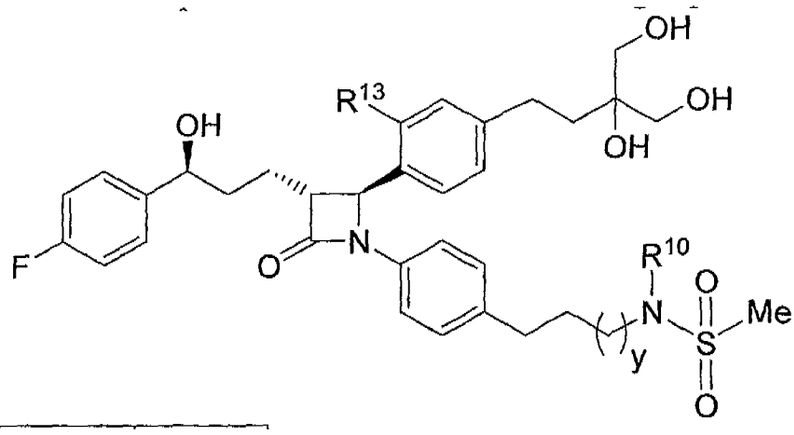
El compuesto de la reivindicación 1 seleccionado entre el grupo constituido por:



El compuesto de la reivindicación 1 seleccionado entre el grupo constituido por:



El compuesto de la reivindicación 1 seleccionado entre el grupo constituido por:



Sales farmacéuticas y ésteres farmacéuticamente aceptables de los mismos; una composición farmacéutica que comprende dichos compuestos farmacéuticos, que puede comprender adicionalmente un inhibidor de la biosíntesis del colesterol; útiles en un procedimiento para reducir los niveles de colesterol LDL en plasma; carece de novedad y nivel inventivo como se argumenta a continuación:

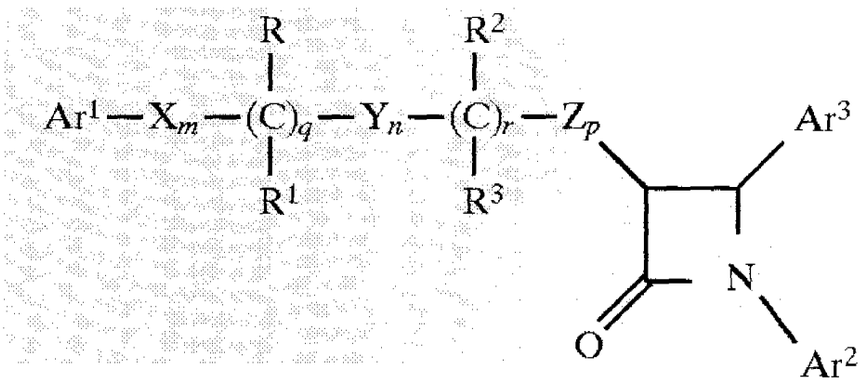
En primera instancia, las reivindicaciones 14 a 18 de dicha solicitud colombiana en trámite incurren en una improcedencia directa de patentabilidad, en cuanto a que explícitamente se refieren a un tratamiento terapéutico, que involucra reducir los niveles de colesterol LDL, para así tratar la hipercolesterolemia, reducir y/o eliminar el riesgo de desarrollar aterosclerosis y/o una enfermedad aterosclerótica; lo cual va en contra de lo expuesto por la decisión 486 de 2000 que explícitamente revela en su articulo 20 literal d) "*No serán patentables (...) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnostico aplicados a los seres humanos o a animales.*"

#144
145

Por otro lado, existen documentos que revelan con anterioridad la obtención de compuestos del mismo tipo que los revelados por la solicitud colombiana en trámite (derivados de azetidinona), lo que afecta directamente el nivel inventivo de dicha invención, veamos:

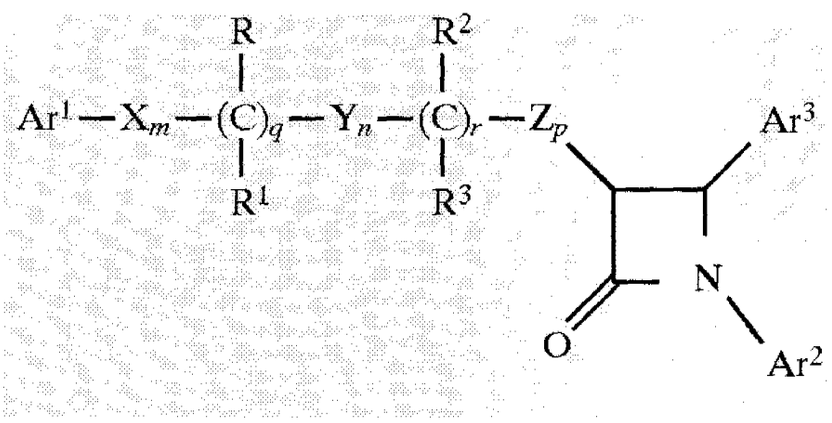
- La patente americana US 5846966 publicada el 08 de Diciembre de 1998 y titulada "COMBINATIONS OF HYDROXY-SUSBSITUTED AZETIDINONE COMPOUNDS AND HMG COA REDUCTASE INHIBITORS" revela:

> 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 hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I and a cholesterol biosynthesis inhibitor. That is, the present invention relates to the use of a hydroxy-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 hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I) to treat or prevent atherosclerosis or to reduce plasma cholesterol levels.
>
> (...)
>
> **1**. A pharmaceutical composition for the treatment or prevention of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising an effective amount of a compound represented by the formula I



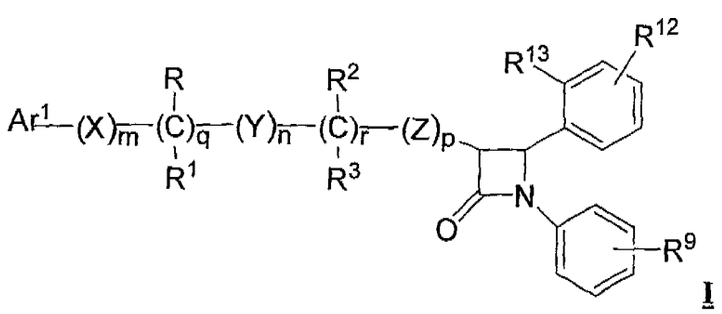
(...)

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



I

Como se puede apreciar claramente, en esta anterioridad se exponen compuestos derivados de azetidinona del mismo tipo que los reivindicados por la solicitud colombiana, específicamente en su reivindicación 1;



I

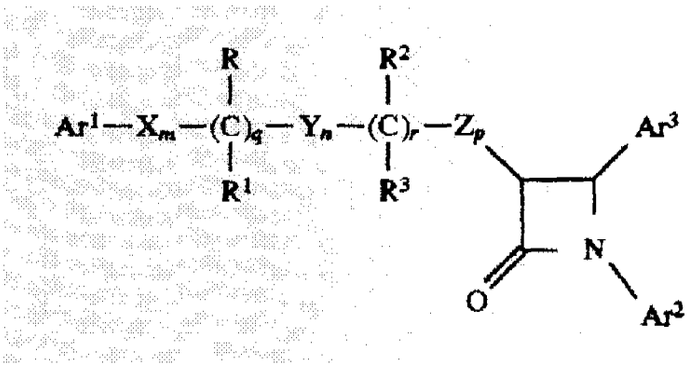
así como la inclusión de los mismos en formulaciones farmacéuticas útiles en el tratamiento de aterosclerosis a partir de la reducción de los niveles de colesterol en el plasma, solos o en combinación con inhibidores de la biosíntesis de colesterol, lo que también afectaría directamente las reivindicaciones 14 a 20 de dicha solicitud en trámite.

- La patente americana US 5767115 publicada el 16 de Junio de 1998 y titulada "HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS" revela:

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

(...)

1. A compound represented by the formula

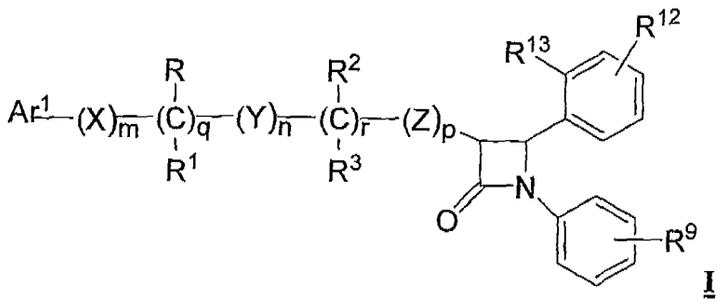


(...)

