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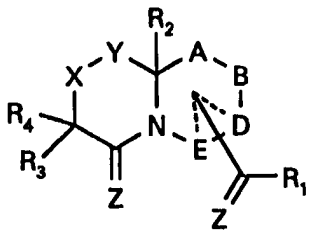
(54) Title: BICYCLIC THROMBIN INHIBITORS

(57) Abstract

This invention relates to heterocyclic inhibitors of the enzyme thrombin, their preparation, and pharmaceutical compositions thereof having general formula (I): wherein A, B, C, D, E, X, Y, Z, R_1, R_2, R_3 and R_4, are as defined herein. Also, the invention relates to the use of such compounds and compositions as anticoagulants and as agents for the treatment and prophylaxis of thrombotic disorders such as venous thrombosis, pulmonary embolism and arterial thrombosis resulting in acute ischemic events such as myocardial infarction or cerebral infarction.



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BICYCLIC THROMBIN INHIBITORS

FIELD OF THE INVENTION

This invention relates to compounds useful for the treatment of thrombotic disorders, and more particularly to novel heterocyclic inhibitors of the enzyme thrombin.

BACKGROUND

Inordinate thrombus formation on blood vessel walls precipitates acute cardiovascular disease states that are the chief cause of death in economically developed societies. Plasma proteins such as fibrinogen, proteases and cellular receptors participating in hemostasis have emerged as important factors that play a role in acute and chronic coronary disease as well as cerebral artery disease by contributing to the formation of thrombus or blood clots that effectively diminish normal blood flow and supply. Vascular aberrations stemming from primary pathologic states such as hypertension, rupture of atherosclerotic plaques or denuded endothelium, activate biochemical cascades that serve to respond and repair the injury site. Thrombin is a key regulatory enzyme in the coagulation cascade; it serves a pluralistic role as both a positive and negative feedback regulator. However, in pathologic conditions the former is amplified through catalytic activation of cofactors required for thrombin generation as well as activation of factor XIII necessary for fibrin cross-linking and stabilization.

In addition to its direct effect on hemostasis, thrombin exerts direct effects on diverse cell types that support and amplify pathogenesis of arterial thrombus disease. The enzyme is the strongest activator of platelets causing them to aggregate and release substances (e.g. ADP TXA_2 NE) that further propagate the thrombotic cycle.

Platelets in a fibrin mesh comprise the principal framework of a white thrombus. Thrombin also exerts direct effects on endothelial cells causing release of vasoconstrictor substances and translocation of adhesion molecules that become sites for attachment of immune cells.

In addition, the enzyme causes mitogenesis of smooth muscle cells and proliferation of fibroblasts.

The principal endogenous neutralizing factor for thrombin activity in mammals is antithrombin III (ATIII), a circulating plasma macroglobulin having low affinity for the enzyme. Heparin has shown clinical efficacy in alleviating venous thrombosis by enhancing ATIII/thrombin binding through catalysis. However, heparin also catalyzes inhibition of other proteases in the coagulation cascade and its efficacy in platelet-dependent thrombosis is largely reduced or abrogated due to inaccessibility of thrombus-bound enzyme. Also, adverse side effects such as thrombocytopenia, osteoporosis and triglyceridemia have been observed following prolonged treatment with heparin.

It has been proposed that thrombin activity can be inhibited by compounds that compete with fibrinogen for thrombin's catalytic site, thereby inhibiting proteolysis of that protein or other protein substrates such as the thrombin receptor. A common strategy for designing enzyme inhibitory compounds relies on mimicking the specificity inherent in the primary and secondary structure of the enzyme's natural substrate. Thrombin inhibitors have been modeled upon the partial sequence of the fibrinogen Aα chain comprising its proteolytically susceptible region (Blomback, et al., J. Clin. Lab. Invest., 24, 59, 1969). This region of fibrinogen minimally includes the residues commencing with phenylalanine:

Ala-Asp-Ser-Gly-Glu-Gly-Asp-Phe-Leu-Ala-Glu-Gly-Gly-Gly-Val-Arg-Gly-Pro-Arg

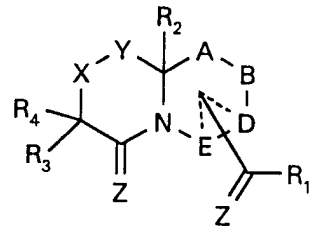
↑ Scissile bond

Systematic replacement of amino acids within this region has led to optimization of the tripeptidyl inhibitory sequence exemplified by the peptide (D)-Phe-Pro-Arg which corresponds to interactions within the P_3-P_2-P_1 local binding sites on thrombin (Bajusz S. et al. in Peptides: Chemistry Structure and Biology: Proceedings of the Fourth American Peptide Symposium, Walter R., Meienhofer J. Eds. Ann Arbor Science Publishers Inc., Ann Arbor MI, 1975, pp. 603).

It is an object of the present invention to provide thrombin inhibitors that display inhibitory activity towards the enzyme thrombin which may be used in the treatment or prophylaxis of thrombotic disorders.

SUMMARY OF THE INVENTION

The present invention provides for novel compounds that display thrombin inhibitory activity as represented by formula I:



(I)

wherein:

A is selected from $(CH\text{-}R_8)_{0\text{-}1}$, S, SO, SO_2, O and NR_8 wherein R_8 is hydrogen, $C_{1\text{-}6}$ alkyl optionally interrupted with 1 or 2 heteroatoms; $C_{6\text{-}16}$ aryl, $C_{3\text{-}7}$ cycloalkyl or heterocyclic ring or a hydrophobic group;

B is selected from S, SO_2, O, -N=, NH, -CH= and CR_6R_7 wherein R_6 and R_7 are independently selected from hydrogen and $C_{1\text{-}6}$ alkyl provided that when A is S, SO, SO_2, O, or NR_8, then B is CR_6R_7;

D is selected from $(CH\text{-}R_9)_{0\text{-}2}$, wherein R_9 is hydrogen, $C_{1\text{-}6}$ alkyl or $-C(O)R_1$; and CH with a double bond to B when B is -N= or -CH=;

E is selected from CH_2 and CH substituted with the $-C(O)R_1$, provided that only one of D and E is substituted with $-C(O)R_1$;

X is selected from O, $N\text{-}R_5$, or $CH\text{-}R_5$;

Y is selected from O, S, SO, SO_2, $N\text{-}R_5$, CO and $CH\text{-}R_8$ provided that when X is $N\text{-}R_5$ then Y is $CH\text{-}R_8$ or O, and when X is O then Y is $CH\text{-}R_8$;

Z is selected from O, S and H_2;

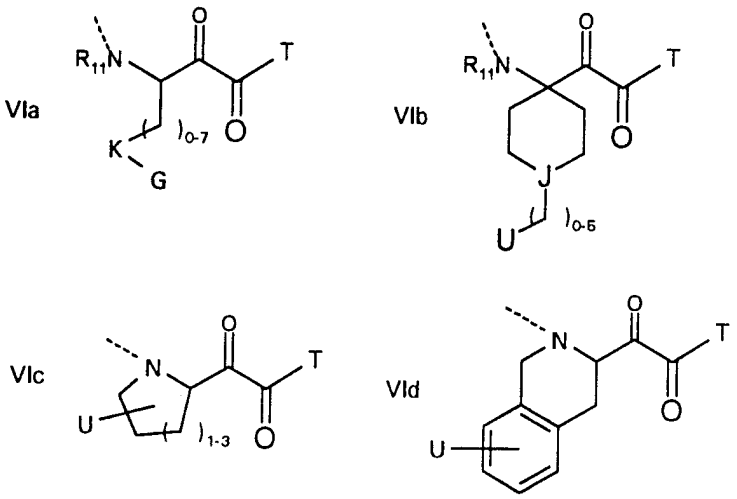
R_2 is selected from H and $C_{1\text{-}6}$ alkyl optionally substituted with C_6 aryl, a 6 member heterocycle or a $C_{3\text{-}7}$ cycloalkyl ring

R_3 is selected from H, NR_6R_7 and $C_{1\text{-}6}$ alkyl;

R_4 and R_5 are independently selected from H; NR_6R_7; $C_{6\text{-}16}$ aryl or $C_{3\text{-}7}$ cycloalkyl optionally substituted with $C_{1\text{-}6}$ alkyl; $C_{1\text{-}16}$ alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_6R_7 or a $C_{6\text{-}16}$ aryl,

heterocycle or C_{3-7} cycloalkyl group optionally substituted with halogen, hydroxyl, C_{1-6} alkyl; an amino acid side chain; and a hydrophobic group; and

R_1 is selected from the group consisting of formula VIa, VIb, VIc and VId:



wherein:

R_{11} is hydrogen or C_{1-6} alkyl;

J is CH or N;

K is a bond or -NH-;

G is C_{1-4} alkoxy; cyano; $-NH_2$; $-CH_2-NH_2$; $-C(NH)-NH_2$; $-NH-C(NH)-NH_2$; $-CH_2-NH-C(NH)-NH_2$; a C_6 cycloalkyl or aryl substituted with cyano, $-NH_2$, $-CH_2-NH_2$, $-C(NH)-NH_2$, $-NH-C(NH)-NH_2$ or $-CH_2-NH-C(NH)-NH_2$; or a 5 or 6 member, saturated or unsaturated heterocycle optionally substituted with cyano, $-NH_2$, $-CH_2-NH_2$, $-C(NH)-NH_2$, $-NH-C(NH)-NH_2$ or $-CH_2-NH-C(NH)-NH_2$;

U is cyano, $-NH_2$, $-C(NH)-NH_2$ or $-NH-C(NH)-NH_2$;

T is H, OH, amino, a peptide of 1 to 4 amino acid residues, C_{1-16} alkyl, C_{1-16} alkoxy, C_{6-20} aralkyl, C_{6-16} aryloxy; C_{6-20} arylalkoxy or an aryl or heterocycle optionally substituted;

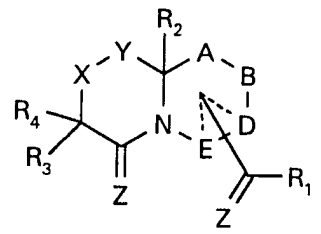
and pharmaceutically acceptable salts thereof.

In another aspect of the present invention, there is provided pharmaceutical compositions comprising compounds of formula (I) in combination with a pharmaceutically acceptable carrier.

In a further aspect, there is provided a method for the treatment or prophylaxis of thrombotic disorders in a mammal, comprising administering to said mammal an effective amount of a compound according to formula (I) or pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to molecules which inhibit the enzyme, thrombin. These molecules are characterized by a heterobicyclic moiety as illustrated in Formula I:



(I)

wherein X, Y, Z, A, B, D, E and R_1 to R_4 are as previously defined.

The term "hydrophobic group" (HG) as used hereinafter, refers to any group which lacks affinity for, or displaces water. Hydrophobic groups include but are not limited to C_{1-20} alkyl, C_{2-20} alkenyl (e.g. vinyl, allyl) or C_{2-20} alkynyl (e.g. propargyl) optionally interrupted by a carbonyl group, (e.g. forming an acyl group); C_{6-16} aryl, C_{3-7} cycloalkyl, C_{6-20} aralkyl, C_{6-20} cycloalkyl substituted C_{1-20} alkyl, wherein the aliphatic portion is optionally interrupted by a carbonyl group (e.g. forming an acyl group) and the ring portion is optionally substituted with C_{1-6} alkyl such as methyl ethyl or t-butyl; or a hydrophobic amino acid side chain. Preferred hydrophobic groups include cyclohexyl, benzyl, benzoyl, phenylmethyl, phenethyl and para-t-butyl-phenylmethyl.

The term "alkyl" represents a straight or branched, saturated or unsaturated chain having a specified total number of carbon atoms.

The term "aromatic" or "aryl" represents an unsaturated carbocyclic ring(s) of 6 to 16 carbon atoms which is optionally mono- or di-substituted with OH, SH, amino (i.e. NR_6R_7) halogen or C_{1-6} alkyl. Aromatic rings include benzene, napththalene, phenanthrene and anthracene. Preferred aromatic rings are benzene and naphthalene.

The term "cycloalkyl" represents a saturated carbocyclic ring of 3 to 7 carbon atoms which is optionally mono- or di-substituted with OH, SH, amino (i.e. NR_6R_7) halogen or C_{1-6} alkyl. Cycloalkyl groups include cyclo- propyl, butyl, pentyl, hexyl and heptyl. A preferred cycloalkyl group is cyclohexyl.

The term "aralkyl" represents a substituent comprising an aryl moiety attached via an alkyl chain (e.g. benzyl, phenethyl) wherein the sum total of carbon atoms for the aryl moiety and the alkyl chain is as specified. The aryl or chain portion of the group is optionally mono- or di-substituted with OH, SH, amino (i.e. NR_6R_7) halogen or C_{1-6} alkyl

The term "heteroatom" as used herein represents oxygen, nitrogen or sulfur (O, N or S) as well as sulfoxyl or sulfonyl (SO or SO_2) unless otherwise indicated. It is understood that alkyl chains interrupted by one or more heteroatoms means that a carbon atom of the chain is replaced with a heteroatom having the appropriate valency. Preferably, an alkyl chain is interrupted by 0 to 4 heteroatoms and that two adjacent carbon atoms are not both replaced.

The term "heterocycle" represents a saturated or unsaturated mono- or polycyclic (i.e. bicyclic) ring incorporating 1 or more (i.e. 1-4) heteroatoms selected from N, O and S. It is understood that a heterocycle is optionally mono- or di-substituted with OH, SH, amino (i.e. NR_6R_7), halogen, CF_3, oxo or C_{1-6} alkyl. Examples of suitable monocyclic heterocycles include but are not limited to pyridine, piperidine, pyrazine, piperazine, pyrimidine, imidazole, thiazole, oxazole, furan, pyran and thiophene. Examples of suitable bicyclic heterocycles include but are not limited to indole, benzimidazole, quinoline, isoquinoline, purine, and carbazole.

The term "hydrophobic amino acid" represents an amino acid residue that bears an alkyl or aryl group attached to the α-carbon atom. Thus glycine, which has no such group attached to the α-carbon atom is not a hydrophobic amino acid. The alkyl or aryl group can be

substituted, provided that the substituent or substituents do not detract from the overall hydrophobic character of the amino acid. Examples of hydrophobic amino acids include natural amino acid residues such as alanine; isoleucine; leucine; phenylalanine; and non-naturally ocurring amino acids such as those described in "The Peptides", vol. 5, 1983, Academic Press, Chapter 6 by D.C. Roberts and F. Vellaccio. Suitable non-naturally ocurring amino acids include cyclohexylalanine and 1-aminocyclohexane-carboxylic.

By "amino acid side chain" is meant the substituent attached to the carbon which is α to the amino group. For example, the side chain of the amino acid alanine is a methyl group and while benzyl is the side chain for phenylalanine.

Preferably R_2 is H or C_{1-6} alkyl. More preferably R_2 is H, methyl or ethyl and most preferably R_2 is H.

Preferably, R_3 is H or C_{1-6} alkyl. More preferably, R_3 is H, methyl or ethyl, and most preferably R_3 is H.

Preferably, one of R_4 or R_5 is a hydrophobic group such as a saturated or unsaturated carbocycle of 5 or 6 members optionally fused to another carbocyclic group while the other is H, C_{1-16} alkyl optionally substituted by NR_6R_7 or carboxy. The hydrophobic moiety may be linked via a spacer such as a C_{1-16} alkyl chain optionally interrupted with 1 or more (i.e. 1-4) heteroatoms, carbonyl or sulfonyl (SO_2) groups. More preferably, one of R_4 and R_5 is phenyl, cyclohexyl, indole, thienyl, quinoline, tetrahydroisoquinoline, naphthyl or benzodioxolane linked via C_{1-16} alkyl optionally interrupted with a heteroatom or a carbonyl while the other is H, carboxymethyl or carboxyethyl.

Preferably, A is absent or CH_2.

Preferably, B is S or CH_2.

Preferably, D is CH_2.

Preferably, E is CH substituted with $-C(O)R_1$ wherein R_1 is as previously defined.

Preferably, X is $CH-R_5$ or $N-R_5$.

Preferably, Y is $CH-R_8$ or S.

Preferably, Z is O.

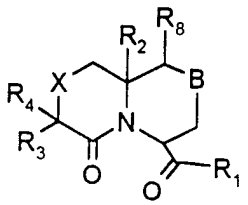
Preferably R_{11} is H or methyl and most preferably H.

Preferably **K** is a bond.

Preferably **G** is -NH-C(NH)-NH_2 attached via a methylene chain of 3-7 carbons or phenyl substituted with -C(NH)-NH_2 attached via a methylene chain of 0 to 3 carbons. More preferably G is -NH-C(NH)-NH_2 attached via a methylene chain of 3 atoms.

In particular embodiments, compounds of the invention are represented by formulas II, III, IV and V, wherein X, Y, B, R_1 to R_4 and R_8 are as previously defined.

(II)



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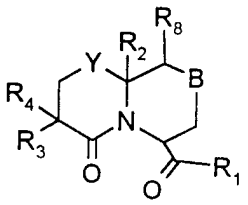

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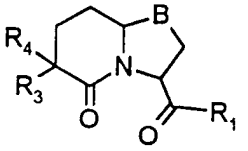

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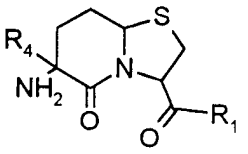
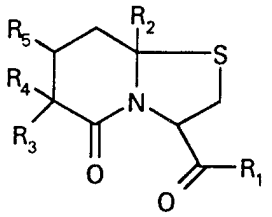
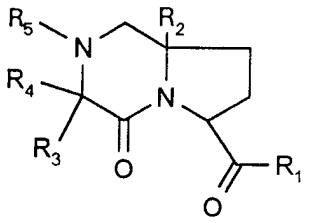
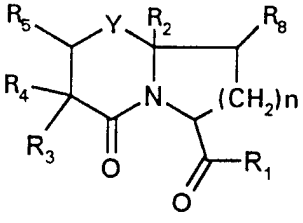
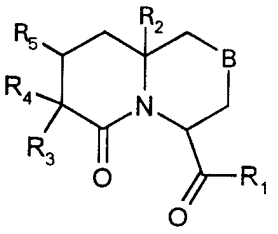


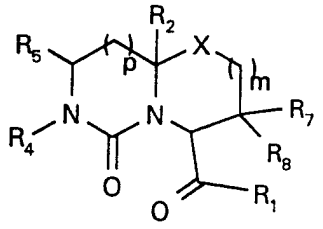
In a particularly preferred embodiment, compounds of the invention are represented by one of formulas VII, VIII, IX, X and XI:











wherein

B is O, S, $-CH_2-$, or -NH-;

Y is selected from O, S, SO, SO_2, N-R_5 and CH-R_8;

R_1 is as previously defined;

R_2 is H or C_{1-6} alkyl;

R_3 is selected from H, NR_6R_7 and C_{1-6} alkyl; and

R_4 and R_5 are independently selected from H; NR_6R_7 wherein R_6 and R_7 are independently hydrogen or C_{1-6} alkyl; C_{6-16} aryl or C_{3-7} cycloalkyl optionally substituted with C_{1-6} alkyl; C_{1-16} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_6R_7 or a C_{6-16} aryl, heterocycle or C_{3-7} cycloalkyl group optionally substituted with halogen, hydroxyl, C_{1-6} alkyl; an amino acid side chain; and a hydrophobic group;

R_8 is hydrogen, C_{1-6} alkyl optionally interrupted with 1 or 2 heteroatoms; C_{6-16} aryl, C_{3-7} cycloalkyl or heterocyclic ring or a hydrophobic group;

m is 0, 1 or 2;

