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ABOGADOS

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Radicación : 00002439 00000005

Fecha (MM/AA): 2002-10-22 16:48:57

Trámite : 002 PATENTES & 1 REGISTRO/ 530 PETICION

Dependencia: 1003 DELEGADO PRODUCCION COMPETENCIA

Folios:

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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

TRÁMITE : 002

EVENTO : 001

ACTUACIÓN : 538

Referencia : Expediente No. 00-002.439

Asunto : Solicitud de patente para COMPUESTOS
HETEROCICLICOS AROMATICOS COMO AGENTES
ANTIINFLAMATORIOS

Solicitante : BOEHRINGER INGELHEIM PHARMACEUTICALS INC.

Fecha de solicitud : 18 de enero de 2000

Publicada en : la Gaceta No. 515 del 29 de Abril de 2002

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo No. 02-60,076 por valor de \$318.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 44691 del 31 de diciembre de 2001.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo, para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Bogotá, 22 OCT 2002
Señora Jefe,


EMILIO FERRERO
T.P.A. No. 31.929

COLO 07612-801-014-7
UBP/JFR/ID-000165/WPCL7612

NIT. 860.041.367-3

37A

Industria y Comercio

NIT : 800176089-2

Radicacion : 00002439 00000005 Folios: 2
Fecha (MM): 2002-10-22 15:48:57
Tramite : 002 PATENTES D 1 REGISTRO/ 536 PETICION
Dependencia: 1000 DELEGADO PRODUCCION COMPETENCIA

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314

RECIBO OFICIAL DE CAJA : 02 - 60,076
FECHA : SEPTIEMBRE 10 DE 2002

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	3344175	10/09/2002	23,267,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	318,000.00
		TOTAL :	318,000.00

SON: TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Colo 07612-801-014-7

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020

Bogotá, DC,

Apoderado: Emillo Ferrero

Oficio

09045

ASUNTO

Radicación: 00-2439

Trámite 002

Evento 001

Actuación 430

Folios

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados:

- ◆capítulo descriptivo, folios 12 a 116;
- ◆capítulo reivindicatorio modificado despues del 2° examen de forma, folios 311 a 321;
- ◆1° examen de forma, folios 101 y 102;
- ◆solicitudes delas cuales se revindica prioridad junto su traducción, 105 a 291;
- ◆respuesta al 1° examen de forma, folios 292 a 299;
- ◆2° examen de forma, folio 308;
- ◆solicitud de examen de patentabilidad, folios 322 y 324.

Objeto de la invención:

El título de la invención "COMPUESTOS HETEROCICLICOS AROMATICOS COMO AGENTES ANTINFLAMATORIOS".

Tienen como objeto los compuestos derivados biaril ureas o biaril tioureas, que tienen un efecto farmacologico como antinflamatorios.

El campo de la invención, según la Clasificación Internacional de Patentes: A61K31/17 // 31/33.

Claridad de la solicitud:

En el artículo 30 de la Decisión 486 de la Comisión de la Comunidad Andina se establece: *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*.

La reivindicación 21 no es clara, puesto que se hace referencia a *"sus derivados farmacéuticamente aceptables"*, son términos especulativos, porque en la descripción no se describe ningún derivado farmacéuticamente aceptable, además con tales términos no se puede identificar inequívocamente ninguna estructura química, entonces es indefinido e ilimitado el alcance de la reivindicación y no esta sustentada enteramente en la descripción.

Excepciones de Patentabilidad:

El artículo 20 de la Decisión 486 de la Comisión de la Comunidad Andina establece en su inciso d) que no serán patentables: *"los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*.

Las reivindicaciones que reclaman métodos de tratamiento para el cuerpo humano o animal son las reivindicaciones 16 a 19.

Por esta razón, las reivindicaciones 16 a 19 no son materia patentable.

