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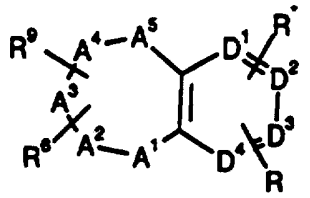
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(54) Title: BICYCLIC FIBRINOGEN ANTAGONISTS

(57) Abstract

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



(I)

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BICYCLIC FIBRINOGEN ANTAGONISTS

Field of the Invention

This invention relates to novel bicyclic 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. These compounds inhibit the GPIIb-IIIa receptor and inhibit platelet aggregation.

Summary of the Invention

In one aspect this invention is a bicyclic compound comprising a substituted seven-membered ring fused to an aromatic six-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).

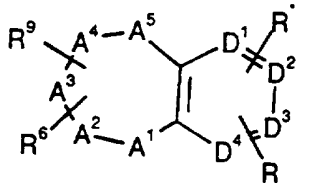
In another aspect, this invention provides a method for inhibiting reocclusion of an artery or vein in a mammal following fibrinolytic therapy, which comprises internally administering an effective amount of a fibrinolytic agent and a compound of formula (I). This invention is also a method for treating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

Detailed Description of the Invention

This invention discloses bicyclic compounds which inhibit platelet aggregation. The novel bicyclic compounds comprise a seven-membered ring fused to an aromatic six-membered ring and having a nitrogen-containing substituent on the seven-membered ring and an aliphatic substituent, preferably containing or being an acidic moiety, on the aromatic six-membered ring. The seven-membered ring may contain heteroatoms, such as nitrogen, oxygen and sulfur, and the aromatic six-membered ring may be carbocyclic or contain up to two nitrogen atoms. The fused 7-6 ring system is believed to interact favorably with the GPIIb-IIIa receptor and to orient the substituent sidechains on the seven and the aromatic six-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 to D^4 form an accessible substituted six membered ring, optionally containing up to two nitrogen atoms;

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, Q-C_{1-4}alkylamino or Q-C_{1-4}alkyloxy, 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, Q-C_{1-4}alkylamino, Q-C_{1-4}alkyloxy, C_{3-6}cycloalkyl, Ar or Het, optionally substituted by one or more of R^{11};

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

R^6 is W-$(CR'_2)_q$-Z-$(CR'R^{10})_r$-U-$(CR'_2)_s$-V-;

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 and Tet;

R^8 is -OR', -NR'R", -NR'SO_2R', -NR'OR', -$OCR'_2C(O)OR'$, -$OCR'_2OC(O)$-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 H, C_{1-4}alkyl or -NR'R";

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', -$C(O)NR'_2$, -$C(O)OR^{15}$, -$S(O)_mR'$ 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 $C(O)OR^{15}$;

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

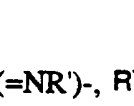
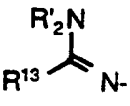
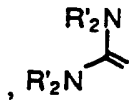
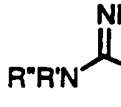
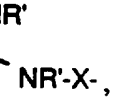
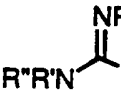
R' is H, C_{1-6}alkyl, C_{3-7}cycloalkyl-C_{0-4}alkyl or Ar-C_{0-4}alkyl;

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

R"' is R" or AA2;

AA1 is an amino acid attached through its amino group and having its carboxyl group optionally protected, and AA2 is an amino acid attached through its carboxyl group, and having its amino group optionally protected;

U and V are absent or CO, CR'$_2$, C(=CR'2), S(O)$_n$, O, NR', CR'OR', CR'(OR")CR'$_2$, CR'$_2$CR'(OR"), C(O)CR'$_2$, CR'$_2$C(O), CONR', NR'CO, OC(O), C(O)O, C(S)O, OC(S), C(S)NR', NR'C(S), S(O)$_n$NR', NR'S(O)$_n$, N=N, NR'NR', NR'CR'$_2$, NR'CR'$_2$, CR'$_2$O, OCR'$_2$, C≡C or CR'=CR', provided that U and V are not simultaneously absent;

W is R'R'"N-, R'R"NR'N-, R'R"NR'NCO-, R'$_2$NR'NC(=NR')-, R'ONR'C(=NR')-, , , , , , , ;

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

Y is absent, S or O;

Z is (CH$_2$)$_t$, Het, Ar or C$_{3-7}$cycloalkyl;

m is 1 or 2;

n is 0 to 3;

p is 0 or 1;

q is 0 to 3;

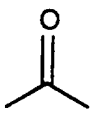
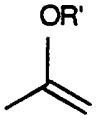
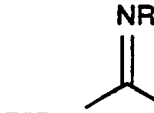
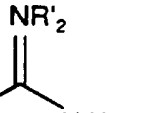
r is 0 to 2;

s is 0 to 2; and

t is 0 to 2; or

pharmaceutically acceptable salts 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 $CR^1R^{1'}$, NR^1, O or $S(O)_x$;

A^2 is $CR^2R^{2'}$ 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-D^4 are CR, CR* or N;

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

R^2 and $R^{2'}$ are hydrogen or together are =O or R^2 is R^6 and $R^{2'}$ is absent or present as hydrogen;

R^3 and $R^{3'}$ are hydrogen or together are =O or R^3 is R^6 and $R^{3'}$ is absent or present as hydrogen;.

R^4 and $R^{4'}$ are hydrogen or R^4 is R^9 and $R^{4'}$ is absent or present as hydrogen; and

R^5 and $R^{5'}$ are hydrogen or together are =O.

More suitably, A^1 is $CR^1R^{1'}$, NR^1, 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^4 are CH; D^2 is CR*; and D^3 is CR.

Preferably, A^1 is $CR^1R^{1'}$, NR" or S; A^2 is $CR^2R^{2'}$ or NR^2; A^3 is $CR^3R^{3'}$; A^4 is $CR^4R^{4'}$ or NR^4; and A^5 is $CR^5R^{5'}$.

Suitably, $(CR'R^{10})_r$-U-$(CR'_2)_s$-V is CO, CONR', NR'CO, CH_2CHOH, $CHOHCH_2$, CH_2CH_2, CH_2O, OCH_2, CH=CH, $C{\equiv}C$, $CH_2CH{=}CH$, $(CH_2)_2O$, CH_2CONR', $CONR'CH_2$, $CH(NR'R")CONR'$, $CH_2CH_2NR'CO$, $CONR'CHR'CH_2$, $CH_2NR'CO_2CH_2$, $CONR'CH_2CO$, $CONR'CH_2CHOH$, $CH{=}CHCONR'$, $(CH_2)_3O$, $NR'CO_2CH{=}CH$, or $SO_2NR'CHR'CH_2$.

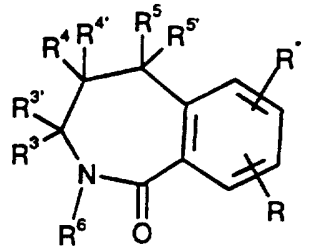
In one embodiment, A^1 is C=O, A^2 is NR^6, A^3, A^4 and A^5 are CH_2.

In another embodiment, A^1 is NH, A^2 is C=O, A^3 is CHR^6, A^4 is $NC(O)R_{1\text{-}6}$alkyl and R^5 is CH_2.

In a more specific embodiment, Z is phenyl, a six-membered Het or $(CH_2)_t$; W is R'_2N, $H_2NC(=NH)$, $H_2NC(=NH)NH$ or ; and $(CR'R^{10})_r$-U-$(CR'_2)_s$-V is $(CR'R^{10})_r$-U- or -U-$(CR'_2)_s$, (*e.g.*, V is absent and s is 0 and one of s and r are 0)

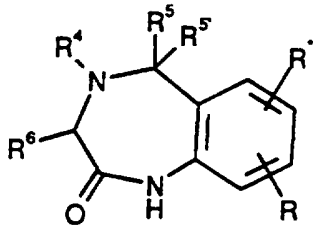
wherein U is CH(NR'R")CONH, NR'CO, CONR', CR'=CR', C≡C, O, CO or CH_2.

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



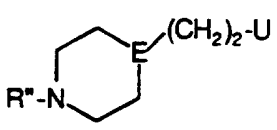
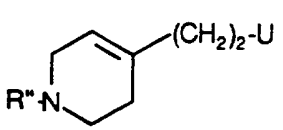
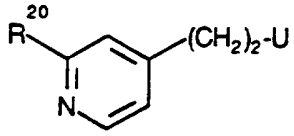
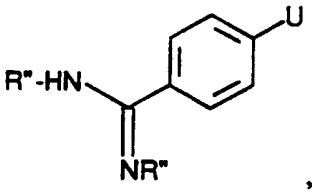
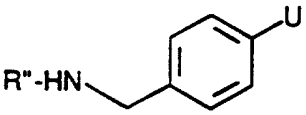
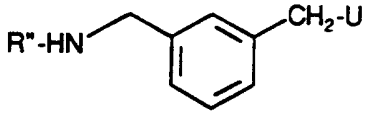
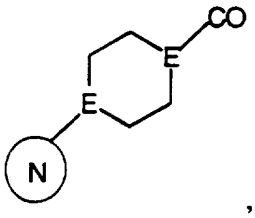
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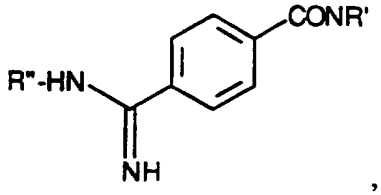
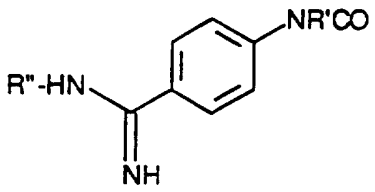
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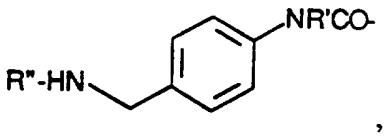
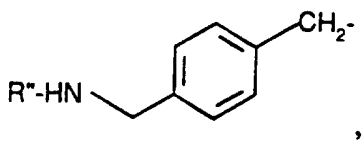
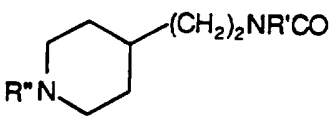
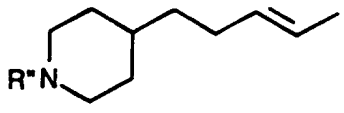
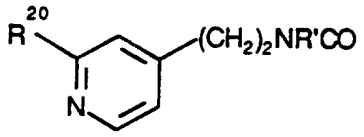
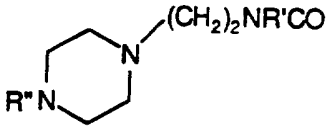
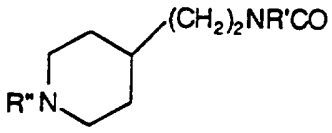
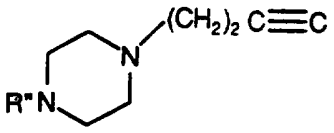
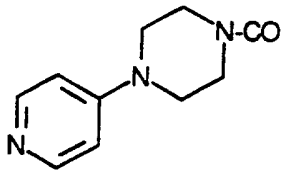
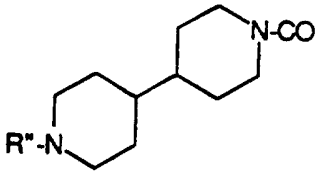
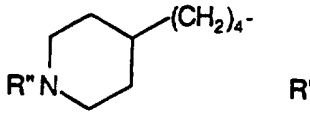
Particular examples of R^6 are:


