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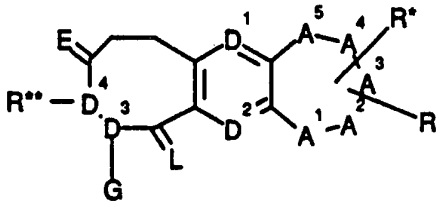
(54) Title: TRICYCLIC COMPOUNDS FOR INHIBITING PLATELET AGGREGATION

(57) Abstract

This invention relates to compounds of formula (I) or a pharmaceutically acceptable salt thereof, which are effective for inhibiting platelet aggregation, pharmaceutical compositions for effecting such activity, and a method for inhibiting platelet aggregation.



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Tricyclic compounds for Inhibiting Platelet Aggregation

Field of the Invention

This invention relates to novel compounds which inhibit platelet aggregation, pharmaceutical compositions containing the compounds and methods of using the compounds.

Background of the Invention

Platelet aggregation is believed to be mediated primarily through the fibrinogen receptor, or GPIIb-IIIa platelet receptor complex, which is a member of a family of adhesion receptors referred to as integrins. It has been found that frequently the natural ligands of integrin receptors are proteins which contain an Arg-Gly-Asp sequence. Von Willebrand factor and fibrinogen, which are considered to be natural ligands for the GPIIb-IIIa receptor, possess an Arg-Gly-Asp (RGD in single letter amino acid code) sequence in their primary structure. Functionally, these proteins are able to bind and crosslink GPIIb-IIIa receptors on adjacent platelets and thereby effect aggregation of platelets.

Fibronectin, vitronectin and thrombospondin are RGD-containing proteins which have also been demonstrated to bind to GPIIb-IIIa. Fibronectin is found in plasma and as a structural protein in the intracellular matrix. Binding between the structural proteins and GPIIb-IIIa may function to cause platelets to adhere to damaged vessel walls.

Linear and cyclic peptides which bind to vitronectin and contain an RGD sequence are disclosed in WO 89/05150 (PCT US88/04403). EP 0 275 748 discloses linear tetra- to hexapeptides and cyclic hexa- to octapeptides which bind to the GPIIb-IIIa receptor and inhibit platelet aggregation. Other linear and cyclic peptides, the disclosure of which are incorporated herein by reference, are reported in EP-A 0 341 915. However, the peptide like structures of such inhibitors often pose problems, such as in drug delivery, metabolic stability and selectivity. Inhibitors of the fibrinogen receptor which are not constructed of natural amino acid sequences are disclosed in EP-A 0 372,486, EP-A 0 381 033 and EP-A 0 478 363. WO 92/07568 (PCT/US91/08166) discloses

fibrinogen receptor antagonists which mimic a conformational γ-turn in the RGD sequence by forming a monocyclic seven-membered ring structure. There remains a need, however, for novel fibrinogen receptor antagonists (e.g. inhibitors of the GPIIb-IIIa protein) which have potent *in vivo* and *in vitro* effects and lack the peptide backbone structure of amino acid sequences.

The present invention discloses novel bicyclic compounds including benzazepines and benzodiazepines, which are inhibitors of the GPIIb-IIIa receptor and inhibit platelet aggregation. Certain 5-phenyl-1,4-benzodiazepines are known as a class of drugs which affect the central nervous system, and have been used as anxiolytics. See Sternbach, L.H., *J. Med. Chem.*, 22, 2 (1979). It has also been disclosed that certain 5-phenyl-1,4-benzodiazepines antagonize the effects of cholecystokinin. See Friedinger, *Med. Res. Rev.*, 9, 271 (1989). However, no such bicyclic compounds have been reported to have anti-platelet activity.

Summary of the Invention

In one aspect this invention is a tricyclic compound comprising a substituted six-membered ring which is fused to both a substituted seven-membered ring and a substituted eight-membered ring as described hereinafter in formula (I).

This invention is also a pharmaceutical composition for inhibiting platelet aggregation or clot formation, which comprises a compound of formula (I) and a pharmaceutically acceptable carrier.

This invention is further a method for inhibiting platelet aggregation in a mammal in need thereof, which comprises internally administering an effective amount of a compound of formula (I).

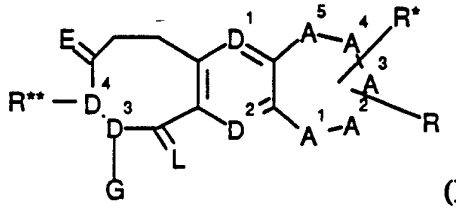
In another aspect, this invention provides a method for inhibiting reocclusion of an artery or vein in a mammal following fibrinolytic therapy, which comprises internally administering an effective amount of a fibrinolytic agent and a compound of formula (I). This invention is also a method for treating stroke, transient ischemia attacks, and myocardial infarction.

Detailed Description of the Invention

This invention discloses novel tricyclic compounds which inhibit platelet aggregation. The novel tricyclic compounds comprise a seven-membered ring fused to an aromatic six-membered ring which is also fused to a nitrogen-containing eight-membered ring. An aliphatic substituent containing an acidic moiety is present on the seven-membered ring. The seven-membered ring may contain heteroatoms, such as nitrogen, oxygen and sulfur, and the six-membered ring may be carbocyclic or contain up to two nitrogen atoms. The fused 8-6-7 ring system is believed to interact favorably with the GPIIb-IIIa receptor and to orient the substituent sidechains on the eight- and seven-membered rings so that they may also interact favorably with the receptor.

Although not intending to be bound to any specific mechanism of action, these compounds are believed to inhibit the binding of fibrinogen to the platelet-bound fibrinogen receptor GPIIb-IIIa, and may interact with other adhesion proteins via antagonism of a putative RGD binding site.

The compounds of this invention are compounds of formula (I):



(I)

wherein:

A^1 to A^5 form an accessible substituted seven-membered ring, which may be saturated or unsaturated, optionally containing up to two heteroatoms chosen from the group of O, S and N wherein S and N may be optionally oxidized;

D^1, D^2, D^3 and D^4 independently are CH or N, with the proviso that at least one of D^3 or D^4 is N;

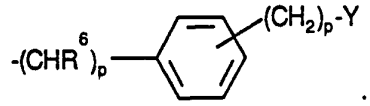
R is at least one substituent chosen from the group of R^7, or Q-C_{1-4}alkyl, Q-C_{2-4}alkenyl, Q-C_{2-4}alkynyl, optionally substituted by one or more of =O, R^{11} or R^7;

R* is H, Q-C_{1-6}alkyl, Q-C_{1-6}oxoalkyl, Q-C_{2-6}alkenyl, Q-C_{3-4}oxoalkenyl, Q-C_{3-4}oxoalkynyl, Q-C_{2-4}alkynyl, C_{3-6}cycloalkyl, Ar, or Het, optionally substituted by one or more of R^{11};

each Q is H, C_{3-6}cycloalkyl, Het or Ar;

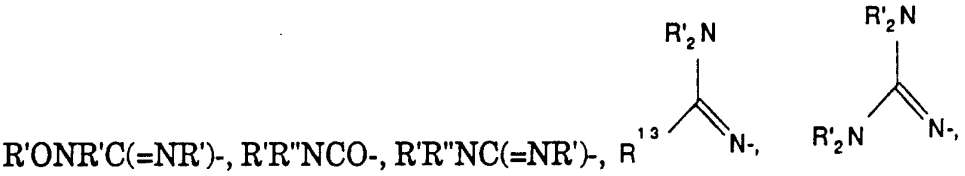
E and L independently are O or (H,H);

G is $(CHR^6)_t$-Y, $(CHR^6)_p$-Het-$(CH_2)_p$-Y, $(CHR^6)_p$-C_{3-7}cycloalkyl-$(CH_2)_p$-Y or

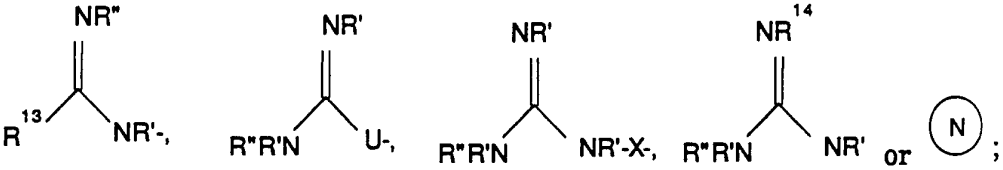


;

Y is R'R"N-, R'R"NR'N-, R'R"NR'NCO-, $R'_2NR'NC(=NR')$-,



R'ONR'C(=NR')-, R'R"NCO-, R'R"NC(=NR')-,



;

X is absent, N=CR', C(O) or O;

U is absent, S or O;

R' is H, C_{1-4}alkyl, C_{3-7}cycloalkyl-C_{0-4}alkyl, or Ar-C_{0-4}alkyl;

R" is R', -C(O)R' or -C(O)OR^{15}

R"' is R" or AA2:

AA2 is an amino acid attached through its carboxyl group, and having its amino group optionally protected;

R** is V-M, wherein V is H, R^{10}, R^{10}-J-CO or R^{10}-J-$S(O)_m$, in which J is O, NH, S or a covalent bond, and M is -NH(CHR^{16})CO- or a covalent bond;

R^6 is H or C_{1-4}alkyl;

R^7 is -COR^8, -$COCR'_2R^9$, -C(S)R^8, -$S(O)_mOR'$, -$S(O)_mNR'R"$, -PO(OR'), -$PO(OR')_2$, -$B(OR')_2$, -NO_2, or Tet;

R^8 is -OR', -NR'R", -NR'SO_2R', -NR'OR', -$OCR'_2CO(O)R'$, -$OCR'_2OC(O)R'$, -$OCR'_2C(O)NR'_2$, CF_3 or AA1;

R^9 is -OR', -CN, -$S(O)_rR'$, -$S(O)_mNR'_2$, -C(O)R', C(O)NR'_2, or -CO_2R';

R^{10} is $(CHR^6)_r$-H, $(CHR^6)_r$-C_{3-6}cycloalkyl, $(CHR^6)_r$-Ar or $(CHR^6)_r$-Het;

R^{11} is H, halo, -OR^{12}, -CN, -$NR'R^{12}$, -NO_2, -CF_3, $CF_3S(O)_r$-, -CO_2R', -$CONR'_2$, Q-C_{0-6}alkyl-, Q-C_{1-6}oxoalkyl-, Q-C_{2-6}alkenyl-, Q-C_{2-6}alkynyl-, Q-C_{0-6}alkyloxy-, Q-C_{0-6}alkylamino- or Q-C_{0-6}alkyl-$S(O)_r$-;

R^{12} is R', -C(O)R', -$C(O)NR'_2$, -C(O)OR', -$S(O)_mR'$, or -$S(O)_mNR'_2$;

R^{13} is R', -CF_3, -SR', or OR';

R^{14} is R', C(O)R', CN, NO_2, SO_2R', or $C(O)OR^{15}$;

each R^{15} independently is C_{1-6}alkyl or Ar-C_{0-4}alkyl;

R^{16} is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, $(CH_2)_n$-Het or $(CH_2)_qZ$, wherein Z is C_{3-6}cycloalkyl, OH, NH_2, SH, SC_{1-4}alkyl, CO_2R^6, $CONH_2$ or $NHC(=NH)NH_2$;

AA1 is an amino acid attached through its amino group and having its carboxyl group optionally protected;

each m independently is 1 or 2;

each n independently is 0 to 2;

each p independently is 0 to 2;

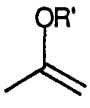
q is 1 to 4;

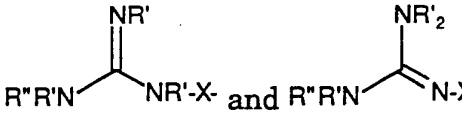
each r independently is 0 to 4; and

t is 2 to 5;

or a pharmaceutically acceptable salt thereof.