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión establece: *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."*

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese

anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

Se realizo la búsqueda del estado de la técnica con fecha anterior a la fecha de presentación de presente solicitud, ya que no se reivindica prioridad, 29 de octubre de 1998. Consultada la fuente de información con que cuenta este despacho se encontró el siguiente documento:

No.	Documento No.	Título	*Fecha de Publicación
D1	US 5.162.360	2-Heteroatom containing urea and thiorea ACAT Inhibitors	10-nov-1992

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece:
"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."

En cumplimiento con este artículo, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

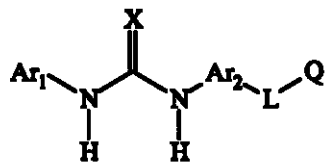
Evaluación de la Novedad:

El art.16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica."* *"El estado de la técnica comprenderá todo lo que haya sido accesible al*

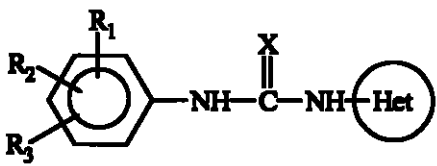
público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

La solicitud en estudio reclama atropismeros de biaril ureas o biaril tioureas de formulas (la):



La anterioridad D1 enseña compuestos biarilureas o biariltioureas de fórmula:



que comprenden las mismas estructuras con los mismos sustituyentes, de la solicitud en estudio de la reivindicación 1.

No existe ninguna diferencia entre los compuestos reclamados como nuevos y los descritos en D1, por lo tanto los compuestos reclamados en la solicitud en estudio, no son nuevos e inventivos.

En conclusión los requisitos de Patentabilidad de la presente solicitud se ven afectados así:

No.	Documento	Reivindicación Afectada	Requisito que afecta
D1.	US 5.162.360	1	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la circular única No. 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
30 SET. 2004

CONCEPTO TÉCNICO No.	EXAMINADOR TÉCNICO Código No.
1177	202012

330
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United States Patent [19]
Creswell et al.

US005162360A
[11] **Patent Number:** 5,162,360
[45] **Date of Patent:** Nov. 10, 1992

[54] **2-HETEROATOM CONTAINING UREA AND THIOUREA ACAT INHIBITORS**

[75] **Inventors:** Mark W. Creswell, Chelsea; Andrew D. White, Lakeland, both of Mich.

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

[21] **Appl. No.:** 719,878

[22] **Filed:** Jun. 24, 1991

[51] **Int. Cl.³** A61K 31/495; C07D 277/04; C07D 401/00; C07D 413/00

[52] **U.S. Cl.** 514/371; 548/196; 546/187; 546/209; 544/367; 544/357; 514/316; 514/326; 514/252

[58] **Field of Search** 548/196; 546/187, 209; 544/367, 357; 514/252, 316, 326, 371

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,551,442 12/1970 Guillot et al. 548/196
3,821,239 6/1974 Guillot et al. 260/306
4,405,644 9/1983 Kabbe et al. 31/275

OTHER PUBLICATIONS

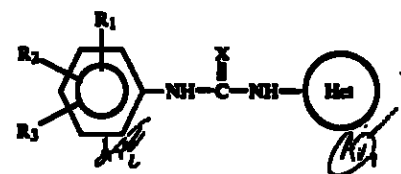
J. Med. Chem., 1979, vol. 22, No. 1, R. K. Y. Zee-Cheng et al., "Antileukemic Activity of Substituted

Ureidothiazoles, Ureidothiadiazoles, and Related Compounds".

Primary Examiner—Mary C. Lee
Assistant Examiner—Robert C. Whittenbaugh
Attorney, Agent, or Firm—Ruth H. Newton; Ronald A. Daignault

[57] **ABSTRACT**

The present invention provides N-substituted aryl-N'-heterocyclic substituted ureas and thioureas of the formula



wherein R₁, R₂ and R₃ are hydrogen, fluorine, chlorine, bromine, alkyl, alkoxy, substituted or unsubstituted benzoyl, substituted or unsubstituted phenyl, amino, substituted amino, or a monocyclic heterocyclic, or a carboxy group; and Het is a substituted monocyclic heterocyclic group containing two hetero atoms selected from nitrogen, oxygen or sulfur; which are useful in treating hypercholesterolemia and atherosclerosis.

