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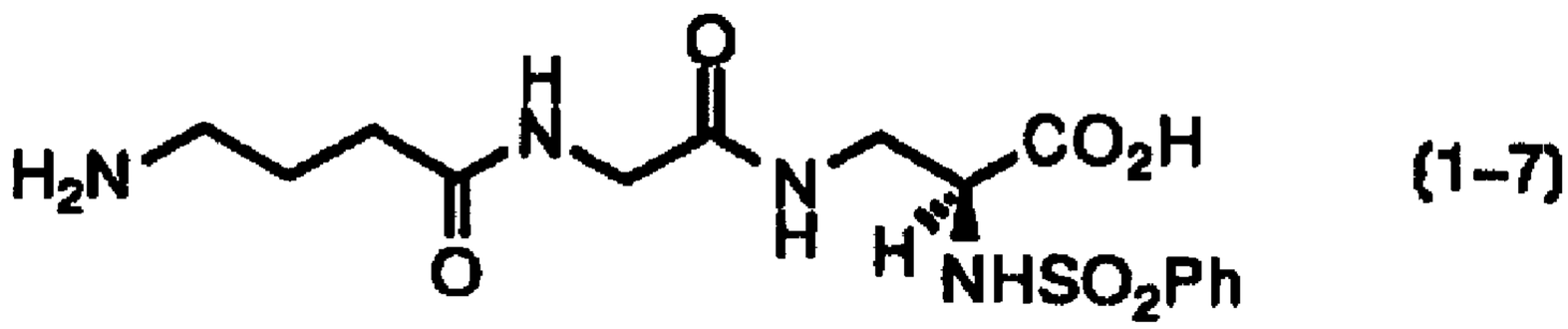
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(54) **ANTAGONISTES DE RECEPTEUR FIBROGENE**

(54) **FIBRINOGEN RECEPTOR ANTAGONISTS**



(1–7)

(57) L'invention concerne des composés représentés par la formule X-$(CH_2)_n$-C(O)NH-A-C($COOR^5$)R^3R^4 ou un sel pharmaceutiquement acceptable de ceux-ci représenté par la formule (1-7). Ces composés sont utiles pour inhiber un fibrogène se liant aux plaquettes sanguines, inhibant de ce fait une agrégation de plaquettes.

(57) Compounds of this invention have the formula: X-$(CH_2)_n$-C(O)NH-A-C($COOR^5$)R^3R^4 or a pharmaceutically acceptable salt thereof, e.g. formula (1-7) which are useful for inhibiting fibrinogen binding to blood platelets, thereby inhibiting platelet aggregation.

PCT

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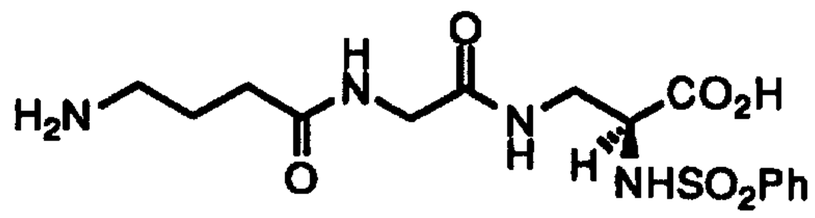
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(54) Title: FIBRINOGEN RECEPTOR ANTAGONISTS



(1–7)

(57) Abstract

Compounds of this invention have the formula: $X–(CH_2)_n–C(O)NH–A–C(COOR^5)R^3R^4$ or a pharmaceutically acceptable salt thereof, e.g. formula (1–7) which are useful for inhibiting fibrinogen binding to blood platelets, thereby inhibiting platelet aggregation.

TITLE OF THE INVENTION
FIBRINOGEN RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

The invention relates generally to inhibition of the binding of fibrinogen and other proteins to blood platelets, and inhibiting the aggregation of blood platelets specifically to the GP IIb/IIIa fibrinogen receptor site. Fibrinogen is a glycoprotein present in blood plasma that participates in platelet aggregation and in fibrin formation. Platelets are cell-like anucleated fragments, found in the blood of all mammals, that also participate in blood coagulation. Interaction of fibrinogen with the IIb/IIIa receptor site is known to be essential for normal platelet function.

When a blood vessel is damaged by an injury or other causative factor, platelets adhere to the disrupted subendothethial surface. The adherent platelets subsequently release biologically active constituents and aggregate. Aggregation is initiated by the binding of agonists, such as thrombin, epinephrine, or ADP to specific platelet membrane receptors. Stimulation by agonists results in exposure of latent fibrinogen receptors on the platelet surface, and binding of fibrinogen to the glycoprotein IIb/IIIa receptor complex.

Attempts have been made to use natural products and synthetic peptides to determine the mechanism of adhesion and platelet aggregation. For example, Rouslahti and Pierschbacher in *Science*, 238, 491-497 (1987), describe adhesive proteins such as fibronectin, vitronectin, osteopontin, collagens, thrombospondin, fibrinogen, and von Willebrand factor that are present in extracellular matrices and in blood. The proteins contain the tripeptide arginine-glycine-aspartic acid (RGD) as their glycoprotein IIb/IIIa recognition site. These arginine-glycine-aspartic acid containing tripeptides are recognized by at least one member of a family of structurally related receptors, integrins, which are heterodimeric proteins with two membrane-spanning subunits. The authors state that the conformation of the tripeptide sequence in the individual proteins may be critical to recognition specificity.

Cheresh in *Proc. Nat'l Acad. Sci. U.S.A.*, 84, 6471-6475, (1987), describes an Arg-Gly-Asp directed adhesion receptor expressed by human endothelial cells that is structurally similar to the IIb/IIIa complex on platelets but is antigenically and functionally distinct. This receptor is directly involved in endothelial cell attachment to fibrinogen, von Willebrand factor, and vitronectin.

Pierschbacher and Rouslahti, in *J. of Biol. Chem.*, 262, (36), 17294-17298 (1987) hypothesized that the Arg-Gly-Asp sequence alone would be a sufficient signal for receptor recognition and binding and that, therefore, the conformation of the tri-peptide sequence would be determinative. Various synthetic peptides were produced and the authors concluded that the stereochemical conformation of Arg-Gly-Asp as influenced by enantiomeric substitutions or additions to this sequence significantly influenced receptor-ligand interaction. The authors further showed that cyclization of a decapeptide by forming a disulfide bridge between non-terminal residues Pen and Cys, rendered the peptide much less effective at inhibiting attachment to fibronectin.

In *Proc. Nat'l Acad. Sci. U.S.A.*, 81, 5985-5988 (1984), the same authors describe tetrapeptide variants of the cell recognition site of fibronectin that retain attachment-promoting activity. Peptides having a tetrapeptide recognition site are described in U.S. Pat. Nos. 4,589,881 and 4,614,517. A number of large polypeptide fragments in the cell-binding domain of fibronectin have cell-attachment activity. For example, see U.S. Pat. Nos. 4,517,686, 4,661,111 and U.S. Pat. No. 4,578,079.

Ruggeri *et al.*, *Proc. Nat'l Acad. Sci. U.S.A.*, 83, 5708-5712 (1986) explore a series of synthetic peptides designed in lengths to 16 residues, that contain RGD and a valine attached to the aspartic acid residue of RGD that inhibit fibrinogen binding to platelets. See also Koczewiak *et al.*, *Biochem.* 23, 1767-1774 (1984); Ginsberg *et al.*, *J. Biol. Chem.* 260(7), 3931-3936 (1985); and Haverstick *et al.*, *Blood* 66(4), 946-952 (1985). Other inhibitors are disclosed in Eur. Pat. App. Nos. 275,748 and 298,820.

A number of low molecular weight polypeptide factors have been isolated from snake venom. These factors apparently have high affinity for the GP IIb/IIIa complex. For example, Huang *et al.*, *J. Biol*

Chem., 262, 16157-16163 (1987); Huang *et al.*, *Biochemistry*, 28, 661-666 (1989) describe the primary structure of the venom trigramin which is a 72 amino acid polypeptide that contains the RGD subunit. Echistatin is another compound which has high affinity for the GP IIb/IIIa complex. This polypeptide contains 49 amino acids and has the RGD subunit and various disulfide bridges. Gan *et al.*, *J. Biol. Chem.*, 263, 19827-19832 (1988). See also, Dennis *et al.*, *Proc. Nat'l Acad. Sci. USA*, 87, 2471-2475 (1989). However, these snake venom factors also have high affinity for other members of the adhesive protein receptor family including the vitronectin and fibronectin receptors so are not selective for the GP IIb/IIIa complex.

While it is known that the tripeptide sequence Arg-Gly-Asp is present in certain polypeptides that can duplicate or inhibit the cell attachment-promoting effects of fibronectin and vitronectin, the tripeptide Arg-Gly-Asp has low activity. At present, there is little understanding of how other amino acids coupled to this sequence influence binding specificity. U.S. Patent No 5,023,233 discloses small cyclic hexapeptides which contain the sequence Arg-Gly-Asp and are useful platelet aggregation inhibitors. U.S. Patent No. 5,037,808 discloses the use of indolyl platelet-aggregation inhibitors which are believed to act by antagonizing interactions between fibrinogen and/or extracellular matrix proteins and the platelet GP IIb/IIIa receptor. U.S. Patent No. 5,037,808 discloses guanidino peptide mimetic compounds that retain an Asp residue which inhibit platelet aggregation. WO9014103 describes the use of antibody-poly-peptide conjugates wherein said polypeptides contain the Arg-Gly-Asp (RGD) sequence.

