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Robl et al.

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(54) **METHOD FOR TREATING
ATHEROSCLEROSIS EMPLOYING AN AP2
INHIBITOR AND COMBINATION**

(75) Inventors: **Jeffrey A. Robl**, Newtown, PA (US);
Rex A. Parker, Titusville, NJ (US);
Scott A. Biller, Lexington, MA (US);
Haris Jamil, Libertyville, IL (US);
Bruce L. Jacobson, Carlsbad, CA
(US); **Krishna Kodukula**, Princeton,
NJ (US); **Gokhan Hotamisligil**,
Wellesley, MA (US)

(73) Assignees: **Bristol-Myers Squibb Company**,
Princeton, NJ (US); **President &
Fellows of Harvard College**,
Cambridge, MA (US)

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548/210; 548/232; 548/235; 548/236; 530/324

(58) **Field of Classification Search** 514/256,
514/12, 374; 548/210, 232, 235, 236; 530/324
See application file for complete search history.

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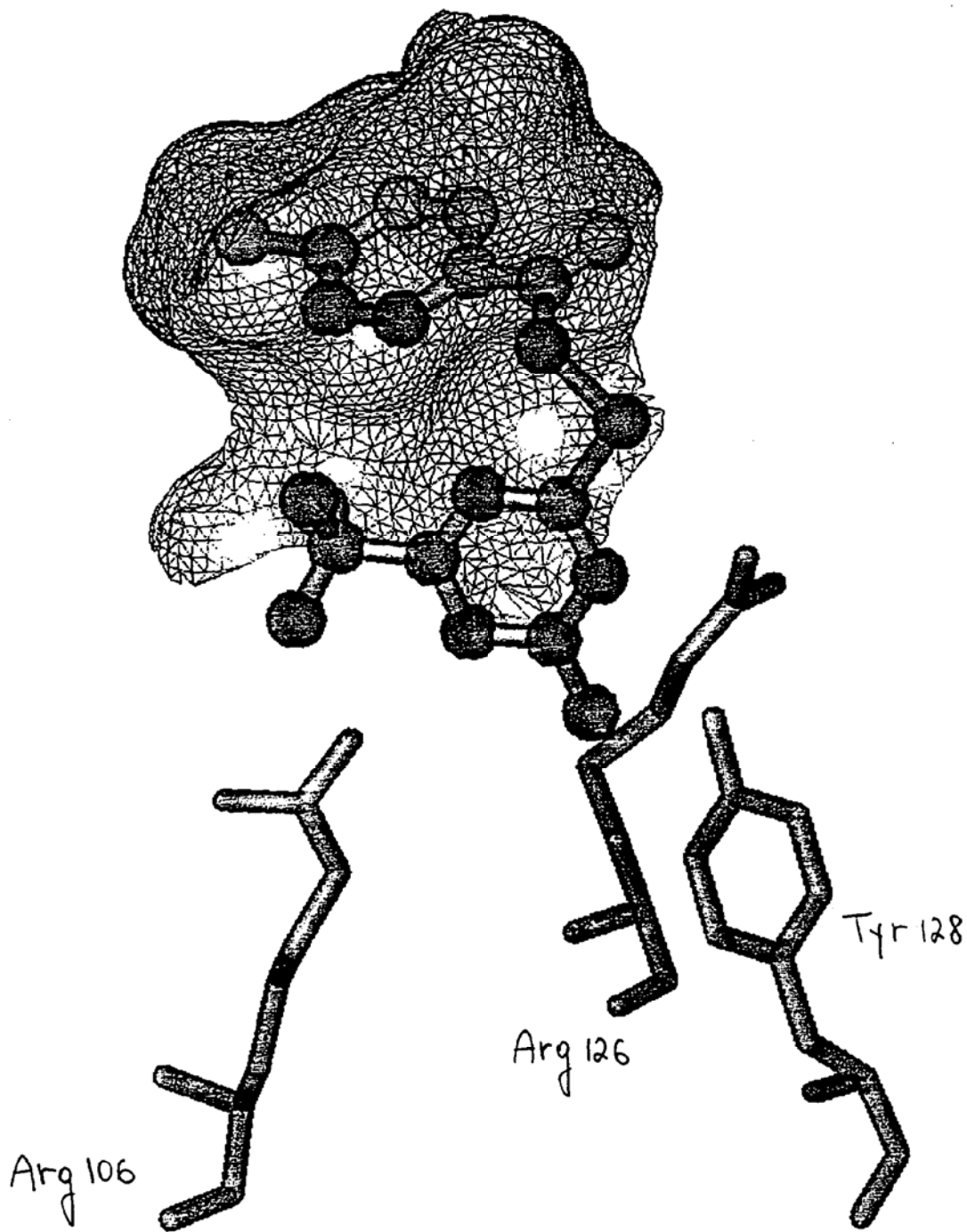
Assistant Examiner—Abdel A Mohamed

(74) *Attorney, Agent, or Firm*—Rosemary M. Miano; Joseph
C. Wang; Laurelee A. Duncan

(57) **ABSTRACT**

A method is provided for treating atherosclerosis and related
diseases, employing an aP2 inhibitor or a combination of an
aP2 inhibitor and another antiatherosclerotic agent, for
example, an HMG CoA reductase inhibitor such as pravastatin.