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

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

Como se puede apreciar claramente, en esta anterioridad se exponen de nuevo compuestos derivados de azetidinona del mismo tipo que los reivindicados por la solicitud colombiana, específicamente en su reivindicación 1;

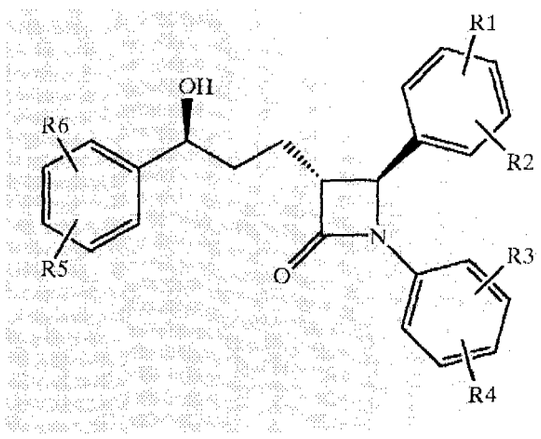


I

así como la inclusión de los mismos en formulaciones farmacéuticas útiles en el tratamiento de aterosclerosis a partir de la reducción de los niveles de colesterol en el plasma, solos o en combinación con inhibidores de la biosíntesis de colesterol, lo que también afectaría directamente las reivindicaciones 14 a 20 de dicha solicitud en trámite.

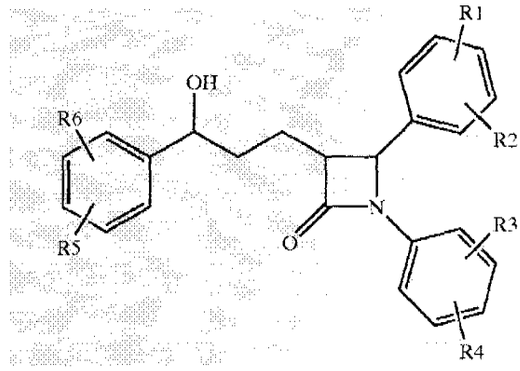
- La patente americana US 2002/0128253 publicada el 12 de septiembre de 2002 y titulada "DIPHENYLAZETIDINONE DERIVATIVCES, PROCESS FOR THEIR PREPARATION, MEDICAMENTS COMPRISING THESE COMPOUNDS AND THEIR USE" revela:

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



(...)

1. A compound of the formula I,



(...)

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

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

(...)

8. A pharmaceutical composition as claimed in claim 6, which comprises, as a further active compound, one or more antidiabetics, hypoglycemically active compounds, HMG-CoA reductase inhibitors, cholesterol absorption inhibitors, PPAR gamma agonists, PPAR alpha agonists, PPAR alpha/gamma agonists, fibrates, MTP inhibitors, bile acid absorption inhibitors, CETP inhibitors, polymeric bile acid adsorbers, LDL receptor inducers, ACAT inhibitors, antioxidants, lipoprotein lipase inhibitors, ATP citrate lyase inhibitors, squalene synthetase inhibitors, lipoprotein(a) antagonists,

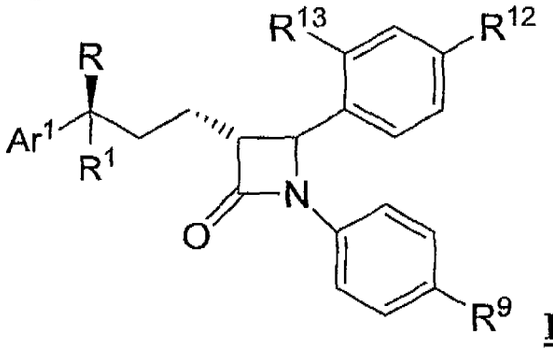
(...)

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

(...)

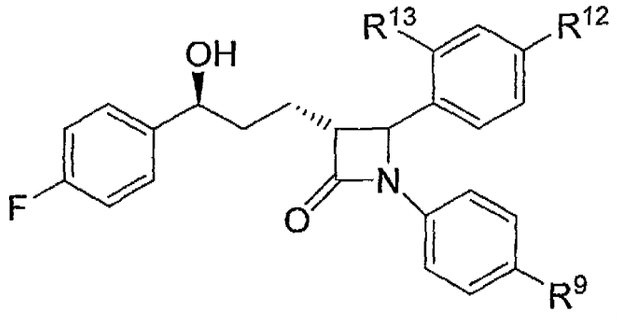
15. A method as claimed in claim 14, wherein the host suffers from an arteriosclerotic manifestation.

Como se puede apreciar claramente, en esta anterioridad se exponen compuestos derivados de azetidinona del mismo tipo que los reivindicados por la solicitud colombiana, específicamente en sus reivindicaciones 5;



Ia.

Y 9:



Ib.

así como la inclusión de los mismos en formulaciones farmacéuticas útiles en el tratamiento de aterosclerosis a partir de la reducción de los niveles de colesterol en el plasma, solos o en combinación con inhibidores de la biosíntesis de colesterol (como lo son por ejemplo los inhibidores de la HMG-CoA reductasa y los inhibidores de la escualeno sintasa), lo que también afectaría directamente las reivindicaciones 14 a 20 de dicha solicitud en trámite.

Para finalizar, existen además otros documentos que exponen la obtención de derivados de azetidinona, que aunque están menos relacionados con los compuestos reivindicados por la solicitud colombiana en trámite, debido a sus sustituyentes sobre el núcleo de azetidinona, son una prueba de la versatilidad y cotidianidad con que se pueden encontrar procesos de obtención de estos compuestos derivados de azetidinona, así como su anterioridad en el uso del

tratamiento de diversos trastornos a través de la reducción de los niveles de colesterol en plasma. Ejemplos de dichos documentos pueden ser la patente americana US 5633246 publicada el 27 de mayo de 1997 y la patente americana US 5744467 publicada el 28 de abril de 1998.

En conclusión la solicitud colombiana en tramite carece de los requisitos fundamentales para otorgársele el privilegio de patente de invención, principalmente porque incurre en una directa improcedencia en la patentabilidad al reivindicar un método de tratamiento. Dicha solicitud carece además tanto de nivel inventivo como de novedad, primero que todo porque el mismo estado de la técnica se encuentran con anterioridad el mismo tipo de compuestos derivados de azetidinona (cuyos sustituyentes pueden variar pero siempre conservan características químicas similares) y finalmente porque dichos compuestos ya se reconocían así mismo con anterioridad, como fármacos útiles en tratamientos donde fuera efectiva la deducción de los niveles de colesterol en el plasma.

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.

VI. ANEXOS

- La patente americana US 5846966 publicada el 08 de Diciembre de 1998 y titulada "COMBINATIONS OF HYDROXY-SUSBSITUTED AZETIDINONE COMPOUNDS AND HMG COA REDUCTASE INHIBITORS" columna 3 y capítulo reivindicatorio.
- La patente americana US 5767115 publicada el 16 de Junio de 1998 y titulada "HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS" columna3 y capítulo reivindicatorio.
- La patente americana US 2002/0128253 publicada el 12 de septiembre de 2002 y titulada "DIPHENYLAZETIDINONE DERIVATIVCES, PROCESS FOR THEIR PREPARATION, MEDICAMENTS COMPRISING THESE COMPOUNDS AND THEIR USE" pagina 4 y capitulo reivindicatorio.

- Reivindicaciones de la patente americana US 5633246 publicada el 27 de mayo de 1997 y la patente americana US 5744467 publicada el 28 de abril de 1998.

Señor Superintendente,

JOSÉ LUIS REYES VILLAMIZAR
C.C. 79'152.473 de Usaquén
T.P.A 44.655 del C.S.J.

US005846966A

United States Patent [19]

Rosenblum et al.

[11] **Patent Number: 5,846,966**

[45] **Date of Patent: Dec. 8, 1998**

[54] **COMBINATIONS OF HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS AND HMG COA REDUCTASE INHIBITORS**

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

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

[21] Appl. No.: **953,825**

[22] Filed: **Oct. 14, 1997**

Related U.S. Application Data

[63] Continuation-in part of Ser. No. 617,751, Mar. 18, 1996, Pat. No. 5,767,115, which is a continuation-in-part of Ser. No. 257,593, Jun. 9, 1994, Pat. No. 5,631,365, which is a continuation-in-part of Ser. No. 102,440, filed as PCT/US94/10099 Sep. 14, 1994, abandoned.