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R"HNC(=NH)NH-$(CH_2)_2$-U, and R"HN-$(CH_2)_5$-U wherein E is N or CH, R^{20} is hydrogen, amino, mono or di-C_{1-4}alkylamino, hydroxy or C_{1-4}alkyl, and U is NR'CO, CONR', (CH_2)CO, CH=CH, , CH_2O, OCH_2, CH_2, and $(CH_2)_2$.

Preferred illustrative examples of R^6 are:


,

,

or

wherein R'are H or C_{1-4}alkyl.

Preferred compounds of this inventions are:

(R,S)-2-[(4-aminomethyl)phenyl]methyl-2,3,4,5-tetrahydro-8-[1-(1,2-dicarboxy)ethyl]amino-1H-2-benzazepin-1-one;

(R,S)-2-[(-aminomethyl)phenyl]methyl-2,3,4,5-tetrahydro-8-[2-(1-carboxy-4-phenyl)butyl]amino-1H-2-benzazepin-1-one;

(+)-4-N-acetyl-1,3,5-trihydro-3-(propyl-3-guanidine)-2-oxo-7,8-dibutyryloxy-1,4-benzodiazapine;

(-)-4-N-acetyl-1,3,5-trihydro-3(R)-(propyl-3-guanidine)-2-oxo-7,8-dioxyacetic acid-1,4-benzodiazapine; and

(+)-4-N-acetyl-1,3,5-trihydro-3(R)-(propyl-3-quanidine)-2-oxo-7,8-diethyletheryloxy-1,4-benzodiazapine;

or a pharmaceutically acceptable salt thereof.

In the above description of formula (I), preferably only one of A^1 to A^5 are substituted by R^6. W represents a nitrogen-containing group which is capable of making a hydrogen bond. Preferably W 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 cation. Preferably R^7 is acidic. It is also preferred that 10-15 (most preferably about 13) intervening covalent bonds via the shortest intramolecular path will exist between the group R^7 and a terminal basic nitrogen moiety of W for optimal spacing between these groups, and the moieties T, U, V and Z, and the alkyl spacers represented by q, r, s, u, v and w are chosen accordingly.

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, tetrahydropyridine, pyridine, thiazole, thiophene, quinoline, isoquinoline, and tetra- and perhydro- quinoline and isoquinoline. A six membered ring heterocycle containing one or two nitrogens, such as piperidine, piperazine, tetrahydropyridine and pyridine, are preferred heterocycles for the moiety Z. 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. A six membered monocyclic ring heterocycle containing one or two nitrogens, such as piperidine, piperazine, tetrahydropyridine and pyridine, are preferred heterocycles for the moiety Z.

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^6 or R^9, 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, pyrazinyl, pyridazinyl or pyrimidinyl ring. Typical of accessible six-membered rings are the common saturated and unsaturated rings of cycloheptane, thiepin, oxapin, azepine, diazepine, thiazepin, oxazepin, dioxepin, oxathiepin, and dithiepin. Preferably, no two adjacent atoms in the seven-membered ring are simultaneously heteroatoms.

An accessible substituted aromatic 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 and R^*, (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 aromatic six-membered rings are phenyl, pyridyl, pyrazinyl, pyridazinyl or pyrimidinyl ring. Representative bicyclic rings formed by the combination of the accessible seven and six-membered rings are: 1,2-benzo-1-cycloheptene, 1,2-benzo-1,3-cycloheptadiene and 1,2-benzo-1,4-cycloheptadiene compounds; 1-, 2- and 3-benzazepine, dihydrobenzazepine and tetrahydrobenzazepine compounds; 1,2-, 1,3-, 1,4-, 1,5-, 2,3- and 2,4-benzodiazepine, dihydrobenzodiazepine and tetrahdyrobenzodiazepine compounds;, 1,2-, 1,3-, 1,4-, 1,5-, 2,1-, 2,3-, 2,4-, 2,5-, 3,1-, 3,2-, and 4,1-benzoxazepine, dihydrobenzoxazepine and tetrabenzoxazepine compounds; 1,2-, 1,3-, 1,4-, 1,5-,

2,1-, 2,3-, 2,5-, 3,1-, 3,2- and 4,1-benzothiazepine, dihydrobenzothiazepine and tetrahydrobenzothiazepine compounds; and other similar saturated and unsatruated stable pyridazepine, pyrazazepine, pyridazin-azepine, pyrimidinazepine, mono- and di-oxo- (e.g., sulfoxyl, sulfonyl) benzothiazepine, benzodioxepin and benzoxathiepin compounds. Phenyl is a preferred accessible six-membered ring, and di- or tetrahydroazepine, diazepine, thiazepine and oxazepine are preferred accessible seven-membered rings. Particularly, preferred ring systems are the benzazepine and benzodiazepine systems.

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 (*e.g.*, 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.

(N) 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 R^{20}, for instance H, C_{1-4}alkoxy, F, Cl, Br, I, NO_2, NR'_2, OH, CO_2R', CONHR', CF_3, Q-C_{0-4}alkyl, Q-C_{1-4}alkyl-$S(O)_u$ (*e.g.*, where u is 0, 1 or 2) or C_{1-4}alkyl substituted by any of the aforementioned sustituents. Representative of (N) 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, (N) may be pyridyl, pyrolidinyl, piperidinyl, piperazinyl, azetidinyl, quinuclidinyl or tetrahydropyridinyl. (N) is preferably 4-pyridyl, 4-(2-amino-pyridyl), 4-tetrahydropyridyl, 4-piperidinyl or 4-piperazinyl.

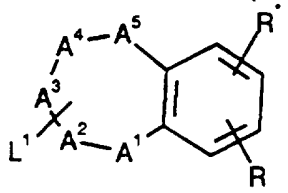
AA1 as referred to herein is an amino acid with its carboxyl group optionally protected, wherein the amino acid may be any of the natural α-amino acids or penicillamine. The unprotected carboxyl group is a free carboxylic acid group. Protecting groups for the carboxyl are esters or amides which are formed, 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 (*e.g.*, carbonyl), C(S) indicates a carbon doubly bonded to sulfur (*e.g.*, 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. Tet refers to 5-tetrazolyl.

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 reacting a compound of the formula (IV) with a compound of the formula (V):



(IV)

$R^{6''}$-L^2

(V)

wherein D^1-D^4 and A^1-A^5, R and R^* are as defined in formula (I), with any reactive functional groups protected;

L^1 and L^2 are functional groups which are capable of reacting to form the linkage $-(CR'R^{10})_r-U-(CR'_2)_s-V-$; and

$R^{6"}$ is $W-(CR'_2)_q-Z-$ and any portion of the group $-(CR'R^{10})_r-U-(CR'_2)_s-V-$ which is connected to L^2, with any reactive functional groups protected;

and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt.

It will be apparent that the precise identity of L^1 and L^2 will be dependent upon the site of the linkage being formed. General methods for preparing the linkage $-(CR'R^{10})_r-U-(CR'_2)_s-V-$ are described, for example, in EP-A 0 372 486 and EP-A 0 381 033 and EP-A 0 478 363, which are incorporated herein by reference.

For instance, if V is CONH, L^1 may be $-NH_2$, L^2 may be OH (as in an acid) or Cl (as in an acid chloride), and $R^{6"}$ may be $W-(CR'_2)_q-Z-(CR'R^{10})_r-U-(CR'_2)_s-C(O)$, with any functional groups optionally protected. For example, $R^{6"}$ may be (benzyloxycarbonyl-amidino)benzoyl- or (N^{α}-Boc,N^{guan}-Tos)arginyl-. When L^2 is OH, a coupling agent is used.

Similarly, if V is NHCO, L^1 may be $-CO_2H$ or CO-Cl, L^2 may be $-NH_2$, and $R^{6"}$ may be $W-(CR'_2)_q-Z-(CR'R^{10})_r-U-(CR'_2)_s-$. For example, $R^{6"}$ may be (benzyloxycarbonyl-amidino)phenyl, (benzyloxycarbonylamino)methylbenzyl- or 6-(benzyloxycarbonylamino)hexyl-.

Where V is $NHSO_2$, L^1 may be SO_2Cl, L^2 may be $-NH_2$ and $R^{6"}$ may be as above. Where V is SO_2NH, L^1 may be $-NH_2$ and L^2 may be SO_2Cl. Methods to prepare such sulfonyl chlorides are disclosed, for instance, in *J. Org. Chem.*, 23, 1257 (1958).

If V is CH=CH, L^1 may be -CHO, L^2 may be $CH=P-Ph_3$ and $R^{6"}$ may be $W-(CR'_2)_q-Z-(CR'R^{10})_r-U-(CR'_2)_s-$. Alternately, L^1 may be $CH=P-Ph_3$, L^2 may be CHO, *e.g.*, $R^{6"}$ may be $W-(CR'_2)_q-Z-(CR'R^{10})_r-U-(CR'_2)_{s-1}-CHO$.