WO9111458 discloses the use of large cyclic peptides containing RGD flanked by proline residues which are platelet aggregation inhibitors. WO9101331 discloses small cyclic platelet aggregation inhibitors which are synthetic cyclic pentapeptides containing the tripeptide sequence Arg-Gly-Asp and a thioether linkage in the cycle. U.S. Patent No. 5,051,405 also discloses the use of peptides and pseudopeptides such as N-amidino-piperidine-3-carboxylglycyl-L-aspartyl-L-valine that inhibit platelet aggregation and thrombus formation in mammalian blood. EP 445 796 discloses linear compounds

which can include internal piperazinyl or piperidinyl derivatives. EP 437 367 discloses linear polypeptide fibrinogen receptor antagonists. U.S. Patent No. 5,256,812 discloses compounds of the R^1-A-$(W)_a$-X-$(CH_2)_b$-$(Y)_c$-B-Z-COOR wherein R^1 is a guanidino or amidino moiety and A and B are chosen from specific monosubstituted aryl or heterocyclic moieties. WO9412181 describes fibrinogen receptor antagonists such as biphenylcarboxamides.

While a multitude of compounds or peptide analogs believed to inhibit platelet aggregation by inhibiting binding to a blood platelet by fibrinogen are known, the present invention provides novel fibrinogen receptor antagonists that have significant binding activity and are, therefore, useful for the reasons stated herein. A number of very serious diseases and disorders involve hyperthrombotic complications which lead to intravascular thrombi and emboli. Myocardial infarction, stroke, phlebitis and a number of other serious conditions create the need for novel and effective fibrinogen receptor antagonists.

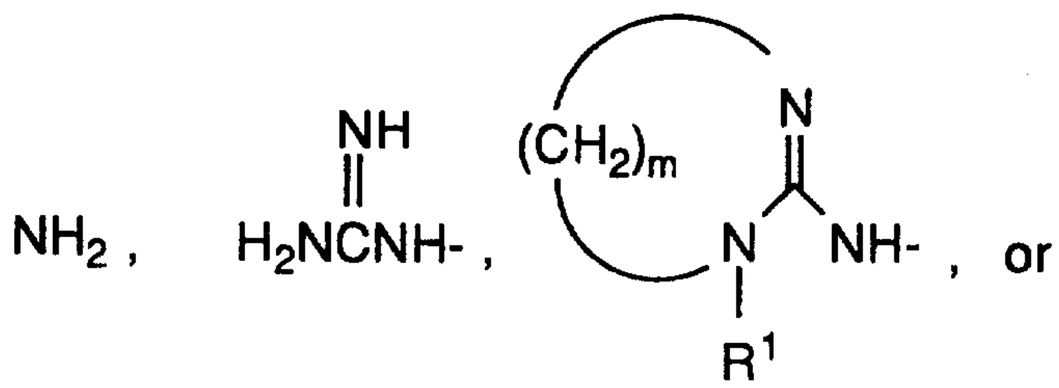
SUMMARY OF THE INVENTION

Compounds of this invention have the formula:

$$X\text{-}(CH_2)_n\text{-}C(O)NH\text{-}A\text{-}C(COOR^5)R^3R^4$$

or a pharmaceutically acceptable salt thereof, wherein

X is



a 5, 6 or 7 membered nonaromatic ring, having 1, 2 or 3 nitrogen atoms and either unsubstituted or monosubstituted on the carbon and nitrogen atoms with R^1, or disubstituted on the carbon and nitrogen atoms with R^1 and R^2, where R^1 and R^2 are independently selected from the group consisting of

hydrogen,
halogen,
$C_{1\text{-}10}$ alkyl,
$C_{3\text{-}8}$ cycloalkyl,
aryl,
aryl $C_{1\text{-}8}$ alkyl,
amino,
amino $C_{1\text{-}8}$ alkyl,
$C_{1\text{-}3}$ acylamino,
$C_{1\text{-}3}$ acylamino $C_{1\text{-}8}$ alkyl,
$C_{1\text{-}6}$ alkylamino $C_{1\text{-}8}$ alkyl,
$C_{1\text{-}6}$ alkylamino,
$C_{1\text{-}6}$ dialkylamino $C_{1\text{-}8}$ alkyl,
$C_{1\text{-}6}$ alkoxy,
$C_{1\text{-}6}$ alkoxy $C_{1\text{-}6}$ alkyl,
aryl $C_{1\text{-}6}$ alkyloxy,
aryl $C_{1\text{-}6}$ alkyloxy $C_{1\text{-}6}$ alkyl,

carboxy,
carboxy C_{1-6} alkyl,
C_{1-3} alkoxycarbonyl,
C_{1-3} alkoxycarbonyl C_{1-6} alkyl,
carboxy C_{1-6} alkyloxy,
hydroxy, and
hydroxy C_{1-6} alkyl;

m is 2, 3, 4, or 5;
n is an integer from 1 to 8;

A is

$-CH_2-$ or $-CH_2C(O)NHC(R^6R^7)-$;

R^5 is

hydrogen,
C_{1-8} alkyl,
aryl,
aryl C_{1-6} alkyl-,
C_{1-8} alkylcarbonyloxy C_{1-4} alkyl-, or
aryl C_{1-8} alkylcarbonyloxy C_{1-4} alkyl-.

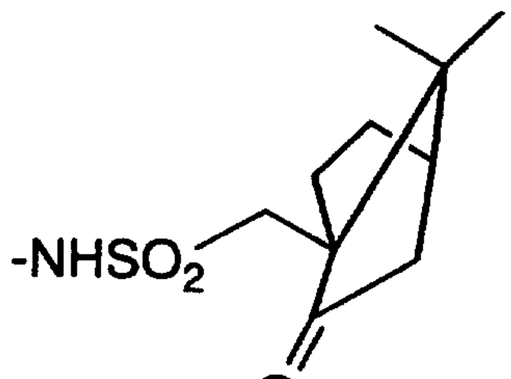
R^3 and R^4 are independently selected from the group consisting of

hydrogen,
fluoro,
hydroxy C_{1-6} alkyl-,
carboxy,
carboxy C_{1-6} alkyl-,
hydroxyl,
C_{1-6} alkyloxy-,
aryl C_{1-6}alkyloxy-,
C_{3-8} cycloalkyl-,
C_{1-8} alkyl,

aryl,
aryl C_{1-6} alkyl-,
C_{1-6} alkylcarbonyloxy-,
amino,
C_{1-6} alkylamino-,
amino C_{1-6} alkyl-,
C_{1-6} alkylamino C_{1-6} alkyl-,
arylamino-,
aryl C_{1-6} alkylamino-,
arylamino C_{1-6} alkyl-,
aryl C_{1-6} alkylamino C_{1-6} alkyl-,
amino C_{1-6} alkyl-,
C_{1-6} dialkylamino-,
C_{1-6} dialkylamino C_{1-6} alkyl-,
aminocarbonyloxy-,
aminocarbonyloxy C_{1-6} alkyl-,
C_{1-6} alkylaminocarbonyloxy-,
C_{1-6} alkylaminocarbonyloxy C_{1-6} alkyl-,
aryl aminocarbonyloxy-,
aryl aminocarbonyloxy C_{1-6} alkyl-,
aryl C_{1-6} alkylaminocarbonyloxy-,
aryl C_{1-6} alkylaminocarbonyloxy C_{1-6} alkyl-,
C_{1-8} alkylsulfonylamino-,
C_{1-8} alkylsulfonylamino C_{1-6} alkyl-,
aryl sulfonylamino-,
aryl sulfonylamino C_{1-6} alkyl-,
aryl C_{1-6} alkylsulfonylamino-,
aryl C_{1-6} alkylsulfonylamino C_{1-6} alkyl-,
C_{1-8} alkyloxycarbonylamino-,
C_{1-8} alkyloxycarbonylamino C_{1-8} alkyl-,
aryloxycarbonylamino-,
aryloxycarbonylamino C_{1-8} alkyl-,
aryl C_{1-8} alkyloxycarbonylamino-,
aryl C_{1-8} alkyloxycarbonylamino C_{1-8} alkyl-,
C_{1-8} alkylcarbonylamino-,

C_{1-8} alkylcarbonylamino C_{1-6} alkyl-,
arylcarbonylamino-,
arylcarbonylamino C_{1-6} alkyl-,
aryl C_{1-8} alkylcarbonylamino-,
aryl C_{1-8} alkylcarbonylamino C_{1-6} alkyl-,
aminocarbonylamino-,
aminocarbonylamino C_{1-6} alkyl-,
C_{1-8} alkylaminocarbonylamino-,
C_{1-8} alkylaminocarbonylamino C_{1-6} alkyl-,
arylaminocarbonylamino-,
arylaminocarbonylamino C_{1-6} alkyl-,
aryl C_{1-8} alkylaminocarbonylamino-,
aryl C_{1-8} alkylaminocarbonylamino C_{1-6} alkyl-,
aminosulfonylamino-,
aminosulfonylamino C_{1-6} alkyl-,
C_{1-8} alkylaminosulfonylamino-,
C_{1-8} alkylaminosulfonylamino C_{1-6} alkyl-,
arylaminosulfonylamino-,
arylaminosulfonylamino C_{1-6} alkyl-,
aryl C_{1-8} alkylaminosulfonylamino-,
aryl C_{1-8} alkylaminosulfonylamino C_{1-6} alkyl-,
C_{1-6} alkylsulfonyl-,
C_{1-6} alkylsulfonyl C_{1-6} alkyl-,
aryl C_{1-6} alkylsulfonyl-,
aryl C_{1-6} alkylsulfonyl C_{1-6} alkyl-,
C_{1-6} alkylcarbonyl-,
C_{1-6} alkylcarbonyl C_{1-6} alkyl-,
aryl C_{1-6} alkylcarbonyl-,
aryl C_{1-6} alkylcarbonyl C_{1-6} alkyl-,
aminocarbonyl-,
aminocarbonyl C_{1-8} alkyl-,
C_{1-8} alkylaminocarbonyl-,
C_{1-8} alkylaminocarbonyl C_{1-8} alkyl-,
arylaminocarbonyl-,

arylaminocarbonyl C_{1-8} alkyl-,
aryl C_{1-8} alkylaminocarbonyl-,
aryl C_{1-8} alkylaminocarbonyl C_{1-8} alkyl-,
aminosulfonyl-,
aminosulfonyl C_{1-8} alkyl-,
C_{1-8} alkylaminosulfonyl-,
C_{1-8} alkylaminosulfonyl C_{1-8} alkyl-,
arylaminosulfonyl-,
arylaminosulfonyl C_{1-8} alkyl-,
aryl C_{1-8} alkylaminosulfonyl-,
aryl C_{1-8} alkylaminosulfonyl C_{1-8} alkyl-,
C_{3-8} cycloalkylsulfonylamino-,
C_{1-8} alkyloxyarylsulfonylamino-,
thiophenylsulfonylamino-, and