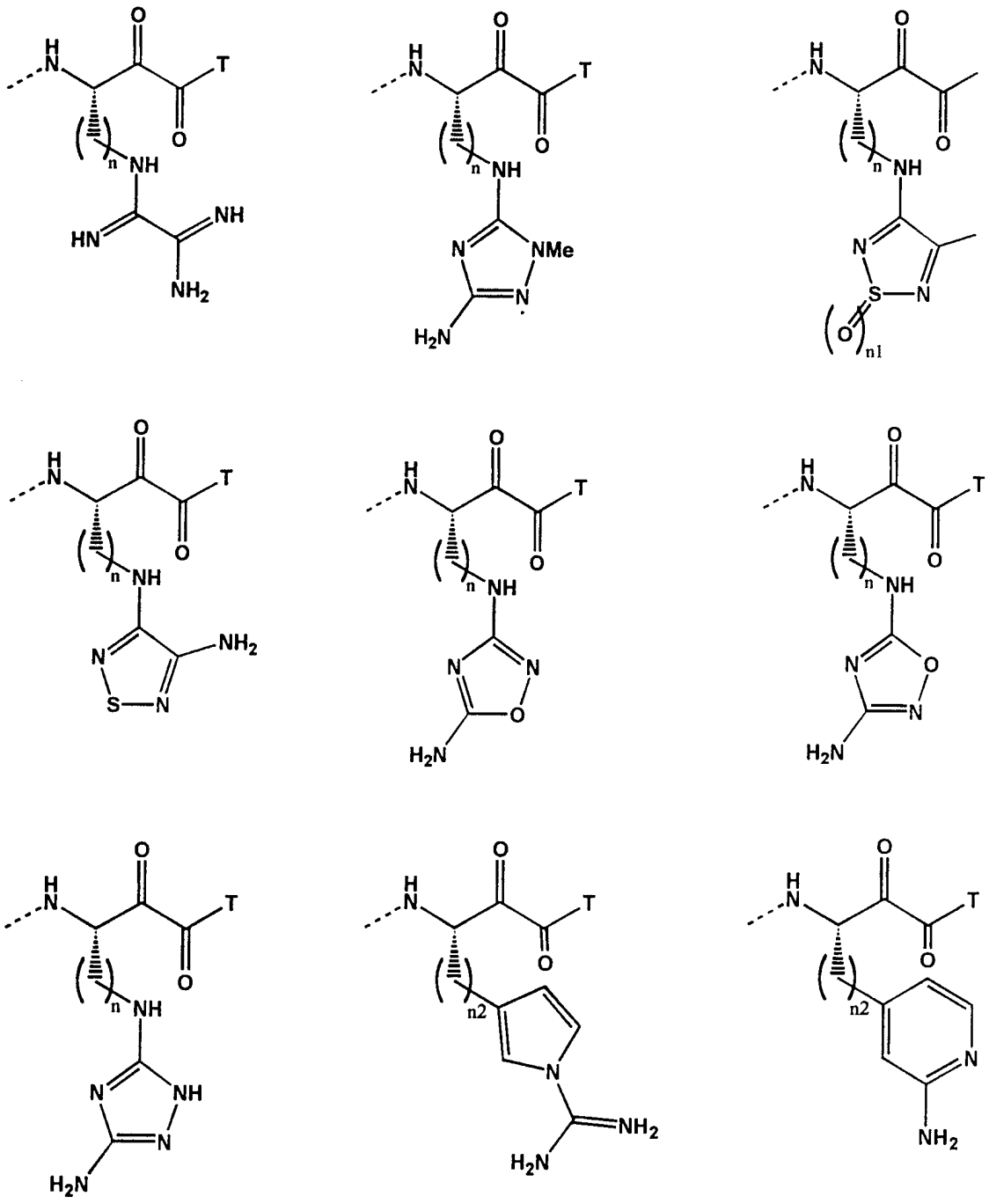
n is 1 or 2; and

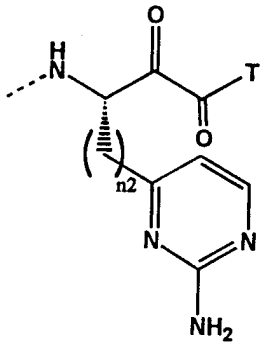
p is 0, 1 or 2.

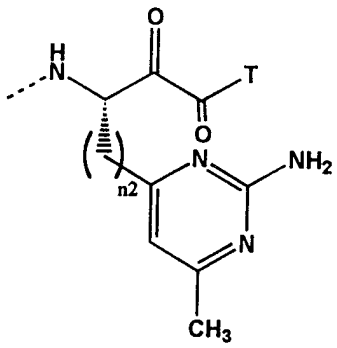
In preferred embodiments one of R_4 and R_5 is H while the other is a C_{1-16} alkyl optionally interrupted by one or more heteroatom (in particular SO_2 or a carbonyl group) and is substituted with C_{6-16} aryl, heterocycle or C_{3-7} cycloalkyl group optionally substituted with halogen, hydroxyl or C_{1-6} alkyl. More preferably R_4 is H and R_5 is C_{1-5} alkyl optionally interrupted adjacent to the bicyclic ring with SO_2 or carbonyl and is terminally substituted with C_{6-16} aryl preferably phenyl. Preferably R_3 where present is H or C_{1-16} alkyl and more preferably H. Preferably R_2 is H.

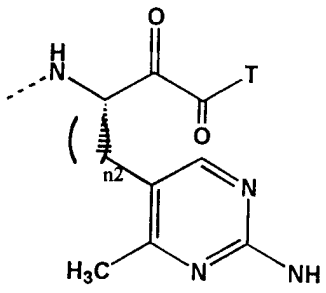
In particular embodiments of the invention, R_1 is selected from the following amino acid derivatives. Preparation of the derivatives in standard C-terminal [C(O)-OH] form is

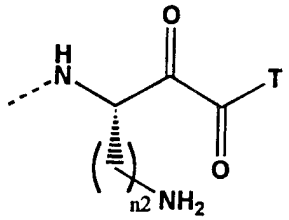
described in Bioorg. Med. Chem., 1995, 3:1145 and international patent applications PCT/CA95/00708 and PCT/CA96/00318 incorporated herein by reference which are subsequently modified to the di-keto [C(O)C(O)-OH] form according to established synthetic techniques (see general Scheme (I)).

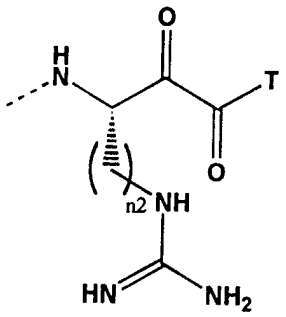


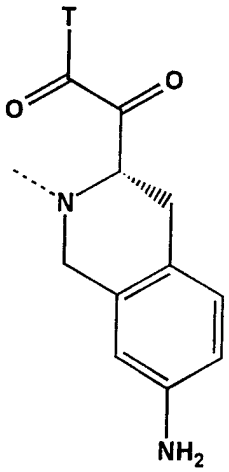












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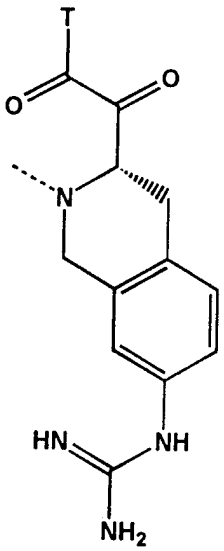

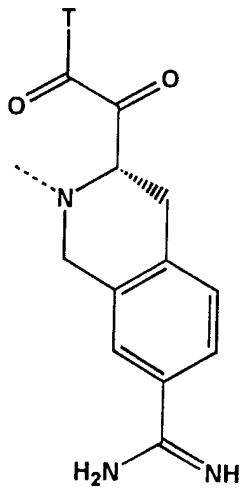

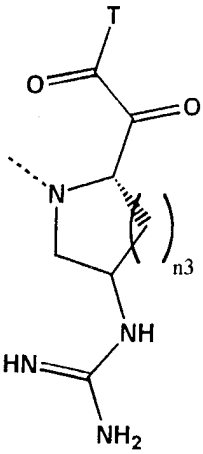

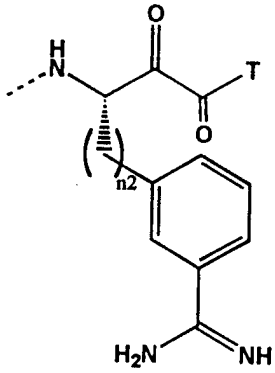
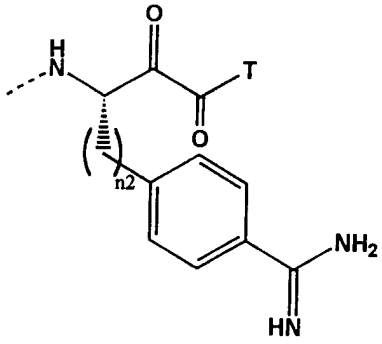
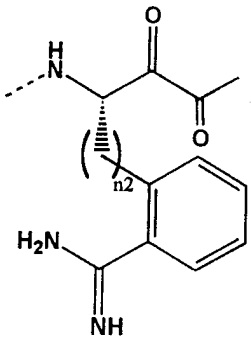
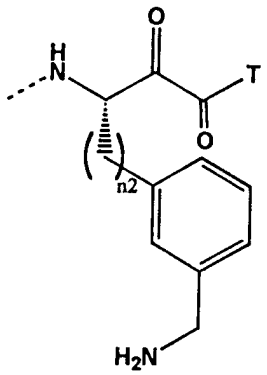
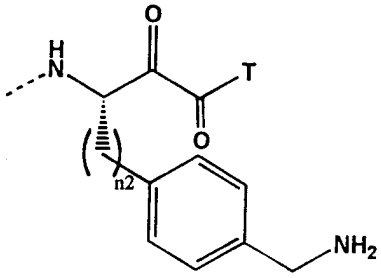
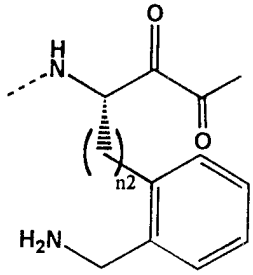
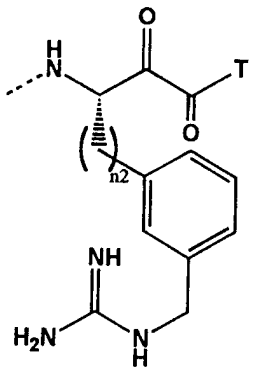
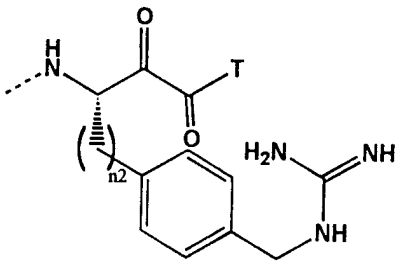
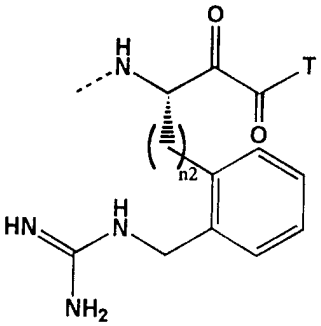
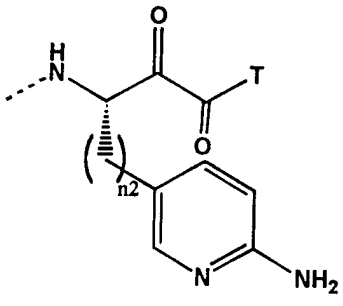
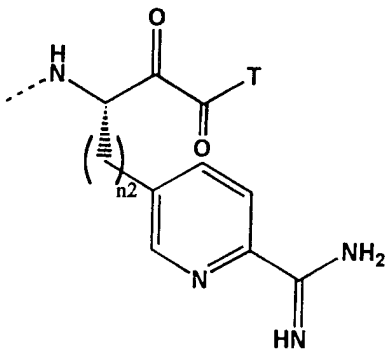
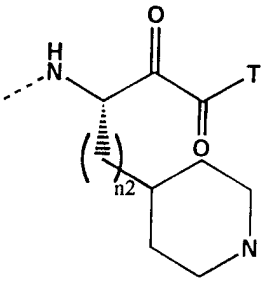

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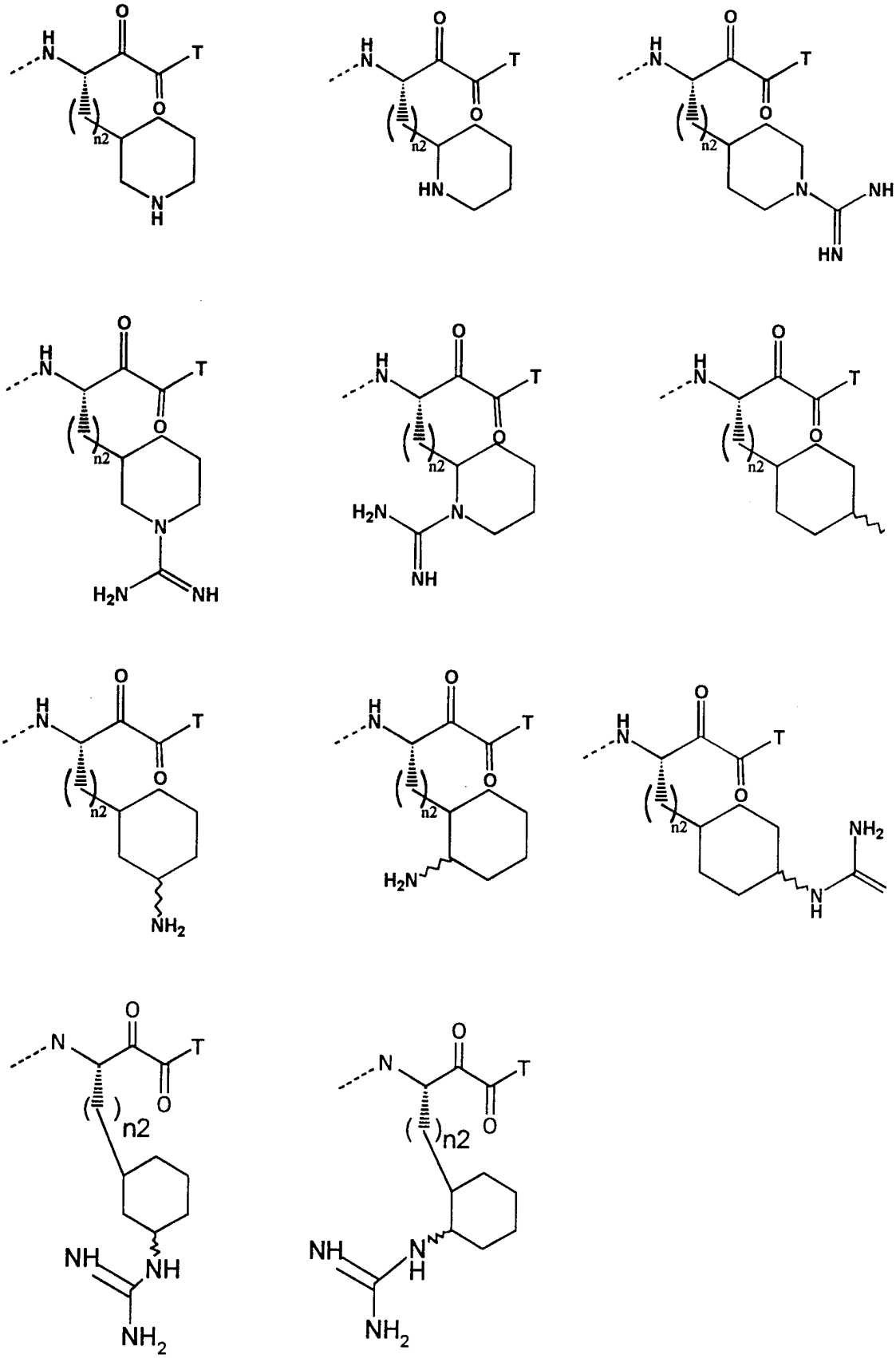
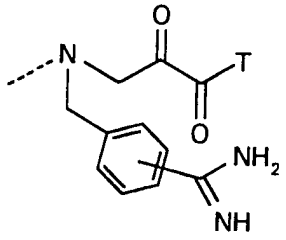
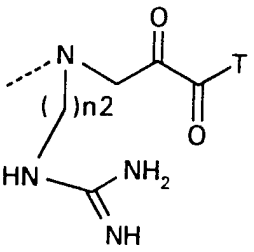
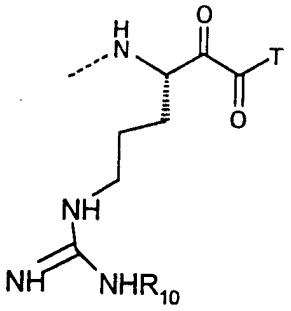


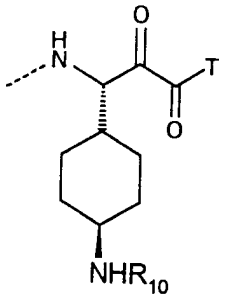


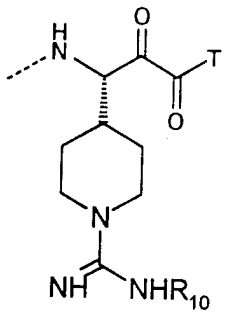


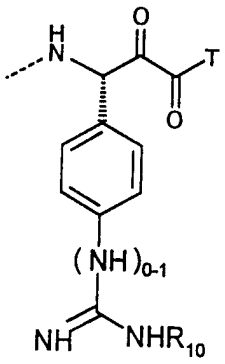
wherein n=1-6, n1=1-2, n2=0-7 and T is as previously defined.

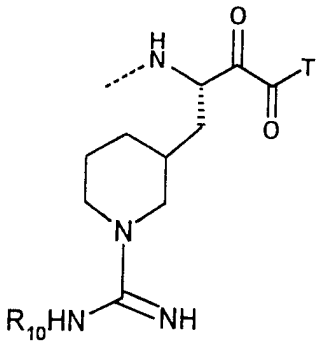
In particularly preferred embodiments, R_1 is selected from the group:

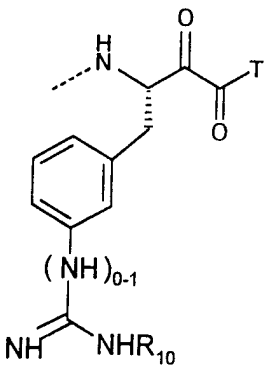


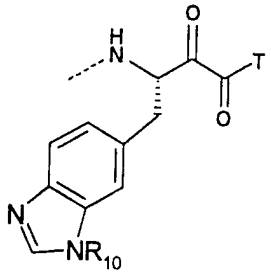


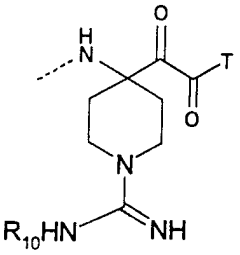


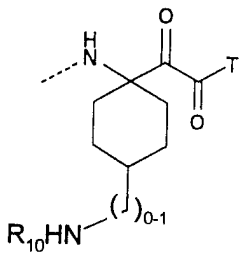


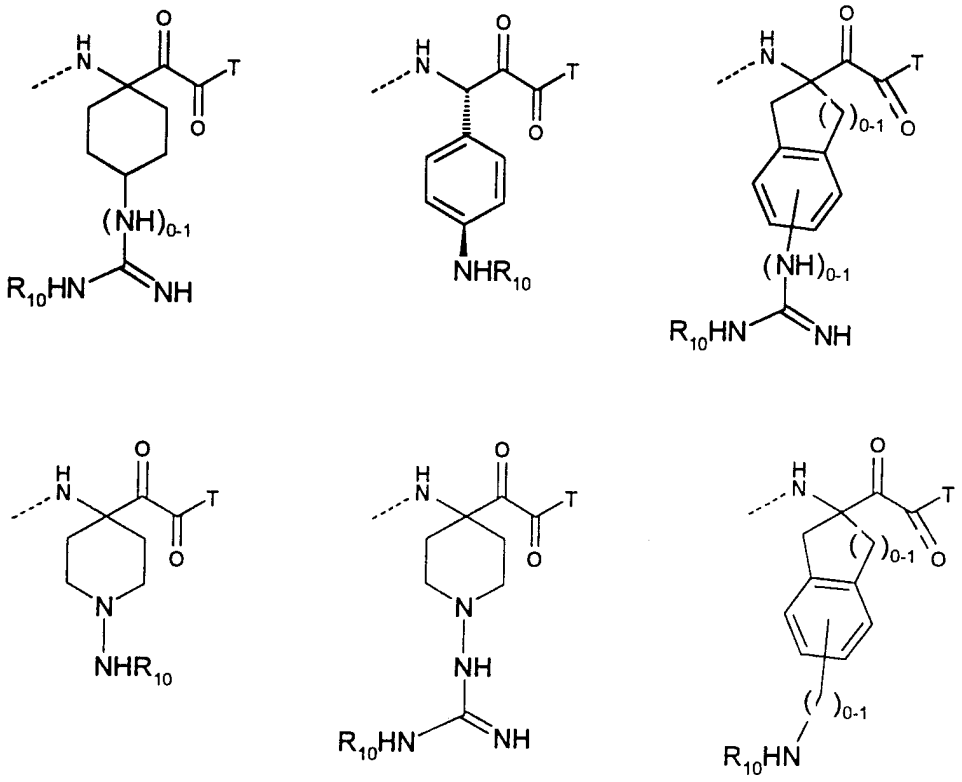










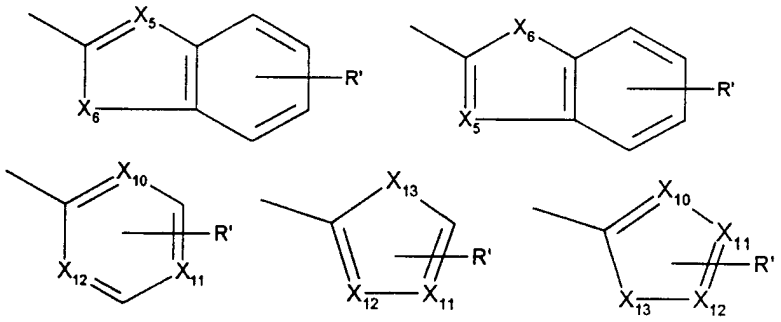


wherein R_{10} is H, C_{1-6} alkyl, aryl, CN, NH_2 or NO_2 and T is as previously defined. Preferably R_{10} is H, NO_2 and most preferably H.

