US 20030109543A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2003/0109543 A1

Ogletree (43) Pub. Date: Jun. 12, 2003

(54) NOVEL COMBINATION OF AN ADP-RECEPTOR BLOCKING ANTIPLATELET DRUG AND A THROMBOXANE A2 RECEPTOR ANTAGONIST AND A METHOD FOR INHIBITING THROMBUS FORMATION EMPLOYING SUCH COMBINATION

(76) Inventor: **Martin L. Ogletree**, Newtown, PA (US)

Correspondence Address:
STEPHEN B. DAVIS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000 (US)

(21) Appl. No.: **10/295,347**

(22) Filed: **Nov. 15, 2002**

Related U.S. Application Data

(62) Division of application No. 09/428,611, filed on Oct. 27, 1999, now Pat. No. 6,509,348.

(60) Provisional application No. 60/106,813, filed on Nov. 3, 1998.

Publication Classification

(51) **Int. Cl.**[7] **A61K 31/557**; A61K 31/4743

(52) **U.S. Cl.** **514/301**; 514/381; 514/374; 514/469

(57) **ABSTRACT**

A method is provided for inhibiting platelet aggregation and thrombus formation by administering to a patient an ADP-receptor blocking antiplatelet drug, such as clopidogrel, in combination with a thromboxane A_2 receptor antagonist, such as ifetroban, and optionally a cholesterol lowering drug, such as an HMG CoA reductase inhibitor, for example, pravastatin.

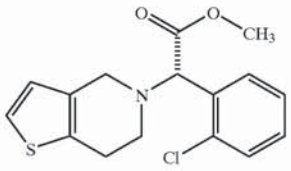
NOVEL COMBINATION OF AN ADP-RECEPTOR BLOCKING ANTIPLATELET DRUG AND A THROMBOXANE A2 RECEPTOR ANTAGONIST AND A METHOD FOR INHIBITING THROMBUS FORMATION EMPLOYING SUCH COMBINATION

FIELD OF THE INVENTION

[0001] The present invention relates to a novel combination of an ADP-receptor blocking antiplatelet drug, such as clopidogrel, and a thromboxane A_2 receptor antagonist such as ifetroban, and optionally a cholesterol lowering drug, such as pravastatin, and to a method for inhibiting platelet aggregation and thrombus formation employing such combination.

BACKGROUND OF THE INVENTION

[0002] Clopidogrel is a thieno-[3,2-c]pyridine derivative which has the chemical name methyl (4)-(S)-α-(o-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5-acetate and the formula



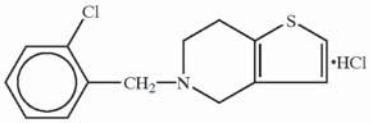
[0003] including pharmaceutically acceptable acid addition salts thereof, preferably the hydrogen sulfate salt, and is disclosed in U.S. Pat. Nos. 4,529,596 to Aubert et al and 4,847,265 to Badorc et al as having blood platelet aggregation inhibiting activity and anti-thrombotic activity and thus useful in inhibiting or preventing arterial and venous thrombosis.

[0004] U.S. Pat. No. 5,576,328 to Herbert et al discloses that clopidogrel may be employed in secondary prevention of ischemic events such as myocardial infarction, unstable or stable angina, acute reocclusion after percutaneous transluminal coronary angioplasty (PTCA), restenosis after PTCA, thrombotic stroke, transient ischemic attack, reversible ischemic neurological deficit, and intermittent claudication.

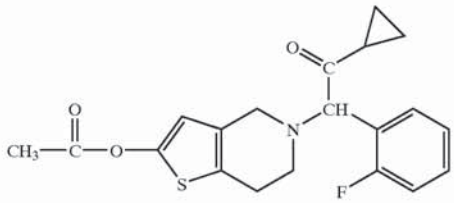
[0005] The above patents are incorporated herein by reference.