Where V is CH_2CH_2 may be obtained by reduction of a suitably protected compound wherein V is CH=CH.

Where V is CH_2O, CH_2N or $C{\equiv}C$, L^1 may be -OH, -NH or $-C{\equiv}CH$, respectively; L^2 may be -Br; and $R^{6"}$ may be $W-(CR'_2)_q-Z-(CR'R^{10})_r-U-(CR'_2)_s-$. For example, $R^{6"}$ may be (benzyloxycarbonylamino)-methylbenzyl- or 2-(N-benzyl-4-piperidinyl)-ethyl. Similarly where U or V is OCH_2, $NR'CH_2$ or , L^1 may be $-CH_2Br$ and L^2 may be -OH, -NH or -H, respectively. Alternately, when U or V

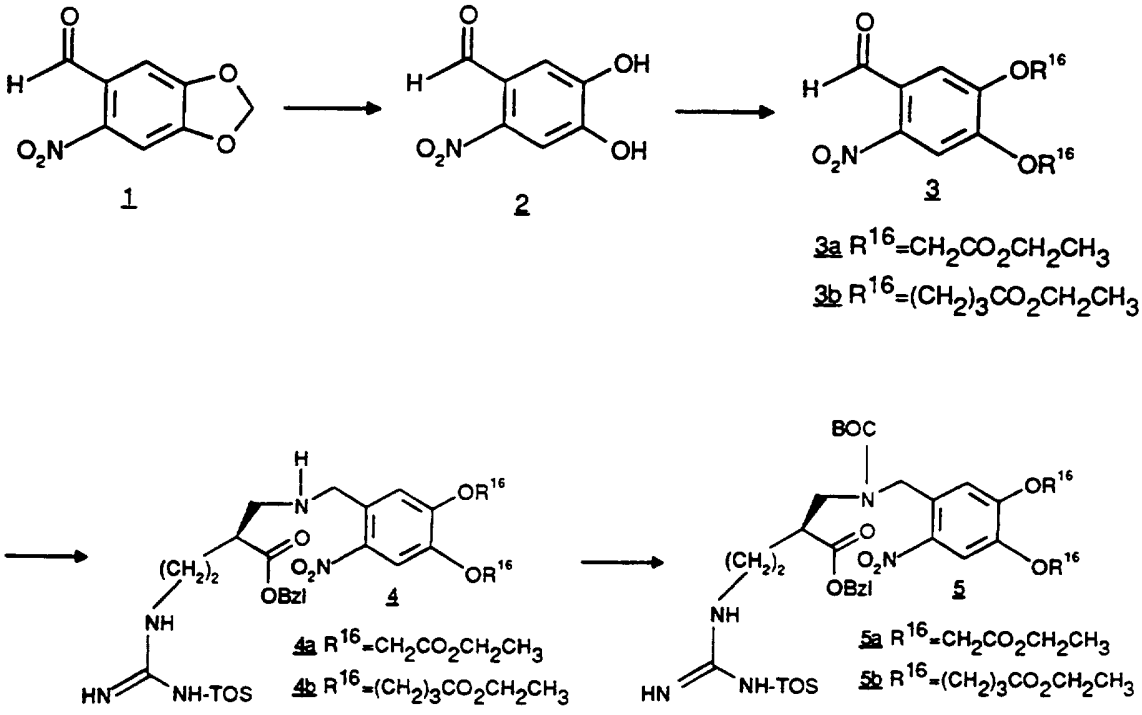
is C≡C, L^1 may be Br, I or CF_3SO_3, L^2 may be C≡CH and the coupling may be catalyzed by palladium and a base.

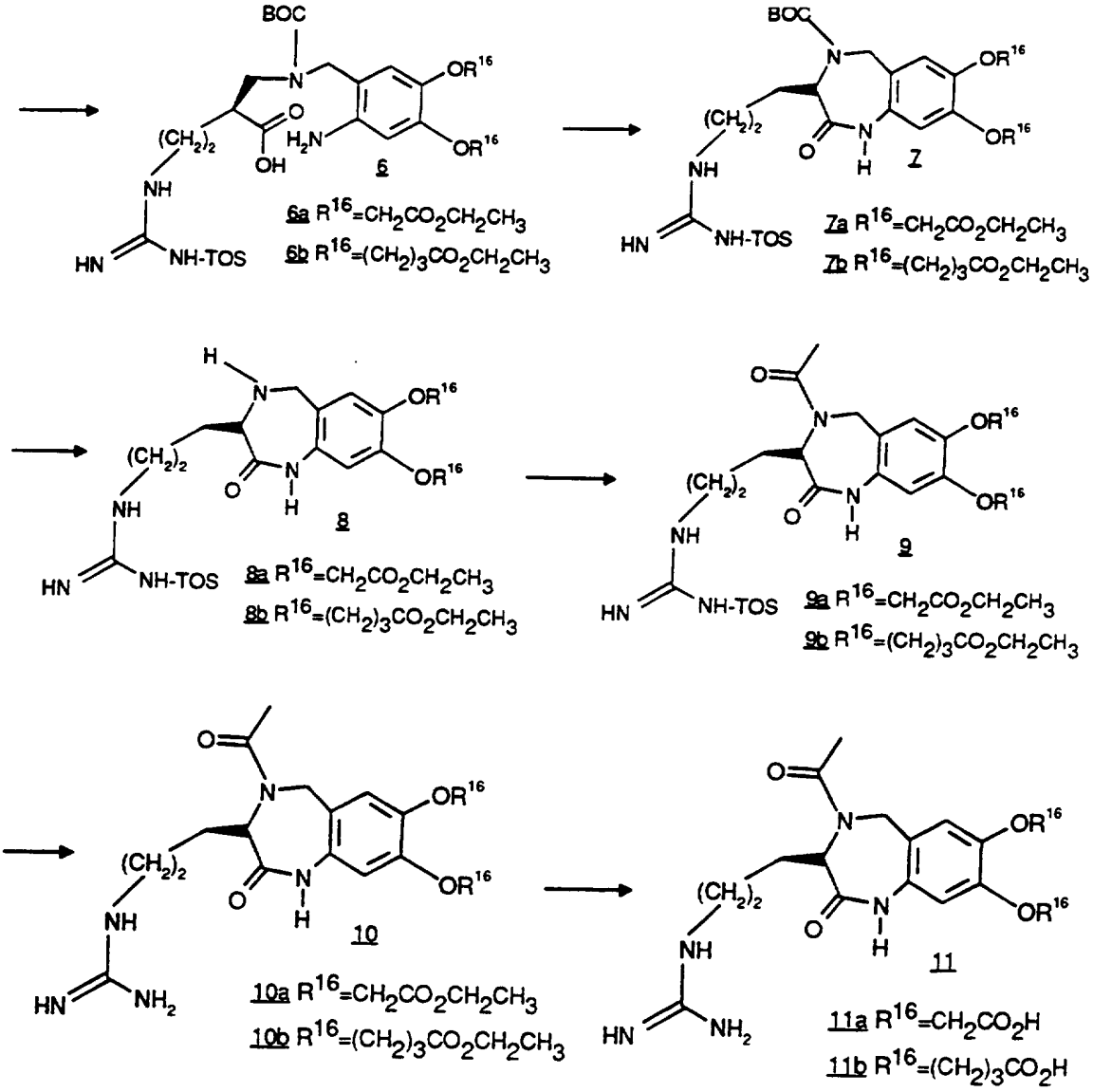
Compounds wherein V is $CHOHCH_2$ may be prepared from a suitably protected compound where V is CH=CH by the procedure disclosed in *J. Org. Chem.*, 54, 1354 (1989).

Compounds wherein V is CH_2CHOH may be obtained from a suitably protected compound where V is CH=CH by hydroboration and basic oxidation as disclosed in *Tet. Lett.*, 31, 231 (1990).

The compounds of formula (IV), wherein two of A^1 to A^5 are nitrogen, are benzodiazepines and are prepared by the general methods illustrated by Scheme I. Representative methods for preparing benzodiazepines are well known in the art (*e.g.*, Hynes, et al., J. Het. Chem., 25:1173 (1988); Muller, et al., Helv. Chim. Acta., 65:2118 (1982); Mori, et al., Heterocycles, 16:1491 (1981)).

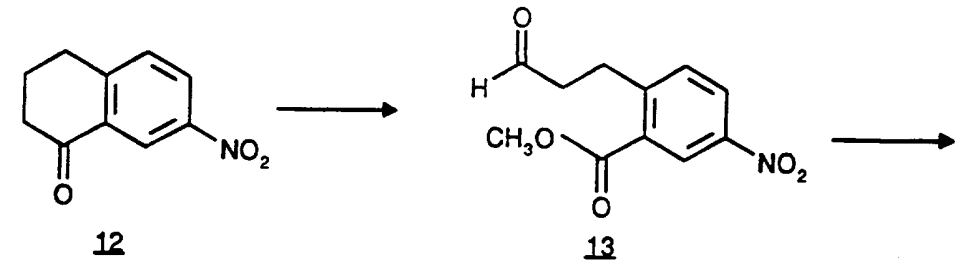
Scheme I



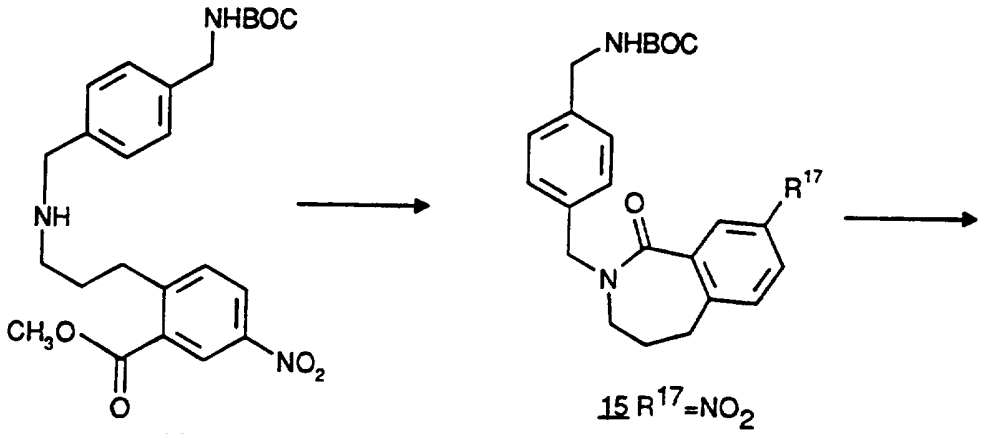

BOC
OR16
(CH2)2
NH
HN
NH-TOS
OH
H2N
6
6a R16=CH2CO2CH2CH3
6b R16=(CH2)3CO2CH2CH3
7
7a R16=CH2CO2CH2CH3
7b R16=(CH2)3CO2CH2CH3
8
8a R16=CH2CO2CH2CH3
8b R16=(CH2)3CO2CH2CH3
9
9a R16=CH2CO2CH2CH3
9b R16=(CH2)3CO2CH2CH3
10
10a R16=CH2CO2CH2CH3
10b R16=(CH2)3CO2CH2CH3
NH2
11
11a R16=CH2CO2H
11b R16=(CH2)3CO2H