[51] **Int. Cl.**[6] **A61K 31/395**; A61K 31/40; A61K 31/35; A61K 31/21

[52] **U.S. Cl.** **514/210**; 514/423; 514/451; 514/460; 514/510; 514/824

[58] **Field of Search** 514/210, 423, 514/451, 460, 510, 824

[56] **References Cited**

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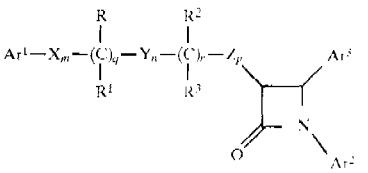
Primary Examiner—Kimberly Jordan

Attorney, Agent, or Firm—Anita W. Magatti

[57] **ABSTRACT**

Hydroxy-substituted azetidinone hypocholesterolemic agents of the formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 and Ar^2 are aryl or R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are $—CH_2—$, —CH(lower alkyl)- - or —C(dilower alkyl)—;

R and R^2 are - OR^6, -O(CO)R^6, —O(CO)OR^9 or —O(CO)NR^6R^7;

R^1 and R^3 are H or lower alkyl;

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

R^4 is selected from lower alkyl, R^5, $—CF_3$, —CN, $—NO_2$ and halogen;

R^5 is selected from $—OR^6$, - O(CO)R^6, -O(CO)OR^9, $—O(CH_2)_{1-5}OR^6$, —O(CO)NR^6R^7, $—NR^6R^7$, $—NR^6(CO)R^7$, —NR^6(CO)OR^9, —NR^6(CO)NR^7R^8, $—NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, $—SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $—O(CH_2)_{1-10}—COOR^6$, $—O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$ and —CH=CH–-$COOR^6$;

R^6, R^7 and R^8 are H, lower alkyl, aryl or aryl-substituted lower alkyl;

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

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

10 Claims, No Drawings

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

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

R^4 is preferably 1–3 independently selected substituents, and R^5 is preferably 1–3 independently selected substituents. Preferred are compounds of formula I wherein Ar^1 is phenyl or R^4-substituted phenyl, especially (4-R^4)-substituted phenyl. Ar^2 is preferably phenyl or R^4-substituted phenyl, especially (4-R^4)-substituted phenyl. Ar^3 is preferably R^5-substituted phenyl, especially (4-R^5)-substituted phenyl. When Ar^1 is (4-R^4)-substituted phenyl, R^4 is preferably a halogen. When Ar^2 and Ar^3 are R^4- and R^5-substituted phenyl, respectively, R^4 is preferably halogen or —OR^6 and R^5 is preferably —OR^6, wherein R^6 is lower alkyl or hydrogen. Especially preferred are compounds wherein each of Ar^1 and Ar^2 is 4-fluorophenyl and Ar^3 is 4-hydroxyphenyl or 4-methoxyphenyl.

X, Y and Z are each preferably —CH_2—. R^1 and R^3 are each preferably hydrogen. R and R^2 are preferably —OR^6 wherein R^6 is hydrogen, or a group readily metabolizable to a hydroxyl (such as —$O(CO)R^6$, —$O(CO)OR^9$ and —$O(CO)NR^6R^7$, defined above).

The sum of m, n, p, q and r is preferably 2, 3 or 4, more preferably 3. Preferred are compounds wherein m, n and r are each zero, q is 1 and p is 2. Also preferred are compounds wherein p, q and n are each zero, r is 1 and m is 2 or 3. More preferred are compounds wherein m, n and r are each zero, q is 1, p is 2, Z is —CH_2— and R is —OR^6, especially when R^6 is hydrogen. Also more preferred are compounds wherein p, q and n are each zero, r is 1, m is 2, X is —CH_2— and R^2 is —OR^6, especially when R^6 is hydrogen.

Another group of preferred compounds is that wherein Ar^1 is phenyl or R^4-substituted phenyl, Ar^2 is phenyl or R^4-substituted phenyl and Ar^3 is R^5-substituted phenyl. Also preferred are compounds wherein Ar^1 is phenyl or R^4-substituted phenyl, Ar^2 is phenyl or R^4-substituted phenyl, Ar^3 is R^5-substituted phenyl, and the sum of m, n, p, q and r is 2, 3 or 4, more especially 3. More preferred are compounds wherein Ar^1 is phenyl or R^4-substituted phenyl, Ar^2 is phenyl or R^4-substituted phenyl, Ar^3 is R^5-substituted phenyl, and wherein m, n and r are each zero, q is 1 and p is 2, or wherein p, q and n are each zero, r is 1 and m is 2 or 3.

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.

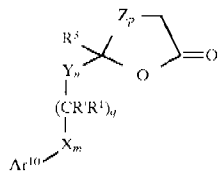
In still another aspect, the present invention relates to a pharmaceutical composition comprising a serum cholesterol-lowering effective amount of a compound of formula I in a pharmaceutically acceptable carrier.

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 hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I and a cholesterol biosynthesis inhibitor. That is, the present invention relates to the use of a hydroxy-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 hydroxy-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 hydroxy-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 hydroxy-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.

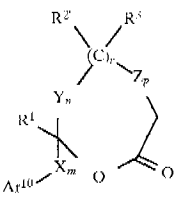
In yet another aspect, the invention relates to a process for preparing certain compounds of formula I comprising the steps:

(a) treating with a strong base a lactone of the formula



A

or



B

wherein R' and $R^{2'}$ are R and R^2, respectively, or are suitably protected hydroxy groups; Ar^{10} is Ar^1, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl; and the remaining variables are as defined above, provided that in lactone of formula B, when n and r are each zero, p is 1–4;

(b) reacting the product of step (a) with an imine of the formula

wherein Ar^{20} is Ar^2, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl; and Ar^{30} is Ar^3, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl;

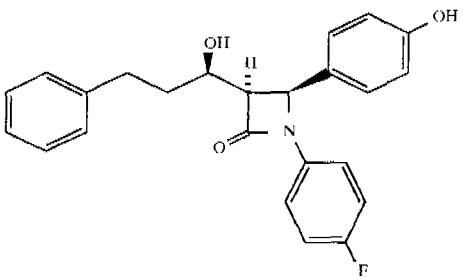
c) quenching the reaction with an acid;

d) optionally removing the protecting groups from R', $R^{2'}$, Ar^{10}, Ar^{20} and Ar^{30}, when present; and

e) optionally functionalizing hydroxy or amino substituents at R, R^2, Ar^1, Ar^2 and Ar^3.

Using the lactones shown above, compounds of formula IA and IB are obtained as follows:

EXAMPLE 10



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

Step 2: Treat a solution of the cis-azetidinone of Step 1 (0.25 g) in CH_3CN (21 ml) with 48% aqueous HF (2.5 ml). After 18 h, dilute the reaction mixture with cold H_2O and extract with Et_2O. Wash (2× H_2O, dilute $NaHCO_3$ and brine), dry ($MgSO_4$) and concentrate the Et_2O layer. Crystallize the residue from EtOAc:hexane (1:2) to obtain the title compound as colorless needles (123 mg, y=64%), mp 168°–171° C. Elemental analysis calc for $C_{24}H_{22}O_3FN$: C 73.64; H 5.66; N 3.58. found C 73.32; H 5.65; N 3.68.

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

EXAMPLE A

Tablets

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

Method of Manufacture

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

EXAMPLE B

Capsules

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

-continued

Capsules

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

Method of Manufacture

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

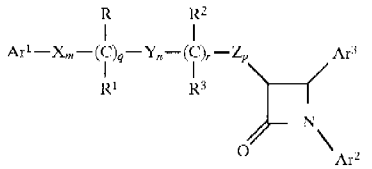
Representative formulations comprising a cholesterol biosynthesis inhibitor-are well known in the art. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms disclosed above for substituted azetidinone compounds may readily be modified using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

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

	% Reduction		
Ex. #	Serum Cholest.	Cholest. Esters	Dose mg/kg
1A	−23	0	50
1B	−15	−39	50
1C	14	0	50
2	0	0	50
3A	−31	−69	50
3C	−60	−92	50
3D	17	−61	10
3E	0	0	10
3F	−29	−77	10
3G	16	−38	10
3H	−41	−86	10
3I	0	−22	10
3J	0	0	3
3K	0	0	10
3L	−15	−21	10
3M	0	−22	10
4A	0	−54	5
4B	−37	−89	8
4C	−12.5	0	3
4D	9	0	7
4E	0	−46	3
4F	−29	−95	3
5	0	−64	10
6A	−59	−98	1
6A-1	−43	−93	1
6B	−40	−92	3
6C	0	−48	3
6D	−46	−95	10
8A	0	−44	3
8B	−50	−95	3
8C	−14	−37	1
8D	−49	−98	1
8E	−22	−66	3
8F	−43	−94	1
10	−26	77	3

We claim:

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



I

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of —CH_2—, —CH(lower alkyl)— and —C(dilower alkyl)—;

R and R^2 are independently selected from the group consisting of —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$ and —$O(CO)NR^6R^7$;

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

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

R^4 is 1–5 substituents independently selected from the group consisting of lower alkyl, —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{2-5}OR^6$, —$O(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$, —CH═CH—$COOR^6$, —CF_3, —CN, —NO_2 and halogen;

R^5 is 1–5 substituents independently selected from the group consisting of —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$ and —CH═CH—$COOR^6$;

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

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

in combination with an HMG CoA reductase inhibitor in a pharmaceutically acceptable carrier.