[0006] WO 97/29753 published Aug. 21, 1997, discloses a pharmaceutical composition containing clopidogrel and aspirin.

[0007] Ticlopidine hydrochloride is disclosed in U.S. Pat. No. 4,591,592 as a platelet aggregation inhibitor and is marketed in the U.S. under the name Ticlid® by Roche Laboratories and has the chemical name 5-[(2-chlorophenyl)methyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride and the structure

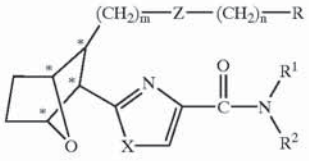


[0008] U.S. Pat. No. 5,288,726 (assigned to Sankyo) discloses a platelet aggregation inhibitor CS-747 which has the structure and name as follows:



[0009] 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

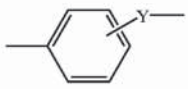
[0010] U.S. Pat. No. 5,100,889 to Misra et al discloses 7-oxabicycloheptyl substituted heterocyclic amide prostacyclin analogs which are potent thromboxane A_2 receptor antagonists and thus are useful in inhibiting platelet aggregation and thrombus formation. The Misra et al compounds have the structure



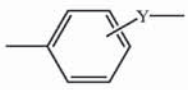
[0011] and including all stereoisomers thereof, wherein

[0012] m is 1, 2 or 3; n is 0, 1, 2, 3 or 4;

[0013] Z is —$(CH_2)_2$—, —CH═CH— or

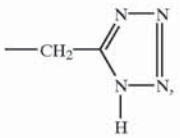


[0014] wherein Y is O, a single bond or vinyl (—CH═CH—), with the provisos that when n is 0, if Z is



[0015] then Y cannot be 0; and when Z is —CH═CH—, n is 1,2,3, or 4; and when Y=vinyl, n=0;

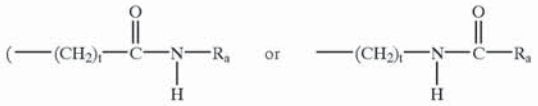
[0016] R is CO_2H, CO_2lower alkyl, CO_2alkali metal, CH_2OH, $CONHSO_2R^3$, $CONHR^{3a}$, or



[0017] (—CH_2-5-tetrazolyl);

[0018] X is O, S or NH;

[0019] R^1 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aralkyl, aryl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, heteroaryl or heteroarylalkyl, or amide



[0020] wherein t is 1 to 12 and R_a is lower alkyl, aryl, cycloalkyl, or cycloalkylalkyl);

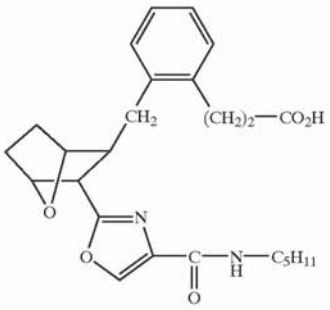
[0021] R^2 is hydrogen, lower alkyl, aryl, or aralkyl; or

[0022] R^1 and R^2 together with the nitrogen to which they are linked may form a 5- to 8-membered ring;

[0023] R^3 is lower alkyl, aryl or aralkyl; and

[0024] R^{3a} is hydrogen, lower alkyl, aryl or aralkyl.

[0025] Ifetroban which is a particularly potent thromboxane A_2 antagonist is disclosed in the Misra et al patent and has the structure



[0026] and the name [1S-(1α, 2α, 3α, 4α)]-2-[[3-[4-[(pentylamino)-carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]-benzenepropanoic acid or a pharmaceutically acceptable salt thereof such as its sodium salt.

[0027] U.S. Pat. No. 5,312,818 to Rubin et al discloses use of thromboxane A_2 receptor antagonists in combination with anti-inflammatory agents including aspirin to prevent or treat ulcerative conditions caused by anti-inflammatory agents.