; and

R^6 and R^7 are independently selected from
hydrogen,
halogen,
C_{1-10} alkyl,
C_{3-8} cycloalkyl,
aryl,
aryl C_{1-8} alkyl,
amino,
amino C_{1-8} alkyl,
C_{1-3} acylamino,
C_{1-3} acylamino C_{1-8} alkyl,
C_{1-6} alkylamino C_{1-8} alkyl,
C_{1-6} alkylamino,
C_{1-6} dialkylamino C_{1-8} alkyl,

C_{1-6} alkoxy,
C_{1-6} alkoxy C_{1-6} alkyl,
aryl C_{1-6} alkyloxy,
aryl C_{1-6} alkyloxy C_{1-6} alkyl,
carboxy,
carboxy C_{1-6} alkyl,
C_{1-3} alkoxycarbonyl,
C_{1-3} alkoxycarbonyl C_{1-6} alkyl,
carboxy C_{1-6} alkyloxy,
hydroxy, and
hydroxy C_{1-6} alkyl.

Compounds of the invention are useful for inhibiting the binding of fibrinogen to blood platelets and for inhibiting the aggregation of blood platelets. The above-mentioned compounds can be used in a method of acting upon a fibrinogen receptor which comprises administering a therapeutically effective amount of such compound to a mammal, preferably a human. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, dispersed therein, an effective amount of such compound is another feature of this invention. The use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting the binding of fibrinogen to blood platelets and for inhibiting the aggregation of blood platelets in a mammal.

DETAILED DESCRIPTION OF THE INVENTION

One class of compounds of the invention includes those having the formula

$$X\text{-}(CH_2)_n\text{-}C(O)NH\text{-}A\text{-}C(COOH)R^3R^4$$

or a pharmaceutically acceptable salt thereof, wherein

X is NH_2, or

a 6 membered nonaromatic ring having 2 nitrogen atoms and either unsubstituted or monosubstituted on the carbon and nitrogen atoms with R^1, or disubstituted on the carbon and nitrogen atoms with R^1 and R^2, where R^1 and R^2 are independently selected from the group consisting of

hydrogen,
halogen,
C_{1-10} alkyl,
C_{3-8} cycloalkyl,
aryl,
aryl C_{1-8} alkyl,
amino,
amino C_{1-8} alkyl,
C_{1-3} acylamino,
C_{1-3} acylamino C_{1-8} alkyl,
C_{1-6} alkylamino C_{1-8} alkyl,
C_{1-6} alkylamino,
C_{1-6} dialkylamino C_{1-8} alkyl,
C_{1-6} alkoxy,
C_{1-6} alkoxy C_{1-6} alkyl,
aryl C_{1-6} alkyloxy,
aryl C_{1-6} alkyloxy C_{1-6} alkyl,
carboxy,
carboxy C_{1-6} alkyl,
C_{1-3} alkoxycarbonyl,
C_{1-3} alkoxycarbonyl C_{1-6} alkyl,
carboxy C_{1-6} alkyloxy,
hydroxy, and
hydroxy C_{1-6} alkyl;

n is an integer from 1 to 8;

A is

$-CH_2-$ or $-CH_2C(O)NHCH_2-$;

R^3 and R^4 are independently selected from the group consisting of

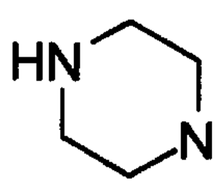
hydrogen,
aryl sulfonylamino-,
aryl sulfonylamino C_{1-6} alkyl-,
aryl C_{1-6} alkylsulfonylamino-, and
aryl C_{1-6} alkylsulfonylamino C_{1-6} alkyl-.

A group of this class of compounds includes those having the formula

$$X\text{-}(CH_2)_n\text{-}C(O)NH\text{-}A\text{-}CH(COOH)(NHSO_2Ph)$$

or a pharmaceutically acceptable salt thereof, wherein

X is



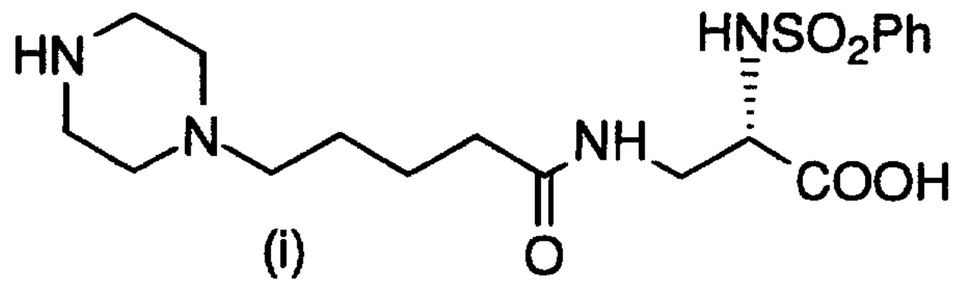
or NH_2;

n is 3, 4, 5, or 6;

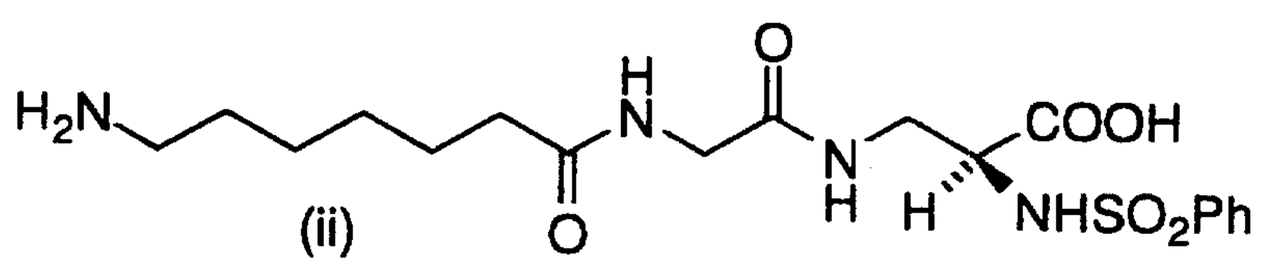
A is

CH_2 or $CH_2C(O)NHCH_2$.

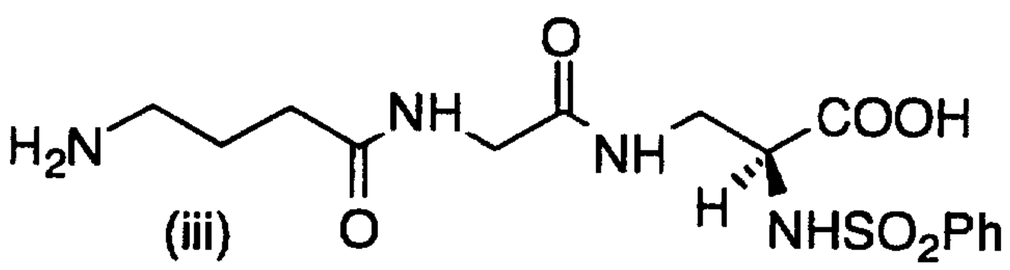
A subgroup of this group of compounds of the invention, includes those consisting essentially of



(i) ,



(ii) , and



(iii) .

or a pharmaceutically acceptable salt thereof.

One test which is used to evaluate fibrinogen receptor antagonist activity is based on evaluation of inhibition of ADP-stimulated platelets. Aggregation requires that fibrinogen bind to and occupy the platelet fibrinogen receptor site. Inhibitors of fibrinogen binding inhibit aggregation. In the ADP-stimulated platelet aggregation assay used to determine inhibition associated with the compounds claimed in the instant invention, human platelets are isolated from fresh blood, collected into acid citrate/dextrose by differential centrifugation followed by gel filtration on Sepharose 2B in divalent ion-free Tyrode's buffer (pH 7.4) containing 2% bovine serum albumin.

Platelet aggregation is measured at 37°C in a Chronolog aggregometer. The reaction mixture contains gel-filtered human platelets (2 x 10^8 per ml), fibrinogen (100 micrograms per ml (μg/ml)), Ca^{2+} (1 mM), and the compound to be tested. The aggregation is initiated by adding 10 mM ADP 1 minute after the other components are added. The reaction is then allowed to proceed for at least 2 minutes. The extent of inhibition of aggregation is expressed as the percentage of the rate of aggregation observed in the absence of inhibitor. The IC_{50} is

the dose of a particular compound inhibiting aggregation by 50% relative to a control lacking the compound.

