US 20020035064A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2002/0035064 A1**

Robl et al. (43) **Pub. Date: Mar. 21, 2002**

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

(76) Inventors: **Jeffrey A. Robl**, Newtown, PA (US); **Rex A. Parker**, Titusville, NJ (US); **Scott A. Biller**, Hopewell, NJ (US); **Haris Jamil**, Newtown, PA (US); **Bruce L. Jacobson**, Mercerville, NJ (US); **Krishna Kodukula**, Princeton, NJ (US)

Correspondence Address:
MARLA J MATHIAS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000 (US)

(21) Appl. No.: **09/905,235**

(22) Filed: **Jul. 13, 2001**

Related U.S. Application Data

(63) Continuation of application No. 09/390,275, filed on Sep. 7, 1999, now abandoned, which is a non-provisional of provisional application No. 60/100,677, filed on Sep. 17, 1998.

Publication Classification

(51) **Int. Cl.**[7] **A61K 38/17**; C12N 9/99

(52) **U.S. Cl.** **514/12**; 435/184

(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.

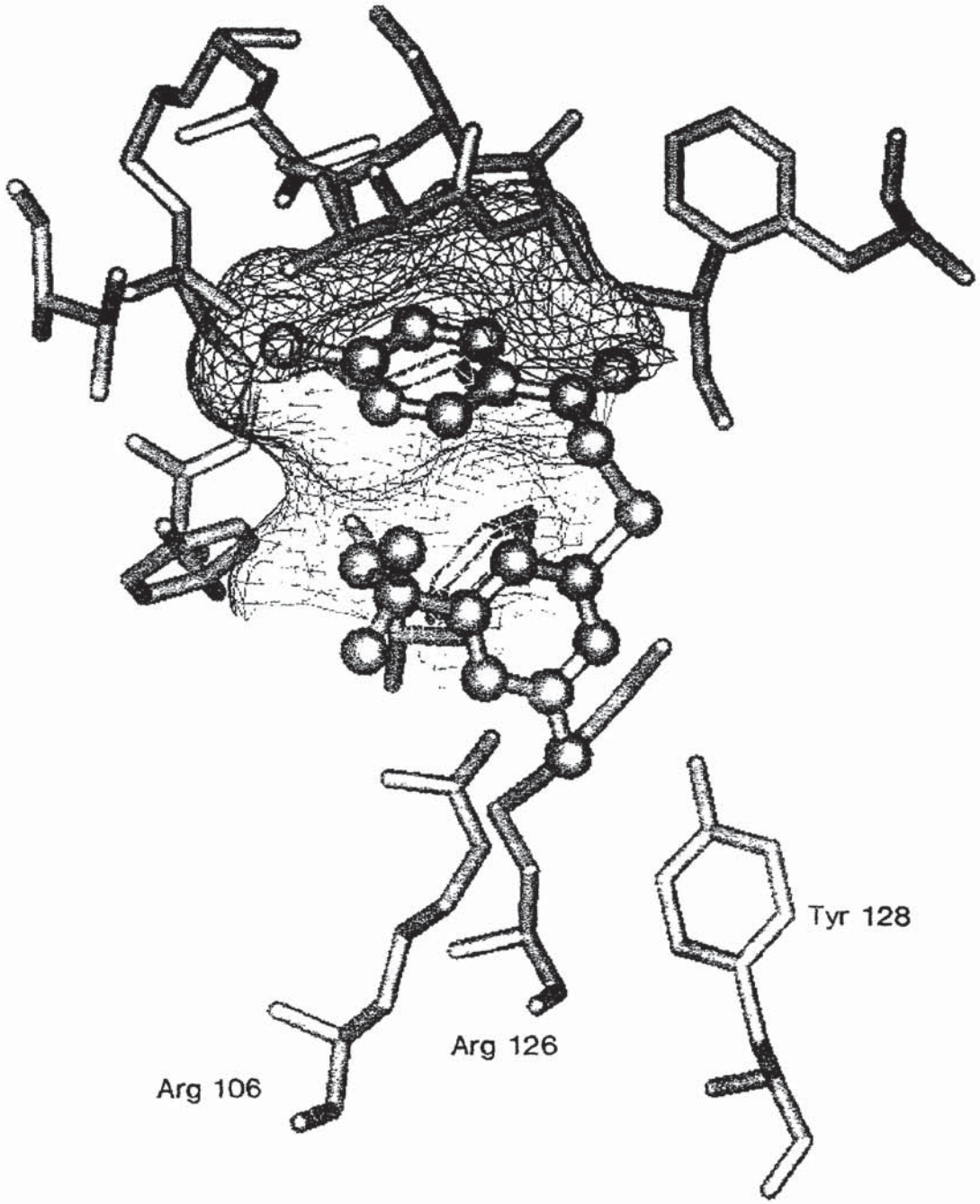


FIGURE 1

METHOD FOR TREATING ATHEROSCLEROSIS EMPLOYING AN AP2 INHIBITOR AND COMBINATION

FIELD OF THE INVENTION

[0001] 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

[0002] 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).

[0003] 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

[0004] 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.

[0005] 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.

[0006] 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.

[0007] 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 encompasses treating, reducing risk of, inhibiting, preventing and/or reducing or causing regression of atherosclerosis.

[0008] The method of the invention also encompasses preventing, inhibiting or reducing risk of cardiovascular and cerebrovasculer diseases resulting from atherosclerosis, such as cardiac and/or cerebral ischemia, myocardial infarction, angina, peripheral vascular disease and stroke.