5 Claims, No Drawings

33T
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1

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2-HETEROATOM CONTAINING UREA AND THIOUREA ACAT INHIBITORS

BACKGROUND OF THE INVENTION

This invention relates to chemical compounds having pharmacological activity, to pharmaceutical compositions which include these compounds, and to a pharmaceutical method of treatment. More particularly, this invention concerns certain 2-heteroatom aryl ureas and thioureas which inhibit the enzyme acyl-coenzyme A:cholesterol acyltransferase (ACAT), pharmaceutical compositions containing these compounds, and a method of treating hypercholesterolemia and atherosclerosis.

In recent years the role which elevated blood plasma levels of cholesterol plays in pathological conditions in man has received much attention. Deposits of cholesterol in the vascular system have been indicated as causative of a variety of pathological conditions including coronary heart disease.

Initially, studies of this problem were directed toward finding therapeutic agents which would be effective in lowering total serum cholesterol levels. It is now known that cholesterol is transported in the blood in the form of complex particles consisting of a core of cholesteryl esters plus triglycerides and an exterior consisting primarily of phospholipids and a variety of types of protein which are recognized by specific receptors. For example, cholesterol is carried to the sites of deposit in blood vessels in the form of low density lipoprotein cholesterol (LDL cholesterol) and away from such sites of deposit by high density lipoprotein cholesterol (HDL cholesterol).

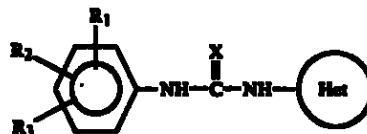
Following these discoveries, the search for therapeutic agents which control serum cholesterol turned to finding compounds which are more selective in their action; that is, agents which are effective in elevating the blood serum levels of HDL cholesterol and/or lowering the levels of LDL cholesterol. While such agents are effective in moderating the levels of serum cholesterol, they have little or no effect on controlling the initial absorption of dietary cholesterol in the body through the intestinal wall.

In intestinal mucosal cells, dietary cholesterol is absorbed as free cholesterol which must be esterified by the action of the enzyme acyl-CoA: cholesterol acyltransferase (ACAT) before it can be packaged into the chylomicrons which are then released into the blood stream. Thus, therapeutic agents which effectively inhibit the action of ACAT prevent the intestinal absorption of dietary cholesterol into the blood stream or the reabsorption of cholesterol which has been previously released into the intestine through the body's own regulatory action.

SUMMARY OF THE INVENTION

The present invention provides N-substituted aryl N'-heterocyclic substituted ureas and thioureas which are inhibitors of acyl-CoA: cholesterol acyltransferase (ACAT). More particularly, the present invention provides ACAT inhibitors wherein the acyl moiety is a substituted phenyl group and the heterocyclic moiety is a monocyclic heterocyclic group containing 2-hetero atoms selected from nitrogen, oxygen, and sulfur. The compounds of the present invention may be depicted by the following Formula I

Formula I



wherein

X is oxygen or sulfur;

wherein each of R₁, R₂, and R₃ is the same or different and is selected from

hydrogen,

fluorine,

chlorine,

bromine,

a straight or branched alkyl group having from one to six carbon atoms,

a straight or branched alkoxy group having from one to six carbon atoms,

benzoyl which is unsubstituted or is substituted on the aromatic ring with from one to three substituents selected from fluorine, chlorine, bromine, iodine, a

straight or branched alkyl group having from one to six carbon atoms, or a straight or branched alkoxy group having from one to six carbon atoms,

benzyl which is unsubstituted or is substituted on the aromatic ring with from one to three substituents selected from fluorine, chlorine, bromine, iodine, a

straight or branched alkyl group having from one to six carbon atoms, or a straight or branched alkoxy group having from one to six carbon atoms,