Compounds i, ii, and iii shown above were tested and found to have an IC_{50} of less than 5000 nM.

The term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following salts: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, valerate.

Compounds of the present invention are chiral; included within the scope of the present invention are racemic mixtures and separated enantiomers of the general formula. Furthermore, all diastereomers, including E, Z isomers, of the general formula are included in the present scope. Furthermore, hydrates as well as anhydrous compositions and polymorphs of the general formula are within the present invention.

Prodrugs, such as ester derivatives of described compounds, are compound derivatives which, when absorbed into the bloodstream of a warm-blooded animal, cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

The term "therapeutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system or animal that is being sought by a researcher or clinician. The term "anti-coagulant" shall

include heparin, and warfarin. The term "thrombolytic agent" shall include agents such as streptokinase and tissue plasminogen activator. The term "platelet anti-aggregation agent" shall include agents such as aspirin and dipyridamole.

The term "alkyl" means straight or branched alkane containing 1 to about 10 carbon atoms, e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexy, octyl radicals and the like, straight or branched alkene containing 2 to about 10 carbon atoms, e.g., propylenyl, buten-1-yl, isobutenyl, pentenylen-1-yl, 2,2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, hepten-1-yl, and octen-1-yl radicals and the like, or straight or branched alkyne containing 2 to about 10 carbon atoms, e.g., ethynyl, propynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals and the like.

The term "aryl" means a 5- or 6-membered aromatic ring containing 0, 1, or 2 heteroatoms selected from O, N, and S, e.g., phenyl, pyridine, pyrimidine, imidazole, thiophene, oxazole, isoxazole, and thiazole.

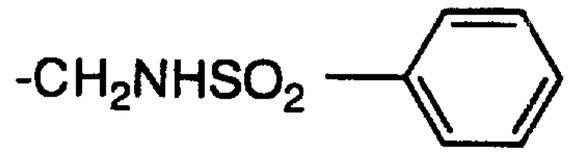
The terms "alkyloxy" or "alkoxy" include an alkyl portion where alkyl is as defined above, e.g., methyloxy, propyloxy, and butyloxy.

The terms "arylalkyl" and "alkylaryl" include an alkyl portion where alkyl is as defined above and to include an aryl portion where aryl is as defined above. The C_{1-n} designation where n may be an integer from 1-10 or 2-10 respectively refers to the alkyl component of the arylalkyl or alkylaryl unit. Examples of arylalkyl include benzyl, fluorobenzyl, chlorobenzyl, phenylethyl, phenylpropyl, fluorophenylethyl, chlorophenylethyl, thienylmethyl, thienylethyl, and thienylpropyl. Examples of alkylaryl include toluene, ethylbenzene, propylbenzene, methylpyridine, ethylpyridine, propylpyridine, butylpyridine, butenylpyridine, and pentenylpyridine.

The term "halogen" includes fluorine, chlorine, iodine and bromine.

The term "oxy" means an oxygen (O) atom. The term "thio" means a sulfur (S) atom.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first followed by the adjacent functionality toward the point of attachment. For example, a methylene group substituted with benzenesulfonylamino is equivalent to



In the schemes and examples below, various reagent symbols have the following meanings:

BOC (or Boc):	t-butyloxycarbonyl
Pd-C:	Palladium on activated carbon catalyst
DMF:	Dimethylformamide
DMSO:	Dimethylsulfoxide
CBZ:	Carbobenzyloxy
CH_2Cl_2:	Methylene chloride
$CHCl_3$:	chloroform
BOP:	Benzotriazol-1-yloxytris(dimethylamino)phosphonium, hexafluorophosphate
EDC:	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Oxone:	Potassium peroxymonosulfate
LDA:	Lithium diisopropylamide

The compounds of the present invention can be administered in such oral forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Likewise, they may be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an anti-aggregation agent.

Compounds of the invention may be administered to patients where prevention of thrombosis by inhibiting binding of fibrinogen to the platelet membrane glycoprotein complex IIb/IIIa receptor is desired. They are useful in surgery on peripheral arteries (arterial grafts, carotid endarterectomy) and in cardiovascular surgery where manipulation of arteries and organs, and/or the interaction of platelets with artificial surfaces, leads to platelet aggregation and consumption. The aggregated platelets may form thrombi and thromboemboli. Compounds of this invention may be administered to these surgical patients to prevent the formation of thrombi and thromboemboli.

Extracorporeal circulation is routinely used for cardiovascular surgery in order to oxygenate blood. Platelets adhere to surfaces of the extracorporeal circuit. Adhesion is dependent on the interaction between GP IIb/IIIa on the platelet membranes and fibrinogen adsorbed to the surface of the circuit. (Gluszko *et al., Amer. J. Physiol.,* 252(H), 615-621 (1987)). Platelets released from artificial surfaces show impaired hemostatic function. Compounds of the invention may be administered to prevent adhesion.

Other applications of these compounds include prevention of platelet thrombosis, thromboembolism and reocclusion during and after thrombolytic therapy and prevention of platelet thrombosis, thromboembolism and reocclusion after angioplasty or coronary artery bypass procedures. They may also be used to prevent myocardial infarction.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 300 mg/kg/day and preferably 0.01-100 mg/kg/day and most preferably 0.01-20 mg/kg/day. Typically, oral dosages for an adult patient are, for example, 1 mg, 10 mg or 100 mg. Intravenously, doses of compounds of the invention will range from about 0.001 μg/kg/minute and 1 mg/kg/minute, during a constant rate of infusion, e.g., 0.1, 0.15, and 0.2 μg/kg/minute. In order to administer such amounts of tirofiban, an intravenous composition having 0.05 mg/ml of active ingredient can be administered at rates of 0.002, 0.003 or 0.004 ml/kg/min, respectively. Compositions of the invention containing higher concentrations of active ingredients should be administered at correspondingly lower rates.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with convention pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn-sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium

benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch methyl cellulose, agar, bentonite, xanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

The compounds of the present invention can also be co-administered with suitable anticoagulation agents or thrombolytic agents such as plasminogen activators or streptokinase in the treatment of various vascular pathologies. They may also be combined with heparin, aspirin, or warfarin. Coadministration includes administration together or separately in order to achieve beneficial thrombosis prevention or thrombolysis.

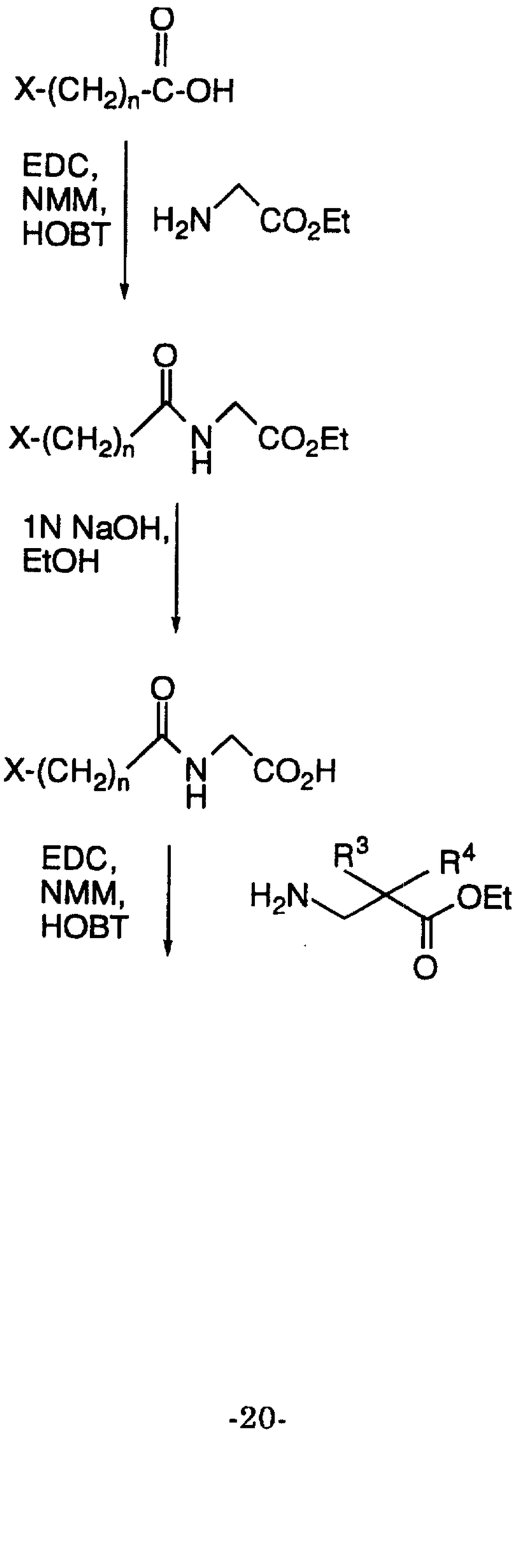
Furthermore, compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage

administration will, or course, be continuous rather that intermittent throughout the dosage regime.