Also included in this invention are pharmaceutically acceptable addition salts, complexes or prodrugs of the compounds of this invention. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo*.

In cases wherein the compounds of this invention may have one or more chiral centers, unless specified, this invention includes each unique nonracemic compound which may be synthesized and resolved by conventional techniques. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, such as  and  , and tautomers of guanidine-type groups, such as



and , each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or locked in one form by appropriate substitution with R'. The meaning of any substituent at any one occurrence is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

With reference to formula (I), suitably,

A^1 is $CR^1R^{1'}$, CR^1, NR^1, N, O, or $S(O)_x$;

A^2 is $CR^2R^{2'}$, CR^2, or NR^2;

A^3 is $CR^3R^{3'}$, CR^3, NR^3, N, O, or $S(O)_x$;

A^4 is $CR^4R^{4'}$, CR^4, NR^4, or N;

A^5 is $CR^5R^{5'}$, CR^5, NR^5, N, O, or $S(O)_x$;

D^1 and D^2 are CH;

R is $(CR^{14}R^{15})_u$-$(T)_v$-$(CR^{17}R^{18})_w$-R^7 or =CR'-$(T)_v$-$(CR^{17}R^{18})_w$-R^7 wherein T is $CR^{17}R^{18}$-$CR^{17}R^{18}$, CR'=CR' or $C \equiv C$, and R^{17} and R^{18} are R', OR' or together are =O, provided that R^{16} and R^{17} are not simultaneously OR' when they are attached to the same carbon;

R^1 and $R^{1'}$ are R^* or R, or together are =O;

R^2 and $R^{2'}$ are R^*, R or =O;

R^3 and $R^{3'}$ are R^*, R or =O;

R^4 and $R^{4'}$ are R^*, R or =O;

R^5 and $R^{5'}$ are R^*, R or =O;

x is 0 to 2; and

u, v and w independently are 0 or 1.

More suitably,

A^1 is $CR^1R^{1'}$, CR^1, NR^1, N, O, or S;

A^2 is $CR^2R^{2'}$, NR^2 or CR^2;

A^3 is $CR^3R^{3'}$

A^4 is $CR^4R^{4'}$, CR^4, NR^4, or N;

A^5 is $CR^5R^{5'}$, CR^5 NR^5, N or O;

D^1 and D^2 are CH;

R^2 or R^4 are R;

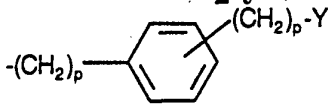
R^3, $R^{3'}$ and R^5, $R^{5'}$ are =O or R^*, H.

With reference to compounds of formula (I) preferably

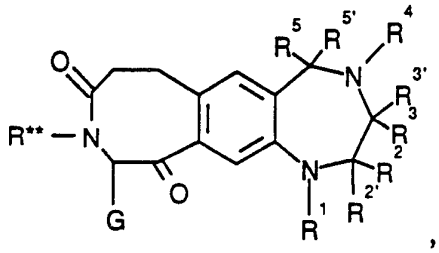
L is O and E is O or (H,H);

R** is methyl, acetyl or benzoyl; and

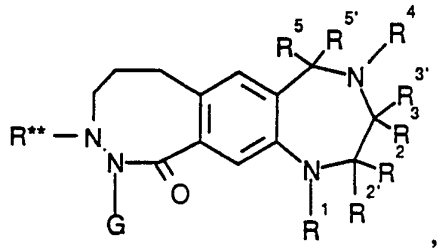
G is $(CH_2)_t$-Y, $(CH_2)_p$-Het-$(CH_2)_p$-Y, or



Representative compounds of this invention are given by each of formulas (II) - (IX):



(II)



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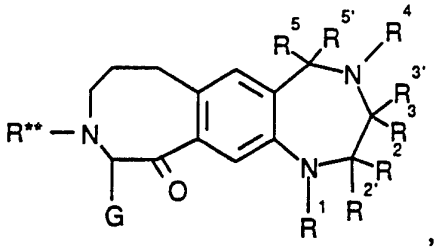

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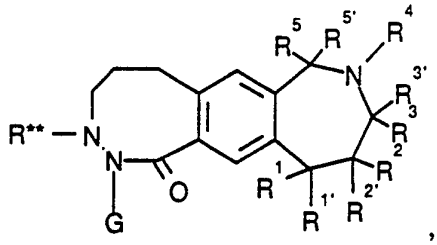

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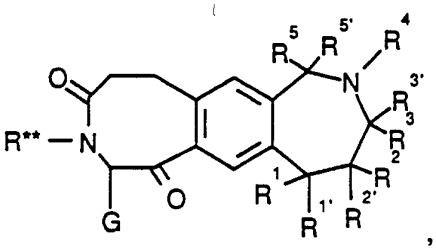

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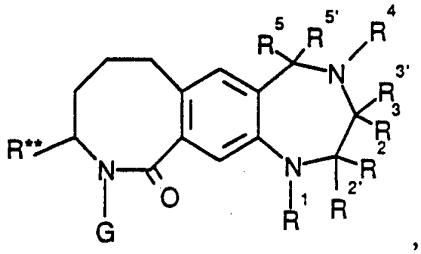

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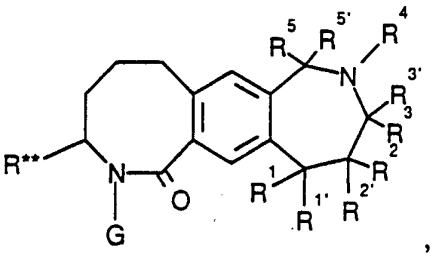
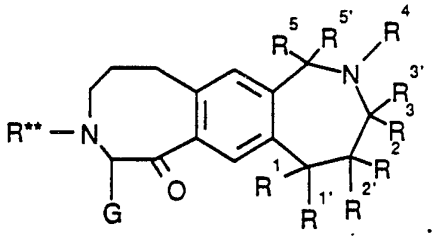


(VIII), or

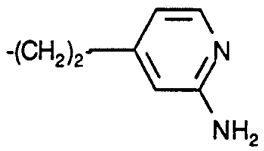


(IX).

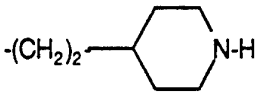
Preferably, R^1 is H, C_{1-4}alkyl, or C(O)R';

R^2 is CH_2CO_2H;
R^3,$R^{3'}$ is =O or H,H;
R^4 is H, C_{1-6}alkyl or C_{1-4}alkyl-Ar; and
R^5 is H.

Preferably, Y is H_2N-, $H_2NC(=NH)$-, $H_2NC(=NH)NH$- or  .
Most preferably, G is



$-(CH_2)_3NHC(=NH)NH_2$,



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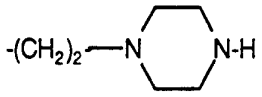
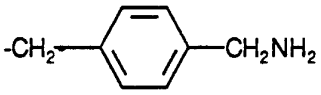
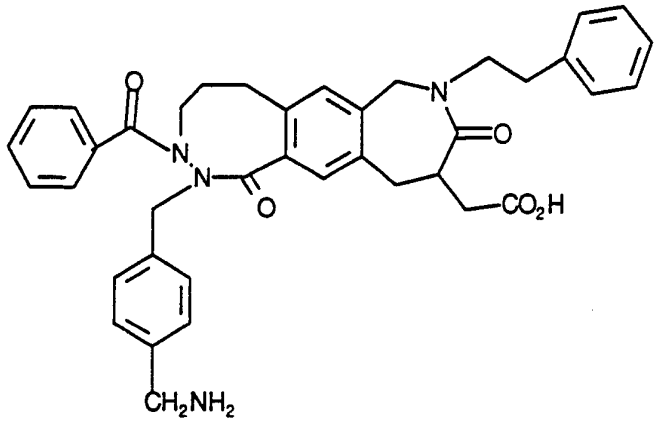


, or



A preferred compound of this invention is:



In the above description of formula (I), preferably only one or two of A^1 to A^5 are substituted by R. Y represents a nitrogen-containing group which is capable of making a hydrogen bond. Preferably, Y is a basic nitrogen moiety. R^7 represents a group with a non-bonding pair of electrons which is capable of forming a hydrogen bond or chelating with a metal. Preferably R^7 is acidic. It is also preferred that 10-15 intervening covalent bonds via the shortest intramolecular path will exist between the group R^7 and Y for optimal spacing between these groups.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of this invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984).

Arg refers to arginine, MeArg refers to N^{α}-methyl-arginine, HArg refers to homoarginine, NArg refers to norarginine, (Me_2)Arg refers to N',N"-dimethyl arginine, (Et_2)Arg refers to N',N"-diethyl arginine and Orn refers to ornithine. These radicals are suitable components of the substituent R^6. N^{α}-Substituted derivatives of these amino acid are also useful in this invention. Representative methods for preparing α-substituted derivatives are disclosed in U.S. Patent No. 4,687,758; Cheung *et al.*, *Can. J. Chem.*, 55, 906 (1977); Freidinger *et al.*, *J. Org. Chem.*, 48, 77, (1982); and Shuman *et al.*, PEPTIDES: PROCEEDINGS OF THE 7TH AMERICAN PEPTIDE SYMPOSIUM, Rich, D., Gross, E., Eds, Pierce Chemical Co., Rockford, Ill.,617 (1981), which are incorporated herein by reference.