2 Claims, 1 Drawing Sheet



FIGURE

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METHOD FOR TREATING ATHEROSCLEROSIS EMPLOYING AN aP2 INHIBITOR AND COMBINATION

FIELD OF THE INVENTION

The present invention relates to a method for treating atherosclerosis and related diseases, employing an aP2 inhibitor alone or in combination with another type antiatherosclerotic agent.

BACKGROUND OF THE INVENTION

Fatty acid binding proteins (FABPs) are small cytoplasmic proteins which bind to fatty acids such as oleic acids which are important metabolic fuels and cellular regulators. Dysregulation of fatty acid metabolism in adipose tissue is a prominent feature of insulin resistance and the transition from obesity to non-insulin dependent diabetes mellitus (NIDDM or Type II diabetes).

aP2, an abundant 14.6 KDa cytosolic protein in adipocytes, and one of a family of homologous intracellular fatty acid binding proteins (FABPs), is involved in the regulation of fatty acid trafficking in adipocytes and mediates fatty acid fluxes in adipose tissue. G. S. Hotamisligil et al, "Uncoupling of Obesity from Insulin Resistance Through a Targeted Mutation in aP2, the Adipocyte Fatty Acid Binding Protein", Science, Vol. 274, Nov. 22, 1996, pp. 1377-1379, report that aP2-deficient mice placed on a high fat diet for several weeks developed dietary obesity, but, unlike control-mice on a similar diet, did not develop insulin resistance or diabetes. Hotamisligil et al conclude that "aP2 is central to the pathway that links obesity to insulin resistance" (Abstract, page 1377).

DIALOG ALERT DBDR928 dates Jan. 2, 1997, Pharmaprojects No. 5149 (Knight-Ridder Information) discloses that a major drug company "is using virtual screening techniques to identify potential new antidiabetic compounds." It is reported that "the company is screening using aP2, a protein related to adipocyte fatty acid binding protein."

DESCRIPTION OF THE INVENTION

In accordance with the present invention, a method is provided for treating atherosclerosis wherein a therapeutically effective amount of a drug which inhibits aP2 (aP2 inhibitor) is administered to a human patient in need of treatment.

In addition, in accordance with the present invention, a method is provided for treating atherosclerosis, wherein a therapeutically effective amount of a combination of an aP2 inhibitor and another type of antiatherosclerotic agent is administered to a human patient in need of treatment.

Furthermore, in accordance with the present invention, a novel antiatherosclerotic combination is provided which is formed of a drug which inhibits aP2 and an antiatherosclerotic agent which functions by a mechanism other than by inhibiting aP2. The aP2 inhibitor will be employed in a weight ratio to the antiatherosclerotic agent (depending upon its mode of operation) within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 10:1.

It will be appreciated that the method of the invention for treating atherosclerosis employing an aP2 inhibitor alone or in combination with an antiatherosclerotic agent encom-

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The method of the invention also encompasses preventing, inhibiting or reducing risk of cardiovascular and cerebrovascular diseases resulting from atherosclerosis, such as cardiac and/or cerebral ischemia, myocardial infarction, angina, peripheral vascular disease and stroke.

The aP2 inhibitors suitable for use in the method of the invention are compounds which bind to the aP2 protein and inhibits its function and/or its ability to bind free fatty acids. The compounds will preferably contain less than 60 carbon atoms, more preferably less than 45 carbon atoms, and will contain less than 20 heteroatoms, more preferably less than 12 heteroatoms. They contain a hydrogen bond donor or acceptor group, preferably acidic in nature, which includes, but is not limited to, CO₂H, tetrazole, SO₃H, PO₃H, P(R)(O)OH (where R is lower alkyl or lower alkoxy), OH, NHSO₂R' or CONHSO₂R' (where R' is lower alkyl), and thiazolidindione, and interacts (directly or through an intervening water molecule), either by ionic or hydrogen bonding interactions, with one, two, or three of the three amino acid residues, designated as Arg 106, Arg 126 and Tyr 128 in human aP2, within the aP2 protein.