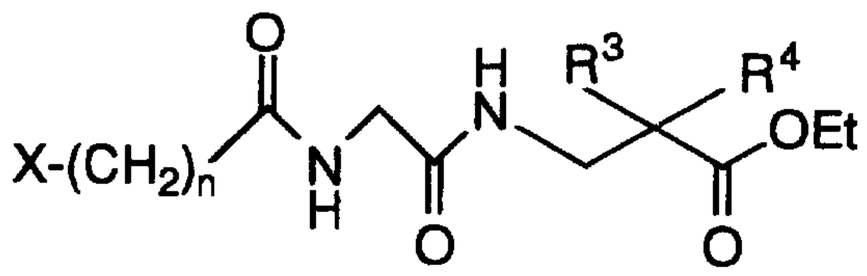
Compounds of the invention may be prepared according to the general synthetic procedures outlined below:

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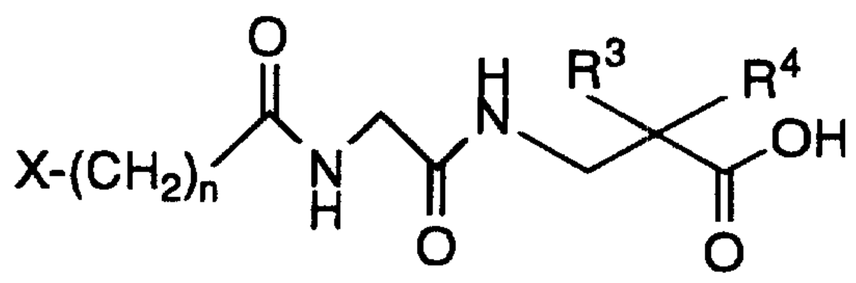
Scheme 1



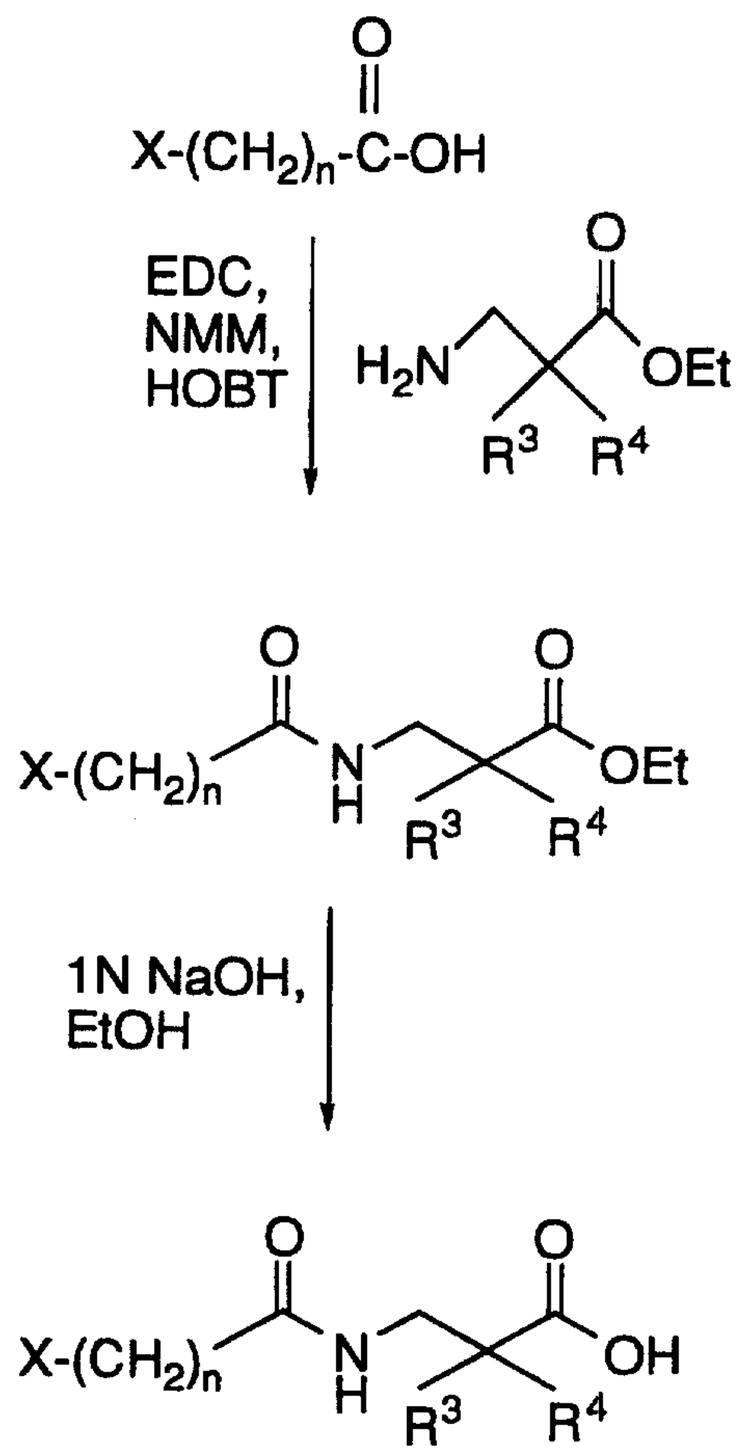
Scheme 1 (continued)



1N NaOH,
EtOH

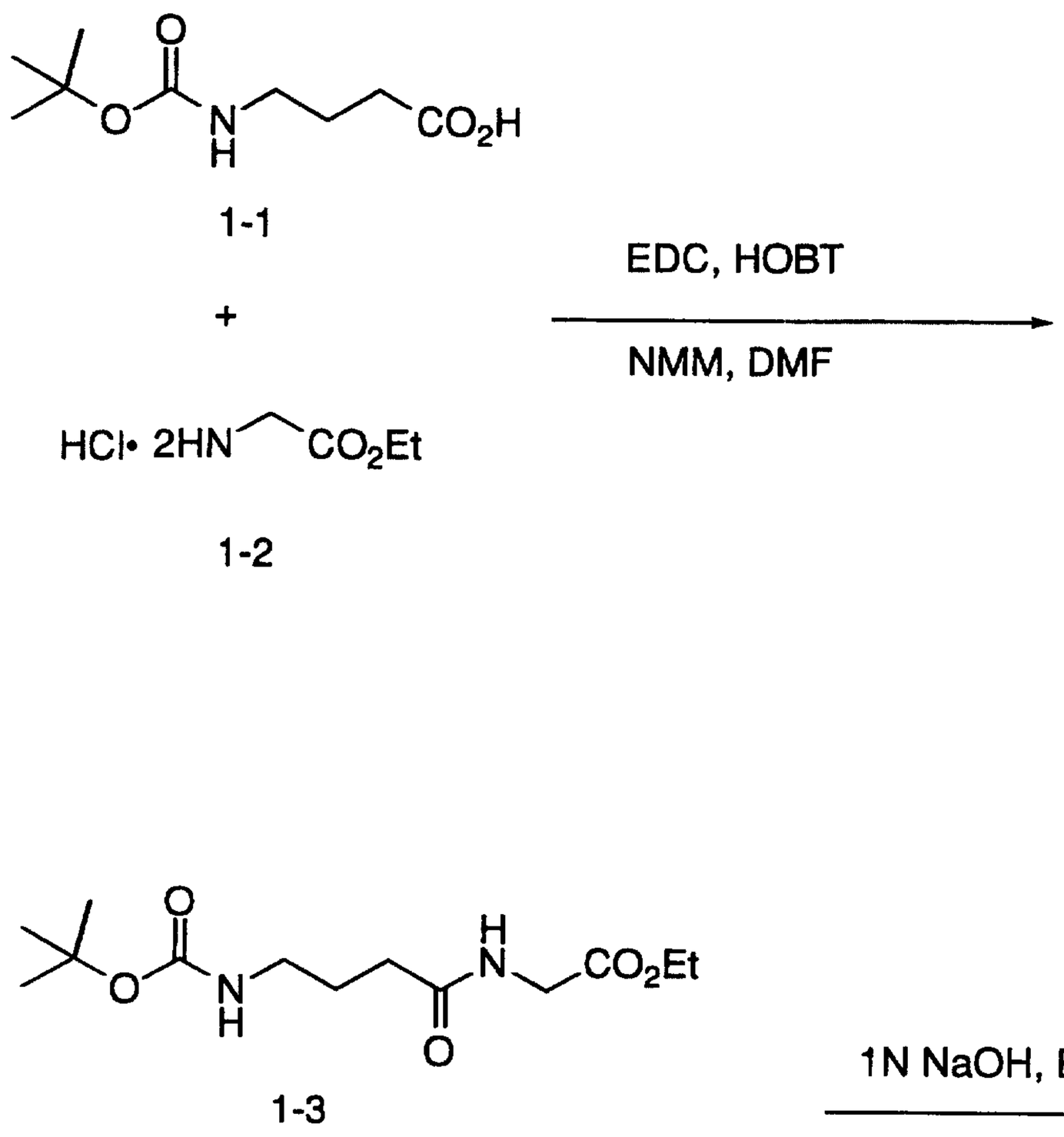


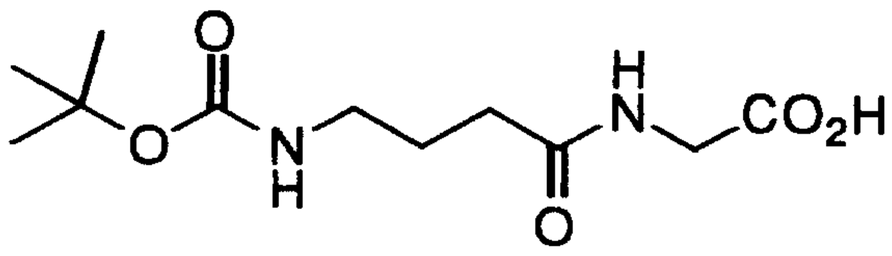
Scheme 2



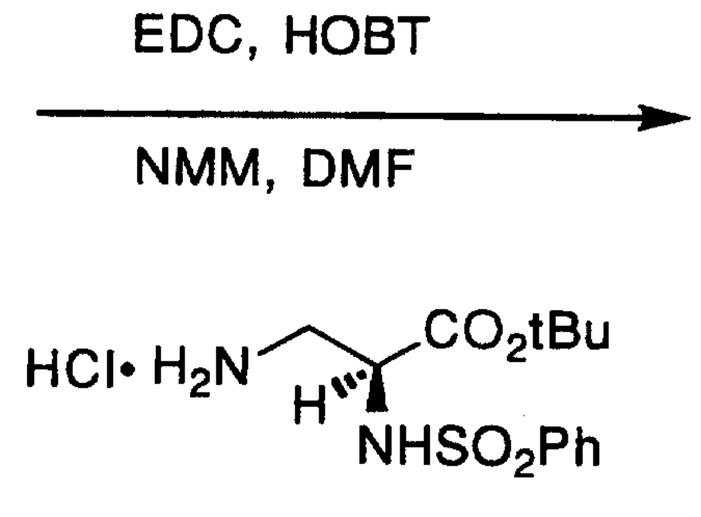
Novel compounds of the present invention were prepared according to the procedures shown below which illustrate the general synthetic procedures in Scheme 1 and Scheme 2.