[0009] 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 donator or acceptor group, preferably acidic in nature, which includes, but is not limited to, CO_2H, tetrazole, SO_3H, PO_3H, P(R) (O)OH (where R is lower alkyl or lower alkoxy), OH, $NHSO_2R'$ or $CONHSO_2R'$ (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 Tvr 128 in human aP2, within the aP2 protein.

[0010] 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.

[0011] 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.

[0012] The above compounds may be employed in the form of pharmaceutically acceptable salts thereof and prodrug esters thereof.

[0013] 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, lipoxygenase inhibitors, ACAT inhibitors, and PPAR α/γ dual agonists as disclosed hereinafter.

BRIEF DESCRIPTION OF FIGURE

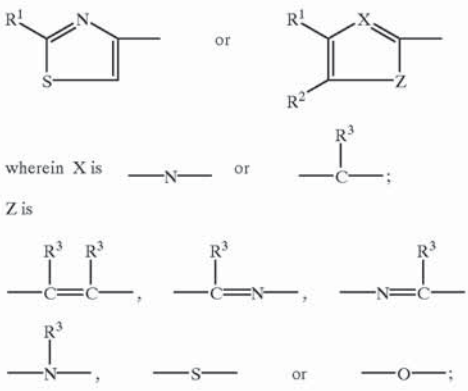
[0014] The accompanying Figure is a computer generated image of a partial X-ray structure of compound XVIA (described hereinafter) bound to human aP2.

DETAILED DESCRIPTION OF THE INVENTION

[0015] 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, bipheny-and 2-oxazole-alkanoic acid derivatives having the following structure: I $A(CH_2)_nO$-B

[0016] wherein A is a group having the formula



[0017] wherein

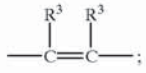
[0018] X is -N- or

[0019] Z is

[0020] R^1 is hydrogen, lower alkyl or phenyl;

[0021] R^2 is hydrogen or lower alkyl; or

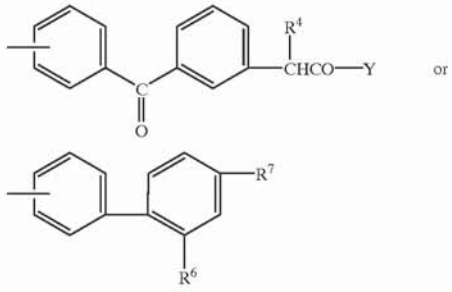
[0022] R^1 and R^2 taken together form a benzene ring, with the proviso that when X is -N-, Z is other than



[0023] R^3 is hydrogen or lower alkyl;

[0024] n is 1-2;

[0025] B is



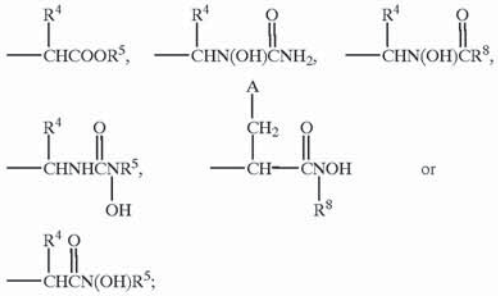
[0026] wherein

[0027] Y is OR^5 or $N(OH)R^8$;

[0028] R^4 and R^5 are each, independently, hydrogen or lower alkyl;

[0029] R^6 is hydrogen, halo or nitro;

[0030] R^7 is

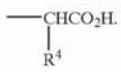


[0031] R^8 is lower alkyl;

[0032] m is 0-3; and the pharmacologically acceptable salts thereof.

