



[54] METHOD FOR LOWERING SERUM LIPID LEVELS EMPLOYING AN MTP INHIBITOR IN COMBINATION WITH ANOTHER CHOLESTEROL LOWERING DRUG

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[21] Appl. No.: 854,311

[22] Filed: May 12, 1997

Related U.S. Application Data

[60] Provisional application No. 60/022,866 Jul. 24, 1996.

[51] Int. Cl.⁶ A61K 31/445

[52] U.S. Cl. 514/321; 514/325; 514/824

[58] Field of Search 514/321, 325, 514/824

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Table with 3 columns: Patent Number, Date, Inventor/Assignee, and Patent Number. Includes entries like 3,674,836 7/1972 Creger, 3,910,931 10/1975 Cavalla et al., etc.

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[57] ABSTRACT

A method is provided for lowering serum lipids, cholesterol and/or triglycerides and thereby inhibiting atherosclerosis by administering to a patient an MTP inhibitor, in combination with a cholesterol lowering drug, such as pravastatin.

22 Claims, No Drawings

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METHOD FOR LOWERING SERUM LIPID LEVELS EMPLOYING AN MTP INHIBITOR IN COMBINATION WITH ANOTHER CHOLESTEROL LOWERING DRUG

This application claims the benefit of U.S. Provisional Application No. 60/022,866, filed Jul. 24, 1996.

FIELD OF THE INVENTION

The present invention relates to a method for lowering serum lipids, cholesterol and/or triglycerides in mammalian species by administering an MTP inhibitor in combination with another cholesterol lowering drug, for example, an HMG CoA reductase inhibitor, such as pravastatin, lovastatin or simvastatin.

BACKGROUND OF THE INVENTION

The use of microsomal triglyceride transfer protein (MTP) inhibitors for decreasing serum lipids including cholesterol and triglycerides and their use in treating atherosclerosis, obesity and pancreatitis is disclosed in Canadian Patent Application No. 2,091,102 (corresponding to U.S. application Ser. No. 117,362, now U.S. Pat. No. 5,595,872), U.S. application Ser. No. 472,067, filed Jun. 6, 1995, now U.S. Pat. No. 5,739,135 (file DC21e), U.S. application Ser. No. 548,811, now U.S. Pat. No. 5,712,279 (file DC21h), U.S. provisional application No. 60/017,224, (file HX79a*), U.S. provisional application No. 60/017,253, (file HX82*) and U.S. provisional application No. 60/017,254, (file HX84*).

All of the above U.S. applications are incorporated herein by reference.

DESCRIPTION OF THE INVENTION

In accordance with the present invention, a method for preventing, inhibiting or treating atherosclerosis, pancreatitis or obesity is provided, wherein an MTP inhibitor in combination with another cholesterol lowering drug is administered in therapeutically effective amounts to lower LDL cholesterol and triglycerides.

Furthermore, in accordance with the present invention, a method is provided for lowering serum lipid levels, cholesterol and/or triglycerides, or inhibiting and/or treating hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia, wherein a combination of an MTP inhibitor and another cholesterol lowering drug is administered in therapeutically effective amounts.

In addition, in accordance with the present invention, a novel combination of cholesterol lowering agents is provided which includes an MTP inhibitor and another cholesterol lowering drug.

Cholesterol lowering drugs or drugs which are inhibitors of cholesterol biosynthesis which may be used in the method of the invention in combination with the MTP inhibitor include HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, bile acid sequestrants, probucol, niacin, niacin derivatives, neomycin, aspirin, and the like.

It is believed that the combination of MTP inhibitor and other cholesterol lowering drug, which works by a mechanism other than inhibiting MTP, is a surprising and unique concept in treating diseases involved with elevated cholesterol and/or triglycerides and atherosclerosis, obesity and/or pancreatitis, in that the combination may provide additional

anticholesterolemic effects over that which may be obtained using each of the components of the combination alone. It is expected that reduced levels of each of the MTP inhibitor and other cholesterol lowering drug may be employed to achieve desired results, albeit with reduced side effects.

