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United States Patent [19]

Gregg et al.

[11] Patent Number: 5,883,109

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

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[73] Assignee: **Bristol-Myers Squibb Company**, Princeton, N.J.

[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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[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.

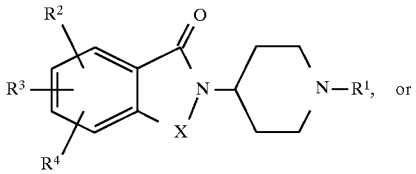
The phrase "causing the regression of" atherosclerosis as used in the present application refers to reducing and/or eliminating atherosclerotic lesions.

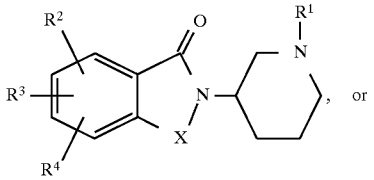
The combination of the MTP inhibitor and other cholesterol lowering drug will be employed in a weight ratio to each other of within the range of from about 1000:1 to about 0.001:1 and preferably from about 0.05:1 to about 100:1.

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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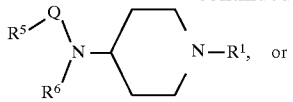
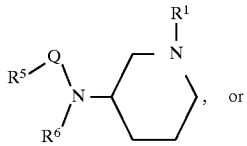
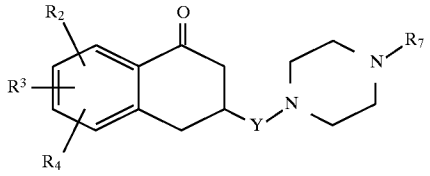
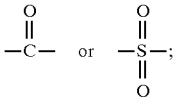


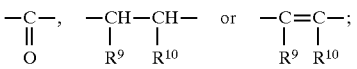




where Q is



X is: CHR^8,



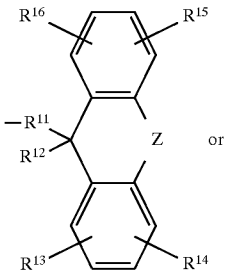
R^8, R^9 and R^{10} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

Y is $-(CH_2)_m-$ or 

wherein m is 2 or 3;

R^1 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 R^1 is a fluorenyl-type group of the structure

A 

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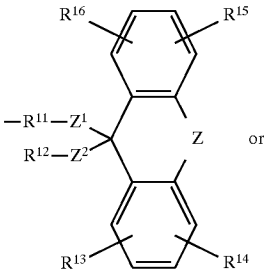
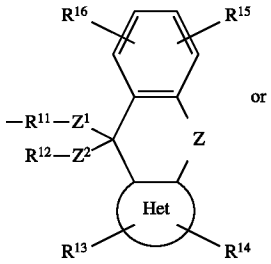
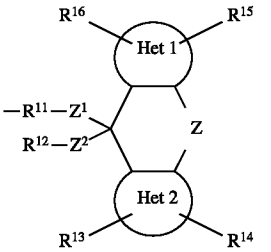
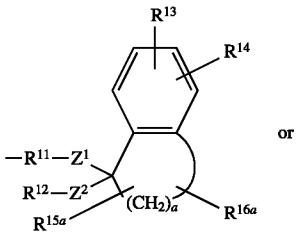
B 

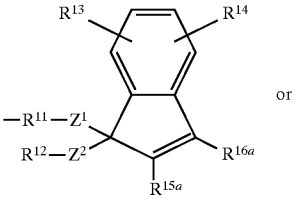
C 

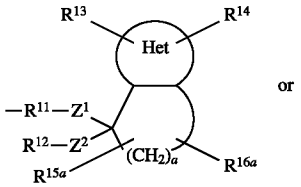
D 

R^1 is an indenyl-type group of the structure

E 

(a = 2,3 or 4)

F 

G 

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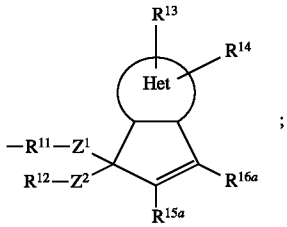
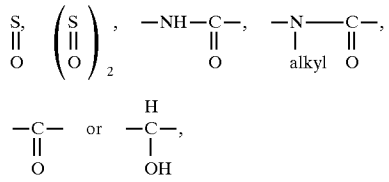
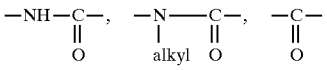


Z^1 and Z^2 are the same or different and are independently a bond, O, S,



with the proviso that with respect to B, at least one of Z^1 and Z^2 will be other than a bond; R^{11} is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms; arylene or mixed arylene-alkylene; R^{12} 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 R^{12} is H, aryloxy, alkoxy or arylalkoxy, then Z^2 is



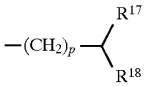
or a bond and

(2) when Z^2 is a bond, R^{12} cannot be heteroaryl or heteroarylalkyl;

Z is bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene from 1 to 5 carbon atoms; R^{13}, R^{14}, R^{15}, and R^{16} 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;

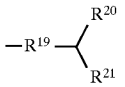
R^{15a} and R^{16a} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

or R^1 is a group of the structure



wherein p is 1 to 8 and R^{17} and R^{18} are each independently H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl at least one of R^{17} and R^{18} being other than H;

or R^1 is a group of the structure



wherein R^{19} is aryl or heteroaryl;

R^{20} is aryl or heteroaryl;

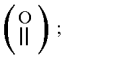
R^{21} is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

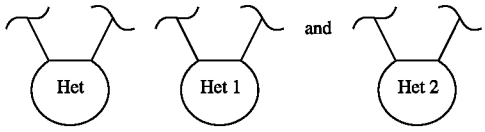
R^2, R^3, R^4 are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

R^5 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, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, alkylsulfinyl;

R^6 is hydrogen or C_1–C_4 alkyl or C_1–C_4 alkenyl; all optionally substituted with 1, 2, 3 or 4 groups which may independently be any of the substituents listed in the definition of R^5 set out above;

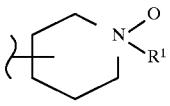
R^7 is alkyl, aryl or arylalkyl wherein alkyl by itself or as part of arylalkyl is optionally substituted with oxo





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

N-oxides



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