C_{1-4}alkyl as applied herein is meant to include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl. C_{1-6}alkyl additionally includes pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. C_{0-4}alkyl and C_{0-6}alkyl additionally indicates that no alkyl group need be present (*e.g.*, that a covalent bond is present).

C_{2-6} alkenyl as applied herein means an alkyl group of 2 to 6 carbons wherein a carbon-carbon single bond is replaced by a carbon-carbon double bond. C_{2-6}alkenyl includes ethylene, 1-propene, 2-propene, 1-butene, 2-butene, isobutene and the several isomeric pentenes and hexenes. Both cis and trans isomers are included.

C_{2-6} alkynyl means an alkyl group of 2 to 6 carbons wherein one carbon-carbon single bond is replaced by a carbon-carbon triple bond. C_{2-6} alkynyl includes acetylene, 1-propyne, 2-propyne, 1-butyne, 2-butyne, 3-butyne and the simple isomers of pentyne and hexyne.

C_{1-4}oxoalkyl refers to an alkyl group of up to four carbons wherein a CH_2 group is replaced by a C(O), or carbonyl, group. Substituted formyl, acetyl, 1-propanal, 2-propanone, 3-propanal, 2-butanone, 3-butanone, 1- and 4-butanal groups are representative. C_{1-6}oxoalkyl includes additionally the higher analogues and isomers of five and six

carbons substituted by a carbonyl group. C_{3-6}oxoalkenyl and C_{3-6}oxoalkynyl refers to a C_{3-6}alkenyl or C_{3-6}alkynyl group wherein a CH_2 group is replaced by C(O) group. C_{3-4}oxoalkenyl includes 1-oxo-2-propenyl, 3-oxo-1-propenyl, 2-oxo-3-butenyl and the like.

A substituent on a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{1-6} oxoalkyl group, such as R^{11}, may be on any carbon atom which results in a stable structure, and is available by conventional synthetic techniques.

Q-C_{1-6} alkyl refers to a C_{1-6} alkyl group wherein in any position a carbon-hydrogen bond is replaced by a carbon-Q bond. Q-C_{2-6} alkenyl and Q-C_{2-6} alkynyl have a similar menaing with respect to C_{2-6} alkenyl and C_{2-6} alkynyl.

Ar, or aryl, as applied herein, means phenyl or naphthyl, or phenyl or naphthyl substituted by one to three moieties R^{11}. In particular, R^{11} may be C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkthio, trifluoroalkyl, OH, F, Cl, Br or I.

Het, or heterocycle, indicates an optionally substituted five or six membered monocyclic ring, or a nine or ten-membered bicyclic ring containing one to three heteroatoms chosen from the group of nitrogen, oxygen and sulfur, which are stable and available by conventional chemical synthesis. Illustrative heterocycles are benzofuryl, benzimidazole, benzopyran, benzothiophene, furan, imidazole, indoline, morpholine, piperidine, piperazine, pyrrole, pyrrolidine, pyridine, thiazole, thiophene, quinoline, isoquinoline, and tetra- and perhydro-quinoline and isoquinoline. Any accessible combination of up to three substituents, such as chosen from R^{11}, on the Het ring that is available by chemical synthesis and is stable is within the scope of this invention.

C_{3-7}cycloalkyl refers to an optionally substituted carbocyclic system of three to seven carbon atoms, which may contain up to two unsaturated carbon-carbon bonds. Typical of C_{3-7}cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl and cycloheptyl. Any combination of up to three substituents, such as chosen from R^{11}, on the cycloalkyl ring that is available by conventional chemical synthesis and is stable, is within the scope of this invention.

An accessible substituted seven-membered ring as referred to herein is any saturated or unsaturated seven-membered ring which (i)

has up to five substituents, such as R or R*, wherein the substituents may be present on any atom or heteroatom that results in a stable structure, and (ii) contains up to two heteroatoms selected from the group of N, O and S, wherein S and N may optionally be oxidized, and (iii) is stable and may be synthesized by one skilled in the chemical arts in a form fused via two adjacent ring carbon atoms to a phenyl, pyridyl, or pyrazinyl ring. Typical of accessible seven-membered rings are the common saturated and unsaturated rings of cycloheptane, thiepin, oxapin, azepine, diazepine, thiazepin, oxazepin, dioxepin, oxathiepin and dithiepin.

An accessible substituted six-membered ring as referred to herein is an unsaturated (e.g. aromatic) six-membered ring which (i) has one to three substituents, such as chosen from R^6 and R^{11}, (ii) optionally contains up to two nitrogens, (iii) is fused via two adjacent carbon atoms to an accessible substituted seven-membered ring, and (iv) is stable and may be prepared by one skilled in the chemical arts. Typical of accessible six-membered rings are phenyl, pyridyl or pyrazinyl ring.

Phenyl is a preferred accessible six-membered ring, and di- or tetrahydroazepine, diazepine, thiazepine and oxazepine are preferred accessible seven-membered rings.

Any accessible substituted eight-membered ring as referred to herein is a saturated eight-membered ring which (i) has up to two substituents, such as G and R**, (ii) contains one or two nitrogen atoms, and (iii) is stable and may be synthesized by one skilled in the chemical arts in a form fused via two adjacent ring carbon atoms to a phenyl, pyridyl, or pyrazinyl ring. Typical of accessible eight-membered rings are diazocine and azocine.

It will be understood that, with respect to A^1-A^5, $CR^1R^{1'}$-$CR^5R^{5'}$ and NR^1-NR^5 are saturated sp^3 carbon and nitrogen atoms respectively which are singly bonded to the adjacent ring atoms, except that when $R^1/R^{1'}$, $R^2/R^{2'}$, $R^3/R^{3'}$, $R^4/R^{4'}$ and $R^5/R^{5'}$ represent a doubly bonded substituent exo to the ring (eg. such as =O or an alkylene side chain), $CR^1R^{1'}$-CR^5R^5 may also represent an sp^2 carbon atom. It will be further understood that, with respect to A^1-A^5, CR^1-CR^5 and N represent an unsaturated sp^2 carbon or nitrogen atom, which may be connected by an endocyclic double bond to an adjacent atom in the ring, provided such arrangement results in the creation of a stable compound.

 as used herein indicates a nitrogen heterocycle, which may be a saturated or unsaturated stable five-, six- or seven-membered monocyclic ring, or a seven- to ten-membered bicyclic ring containing up to three nitrogen atoms or containing one nitrogen atom and a heteroatom chosen from oxygen and sulfur, and which may be substituted on any atom that results in a stable structure. The nitrogen atom in such ring may be substituted so as to result in a quaternary nitrogen. The nitrogen heterocycle may be substituted in any stable position by C_{1-4}alkoxy, C_{1-4}alkylthio, F, Cl, Br, I, NO_2, NR'_2, OH, CO_2R', CONHR' or C_{1-4}alkyl, optionally substituted by any of the aforementioned sustituents. Representative of  are pyrroline, pyrrolidine, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, piperidine, piperazine, morpholine, pyridine, pyridinium, tetrahydropyridine, tetrahydro- and hexahydro-azepine, quinuclidine, quinuclidinium, quinoline, isoquinoline, and tetra- and perhydro-quinoline and isoquinoline. In particular,  may be pyridyl, pyrolidinyl, piperidinyl, piperazinyl, azetidinyl, quinuclidinyl or tetrahydropyridinyl.  is preferably 4-piperidinyl, 4-pyridyl or 4-piperazinyl.

AA1 as referred to herein is an amino acid with its carboxyl group optionally protected, wherein the amino acid may be any of the natural amino acids or penicillamine. The unprotected carboxyl group is a free carboxylic acid group. Protecting groups for the carboxyl are esters or amides which are formed, for instance, when the OH of the carboxy group is replaced by R^8. AA2 is an amino acid, as above, with its amino group optionally protected. Amino protecting groups are well known in the art, for instance, when the amino group is substituted by R^{12}. An unprotected amino group is a free NH_2 group.

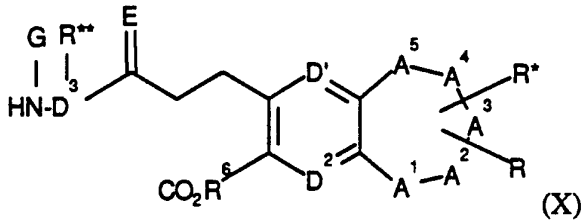
C(O) indicates a carbon doubly bonded to oxygen (eg. carbonyl), C(S) indicates a carbon doubly bonded to sulfur (eg. thiocarbonyl).

t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz refers to the benzyloxycarbonyl radical, BrZ refers to the o-bromobenzyloxycarbonyl radical, ClZ refers to the o-chlorobenzyloxycarbonyl radical, Bzl refers to

the benzyl radical, 4-MBzl refers to the 4-methyl benzyl radical, Me refers to methyl, Et refers to ethyl, Ac refers to acetyl, Alk refers to C_{1-4}alkyl, Nph refers to 1- or 2-naphthyl and cHex refers to cyclohexyl. MeArg is N^{α}-methyl arginine.

DCC refers to dicyclohexylcarbodiimide, DMAP refers to dimethylaminopyridine, DIEA refers to diisopropylethyl amine, EDC refers to N-ethyl-N'(dimethylaminopropyl)-carbodiimide. HOBt refers to 1-hydroxybenzotriazole, THF refers to tetrahydrofuran, DIEA refers to diisopropylethylamine, DMF refers to dimethyl formamide, NBS refers to N-bromo-succinimide, Pd/C refers to a palladium on carbon catalyst, PPA refers to 1-propanephosphonic acid cyclic anhydride, DPPA refers to diphenylphosphoryl azide, BOP refers to benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate, HF refers to hydrofluoric acid, TEA refers to triethylamine, TFA refers to trifluoroacetic acid, PCC refers to pyridinium chlorochromate.