2. A pharmaceutical composition of claim **1** wherein, in the compound of formula I, Ar^1 is phenyl or R^4-substituted phenyl, wherein R^4 is halogen; Ar^2 is phenyl or R^4-substituted phenyl, wherein R^4 is halogen or —OR^6, wherein R^6 is lower alkyl or hydrogen; Ar^3 is R^5-substituted phenyl, wherein R^5 is —OR^6, wherein R^6 is lower alkyl or hydrogen; X, Y, and Z are each —CH_2—; R^1 and R^3 are each hydrogen; R and R^2 are each —OR^6, wherein R^6 is hydrogen; and the sum of m, n, p, q and r is 2, 3 or 4.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

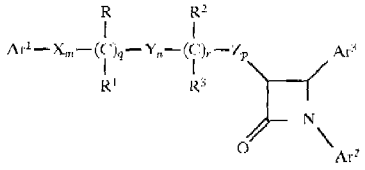
3(R)-[3(R)-(acetyloxy)-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-11-(4-chlorophenyl)-2-azetidinone;

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

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

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

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



or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of $—CH_2—$, —CH(lower alkyl)— and —C(dilower alkyl)—;

R and R^2 are independently selected from the group consisting of $—OR^6$, $—O(CO)R^6$, $—O(CO)OR^9$ and $—O(CO)NR^6R^7$;

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

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

R^4 is 1–5 substituents independently selected from the group consisting of lower alkyl, $—OR^6$, $—O(CO)R^6$, $—O(CO)OR^9$, $—O(CH_2)_{1-5}OR^6$, $—O(CO)NR^6R^7$, $—NR^6R^7$, $—NR^6(CO)R^7$, $—NR^6(CO)OR^9$, $—NR^6(CO)NR^7R^8$, $—NR^6SO_2R^9$, —COOR⁶, —CONR⁶R⁷, —COR⁶, $—SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $—O(CH_2)_{1-10}—COOR^6$, $—O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)COOR⁶, —CH=CH—COOR⁶, $—CF_3$, —CN, $—NO_2$ and halogen;

R^5 is 1–5 substituents independently selected from the group consisting of $—OR^6$, $—O(CO)R^6$, $—O(CO)OR^9$, $—O(CH_2)_{1-5}OR^6$, $—O(CO)NR^6R^7$, $—NR^6R^7$, $—NR^6(CO)R^7$, $—NR^6(CO)OR^9$, $—NR^6(CO)NR^7R^8$, $—NR^6SO_2R^9$, —COOR⁶, —CONR⁶R⁷, —COR⁶, $—SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $—O(CH_2)_{1-10}—COOR^6$, $—O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)COOR⁶ and —CH=CH—COOR⁶;

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

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl; in combination with an effective amount of a cholesterol biosynthesis inhibitor selected from the group consisting of HMG CoA reductase inhibitors.

7. A method of claim **6** wherein, in the compound of formula I, Ar^1 is phenyl or R^4-substituted phenyl, wherein R^4 is halogen; Ar^2 is phenyl or R^4-substituted phenyl, wherein R^4 is halogen or $—OR^6$, wherein R^6 is lower alkyl or hydrogen; Ar^3 is R^5-substituted phenyl, wherein R^5 is $—OR^6$, wherein R^6 is lower alkyl or hydrogen; X, Y, and Z are each $—CH_2—$; R^1 and R^3 are each hydrogen; R and R^2 are each $—OR^6$, wherein R^6 is hydrogen; and the sum of m, n, p, q and r is 2, 3 or 4.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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US005767115A

United States Patent [19]

Rosenblum et al.

[11] **Patent Number: 5,767,115**

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

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

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

[21] Appl. No.: **617,751**

[22] Filed: **Mar. 18, 1996**

Related U.S. Application Data

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

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

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

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

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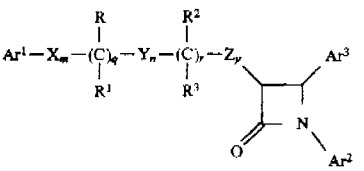
Primary Examiner—Mark L. Berch

Attorney, Agent, or Firm—Anita W. Magatti

[57] **ABSTRACT**

Hydroxy-substituted azetidinone hypocholesterolemic agents of the formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 and Ar^2 are aryl or R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are —CH_2—, —CH(lower alkyl)— or —C(dilower alkyl)—;

R and R^2 are —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$ or —$O(CO)NR^6R^7$;

R^1 and R^3 are H or lower alkyl;

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

R^4 is selected from lower alkyl, R^5, —CF_3, —CN, —NO_2, and halogen R^5 is selected from —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —NR_6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$ and —CH=CH—$COOR^6$;

R^6, R^7 and R^8 are H, lower alkyl, aryl or aryl-substituted Ic

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

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

9 Claims, No Drawings

substituted phenyl. Ar^2 is preferably phenyl or R^4-substituted phenyl, especially (4-R^4)-substituted phenyl. Ar^3 is preferably R^5-substituted phenyl, especially (4-R^5)-substituted phenyl. When Ar^1 is (4-R^4)-substituted phenyl, R^4 is preferably a halogen. When Ar^2 and Ar^3 are R^4- and R^5-substituted phenyl, respectively, R^4 is preferably halogen or —OR^6 and R^5 is preferably —OR^6, wherein R_6 is lower alkyl or hydrogen. Especially preferred are compounds wherein each of Ar^1 and Ar^2 is 4-fluorophenyl and Ar^3 is 4-hydroxyphenyl or 4-methoxyphenyl.

X, Y and Z are each preferably —CH_2—. R^1 and R^3 are each preferably hydrogen. R and R^2 are 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^9 and —O(CO)NR^6R^7, defined above).

The sum of m, n, p, q and r is preferably 2, 3 or 4, more preferably 3. Preferred are compounds wherein m, n and r are each zero, q is 1 and p is 2. Also preferred are compounds wherein p, q and n are each zero, r is 1 and m is 2 or 3. More preferred are compounds wherein m, n and r are each zero, q is 1, p is 2, Z is —CH_2 and R is —OR^6OR_6, especially when R^6 is hydrogen. Also more preferred are compounds wherein p, q and n are each zero, r is 1, m is 2, X is —CH_2— and R^2 is —OR^6, especially when R^6 is hydrogen.

Another group of preferred compounds is that wherein Ar^1 is phenyl or R^4-substituted phenyl, Ar^2 is phenyl or R^4-substituted phenyl and Ar^3 is R^5-substituted phenyl. Also preferred are compounds wherein Ar^1 is phenyl or R^4-substituted phenyl, Ar^2 is phenyl or R^4-substituted phenyl, Ar^3 is R^5-substituted phenyl, and the sum of m, n, p, q and r is 2, 3 or 4, more especially 3. More preferred are compounds wherein Ar^1 is phenyl or R^4-substituted phenyl, Ar^2 is phenyl or R^4-substituted phenyl Ar^3 is R^5-substituted phenyl, and wherein m, n and r are each zero, q is 1 and p is 2, or wherein p, q and n are each zero, r is 1 and m is 2 or 3.

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.

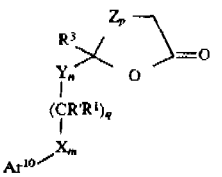
In still another aspect, the present invention relates to a pharmaceutical composition comprising a serum cholesterol-lowering effective amount of a compound of formula I in a pharmaceutically acceptable carrier.

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 hydroxy-substituted azetidinone cholesterol absorption inhibitor of formula I and a cholesterol biosynthesis inhibitor. That is, the present invention relates to the use of a hydroxy-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 hydroxy-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 hydroxy-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 hydroxy-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.

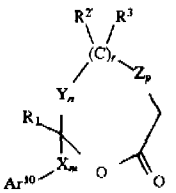
In yet another aspect, the invention relates to a process for preparing certain compounds of formula I comprising the steps:

(a) treating with a strong base a lactone of the formula



A

or



B

wherein R' and $R^{2'}$ are R and R^2, respectively, or are suitably protected hydroxy groups; Ar^{10} is Ar^1, a suitably protected hydroxy substituted aryl or a suitably protected amino-substituted aryl; and the remaining variables are as defined above, provided that in lactone of formula B when n and r are each zero, p is 1–4;

(b) reacting the product of step (a) with an imine of the formula

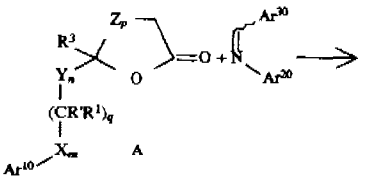
wherein Ar^{20} is Ar^2, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl; and Ar^{30} is Ar^3, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl;

c) quenching the reaction with an acid;

d) optionally removing the protecting groups from R', $R^{2'}$, Ar^{10}, Ar^{20} and Ar^{30}, when present; and

e) optionally functionalizing hydroxy or amino substituents at R, R^2, Ar^1, Ar^2 and Ar^3.