In particularly preferred embodiments, T is OH; C_{1-16} alkoxy such as methoxy, ethoxy, propyloxy, or (n-, i-, s-, t-) butoxy; C_{6-16} aryloxy such as phenoxy; or C_{6-20} arylalkoxy such as benzyloxy or phenylethoxy. In a more preferred embodiments T is OH; C_{1-16} alkoxy and in a most preferred embodiment T is OH.

In alternative embodiments, T is a peptide of 1 to 4 amino acid residues in length having a free C-terminus or an alkyl ester thereof and may be fibrinogen's A or B chain or fragment or derivative thereof. Preferred amino acids are neutral such as Gly, Ala, Val, Leu or Ile or acidic such as Asp or Glu. More preferred amino acids include Gly, Asp and Glu, and most preferably Gly.

In other alternative embodiments, T is a heterocycle selected from the group consisting of:



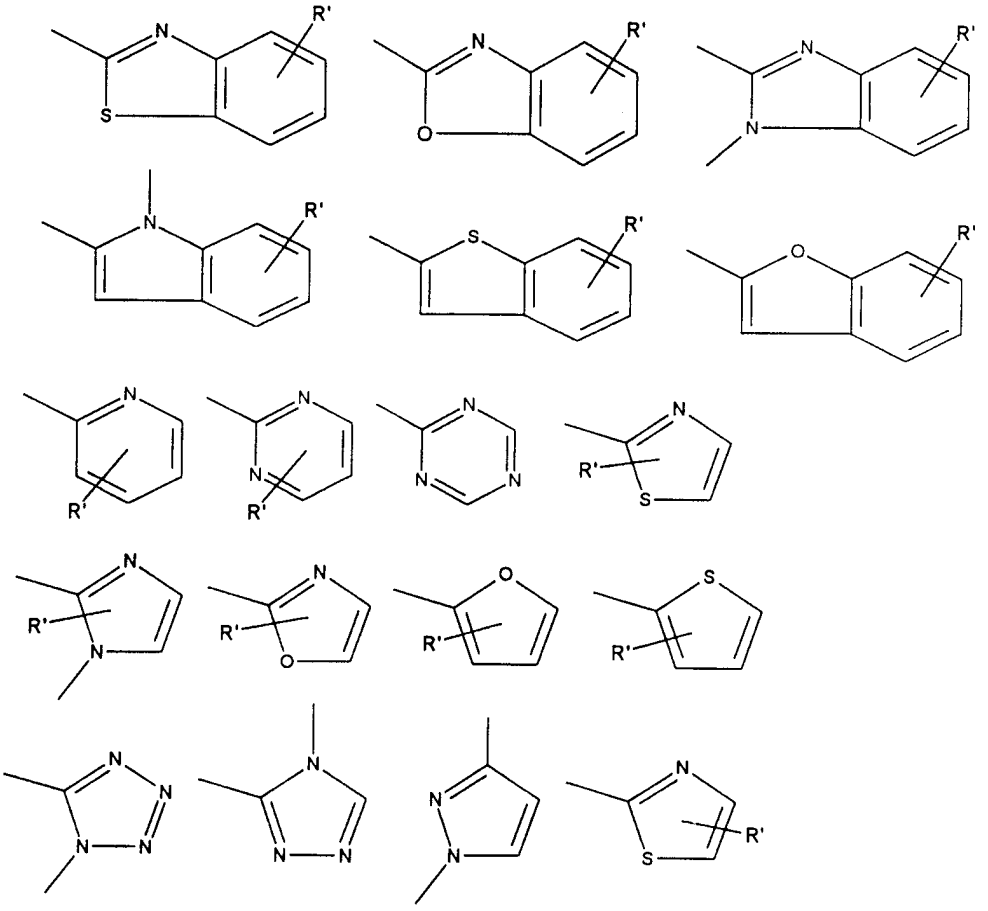
wherein

X_5, X_{10}, X_{11} and X_{12} are each independently selected from the group consisting of N, or C-X_7 where X_7 is hydrogen, C_{1-4} alkyl, or C_{6-16} aryl;

X_6 and X_{13} are each independently selected from the group consisting of C, O, N, S, N-X_7, or CH-X_7;

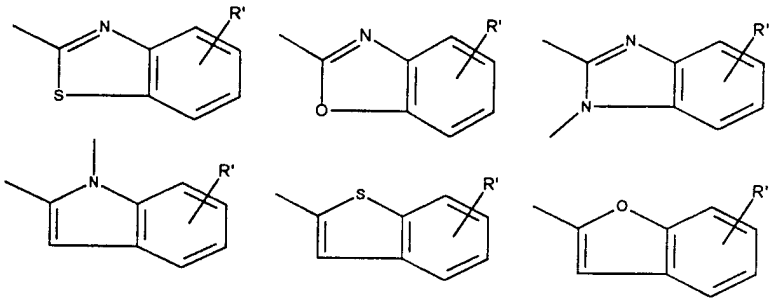
R' is hydrogen, C_{1-16} alkyl optionally carboxyl substituted, carboxyl, -C_{0-16} alkyl-CO_2-C_{1-16} alkyl, C_{6-20} aralkyl, C_{3-7} cycloalkyl, aryl or an aromatic heterocycle.

Preferably T is selected from the group consisting of:



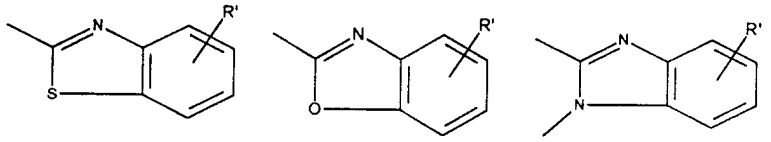
wherein R' is as defined above.

More preferably T is selected from the group consisting of:



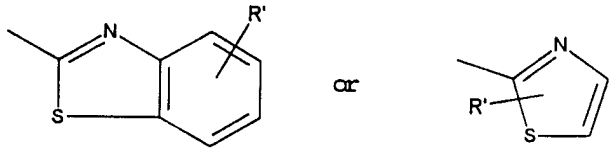
wherein R' is as defined above.

More preferably T is selected from the group consisting of:



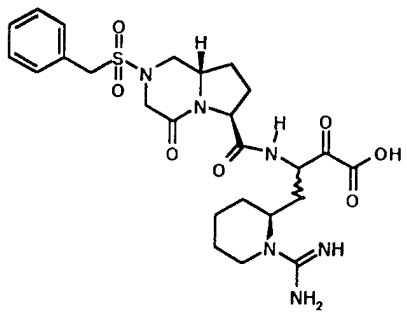
wherein R' is as defined above.

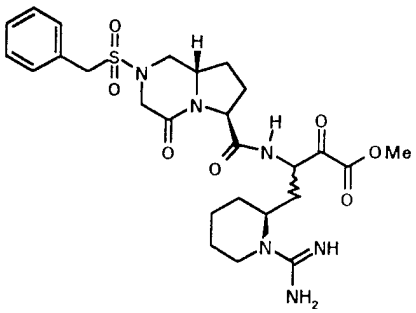
Most preferably T is

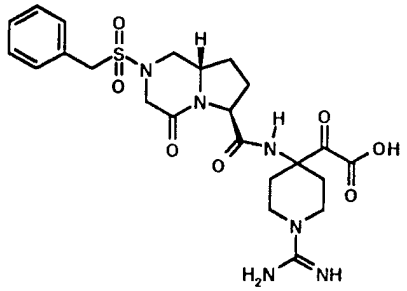


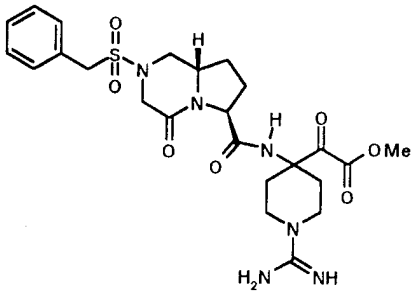
wherein R' is H or C_{1-4} alkyl such as methyl, ethyl, propyl or butyl and most preferably wherein R' is hydrogen,. In another embodiment, T is a 1,2 thiazole optionally substituted with R' and/or is attached to J at the 2, 3, 4 or 5 position of the ring.

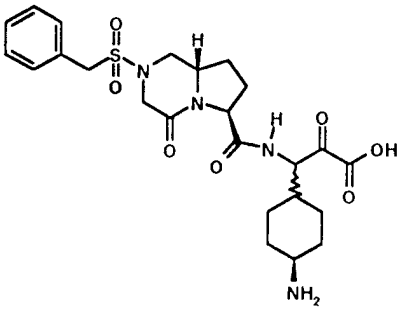
Preferred compounds according to the present invention include any one of the following:

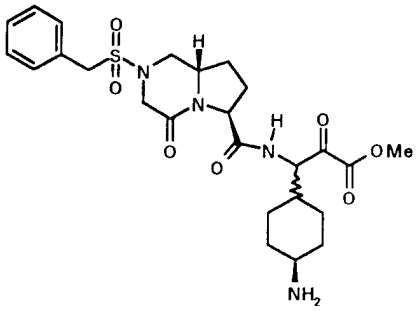


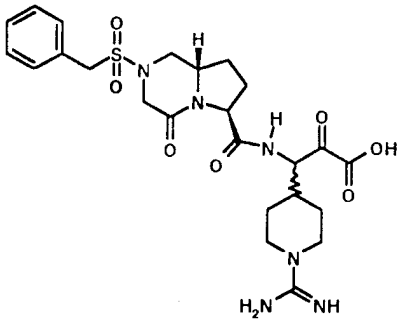


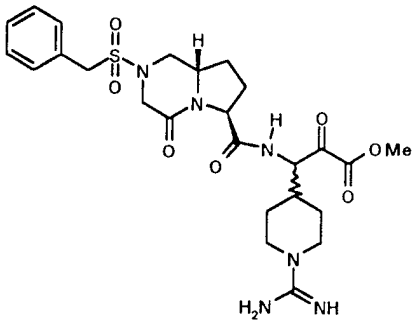


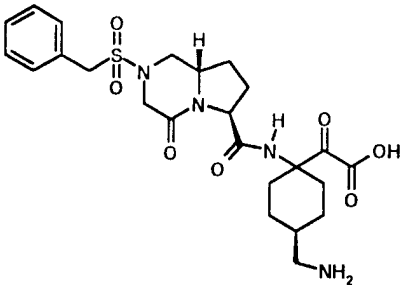


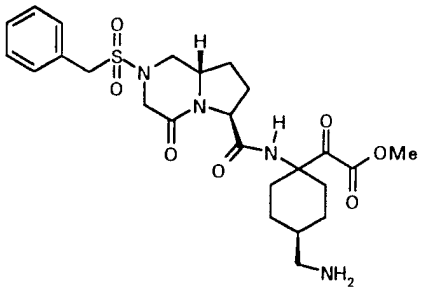


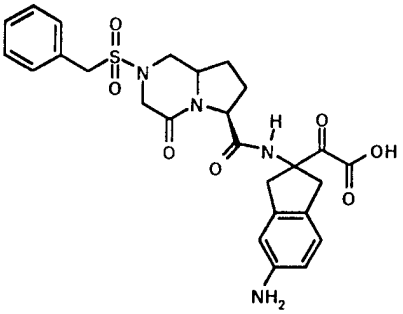


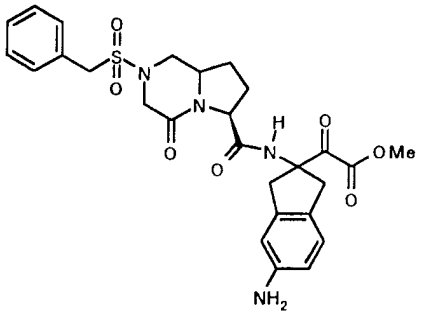


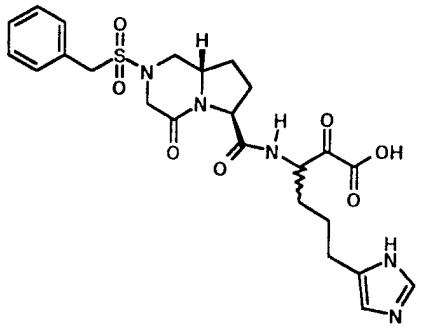


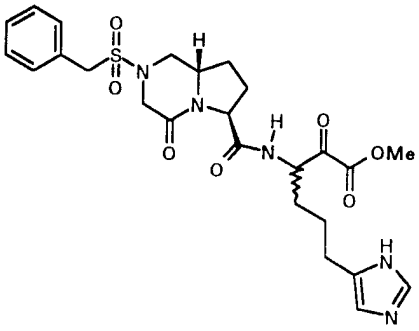


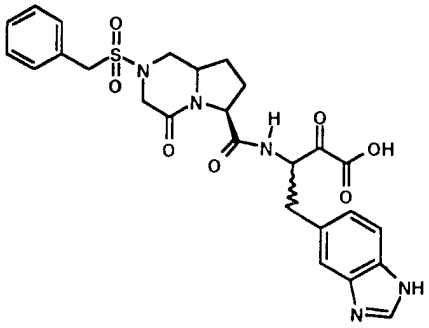


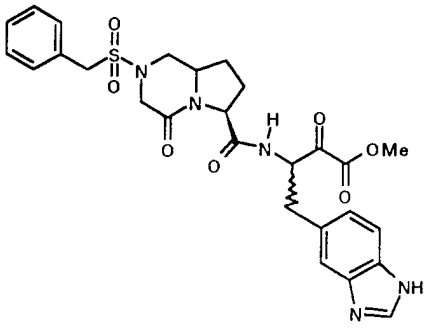


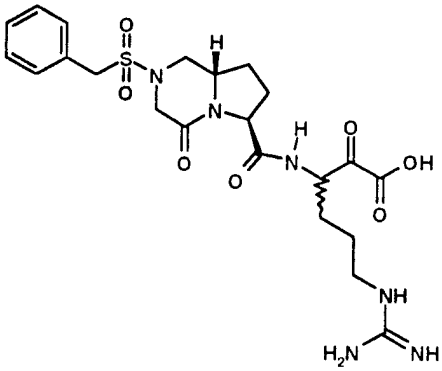


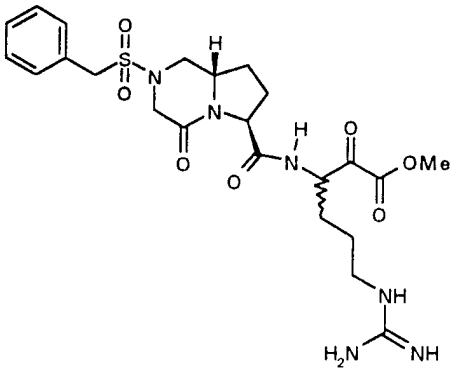


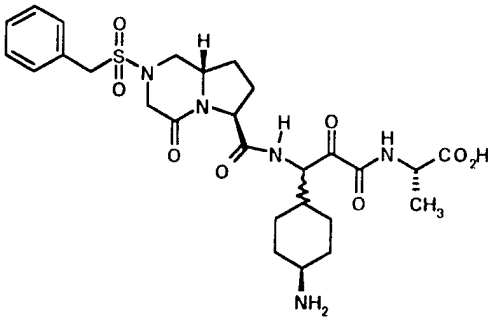


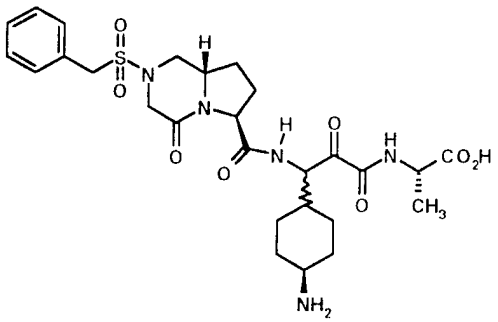












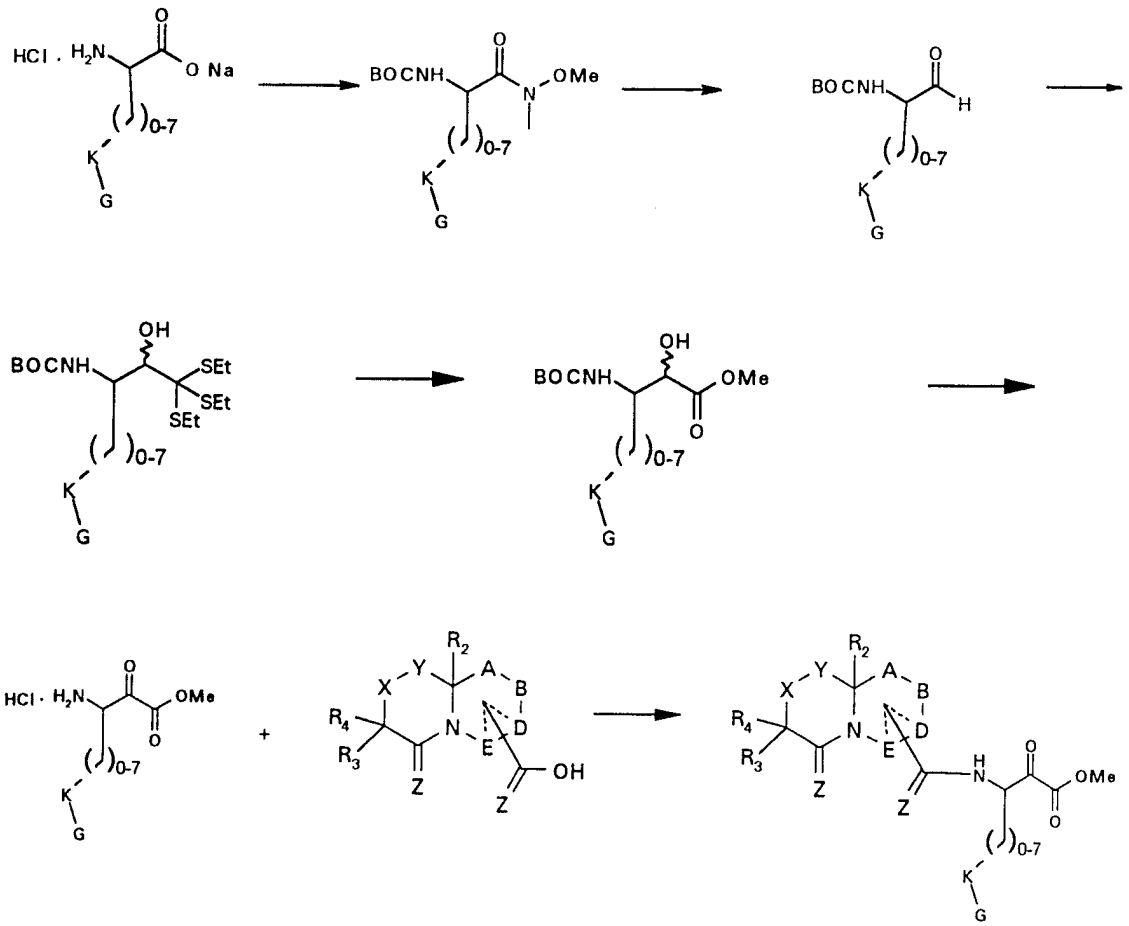
5

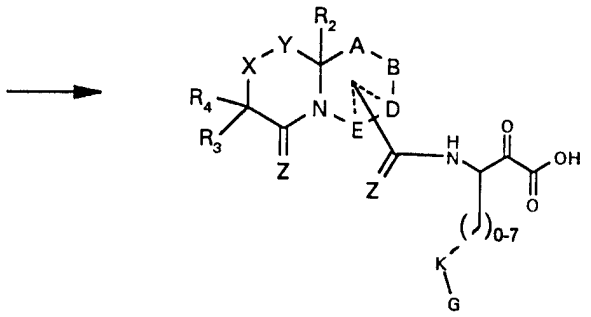
and stereoisomers thereof.