Scheme I provides a method for preparing compounds wherein A^1 is NH, A^2 is C=O, A^3 is CHR^6, A^4 is $NC(O)C_{1-6}$alkyl and A^5 is CH_2. According to Scheme I, the methylene acetal group of the formula 1 compound is converted to the corresponding diol compound of formula 2 by reacting the formula 1 compound with a Lewis Acid, such as aluminum chloride, in a suitable solvent, such as 1,2-dichloroethane, followed by reaction with aqueous hydrobromic acid. Alkylation of the hydroxyl groups using, for example, ethyl bromoacetate or ethyl 4-bromobutyrate, takes place in the presence of a base, such as potassium carbonate, in a suitable solvent, such as dimethylformamide to give the formula 3 compound, which is reductively aminated in a reaction with an appropriately protected amine in the presence of sodium cyanoborohydride at a pH of 6-7. Protection of the secondary amine functionality of the formula 4 compound, using, for example, di-tert-butyl dicarbonate yielded the formula 5 BOC derivative. Concomitant removal of the benzyl protecting group with reduction of the nitro group to an amine group in the formula 5 compound using, for example, hydrogenation in the presence of a catalyst, such as palladium on barium sulfate, results in the formation of the formula 6 amino acid compound. The formula 7 oxo-benzodiazepine ring system is formed in the presence of an amide-forming agent, such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, in the presence of 1-hydroxybenzotriazole and a base, such as diisoproplyethylamine, in a suitable solvent, such as dimethylformamide. The Boc protecting group on the 4-nitrogen of the formula 7 1,4-benzodiazepine compound is removed under acidic conditions, using, for example, trifluoroacetic acid in methylene chloride. Acetylation of the 4-nitrogen of the formula 8 compound using, for example, acetyl chloride in the presence of a base, such as diisopropylethylamine, yields the formula 9 compound. Protecting groups, such as those for amino or carboxy groups, are selectively removed by methods known in the art. For example, a TOS group on a nitrogen atom may be removed by condensing the formula 9 compound with hydrogen fluoride to give the formula 10 compound, which is also a formula (I) compound, and a C_{1-6}alkyl ester group on a carboxylic acid moiety may be removed by saponification using base, for example, sodium hydroxide in a suitable solvent system, such as water/methanol, to give the formula 11 compound, which is also a formula (I) compound.

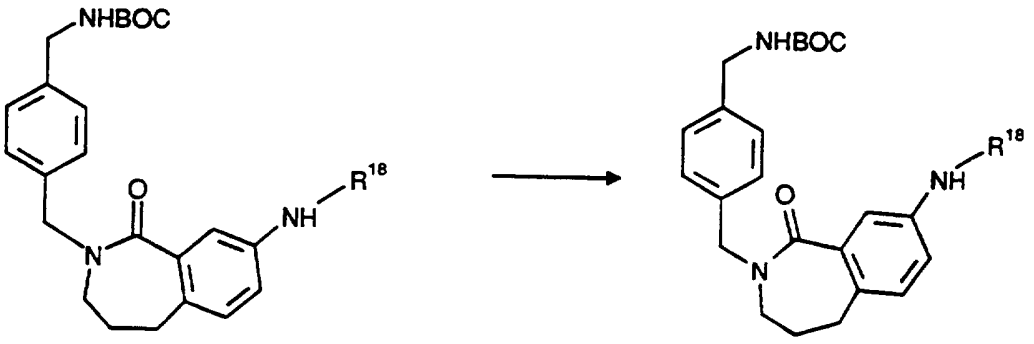
Scheme II



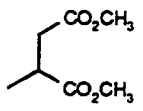
12 13

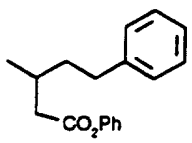


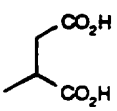
14 15 $R^{17}=NO_2$ 16 $R^{17}=NH_2$

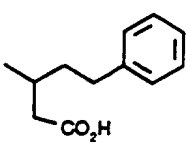


17 18

17a R^{18}= 

17b R^{18}= 

18a R^{18}= 

18b R^{18}= 

Scheme II provides a method for preparing compounds wherein A^1 is C=O, A^2 is NR^6, and A^3, A^4, and A^5 are CH_2. Thus, Scheme II presents a method for the preparation of the benzazepine ring system. Generally the synthesis is begun with a tetralone, substituted by R and R*, or precussors thereto, such as a nitro group, which are commercially available or are well known in the art. According to Scheme II, the tetralone of formula 12 is treated with a base, such as lithium bis(trimethylsilyl)amide, followed by reaction with a C_{1-4}alkyl chloroformate, such as methyl chloroformate, to give the corresponding enol carbonate. Ozonolysis of the enol carbonate with reductive workup, for example, using methyl sulfide, gives the formula 13 ring-opened intermediate. Reductive amination of the formula 13 compound with a $R^{6"}$-amine, wherein $R^{6"}$ is as defined in formula (V), such as 1-tert-butyloxycarbonylaminomethyl-4-aminomethylbenzene, in the presence of sodium cyanoborohydride at a pH of 6-7 yields the compound of the formula 14. Cyclization to form the azepine ring is accomplished by hydrolyzing the ester of the formula 14 compound, for example, using base, such as sodium hydroxide, followed by reaction with a peptide-coupling agent, such as benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate, in the presence of 1-hydroxybenzotriazole and a base, such as N-methylmorpholine, in a suitable solvent, such as dimethylformamide, to give the formula 15 compound. Reduction of the nitro group in the formula 15 compound using, for example, hyrogenation in the presence of a catalyst, such as palladium on carbon, gives the formula 16 amino compound. The amine group is further elaborated to give the desired R-substituent on the benzazepine ring. For example, the formula 16 amine is reacted with dimethylacetylene dicarboxylate to give the corresponding enamine, which is then reduced to the formula 17a compound, which is also a formula (I) compound. Additionally, the formula 16 amine may be reacted with imine-forming reagents, such as benzyl 3-keto-5-phenyl-pentanoate, which may be reduced using, for example, sodium triacetoxyborohydride to give a compound represented by formula 17b, which is also a formula (I) compound. Protecting groups, such as those for amino or carboxy groups, are selectively removed by methods known in the art to give the formula 18 compound, which is also a formula (I) compound.

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 (V) are prepared by conventional methods known in the art from commercially available materials. W is a generally a basic functional group attached to Z, optionally via an alkyl chain, and is protected during the synthesis of R^6 or is introduced into the molecule after the $-(CR'R^{10})_r-U-(CR'_2)_s-V-$ linkage has been formed. For example, compounds of formula (XII) or formula (I) wherein W is a suitably substituted R'R"N-, R"R'NC(=NR'), $R'_2N(R^{13})C{=}N-$, $R"N{=}(R^{13})C-NR'-$, $R'_2N(R'_2N)C{=}N-$ 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 (V) wherein W is  are prepared, *inter alia*, by methods disclosed in EP-A 0 478 363.

Compounds wherein W is $R'_2N(R'_2N)C{=}N-X-$ 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 W is $R'_2N(R'_2N)C{=}N-X-$ 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 W is$R'_2N(R'_2N)C=N-X-$ 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 W 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 W is $R'_2NR'NC(=NR')$- are prepared by conventional methods including those disclosed in Syn., 583 (1974).

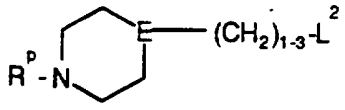
Compounds wherein W is R'R"NR'N- are prepared, *inter alia*, by methods disclosed in *J. Prakt. Chem.*, 36, 29 (1967).

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

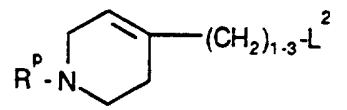
Compounds wherein W is R"R'NC(=NR')Y, and Y is S, are prepared, *inter alia*, by methods disclosed in *Chem. Lett.*, 1379 (1986).

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

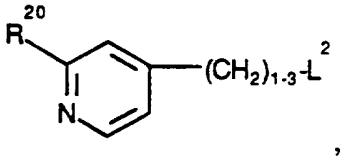
Useful intermediates of formula (V) include compounds of the formula $W'-(CR'_2)_q-Z-(CR'R^{10})_r-U-(CR'_2)_s-L^2$, wherein Z, R', R", R^{10}, U, q, r, and s are as defined for formula (I); L^2 is CHO, CO_2R', , OH, Cl, Br, I, CH_2-T or NR'R", and T is CF_3SO_3, OH, NHR", Cl, Br or I; and W' is W with any reactive basic nitrogen group protected as herein described. $R'SO_2$, R'OCO and R'CO (*e.g.*, Tos, Boc, Cbz or acetyl) are typical nitrogen protecting groups. Particular examples of such intermediates are:



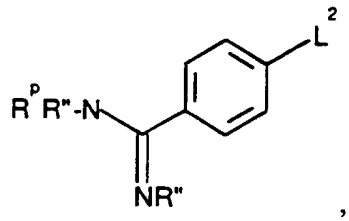
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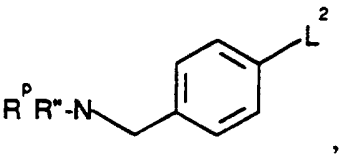
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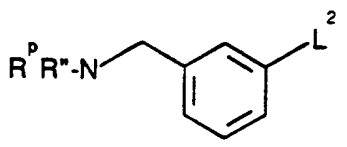
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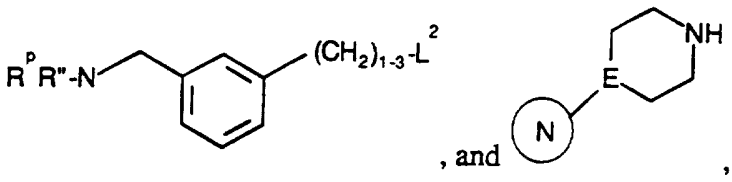
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wherein E is N or CH, R^{20} is hydrogen, amino, mono or di-C_{1-4}alkylamino, hydroxy or C_{1-4}alkyl.