EXAMPLE 1

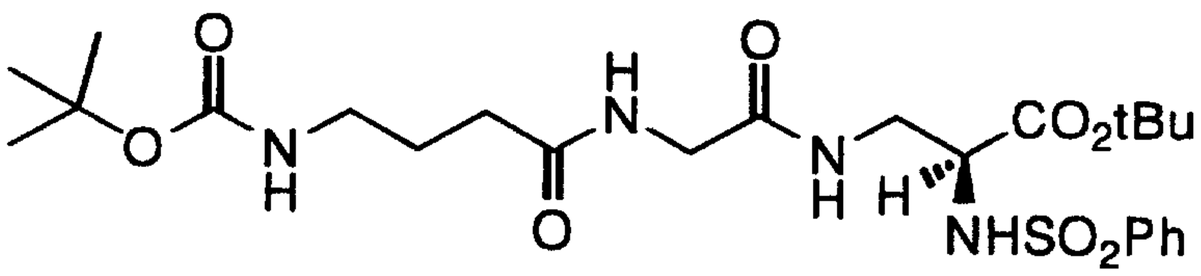

O
O
N
H
CO2H
1-1
+
EDC, HOBT
NMM, DMF
HCl• 2HN
CO2Et
1-2
O
O
N
H
H
N
CO2Et
O
1-3
1N NaOH, EtOH



1-4

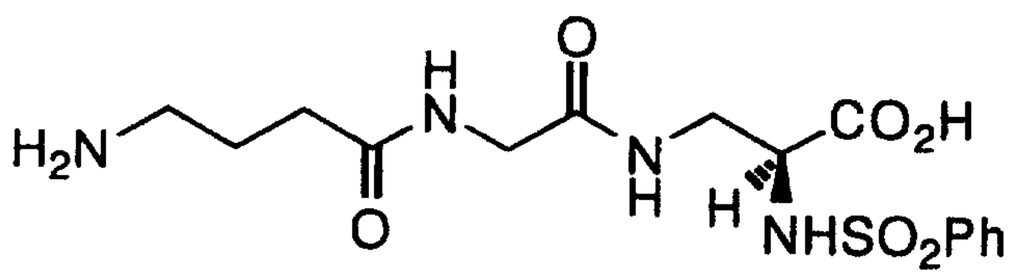


1-5



1-6





1-7

(4-*tert*-Butoxycarbonylamino-butyrylamino)-acetic acid ethyl ester (1-3)

A mixture of 1-2 (1 g, 4.93 mmol), 1-2 (687 mg, 4.93 mmol), EDC (1.89 g, 9.86 mmol), HOBT (800 g, 5.92 mmol) and NMM (2.71 mL, 24.65 mmol) in DMF (24 mL) was stirred for 20 h. The mixture was diluted with EtOAc, washed with H_2O, sat. $NaHCO_3$, 10% KHSO brine, and dried over $MgSO_4$. Following evaporative removal of the solvent, the

residue was chromatographed (silica, 80% EtOAc/hexane) to give 1-3 as a white solid.
TLC R_f = 0.46 (silica, EtOAc).
^{1}H NMR (300 MHz, CDCl3) δ 6.61 (bd, 1H), 4.77 (bd, 1H), 4.22 (q, 2H, J=7.3 Hz), 4.03 (d, 2H, J=5.3 Hz), 3.21 (m, 2H), 2.29 (t, 2H, J=7.1 Hz), 1.83 (m, 2H), 1.44 (s, 9H), 1.25 (t, 3H, J=7.1 Hz).

(4-*tert*-Butoxycarbonylamino-butyrylamino)-acetic acid 1-4

To a solution 1-3 (1 g, 3.47 mmol) in EtOH (20 mL) was added 1N NaOH (5.2 mL, 5.2 mmol). After stirring for 1 h, the solvents were evaporated, the mixture was diluted with EtOAc, acidified with 10% $KHSO_4$, washed with brine, dried over $MgSO_4$, and evaporated to give 1-4 as a white solid.
TLC Rf = 0.48 (silica,9.5/0.5/0.5 CH_2Cl_2/MeOH/AcOH)
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (bs, 1H), 6.54 (bs, 1H), 4.14 (m, 2H), 3.18 (m, 2H), 2.30 (m, 2H), 1.85 (m, 2H), 1.44 (d, 9H, J=11 Hz).

2(S)-Benzenesulfonylamino-3-[2-(4-*tert*-butoxycarbonylamino-butyrylamino)-acetylaminol-propionic acid *tert*-butyl ester (1-6)

A mixture of 1-4 (290 mg, 1.11 mmol), 1-5 (375 mg, 1.11 mmol), EDC (425 mg, 2.22 mmol), HOBT (180 mg, 1.33 mmol) and NMM (0.73 mL, 6.66 mmol) in DMF (5 mL) was stirred for 20 h. The mixture was diluted with EtOAc, washed with H_2O, sat. $NaHCO_3$, 10% $KHSO_4$ brine, and dried over $MgSO_4$. Following evaporative removal of the solvent, the residue was chromatographed (silica, EtOAc) to give 1-6 as a clear oil.
TLC R_f = 0.36 (silica, EtOAc).
^{1}H NMR (300 MHz, CDCl3) δ 7.85 (d, 2H, J=7 Hz), 7.55 (m, 3H), 6.98 (bs, 1H), 6.62 (bs, 1H), 5.76 (bd, 1H), 4.83 (s, 1H), 3.95 (m, 3H), 3.66 (m, 1H), 3.41 (m, 1H), 3.20 (m, 2H), 2.33 (t, 2H, J=7 Hz), 1.86(m, 2H), 1.62 (s, 9H), 1.44 (s, 9H).

3-[2-(4-Amino-butyrylamino)-acetylamino]-2(S)-benzenesulfonyl-aminopropionic acid (1-7)

To a solution of 1-6 in CH_2Cl_2 (1.5 mL) was added TFA (1.5 mL). The reaction was stirred for 6h. Following evaporative removal of the solvent, the residue was chromatographed (silica, 10/1/1: EtOH, NH_4OH, H_2O) to give 1-7 as a white solid.

TLC R_f = 0.23 (silica, 10/1/1: EtOH, NH_4OH, H_2O).

^1H NMR (300 MHz, D_2O) δ 7.84 (m, 2H), 7.64 (m, 3H), 3.79 (m, 3H), 3.53 (m, 2H), 3.04 (t, 2H, J=8 Hz), 2.46 (t, 2H, J=8 Hz), 1.97 (m, 2H).

EXAMPLE 2

Tablet Preparation

Tablets containing 25.0, 50.0, and 100.0 mg., respectively, of the active compound 3-[2-(4-Amino-butyrylamino)-acetylamino]-2(S)-benzenesulfonylamino-propionic acid (1-7) are prepared as illustrated below:

TABLE FOR DOSES CONTAINING
FROM 25-100MG OF THE ACTIVE COMPOUND

	Amount-mg		
Active Compound (1-7)	25.0	50.0	100.0
Microcrystalline cellulose	37.25	100.0	200.0
Modified food corn starch	37.25	4.25	8.5
Magnesium stearate	0.50	0.75	1.5

All of the active compound, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 25.0, 50.0, and 100.0 mg, respectively, of active ingredient per tablet.

EXAMPLE 3

Intravenous formulations

An intravenous dosage form of the above-indicated active compound is prepared as follows:

Active Compound (1-7)	0.5-10.0mg
Sodium Citrate	5-50mg
Citric Acid	1-15mg
Sodium Chloride	1-8mg
Water for Injection (USP)	q.s. to 1 L

Utilizing the above quantities, the active compound is dissolved at room temperature in a previously prepared solution of sodium chloride, citric acid, and sodium citrate in Water for Injection (USP, see page 1636 of United States Pharmacopeia/National Formulary for 1995, published by United States Pharmacopeial Convention, Inc., Rockville, Maryland, copyright 1994.

EXAMPLE 4

Intravenous formulation

A pharmaceutical composition was prepared at room temperature using 3-[2-(4-amino-butyrylamino)-acetylamino]-2(S)-benzenesulfonylamino-propionic acid, a citrate buffer, and sodium chloride, to obtain a concentration of 0.25 mg/ml.