The bicyclic portion of compounds of formula VII, VIII, IX, X and XI are prepared according to the procedures described in international patent applications PCT/CA95/00708 and PCT/CA96/00318 incorporated herein by reference. The bicycle is subsequently coupled with a di-keto R_1 portion of the present invention according to standard amide bond formation techniques and described in further detail herein.

For preparation of compounds according to formula (I) where R_1 is a group according to formula (VIa) the following general synthetic scheme (I) may be employed.

Scheme (I)





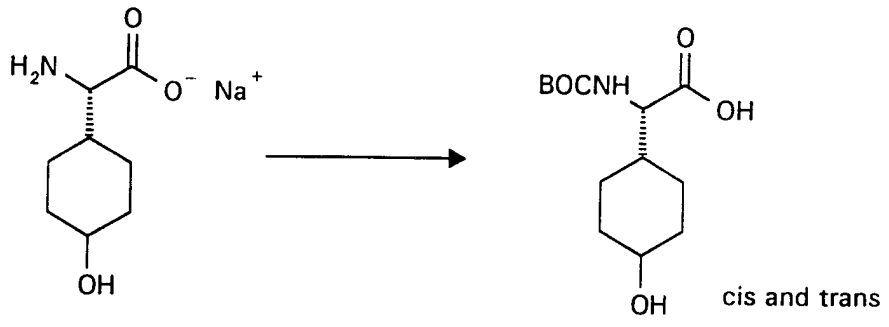
In a like manner, compounds of formula (I) may be prepared wherein R_1 is a group according to formula VIb, VIc or VId.

In another aspect of the invention, there is provided a method for the treatment or prophylaxis of thrombotic disorders, comprising administering to a mammal i.e. a human, an effective amount of a compound according to formula (I) or pharmaceutically acceptable salts thereof. Particular thrombotic disorders include venous thrombosis, pulmonary embolism, arterial thrombosis, myocardial infarction and cerebral infarction. By "effective amount" is meant the amount of compound administered to an individual which is necessary to prevent, alleviate or inhibit the progression of a thrombotic disorder caused by the activity of thrombin. Compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers, diluents or adjuvants. The amount of active ingredient and proportion of carrier is determined by the solubility and chemical nature of the compound, the route of administration. For example, the compounds may be injected parenterally i.e. intramuscularly, intravenously, or subcutaneously. For parenteral administration, the compound may be used in the form of sterile solutions containing other solutes, for example, sufficient saline or glucose to make the solution isotonic. The compounds may be administered orally in the form of tablets, capsules, or granules containing suitable excipients such as starch, lactose, white sugar and the like. The compounds may also be administered sublingually in the form of troches or lozenges in which each active ingredient is mixed with sugar or corn syrups, flavoring agents and dyes, and then dehydrated sufficiently to make the mixture suitable for pressing into solid form. The compounds may be administered orally in the form of solutions which may contain coloring and/or flavoring agents.

The compounds of the present invention may also be used as anti-coagulants *in vitro* or *ex vivo* as in the case of contact activation with foreign thrombogenic surfaces such as is found in tubing used in extracorporeal shunts. The compounds of the invention may also be used to coat the surface of such thrombogenic conduits. To this end, the compounds of the invention are obtained as lyophilized powders, redissolved in isotonic saline and added in an amount sufficient to maintain blood in an anticoagulated state.

Compounds of the present invention are characterized by their ability to inhibit the catalytic activity of thrombin, which may be demonstrated in standard binding assays as follows. Compounds of the present invention may be prepared for assay by dissolving them in buffer to give solutions ranging in concentrations from 1 to 100μM. In an assay to determine the inhibitory dissociation constant, K_i, for a given compound, a chromogenic or fluorogenic substrate of thrombin would be added to a solution containing a test compound and thrombin; the resulting catalytic activity of the enzyme would be spectrophotometrically determined. This type of assay is well known to those skilled in the art.

EXAMPLE 1



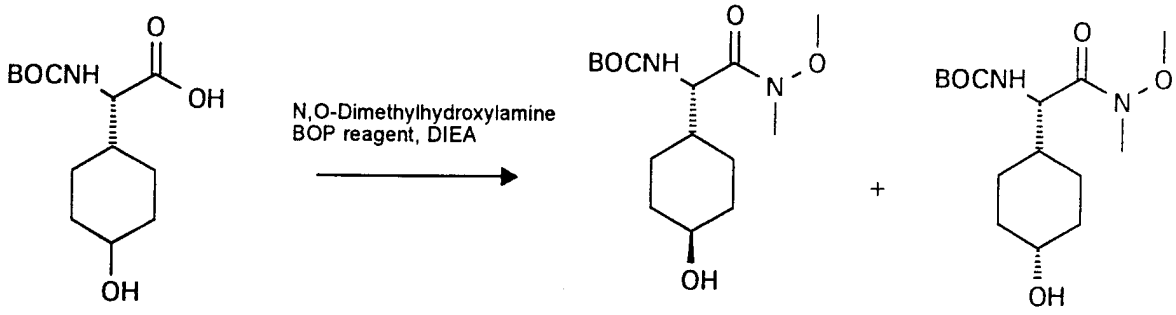
cis and trans

To a suspension of the amine (5g, 26mmol) in a mixture of dioxane and water (35mL/50mL) were added triethylamine (6,5mL, 47mmol, 1.8eq.) and Boc anhydride (6,8g, 31.2mmol, 1.2eq.). The reaction mixture was stirred at room temperature for 32 hours then the solution was concentrated to 50 mL, cooled to 0°C and 5% HCl solution was added (pH 2), sodium chloride was added and the mixture was extracted with EtOAc (3X). Combined organic extract were dried (Na_2SO_4) and concentrated.

The trans isomer was then recrystalized from the mixture. It was also possible to separate the two isomers at the next step.

^{1}HRMN of the trans isomer: 6.92 (d, 1H, J=8.4Hz); 4.45 (d, 1H, J=4.5Hz); 3.75 (t, 1H, J=8.1 and 6,4Hz); 1.80 (m, 2H); 1.56 (m, 3H); 1.37 (s, 9H +2H) and 1.10-1.05 (m, 3H) ppm

EXAMPLE 2



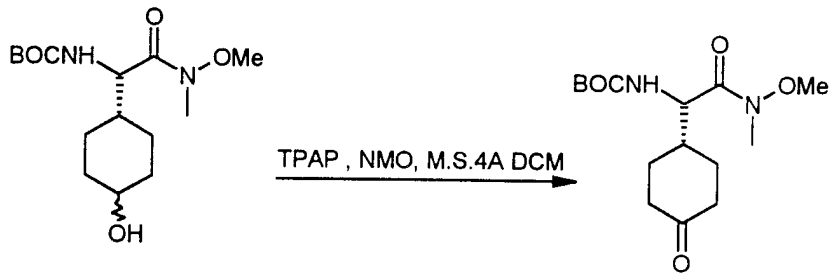
trans cis

BOP reagent (6.31 g, 14.3mmol, 1.4eq.) was added to a solution of the acid (2.8g, 10.2mmol), N,O-dimethylhydroxylamine hydrochloride (1.19g, 12.24mmol, 1.2eq .) and DIEA (5.3mL, 3eq.) in dry DMF (100 mL) at room temperature. Reaction mixture was stirred overnight, then poured into brine/water, extracted with EtOAc, and combined extracts were washed with citric acid 10%, $NaHCO_3$ sat., brine (2X), dried over Na2SO4 and concentrated to give a pale yellow oil. Purified by flash chromatography using Acetone/Toluene 40% to give two isomers cis: 47% and trans: 28% as a white solid.

^{1}HNMR (cis): 5.19 (d, 1H, J=9.7Hz); 4.64 (m, 1H); 3.97 (s, 1H); 3.77 (s, 1H); 3.20 (s, 3H); 1.78 (m, 3H); 1.63-1.24 (m, ?H) ppm

^{1}HNMR (trans): 5.15 (d, 1H, J=9.4Hz); 4.61 (m, 1H); 3.78 (s, 1H); 3.56 (m, 1H); 3.23 (s, 1H); 2.00 (m, 2H); 1.82-1.78 (m, 1H); 1.60 (m, 6H); 1.44 (s, 1H); 1.32-1.12 (m, H)ppm

EXAMPLE 3

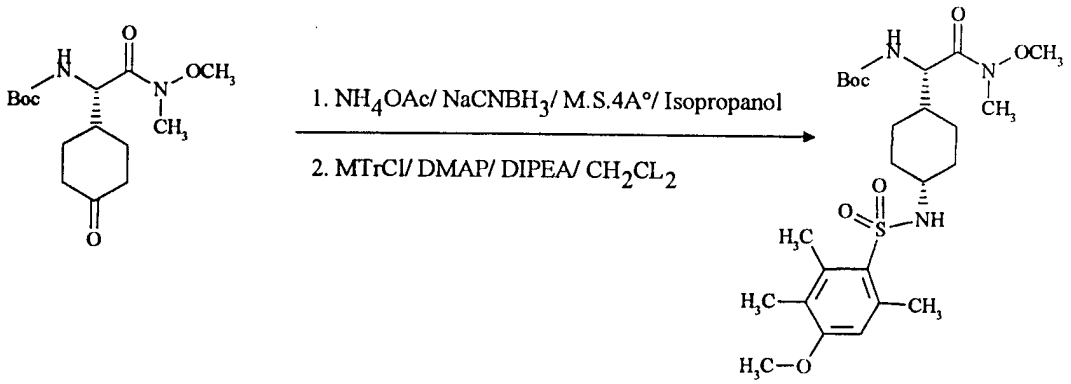


To a mixture of the alcohol (21.7 g; 0.686 mol) and powdered molecular sieves 4A (40 g) in methylene chloride (500 mL) was added NMO (17 g; 0.14 mol) followed by TPAP (2.0 g). The mixture was stirred at room temperature for 40 minutes and then filtered on celite pad and washed thoroughly with dichloromethane.

Silica gel was added to the filtrate and solvent was evaporated *in vacuo*. The adsorbed product was purified on silica gel (EtOAc 60 %, hexanes 40 %) to yield the pure ketone (15.7 g; 73 %) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.25 (d, J = 10.6 Hz, 1H), 4.69 (m, 1H), 3.74 (s, 3H), 3.19 (s, 3H), 2.39-2.33 (m, 2H), 2.32-2.22 (m, 2H), 2.11-2.03 (m, 2H), 1.93-1.90 (m, 1H), 1.65-1.46 (m, 2H), 1.38 (s, 9H).

EXAMPLE 4

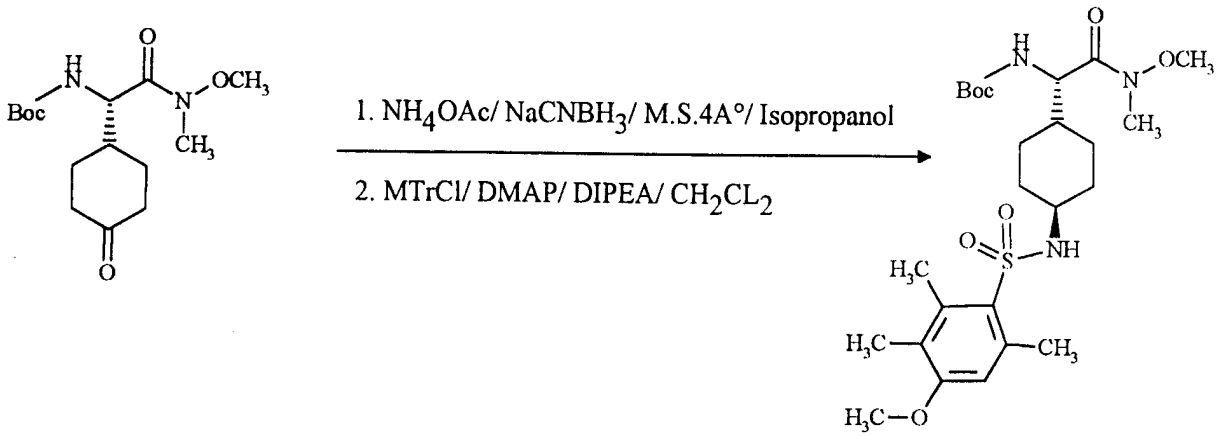


To the heterogeneous mixture of the ketone (15.72 g, 0.05 mol) in isopropanol (450 ml) was added molecular sieve powder 4A° (38 g) followed by ammonium acetate (38 g, 0.49 mol) and sodium cyanoborohydride (3.5 g, 0.055 mol). The mixture was left to stir at room temperature for 18 hours. It was then filtered over celite and washed with MeOH (1L). Solvent was evaporated until dryness and the residue thrown in NaOH 15% (800ml) and CH_2Cl_2 (800 ml). The organic phase was separated and the aqueous phase was washed again with CH_2Cl_2 (2x 800 ml). The organic phases were combined dried over $MgSO_4$ and evaporated giving an off-white foam of the crude amine (15.06 g, 0.55mol) which was used in the next step without purification.

To the crude amine in CH_2Cl_2 (400ml) was added DIPEA (30.3 ml), DMAP (1.94 g) and Mtr-Cl (33.25 g). The mixture was left to stir at room temperature for 65 hrs. 10% citric acid (500 ml) was added and the organic phase was separated and washed with 10% citric acid (200 ml), $NaHCO_3$ (sat) (200 ml) and brine (2x 200 ml). The original aqueous phase separated from the CH_2Cl_2 layer was further extracted using ETOAc (3x 600 ml). The combined ETOAc layers were also washed with 10% citric acid (300 ml), $NaHCO_3$ (sat) (300 ml) and brine (300 ml). The organic phases were then all combined, dried over $MgSO_4$ and evaporated. The crude residue was purified by flash column chromatography using a gradient of solvents starting with 30% ETOAc/Hexane followed by 40% ETOAc/Hexane and the cis diastereoisomer was isolated in 7.2% yield as the fast moving isomer by TLC.

^{1}H NMR (CD_3Cl, 400 MHz) d 1.19-1.56 (m,18H), 1.59-1.65 (m, 8H), 2.16 (s, 3H), 2.60 (s, 3H), 2.68 (s, 3H), 3.20 (s, 3H), 3.40 (m, 1 H), 3.78 (s, 3H), 3.85 (s, 3H), 4.53-4.55 (d, 1H, J = 6.74 Hz), 4.63-4.65 (m,1H), 5.09-5.11 (d, 1H, J=9.82 Hz), 6.57 (s, 1 H).

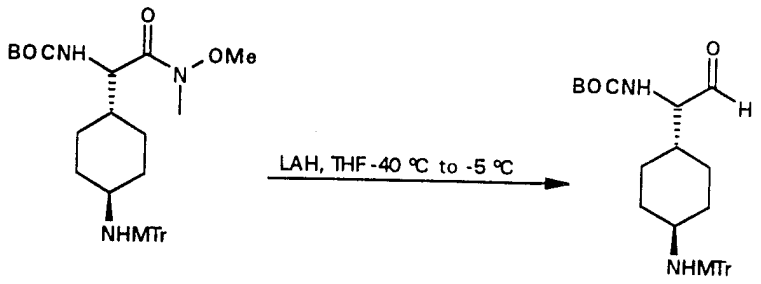
EXAMPLE 5



From example 1d, the trans diastereoisomer was isolated from the flash column chromatography in 38.3% yield as the slow moving isomer by TLC.

^{1}H NMR (CD_3Cl, 400 MHz) d 1.01-1.19 (m,5H), 1.41-1.44 (d, 10H), 1.52-1.72 (m, 5H), 1.86 (broad s, 2H), 2.15 (s, 3H), 2.56 (s, 3H), 2.67 (s, 3H), 2.98-3.00 (m, 1 H), 3.19 (s, 3H), 3.74 (s, 3H), 3.86 (s, 3H), 4.35 (d,1H), 4.54 (m,1H), 5.08-5.11 (d, 1H, J=9.66 Hz), 6.58 (s, 1 H).

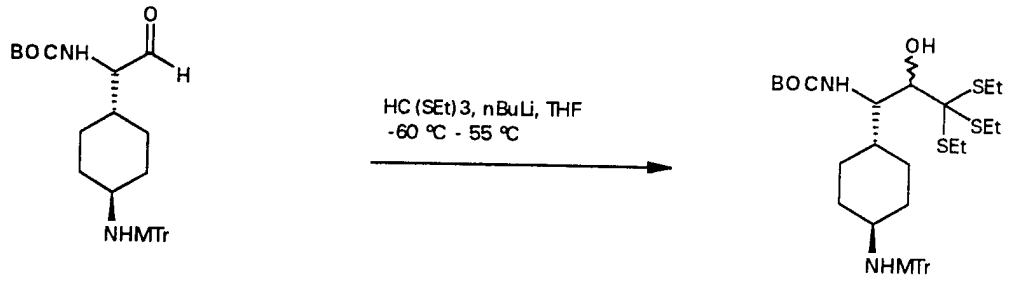
EXAMPLE 6



To a solution of the amide (1.16 g, 2.21 mmols) in THF (30 mL) was added at -40 °C a 1.0 M solution of LAH in ether (2.9 mL). The solution was warmed to ~ -5 °C - 10 °C and stirred for 50 minutes. The solution was cooled to ~ -25 °C and quenched with 1 M aqueous solution of $KHSO_4$ (10 mL). The mixture was stirred at 0 °C for 40 minutes then brine was added (30 mL). The organic phase was separated and the aqueous layer was extracted with ether (2 x 30 mL). The combined organic layers were washed successively with cold 1.0 M aqueous HCl (20 mL), cold $NaHCO_3$ (s) (20 mL), cold brine (20 mL) then dried ($MgSO_4$). Evaporation of the solvent left a white foamy solid (952 mg; 92 %) that was used in the next step without further purification.

^1H NMR ($CDCl_3$, 300 MHz) δ 9.58 (s, 1H), 6.57 (s, 1H), 5.08-5.05 (m, 1H), 4.42 (d, J = 7.7 Hz, 1H), 4.22-4.18 (m, 1H), 3.85 (s, 3H), 3.02-2.98 (m, 1H), 2.66 (s, 3H), 2.56 (s, 3H), 2.14 (s, 3H), 1.87-1.35 (m, 5 H), 1.42 (s, 9H), 1.20-1.13 (m, 4H).