DETAILED DESCRIPTION OF THE INVENTION

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

The term "MTP" refers to a polypeptide or protein complex that (1) if obtained from an organism (e. g., cows, humans, etc.), can be isolated from the microsomal fraction of homogenized tissue; and (2) stimulates the transport of triglycerides, cholesterol esters, or phospholipids from synthetic phospholipid vesicles, membranes or lipoproteins to synthetic vesicles, membranes, or lipoproteins and which is distinct from the cholesterol ester transfer protein [Drayna et al., *Nature* 327, 632-634 (1987)] which may have similar catalytic properties.

The phrase "stabilizing" atherosclerosis as used in the present application refers to slowing down the development of and/or inhibiting the formation of new atherosclerotic lesions.

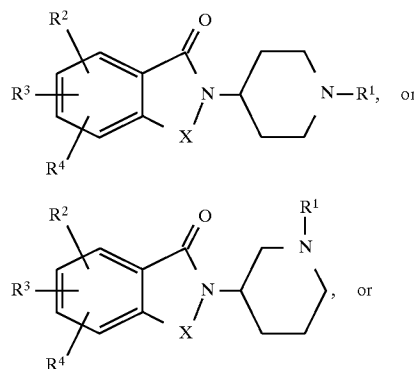
The phrase "causing the regression of" atherosclerosis as used in the present application refers to reducing and/or eliminating atherosclerotic lesions.

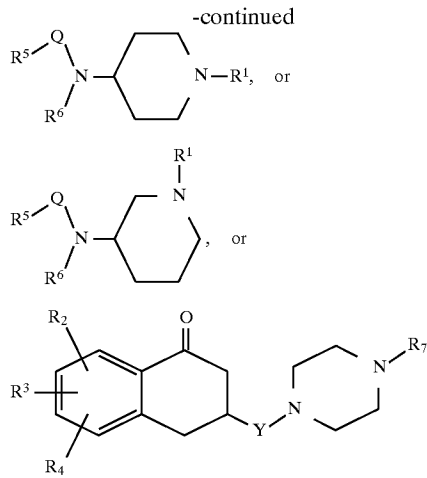
The combination of the MTP inhibitor and other cholesterol lowering drug will be employed in a weight ratio to each other of within the range of from about 1000:1 to about 0.001:1 and preferably from about 0.05:1 to about 100:1.

MTP inhibitors to be employed in the methods of the invention include MTP inhibitors disclosed in Canadian Patent Application No. 2,091,102 (corresponding to U.S. application Ser. No. 117,362, now U.S. Pat. No. 5,595,872), U.S. application Ser. No. 472,067, filed Jun. 6, 1995, now U.S. Pat. No. 5,739,135 (file DC21e), U.S. application Ser. No. 548,811, now U.S. Pat. No. 5,712,279 (file DC21h), U.S. provisional application No. 60/017,224, (file HX79a*), U.S. provisional application No. 60/017,253, (file HX82*) and U.S. provisional application No. 60/017,254, (file HX84*).

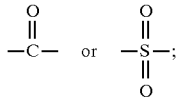
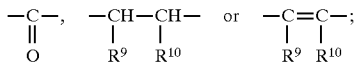
All of the above U.S. applications are incorporated herein by reference.

The MTP inhibitors disclosed in U.S. application Ser. No. 472,067, filed Jun. 6, 1995, now U.S. Pat. No. 5,739,135 (file DC21e) are piperidine compounds of the structure

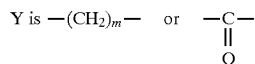


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where Q is

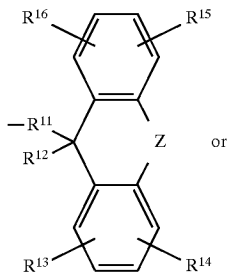
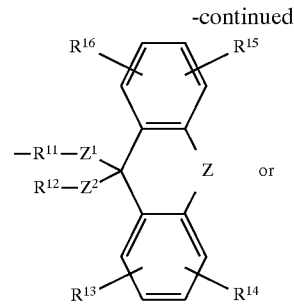
X is: CHR⁸,

R⁸, R⁹ and R¹⁰ are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;