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 (*e.g.*, 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 bicyclic system, may be accomplished by alkylation, sulfonylation, cyanation or acylation as is generally known in the art.

Acid addition salts of the compounds of this invention 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 this invention 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 compounds of this invention 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 compounds of formula (I) are 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 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 peptide 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 this invention 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 an peptide 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 peptide 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 compound of this invention 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 compound of this invention 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. The compounds of this invention inhibit [3H]-SK&F 107260 binding with Ki in the range of about 40 μM to about 100 μM.

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.

EXAMPLE 1

Preparation of (+)-4-N-Acetyl-1,3,5-trihydro-3(R)-(propyl-3-guanidine)-2-oxo-7,8-diethyletheryloxy-1, 4-benzodiazapine

a) 4,5-dihydroxy-2-nitrobenzaldehyde

To a cold (-50°C) suspension of aluminium chloride (55g, 0.43mol) in dichloroethane (150mL) a solution of 6-nitropiperonal (30g, 0.15mol) in dichloroethane (400mL) was added in one portion at room temperature. The mixture was then allowed to come to 0°C and stirred at this temperature for 1.5 hours. The suspension was diluted with cold water (1L), extracted with ethyl acetate and the then dried over sodium sulfate. Recrystallization from hot ethyl acetate/hexane (2/1) afforded a pure yellow solid. The solid was then mixed with 48% aqueous hydrobromic acid and allowed to stir at room temperature for 48 hours. The mixture was filtered, the solid was washed with water and pressed dry, followed by drying in vacuo to afford the title compound (22.19g 80%). MS(ES) m/e 184$(m+H)^+$.

b) bis ethyl-2-nitro-4,5-dioxyacetoacetate-benzaldehyde

A mixture of 4,5-dihydroxy-2-nitrobenzaldehyde (4.33g, 24mmol), potassium carbonate (13.8g, 0.1mol), ethyl bromoacetate (8.02g, 48mmol), in dimethylformamide (25mL) was stirred under argon at room temperature for 48 hours. The suspension was then poured into diethyl ether/ water (1/1, 500mL) and the resulting layers were separated. The aqueous layer was extracted with an additional volume of diethyl ether, the etheral layers were combined, washed with water and dried over magnesium sulfate. Concentration by rotary evaporation produced a solid which was triturated with hexane, filtered and dried in vacuo to give the title compound (7.0g, 84%). MS(ES) m/e 356$(m+H)^+$.

c) N-(benzyl-2-nitro-4,5-dioxyacetoacetate ethyl ester)-D-Arg(tos)OBzl

To a stirring solution of bis ethyl-2-nitro-4,5-dioxyacetoacetate-benzaldehyde (2.66g, 7.5mmol), in methanol (20mL) was added a solution of D-Arg(tos)OBzl (4.18g, 10mmol) in MeOH that was previously adjusted to pH 6.0

with sodium acetate. The resulting solution was allowed to stirr at room temperature for 1.5h, after which time sodium cyanoborohydride (0.68g, 10mmol) was added. After 18 hours the solution was diluted with ethyl acetate (200mL) and washed with 5% sodium bicarbonate, water, brine and dried over magnesium sulfate. The red oil was then purified by chromatography (silica gel, 1-4% methanol in chloroform) to afford the title compound (5.3g, 92%). MS(ES) m/e 758(m+H)$^+$.

d) N,N-(BOC)-(benzyl-2-nitro-4,5-dioxyacetoacetate ethyl ester)-D-Arg(tos)OBzl

A solution of N-(benzyl-2-nitro-4,5-dioxyacetoacetate ethyl ester)-D-Arg(tos)OBzl (5.0g, 6.6mmol), di-tert-butyl dicarbonate (5.0g, 23mmol) in methylene chloride (150mL) was heated to reflux for 48 hours. The solution was concentrated by rotary evaporation and purified by chromatography (silica gel, 35% hexane/ ethyl acetate) to afford the title compound 4.90g, 89%). MS(ES) m/e 858(m+H)$^+$.

e) N,N-(BOC)-(benzyl-2-amino-4,5-dioxyacetoacetate ethyl ester)-D-Arg(tos)OH

A mixture of N,N(BOC)(benzyl-2-nitro-4,5-dioxyacetoacetate ethyl ester)-D-Arg(tos)OBzl (4.2g, 4.9mmol) and 5% palladium on barium sulfate (3g) in methanol (100mL) was hydrogenated at 50 psi for 2 hours. The catalyst was filtered off through Celite®, and the filtrate was concentrated by rotary evaporation to afford the title compound as a white solid, (3.5g, 96%). MS(ES) m/e 738(m+H)$^+$.

f) (-)-4-N-(BOC)-1,3,5-trihydro-3(R)-(propyl-3-guanidine(tos))-2-oxo-7,8-dioxyacetoacetate-1,4-benzodiazapine bis ethyl ester

A cold (0°C) solution of N,N-(BOC)-(benzyl-2-amino-4,5-dioxyacetoacetate ethyl ester)-D-Arg(tos)OH (4.8g, 6.5mmol), DIEA (0.84g, 6.5mmol), 1-hydroxybenzotrazole hydrate (1.0g, 7.4mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.3g, 6.8mmol) in dimethylformamide (25mL) was made under argon. After which the reaction was allowed to come to room temperature for 18 hours. The majority of the solvents were removed and the resulting residue was treated with 10% potassium carbonate. The solid precipitate was filtered off and washed well with water and dried in vacuo. The desired product was purified by chromatogrphy (silica gel, ethyl acetate/hexane, 1/1) to afford the title compound (3.9g, 83%). MS(ES) m/e 720(m+H)$^+$.

g) (-)-4-N-1,3,5-trihydro-3(R)-(propyl-3-guanidine(tos))-2-oxo-7,8-dioxyacetoacetate-1,4-benzodiazapine bis ethyl ester

(-)-4-N-(BOC)-1,3,5-trihydro-3(R)-(propyl-3-guanidine(tos))-2-oxo-7,8-dioxyacetoacetate-1,4-benzodiazapine bis ethyl ester (3.9g, 5.4mmol) was treated with a 20% solution of trifluoroacetic acid in methylene chloride (60mL). After 1 hour, the solution was concentrated and the resulting wax was triturated with diethyl ether. Filtration of the white solid followed by drying in vacuo afforded the title compound as the bis trifluoroacetic acid salt (4.2g, 95%). MS(ES) m/e 520(m+H)$^+$.

h) (-)-4-N-acetyl-1,3,5-trihydro-3(R)-(propyl-3-guanidine(tos))-2-oxo-7,8-dioxyacetoacetate-1,4-benzodiazapine bis ethyl ester

A solution of (-)-4-N-1,3,5-trihydro-3(R)-(propyl-3-guanidine(tos))-2-oxo-7,8-oxyacetoacetate-1,4-benzodiazapine bis ethyl ester (4.2g, 5.4mmol) in dimethylformamide (40mL) was treated with DIEA until the pH was at 7.0. Acetyl chloride (0.426, 6mmol) was then added, and the pH was adjusted to 8.0 using an additional amount of DIEA. The resulting mixture was allowed to stir at room temperature for 2 hours. The solution was concentrated by rotary evaporation, and the residue was taken into ethyl acetate. The organics were then washed with water and dried over magnesium sulfate. Removal of the solvents afforded the title compound (2.5g, 70%). MS(ES) m/e 662(m+H)$^+$.

i) (+)-4-N-acetyl-1,3,5-trihydro-3(R)-(propyl-3-guanidine)-2-oxo-7,8-diethyletheryloxy-1,4-benzodiazapine

Under standard hydrogen fluoride (hydrogen fluoride (HF)) reaction conditions, (-)-4-N-acetyl-1,3,5-trihydro-3(R)-(propyl-3-guanidine(tos))-2-oxo-7,8-dioxyacetoacetate -1,4-benzodiazapine bis ethyl ester (1.6g, 2.4mmol) was condensed with hydrogen fluoride (15mL) at -78^{0}C. The solution was then allowed to warm to 0°C for 90 minutes. The hydrogen fluoride was removed in vacuo and the resulting wax was triturated with diethl ether. The solid was filtered off dried in vacuo and taken into water. The solution was washed with diethyl ether, ethyl acetate, then lyophillized to afford the titled compound as a white powder, 1.04g, (82%):MS(ES) m/e 508(m+H)$^+$.

EXAMPLE 2

Preparation of (-)-4-N-Acetyl-1,3,5-trihydro-3(R)-(propyl-3-guanidine)-2-oxo-7,8-dioxyacetic acid-1,4-benzodiazapine

A solution of (+)-4-N-acetyl-1,3,5-trihydro-3(R)-(propyl-3-guanidine)-2-oxo-7,8-diethyletheryloxy-1,4-benzodiazapine, prepared in Example 1, (100mg, 0.2mmol), in methanol (2.0mL) was treated with 1N sodium hydroxide (0.4mL, 0.4mmol). After 1 hour, the mixture was diluted with diethyl ether (10mL), filtered and the solid washed with diethyl ether. The solid was then dried, ground with diethyl ether, filtered and dried in vacuo. The material was then desalted by non-ionic XAD-2 absorbant (equilibrated with water, eluted with 30% acetonitrile) to give the title compound (80mg, 88%). MS(ES) m/e 452(m+H)$^+$.