The compounds of formula (I) are generally prepared by cyclizing a compound of the formula (X):

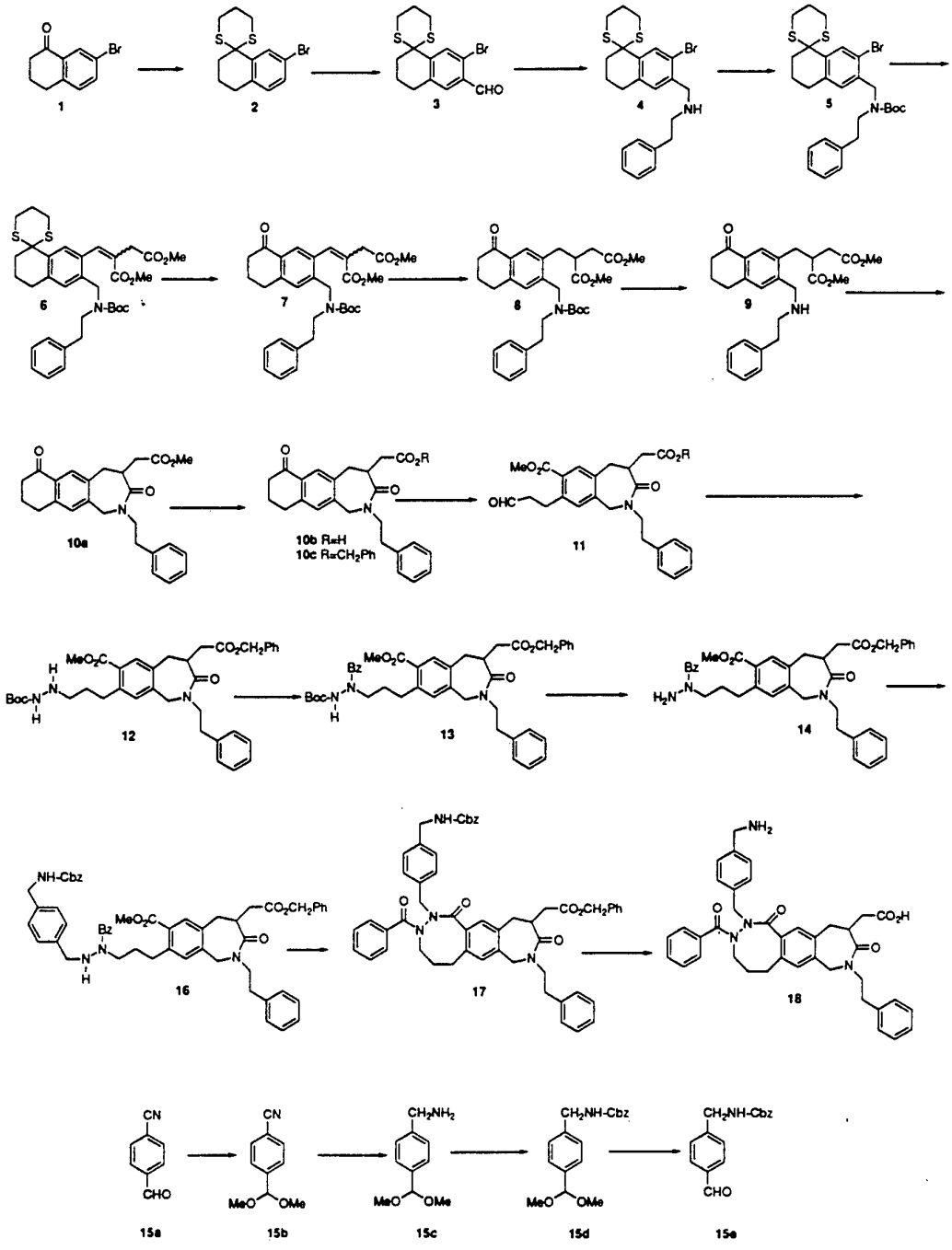


(X)

wherein D^1, D^2, D^3, A^1-A^5, R, R*, R**, R^6, E, and G are as defined in formula (I), except any reactive functional groups are protected, and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt.

The compounds of formula (I) are prepared starting from commercially available reagents, such as substituted tetralones, using conventional synthetic techniques. The scheme disclosed herein is illustrative of the methods of this invention.

Scheme 1


1
2
3
4
5
6
7
8
9
10a
10b R=H
10c R=CH2Ph
11
12
13
14
15a
15b
15c
15d
15e
16
17
18

Scheme 1 provides a method of preparing compounds wherein one of A^1 - A^5 is nitrogen (a benzazepine), the six-membered ring is a phenyl and the eight-membered ring is a diazocine. Generally, the synthesis is begun with a 3-halo-1-tetralone. Protection of the ketone with, for example, a dithioacetal using 1,3-dithiapropane, in the presence of a Lewis Acid, such as boron trifluoride etherate, followed by formylation, using, for example, dichloromethyl methyl ether in the presence of a Lewis Acid, such as aluminum chloride, yields compounds of formula (3). Reductive amination using an appropriately substituted R^4-substituted amine, such as 1-amino-2-phenyl ethane, in the presence of sodium cyanoborohydride, yields formula (4) compounds. Protection of the amine using standard techniques, for example, conversion to the Boc-protected amine, followed by palladium-catalyzed coupling of the aromatic halide of formula (5) with dimethyl itaconate gives formula (6) compounds. Deprotection of the ketone and subsequent reduction of the double bond using, for example, hydrogen in the presence of a catalyst, such as palladium on carbon, gives formula (8) compounds. Deprotection of the amino group, such as by treatment with acid in the case of the Boc-protecting group, yields the free amine compound of formula (9). Upon heating in the presence of a base, the free amino group may be induced to undergo an intramolecular cyclization to form the banzazepine compound of formula (10). Ozonolysis of this intermediate, followed by amination and benzoylation yields formula (13) compounds. Removal of the Boc-group, followed by reduction amination, for example, by reacting a formula (15) compound with a Cbz-protected 4-aminomethyl-benzaldehyde, introduces the G substituent. Intramolecular cyclization and subsequent removal of any protecting groups gives formula (18) compounds, which are also formula (I) compounds.

From Scheme 1, it should be appreciated by those skilled in the art that the R^4 and G groups desired in the formula (I) compounds are introduced into the molecule in the reductive aminations steps detailed above. Scheme 1 presents a representative R^4 group, namely, a 2-phenylethyl group, and a representative G group, namely, a 4-amino-methylbenzyl group. This scheme is illustrative of the methods of this invention.

The benzodiazepines and benzazepines of formula (X) are prepared by the general methods detailed in PCT Publication No.

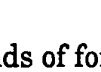
93/00095, published January 7, 1993, assigned to SmithKline Beecham Corporation. Referenced should be made to such publication for its disclosure, which is incorporated herein by reference. (See also Hynes, et al. J. Het. Chem., 25:1173 (1988); Muller, et al. Helv. Chim. Aeta, 65:2118 (1982) and Mori, et al., Heterocycles, 16:1491(1981)). The appropriately substituted benzazepine or benzodiapine, which are the precussors to the tricyclic formula (I) compounds, may be obtained starting from the appropriately substituted tetralone as detailed in Scheme 1.

Coupling reagents as used herein denote reagents which may be used to form peptide bonds. Typical coupling methods employ carbodiimides, activated anhydrides and esters and acyl halides. Reagents such as EDC, DCC, DPPA, PPA, BOP reagent, HOBt, N-hydroxysuccinimide and oxalyl chloride are typical.

Coupling methods to form peptide bonds are generally well known to the art. The methods of peptide synthesis generally set forth by Bodansky *et al.*, THE PRACTICE OF PEPTIDE SYNTHESIS, Springer-Verlag, Berlin, 1984, Ali *et al.* in *J. Med. Chem.*, 29, 984 (1986) and *J. Med. Chem.*, 30, 2291 (1987) are generally illustrative of the technique and are incorporated herein by reference.

Solution synthesis for the formation of amide or peptide bonds is accomplished using conventional methods used to form amide bonds. Typically, the amine or aniline is coupled via its free amino group to an appropriate carboxylic acis substrate using a suitable carbodiimide coupling agent, such as N,N' dicyclohexyl carbodiimide (DCC), optionally in the presence of catalysts such as 1-hydroxybenzotriazole (HOBt) and dimethylamino pyridine (DMAP). Other methods, such as the formation of activated esters, anhydrides or acid halides, of the free carboxyl of a suitably protected acid substrate, and subsequent reaction with the free amine of a suitably protected amine, optionally in the presence of a base, are also suitable. For example, a protected Boc-amino acid or Cbz-amidino benzoic acid is treated in an anhydrous solvent, such as methylene chloride or tetrahydrofuran(THF), in the presence of a base, such as N-methyl morpholine, DMAP or a trialkylamine, with isobutyl chloroformate to form the "activated anhydride", which is subsequently reacted with the free amine of a second protected amino acid or aniline.

Compounds of formula (X) are prepared by conventional methods known in the art from commercially available materials. Y is generally a basic functional group, such as amino, guanidino, amidino ro heterocyclic group, and is protected during the synthesis of Formula (I) compounds. For example, compounds of formula (X) or formula (I) wherein Y is a suitably substituted R'R"N-, R"R'NC(=NR'), R'$_2$N(R^{13})C=N-, R"N=(R^{13})C-NR'-, R'$_2$N(R'$_2$N)C=N- or R"R'N(R'N=)C-NR', are prepared by conventional methods including those disclosed in EP-A 0 372 486, EP-A 0 381 033 or EP-A 0 478 363, which are incorporated herein by reference.

Compounds of formula (X) wherein Y is  are prepared, *inter alia*, by methods disclosed in EP-A 0 478 363.

Compounds wherein W is R'$_2$N(R'$_2$N)C=N-X- or R"R'N(R'N=)C-NR'-X-, and X is O are prepared, *inter alia*, by methods disclosed in *J. Org. Chem.*, 51, 5047 (1986).

Compounds wherein Y is R'$_2$N(R'$_2$N)C=N-X- or R"R'N(R'N=)C-NR'-X-, and X is N=CR', are prepared, *inter alia*, by methods disclosed in United States Patent 3,714,253 and *Eur. J. Med. Chem.-Chim. Ther.*, 20, 25 (1985).

Compounds wherein Y isR'$_2$N(R'$_2$N)C=N-X- or R"R'N(R'N=)C-NR'-X-, and X is C(O), are prepared, *inter alia*, by methods disclosed in United States Patent 3,714,253 and *Can. J. Chem.*, 43, 3103 (1965).

Compounds wherein Y is R'ONR'C(=NR')- may be prepared, *inter alia*, by methods disclosed in J. Het. Chem., 16, 1063 (1979) or J. Het. Chem., 26, 125 (1989).

Compounds wherein Y is R'$_2$NR'NC(=NR')- are prepared by conventional methods including those disclosed in Syn., 583 (1974).

Compounds wherein Y is R'R"NR'N- are prepared, *inter alia*, by methods disclosed in *J. Prakt. Chem.*, 36, 29 (1967).

Compounds wherein Y is R'R"NR'NCO- are prepared, *inter alia*, by methods disclosed in *Bull. Chem. Soc. Jpn.*, 43, 2257 (1970).

Compounds wherein Y is R"R'NC(=NR')Y', and Y' is S, are prepared, *inter alia*, by methods disclosed in *Chem. Lett.*, 1379 (1986).