Using the lactones shown above, compounds of formula IA and IB are obtained as follows:



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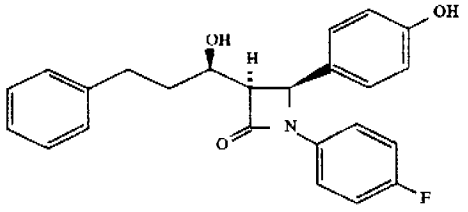
EXAMPLE 10



Step 1:

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

Step 2:

Treat a solution of the cis-azetidinone of Step 1 (0.25 g) in CH3CN (21 ml) with 48% aqueous HF (2.5 ml). After 18 h, dilute the reaction mixture with cold H_2O and extract with Et_2O. Wash (2× H_2O, dilute $NaHCO_3$ and brine), dry ($MgSO_4$) and concentrate the Et_2O layer. Crystallize the residue from EtOAc:hexane (1:2) to obtain the title compound as colorless needles (123 mg, y=64%), mp 168°–171° C. Elemental analysis calc for $C_{24}H_{22}O_3FN$: C 73.64; H 5.66; N 3.58. found C 73.32; H 5.65; N 3.68.

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

EXAMPLE A

Tablets

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

Method of Manufacture

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

EXAMPLE B

Capsules

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

Method of Manufacture

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

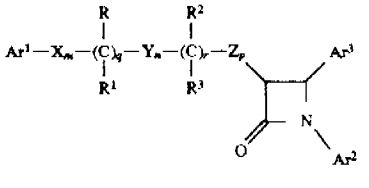
Representative formulations comprising a cholesterol biosynthesis inhibitor are well known in the art. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms disclosed above for substituted azetidinone compounds may readily be modified using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

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

	% Reduction				% Reduction		
Ex. #	Serum Cholest.	Cholest. Esters	Dose mg/kg	Ex. #	Serum Cholest.	Cholest. Esters	Dose mg/kg
1A	–23	0	50	4C	12.5	0	3
1B	–15	–39	50	4D	9	0	7
1C	14	0	50	4E	0	–46	3
2	0	0	50	4F	–29	–95	3
3A	–31	–69	50	5	0	–64	10
3C	–60	–92	50	6A	–59	–95	1
3D	–17	–61	10	6A-1	–43	–93	1
3E	0	0	10	6B	–40	–92	3
3F	–29	–77	10	6C	0	–48	3
3G	–16	–38	10	6D	–46	–95	10
3H	–41	–86	10	8A	0	–44	3
3I	0	–22	10	8B	–50	–95	3
3J	0	0	3	8C	–14	–37	1
3K	0	0	10	8D	–49	–98	1
3L	–15	–21	10	8E	–22	–66	3
3M	0	–22	10	8F	–43	–94	1
4A	0	–54	5	10	–26	–77	3
4B	–37	–89	8				

We claim:

1. A compound represented by the formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of —CH_2—, —CH(lower alkyl)- and —C(dilower alkyl)-;

R and R^2 are independently selected from the group consisting of —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$ and —$O(CO)NR^6R^7$;

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

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

R^4 is 1–5 substituents independently selected from consisting of lower alkyl, —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, -COR^6, -$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, —CH=CH—$COOR^6$, —CF_3, —CN, —NO_2 and halogen;

R^5 is 1–5 substituents independently selected from the group consisting of —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and —CH=CH—$COOR^6$;

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

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

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

3. A compound of claim **2** wherein Ar^1 is R^4-substituted phenyl wherein R^4 is halogen; Ar^2 is R^4-substituted phenyl wherein R^4 is halogen or —OR^6, wherein R^6 is lower alkyl or hydrogen; and Ar^3 R^5-substituted phenyl, wherein R^5 is —OR^6, wherein R6 is lower alkyl or hydrogen.

4. A compound of claim **1** wherein X, Y, and Z are each —CH_2—; R^1 and R^3 are each hydrogen; R and R^2 are each —OR^6, wherein R^6 is hydrogen; and the sum of m, n, p, q and r is 2, 3 or **4**.

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

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

7. A compound selected from the group consisting of

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,767,115
DATED : JUNE 16, 1998
INVENTOR(S) : STUART B. ROSENBLUM, SUNDEEP DUGAR, DUANE A. BURNETT, JOHN W. CLADER AND BRIAN A. MCKITTRICK

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 40, line 3, change "4(3S)" to read --4(S)--.

In column 40, line 17, change "phenyl]-1,4(S)' " to read --phenyl]propyl]-1,4(S)--.

In column 40, line 19, change "(4-hydroxyphenyl)" to read --(4-hydroxyphenyl)--.

In column 40, line 29, change "(4-fluorophenyl)" to read --(4-fluorophenyl)--.

Signed and Sealed this

Fifteenth Day of September, 1998

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

US 20020128253A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2002/0128253 A1**

Glombik et al. (43) **Pub. Date: Sep. 12, 2002**

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

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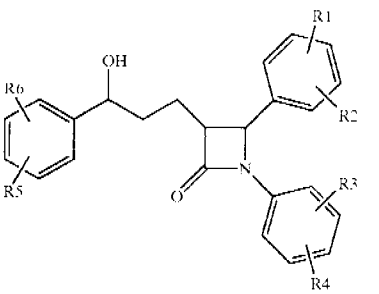
(57) **ABSTRACT**

Compounds of the formula I,



I

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

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

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

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

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

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

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

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

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

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

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

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

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

[0061] In a further embodiment, the compounds of the formula I are administered in combination with CART agonists, NPY agonists, MC4 agonists, orexin agonists, H3 agonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists, β3-agonists, MSH (melanocyte-stimulating hormone) agonists, CCK agonists, serotonin reuptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone-releasing compounds, TRH agonists, decoupling protein 2- or 3 modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR-β agonists.

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

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

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

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

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

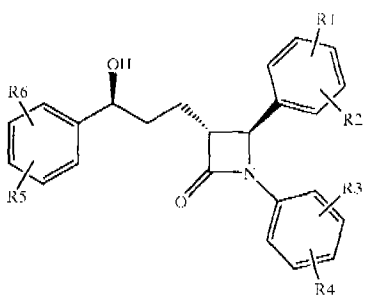
[0067] In one embodiment, the further active compound is mazindol or phentermine.

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

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

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

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



[0106] Effect on Cholesterol Absorption+^{3}H-taurocholic Acid Excretion Using Fecal Excrement of Mice, Rats or Hamsters

[0107] NMRI mice, Wistar rats, or Golden Syrian hamsters (in groups of n=4-6) are kept in metabolic cages, where they are fed with a standard diet (Altromin, Lage (Lippe)). The afternoon prior to the administration of the radioactive tracers (^{14}C-cholesterol), the feed is removed and the animals are adapted to grates.

[0108] Additionally, the animals are labeled s.c. with ^{3}H-TCA (taurocholic acid) (for example 1 μCi/mouse up to 5 μCi/rat) 24 hours prior to the peroral administration of the test meal (^{14}C-cholesterol in Intralipid® 20, Pharmacia-Upjohn).

[0109] Cholesterol absorption test: 0.25 ml/mouse Intralipid® 20 (Pharmacia-Upjohn) ((spiked with 0.25 μCi of ^{14}C-cholesterol in 0.1 mg of cholesterol) is administered perorally by gavage.

[0110] Test substances are prepared separately in 0.5% methylcellulose (Sigma)/5% Solutol (BASF, Ludwigshafen) or a suitable vehicle.

[0111] The administration volume of the test substance is 0.5 ml/mouse. The test substance is administered immediately prior to the test meal (Intralipid labeled with ^{14}C-cholesterol) (cholesterol absorption test).

[0112] The feces are collected over a period of 24 h: fecal elimination of ^{14}C-cholesterol and ^{3}H-taurocholic acid (TCA) is determined after 24 hours.

[0113] The livers are removed and homogenized, and aliquots are incinerated in an oximate (Model 307, Packard) to determine the amount of ^{14}C-cholesterol which had been taken up/absorbed.