DESCRIPTION OF THE INVENTION

[0028] In accordance with the present invention, a method for preventing or inhibiting platelet aggregation and thrombus formation in mammals is provided wherein an ADP-receptor blocking antiplatelet drug, such as clopidogrel, in combination with a thromboxane A_2 receptor antagonist, such as ifetroban, and optionally a cholesterol lowering drug, is administered in therapeutically effective amounts to inhibit platelet aggregation and thrombus formation.

[0029] Furthermore, in accordance with the present invention, a method is provided for preventing or inhibiting onset of ischemic events including cardiovascular, cerebrovascular and peripheral vascular events, such as myocardial infarction, unstable and stable angina, acute reocclusion after percutaneous transluminal coronary angioplasty (PTCA), restenosis after PTCA, thrombotic stroke, transient ischemic attack, reversible ischemic neurological deficit, and intermittent claudication wherein a combination of an ADP-receptor blocking antiplatelet drug, such as clopidogrel, and a thromboxane A_2 receptor antagonist, such as ifetroban, and optionally a cholesterol lowering agent, is administered in therapeutic effective amounts.

[0030] In addition, in accordance with the present invention, a novel combination of antithrombotic agents is provided which includes an ADP receptor blocking antiplatelet drug, such as clopidogrel, and a thromboxane A_2 receptor antagonist, such as ifetroban, and optionally a cholesterol lowering drug, such as an HMG CoA reductase inhibitor such as pravastatin.

[0031] It is believed that the combination of ADP-receptor blocking antiplatelet drug and thromboxane A_2 receptor antagonist, which works by a mechanism other than inhibition of ADP-induced platelet aggregation, is a surprising and unique concept in treating diseases involved with platelet aggregation, thrombus formation and ischemic events, in that the combination may provide additional antiplatelet aggregation, anti-ischemic, anti-thrombus effects over that which may be obtained using each of the components of the combination alone. It may be expected that reduced levels of each of the ADP receptor blocking antiplatelet drug and thromboxane A_2 receptor antagonist may be employed to achieve desired results, albeit with reduced side effects.

[0032] In addition, in accordance with the present invention, a method is provided wherein a combination of an ADP-receptor blocking antiplatelet drug and a thromboxane A_2 receptor antagonist, and optionally aspirin, is employed to prevent or inhibit platelet aggregation and thrombus formation and to prevent or inhibit any of the disease states set out above, including thrombotic stroke.

[0033] The ADP-receptor blocking antiplatelet drug suitable for use herein includes antiplatelet drugs which inhibit ADP-induced platelet aggregation and include clopidogrel and/or ticlopidine and/or CS-747 (described herein), and do not include drugs such as aspirin which inhibit platelet aggregation by other mechanisms.

[0034] The term "clopidogrel" as employed herein includes clopidogrel in its free acid form, ester thereof, including the acetate, and/or pharmaceutically acceptable acid addition salts thereof, including the hydrogen sulfate salt.

[0035] The term "ticlopidine" as employed herein includes all pharmaceutical acceptable salts thereof including the hydrochloride salt thereof.

[0036] The term "CS-747" as employed herein includes 2-acetoxy-5-(α(-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

[0037] Thromboxane A_2 receptor antagonists which may be employed herein include the interphenylene 7-oxabicyclo-heptyl substituted heterocyclic amide prostaglandin analogs as disclosed in U.S. Pat. No. 5,100,889, issued Mar. 31, 1992, including [1S-(1α, 2α, 3α, 4α)]-2-[[3-[4-[[(4-cyclohexylbutyl)amino]carbonyl]-2-oxazolyl]-7-oxabicyclo [2.2.1]-hept-2-yl]methyl]benzenepropanoic acid (SQ 33,961) which is preferred, or esters or salts thereof;

[0038] [1S-(1α, 2α, 3α, 4α)]-2-[[3-[4-[[[(4-chlorophenyl)-butyl]amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic acid or esters, or salts thereof;