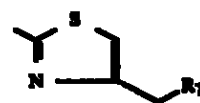
phenyl which is unsubstituted or is substituted with from one to three substituents selected from fluorine, chlorine, bromine, iodine, a straight or

branched alkyl group having from one to six carbon atoms, or a straight or branched alkoxy group having from one to six carbon atoms;

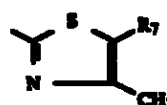
NR₄R₅ wherein each of R₄ and R₅ is the same or different and is hydrogen, a straight or branched alkyl group having from one to four carbon atoms or -NR₄R₅ taken together form a monocyclic heterocyclic group selected from pyrrolidino, piperidino, piperazino, or piperazino substituted on the 4-position with a straight or branched alkyl group having from one to four carbon atoms;

-COR₆ wherein R₆ is hydroxy, a straight or branched alkoxy group having from one to six carbon atoms, benzyloxy which is unsubstituted or is substituted on the aromatic ring with from one to three substituents selected from fluorine, chlorine, bromine, iodine, a straight or branched alkyl group having from one to six carbon atoms, or a straight or branched alkoxy group having from one to six carbon atoms, or R₆ is -NR₄R₅ wherein R₄ and R₅ have the meanings defined above;

wherein Het is selected from



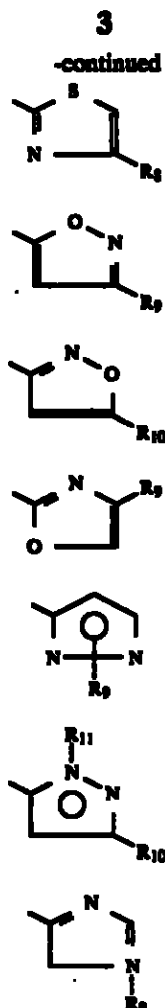
(1)



(2)

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wherein R_7 is hydrogen or straight or branched alkyl having from 1 to 14 carbon atoms;
 wherein R_8 is phenyl;
 wherein R_9 is straight or branched alkyl having from 1 to 16 carbon atoms;
 wherein R_{10} is R_9 or the group $-\text{CH}_2\text{NR}_9\text{R}_9$ wherein each R_9 is an alkyl group of from 1 to 10 carbon atoms;
 wherein R_{11} is benzyl, 2-pyridyl or hydrogen; and pharmaceutically acceptable salts and isomers thereof.

DETAILED DESCRIPTION OF INVENTION

Pharmaceutically acceptable salts of the compounds of Formula I are also included as a part of the present invention.

The acid addition salts may be generated from the free base forms of the compounds by reaction of the latter with one equivalent of a suitable nontoxic, pharmaceutically acceptable acid, followed by evaporation of the solvent employed for the reaction and recrystallization of the salt, if required. The free base may be recovered from the acid addition salt by reaction of the salt with a water solution of the salt with a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate, sodium hydroxide, and the like.

Suitable acids for forming acid addition salts of the compounds of this invention include, but are not necessarily limited to acetic, benzoic, benzenesulfonic, tartaric, hydrobromic, hydrochloric, citric, fumaric, glu-

conic, glucuronic, glutamic, lactic, malic, maleic, methanesulfonic, pantoic, salicylic, stearic, succinic, sulfuric, and tartaric acids. The class of acids suitable for the formation of nontoxic, pharmaceutically acceptable salts is well known to practitioners of the pharmaceutical formulation arts. (See, for example, Stephen N. Berge, et al, *J. Pharm. Sciences* 66:1-19 (1977)).