The compounds suitable for use herein preferably contain an additional substituent, preferably hydrophobic in nature, which include the following groups: alkyl, cycloalkyl, aryl, heteroaryl, cycloheteroalkyl, benzo-fused aryl and heteroaryl, and their substituted counterparts. Especially preferred are aryl and substituted aryl groups. More especially preferred is phenyl and halo or methyl substituted phenyl.

The hydrophobic substituent binds to (in) and/or interacts with a discrete pocket within the aP2 protein defined roughly by the amino acid residues Phe 16, Tyr 19, Met 20, Val 23, Val 25, Ala 33, Phe 57, Thr 74, Ala 75, Asp 76, Arg 78 in human aP2. The through space distance from the hydrogen bond donor/acceptor group and the additional substituent group is within the distance of about 7 to about 15 Angstroms.

The above compounds may be employed in the form of pharmaceutically acceptable salts thereof and prodrug esters thereof.

The term "antiatherosclerotic agent" as employed herein refers to antihyperlipidemic agents including HMG CoA reductase inhibitors, microsomal triglyceride transfer protein (MTP) inhibitors, fibric acid derivatives, squalene synthetase inhibitors and other known cholesterol lowering agents, lipoxigenase inhibitors, ACAT inhibitors, and PPAR α/γ dual agonists as disclosed hereinafter.

BRIEF DESCRIPTION OF FIGURE

The accompanying FIGURE is a computer generated image of a partial X-ray structure of compound XVIIA (described hereinafter) bound to human aP2.

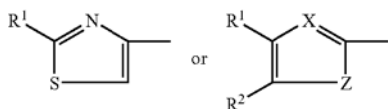
DETAILED DESCRIPTION OF THE INVENTION

Examples of aP2 inhibitors suitable for use herein include compounds which include an oxazole or analogous ring. Thus, U.S. Pat. No. 5,218,124 to Failli et al (the disclosure of which is incorporated herein by reference) discloses compounds, which have activity as aP2 inhibitors and thus suitable for use herein, which include substituted benzoylbenzene, biphenyl- and 2-oxazole-alkanoic acid derivatives having the following structure:

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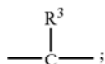
wherein

A is a group having the formula

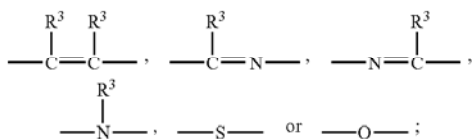
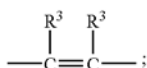


wherein

X is —N— or

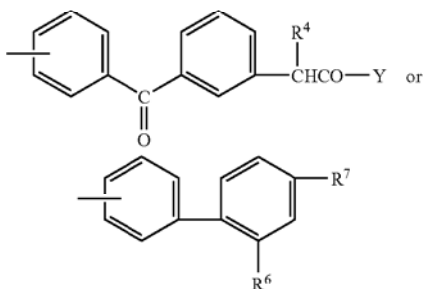


Z is

R¹ is hydrogen, lower alkyl or phenyl;R² is hydrogen or lower alkyl; orR¹ and R² taken together form a benzene ring, with the proviso that when X is —N—, Z is other thanR³ is hydrogen or lower alkyl;

n is 1-2;

B is

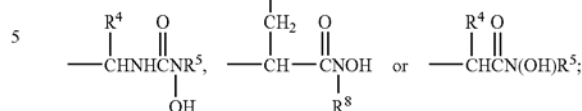


wherein

Y is OR⁵ or N(OH)R⁸;R⁴ and R⁵ are each, independently, hydrogen or lower alkyl;R⁶ is hydrogen, halo or nitro;R⁷ is

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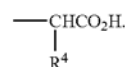
R⁸ is lower alkyl;

m is 0-3;

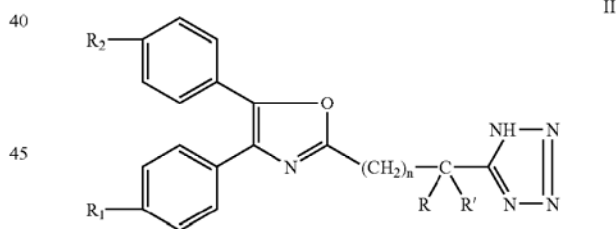
and the pharmacologically acceptable salts thereof.

The grouping A embraces, inter alia, 5- or 6-membered unsaturated nitrogen, sulfur or oxygen containing mono- or benzofused-heterocycles, optionally substituted with lower alkyl or phenyl. The foregoing definition embraces the following heterocyclic moieties; furyl, pyrrolyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, benzofuranyl, benzothienyl, benzothiazolyl, indolyl, benzoxazolyl, quinazoliny, benzimidazolyl, quinoxaliny, quinazoliny and the like.