EXAMPLE 7

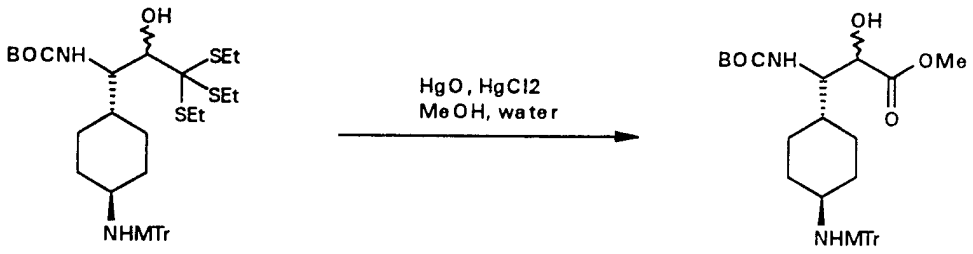


To a solution of ethyl orthothioformate (2.7 mL; 14 mmols) in THF (30 mL) was added at - 60 °C - 55 °C n-BuLi in hexanes (1.3 M, 9.0 mL, 12 mmols). The solution was

stirred at - 60 °C - 55 °C for 30 minutes then a solution of the aldehyde (932 mg; 2.00 mmols) in THF (10 mL) was added so that the temperature was maintained at - 60 °C - 55 °C. The solution was then stirred at - 40 °C for 1.5 hours then quenched at this temperature with a saturated solution of ammonium chloride in water (25 mL) and ether (30 mL) was added. The organic layer was separated and the aqueous phase was extracted with ether (2 x 30 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Purification on silica gel (EtOAc 25 % to 30 % in hexanes) afforded the desired product (975 mg, 73 %) as a mixture of isomers.

Major isomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.58 (s, 1H), 5.26 (d, J = 8.7 Hz, 1H), 4.32 (d, J = 7.5 Hz, 1H), 3.87 (s, 3H),3.87-3.82 (m, 1H) 3.70 (s, 1H), 3.40 (s, 1H), 3.05-2.95 (m,1H), 2.83-2.74 (m, 6H), 2.68 (s, 3H), 2.57 (s, 3H), 2.16(s, 3H), 1.88-1.60 (complex signal, 5H), 1.42 (s, 9H), 1.28-1.21 (m, 9H), 1.16-1.09 (m, 4H).

EXAMPLE 8

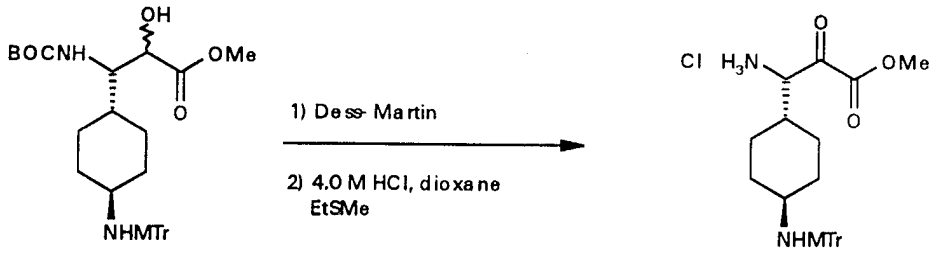


To a solution of the orthothioformate (2.56 g; 3.85 mmols) in methanol (69 mL) and water (4 mL) was added HgO (732 mg) and mercuric chloride (2.69 g). The mixture was stirred at room temperature for 2 hours then at 60 °C for 30 minutes. The mixture was filtered on a celite pad and washed with methanol (2 x 4 mL), and dichloromethane (3 x 20 mL). Water (80 mL) and dichloromethane (40 mL) was added to the filtrate and the organic layer was separated. The aqueous phase was extracted with dichloromethane (2 x 80 mL). The combined organic layers were washed with a 70 % aqueous ammonium acetate solution (200 mL) and the aqueous layer extracted with dichloromethane (2 x 200 mL). The combined organic layers were washed with a saturated aqueous solution of ammonium chloride and dried ($MgSO_4$). Purification on

silica gel (EtOAc 50%, hexanes 50%) afforded the hydroxy ester (1.33 g; 65 %) as a mixture of isomers.

Major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.58 (s, 1H), 5.26 (d, J = 8.7 Hz, 1H), 4.32-4.29 (m, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 3.68 (t, J = 9.0 Hz, 1H), 3.10 (bs, 1H), 3.00 (bs, 1H), 2.68 (s, 3H), 2.58 (s, 3H), 2.16 (s, 3H), 1.93-1.83 (complex signal, 4H), 1.59 (bs, 1H), 1.39 (s, 9H), 1.25-1.00 (complex signal, 4H).

EXAMPLE 9

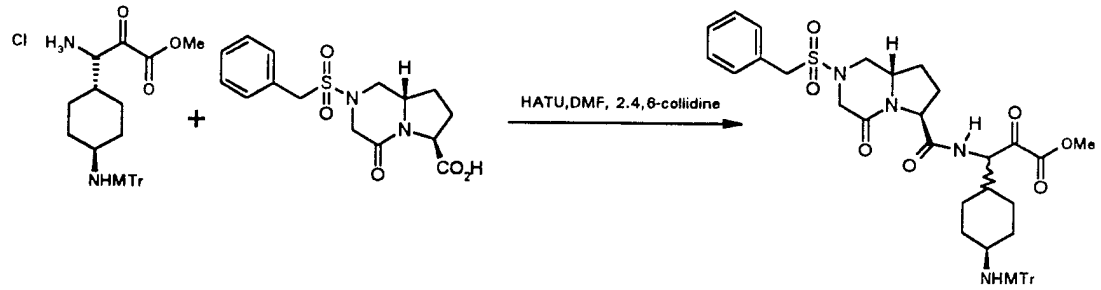


To a solution of the alcohol (812 mg; 1.54 mmols) in dichloromethane (100 mL) was added Dess-Martin reagent (3.0 g, 7.0 mmols). The resulting mixture was stirred at room temperature for 30 minutes then quenched with a solution of sodium thiosulphate (15 g) in a saturated aqueous solution of $NaHCO_3$ (150 mL). The mixture was stirred for about 10 minutes and the organic layer was separated. The aqueous layers were extracted with ethyl acetate (3 x 100 mL) and the combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ then dried ($MgSO_4$). Purification on silica gel (EtOAc 50%, hexanes 50%) afforded the keto ester (772 g; 95 %) pure as a white solid.

This keto ester (772 mg) was dissolved in ethyl methyl sulfide (2 mL) and treated with 4.0 M HCl in dioxane (20 mL). The solution was stirred at room temperature for 30 minutes then volatiles were evaporated *in vacuo* to yield the crude deprotected amine (854 mg) which was used in the next step without further purification.

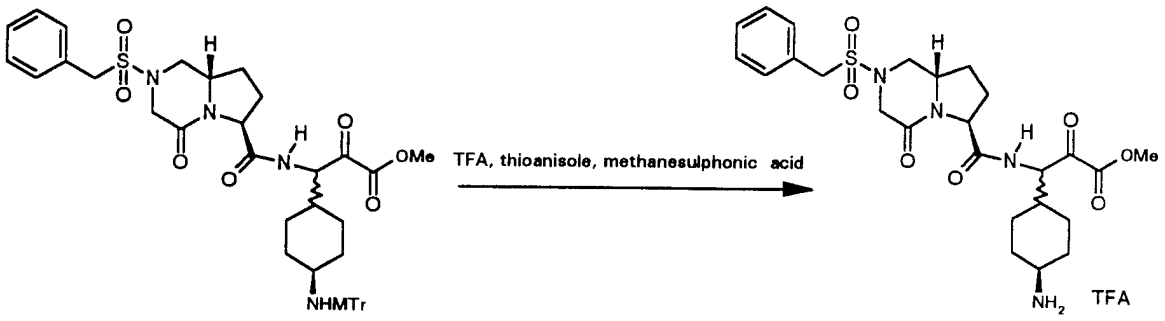
^{1}H NMR (DMSO, 400 MHz) d 8.46 (bs, 3H), 7.41 (d, J = 8.3 Hz, 1H), 6.78 (s, 1H), 4.43 (bs, 1H), 3.82 (s, 6H), 2.85-2.74 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.08 (s, 3H), 1.98-1.88 (m, 1H), 1.61-1.41 (m, 4H), 1.24-1.02 (m, 4H).

EXAMPLE 10



To a solution of the keto ester (830 mg; 1.79 mmols) in DMF (15 mL) was added successively 2,4,6-collidine (1.6 mL), the acid (460 mg; 1.36 mmols) followed by HATU (700 mg; 1.84 mmols). The solution was stirred at room temperature for 18 hours then transferred into brine (50 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 70 mL). The combined organic layers were washed with 10 % aqueous citric acid (100 mL), a saturated aqueous solution of $NaHCO_3$ (100 mL), brine (100 mL) and dried ($MgSO_4$). Purification on silica gel (EtOAc 100%) afforded the coupled product (781 g; 77 %) as foamy solid.

EXAMPLE 11

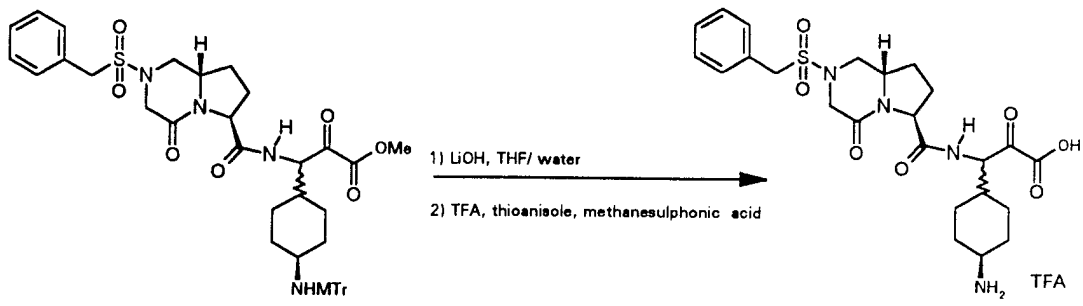


Compound 1

The substrate was dissolved in thioanisole (1.5 mL) and TFA (15 mL) and methanesulphonic acid (44 uL) were added. The solution was stirred at room temperature for 16 hours and TFA was removed *in vacuo*. Ether (20 mL) was added to precipitate the resulting amine salt which was filtered and washed several times with ether. Purification of the crude compound on HPLC gave the compound 1 (71 mg, 24%) as mixture of isomers at the cyclohexyl moiety.

^{1}HNMR (D_2O, 400 MHz) d 7.38-7.31 (m, 5H), 4.53-4.45 (m, 2H), 4.39-4.31 (m, 1H), 4.08-4.04 (m, 1H), 3.95-3.84 (m, 2H), 3.79-3.67 (m, 2H), 3.67 (s, 3H), 3.54 (d, J = 17.4 Hz, 1H), 3.03-2.95 (m, 1H), 2.74-2.68 (m, 1H), 2.43-2.22 (m, 1H), 2.12-1.97 (m, 4H), 1.81-1.56 (m, 3H), 1.46-0.95 (m, 4H).

EXAMPLE 12



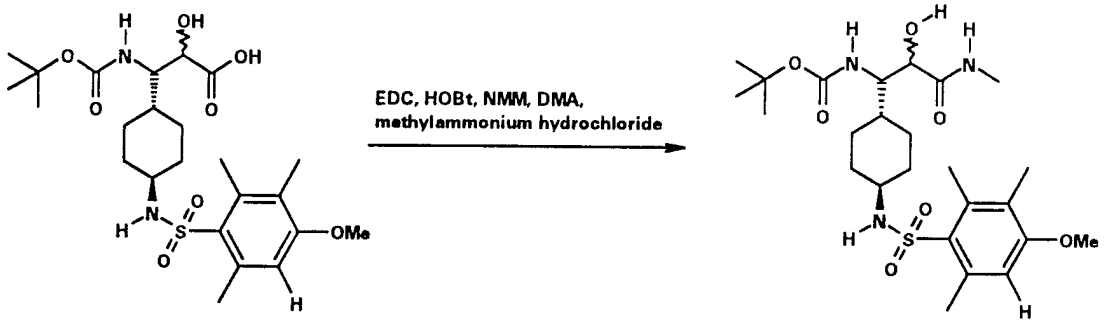
Compound 2

To a solution of the ester (410 mg; 0.548 mmols) in THF (20 mL) was added a solution of $LiOH \bullet H_2O$ (100 mg; 2.38 mmols) in water (20 mL). The solution was stirred at room temperature for one hour then poured into a 5% aqueous solution of hydrochloric acid (80 mL) and extracted with dichloromethane (3 x 80 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to yield the crude acid (376 mg; 94%) that was used in the next step directly.

The substrate was dissolved in thioanisole (1.5 mL) and TFA (15 mL) and methanesulphonic acid (50 uL) were added. The solution was stirred at room temperature for 16 hours and TFA was removed *in vacuo*. Ether (20 mL) was added to precipitate the resulting amine salt which was filtered and washed several times with ether. Purification of the crude compound on HPLC gave compound 2 (77 mg, 24%) as mixture of isomers at the cyclohexyl moiety.

^{1}HNMR (D_2O, 400 Mhz) d 7.39-7.33 (m, 5H), 4.95 (t, J = 4.6 Hz, 1H), 4.54-4.47 (m, 2H), 4.45-4.34 (m, 1H), 3.91-3.85 (complex signal, 2H), 3.78-3.72 (m, 1H), 3.57 (d, J = 16.2 Hz, 1H), 3.03-2.94 (m, 1H), 2.76-2.69 (m, 1H), 2.44-2.31 (m, 1H), 2.06-1.85 (m, 4H), 1.78-1.68 (m, 2H), 1.61-1.48 (m, 1H), 1.45-0.94 (m, 5H).

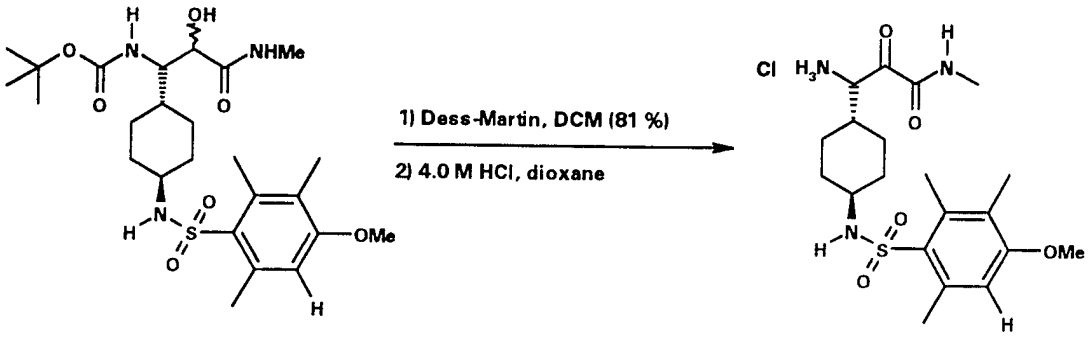
EXAMPLE 13



To a solution of the acid (173 mg; 0.337 mmol) in DMA (10 mL) was added successively NMM (75 uL; 69 mg; 0.682 mmol), HOBt (78 mg; 0.58 mmol), methylammonium hydrochloride (68 mg; 1.0 mmol). The mixture was stirred at roo temperature for 10 minutes then EDC (107 mg; 0.560 mmol) and stirred 16 hours.

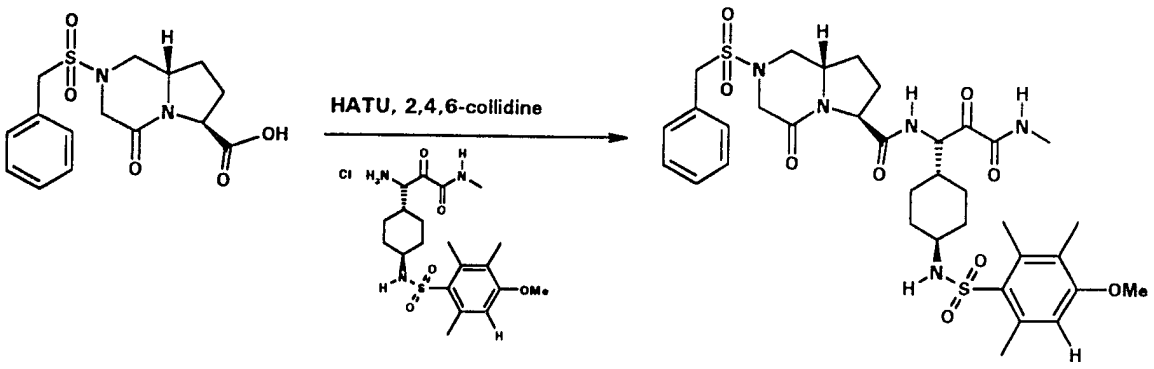
The mixture was poured into ethyl acetate (80 mL) and washed with a 10% aqueous solution of citric acid (30 mL), a saturated aqueous solution of $NaHCO_3$(2 x 30 mL), brine (30 mL) and the organic layer was dried ($MgSO_4$) to afford the amide (167 mg; 94%) that was used in the next step without further purification.

EXAMPLE 14



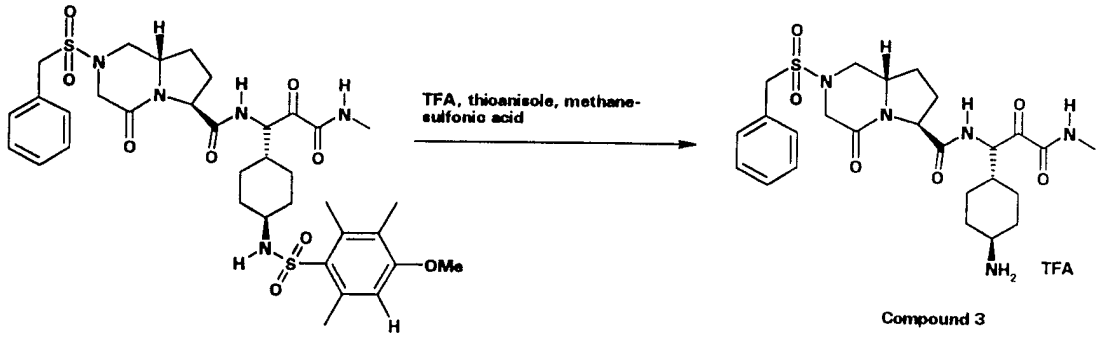
Following exactly the same procedure used in example 5, the alcohol (133 mg; 0.254 mmol) was oxidized and deprotected to the ketoamide (130 mg; 81 %) as a yellow foamy solid.

EXAMPLE 15



Using the same procedure used in Example 6, the carboxylic acid (103 mg; 0.303 mmols) was coupled with the cyclohexylamine derivative (130 mg; 0.282 mmol) to give the product (157 mg; 69 %) as a foamy solid.