Compounds of formula (X) or formula (I), wherein Y is R"R'NC(=NR')Y' and Y' is O, are prepared by conventional methods including those disclosed in Japanese Patent 2022751.

The reactive functional groups of the sidechains of each synthetic fragment are suitably protected as known in the art. Suitable protective groups are disclosed in Greene, PROTECTIVE GROUPS IN ORGANIC CHEMISTRY, John Wiley and Sons, New York, 1981. For example, the Boc, Cbz, phthaloyl or Fmoc group may be used for protection of an amino or amidino group. The Boc group is generally preferred for protection of an α-amino group. A t-Bu, cHex or benzyl ester may be used for the protection of the side chain carboxyl. A benzyl group or suitably substituted benzyl group (eg. 4-methoxy-benzyl or 2,4-dimethoxy-benzyl) is used to protect the mercapto group or the hydroxyl group. The tosyl group may be used for protection of the imidazolyl group and tosyl or nitro group for protection of the guanidino group. A suitably substituted carbobenzyloxy group or benzyl group may be also be used for the hydroxyl group or amino group. Suitable substitution of the carbobenzyloxy or benzyl protecting groups is ortho and/or para substitution with chloro, bromo, nitro or methyl, and is used to modify the reactivity of the protective group. Except for the Boc group, the protective groups for the amino moiety are, most conveniently, those which are not removed by mild acid treatment. These protective groups are removed by such methods as catalytic hydrogenation, sodium in liquid ammonia or HF treatment, as known in the art.

Modification of amino groups especially on the six-membered ring of the tricyclic system, may be accomplished by alkylation, sulfonylation, cyanation or acylation as is generally known in the art.

Acid addition salts of the peptides are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, maleic, succinic or methanesulfonic. The acetate salt form is especially useful. Certain of the compounds form inner salts or zwitterions which may be acceptable. Cationic salts are prepared by treating the parent compound with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation; or with an appropriate organic amine. Cations such as Li+, Na+, K+, Ca++, Mg++ and NH_4+ are specific examples of cations present in pharmaceutically acceptable salts.

This invention provides a pharmaceutical composition which comprises a compound according to formula (I) and a pharmaceutically

acceptable carrier. Accordingly, the compounds of formula (I) may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of formula (I) prepared as hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, the compounds of formula (I) may be encapsulated, tableted or prepared in a emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the formula (I) compounds may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

The compounds of this invention may be used *in vitro* to inhibit the aggregation of platelets in blood and blood products, *e.g.*, for storage, or for *ex vivo* manipulations such as in diagnostic or research use.

This invention also provides a method of inhibiting platelet aggregation and clot formation in a mammal, especially a human, which comprises the internal administration of a compound of formula (I) and a pharmaceutically acceptable carrier. Indications for such therapy include acute myocardial infarction (AMI), deep vein thrombosis, pulmonary embolism, dissecting anurysm, transient ischemia attack (TIA), stroke and other infarct-related disorders, and unstable angina. Chronic or acute states of hyper-aggregability, such as disseminated intravascular coagulation (DIC), septicemia, surgical or infectious shock, post-operative and post-partum trauma, cardiopulmonary bypass surgery, incompatible blood transfusion, abruptio placenta, thrombotic thrombocytopenic purpura (TTP), snake venom and immune diseases, are likely to be responsive to such treatment. In addition, the compounds of this invention may be useful in a method for the prevention of metastatic conditions, the prevention or treatment of fungal or bacterial infection, inducing immunostimulation, treatment of sickle cell disease, and the prevention or treatment of diseases in which bone resorption is a factor.

The formula (I) compound is administered either orally or parenterally to the patient, in a manner such that the concentration of drug in the plasma is sufficient to inhibit platelet aggregation, or other such indication. The pharmaceutical composition containing the compound of this invention is administered at a dose between about 0.2 to about 50 mg/kg in a manner consistent with the condition of the patient. For acute therapy, parenteral administration is preferred. For persistent states of hyperaggregability, an intravenous infusion of the formula (I) compound in 5% dextrose in water or normal saline is most effective, although an intramuscular bolus injection may be sufficient.

For chronic, but noncritical, states of platelet aggregability, oral administration of a capsule or tablet, or a bolus intramuscular injection is suitable. The compound of formula (I) is administered one to four times daily at a level of about 0.4 to about 50 mg/kg to achieve a total daily dose of about 0.4 to about 200 mg/kg/day.

This invention further provides a method for inhibiting the reocclusion of an artery or vein following fibrinolytic therapy, which comprises internal administration of a compound of formula (I) and a fibrinolytic agent. It has been found that administration of a formula (I) compound in fibrinolytic therapy either prevents reocclusion completely or prolongs the time to reocclusion.

When used in the context of this invention the term fibrinolytic agent is intended to mean any compound, whether a natural or synthetic product, which directly or indirectly causes the lysis of a fibrin clot. Plasminogen activators are a well known group of fibrinolytic agents. Useful plasminogen activators include, for example, anistreplase, urokinase (UK), pro-urokinase (pUK), streptokinase (SK), tissue plasminogen activator (tPA) and mutants, or variants, thereof, which retain plasminogen activator activity, such as variants which have been chemically modified or in which one or more amino acids have been added, deleted or substituted or in which one or more or functional domains have been added, deleted or altered such as by combining the active site of one plasminogen activator with the fibrin binding domain of another plasminogen activator or fibrin binding molecule. Other illustrative variants include tPA molecules in which one or more glycosylation sites have been altered. Preferred among plasminogen activators are variants of tPA in which the primary amino acid sequence has been altered in the growth factor domain so as to increase the serum half-life of the plasminogen activator. tPA Growth factor variants are disclosed, e.g., by Robinson et al., EP-A 0 297 589 and Browne et al., EP-A 0 240 334. Other variants include hybrid proteins, such as those disclosed in EP 0 028 489, EP 0 155 387 and EP 0 297 882, all of which are incorporated herein by reference. Anistreplase is a preferred hybrid protein for use in this invention. Fibrinolytic agents may be isolated from natural sources, but are commonly produced by traditional methods of genetic engineering.

Useful formulations of tPA, SK, UK and pUK are disclosed, for example, in EP-A 0 211 592, EP-A 0 092 182 and U.S. Patent 4,568,543, all of which are incorporated herein by reference. Typically the fibrinolytic agent may be formulated in an aqueous, buffered, isotonic solution, such as sodium or ammonium acetate or adipate buffered at pH 3.5 to 5.5. Additional excipients such as polyvinyl pyrrolidone, gelatin,

hydroxy cellulose, acacia, polyethylene, glycol, mannitol and sodium chloride may also be added. Such a composition can be lyophilized.

The pharmaceutical composition may be formulated with both the compound of formula (I) and fibrinolytic in the same container, but formulation in different containers is preferred. When both agents are provided in solution form they can be contained in an infusion/injection system for simultaneous administration or in a tandem arrangement.

Indications for such therapy include myocardial infarction, deep vein thrombosis, pulmonary embolism, stroke and other infarct-related disorders. The compound of formula (I) is administered just prior to, at the same time as, or just after parenteral administration of tPA or other fibrinolytic agent. It may prove desirable to continue treatment with the formula (I) compound for a period of time well after reperfusion has been established to maximally inhibit post-therapy reocclusion. The effective dose of tPA, SK, UK or pUK may be from 0.5 to 5 mg/kg and the effective dose of the peptide may be from about 0.1 to 25 mg/kg.

For convenient administration of the inhibitor and the fibrinolytic agent at the same or different times, a kit is prepared, comprising, in a single container, such as a box, carton or other container, individual bottles, bags, vials or other containers each having an effective amount of the inhibitor for parenteral administration, as described above, and an effective amount of tPA, or other fibrinolytic agent, for parenteral administration, as described above. Such kit can comprise, for example, both pharmaceutical agents in separate containers or the same container, optionally as lyophilized plugs, and containers of solutions for reconstitution. A variation of this is to include the solution for reconstitution and the lyophilized plug in two chambers of a single container, which can be caused to admix prior to use. With such an arrangement, the fibrinolytic and the peptide may be packaged separately, as in two containers, or lyophilized together as a powder and provided in a single container.

When both agents are provided in solution form, they can be contained in an infusion/injection system for simultaneous administration or in a tandem arrangement. For example, the platelet aggregation inhibitor may be in an i.v. injectable form, or infusion bag linked in series, via tubing, to the fibrinolytic agent in a second infusion bag. Using such a system, a patient can receive an initial bolus-type

injection or infusion, of the peptide inhibitor followed by an infusion of the fibrinolytic agent.

The pharmacological activity of the compounds of this invention is assessed by their ability to inhibit the binding of ^{3}H-SK&F 107260, a known RGD-fibrinogen antagonist, to the GPIIbIIIa receptor; their ability to inhibit platelet aggregation, *in vitro*, and their ability to inhibit thrombus formation *in vivo*.

Inhibition of RGD-mediated GPIIb-IIIa binding

Purification of GPIIb-IIIa

Ten units of outdated, washed human platelets (obtained from Red Cross) were lyzed by gentle stirring in 3% octylglucoside, 20 mM Tris-HCl, pH 7.4, 140 mM NaCl, 2 mM $CaCl_2$ at 4°C for 2 h. The lysate was centrifuged at 100,000g for 1 h. The supernatant obtained was applied to a 5 mL lentil lectin sepharose 4B column (E.Y. Labs) preequilibrated with 20 mM Tris-HCl, pH 7.4, 100 mM NaCl, 2 mM $CaCl_2$, 1% octylglucoside (buffer A). After 2 h incubation, the column was washed with 50 mL cold buffer A. The lectin-retained GPIIb-IIIa was eluted with buffer A containing 10% dextrose. All procedures were performed at 4°C. The GPIIb-IIIa obtained was >95% pure as shown by SDS polyacrylamide gel electrophoresis.

Incorporation of GPIIb-IIIa in Liposomes.

A mixture of phosphatidylserine (70%) and phosphatidylcholine (30%) (Avanti Polar Lipids) were dried to the walls of a glass tube under a stream of nitrogen. Purified GPIIb-IIIa was diluted to a final concentration of 0.5 mg/mL and mixed with the phospholipids in a protein:phospholipid ratio of 1:3 (w:w). The mixture was resuspended and sonicated in a bath sonicator for 5 min. The mixture was then dialyzed overnight using 12,000-14,000 molecular weight cutoff dialysis tubing against a 1000-fold excess of 50 mM Tris-HCl, pH 7.4, 100 mM NaCl, 2 mM CaCl2 (with 2 changes). The GPIIb-IIIa-containing liposomes wee centrifuged at 12,000g for 15 min and resuspended in the dialysis buffer at a final protein concentration of approximately 1 mg/mL. The liposomes were stored at -70C until needed.