EXAMPLE 3

Preparation of (+)-4-N-Acetyl-1,3,5-trihydro-3(R)-(propyl-3-guanidine)-2-oxo-7,8-dibutyryloxy acid-1,4-benzodiazapine

a) bis ethyl-2-nitro-4,5-dibutyrloxy-benzaldehyde

4,5-dihydroxy-2-nitrobenzaldehyde was O-alkylated with ethyl 4-bromobutyrate according to the procedure of Example 1(b) to affored the title compound (63%). MS(ES) m/e 412(m+H)$^+$.

b) N-(benzyl-2-nitro-4,5-dibutyrloxy ethyl ester)-D-Arg(tos)OBzl

Bis ethyl-2-nitro-4,5-dibutyrloxy-benzaldehyde was reductivly aminated according to the procedure of Example 1(c) to afford the title compound (82%). MS(ES) m/e 814(m+H)$^+$.

c) N,N-(BOC)-(benzyl-2-nitro-4,5-dibutyrloxy ethyl ester)-D-Arg(tos)OBzl

N(benzyl-2-nitro-4,5-dibutyrloxy ethyl ester)-D-Arg(tos)OBzl was N-protected according to the procedure of Example 1(d) to afford the title compound (95%). MS(ES) m/e 914(m+H)$^+$.

d) N,N-(BOC)-(benzyl-2-amino-4,5-dibutyrloxy ethyl ester)-D-Arg(tos)OH

N,N-(BOC)-(benzyl-2-nitro-4,5-dibutyrloxy ethyl ester)-D-Arg(tos)OBzl was deprotected and reduced according to the procedure of Example I(e) to afford the title compound (77%). MS(ES) m/e 794(m+H)$^+$.

e) (+)-4-N-(BOC)-1,3,5-trihydro-3(R)-(propyl-3-guanidine(tos))-2-oxo-7,8-dibutyrloxy-1,4-benzodiazapine bis ethyl ester

N,N-(BOC)-(benzyl-2-amino-4,5-dibutyrloxy ethyl ester)-D-Arg(tos)OH was cyclized according to the procedure of Example 1(f) to afford the title compound (Quant.). MS(ES) m/e 776(m+H)$^+$.

f) (+)-4-N-1,3,5-trihydro-3(R)-(propyl-3-guanidine(tos))-2-oxo-7,8-dibutyrloxy -1,4-benzodiazapine bis ethyl ester

(+)-4-N-(BOC)-1,3,5-trihydro-3(R)-(propyl-3-guanidine(tos))-2-oxo-7,8-dibutyrloxy-1,4-benzodiazapine bis ethyl ester was N-deprotected according to the procedure of Example 1(g). MS(ES) m/e 676(m+H)$^+$.

g) (+)-4-N-acetyl-1,3,5-trihydro-3(R)-(propyl-3-guanidine(tos))-2-oxo-7,8-diobutyrloxy-1,4-benzodiazapine bis ethyl ester

(+)-4-N-1,3,5-trihydro-3(R)-(propyl-3-guanidine(tos))-2-oxo-7,8-dibutyrloxy-1,4-benzodiazapine bis ethyl ester was N-acetylated according to the procedure of Example 1(h) to afford the title compound (30%). MS(ES) m/e 662(m+H)$^+$.

h) (+)-4-N-acetyl-1,3,5-trihydro-3(R)-(propyl-3-guanidine)-2-oxo-7,8-dibuturloxy-1,4-benzodiazapine

(+)-4-N-acetyl-1,3,5-trihydro-3(R)-(propyl-3-guanidine(tos))-2-oxo-7,8-diobutyrloxy-1,4-benzodiazapine bis ethyl ester was hydrogen fluoride (HF) deprotected according to the procedure of Example 1(i) to afford the title compound (80%). MS(ES) m/e 564(m+H)$^+$.

i) (+)-4-N-Acetyl-1,3,5-trihydro-3(R)-(propyl-3-guanidine)-2-oxo-7,8-dibutyrloxy acid-1,4-benzodiazapine

(+)-4-N-acetyl-1,3,5-trihydro-3(R)-(propyl-3-guanidine)-2-oxo-7,8-dibuturloxy-1,4-benzodiazapine was saponified according to the procedure of Example 2(a) to afford the title compound. MS(ES) m/e 508(m+H)$^+$.

EXAMPLE 4

Preparation of (R, S)-2-[(4-Aminomethyl)phenyl]methyl-2,3,4,5-tetrahydro-8-[1-(1,2-dicarboxy)ethyl]amino-1H-2-benzazepin-1-one

a) 1-t-butyloxycarbonylaminomethyl-4-aminomethylbenzene

p-Xylenediamine (10 g, 73.4 mmol, was dissolved in methylene chloride (150 mL) and was treated at room temperature with di-tert-butyl dicarbonate (5.36 g, 24.5 mmol) and stirred for 50 hours. The reaction was diluted with chloroform, washed with 5% sodium carbonate, dried over magnesium sulfate, filtered and evaporated at reduced pressure. The residue was dissolved in a minimum of 1N aqueous hydrochloric acid (10 mL) and was washed 2 times with diethyl ether. The aqueous

layer was made basic (pH 10) with aqueous 1N sodium hydroxide and was extracted 2 times with ethyl acetate, dried over magnesium sulfate, filtered and evaporated at reduced pressure to give 3.48 g (60 %) of the title compound. ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.48 (s, 9H), 3.85 (s, 2H), 4.31 (d, 2H, J=7.5 Hz), 5.07-5.47 (m, 1H), 7.28 (s, 4H).

b) 1-nitro-3-carbomethoxymethyl-4-(propan-3-alyl)-benzene

A solution of 7-nitro-1-tetralone (3.0 g, 15.7 mmol) in tetrahydrofuran (60 mL) was treated under argon at -78 °C with 16 mL of 1M lithium bis(trimethylsilyl)amide in tetrahydrofuran and stirred for 45 minutes. Then methyl chloroformate (1.3 mL) was added and the reaction was stirred at room temperature for 1 hour. The reaction was then quenched with water and extracted with ethyl acetate to give the crude enol carbonate. The enol carbonate in a 3:2 mixture of methanol : methylene chloride was cooled to -78 °C and treated with excess ozone (until the reaction mixture became blue). The excess ozone was blown off with oxygen and the reaction was then treated with of methyl sulfide (4 mL) and slowly warmed to room temperature and stirred for 18 hours. The reaction was evaporated at reduced pressure and purified by flash chromatography (2x20 cm, 20% ethyl acetate in hexane) to give 1.33 g (41%) of the title compound. ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.85 (t, 2H, J=7.5 Hz), 3.58 (t, 2H, J=7.5Hz), 4.00 (s, 3H), 7.60 (d, 1H, J=9.0 Hz), 8.36 (d of d, 1H, J=9.0,1.5 Hz), 8.88 (d, 1H, J=1.5 Hz), 9.91 (s,1H).

c) 1-nitro-3-carboxymethyl-4-(3-(aminomethyl-(4-t-butyloxycarbonyl aminomethyl)-benzyly)propyl) benzene

1-Nitro-3-carbomethoxymethyl-4-(propan-3-alyl)-benzene (460 mg, 2.0 mmol) in dry methanol (20 mL) was treated with 1-t-butyloxycarbonylaminomethyl-4-aminomethylbenzene (950 mg, 4 mmol) and 288 µL (4 mmol) of acetic acid (pH =7) followed by (126 mg, 2 mmol) sodium cyanoborohydride at room temperature for 24 hours. The reaction was then evaporated at reduced pressure and taken into chloroform. This solution was washed with 5% sodium carbonate, dried over magnesium sulfate, filtered and evaporated at reduced pressure. The residue was purified by flash chromatography (3x20 cm, 5% methanol in chloroform) to give 440 mg of the title compound (48%). ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.40 (s, 9H), 1.73-2.10 (m, 3H), 2.71 (t, 2H, J=7.5 Hz), 3.20-3.05 (m, 2H), 3.82 (s,2H), 3.93 (s, 3H), 4.32 (d, 2H, J=6.0 Hz), 4.87-5.20 (m, 1H), 7.30 (s, 4H), 7.55 (d, 1H, J=9 Hz), 8.30 (d of d, 1H, J=9.0, 1.5 Hz), 8.75 (d, 1H, J=1.5 Hz).

d) 2-[(4-t-butyloxycarbonylaminomethyl)phenyl]methyl-2,3,4,5-tetrahydro-8-nitro-1H-2-benzazepin-1-one

1-Nitro-3-carboxymethyl-4-(3-(aminomethyl-(4-t-butyloxycarbonyl aminomethyl)-benzyly)propyl) benzene (740 mg, 1.62 mmol) in 1,4-dioxane (6.0 mL) was treated with 3.5 mL of aqueous 1N sodium hydroxide at room temperature for 1 hour. The reaction was acidified with 1N hydrochloric acid and stirred 10 minutes. The reaction was evaporated at reduced pressure and then evaporated from toluene. The residue was dissolved in dimethylformamide (200 mL) and was treated at 0°C with the following: N-methyl-morpholine (1.07 mL, 9.72 mL), HOBt (437 mg, 3.24 mmol) and benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (1.43 g, 3.24 mmol). The reaction gradually warmed to room temperature and stirred for 2 days. The reaction mixture was evaporated at reduced pressure and purified by flash chromatography (2x20 cm,50 to 75%, ethyl acetate in hexane) to give 440 mg (64%) of the title compound. ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.50 (s, 9H), 1.67-2.10 (m, 2H), 2.82 (t, 2H J= 7.5 Hz), 3.20 (t, 2H, J= 7.5 Hz), 4.35 (d, 2H, J= 6 Hz), 4.70-5.03 (m, 1H), 4.79 (s, 2H), 7.27-7.40 (m, 5H), 8.27 (d of d, 1H, J=9.0, 1.5 Hz), 8.67 (d, 1H, J= 1.5 Hz).