The compounds of the present invention may also exist in different stereoisomeric forms by virtue of the presence of one or more asymmetric centers in the compound. The present invention contemplates all stereoisomeric forms of the compounds as well as mixtures thereof, including racemic mixtures. Individual stereoisomers may be obtained, if desired, by methods known in the art as, for example, the separation of stereoisomers in chiral chromatographic columns.

Further, the compounds of this invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Preferred compounds of this invention are those wherein Het has the meaning defined in groups 4, 5, and 7 above with the more preferred compounds being those defined in groups 4 and 5. The most preferred compounds are those set forth below as Examples 8 through 17, 19, and 23.

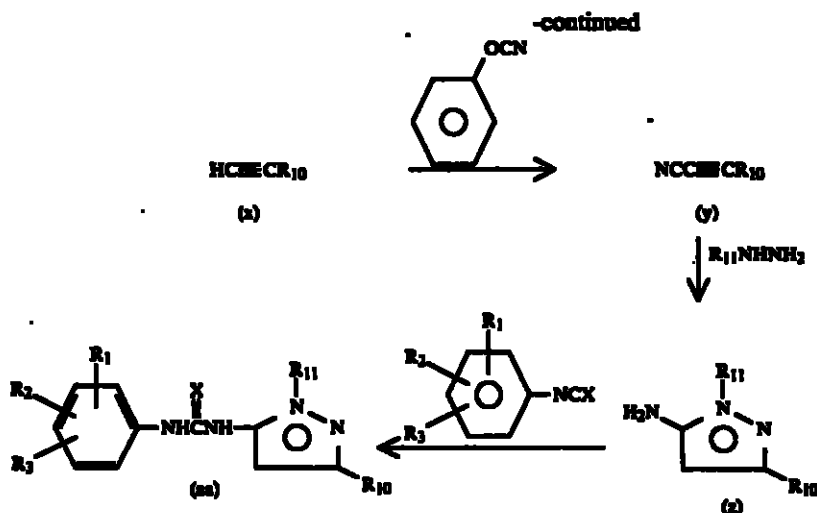
As shown by the data presented in Table 1, the compounds of the present invention are potent inhibitors of the enzyme acyl-CoA:cholesterol acyltransferase (ACAT), and are thus effective in inhibiting the esterification and transport of cholesterol across the intestinal cell wall. The compounds of the present invention are thus useful in pharmaceutical formulations for the treatment of hypercholesterolemia or atherosclerosis.

The ability of representative compounds of the present invention to inhibit ACAT was measured using an in vitro test more fully described by F. J. Field and R. G. Salone, in *Biochemistry and Biophysics* 712:557-570 (1982). The test assesses the ability of a test compound to inhibit the acylation of cholesterol by oleic acid by measuring the amount of radio-labeled cholesterol oleate formed from radiolabeled oleic acid in a tissue preparation containing rabbit intestinal microsomes.

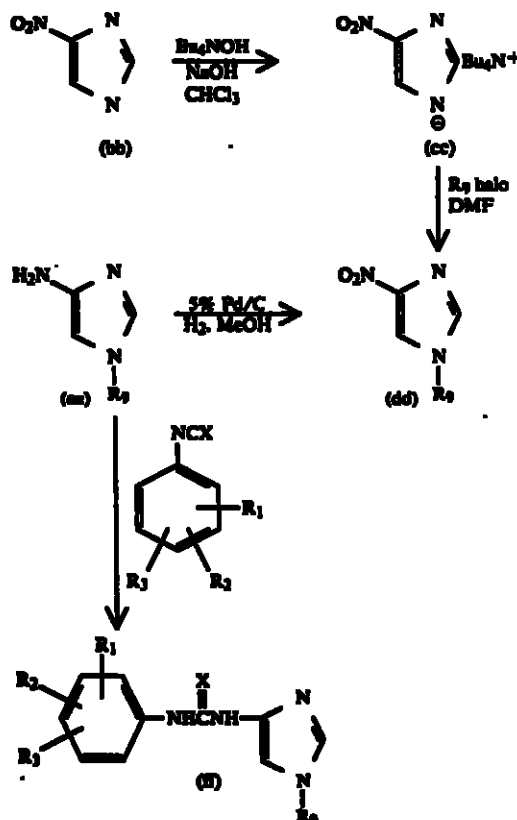
The data appear in Table 1 where they are expressed as IC_{50} values; i.e., the concentration of test compound required to inhibit 50% expression of the enzyme.