Competitive Binding to GPIIb-IIIa

The binding to the fibrinogen receptor (GPIIb-IIIa) was assayed by an indirect competitive binding method using [^{3}H]-SK&F-107260 as an RGD-type ligand. The binding assay was performed in a 96-well filtration plate assembly (Millipore Corporation, Bedford, MA) using 0.22 um hydrophilic durapore membranes. The wells were precoated with 0.2 mL of 10 µg/mL polylysine (Sigma Chemical Co., St. Louis, MO.) at room temperature for 1 h to block nonspecific binding. Various concentrations of unlabeled benzadiazapines were added to the wells in quadruplicate. [^{3}H]-SK&F-107260 was applied to each well at a final concentration of 4.5 nM, followed by the addition of 1 µg of the purified platelet GPIIb-IIIa-containing liposomes. The mixtures were incubated for 1 h at room temperature. The GPIIb-IIIa-bound [3H]-SK&F-107260 was seperated from the unbound by filtration using a Millipore filtration manifold, followed by washing with ice-cold buffer (2 times, each 0.2 mL). Bound radioactivity remaining on the filters was counted in 1.5 mL Ready Solve (Beckman Instruments, Fullerton, CA) in a Beckman Liquid Scintillation Counter (Model LS6800), with 40% efficiency. Nonspecific binding was determined in the presence of 2 µM unlabeled SK&F-107260 and was consistently less than 0.14% of the total radioactivity added to the samples. All data points are the mean of quadruplicate determinations.

Competition binding data were analyzed by a nonlinear least-squares curve fitting procedure. This method provides the IC50 of the antagonists (concentration of the antagonist which inhibits specific binding of [^{3}H]-SK&F-107260 by 50% at equilibrium). The IC50 is related to the equilibrium dissociation constant (Ki) of the antagonist based on the Cheng and Prusoff equation: Ki = IC50/(1+L/Kd), where L is the concentration of [3H]-SK&F-107260 used in the competitive binding assay (4.5 nM), and Kd is the dissociation constant of [3H]-SK&F-107260 which is 4.5 nM as determined by Scatchard analysis.

Inhibition of Platelet Aggregation

Blood was collected (citrated to prevent coagulation) from, naive, adult mongrel dogs. Platelet rich plasma, PRP, was prepared by centrifugation at 150 x g for 10 min at room temperature. Washed platelets were prepared by centrifuging PRP at 800 x g for 10 min. The cell pellet thus obtained was washed twice in Tyrode's buffer (pH 6.5)

without Ca^{++} and resuspended in Tyrode's buffer (pH 7.4) containing 1.8 mM Ca^{++} at 3 x 10^5 cells/ml. Peptides were added 3 min prior to the agonist in all assays of platelet aggregation. Final agonist concentrations were 0.1 unit/ml thrombin and 2 mM ADP (Sigma). Aggregation was monitored in a Chrono-Log Lumi-Aggregometer. Light transmittance 5 min after addition of the agonist was used to calculate percent aggregation according to the formula % aggregation = [(90-CR) ÷ (90-10)] x 100, where CR is the chart reading, 90 is the baseline, and 10 is the PRP blank reading. IC50's were determined by plotting [% inhibition of aggregation] vs. [concentration of peptide]. Peptides were assayed at 200 mM and diluted sequentially by a factor of 2 to establish a suitable dose response curve.

To assess the stability of the compounds to plasma proteases, the compounds were incubated for 3 h (rather than 3 min) in the PRP prior to addition of the agonist.

In Vivo Inhibition of Platelet Aggregation

In vivo inhibition of thrombus formation is demonstrated by recording the systemic and hemodynamic effects of infusion of the peptides into anesthetized dogs according to the methods described in Aiken *et al.*, *Prostaglandins*, 19, 629 (1980).

The examples which follow are intended to in no way limit the scope of this invention, but are provided to illustrate how to make and use the compounds of this invention. Many other embodiments will be readily apparent and available to those skilled in the art.

EXAMPLES

Example 1

Synthesis of (18)

Synthesis of 1-[S,S-Dithianyl]-7-bromo-1,2,3,4-tetrahydro-naphthalene (**2**).

A solution of **1** (prepared using the method of M. Adamczyk, et al.; *J. Org. Chem.* **1984**, *49*, 4226) and 1,3-dithiapropane in CH_2Cl_2 are treated, using the method of J. A. Marshall, et al. (*Tetr.Lett.* **1971**, 871), with BF_3oEt_2O at room temperature for 12 h. Purification by flash chromatography give **2**.

Synthesis of 1-[S,S-Dithianyl]-6-formyl-7-bromo-1,2,3,4-tetrahydro-naphthalene (**3**).

Compound **2** is formylated using the method of Lewin, et al. (*Org. Prep. Proced. Int.* **1978**, *10*, 201) with dichloromethyl methyl ether and $AlCl_3$ to give a mixture of 6- and 8- formyl products which are separated by chromatography to give the desired **3**.

Synthesis of 1-[S,S-Dithianyl]-6-[[N-2-phenylethyl]amino-methyl]-7-bromo-1,2,3,4-tetrahydro-naphthalene (**4**).

A solution of **3** and 1-amino-2-phenyl ethane in MeoH is treated with NaBH3CN at room temperature (pH=6) for 18 h. The reaction is evaporated and the residue is taken into ethyl acetate. The solution is washed with 5% $NaHCO_3$ (aqueous), dried over anhydrous $MgSO_4$ and evaporated at reduced pressure. Purication by flash chromatography gives **4**.

Synthesis of 1-[S,S-Dithianyl]-6-[[N-2-phenylethyl, N'-tert-butyloxycarobonyl]amino-methyl]-7-bromo-1,2,3,4-tetrahydro-naphthalene (**5**).

A solution of **4** in CH_2Cl_2 is treated with Et_3N (1 equiv.) and di-*tert*-butyldicarbonate (1 equiv.) at room temperature for 18 h. The reaction mixture is then washed with 5% $NaHCO_3$ (aqueous), dried over anhydrous $MgSO_4$ and evaporated at reduced pressure. Purication by flash chromatography gives **5**.

Synthesis of 1-[S,S-Dithianyl]-6-[[N-2-phenylethyl, N'-tert-butyloxycarobonyl]amino-methyl]-7-[4-[3-methylcarboxyl]-methyl but-3-enate]-1,2,3,4-tetrahydro-naphthalene (**6**).

A solution of **5** in propionitrile is treated with diisopropylethylamine, dimethyl itaconate and catalytic $Pd(OAc)_2$ and heated at reflux for 1 h. Purifcation of the crude product by flash chromatography gives **6**.

Synthesis of 1-Oxo-6-[[N-2-phenylethyl, N'-tert-butyloxycarobonyl]amino-methyl]-7-[4-[3-methylcarboxyl]-methyl but-3-enate]-1,2,3,4-tetrahydro-naphthalene (**7**).

A solution of **6** in $MeOH/CHCl_3$ is treated, using the method of E. Fujita, et al. (*Chem. Pharm. Bull.* **1978**, *26*, 3743), with $Hg(ClO_4)_2$ at room temperature for 5 min. After workup the residue is purified by flash chromatography to give **7**.

Synthesis of 1-Oxo-6-[[N-2-phenylethyl, N'-tert-butyloxycarobonyl]amino-methyl]-7-[4-[3-methylcarboxyl]-methyl butanate]-1,2,3,4-tetrahydro-naphthalene (**8**).

A solution of **7** in MeOH with 5% Pd/C is treated with H_2 (Parr apparatus, room temperature, 50 psi) to give **8** which is used without further purification.

Synthesis of 1-Oxo-6-[[N-2-phenylethyl]amino-methyl]-7-[4-[3-methylcarboxyl]-methyl butanate]-1,2,3,4-tetrahydro-naphthalene (**9**).

Compound **8** is treated with TFA at 0 °C for 1 h. to give after evaporation at reduced pressure **9** which is used without further purification.

Synthesis of (**10a**).

A solution of **9** in toluene is treated with pyridine and the mixture heated at reflux for 24 h. The reaction mixture is diluted with ethyl acetate, washed with 5% $NaHCO_3$ (aqueous), 1N HCl (aqueous), dried over anhydrous $MgSO_4$ and evaporated. The residue is purified by flash chromatography to give **10a**.

Synthesis of (**10b**).

A solution of **10a** in MeOH is treated with LiOH at room temperature for 24 h. The reaction is then acidified and evaporated to give **10b** which is used without further purification.

Synthesis of (**10c**).

A solution of **10b** in CH2Cl2 is treated with DCC, DMAP and benzyl alcohol at room temperature for 18 h. The reaction is washed with 5% $NaHCO_3$ (aqueous), 1N HCl (aqueous), dried over anhydrous $MgSO_4$ and evaporated. The residue is purified by flash chromatography to give **10c**.

Synthesis of (**11**).

A solution of **10c** in THF is treated under argon at -78 °C with 1 equiv. of 1M lithium bis(trimethylsilyl)amide and stirred for 45 min. Then methyl chloroformate is added and the reaction is stirred at room temperature for 1 h. The reaction is then quenched with water and extracted with EtOAc to give the crude enol carbonate. The enol carbonate in a 3:2 mixture of methanol : methylene chloride is cooled to -78 °C and treated with excess ozone. The excess O_3 is then blown off with oxygen and the reaction is then treated with of methyl sulfide and slowly warmed to room temperature and stirred for 18 h. The reaction is evaporated at reduced pressure and purified by flash chromatography to give **11**.

Synthesis (**12**).

A solution of **11** and *tert*-butyl carbazate in ethyl acetate/hexane is heated at reflux for 1 h and then stirred at room temperature for 18 h. The reaction mixture is evaporated at reduced pressure and the residue dissolved in dry THF. This solution is treated with 1M BH_3oTHF in THF and stirred at room temperature for 3 h. At this time, an equal volume of 3N HCl (aqueous) is added and the reaction stirred for 18 h. The reaction mixture is then diluted with ethyl acetate, the organic fraction separated, dried over anhydrous $MgSO_4$ and evaporated at reduced pressure. The residue is purified by flash chromatography to give **12**.

Synthesis of (**13**).

A solution of **12** in CH_2Cl_2 is treated with triethylamine and benzoyl chloride at room temperature for 18 h. The reaction mixture is diluted with $CHCl_3$, washed with 5% Na_2CO_3 (aqueous), dried over anhydrous $MgSO_4$ and evaporated at reduced pressure. The residue is purified by flash chromatography to give **13**.