800 grams of water was introduced into a standard pharmaceutical mixing vessel. 0.25 grams of 3-[2-(4-amino-butyrylamino)-acetylamino]-2(S)-benzenesulfonylamino-propionic acid was dissolved in the water. 2.7 grams sodium citrate and 0.16 grams citric acid were added to obtain a finished citrate concentration of 10 mM. 8 grams of sodium chloride was added. 200 grams of water was then added to achieve the desired final concentrations of ingredients. The resulting aqueous formulation had the following concentrations:

Ingredient	Amount
3-[2-(4-amino-butyrylamino)-acetylamino]-2(S)-benzenesulfonylamino-propionic acid	0.25 mg/ml
citrate buffer	10 mM
sodium chloride	8 mg/ml

The finished concentrated formulation is stored in a standard USP Type I borosilicate glass container at 30-40 degrees C. Prior to compound administration, the concentrated formulation is diluted in a 4:1 ratio resulting in a finished concentration of 0.05 mg/ml and transferred to an infusion bag.

Therapeutic Treatment

Compounds of the invention may be administered to patients where inhibition of human or mammalian platelet aggregation or adhesion is desired.

Compounds of the invention are useful in inhibiting platelet aggregation and thus, they may find utility in surgery on peripheral

arteries (arterial grafts, carotid endaterectomy) and in cardiovascular surgery where manipulation of arteries and organs, and/or the interaction of platelets with artificial surfaces, leads to platelet aggregation and consumption. The aggregated platelets may form thrombi and thromboemboli. Compounds of the invention may be administered to these surgical patients to prevent the formation of thrombi and thromboemboli.

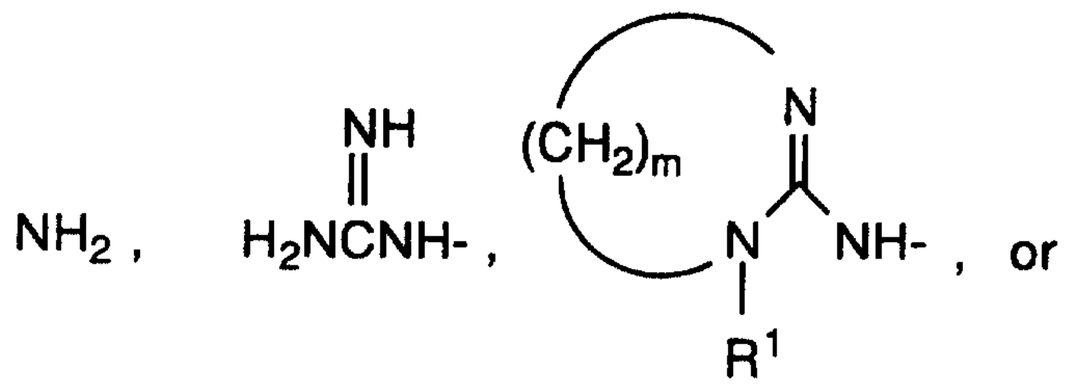
WHAT IS CLAIMED IS:

1. A compound having the structure

$$X\text{-}(CH_2)_n\text{-}C(O)NH\text{-}A\text{-}C(COOR^5)R^3R^4$$

or a pharmaceutically acceptable salt thereof, wherein

X is



a 5, 6 or 7 membered nonaromatic ring, having 1, 2 or 3 nitrogen atoms and either unsubstituted or monosubstituted on the carbon and nitrogen atoms with R^1, or disubstituted on the carbon and nitrogen atoms with R^1 and R^2, where R^1 and R^2 are independently selected from the group consisting of

hydrogen,
halogen,
$C_{1\text{-}10}$ alkyl,
$C_{3\text{-}8}$ cycloalkyl,
aryl,
aryl $C_{1\text{-}8}$ alkyl,
amino,
amino $C_{1\text{-}8}$ alkyl,
$C_{1\text{-}3}$ acylamino,
$C_{1\text{-}3}$ acylamino $C_{1\text{-}8}$ alkyl,
$C_{1\text{-}6}$ alkylamino $C_{1\text{-}8}$ alkyl,
$C_{1\text{-}6}$ alkylamino,
$C_{1\text{-}6}$ dialkylamino $C_{1\text{-}8}$ alkyl,
$C_{1\text{-}6}$ alkoxy,
$C_{1\text{-}6}$ alkoxy $C_{1\text{-}6}$ alkyl,
aryl $C_{1\text{-}6}$ alkyloxy,

aryl C_{1-6} alkyloxy C_{1-6} alkyl,
carboxy,
carboxy C_{1-6} alkyl,
C_{1-3} alkoxycarbonyl,
C_{1-3} alkoxycarbonyl C_{1-6} alkyl,
carboxy C_{1-6} alkyloxy,
hydroxy, and
hydroxy C_{1-6} alkyl;

m is 2, 3, 4, or 5;
n is an integer from 1 to 8;

A is

$-CH_2-$ or $-CH_2C(O)NHC(R^6R^7)-$;

R^5 is

hydrogen,
C_{1-8} alkyl,
aryl,
aryl C_{1-6} alkyl-,
C_{1-8} alkylcarbonyloxy C_{1-4} alkyl-, or
aryl C_{1-8} alkylcarbonyloxy C_{1-4} alkyl-.

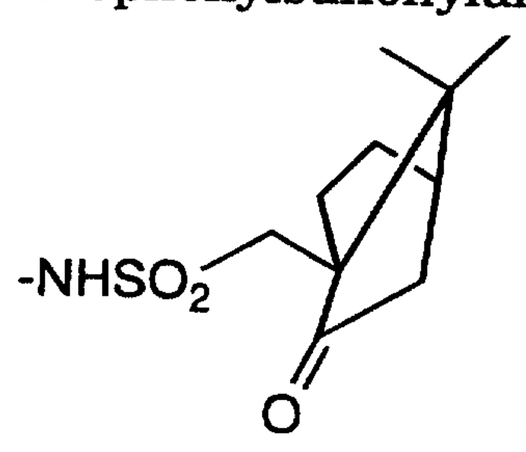
R^3 and R^4 are independently selected from the group consisting of

hydrogen,
fluoro,
hydroxy C_{1-6} alkyl-,
carboxy,
carboxy C_{1-6} alkyl-,
hydroxyl,
C_{1-6} alkyloxy-,
aryl C_{1-6}alkyloxy-,
C_{3-8} cycloalkyl-,

C_{1-8} alkyl,
aryl,
aryl C_{1-6} alkyl-,
C_{1-6} alkylcarbonyloxy-,
amino,
C_{1-6} alkylamino-,
amino C_{1-6} alkyl-,
C_{1-6} alkylamino C_{1-6} alkyl-,
arylamino-,
aryl C_{1-6} alkylamino-,
arylamino C_{1-6} alkyl-,
aryl C_{1-6} alkylamino C_{1-6} alkyl-,
amino C_{1-6} alkyl-,
C_{1-6} dialkylamino-,
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aryl aminocarbonyloxy C_{1-6} alkyl-,
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aryl C_{1-6} alkylaminocarbonyloxy C_{1-6} alkyl-,
C_{1-8} alkylsulfonylamino-,
C_{1-8} alkylsulfonylamino C_{1-6} alkyl-,
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C_{1-8} alkylaminosulfonylamino C_{1-6} alkyl-,
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arylaminosulfonylamino C_{1-6} alkyl-,
aryl C_{1-8} alkylaminosulfonylamino-,
aryl C_{1-8} alkylaminosulfonylamino C_{1-6} alkyl-,
C_{1-6} alkylsulfonyl-,
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aryl C_{1-6} alkylsulfonyl C_{1-6} alkyl-,
C_{1-6} alkylcarbonyl-,
C_{1-6} alkylcarbonyl C_{1-6} alkyl-,
aryl C_{1-6} alkylcarbonyl-,
aryl C_{1-6} alkylcarbonyl C_{1-6} alkyl-,
aminocarbonyl-,
aminocarbonyl C_{1-8} alkyl-,
C_{1-8} alkylaminocarbonyl-,

C_{1-8} alkylaminocarbonyl C_{1-8} alkyl-,
arylaminocarbonyl-,
arylaminocarbonyl C_{1-8} alkyl-,
aryl C_{1-8} alkylaminocarbonyl-,
aryl C_{1-8} alkylaminocarbonyl C_{1-8} alkyl-,
aminosulfonyl-,
aminosulfonyl C_{1-8} alkyl-,
C_{1-8} alkylaminosulfonyl-,
C_{1-8} alkylaminosulfonyl C_{1-8} alkyl-,
arylaminosulfonyl-,
arylaminosulfonyl C_{1-8} alkyl-,
aryl C_{1-8} alkylaminosulfonyl-,
aryl C_{1-8} alkylaminosulfonyl C_{1-8} alkyl-,
C_{3-8} cycloalkylsulfonylamino-,
C_{1-8} alkyloxyarylsulfonylamino-,
thiophenylsulfonylamino-, and



; and

R^6 and R^7 are independently selected from
hydrogen,
halogen,
C_{1-10} alkyl,
C_{3-8} cycloalkyl,
aryl,
aryl C_{1-8} alkyl,
amino,
amino C_{1-8} alkyl,
C_{1-3} acylamino,
C_{1-3} acylamino C_{1-8} alkyl,
C_{1-6} alkylamino C_{1-8} alkyl,

C_{1-6} alkylamino,
C_{1-6} dialkylamino C_{1-8} alkyl,
C_{1-6} alkoxy,
C_{1-6} alkoxy C_{1-6} alkyl,
aryl C_{1-6} alkyloxy,
aryl C_{1-6} alkyloxy C_{1-6} alkyl,
carboxy,
carboxy C_{1-6} alkyl,
C_{1-3} alkoxycarbonyl,
C_{1-3} alkoxycarbonyl C_{1-6} alkyl,
carboxy C_{1-6} alkyloxy,
hydroxy, and
hydroxy C_{1-6} alkyl.

2. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

$$X\text{-}(CH_2)_n\text{-}C(O)NH\text{-}A\text{-}C(COOH)R^3R^4$$

or a pharmaceutically acceptable salt thereof, wherein

X is NH_2, or

a 6 membered nonaromatic ring having 2 nitrogen atoms and either unsubstituted or monosubstituted on the carbon and nitrogen atoms with R^1, or disubstituted on the carbon and nitrogen atoms with R^1 and R^2, where R^1 and R^2 are independently selected from the group consisting of
hydrogen,
halogen,
C_{1-10} alkyl,
C_{3-8} cycloalkyl,
aryl,
aryl C_{1-8} alkyl,
amino,

amino C_{1-8} alkyl,
C_{1-3} acylamino,
C_{1-3} acylamino C_{1-8} alkyl,
C_{1-6} alkylamino C_{1-8} alkyl,
C_{1-6} alkylamino,
C_{1-6} dialkylamino C_{1-8} alkyl,
C_{1-6} alkoxy,
C_{1-6} alkoxy C_{1-6} alkyl,
aryl C_{1-6} alkyloxy,
aryl C_{1-6} alkyloxy C_{1-6} alkyl,
carboxy,
carboxy C_{1-6} alkyl,
C_{1-3} alkoxycarbonyl,
C_{1-3} alkoxycarbonyl C_{1-6} alkyl,
carboxy C_{1-6} alkyloxy,
hydroxy, and
hydroxy C_{1-6} alkyl;

n is an integer from 1 to 8;

A is

$-CH_2-$ or $-CH_2C(O)NHCH_2-$;

R^3 and R^4 are independently selected from the group consisting of

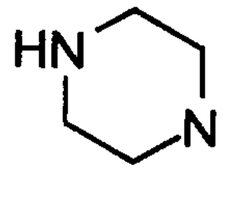
hydrogen,
aryl sulfonylamino-,
aryl sulfonylamino C_{1-6} alkyl-,
aryl C_{1-6} alkylsulfonylamino-, and
aryl C_{1-6} alkylsulfonylamino C_{1-6} alkyl-.

3. A compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein

$$X\text{-}(CH_2)_n\text{-}C(O)NH\text{-}A\text{-}CH(COOH)(NHSO_2Ph)$$

or a pharmaceutically acceptable salt thereof, wherein

X is



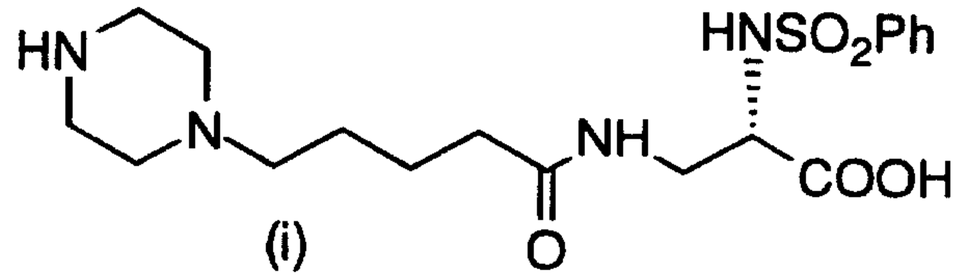
or NH_2;

n is 3, 4, 5, or 6;

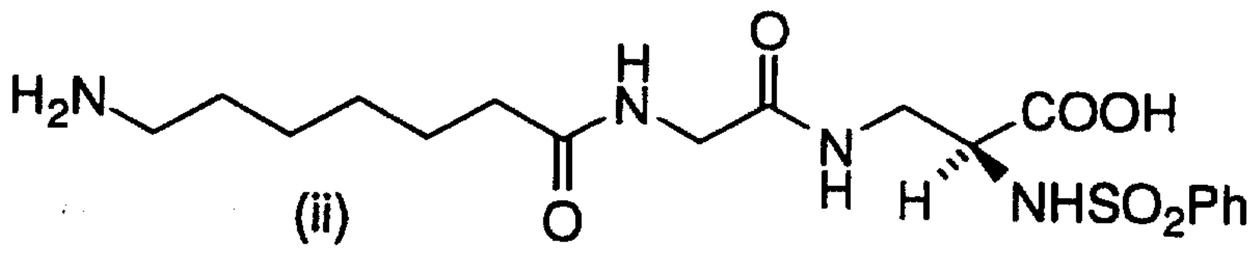
A is

CH_2 or $CH_2C(O)NHCH_2$.

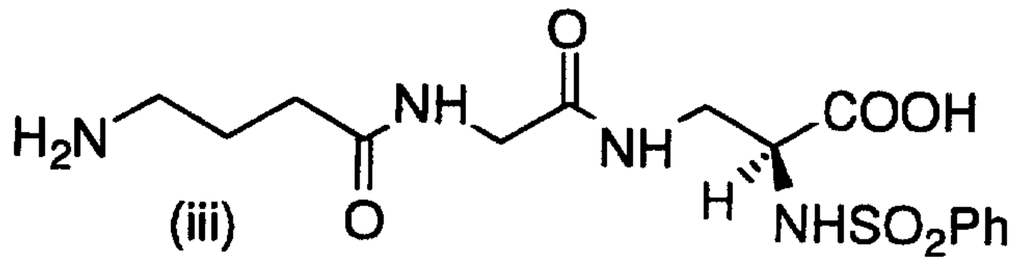
4. A compound of claim 3, or a pharmaceutically acceptable salt thereof, selected from the group consisting of



(i) ,



(ii) , and



(iii) .

5. A compound of Claim 1 for use in inhibiting the binding of fibrinogen to blood platelets, inhibiting the aggregation of

blood platelets, treating thrombus formation or embolus formation, or preventing thrombus or embolus formation in a mammal.

6. A composition for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising a therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

7. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising treating the mammal with a therapeutically effective amount of a composition of Claim 6.

8. A method for inhibiting the aggregation of blood platelets in a mammal, by blocking fibrinogen from acting at its receptor site, comprising treating the mammal with a therapeutically effective amount of a composition of Claim 6.

9. A composition for inhibiting the aggregation of blood platelets in a mammal, by blocking fibrinogen from acting at its receptor site, comprising a therapeutically effective amount of a compound of Claim 1 in combination with a thrombolytic agent and a pharmaceutically acceptable carrier.

10. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising treating the mammal with a therapeutically effective amount of a composition of Claim 9.

11. A method for inhibiting the aggregation of blood platelets in a mammal, by blocking fibrinogen from acting at its receptor site, comprising treating the mammal with a therapeutically effective amount of a composition of Claim 9.

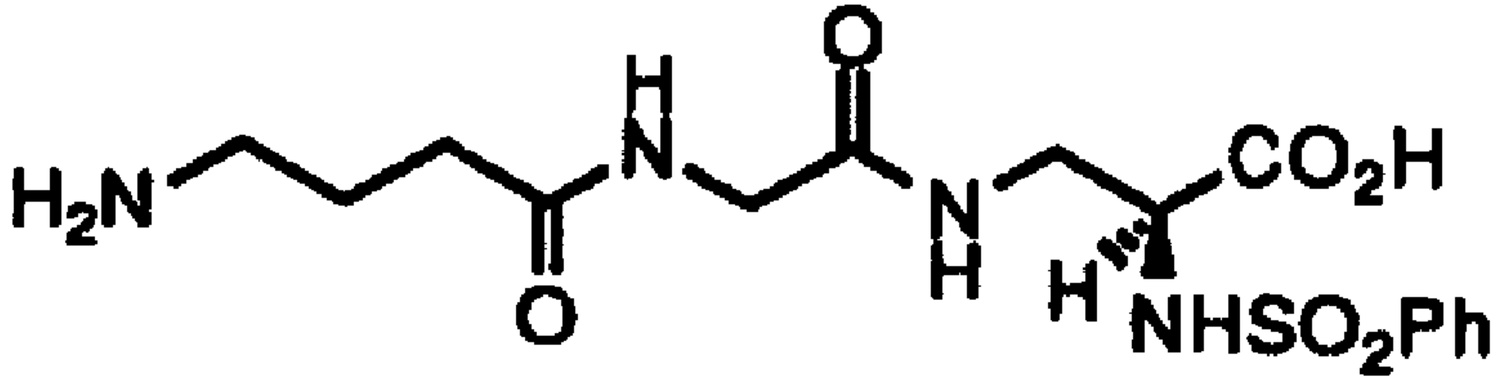
12. A composition for inhibiting the aggregation of blood platelets in a mammal, by blocking fibrinogen from acting at its receptor site, comprising a therapeutically effective amount of a compound of

Claim 1 in combination with an anticoagulant agent and pharmaceutically acceptable carrier.

13. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising treating the mammal with a therapeutically effective amount of a composition of Claim 12.

14. A method for inhibiting the aggregation of blood platelets in a mammal, by blocking fibrinogen from acting at its receptor site, comprising treating the mammal with a therapeutically effective amount of a composition of Claim 13.

15. The use of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting the binding of fibrinogen to blood platelets and for inhibiting the aggregation of blood platelets in a mammal.



(1-7)