[0114] Evaluation:

[0115] Feces Samples:

[0116] The total weight is determined, the sample is made up with water to a defined volume and then homogenized, and an aliquot is evaporated to dryness and incinerated in an oximate (Model 307 from Packard for the incineration of radioactively labeled samples): the amount of radioactive ^{3}H—H_2O and ^{14}C—CO_2 is extrapolated to the amount of ^{3}H-taurocholic acid and ^{14}C-cholesterol, respectively, that is excreted (dual isotope technique). The ED_{200} values as dose from a dose-effect curve are interpolated as those doses at which the excretion of TCA or cholesterol is doubled, based on a control group treated at the same time.

[0117] Liver Samples:

[0118] The amount of ^{14}C-cholesterol taken up by the liver is based on the administered dose. The ED_{50} values are interpolated from a dose-effect curve as the dose at which the uptake of ^{14}C-cholesterol by the liver is halved (50%), based on a control group.

[0119] The ED_{50} values below demonstrate the activity of the compounds of the formula I according to the invention

Example No.	ED_{50} (liver) [mg/mouse]
XVI	0.03
XVIII	0.3
XIX	0.1

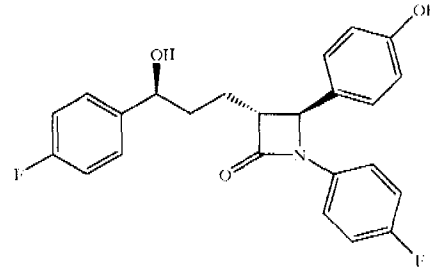
[0120] As can be seen from the table, the compounds of the formula I have very good cholesterol-lowering action. The compounds can thus be used to control cholesterol concentration. Such control can be by lowering the cholesterol concentation, or maintaining a desired level of cholesterol concentation.

[0121] Bioabsorption:

[0122] The bioabsorption of the compounds of the formula I can be examined using the Caco cell model (A. R. Hilgers et al., Caco-2 cell monolayers as a model for drug transport across the intestinal mucosa, Pharm. Res. 1990, 7, 902).

[0123] Below is a bioabsorption measurement for a reference compound

	Reference structure	Example
Apparent partition coefficient P_{app} [cm/s] (according to Lit. Hilgers)	4.88×10^{-06}	
Estimated human bioabsorption	100%	

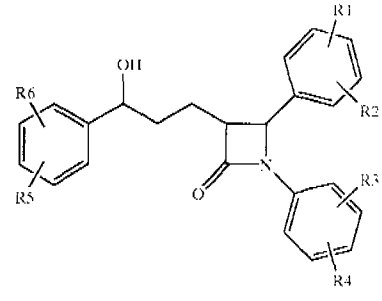


Reference structure: Ezetimibe

We claim:

1. A compound of the formula I,

I



or a pharmaceutically acceptable salt or ester thereof, in which

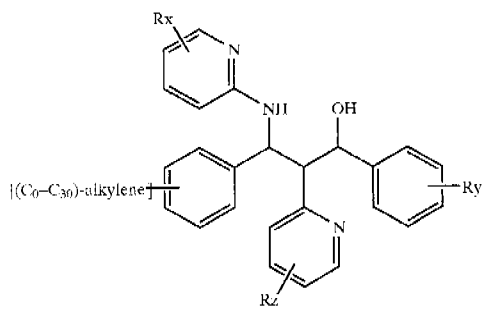
R1, R2, R3, R4, R5, R6 independently of one another are (C_0-C_{30})-alkylene-L, where one or more carbon atoms of the alkylene radical may be replaced by —O—, —(C=O)—, —CH=CH—, —C≡C—, —N((C_1-C_6)-alkyl)- or —NH—, or

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

SO_2—NH_2, $SO_2NH(C_1-C_6)$-alkyl, $SO_2N[(C_1-C_6)$-alkyl$]_2$, S—(C_1-C_6)-alkyl, S—$(CH_2)_n$-phenyl, SO—(C_1-C_6)-alkyl, SO—$(CH_2)_n$-phenyl, SO_2—(C_1-C_6)-alkyl or SO_2—$(CH_2)_n$-phenyl, where n=0-6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, (C_1-C_6)-alkyl or NH_2; or

NH_2, NH—(C_1-C_6)-alkyl, N((C_1-C_6)-alkyl$)_2$, NH(C_1-C_7)-acyl, phenyl or O—$(CH_2)_n$-phenyl, where n=0-6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, NH_2, NH(C_1-C_6)-alkyl, N((C_1-C_6)-alkyl$)_2$, SO_2—CH_3, COOH, COO—(C_1-C_6)-alkyl or $CONH_2$;

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



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

SO_2—NH_2, SO_2NH—(C_1-C_6)-alkyl, SO_2N—$[(C_1-C_6)$-alkyl$]_2$, S—(C_1-C_6)-alkyl, S—$(CH_2)_n$-phenyl, SO—(C_1-C_6)-alkyl, SO—$(CH_2)_n$-phenyl, SO_2—(C_1-C_6)-alkyl or SO_2—$(CH_2)_n$-phenyl, where n=0-6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, (C_1-C_6)-alkyl or NH_2; or

NH_2, NH—(C_1-C_6)-alkyl, N—$((C_1-C_6)$-alkyl$)_2$, NH—(C_1-C_7)-acyl, phenyl or O—$(CH_2)_n$-phenyl, where n=0-6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, NH_2, NH—(C_1-C_6)-alkyl, N—$((C_1-C_6)$-alkyl$)_2$, SO_2—CH_3, COOH, COO—(C_1-C_6)-alkyl or $CONH_2$;

wherein at least one of the radicals R1 to R6 has the meaning (C_0-C_{30})-alkylene-L, where one or more carbon atoms of the alkylene radical may be replaced by —O—, —(C=O)—, —CH=CH—, —C≡C—, —N((C_1-C_6)-alkyl)-, or —NH—.

2. A compound as claimed in claim 1, wherein

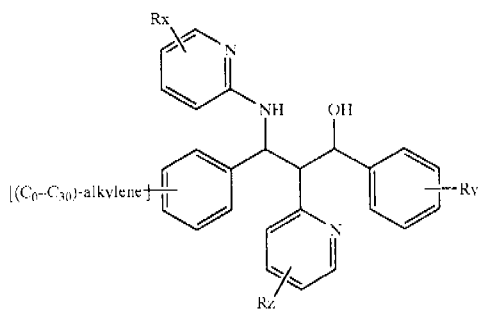
R1, R2, R3, R4, R5, R6 independently of one another are (C_0-C_{30})-alkylene-L, where one or more carbon atoms of the alkylene radical may be replaced by —O—, —(C=O)— or —NH—, or

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

SO_2-NH_2, $SO_2NH(C_1-C_6)$-alkyl, $SO_2N[(C_1-C_6)$-alkyl$]_2$, S—(C_1-C_6)-alkyl, S—$(CH_2)_n$-phenyl, SO—(C_1-C_6)-alkyl, SO—$(CH_2)_n$-phenyl, SO_2—(C_1-C_6)-alkyl or SO_2—$(CH_2)_n$-phenyl, where n=0-6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, (C_1-C_6)-alkyl or NH_2; or

NH_2, NH—(C_1-C_6)-alkyl, N$((C_1-C_6)$-alkyl$)_2$, NH(C_1-C_7)-acyl, phenyl or O—$(CH_2)_n$-phenyl, where n=0-6 and the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, NH_2, NH(C_1-C_6)-alkyl, N$((C_1-C_6)$-alkyl$)_2$, SO_2—CH_3, COOH, COO—(C_1-C_6)-alkyl or $CONH_2$;

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



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

SO_2—NH_2, SO_2NH—(C_1-C_6)-alkyl, SO_2N—$[(C_1-C_6)$-alkyl$]_2$, S—(C_1-C_6)-alkyl, S—$(CH_2)_n$-phenyl,

SO—(C_1-C_6)-alkyl, SO—(CH_2)$_n$-phenyl, SO_2—(C_1-C_6)-alkyl or SO_2—(CH_2)$_n$-phenyl, where n=0-6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, (C_1-C_6)-alkyl or NH_2; or

NH_2, NH—(C_1-C_6)-alkyl, N—((C_1-C_6)-alkyl)$_2$, NH—(C_1-C_7)-acyl, phenyl or O—(CH_2)$_n$-phenyl, where n=0-6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, NH_2, NH—(C_1-C_6)-alkyl, N—((C_1-C_6)-alkyl)$_2$, SO_2—CH_3, COOH, COO—(C_1-C_6)-alkyl or $CONH_2$;

wherein at least one of the radicals R1 to R6 has the meaning (C_0-C_{30})-alkylene-L, where one or more carbon atoms of the alkylene radical may be replaced by —O—, —(C═O)— or —NH—.