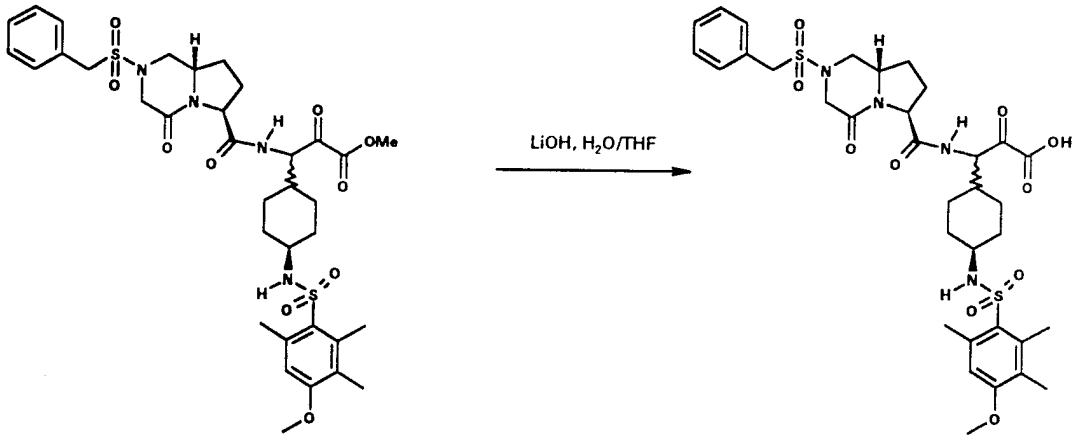
EXAMPLE 16



Compound 3

The substrate (157 mg; 0.210 mmol) was dissolved in thioanisole (0.8 mL) and TFA (8 mL) and methanesulphonic acid (20 uL) were added. The solution was stirred at room temperature for 16 hours and TFA was removed *in vacuo*. Ether (20 mL) was added to precipitate the resulting amine salt which was filtered and washed several times with ether. Purification of the crude compound on HPLC gave the analog **compound 3** (79 mg, 58 %) as mixture of isomers at the cyclohexyl moiety.

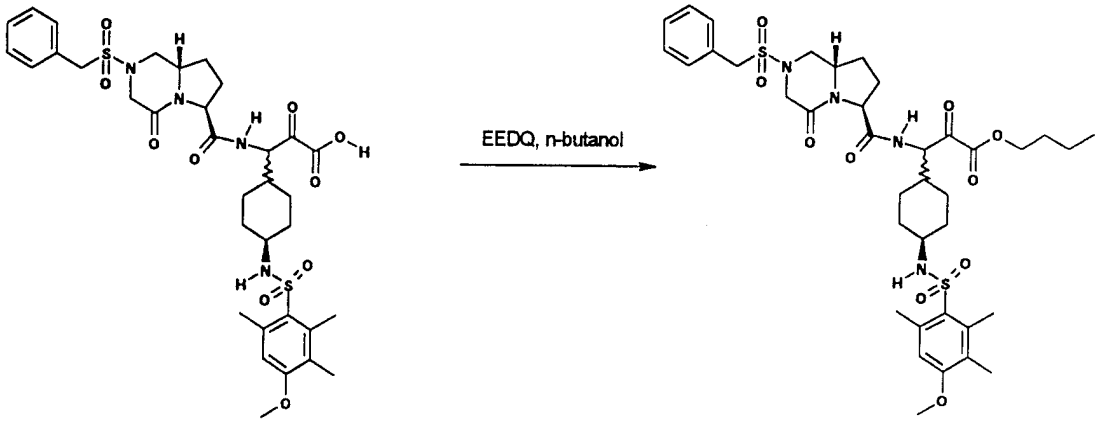
EXAMPLE 17



To a solution of the ester (1.35 g, 1.81 mmols) in THF (40 mL) was added $LiOH \cdot H_2O$ (150 mg; 3.57 mmols) in water (40 mL). The solution was stirred at room temperature for two hour then poured into 5 % HCl (100 mL) and extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to

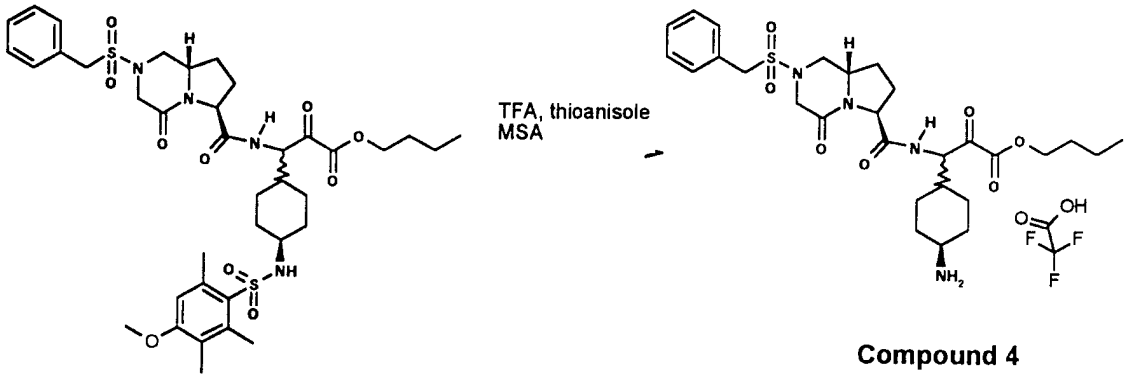
afford the acid (1.34 mg, 100 %) which was used in the next step without further purification.

EXAMPLE 18



To a solution of the acid (735 mg, 1.00 mmols) in butanol (20 mL) was added EEDQ (300 mg, 1.21 mmols) and stirred overnight at room temperature. The mixture was poured into ethyl acetate (200 mL) and washed successively with HCl 5% (100 mL), saturated $NaHCO_3$ (100 mL), brine, dried ($MgSO_4$) and evaporated. The residue was purified on silica gel (EtOAc 80%, hexanes 20%) to afford the butyl ester ((353 mg, 44%).

EXAMPLE 19



Compound 4

To a solution of the protected compound (350 mg, 0.444 mmols) in TFA (18 mL) was added thioanisole (2 mL) and methanesulfonic acid (50 ml. 0.77 mmols). The solution

was stirred overnight and TFA was evaporated. Ether was added to the residue and the resulting solid was filtered and washed several times with ether. This solid was purified by preparative HPLC to afford, after lyophilization, **compound 4** (211 mg, 69 %) as white powder.

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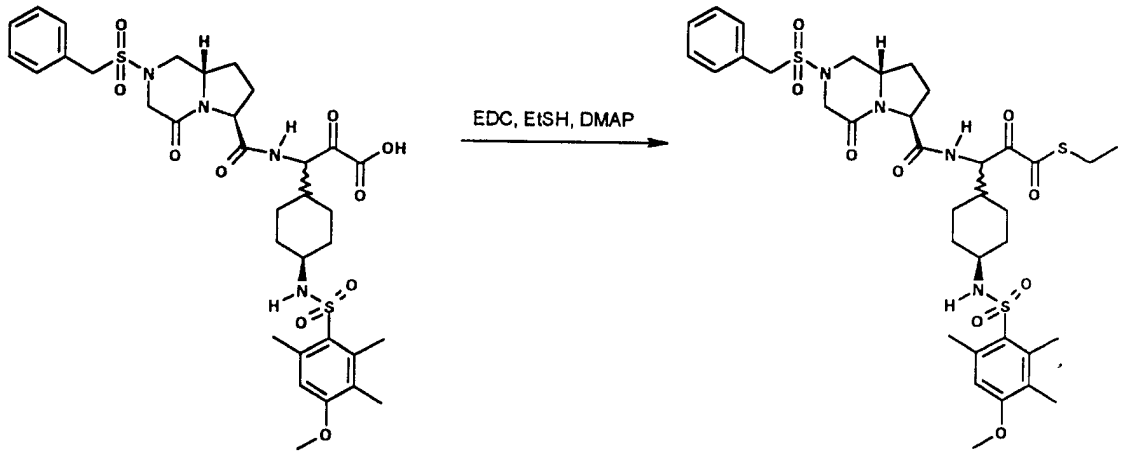
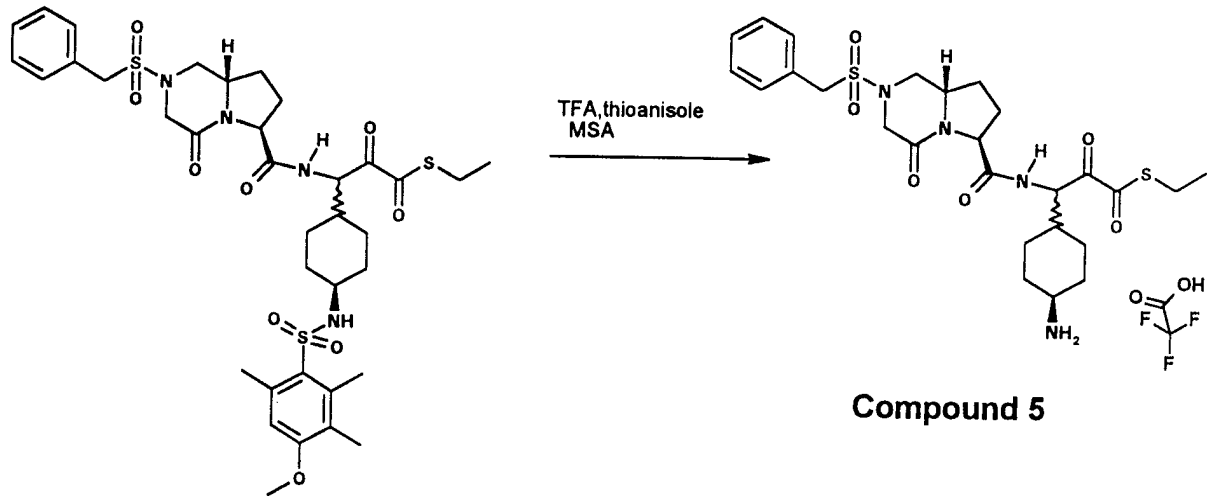
EXAMPLE 20



10 To a solution of the acid (605 mg, 0.825 mmols) in dichloromethane (10 mL) was added EtSH (0.2 mL, 2.70 mmols), DMAP (10 mg) followed by EDC (180 mg, 0.94 mmols). The solution was stirred over the weekend at room temperature then poured into a 10% aqueous citric acid solution and extracted with ethyl acetate 3 times. The combined organic layers were washed successively with a 10% aqueous citric acid
15 solution, a saturated $NaHCO_3$ solution, brine, dried ($MgSO_4$) and evaporated. The residue was purified on silica gel (EtOAc 80%, hexanes 20%) to afford the thioester (149 mg, 23%).

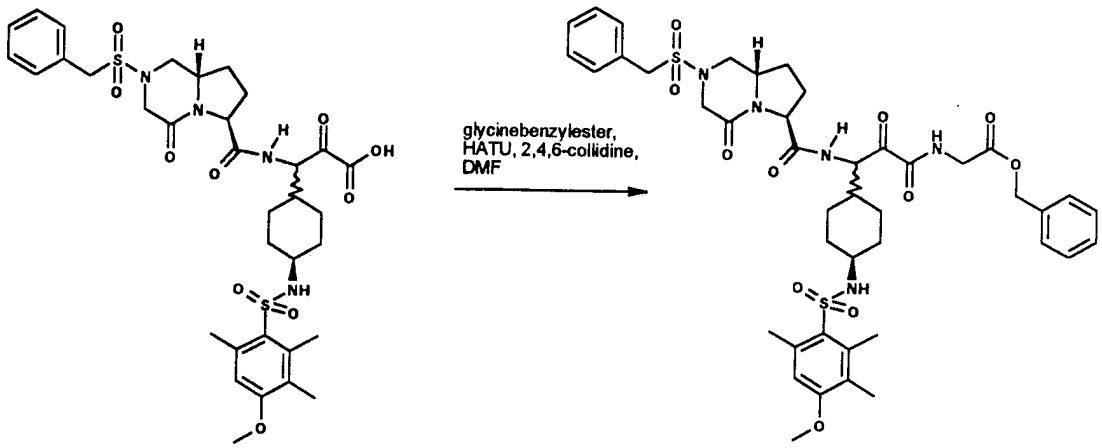
EXAMPLE 21



Compound 5

To a solution of the protected compound (149 mg, 0.192 mmols) in TFA (9 mL) was added thioanisole (1 mL) amd methanesulfonic acid (20 ml. 0.31 mmols). The solution was stirred overnight and TFA was evaporated. Ether was added to the residue and the resulting solid was filtered and washed several times with ether. This solid was purified by preparative HPLC to afford, after lyophilization, **compound 5** (77 mg, 59 %) as white powder.

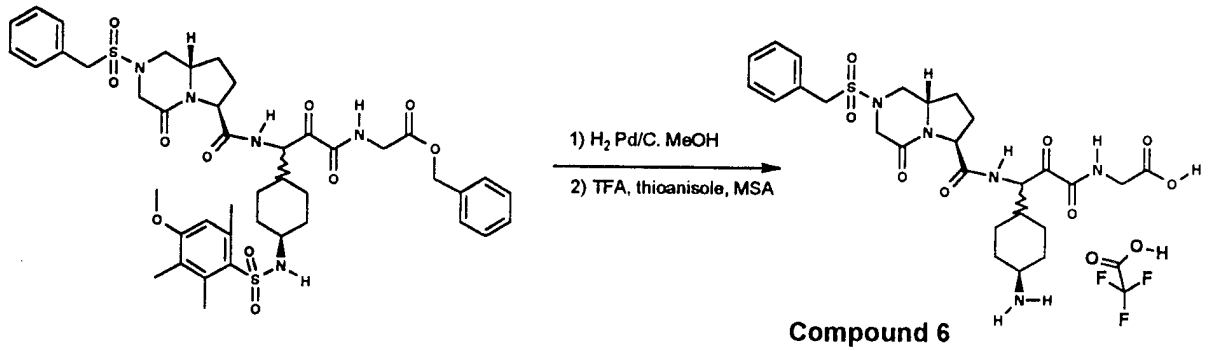
EXAMPLE 22



To a solution of the acid (400 mg, 0.546 mmol) in dry DMF (4 mL) was added the glycine (131 mg, 0.652 mmols) followed by collidine (0.5 mL) and by HATU (270 mg,

0.710 mmols). The solution was stirred at room temperature overnight, poured into a 10% citric acid solution , extracted with ethyl acetate (3 times). The combined organic layers were washed successsively with a saturated solution of $NaHCO_3$, a 10 % citric acid solution, brine then dried ($MgSO_4$). The residue was purified on silica gel (EtOAC 100 %) to afford the coupled product (305 mg, 63 %).

EXAMPLE 23



Compound 6

To a solution of the benzyl ester (300 mg, 0.340 mmol) in dry methanol (20 mL) was added the palladium (500 mg) and hydrogenated with H_2 (1 atm). The mixture was stirred at room temperature for 3.5 hours then filtered on celite and volatiles evaporated.

The resulting residue was dissolved in TFA (14 mL) and thioanisole (1.4 mL) was added followed by methanesulfonic acid (27 ml. 0.416 mmols). The solution was stirred overnight and TFA was evaporated. Ether was added to the residue and the resulting solid was filtered and washed several times with ether. This solid was purified by preparative HPLC to afford, after lyophilization, **compound 6** (50 mg, 21 %) as white powder.

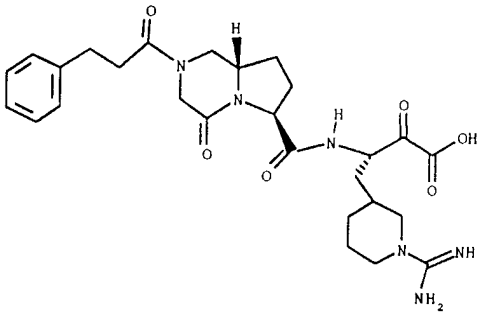
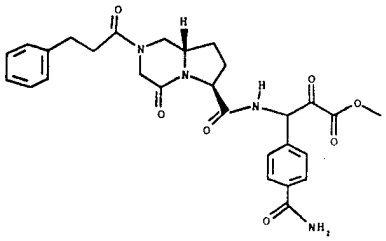
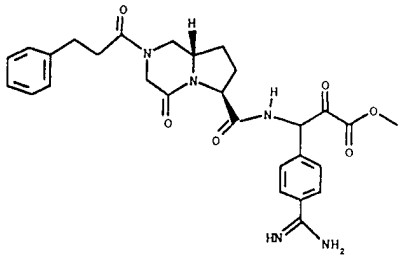
EXAMPLE 24

The affinity of inhibitors for thrombin is measured according to the procedures described in (DiMaio et al, J. Bio. Chem., 1990, 265:21698). Inhibition of amidolytic activity of human thrombin is measured fluorometrically using Tos-Gly-Pro-Arg-AMC as a fluorogenic substrate in 50 mM Tris-HCl buffer (pH 7.52 at 37°C) containing 0.1 M NaCl and 0.1% poly(ethylene glycol) 8000 at room temperature, and (Szewczuk et al., Biochemistry, 1992 31:9132).

The hydrolysis of the substrate by thrombin is monitored on a Varian-Cary 2000™ spectrophotometer in the fluorescence mode (λeX = 383 nm, λem = 455 nm) or on a Hitachi F2000™ fluorescence spectrophotometer (λ_{eX} = 383 nm, λ_{em} = 455 nm), and the fluorescent intensity is calibrated using AMC. The reaction reaches a steady-state within 3 minutes after mixing thrombin with the substrate and an inhibitor. The steady-state velocity is then measured for a few minutes. The compounds may be pre-incubated with thrombin for 20 minutes at room temperature before adding the substrate. The steady-state is achieved within 3 min and measured for a few min. The kinetic data (the steady-state velocity at various concentrations of the substrate and the inhibitors) of the competitive inhibition is analyzed using the methods described by Segel (1975). A non-linear regression program, RNLIN in the IMSL library (IMSL, 1987), LMDER in MINPACK library (More et al., 1980) or Microsoft™ Excell™ , may be used to estimate the kinetic parameters (K_m V_{max} and K_i).