Preferred are the examples where A is defined as above and B is

and R⁷ is

In another embodiment of the present invention, compounds which have activity as aP2 inhibitors suitable for use herein are disclosed in U.S. Pat. No. 5,403,852 to Barreau et al (which is incorporated herein by reference) which are oxazole derivatives and have the structure



in which;

R and R' are identical or different and represent a hydrogen atom or an alkyl radical containing 1 or 2 carbon atoms,

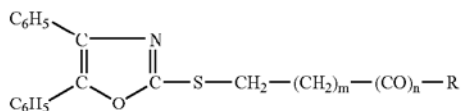
R₁ and R₂ are identical or different and represent hydrogen or halogen atoms or alkyloxy radicals in which the alkyl portion contains 1 to 4 carbon atoms in a straight or branched chain, and

n equals 3 to 6,

as well to their salts, to their isomers where they exist and to pharmaceutical compositions containing them.

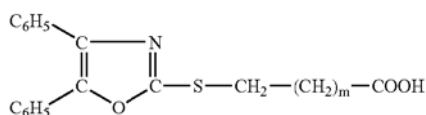
In addition, other compounds which have activity as aP2 inhibitors suitable for use in the method of the invention are compounds disclosed in U.S. Pat. No. 4,001,228 to Mattalia (which is incorporated herein by reference) which are

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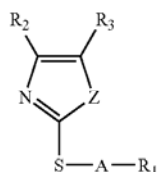
wherein m is 0, 1 or 2, n is 1 and R represents hydroxy, alkoxy or amino. Also included within the scope of this invention are salts of the compounds of formula III above, particularly pharmaceutically acceptable addition salts thereof.

Preferred are S-(4,5-diphenyloxazol-2-yl)-mercaptocarboxylic acids of the formula:



wherein m is 0, 1 or 2, and pharmaceutically acceptable lower alkyl esters and salts thereof.

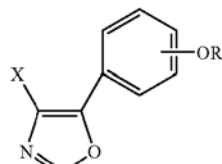
In another embodiment of the present invention, compounds which have activity as aP2 inhibitors suitable for use herein are disclosed in U.S. Pat. No. 4,051,250 to Dahm et al (the disclosure of which is incorporated herein by reference) which discloses azole derivatives of the structure



wherein R_1 is carboxyl, esterified carboxyl or other functionally modified carboxyl group; R_2 and R_3 each are aryl of up to 10 carbon atoms; A is C_nH_{2n} , in which n is an integer from 1 to 10, inclusive; and Z is O or S, and the physiologically acceptable salts thereof.

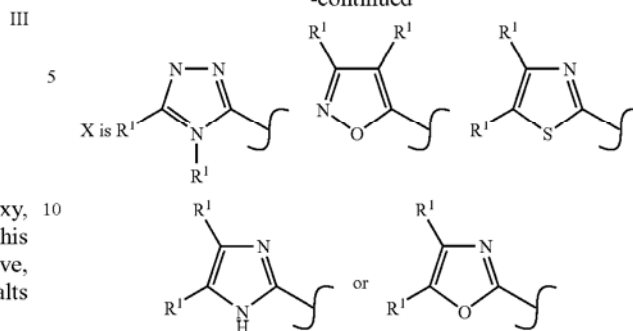
Preferred are preferred compounds as disclosed in the Dahm et al patent.

In still another embodiment of the invention, compounds which have activity as aP2 inhibitors suitable for use herein are disclosed in U.S. Pat. No. 5,380,854 to Romine et al (the disclosure of which is incorporated herein by reference) and are phenyl-heterocyclic oxazole derivatives which have the structure

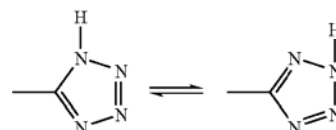


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R is CH_2R^2 ;
 R^1 is Ph or Th;
 R^2 is



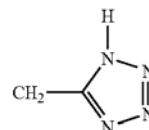
CO_2R^3 , and
 R^3 is H, or C_1 - C_4 lower alkyl;

or pharmaceutically acceptable salt thereof.

Preferred are the compounds where R is CH_2CO_2H and

IV 35

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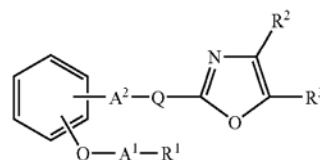


or its tautomer and R^1 is Ph.

In yet another embodiment of the method of the invention, compounds which have activity as aP2 inhibitors suitable for use herein are disclosed in PCT application WO 95/17393 which are diaryloxazole derivatives having the structure

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V 60

wherein R^1 is carboxy or protected carboxy,

R^2 is aryl which may have suitable substituent(s),

R^3 is aryl which may have suitable substituent(s),

A^1 is lower alkylene,

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A^2 is bond or lower alkylene and

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