3. A compound as claimed in claim 1, wherein

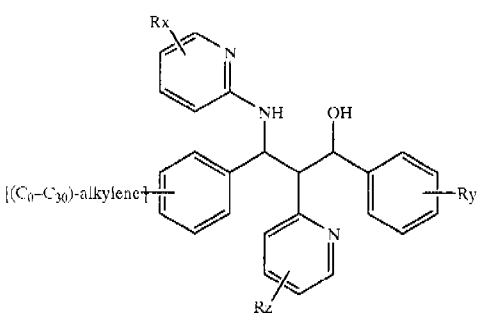
R1, R2, R3, R4, R5, R6 independently of one another are (C_0-C_{30})-alkylene-L, where one or more carbon atoms of the alkylene radical may be replaced by —O—, —(C═O)— or —NH—, or

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

SO_2—NH_2, SO_2NH(C_1-C_6)-alkyl, SO_2N[(C_1-C_6)-alkyl]$_2$, S—(C_1-C_6)-alkyl, S—(CH_2)$_n$-phenyl, SO—(C_1-C_6)-alkyl, SO—(CH_2)$_n$-phenyl, SO_2—(C_1-C_6)-alkyl or SO_2—(CH_2)$_n$-phenyl, where n=0-6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, (C_1-C_6)-alkyl or NH_2; or

NH_2, NH—(C_1-C_6)-alkyl, N((C_1-C_6)-alkyl)$_2$, NH(C_1-C_7)-acyl, phenyl or O—(CH_2)$_n$-phenyl, where n=0-6 and the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, NH_2, NH(C_1-C_6)-alkyl, N((C_1-C_6)-alkyl)$_2$, SO_2—CH_3, COOH, COO—(C_1-C_6)-alkyl or $CONH_2$;

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



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

SO_2—NH_2, SO_2NH—(C_1-C_6)-alkyl, SO_2N—[(C_1-C_6)-alkyl]$_2$, S—(C_1-C_6)-alkyl, S—(CH_2)$_n$-phenyl, SO—(C_1-C_6)-alkyl, SO—(CH_2)$_n$-phenyl, SO_2—(C_1-C_6)-alkyl or SO_2—(CH_2)$_n$-phenyl, where n=0-6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, (C_1-C_6)-alkyl or NH_2; or

NH_2, NH—(C_1-C_6)-alkyl, N—((C_1-C_6)-alkyl)$_2$, NH—(C_1-C_7)-acyl, phenyl or O—(CH_2)$_n$-phenyl, where n=0-6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, NH_2, NH—(C_1-C_6)-alkyl, N—((C_1-C_6)-alkyl)$_2$, SO_2—CH_3, COOH, COO—(C_1-C_6)-alkyl or $CONH_2$;

where one of the radicals R1 or R3 has the meaning (C_0-C_{30})-alkylene-L, where one or more carbon atoms of the alkylene radical may be replaced by —O—, —(C═O)— or —NH—.

4. A compound as claimed in claim 1, wherein

R1, R2, R3, R4, R5, R6 independently of one another are

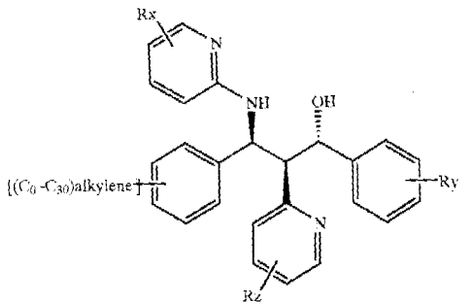
–(CH_2)$_{0-1}$—NH—(C═O)$_{0-1}$—(C_3-C_{25})-alkylene-(C═O)$_{0-1}$—NH—L, where one or more carbon atoms of the alkylene radical may be replaced by oxygen atoms, or

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

SO_2—NH_2, SO_2NH(C_1-C_6)-alkyl, SO_2N[(C_1-C_6)-alkyl]$_2$, S—(C_1-C_6)-alkyl, S—(CH_2)$_n$-phenyl, SO—(C_1-C_6)-alkyl, SO—(CH_2)$_n$-phenyl, SO_2—(C_1-C_6)-alkyl or SO_2—(CH_2)$_n$-phenyl, where n=0-6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, (C_1-C_6)-alkyl or NH_2; or

NH_2, NH—(C_1-C_6)-alkyl, N((C_1-C_6)-alkyl)$_2$, NH(C_1-C_7)-acyl, phenyl or O—(CH_2)$_n$-phenyl, where n=0-6 and the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, NH_2, NH(C_1-C_6)-alkyl, N((C_1-C_6)-alkyl)$_2$, SO_2—CH_3, COOH, COO—(C_1-C_6)-alkyl or $CONH_2$;

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



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

SO_2—NH_2, SO_2NH—$(C_1$-$C_6)$-alkyl, SO_2N—$[(C_1$-$C_6)$-alkyl$]_2$, S—$(C_1$-$C_6)$-alkyl, S—$(CH_2)_n$-phenyl, SO—$(C_1$-$C_6)$-alkyl, SO—$(CH_2)_n$-phenyl, SO_2—$(C_1$-$C_6)$-alkyl or SO_2—$(CH_2)_n$-phenyl, where n=0-6 and the phenyl radical may be substituted up to two times by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O—$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl or NH_2; or

NH_2, NH—$(C_1$-$C_6)$-alkyl, N—$((C_1$-$C_6)$-alkyl$)_2$, NH—$(C_1$-$C_7)$-acyl, phenyl or O—$(CH_2)_n$-phenyl, where n=0-6, where the phenyl ring may be mono- to trisubstituted by F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl, NH_2, NH—$(C_1$-$C_6)$-alkyl, N—$((C_1$-$C_6)$-alkyl$)_2$, SO_2—CH_3, COOH, COO—$(C_1$-$C_6)$-alkyl or $CONH_2$;

where one of the radicals R1 or R3 has the meaning —$(CH_2)_{0-2}$—NH—$(C{=}O)_{0-1}$—$(C_3$-$C_{25})$-alkylene-$(C{=}O)_{0-1}$—NH—L, where one or more carbon atoms of the alkylene radical may be replaced by oxygen atoms.

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

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

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

8. A pharmaceutical composition as claimed in claim 6, which comprises, as a further active compound, one or more antidiabetics, hypoglycemically active compounds, HMG-CoA reductase inhibitors, cholesterol absorption inhibitors, PPAR gamma agonists, PPAR alpha agonists, PPAR alpha/gamma agonists, fibrates, MTP inhibitors, bile acid absorption inhibitors, CETP inhibitors, polymeric bile acid adsorbers, LDL receptor inducers, ACAT inhibitors, antioxidants, lipoprotein lipase inhibitors, ATP citrate lyase inhibitors, squalene synthetase inhibitors, lipoprotein(a) antagonists, lipase inhibitors, insulins, sulfonyl ureas, biguanides, meglitinides, thiazolidindiones, α-glucosidase inhibitors, active compounds which act on the ATP-dependent potassium channel of the beta cells, CART agonists, NPY agonists, MC4 agonists, orexin agonists, H3 agonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists, β3 agonists, MSH (melanocyt-stimulating hormone) agonists, CCK agonists, serotonin-reuptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT agonists, bombesin agonists, galanin antagonists, growth hormones, growth hormone-releasing compounds, TRH agonists, decoupling protein 2- or 3-modulators, leptin agonists, DA agonists, lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR-β-agonists or amphetamines.

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

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

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

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

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

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

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

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

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

* * * * *

US005633246A

United States Patent [19]

McKittrick et al.

[11] Patent Number: 5,633,246

[45] Date of Patent: May 27, 1997

[54] **SULFUR-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS**

[75] Inventors: **Brian A. McKittrick**, Bloomfield; **Sundeep Dugar**, Bridgewater; **Duane A. Burnett**, Fanwood, 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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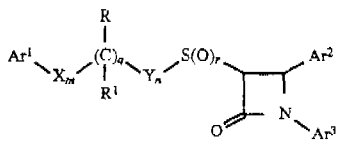
Primary Examiner—Mark L. Berch
Attorney, Agent, or Firm—Anita W. Magatti; Eric S. Dicker

[57] **ABSTRACT**

Sulfur-substituted azetidinone hypocholesterolemic agents of the formula



I

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is aryl, R^{10}-substituted aryl or heteroaryl;

Ar^2 is aryl or R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X and Y are —CH_2—, —CH(lower alkyl)— or —C(dilower alkyl)—;

R is —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$ or —$O(CO)NR^6R^7$; R^1 is hydrogen, lower alkyl or aryl; or R and R^1 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;

R^4 is selected from lower alkyl, —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)—$COOR^6$ and —CH=CH—$COOR^6$;

R^5 is selected from —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —CF_3, —CN, —NO_2, halogen, —(lower alkylene)$COOR^6$ and —CH=CH—$COOR^6$;

R^6, R^7 and R^8 are H, lower alkyl, aryl or aryl-substituted lower alkyl;

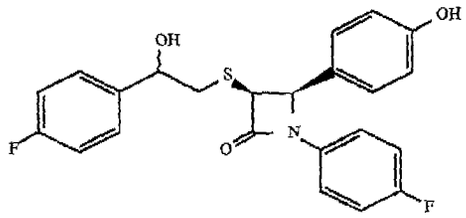
R^9 is lower alkyl, aryl or aryl-substituted lower alkyl; and

R^{10} is selected from lower alkyl, —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —CF_3, —CN, —NO_2 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 inhibitor.