e) 2-[(4-t-butyloxycarbonylaminomethyl)phenyl]methyl-2,3,4,5-tetrahydro-8-amino-1H-2-benzazepin-1-one

2-[(4-t-butyloxycarbonylaminomethyl)phenyl]methyl-2,3,4,5-tetrahydro-8-nitro-1H-2-benzazepin-1-one (200 mg, 0.471 mmol) in dry methanol with 20 mg of 5% palladium on carbon was treated with hydrogen at 50 psi for 2 hours. The reaction mixture was filtered through Celite®, evaporated at reduced pressure and purified by flash chromatography (2x20 cm, 98:2 methanol in chloroform) to give 160 mg (85%) of the title compound ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.46 (s, 9H), 1.64-1.80 (m, 2H), 2.62 (t, 2H, J=7.1 Hz), 3.17 (t, 2H, J=6.4 Hz), 4.31 (d, 2H, J=5.8 Hz), 4.74 (s, 2H), 4.80-4.90 (m, 1H), 6.69 (d of d, 1H, J=6.0, 2.5 Hz), 6.90 (d, 1H, 6.0 Hz), 7.06 (d, 1H, 2.5 Hz), 7.29 (AB, 4H).

f) (R, S)-2-[(4-t-butyloxycarbonylaminomethyl)phenyl]methyl-2,3,4,5-tetrahydro-8-[1-(1,2-dimethylcarboxy)ethyl]amino-1H-2-benzazepin-1-one

A mixture of 2-[(4-t-butyloxycarbonylaminomethyl)phenyl]methyl-2,3,4,5-tetrahydro-8-amino-1H-2-benzazepin-1-one (160 mg, 0.405 mmol) and dimethylacetylene dicarboxylate (248 μL, 2.025 mmol) in dry methanol (3 mL) was treated at reflux (76°C) 1.5 hours. The reaction was evaporated and filtered

through a layer of silica (4 inch) with 50-75-100% ethyl acetate in hexane to give 200 mg of enamine which was dissolved in dry methanol with 20 mg Pd on carbon and treated with hydrogen at 50 psi) for 2 hours. The reaction was then filtered through Celite®, evaporated at reduced pressure and the residue purified by flash chromatography (1x20 cm, 40-60% ethyl acetate in hexane) to give 200 mg (75%) of the title compound. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.49 (s, 9H), 1.60-1.80 (m, 3H), 2.62 (t, 2H, J= 6.6 Hz), 2.92 (d, 2H, J= 6.0 Hz), 3.15 (t, 2H, J= 6.6 Hz), 3.70 (s, 3H), 3.79 (s, 3H), 4.31 (d, 2H, J=4.1 Hz), 4.49 (t, 1H, J=5.0 Hz), 4.75 (s, 2H), 4.80-4.90 (m, 1H), 6.68 (d of d, 1H, J=8.0, 2.0 Hz), 6.92 (d, 1H, J= 8.0 Hz), 7.01 (d, 1H, J= 2.0 Hz), 7.21-7.38 (m, 4H).

g) (R, S)-2-[(4-aminomethyl)phenyl]methyl-2,3,4,5-tetrahydro-8-[1-(1,2-dicarboxy)ethyl]amino-1H-2-benzazepin-1-one

A solution of (R, S)-2-[(4-t-butyloxycarbonylaminomethyl)phenyl]methyl-2,3,4,5-tetrahydro-8-[1-(1,2-dimethylcarboxy)ethyl]amino-1H-2-benzazepin-1-one (200 mg, 0.371 mmol) in 1,4-dioxane (5mL) was treated with 1.86 mL of aqueous 1N sodium hydroxide at room temperature for 2 hours. The reaction mixture was acidified with 1N hydrochloric acid and evaporated at reduced pressure and then evaporated from toluene. The residue methylene chloride (2 mL) was treated with trifluoroacetic acid (2 mL) and stirred at room temperature for 2 hours. The reaction mixture was then evaporated at reduced pressure and evaporated from toluene. The residue was purified by reverse phase hplc [5 μ Hamilton PRP-1; 21.5x250 mm column; 82:18 (0.1% trifluoroacetic acid (aqueous) : 0.1% trifluoroacetic acid in acetonitrile)] to give, after lyophilization from 1% aqueous acetic acid, 56 mg of the title compound. MS(ES) m/e 412 $[M+H]^+$; HPLC k' 3.47 [5 μ PRP-1®: Hamilton, 4.6x250 mm, flow = 1.5 mL/min., UV detection at 220 nm, 80:20 (0.1% trifluoroacetic acid (aqueous) : 0.1% trifluoroacetic acid in acetonitrile)]; TLC R_f 0.25 (silica gel, 4:1:1 butanol : acetic acid : water); ^{1}H NMR (CD_3OD, 250 MHz) δ 1.69-1.80 (m, 2H), 2.52 (t, 2H, J= 6.6 Hz), 2.78 (t, 2H, J= 6.6 Hz), 3.15 (t, 2H, J= 6.6 Hz), 4.02 (s, 2H), 4.31-4.40 (m, 1H), 4.70 (s, 2H), 6.86-6.91 (m, 3H), 7.31-7.41 (m, 4H); elemental analysis: calcd. for $C_{22}H_{25}N_3O_5 \cdot 2.5$ $C_2HO_2F_3 \cdot 2$ water: C, 44.27; H, 4.33; N, 5.74. Found:.C, 44.52; H, 4.33; N, 5.70.

EXAMPLE 5

Preparation of (R,S)-2-[(4-Aminomethyl)phenyl]methyl-2,3,4,5-tetrahydro-8-[2-(1-carboxy-4-phenyl)butyl]amino-1H-2-benzazepin-1-one

a) benzyl 3-keto-5-phenyl-pentanoate

A solution of hydrocinnamoyl chloride (5.0 mL, 33.7 mmol) in methylene chloride was treated with 2,2-dimethyl-1,3-dioxane-4,6-dione (4.8 g, 33.3 mmol) and pyridine (5.3 mL) and stirred at room temperature for 24 hours. The reaction mixture was diluted with chloroform, washed with 1N hydrochloric acid (aqueous), dried over anhydrous magnesium sulfate and evaporated at reduced pressure. The residue was dissolved in dry toluene (250 mL) with benzyl alcohol (11 mL, 100 mmol) and the mixture was heated at 127 °C (bath temperature) for 20 hours and at reflux for 48 hours. The reaction mixture was evaporated and the residue was taken into ethyl acetate. This solution was washed with 5% sodium bicarbonate (aqueous), 1 N hydrochloric acid (aqueous), dried over anhydrous magnesium sulfate and evaporated at reduced pressure. The residue was purified by flash chromatography (silica gel, 6x20 cm, 12% ethyl acetate in hexane) to give 6.12 g (21.7 mmol, 64%) of benzyl 3-keto-5-phenyl-pentanoate.

b) (R,S)-2-[(4-butyloxycarbonyl-aminomethyl)phenyl] methyl-2,3,4,5-tetrahydro-8-[2-(1-benzylcarboxyl-4-phenyl)butyl]amino-1H-2-benzazepin-1-one

A solution of 2-[(4-t-butyloxycarbonylaminomethyl)phenyl]methyl-2,3,4,5-tetrahydro-8-amino-1H-2-benzazepin-1-one (103 mg, 0.26 mmol) and benzyl 3-keto-5-phenyl-pentanoate (166 mg, 0.588 mmol) was treated with acetic acid (89 µL, 1.56 mmol) and sodium triacetoxyborohydride (165 mg, 0.78 mmol) and stirred at room temperature for 42 hours. The reaction mixture was diluted with ethyl acetate, washed with 5% sodium bicarbonate (aqueous), dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography (silica gel, 30% ethyl acetate in hexane) to give 83 mg (0.125 mmol, 48%) of the title compound. MS (ES) m/e 662 $(M+H)^+$.

c) (R,S)-2-[(4-butyloxycarbonyl-aminomethyl)phenyl] methyl-2,3,4,5-tetrahydro-8-[2-(1-carboxy-4-phenyl)butyl]amino-1H-2-benzazepin-1-one

A solution of (R,S)-2-[(4-butyloxycarbonyl-aminomethyl)phenyl] methyl-2,3,4,5-tetrahydro-8-[2-(1-benzylcarboxyl-4-phenyl)butyl]amino-1H-2-benzazepin-1-one (83 mg, 0.125 mmol) and 20 mg of 5% palladium on carbon in methanol was treated with Hydrogen at room temperature (50 psi) for 4 hours. The reaction mixture was filtered through a pad of Celite® and the filtrate evaporated at reduced pressure. The residue was purified by flash chromatography (silica gel, 3x20 cm, 98:2:0.1-chloroform methanol acetic acid) to give 52.3 mg (0.091 mmol, 73%) of the title compound. MS (ES) m/e 572 $(M+H)^+$.

d) (R,S)-2-[(4-aminomethyl)phenyl]methyl-2,3,4,5-tetrahydro-8-[2-(1-carboxy-4-phenyl)butyl]amino-1H-2-benzazepin-1-one

(R,S)-2-[(4-Butyloxycarbonyl-aminomethyl)phenyl] methyl-2,3,4,5-tetrahydro-8-[2-(1-carboxy-4-phenyl)butyl]amino-1H-2-benzazepin-1-one(52.3 mg, 0.091 mmol) was treated with trifluoroacetic acid at room temperature for 1 hour. The reaction mixture was evaporated at reduced pressure and the residue evaporated from toluene. The residue was taken into 1% aqueous acetic acid and lyophilized. The crude product was purified by preparative Prep-HPLC on a Hamilton PRP-1 column [10 μ PRP-1®: Hamilton; 21.5 x 250 mm column; flow rate = 16.2 mL/min.; 65:35 (0.1% trifluoroacetic acid (aqueous) : 0.1% trifluoroacetic acid in acetonitrile)] to give, after lyophilization, 34 mg of product. MS(ES) m/e 472 $[M+H]^+$; HPLC k' = 0.98 [5 μ PRP-1®: Hamilton, 4.6 x 250 mm, flow = 1.5 mL/min., UV detection at 220 nm, 50:50 (0.1% trifluoroacetic acid (aqueous) : 0.1% trifluoroacetic acid in acetonitrile)]; HPLC k' = 4.42 [5 m PRP-1®: Hamilton, 4.6 x 250 mm, flow = 1.5 mL/min., UV detection at 220 nm, gradient elution (0.1% trifluoroacetic acid (aqueous) : 0.1% trifluoroacetic acid in acetonitrile) start at 70:30, to 20 min. 20:80, hold for 5 min., return in 5 min. to 70:30].