Table 1 *In vitro* Activity of Inhibitors Against Human α Thrombin

Compound	Ki(nM)	$Ki^{(try/th)*}$
1	0.131	-
2	0.09	24000
3	0.33	7000
4	low nM	-
5	0.258	600
6	2.136	14000

Compound	
	IC_{50}= 5nM
	55% inhibition at 100 uM
	IC_{50} = 11400 nM

*$Ki^{(try/th)}$= Ki for Trypsin/Ki for Thrombin

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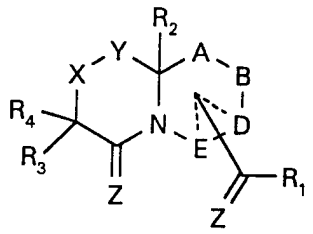
We claim

1. A compound of formula (I):



(I)

wherein:

A is selected from the group consisting of $(CH\text{-}R_8)_{0\text{-}1}$, S, SO, SO_2, O and NR_8 wherein R_8 is hydrogen, $C_{1\text{-}6}$ alkyl optionally interrupted with 1 or 2 heteroatoms; $C_{6\text{-}16}$ aryl, $C_{3\text{-}7}$ cycloalkyl or heterocyclic ring or a hydrophobic group;

B is selected from the group consisting of S, SO_2, O, -N=, NH, -CH= and CR_6R_7 wherein R_6 and R_7 are independently selected from hydrogen and $C_{1\text{-}6}$ alkyl provided that when A is S, SO, SO_2, O, or NR_8, then B is CR_6R_7;

D is selected from the group consisting of$(CH\text{-}R_9)_{0\text{-}2}$, wherein R_9 is hydrogen, $C_{1\text{-}6}$ alkyl or $-C(O)R_1$; and CH with a double bond to B when B is -N= or -CH=;

E is selected from the group consisting of CH_2 and CH substituted with the $-C(O)R_1$, provided that only one of D and E is substituted with $-C(O)R_1$;

X is $N\text{-}R_5$;

Y is selected from the group consisting of $CH\text{-}R_8$ or O

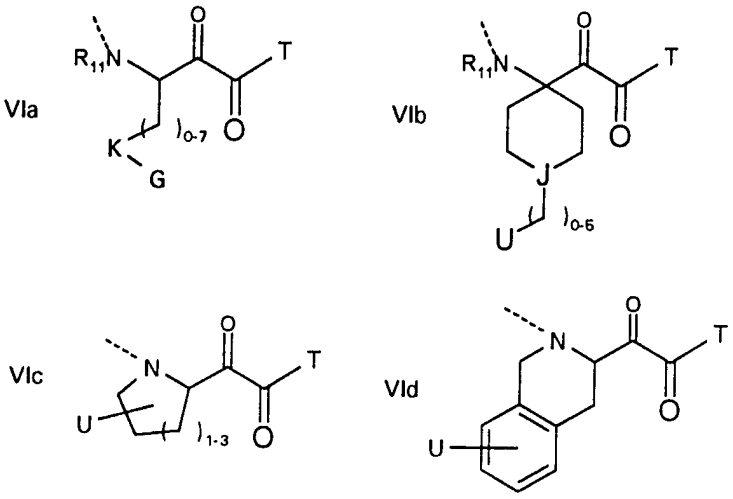
Z is selected from the group consisting of O, S and H_2

R_2 is selected from the group consisting of H and $C_{1\text{-}6}$ alkyl optionally substituted with C_6 aryl, a 6 member heterocycle or a $C_{3\text{-}7}$ cycloalkyl ring

R_3 is selected from H, NR_6R_7 and $C_{1\text{-}6}$ alkyl;

R_4 and R_5 are independently selected from the group consisting of H; NR_6R_7; $C_{6\text{-}16}$ aryl or $C_{3\text{-}7}$ cycloalkyl optionally substituted with $C_{1\text{-}6}$ alkyl; $C_{1\text{-}16}$ alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_6R_7 or a $C_{6\text{-}16}$ aryl, heterocycle or $C_{3\text{-}7}$ cycloalkyl group optionally substituted with halogen, hydroxyl, $C_{1\text{-}6}$ alkyl; an amino acid side chain; and a hydrophobic group; and

R_1 is selected from the group consisting of formula VIa, VIb, VIc and VId:



wherein:

R_{11} is selected from the group consisting of hydrogen or C_{1-6} alkyl;

J is selected from the group consisting of CH or N;

K is selected from the group consisting of a bond and -NH-;

G is selected from the group consisting of C_{1-4} alkoxy; cyano; $-NH_2$; $-CH_2-NH_2$; $-C(NH)-NH_2$; $-NH-C(NH)-NH_2$; $-CH_2-NH-C(NH)-NH_2$; a C_6 cycloalkyl or aryl substituted with cyano, $-NH_2$, $-CH_2-NH_2$, $-C(NH)-NH_2$, $-NH-C(NH)-NH_2$ or $-CH_2-NH-C(NH)-NH_2$; or a 5 or 6 member, saturated or unsaturated heterocycle optionally substituted with cyano, $-NH_2$, $-CH_2-NH_2$, $-C(NH)-NH_2$, $-NH-C(NH)-NH_2$ or $-CH_2-NH-C(NH)-NH_2$;

U is selected from the group consisting of cyano, $-NH_2$, $-C(NH)-NH_2$ or $-NH-C(NH)-NH_2$;

T is selected from the group consisting of H, OH, amino, a peptide of 1 to 4 amino acid residues, C_{1-16} alkyl, C_{1-16} alkoxy, C_{6-20} aralkyl, C_{6-16} aryloxy; C_{6-20} arylalkoxy or an aryl or heterocycle optionally substituted; and

pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein one of R_4 and R_5 is a hydrophobic group selected from the group consisting of C_{1-20} alkyl, C_{2-20} alkenyl or C_{2-20} alkynyl optionally interrupted by a carbonyl group, C_{6-16} aryl, C_{3-7} cycloalkyl, C_{6-20} aralkyl, C_{6-20} cycloalkyl substituted C_{1-20} alkyl, wherein the aliphatic portion

is optionally interrupted by a carbonyl group and the ring portion is optionally substituted with C_{1-6} alkyl; and a hydrophobic amino acid side chain.

3. A compound according to claim 1, wherein R_3 is selected from the group consisting of H, methyl and ethyl .

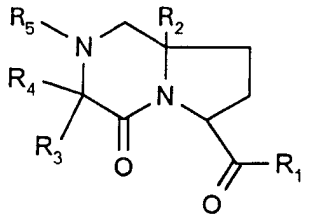
4. A compound according to claim 1, wherein R_3 is H.

5. A compound according to claim 1, wherein Z is O.

6. A compound according to claim 1, wherein R_2 is selected from H, methyl and ethyl .

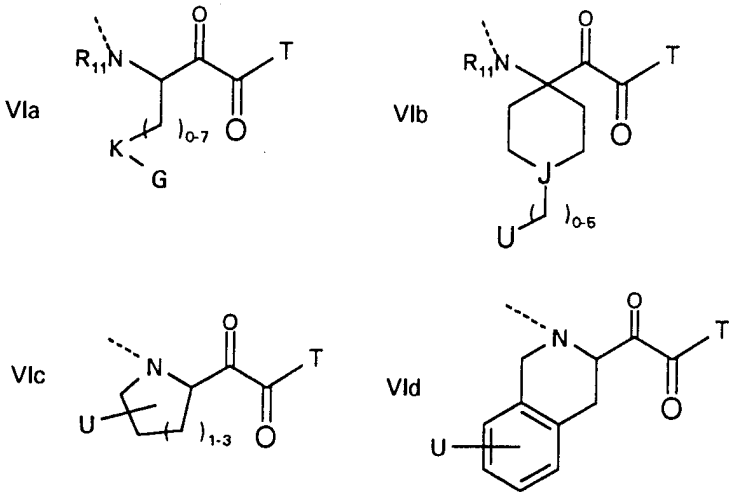
7. A compound according to claim 1, wherein R_2 is H.

8. A compound of formula (VIII):



wherein

R_2 is selected from the group consisting of H and C_{1-6} alkyl;
R_3 is selected from the group consisting of H, NR_6R_7 and C_{1-6} alkyl; and
R_4 and R_5 are independently selected from the group consisting of H; NR_6R_7 wherein R_6 and R_7 are independently hydrogen or C_{1-6} alkyl; C_{6-16} aryl or C_{3-7} cycloalkyl optionally substituted with C_{1-6} alkyl; C_{1-16} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_6R_7 or a C_{6-16} aryl, heterocycle or C_{3-7} cycloalkyl group optionally substituted with halogen, hydroxyl, C_{1-6} alkyl; an amino acid side chain; and a hydrophobic group;
R_1 is selected from the group consisting of formula VIa, VIb, VIc and VId:



wherein:

R_{11} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

J is selected from the group consisting of CH and N;

K is selected from the group consisting of a bond and -NH-;

G is selected from the group consisting of C_{1-4} alkoxy; cyano; $-NH_2$; $-CH_2-NH_2$; $-C(NH)-NH_2$; $-NH-C(NH)-NH_2$; $-CH_2-NH-C(NH)-NH_2$; a C_6 cycloalkyl or aryl substituted with cyano, $-NH_2$, $-CH_2-NH_2$, $-C(NH)-NH_2$, $-NH-C(NH)-NH_2$ or $-CH_2-NH-C(NH)-NH_2$; or a 5 or 6 member, saturated or unsaturated heterocycle optionally substituted with cyano, $-NH_2$, $-CH_2-NH_2$, $-C(NH)-NH_2$, $-NH-C(NH)-NH_2$ or $-CH_2-NH-C(NH)-NH_2$;

U is selected from the group consisting of cyano, $-NH_2$, $-C(NH)-NH_2$ or $-NH-C(NH)-NH_2$;

T is s selected from the group consisting of of H, OH, amino, a peptide of 1 to 4 amino acid residues, C_{1-16} alkyl, C_{1-16} alkoxy, C_{6-20} aralkyl, C_{6-16} aryloxy; C_{6-20} arylalkoxy , a C_{6-16} aryl or heterocycle optionally substituted.

9. A compound according to claim 8 wherein either of R_4 and R_5 is H while the other is a C_{1-16} alkyl optionally interrupted by one or more heteroatom selected from the group consisting of SO_2 and a carbonyl group and is substituted with C_{6-16} aryl, heterocycle or C_{3-7} cycloalkyl group optionally substituted with halogen, hydroxyl or C_{1-6} alkyl.

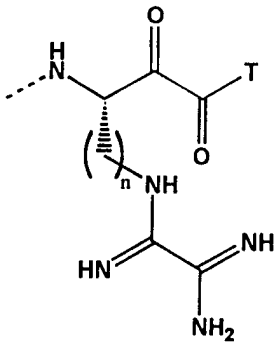
10. A compound according to claim 9 wherein R_4 is H and R_5 is C_{1-5} alkyl optionally interrupted adjacent to the bicyclic ring with SO_2 or carbonyl and is terminally substituted with C_{6-16} aryl.

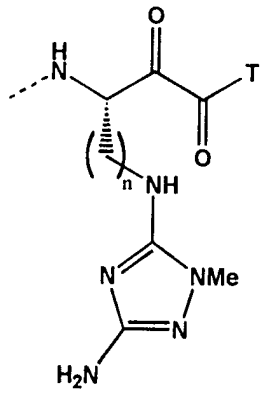
11. A compound according to claim 10 wherein R_3 where is selected from the group consisting of H and C_{1-16} alkyl .

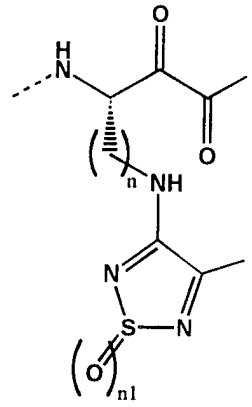
12. A compound according to claim 11 wherein R_3 where is H.

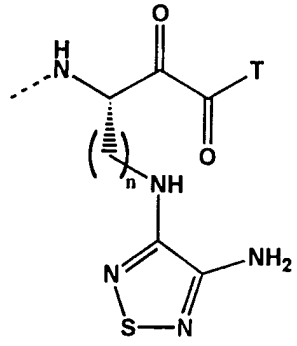
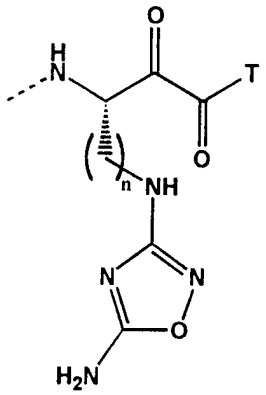
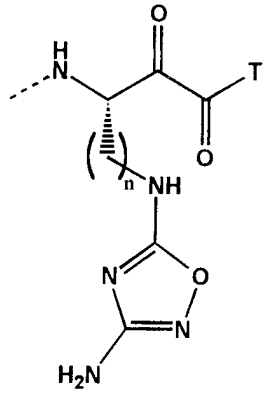
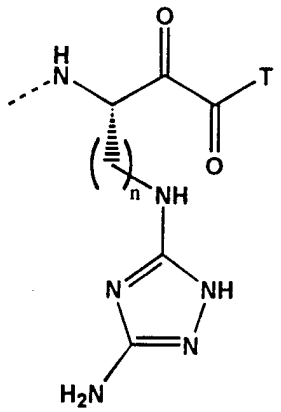
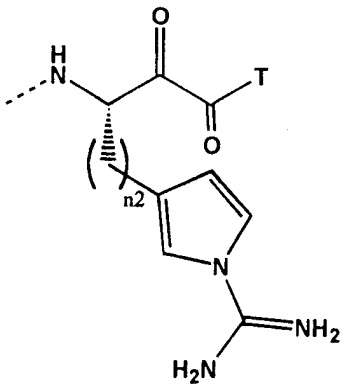
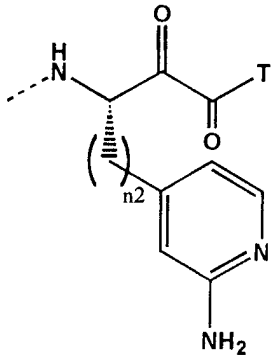
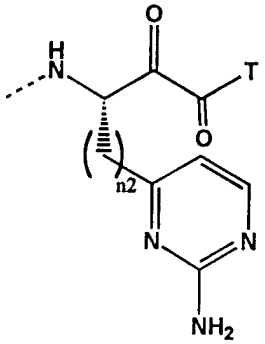
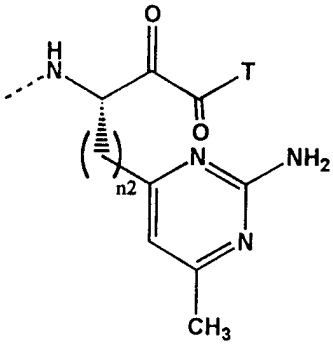
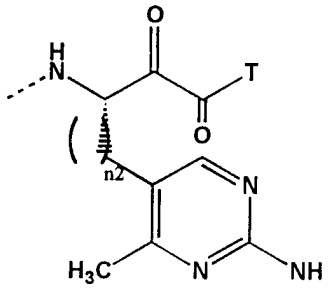
13. A compound according to claim 8 wherein R_2 is H.

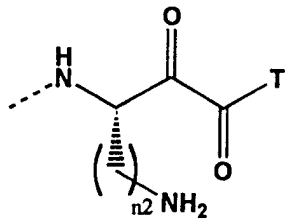
14. A compound according to claim 8 wherein R_1 is selected from the group consisting of