15 Claims, No Drawings

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.

EXAMPLE A

Tablets

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

Method of Manufacture

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

EXAMPLE B

Capsules

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

Method of Manufacture

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

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

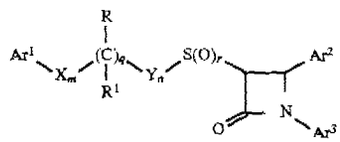
Using the test procedures described above, the following in vivo data were obtained for representative preferred compounds of formula I. Data is reported as percent change (i.e., percent reduction in cholesterol esters) versus control, therefore, negative numbers indicate a positive lipic-lowering effect.

	% Reduction		
Ex. #	Serum Cholest.	Cholest. Esters	Dose mg/kg
1	–27	–83	1
2b	–28	–82	1
5	–42	–97	1
6a	–42	–95	1
6b	–38	–95	1
7a	0	–48	0.1
7d	0	–42	0.1
9b	–24	–63	0.1
11	–55	–95	3
14	–20	–64	3
15	–27	–88	1
18	–27	–68	3

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

We claim:

1. A compound represented by the formula



I

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is heteroaryl;

Ar^2 is aryl or R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X and Y are independently selected from the group consisting of $—CH_2—$, —CH(lower alkyl)— and —C(dilower alkyl)—;

R is $—OR^6$, $—O(CO)R^6$, $—O(CO)OR^9$ or $—O(CO)NR^6R^7$; R^1 is hydrogen, lower alkyl or aryl; or R and R^1 together are =O;

q is 0 or 1;

r is 0, 1 or 2;

m and n are independently 0, 1, 2, 3, 4 or 5; provided that the sum of m, n and q is 1, 2, 3, 4 or 5;

R^4 is 1–5 substituents independently selected from the group consisting of lower alkyl, $—OR^6$, $—O(CO)R^6$, $—O(CO)OR^9$, $—O(CH_2)_{1-5}OR^6$, $—O(CO)NR^6R^7$, $—NR^6R^7$, $—NR^6(CO)R^7$, $—NR^6(CO)OR^9$, $—NR^6(CO)NR^7R^8$, $—NR^6SO_2R^9$, $—COOR^6$, $—CONR^6R^7$, $—COR^6$, $—SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $—O(CH_2)_{1-10}—COOR^6$, $—O(CH_2)_{1-10}CONR^6R^7$, —(lower alkylene)$COOR^6$ and $—CH=CH—COOR^6$;

R^5 is 1–5 substituents independently selected from the group consisting of —OR^6, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —CF_3, —CN, —NO_2, halogen, —(lower alkylene)$COOR^6$ and —CH=CH—$COOR^6$;

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

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, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)NR^6R^7$, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —CF_3, —CN, —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 —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 —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 —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 —OR^6, wherein R^6 is hydrogen, or wherein R and R^1 together form a =O group.

10. A compound of claim **7** wherein X and Y are each —CH_2—; the sum of m and n is 1, 2 or 3; and R^1 is hydrogen and R is —OR^6, wherein R^6 is hydrogen, or wherein R and R^1 together form a =O group.

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.

* * * * *

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; **Sundeep Dugar**, 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, Jun. 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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WO 95/26334	10/1995	WIPO .
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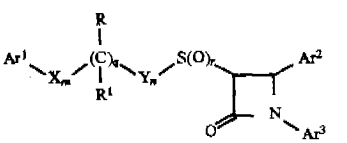
Primary Examiner—C. Warren Ivy
Assistant Examiner—D. Margaret M. Mach
Attorney, Agent, or Firm—Anita W. Magatti

[57] **ABSTRACT**

Sulfur-substituted azetidinone hypocholesterolemic agents of the formula



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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.

12 Claims, No Drawings

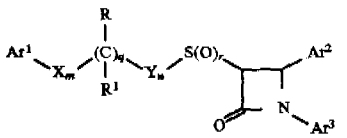
-continued

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

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

We claim:

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



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or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is aryl, R^{10}-substituted aryl or heteroaryl;

Ar^2 is aryl or R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X and Y are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and -C(dilower alkyl)-;

R is $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$ or $-O(CO)NR^6R^7$; R^1 is hydrogen, lower alkyl or aryl; or R and R^1 together are =O;

q is 0 or 1;

r is 0, 1 or 2;

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

R^4 is 1–5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and $-CH=CH-COOR^6$;

R^5 is 1–5 substituents independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, $-CF_3$, -CN, $-NO_2$, halogen, -(lower alkylene)$COOR^6$and $-CH=CH-COOR^6$;

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

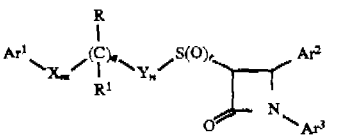
R^9 is lower alkyl, aryl or aryl-substituted lower alkyl; and

R^{10} is 1–5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, $-CF_3$, -CN, $-NO_2$ 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 atorvastastin.

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



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or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is aryl, R^{10}-substituted aryl or heteroaryl;

Ar^2 is aryl or R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X and Y are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and -C(dilower alkyl)-;

R is $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$ or $-O(CO)NR^6R^7$; R^1 is hydrogen, lower alkyl or aryl; or R and R^1 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;

R^4 is 1–5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and $-CH=CH-COOR^6$;

R^5 is 1–5 substituents independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, $-CF_3$, -CN, $-NO_2$, halogen, -(lower alkylene)$COOR^6$and $-CH=CH-COOR^6$;

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

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, —$O(CO)R^6$, —$O(CO)OR^9$, —$O(CH_2)_{1-5}OR^6$, —$O(CO)$ NR^6R^7, —NR^6R^7, —$NR^6(CO)R^7$, —$NR^6(CO)OR^9$, —$NR^6(CO)NR^7R^8$, —$NR^6SO_2R^9$, —$COOR^6$, —$CONR^6R^7$, —COR^6, —$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, —$O(CH_2)_{1-10}$—$COOR^6$, —$O(CH_2)_{1-10}CONR^6R^7$, —CF_3, —CN, —NO_2 and halogen.

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

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

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

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

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

trans-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-thio]-2-azetidinone;

trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl) thio]-2-azetidinone;

cis-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl) thio]-2-azetidinone;

trans-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;

cis-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;

trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl) sulfinyl]-2-azetidinone;

cis-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl) sulfinyl]-2-azetidinone;

trans-4-[1-(4-fluorophenyl)-4-oxo-3-[(2-phenylethyl) sulfinyl]-2-azetidinyl]-phenyl acetate;

cis-4-[1-(4-fluorophenyl)-4-oxo-3-[(2-phenylethyl) sulfinyl]-2-azetidinyl]-phenyl acetate; and

(+/−)-trans-4-(4-methoxyphenyl)- 1-phenyl-3-[(2-phenylethyl)-sulfonyl]-2-azetidinone;

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

trans-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-hydroxyethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

trans-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-thio]-2-azetidinone;

trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl) thio]-2-azetidinone;

cis-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl) thio]-2-azetidinone;

trans-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;

cis-1-(4-fluorophenyl)-4-(4-hydroxyphenyl)-3-[(2-phenylethyl)-sulfinyl]-2-azetidinone;

trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl) sulfinyl]-2-azetidinone;

cis-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl) sulfinyl]-2-azetidinone;

trans-4-[1-(4-fluorophenyl)-4-oxo-3-[(2-phenylethyl) sulfinyl]-2-azetidinyl]-phenyl acetate;

cis-4-[1-(4-fluorophenyl)-4-oxo-3-[(2-phenylethyl) sulfinyl]-2-azetidinyl]-phenyl acetate; and

(+/−)-trans-4-(4-methoxyphenyl)-1-phenyl-3-[(2-phenylethyl)-sulfonyl]-2-azetidinone;

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

trans-1-(4-fluorophenyl)-3-[[2-(4-fluorophenyl)-2-hydroxyethyl]thio]-4-(4-hydroxyphenyl)-2-azetidinone;

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

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

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

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

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

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

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

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

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

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

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

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

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