[0039] [1S-((1α, 2α, 3α, 4α)]-3-[[3-[4-[[(4-cyclohexylbutyl)-amino]carbonyl]-2-oxazolyl]-7-oxabicyclo]2.2.1]hept-2-yl]benzeneacetic acid, or esters or salts thereof;

[0040] [1S-((1α, 2α, 3α, 4α)]-[2-[[3-[4-[[(4-cyclohexyl-butyl)amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]phenoxy]acetic acid, or esters or salts thereof;

[0041] [1S-((1α, 2α, 3α, 4α)]-2-[[3-[4-[[(7,7-dimethyloctyl)-amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-methyl]benzenepropanoic acid, or esters or salts thereof and ifetroban, with ifetroban being most preferred;

[0042] 7-oxabicycloheptyl substituted heterocyclic amide prostaglandin analogs as disclosed in U.S. Pat. No. 5,100,889, issued Mar. 31, 1992, including [1S-[1α, 2α(Z), 3α, 4α)]-6-[3-[4-[[(4-cyclohexylbutyl)amino]-carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0043] [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[4-[[(4-cyclohexyl-butyl)amino]carbonyl]-2-thiazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0044] [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[4-[[(4-cyclohexyl-butyl)methylamino]carbonyl]-2-oxazolyl]-7-oxabicyclo-[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0045] [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[4-[(1-pyrrolidinyl)-carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0046] [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[4-[(cyclohexylamino)-carbonyl]-2-oxazolyl]-7-oxabicyclo [2.2.1]hept-2-yl-4-hexenoic acid or esters or salts thereof;

[0047] [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[4-[[(2-cyclohexyl-ethyl)amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0048] [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[4-[[[2-(4-chloro-phenyl)ethyl]amino]carbonyl]-2-oxazolyl]-7-oxabicyclo-[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0049] [1S-[1α, 2α(Z), 3α, 4α)]-6-[3-[4-[[(4-chlorophenyl)-amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0050] [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[4-[[[4-(4-chloro-phenyl)butyl]amino]carbonyl]-2-oxazolyl]-7-oxabicyclo-[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0051] [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[4α-[[(6-cyclohexyl-hexyl)amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid, or esters, or salts thereof;

[0052] [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[4-[[(6-cyclohexyl-hexyl)amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0053] [1S-[1α, 2α(Z) , 3α, 4α)]]-6-[3-[4-[(propylamino)-carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1] hept-2-yl]-4-hexenoic acid, or esters or salts thereof

[0054] [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[4-[[(4-butylphenyl)-amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0055] [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[4-[(2,3-dihydro-1H-indol-1-yl)carbonyl]-2-oxazolyl]-7-oxabicyclo(2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0056] [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[4-[[(4-cyclohexyl-butyl)amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-N-(phenylsulfonyl)-4-hexenamide;

[0057] [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[4-[[(4-cyclohexyl-butyl)amino]carbonyl]-2-oxazolyl]-N-(methylsulfonyl)-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenamide;

[0058] [1S-[1α, 2α(Z), 3α, 4α)]]-7-[3-[4-[[(4-cyclohexyl-butyl)amino]carbonyl]-2-oxazolyl]-7-oxabicyclo (2.2.1]hept-2-yl]-5-heptenoic acid, or esters or salts threof;

[0059] [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[4-[[(4-cyclohexyl-butyl)amino]carbonyl]-1H-imidazol-2-yl]-7-oxabicyclo-[2.2.1]hept-2-yl]-4-hexenoic acid or esters or salts thereof;

[0060] [1S-[1α, 2α, 3α, 4α)]-6-[3-[4-[[(7, 7-dimethyloctyl)-amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0061] [1S-[1α, 2α(E), 3α, 4α)]]-6-[3-[4-[[(4-cyclohexyl-butyl)amino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid;