EXAMPLE 6

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 7

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 8

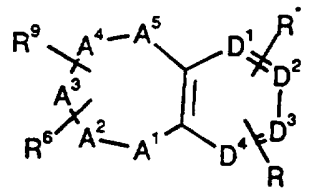
Oral Dosage Unit Composition

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 to D^4 form an accessible substituted six membered ring, optionally containing up to two nitrogen atoms;

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, Q-C_{1-4}alkylamino or Q-C_{1-4}alkyloxy, 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, Q-C_{1-4}alkylamino, Q-C_{1-4}alkyloxy, C_{3-6}cycloalkyl, Ar or Het, optionally substituted by one or more of R^{11};

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

R^6 is W-$(CR'_2)_q$-Z-$(CR'R^{10})_r$-U-$(CR'_2)_s$-V-;

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 and Tet;

R^8 is -OR', -NR'R'', -NR'SO_2R', -NR'OR', -$OCR'_2C(O)OR'$, -$OCR'_2OC(O)$-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 H, C_{1-4}alkyl or -NR'R'';

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', -$C(O)NR'_2$, -$C(O)OR^{15}$, -$S(O)_mR'$ 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 $C(O)OR^{15}$;

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

R' is H, C_{1-6}alkyl, C_{3-7}cycloalkyl-C_{0-4}alkyl or Ar-C_{0-4}alkyl;

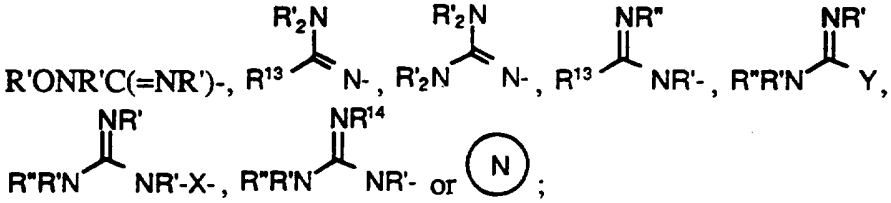
R'' is R', -C(O)R' or -$C(O)OR^{15}$;

R''' is R'' or AA2;

AA1 is an amino acid attached through its amino group and having its carboxyl group optionally protected, and AA2 is an amino acid attached through its carboxyl group, and having its amino group optionally protected;

U and V are absent or CO, CR'_2, C(=CR'2), $S(O)_n$, O, NR', CR'OR', CR'(OR")CR'_2, CR'_2CR'(OR"), C(O)CR'_2, CR'_2C(O), CONR', NR'CO, OC(O), C(O)O, C(S)O, OC(S), C(S)NR', NR'C(S), $S(O)_nNR'$, $NR'S(O)_n$, N=N, NR'NR', $NR'CR'_2$, $NR'CR'_2$, CR'_2O, OCR'_2, C≡C or CR'=CR', provided that U and V are not simultaneously absent;

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



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

Y is absent, S or O;

Z is $(CH_2)_t$, Het, Ar or C_{3-7}cycloalkyl;

m is 1 or 2;

n is 0 to 3;

p is 0 or 1;

q is 0 to 3;

r is 0 to 2;

s is 0 to 2; and

t is 0 to 2; or

pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein

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

A^2 is $CR^2R^{2'}$ 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-D^4 are CR, CR^* or N;

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

R^2 and $R^{2'}$ are hydrogen or together are =O or R^2 is R^6 and $R^{2'}$ is absent or present as hydrogen;

R^3 and $R^{3'}$ are hydrogen or together are =O or R^3 is R^6 and $R^{3'}$ is absent or present as hydrogen;.

R^4 and $R^{4'}$ are hydrogen or R^4 is R^9 and $R^{4'}$ is absent or present as hydrogen; and

R^5 and $R^{5'}$ are hydrogen or together are =O.

3. A compound according to claim 2, wherein

A^1 is $CR^1R^{1'}$, NR^1, 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^4 are CH;

D^2 is CR*; and

D^3 is CR.

4. A compound according to claim 3, wherein

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

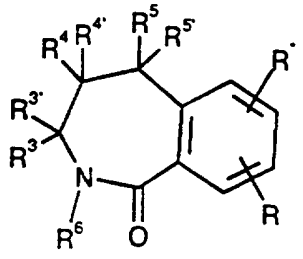
A^2 is $CR^2R^{2'}$ or NR^2;

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

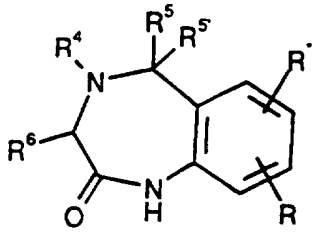
A^4 is $CR^4R^{4'}$ or NR^4; and

A^5 is $CR^5R^{5'}$.

5. A compound according to claim 2, which is:



or



6. A compound according to claim 2, wherein $(CR'R^{10})_r$-U-$(CR'_2)_s$-V is CO, CONR', NR'CO, CH_2CHOH, $CHOHCH_2$, CH_2CH_2, CH_2O, OCH_2, CH=CH, C≡C, CH_2CH=CH, $(CH_2)_2O$, CH_2CONR', $CONR'CH_2$, $CONR'CH_2$, CH(NR'R")CONR', $CH_2CH_2NR'CO$, $CONR'CHR'CH_2$, $CH_2NR'CO_2CH_2$, $CONR'CH_2CO$,

$CONR'CH_2CHOH$, $CH=CHCONR'$, $(CH_2)_3O$, $NR'CO_2CH=CH$, or $SO_2NR'CHR'CH_2$.

7. A compound according to claim 6 wherein R is Q-C_{1-4}alkyl, Q-C_{1-4}alkylamino, or Q-C_{1-4}alkyloxy, substituted by one or more R^7.

8. A compound according to claim 7 wherein A^1 is C=O, A^2 is NR^6 and A^3, A^4 and A^5 are CH_2.

9. A compound according to claim 7 wherein A^1 is NH, A^2 is C=O, A^3 is CHR^6, A^4 is $NC(O)C_{1-6}$alkyl and A^5 is CH_2.

10. A compound according to claim 6 wherein

Z is phenyl, a six-membered Het or $(CH_2)_t$;

W is R'2`:. $H_2NC(=NH)$, $H_2NC(=NH)NH$ or ; and

$(CR'R^{10})_r$-U-$(CR'_2)_s$-V is $(CR'R^{10})_r$-U- or -U-$(CR'_2)_s$, wherein U is $CH(NR'R'')CONH$, NR'CO, CONR', CR'=CR', C≡C , O, CO or CH_2.

11. A compound according to claim 1 which is:

(R,S)-2-[(4-aminomethyl)phenyl]methyl-2,3,4,5-tetrahydro-8-[1-(1,2-dicarboxy)ethyl]amino-1H-2-benzazepin-1-one;

(R,S)-2-[(-aminomethyl)phenyl]methyl-2,3,4,5-tetrahydro-8-[2-(1-carboxy-4-phenyl)butyl]amino-1H-2-benzazepin-1-one;

(+)-4-N-acetyl-1,3,5-trihydro-3-(propyl-3-guanidine)-2-oxo-7,8-dibutyryloxy-1,4-benzodiazapine;

(-)-4-N-acetyl-1,3,5-trihydro-3(R)-(propyl-3-guanidine)-2-oxo-7,8-dioxyacetic acid-1,4-benzodiazapine; or

(+)-4-N-acetyl-1,3,5-trihydro-3(R)-(propyl-3-quanidine)-2-oxo-7,8-diethyletheryloxy-1,4-benzodiazapine;

or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

13. A method for effecting inhibition of platelet aggregation which comprises administering a compound according to claim 1.

14. A method for treating stroke or a transient ischemia attack or myocardial infarction which comprises administering a compound according to claim 1.

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/15932

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 243/14, 243/24, 243/16; A61K 31/55
US CL :540/487, 510, 512, 504; 514/221, 81, 64
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. : 540/487, 510, 512, 504; 514/221, 81, 64

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

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

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, Volume 79, Number 11, issued 17 September 1973, Gogolak et al, "Anticonvulsant Activity of Clonazepam and Ro 8-4192 against Penicillin- and Lidocaine-Induced Seizures", page 20, abstract no. 61480, Arzneim.-Forsch., 23(4), pages 545-549, see the compound with RN 41544-25-6.	1
X	WO, A, 94/22825 (MERCK & CO., INC.) 13 October 1994, see pages 4-8, especially page 4, lines 20-23 and 30-33, page 5, lines 13 and 21-28, page 6, lines 2 and 11-14, and page 8, line 6, page 16, lines 13-42, page 17, lines 5-9 and 18-33, and page 42, claims 20-22.	1-7, 10, and 12-15

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"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)

"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

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search
05 FEBRUARY 1996

Date of mailing of the international search report
04 MAR 1996

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/15932

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	US, A, 5,389,631 (CLAREMON ET AL) 14 February 1995, see abstract, column 2, line 54 to column 4, line 57, column 12, lines 31-44,column 13, lines 2-12 and 46-49, column 14, lines 1-19, and column 88, claim 11.	1-4, 6, 7, 10 and 12-15
X	US, A, 4,820,834 (EVANS ET AL) 11 April 1989, see abstract, column 4, line 1 to column 10, line 26, and column 11, lines 49-55.	1-7, 9, 10 and 12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/15932

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-7 and 9-15, drawn to compounds, compositions, and methods wherein A1 and A4 are N atoms and A2, A3, A5 and D1 to D4 are C atoms.
Group II, claim(s) 1-8 and 10-15, drawn to compounds, compositions, and methods wherein A2 is N and A1, A3 to A5 and D1 to D4 are C atoms.
The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature of Group I is benzodiazepine derivatives and that of Group II is benzazepine derivatives. These special technical features are different and they are not art recognized equivalence.