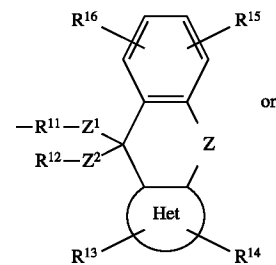
wherein m is 2 or 3;

R¹ is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl wherein alkyl has at least 2 carbons, diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl wherein alkyl has at least 2 carbons, cycloalkyl, or cycloalkylalkyl wherein alkyl has at least 2 carbons, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cyclo-alkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo;

or R¹ is a fluorenyl-type group of the structure**4**

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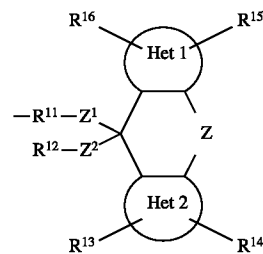
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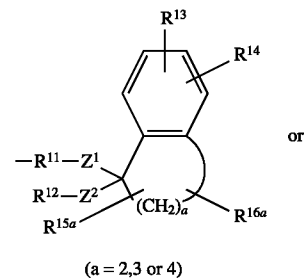
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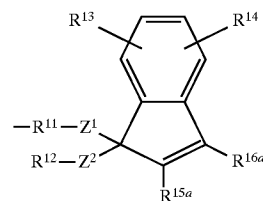
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R¹ is an indenyl-type group of the structure

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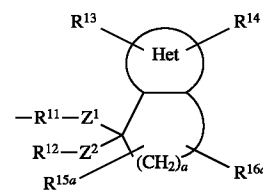


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A

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65



B

C

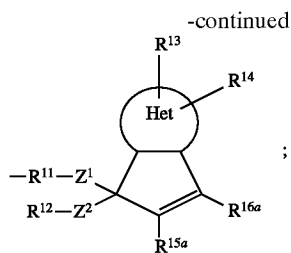
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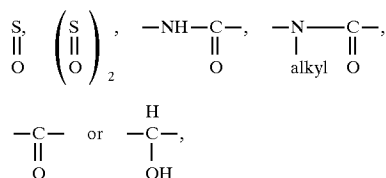
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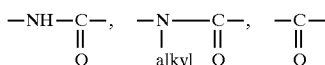


Z¹ and Z² are the same or different and are independently a bond, O, S,



with the proviso that with respect to B, at least one of Z¹ and Z² will be other than a bond; R¹¹ is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms; arylene or mixed arylene-alkylene; R¹² is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cyclo-alkyl, aryloxy, alkoxy, arylalkoxy or cycloalkyl-alkyl, with the provisos that

(1) when R¹² is H, aryloxy, alkoxy or arylalkoxy, then Z² is



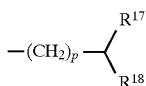
or a bond and

(2) when Z² is a bond, R¹² cannot be heteroaryl or heteroarylalkyl;

Z is bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene from 1 to 5 carbon atoms; R¹³, R¹⁴, R¹⁵, and R¹⁶ are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl or aryloxy;

R^{15a} and R^{16a} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

or R¹ is a group of the structure

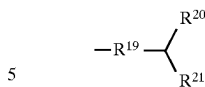


wherein p is 1 to 8 and R¹⁷ and R¹⁸ are each independently H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl at least one of R¹⁷ and R¹⁸ being other than H;

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or R¹ is a group of the structure

H



wherein R¹⁹ is aryl or heteroaryl;

R²⁰ is aryl or heteroaryl;

R²¹ is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

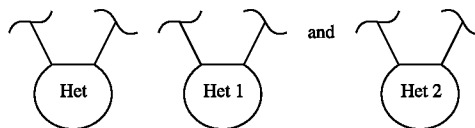
R², R³, R⁴ are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

R⁵ is independently alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from

hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxy, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxy carbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, alkylsulfinyl;

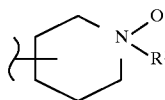
R⁶ is hydrogen or C₁–C₄ alkyl or C₁–C₄ alkenyl; all optionally substituted with 1, 2, 3 or 4 groups which may independently be any of the substituents listed in the definition of R⁵ set out above;

R⁷ is alkyl, aryl or arylalkyl wherein alkyl by itself or as part of arylalkyl is optionally substituted with oxo



are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and

N-oxides



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