Synthesis (**14**).

A mixture of **13** and TFA are stirred at room temperature for 2 h. The reaction mixture is evaporated at reduced pressure and the residue taken into $CHCl_3$. The resulting solution is washed with 5% Na_2CO_3,

dried over anhydrous $MgSO_4$ and evaporated at reduced pressure to give **14** which is used without further purification.

Synthesis of 4-Cyanobenzaldehyde dimethyl acetal (**15b**).

A mixture of 4-cyanobenzaldehyde (**15a**) (5.0 g, 38.1 mmol) and methyl orthoformate (8.34 mL, 76.3 mmol) in MeOH was treated with a catalytic amount of NH_4Cl (~50-100 mg) and heated at reflux for 18 h. The reaction mixture was evaporated at reduced pressure and the residue taken into H_2O/ethyl acetate. The organic layer was washed with 5% $NaHCO_3$ (aqueous), dried over anhydrous $MgSO_4$ and evaporated at reduced pressure to give **15b** which was used without further purification.

Synthesis of 4-Aminomethyl-benzaldehyde dimethylacetal (**15c**).

A solution of **15b**, from above, in THF was treated with 1M $LiAlH_4$ in THF (38.1 mL, 38.1 mmol) at 0 °C and the reaction was stirred at room temperature for 18 h. The reaction was quenched with H_20, followed by 10% NaOH (aqueous) and then H_2O, then filtered and evaporated at reduced pressure to give **15c** which was used without further purification.

Synthesis of 4-(Benzyloxycarbonyl)aminomethyl-benzaldehyde dimethylacetal (**15d**).

A solution of **15c**, from above, in DMF was treated with triethylamine (8 mL, 57.2 mmol) and N-(benzyloxycarbonyloxy) succinimide (14.3 g, 57.2 mmol) and stirred for 3 d. The reaction mixture was evaporated under vacuum and the residue dissolved in ethyl acetate. The solution was washed with 5% Na_2CO_3 (aqueous), dried over anhydrous $MgSO_4$ and evaporated at reduced pressure. Purification of the solid residue by flash chromatography (silica gel, 8x20 cm, 75% ethyl acetate in hexane) gave 9.86 g (31.3 mmol, 82% from **15a**) of **15d**. Compound **15d**: ^1H NMR ($CDCl_3$, 90 MHz) δ 3.30 (s, 6H), 4.38 (d, 2H, J=6Hz), 5.13 (s, 3H), 5.38 (s, 1H), 7.20-7.55 (m, 9H).

Synthesis of 4-aminomethyl-benzaldehyde (**15e**).

A solution of **15d** (4.68 g, 14.8 mmol) in ethyl acetate was treated with an equal volume of 1N HCl (aqueous) and the reaction stirred

vigorously at room temperature for 4 d. The layers were separated and the organic layer was dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by flash chromatography (silica gel, 6x20 cm, 30% ethyl acetate in hexane) to give 2.59 g (9.62 mmol, 65%) of **15d**.

Synthesis (**16**).

A solution of **14** and **15e** in ethyl acetate with a few 4Å molecular sieves is heated at reflux for 18 h. After this time additional ethyl acetate is added and the solution heated at reflux for 2 h. The reaction is filtered and evaporated at reduced pressure. The residue is dissolved in THF and treated with 1M BH_3oTHF at room temperature for 1 h. An equal volume of 1N HCl (aqueous) is added and the mixture stirred vigorously for 3 d. The reaction mixture pH is adjusted to 8 with 5% Na_2CO_3 (aqueous) and then extracted with $CHCl_3$. The $CHCl_3$ extracts are dried over anhydrous $MgSO_4$ and evaporated at reduced pressure. The residue is purified by flash chromatography to give **16**.

Synthesis of (**17**).

The methyl eater in **16** is selectively hydrolyzed, using the method of L.M. Weinstock (Tetrahedron Lett 1975, 3979), with NaCN and HMPA at 75 °C for 24 h. The crude acid after workup is dissolved in CH_3CN with triethylamine and this solution is added dropwise to a refluxing solution of 2-chloro-1-methylpyridinium iodide. After the addition is completed, the reaction is continued at reflux for 4 d. The reaction mixture is evaporated at reduced pressure and the residue is taken into $CHCl_3$, washed with 5% Na_2CO_3 (aqueous) and 1N HCl (aqueous), dried over anhydrous $MgSO_4$ and evaporated at reduced pressure. The residue is purified by flash chromatography to give **17**.

Synthesis (**18**).

A solution of **17** in MeOH with 5% Pd/C is treated with H_2 (Parr apparatus, room temperature, 50 psi) to give crude **18** which is then purified by preparative RP-HLPC.

Example 2

Parenteral Dosage Unit Composition

A preparation which contains 20 mg of the compound of Example 1 as a sterile dry powder is prepared as follows: 20 mg of the compound is dissolved in 15 ml of distilled water. The solution is filtered under sterile conditions into a 25 ml multi-dose ampoule and lyophilized. The powder is reconstituted by addition of 20 ml of 5% dextrose in water (D5W) for intravenous or intramuscular injection. The dosage is thereby determined by the injection volume. Subsequent dilution may be made by addition of a metered volume of this dosage unit to another volume of D5W for injection, or a metered dose may be added to another mechanism for dispensing the drug, as in a bottle or bag for IV drip infusion or other injection-infusion system.

Example 3

Oral Dosage Unit Composition

A capsule for oral administration is prepared by mixing and milling 50 mg of the compound of Example 1 with 75 mg of lactose and 5 mg of magnesium stearate. The resulting powder is screened and filled into a hard gelatin capsule.

Example 4

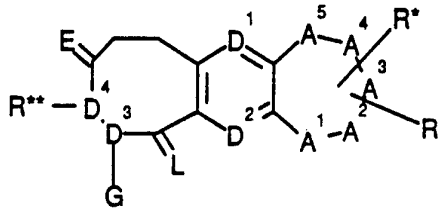
Oral Dosage Unit Composition

A tablet for oral administration is prepared by mixing and granulating 20 mg of sucrose, 150 mg of calcium sulfate dihydrate and 50 mg of the compound of Example 1 with a 10% gelatin solution. The wet granules are screened, dried, mixed with 10 mg starch, 5 mg talc and 3 mg stearic acid; and compressed into a tablet.

The foregoing is illustrative of the making and using of this invention. This invention, however, is not limited to the precise embodiments described herein, but encompasses all modifications within the scope of the claims which follow.

What is claimed is:

1. A compound of the formula:



wherein:

A^1 to A^5 form an accessible substituted seven-membered ring, which may be saturated or unsaturated, optionally containing up to two heteroatoms chosen from the group of O, S and N wherein S and N may be optionally oxidized;

D^1, D^2, D^3 and D^4 independently are CH or N, with the proviso that at least one of D^3 or D^4 is N;

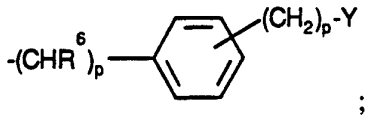
R is at least one substituent chosen from the group of R^7, or Q-C_{1-4}alkyl, Q-C_{2-4}alkenyl, Q-C_{2-4}alkynyl, optionally substituted by one or more of =O, R^{11} or R^7;

R^* is H, Q-C_{1-6}alkyl, Q-C_{1-6}oxoalkyl, Q-C_{2-6}alkenyl, Q-C_{3-4}oxoalkenyl, Q-C_{3-4}oxoalkynyl, Q-C_{2-4}alkynyl, C_{3-6}cycloalkyl, Ar, or Het, optionally substituted by one or more of R^{11};

each Q is H, C_{3-6}cycloalkyl, Het or Ar;

E and L independently are O or (H,H);

G is $(CHR^6)_t$-Y, $(CHR^6)_p$-Het-$(CH_2)_p$-Y, $(CHR^6)_p$-C_{3-7}cycloalkyl-$(CH_2)_p$-Y or



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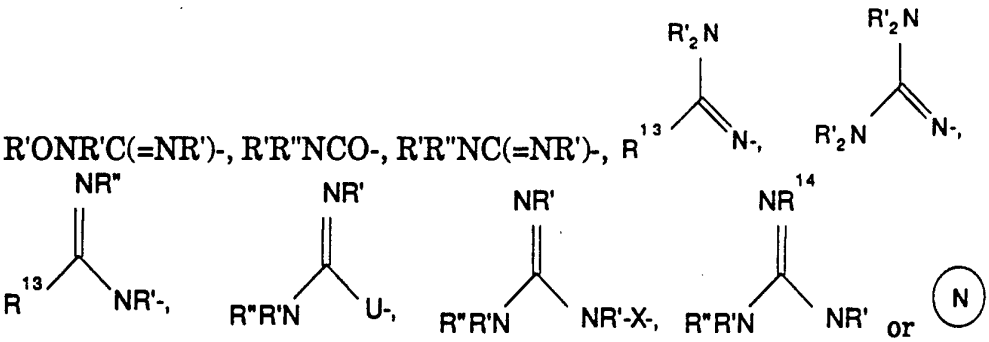
Y is R'R"N-, R'R"NR'N-, R'R"NR'NCO-, $R'_2NR'NC(=NR')$-,



R'ONR'C(=NR')-, R'R"NCO-, R'R"NC(=NR')-,

X is absent, N=CR', C(O) or O;

U is absent, S or O;

R' is H, C_{1-4}alkyl, C_{3-7}cycloalkyl-C_{0-4}alkyl, or Ar-C_{0-4}alkyl;

R" is R', -C(O)R' or -C(O)OR^{15}

R"' is R" or AA2:

AA2 is an amino acid attached through its carboxyl group, and having its amino group optionally protected;

R** is V-M, wherein V is H, R^{10}, R^{10}-J-CO or R^{10}-J-$S(O)_m$, in which J is O, NH, S or a covalent bond, and M is -NH(CHR^{16})CO- or a covalent bond;

R^6 is H or C_{1-4}alkyl;

R^7 is -COR^8, -$COCR'_2R^9$, -C(S)R^8, -$S(O)_mOR'$, -$S(O)_mNR'R"$, -PO(OR'), -$PO(OR')_2$, -$B(OR')_2$, -NO_2, or Tet;

R^8 is -OR', -NR'R", -$NR'SO_2R'$, -NR'OR', -$OCR'_2CO(O)R'$, -$OCR'_2OC(O)R'$, -$OCR'_2C(O)NR'_2$, CF_3 or AA1;