[0062] [1S-[1α, 2α, 3α, 4α)]-3-[4-[[(4-(cyclohexyl-butyl)-amino]carbonyl]-2-oxazolyl]-7-oxabicyclo [2.2.1]heptane-2-hexanoic acid or esters or salts

thereof, with a preferred compound being [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[4-[[(4-cyclohexylbutyl)amino]carbonyl]-2-oxazolyl]-7-oxabicyclo-[2.2.1]hept-2-yl]-4-hexenoic acid, or esters or salts thereof;

[0063] 7-oxabicycloheptane and 7-oxabicycloheptene compounds disclosed in U.S. Pat. No. 4,537,981 to Snitman et al, especially [1S-(1α, 2α(Z), 3α(1E, 3S*, 4R*), 4α)]]-7-[3-(3-hydroxy-4-phenyl-1-pentenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid (SQ 29,548); the 7-oxabicycloheptane substituted aminoprostaglandin analogs disclosed in U.S. Pat. No. 4,416,896 to Nakane et al, especially, [1S-[1α, 2α(Z), 3α, 4α)]]-7-[3-[[2-(phenylamino)carbonyl]-hydrazino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid; the 7-oxabicycloheptane substituted diamide prostaglandin analogs disclosed in U.S. Pat. No. 4,663,336 to Nakane et al, especially, [1S-[1α, 2α(Z), 3α, 4α)]]-7-[3-[[[[(1-oxoheptyl)amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid and the corresponding tetrazole, and [1S-[1α, 2α(Z), 3α, 4α)]]-7-[3-[[[[(4-cyclohexyl-1-oxobutyl)-amino]acetyl]amino]methyl]-7-oxabicyclo]2.2.1]hept-2-yl]-5-heptenoic acid;

[0064] 7-oxabicycloheptane imidazole prostaglandin analogs as disclosed in U.S. Pat. No. 4,977,174, issued Dec. 11, 1990, including [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[[4-(4-cyclohexyl-1-hydroxybutyl)-1H-imidazole-1-yl]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid or its methyl ester;

[0065] [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[[4-(3-cyclohexyl-propyl)-1H-imidazol-1-yl]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid or its methyl ester;

[0066] [1S-[1α, 2α(X(Z), 3α, 4α)]]-6-[3-[[4-(4-cyclohexyl-1-oxobutyl)-1H-imidazol-1-yl]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid or its methyl ester;

[0067] [1S-[1α, 2α(Z), 3α, 4α]]-6-[3-(1H-imidazol-1-ylmethyl)-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenoic acid or its methyl ester; or

[0068] [1S-[1α, 2α(Z), 3α, 4α)]]-6-[3-[[4-[[(4-cyclohexyl-butyl)amino]carbonyl]-1H-imidazol-1-yl] methyl-7-oxabicyclo-[2.2.1]hept-2-yl]-4-hexenoic acid, or its methyl ester;

[0069] the phenoxyalkyl carboxylic acids disclosed in U.S. Pat. No. 4,258,058 to Witte et al, especially 4-[2-(benzenesulfamido)ethyl]phenoxyacetic acid (BM 13,177-Boehringer Mannheim), the sulphonamidophenyl carboxylic acids disclosed in U.S. Pat. No. 4,443,477 to Witte et al, especially 4-[2-(4-chlorobenzenesulfonamido)ethyl]-phenylacetic acid (BM 13,505, Boehringer Mannheim), the arylthioalkylphenyl carboxylic acids disclosed in U.S. Pat. No. 4,752,616, especially 4-(3-((4-chlorophenyl)-sulfonyl)propyl)benzeneacetic acid.