TABLE 1

Compound of Example	IC_{50} (μM)
1	0.12
2	0.13
3	1.9
4	1.6
5	>5
6	>5
7	>1
8	0.019
9	0.027
10	0.029
11	0.030
12	0.013
13	0.028
14	0.028
15	0.027
16	0.014
17	0.11
18	>5
19	0.51
20	2.7

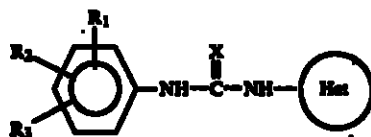


Scheme VIII:



We claim:

1. A compound of the formula



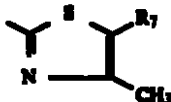
wherein
X is oxygen or sulfur;

wherein each of R_1 , R_2 , and R_3 is the same or different and is selected from
hydrogen,
fluorine,
chlorine,
bromine,
a straight or branched alkyl group having from one to six carbon atoms,
a straight or branched alkoxy group having from one to six carbon atoms,
benzoyl which is unsubstituted or is substituted on the aromatic ring with from one to three substituents selected from fluorine, chlorine, bromine, iodine, a straight or branched alkyl group having from one to six carbon atoms, or a straight or branched alkoxy group having from one to six carbon atoms,
benzyl which is unsubstituted or is substituted on the aromatic ring with from one to three substituents selected from fluorine, chlorine, bromine, iodine, a straight or branched alkyl group having from one to six carbon atoms, or a straight or branched alkoxy group having from one to six carbon atoms,
phenyl which is unsubstituted or is substituted with from one to three substituents selected from fluorine, chlorine, bromine, iodine, a straight or branched alkyl group having from one to six carbon atoms, or a straight or branched alkoxy group having from one to six carbon atoms,
 NR_4R_5 wherein each of R_4 and R_5 is the same or different and is hydrogen, a straight or branched alkyl group having from one to four carbon atoms or $-\text{NR}_4\text{R}_5$ taken together from a monocyclic heterocyclic group selected from pyrrolidino, piperidino, piperazine, or piperazine substituted on the 4-position with a straight or branched alkyl group having from one to four carbon atoms;
 $-\text{COR}_6$ wherein R_6 is hydroxy, a straight or branched alkoxy group having from one to six carbon atoms, benzoyloxy which is unsubstituted or is substituted on the aromatic ring with from one to three substituents selected from fluorine, chlorine, bromine, iodine, a straight or branched alkyl group having from one to six carbon atoms, or a straight or branched alkoxy group having from one to six carbon atoms, or R_6 is $-\text{NR}_4\text{R}_5$ wherein R_4 and R_5 have the meanings defined above;
wherein Het is selected from

23



or



wherein R₇ is straight or branched alkyl having from 9 to 14 carbon atoms;

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and pharmaceutically acceptable salts and isomers thereof

- (1) 2. A method for treating hypercholesterolemia and atherosclerosis in a patient in need thereof which comprises administering to said patient an effective amount of a compound of claim 1 together with a pharmaceutically acceptable carrier

3. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier

- (2) 4. A compound of claim 1 which is N-[2,6-bis(1-methylethyl)phenyl]-N'-(3-decyl-4-methyl-2-thiazolyl)urea or a pharmaceutically acceptable salt thereof

5. A compound of claim 1 which is N-[2,6-bis(1-methylethyl)phenyl]-N'-(4-undecyl-2-thiazolyl)urea or a pharmaceutically acceptable salt thereof

* * * * *

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