R^9 is -OR', -CN, -$S(O)_rR'$, -$S(O)_mNR'_2$, -C(O)R', C(O)NR'_2, or -CO_2R';

R^{10} is $(CHR^6)_r$-H, $(CHR^6)_r$-C_{3-6}cycloalkyl, $(CHR^6)_r$-Ar or $(CHR^6)_r$-Het;

R^{11} is H, halo, -OR^{12}, -CN, -$NR'R^{12}$, -NO_2, -CF_3, $CF_3S(O)_r$-, -CO_2R', -$CONR'_2$, Q-C_{0-6}alkyl-, Q-C_{1-6}oxoalkyl-, Q-C_{2-6}alkenyl-, Q-C_{2-6}alkynyl-, Q-C_{0-6}alkyloxy-, Q-C_{0-6}alkylamino- or Q-C_{0-6}alkyl-$S(O)_r$-;

R^{12} is R', -C(O)R', -C(O)NR'_2, -C(O)OR', -$S(O)_mR'$, or -$S(O)_mNR'_2$;

R^{13} is R', -CF_3, -SR', or OR';

R^{14} is R', C(O)R', CN, NO_2, SO_2R', or C(O)OR^{15};

each R^{15} independently is C_{1-6}alkyl or Ar-C_{0-4}alkyl;

R^{16} is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, $(CH_2)_n$-Het or $(CH_2)_qZ$, wherein Z is C_{3-6}cycloalkyl, OH, NH_2, SH, SC_{1-4}alkyl, CO_2R^6, $CONH_2$ or $NHC(=NH)NH_2$;

AA1 is an amino acid attached through its amino group and having its carboxyl group optionally protected;

each m independently is 1 or 2;

each n independently is 0 to 2;

each p independently is 0 to 2;

q is 1 to 4;

each r independently is 0 to 4; and

t is 2 to 5;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 wherein:

A^1 is $CR^1R^{1'}$, CR^1, NR^1, N, O, or $S(O)_x$;

A^2 is $CR^2R^{2'}$, CR^2, or NR^2;

A^3 is $CR^3R^{3'}$, CR^3, NR^3, N, O, or $S(O)_x$;

A^4 is $CR^4R^{4'}$, CR^4, NR^4, or N;

A^5 is $CR^5R^{5'}$, CR^5, NR^5, N, O, or $S(O)_x$;

D^1 and D^2 are CH;

R is $(CR^{14}R^{15})_u$-$(T)_v$-$(CR^{17}R^{18})_w$-R^7 or =CR'-$(T)_v$-$(CR^{17}R^{18})_w$-R^7 wherein T is $CR^{17}R^{18}$-$CR^{17}R^{18}$, CR'=CR' or $C\equiv C$, and R^{17} and R^{18} are R', OR' or together are =O, provided that R^{16} and R^{17} are not simultaneously OR' when they are attached to the same carbon;

R^1 and $R^{1'}$ are R^* or R, or together are =O;

R^2 and $R^{2'}$ are R^*, R or =O;

R^3 and $R^{3'}$ are R^*, R or =O;

R^4 and $R^{4'}$ are R^*, R or =O;

R^5 and $R^{5'}$ are R^*, R or =O;

x is 0 to 2; and

u, v and w independently are 0 or 1.

3. The compound according to claim 2 wherein:

A^1 is $CR^1R^{1'}$, CR^1, NR^1, N, O, or S;

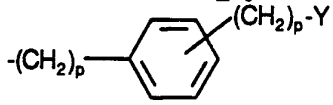
A^2 is $CR^2R^{2'}$, NR^2 or CR^2;

A^3 is $CR^3R^{3'}$

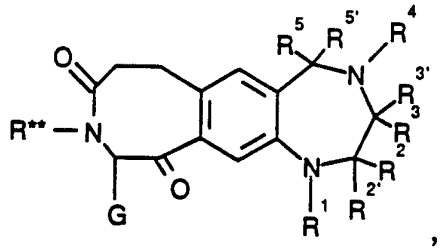
A^4 is $CR^4R^{4'}$, CR^4, NR^4, or N;

A^5 is $CR^5R^{5'}$, CR^5NR^5, N or O;
D^1 and D^2 are CH;
R^2 or R^4 are R;
R^3, $R^{3'}$ and R^5, $R^{5'}$ are =O or R^*, H.

4. The compound according to claim 3 wherein:
L is O and E is O or (H,H);
R** is methyl, acetyl or benzoyl; and
G is $(CH_2)_t$-Y, $(CH_2)_p$-Het-$(CH_2)_p$-Y, or



5. The compound according to claim 4 which is:



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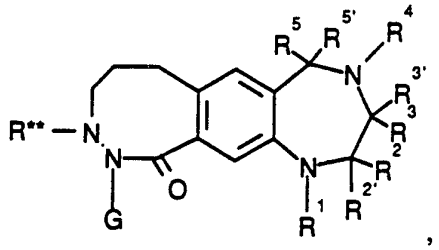

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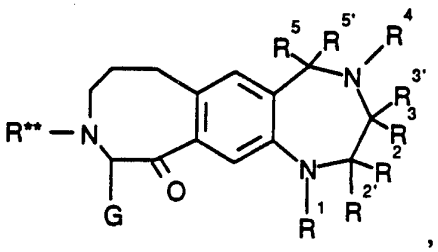

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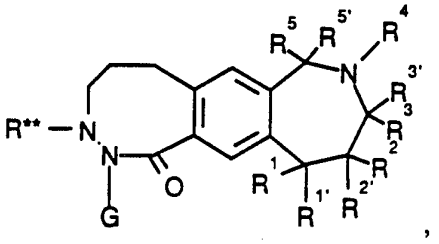

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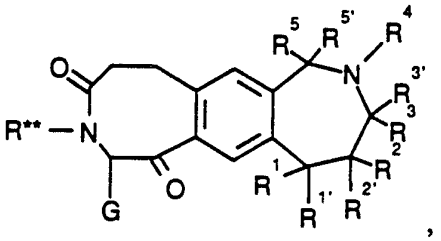

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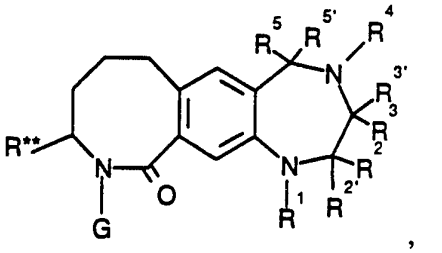

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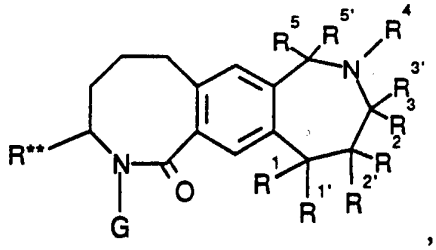
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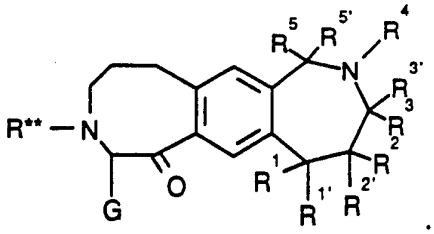
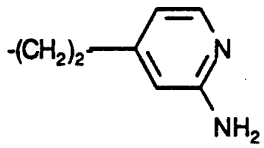

.

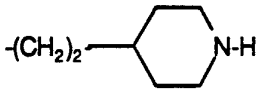
6. The compound according to claim 5 wherein:
R^1 is H, C_{1-4}alkyl, or C(O)R';
R^2 is CH_2CO_2H;
R^3,$R^{3'}$ is =O or H,H;
R^4 is H, C_{1-6}alkyl or C_{1-4}alkyl-Ar; and
R^5 is H.

7. The compound according to claim 6 wherein Y is H_2N-, $H_2NC(=NH)$-, $H_2NC(=NH)NH$- or .

8. The compound according to claim 6 wherein G is


,

$-(CH_2)_3NHC(=NH)NH_2$,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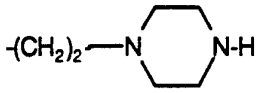
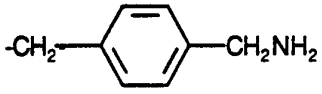
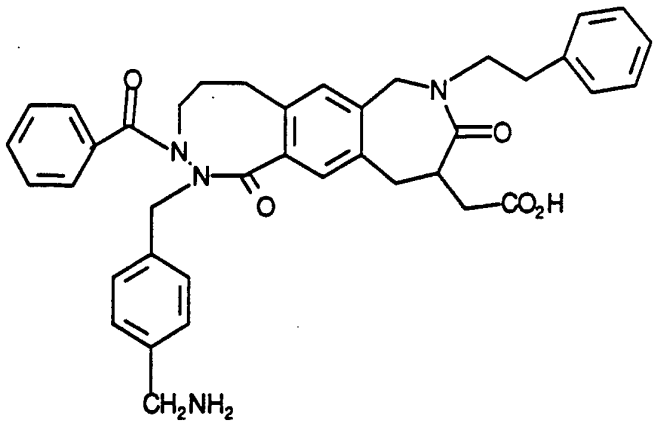

, or


.

9. The compound according to claim 6 which is



10. A pharmaceutical composition which comprises a compound according to claim 1 and a pharmaceutically acceptable carrier.

11. A method for effecting inhibition of platelet aggregation which comprises administering to a mammal in need thereof a compound according to claim 1.

12. A method for treating stroke which comprises administering to a mammal in need thereof a compound according to claim 1.

13. A method for treating transient ischemia attacks which comprises administering to a mammal in need thereof a compound according to claim 1.

14. A method for treating myocardial infarction which comprises administering to a mammal in need thereof a compound according to claim 1.

15. A method for promoting reperfusion of an artery or vein and inhibiting reocclusion which comprises administering to a mammal in need thereof a fibrinolytic agent and a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

Inte...ational application No.
PCT/US94/03383

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/44; C07D 487/04; A61K 31/395

US CL :540/460, 461; 314/183, 217 -

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 540/460, 461; 514/183, 217

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Please See Extra Sheet.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,957,911 (ASCHWANDEN ET AL.) 18 SEPTEMBER 1990, SEE ENTIRE DOCUMENT.	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 06 JUNE 1994	Date of mailing of the international search report JUN 2[illegible] 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ROBERT T. BOND jd Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

Int...ational application No.
PCT/US94/03383

B. FIELDS SEARCHED
Documentation other than minimum documentation that are included in the fields searched:

RING INDEX PLUS I, II, III SUPPS
RING SYSTEMS HANDBOOK
RING SYSTEMS FILE I, RING SYSTEMS FILE II 1993 EDITION