[0070] Other examples of thromboxane A_2 receptor antagonists suitable for use herein include, but are not limited to vapiprost (which is a preferred example), (E)-5-[[[(pyridinyl)]3-(trifluoromethyl)phenyl]methylene]amino]-oxy]pentanoic acid also referred to as R68,070-Janssen Research Laboratories, 3-[1-(4-chlorophenylmethyl)-5-fluoro-3-methylindol-2-yl]-2,2-dimethylpropanoic acid [(L-655240 Merck-Frosst) Eur. J. Pharmacol. 135(2):193, Mar. 17, 87], 5(Z)-7-([2,4,5-cis]-4-(2-hydroxyphenyl)-2-trifluoromethyl-1,3-dioxan-5-yl)heptenoic acid (ICI 185282, Brit. J. Pharmacol. 90 (Proc. Suppl):228 P-Abs, March 87), 5(Z)-7-[2,2-dimethyl-4-phenyl-1,3-dioxan-cis-5-yl]heptenoic acid (ICI 159995, Brit. J. Pharmacol. 86 (Proc. Suppl):808 P-Abs., December 85), N,N'-bis[7-(3-chlorobenzeneamino-sulfonyl)-1,2,3,4-tetrahydro-isoquinolyl]disulfonylimide (SKF 88046, Pharmacologist 25(3):116 Abs., 117 Abs, August 83), (1α(Z)-2β, 5α]-(+)-7-[5-[[(1,1'-biphenyl)-4-yl]-methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid (AH 23848 -Glaxo, Circulation 72(6):1208, December 85, levallorphan allyl bromide (CM 32,191 Sanofi, Life Sci. 31 (20-21):2261, Nov. 15, 82), (Z,2-endo-3-oxo)-7-(3-acetyl-2-bicyclo [2.2.1]heptyl-5-hepta-3Z-enoic acid, 4-phenyl-thiosemicarbazone (EP092-Univ. Edinburgh, Brit. J. Pharmacol. 84(3):595, March 85); GR 32,191 (Vapiprost)-[1R-[1α(Z), 2β, 3β, 5α]]-(+)-7-[5-([1,1'-biphenyl]-4-ylmethoxy)-3-hydroxy-2-(1-piperidinyl-)cyclopentyl]-4-heptenoic acid; ICI 192,605-4(Z)-6-[(2,4,5-cis)2-(2-chlorophenyl)-4-(2-hydroxyphenyl)-1,3-dioxan-5-yl]hexenoic acid; BAY u 3405 (ramatroban)-3-[[(4-fluorophenyl)-sulfonyl]amino]-1,2,3,4-tetrahydro-9H-carbazole-9-propanoic acid; or ONO 3708-7-[2α, 4α-(dimethylmethano)-6β-(2-cyclopentyl-2β-hydroxyacetamido)-1α-cyclohexyl]-5(Z)-heptenoic acid; (±)(5Z)-7-[3-endo-((phenylsulfonyl)amino]-bicyclo[2.2.1]hept-2-exo-yl]-heptenoic acid (S-1452, Shionogi domitroban, Anboxan®); (−)6,8-difluoro-9-p-methylsulfonylbenzyl-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid (L670596, Merck) and (3-[l-(4-chlorobenzyl)-5-fluoro-3-methyl-indol-2-yl]-2,2-dimethyl-propanoic acid (L655240, Merck).

[0071] The disclosure of the above-mentioned U.S. patents are incorporated herein by reference.

[0072] The optional cholesterol lowering drug employed herein includes, but is not limited to, HMG CoA reductase inhibitors, MTP inhibitors, squalene synthetase inhibitors, fibrates, resins and the like.

[0073] The term "MTP" as employed herein 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.

[0074] The combination of the invention will include the ADP-receptor blocking antiplatelet drug and thromboxane A_2 receptor antagonist in a weight ratio to each other within the range from about 1000:1 to about 0.001:1, preferably from about 0.05:1 to about 100:1.

[0075] When employed, the cholesterol lowering drug will be employed in a weight ratio to the ADP-receptor blocking antiplatelet drug 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.

[0076] When present, the cholesterol lowering drug to be used in combination with the ADP-receptor blocking anti-

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.