[0033] 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, quinazolinyl, benzimidazolyl, guinoxalinyl, quinazolinyl and the like.

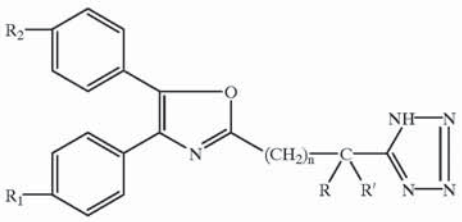
[0034] Preferred are the examples where A is defined as above and B is



[0035] and R^7 is

[0036] 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

II



[0037] in which;

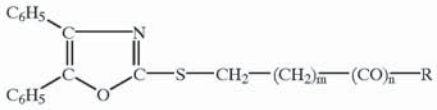
[0038] R and R' are identical or different and represent a hydrogen atom or an alkyl radical containing 1 or 2 carbon atoms,

[0039] R_1 and R_2 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

[0040] n equals 3 to 6, as well to their salts , to their isomers where they exist and to pharmaceutical compositions containing them.

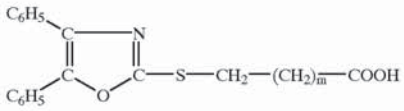
[0041] In addition, other compounds which have activity as aP2 inhibitors suitable for use in the method of the invention are compounds disclosed in U.S. Pat. No. 4,001,228 to Mattalia (which is incorporated herein by reference) which are 2-thiol-4,5-diphenyloxazole S-derivatives which have the structure

III



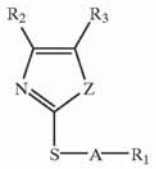
[0042] wherein m is 0, 1 or 2, n is 1 and R represents hydroxy, alkoxy or amino. Also included within the scope of this invention are salts of the compounds of formula III above, particularly pharmaceutically acceptable addition salts thereof.

[0043] Preferred are S-(4,5-diphenyloxazol-2-yl)-mercaptocarboxylic acids of the formula:



[0044] wherein m is 0, 1 or 2, and pharmaceutically acceptable lower alkyl esters and salts thereof.

[0045] 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

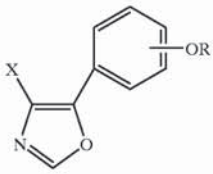


[0046] wherein R_1 is carboxyl, esterified carboxyl or other functionally modified carboxyl group; R_2 and R_3 each are aryl of up to 10 carbon atoms; A is C_nH_{2n} in which n is an integer from 1 to 10, inclusive; and Z is O or S, and the physiologically acceptable salts thereof.

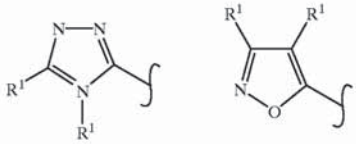
[0047] Preferred are preferred compounds as disclosed in the Dahm et al patent.

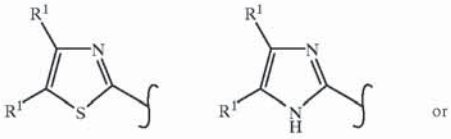
[0048] In still another embodiment of the invention, compounds which have activity as aP2 inhibitors suitable for ue herein are disclosed in U.S. Pat. No. 5,380,854 to Romine et al (the disclosure of which is incorporated herein by reference) and are phenyl-heterocyclic oxazole derivatives which have the structure

V

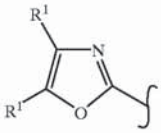


X is





or



R is CH_2R^2;

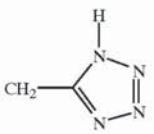
R^1 is Ph or Th;

R^2 is

[0049] CO_2R^3, and

[0050] R^3 is H, or C_1-C_4 lower alkyl; or pharmaceutically acceptable salt thereof.

[0051] Preferred are the compounds where R is CH_2CO_2H and



[0052] or its tautomer and R^1 is Ph.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.