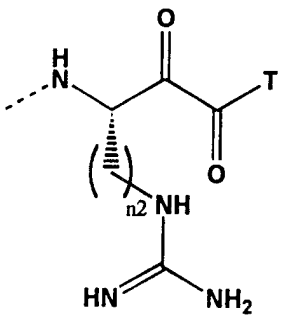


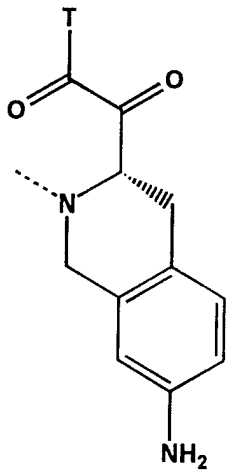


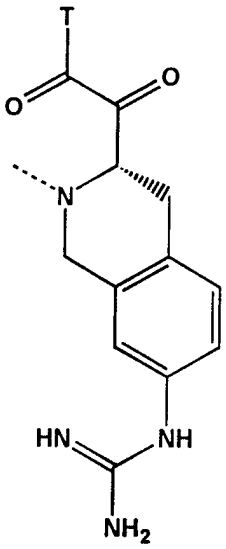


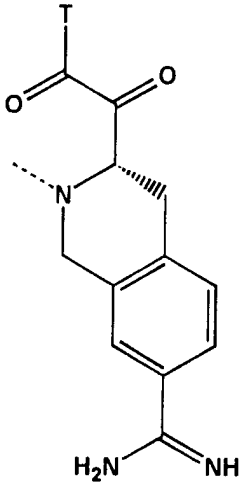










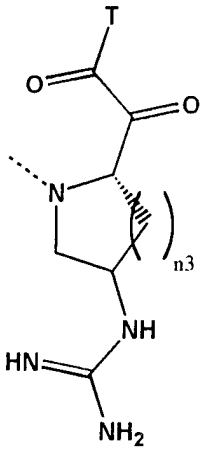


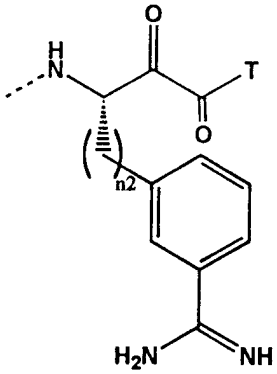


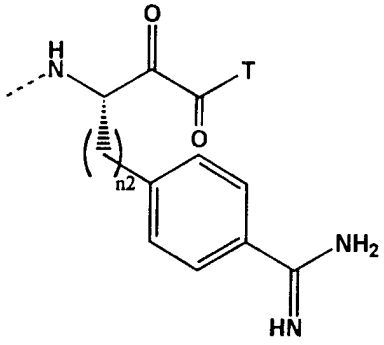


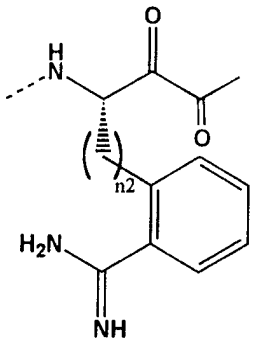


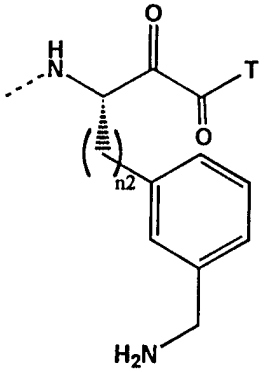


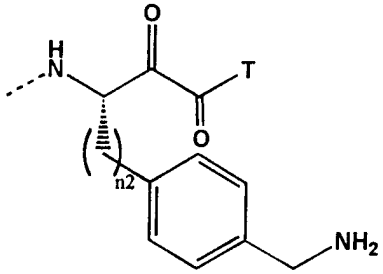


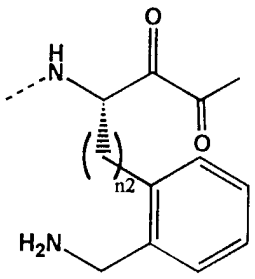


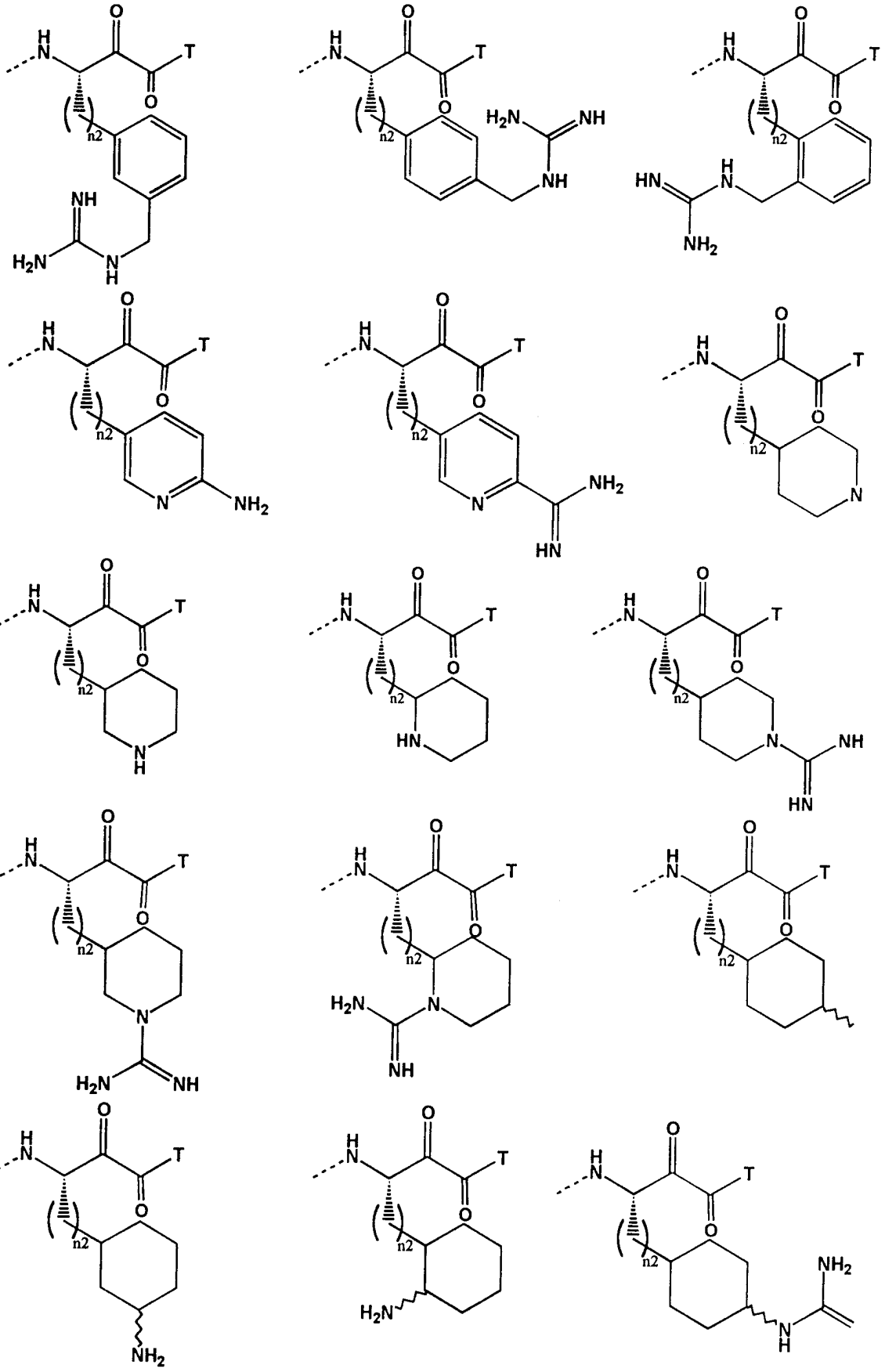


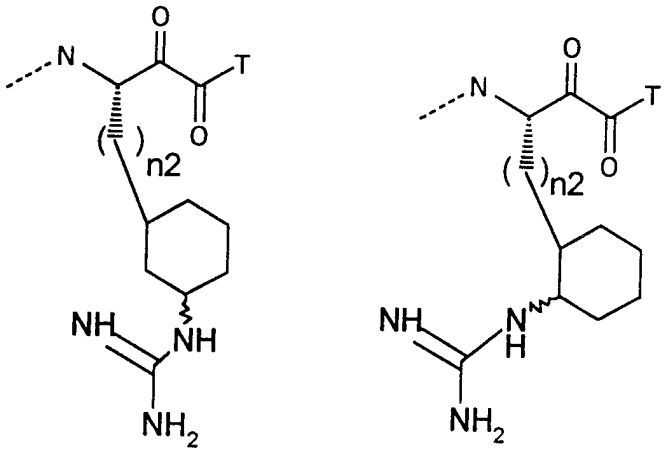






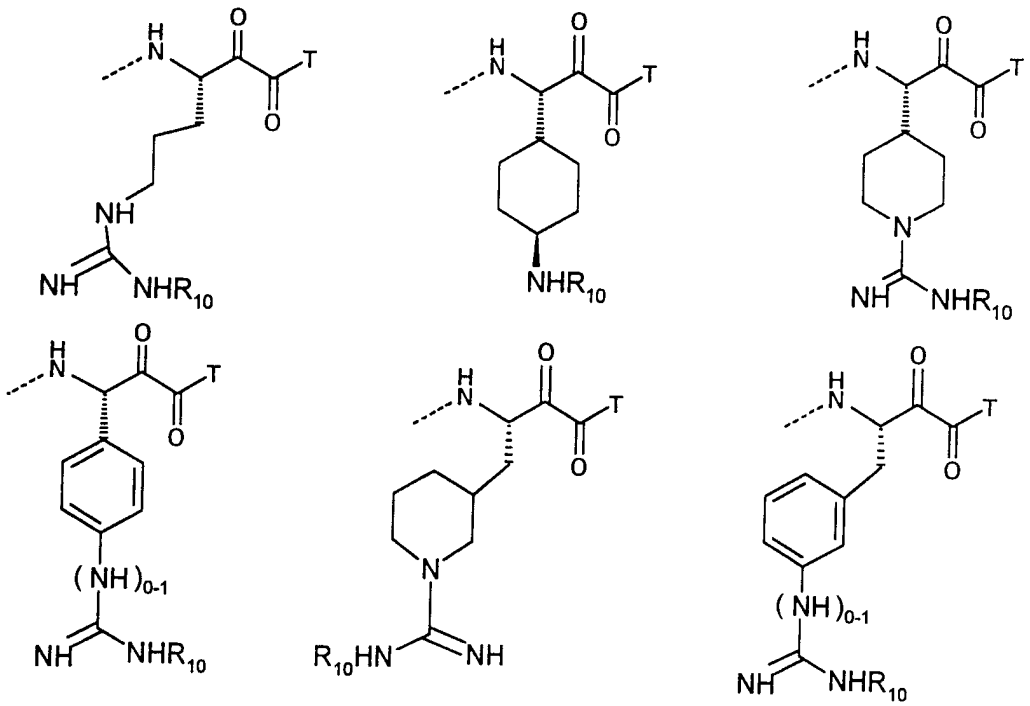


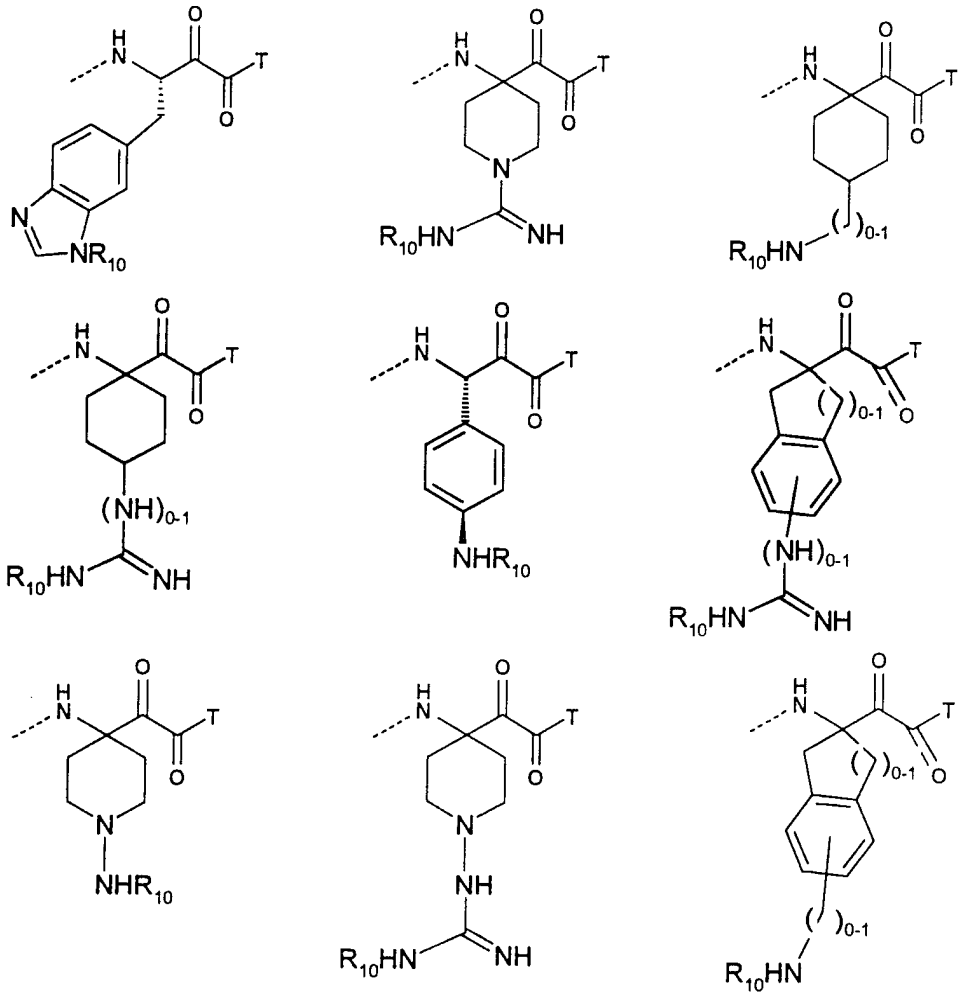




wherein n is an integer between 1 and -6, n1 is either 1 or 2, n2 is an integer between 0 and 7 and T is selected from the group consisting of H, OH, amino, a peptide of 1 to 4 amino acid residues, C_{1-16} alkyl optionally interrupted with 1 or 2 heteroatoms, C_{1-16} alkoxy, C_{6-20} aralkyl, C_{6-16} aryloxy; C_{6-20} arylalkoxy , a C_{6-16} aryl or heterocycle optionally substituted.

15. A compound according to claim 14 wherein R_1 is selected from the group consisting of

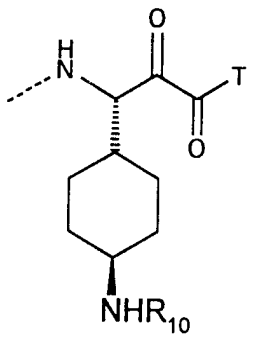




wherein

R_{10} is selected from the group consisting of H, C_{1-6} alkyl, C_{6-16} aryl, CN, NH_2 and NO_2

16. A compound according to claim 15 wherein R_1 is



wherein

R_{10} is selected from the group consisting of H, C_{1-6} alkyl, C_{6-16} aryl, CN, NH_2 and NO_2

17. A compound according to claim 15 wherein R_{10} is selected from the group consisting of H and NO_2

18. A compound according to claim 16 wherein R_{10} is H.

19. A compound according to claim 14 wherein T is selected from the group consisting of OH; C_{1-16} alkoxy, (n-, i-, s-, t-) butoxy; C_{6-16} aryloxy and C_{6-20} arylalkoxy.

20. A compound according to claim 18 wherein T is selected from the group consisting of OH and C_{1-16} alkoxy.

21. A compound according to claim 19 wherein T is OH

22. A compound according to claim 14 wherein T is a peptide of 1 to 4 amino acid residues in length selected from the group consisting of amino acids having a free C-terminus, amino acids having a free alkyl ester and mixtures thereof

23. A compound according to claim 14 wherein T is a peptide of 1 to 4 amino acid residues in length selected from the group consisting fibrinogen's A chain, fibrinogen's B chain, fragments of either chain or derivatives thereof.

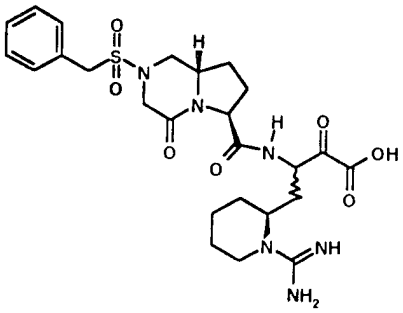
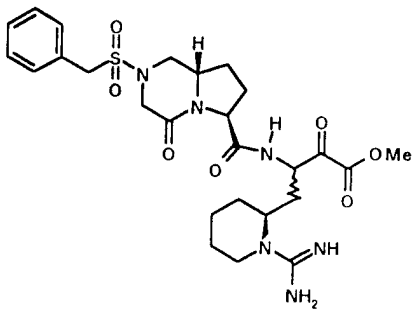
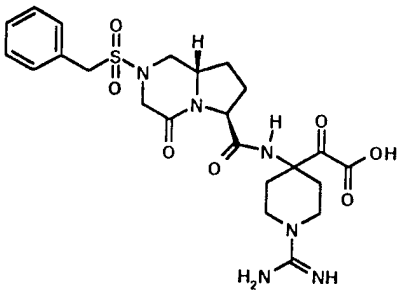
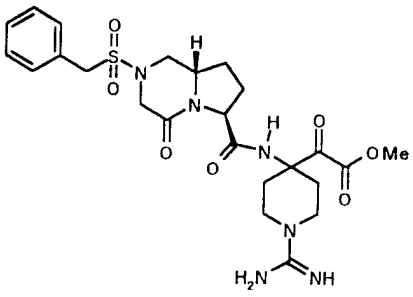
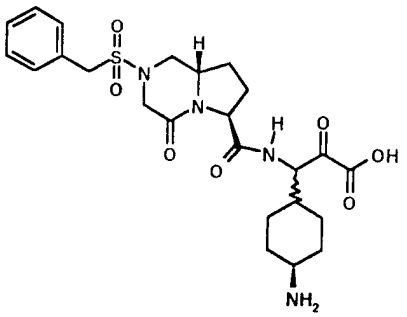
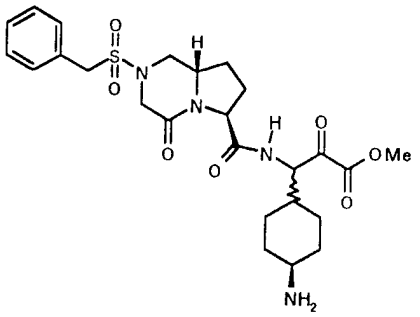
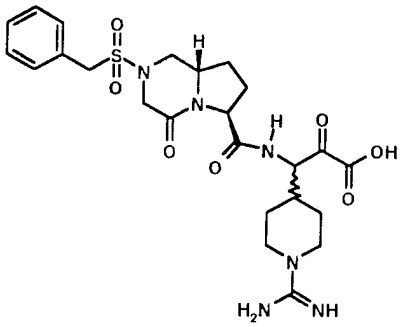
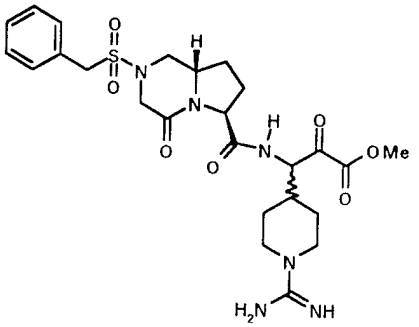
24. A compound according to claim 14 wherein T is a peptide of 1 to 4 amino acid residues in length selected from the group consisting neutral and acidic amino acids

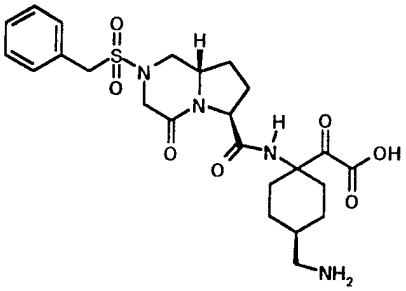
25. A compound according to claim 23 wherein T is a peptide of 1 to 4 amino acid residues in length selected from the group consisting of Gly, Ala, Val, Leu, Ile, Asp and Glu.

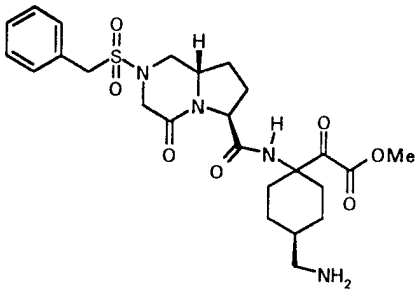
26. A compound according to claim 24 wherein T is a peptide of 1 to 4 amino acid residues in length selected from the group consisting of Gly, Asp and Glu.

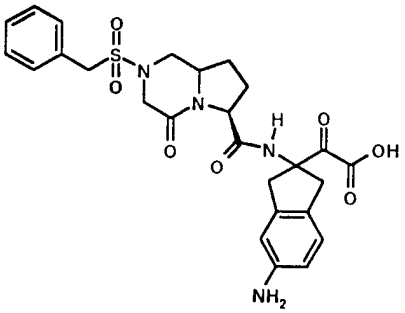
27. A compound according to claim 14 wherein T is a peptide of 1 to 4 Gly amino acid residues in length.

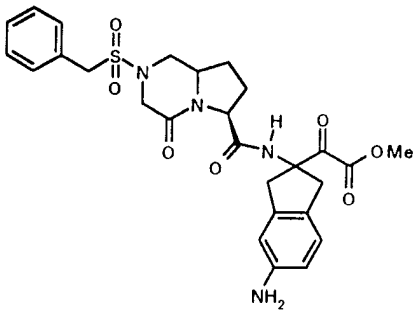
28. A compound according to claim 8 selected from the group consisting of

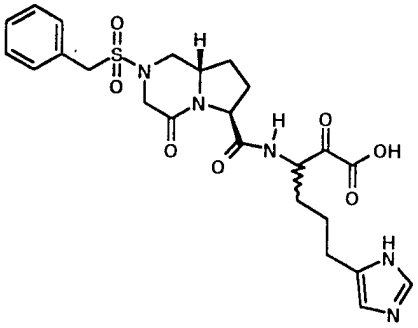









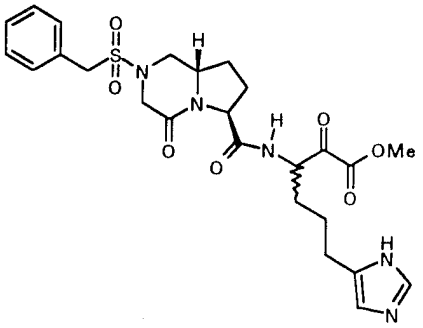


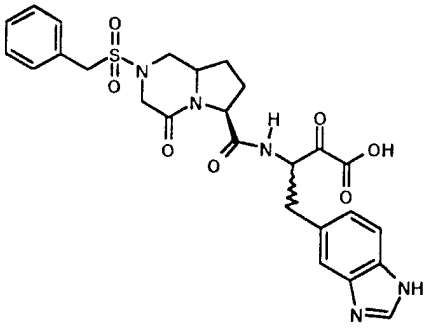


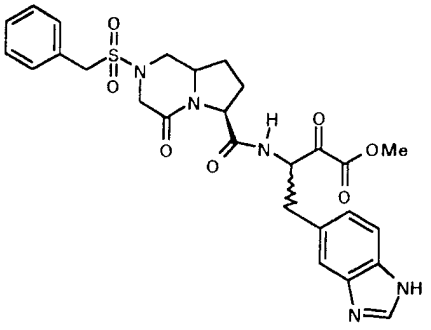












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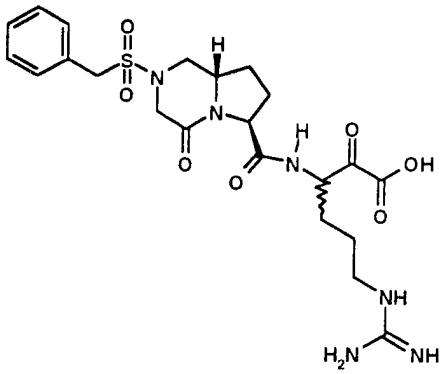
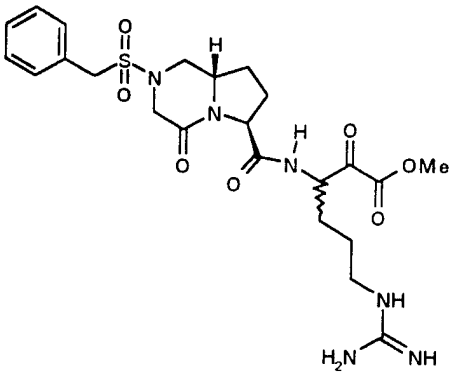
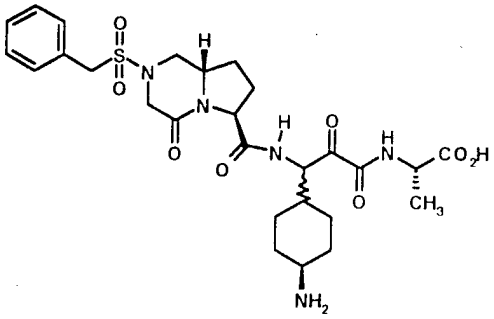
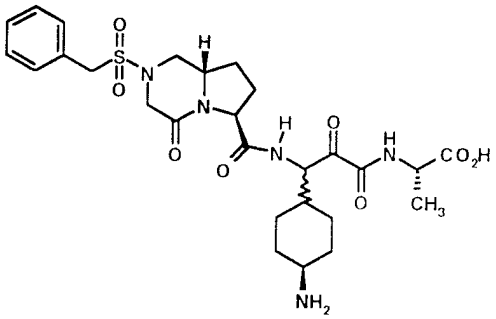
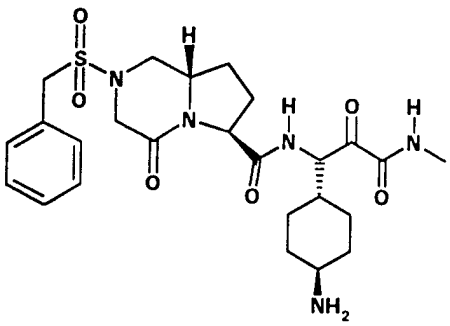
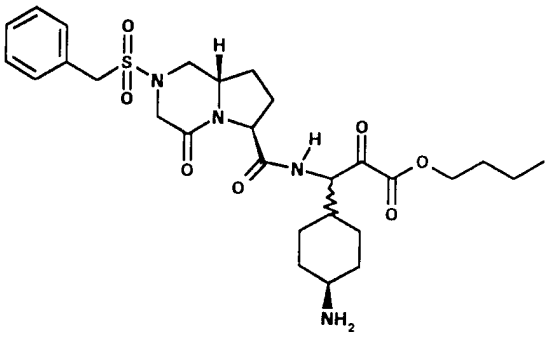


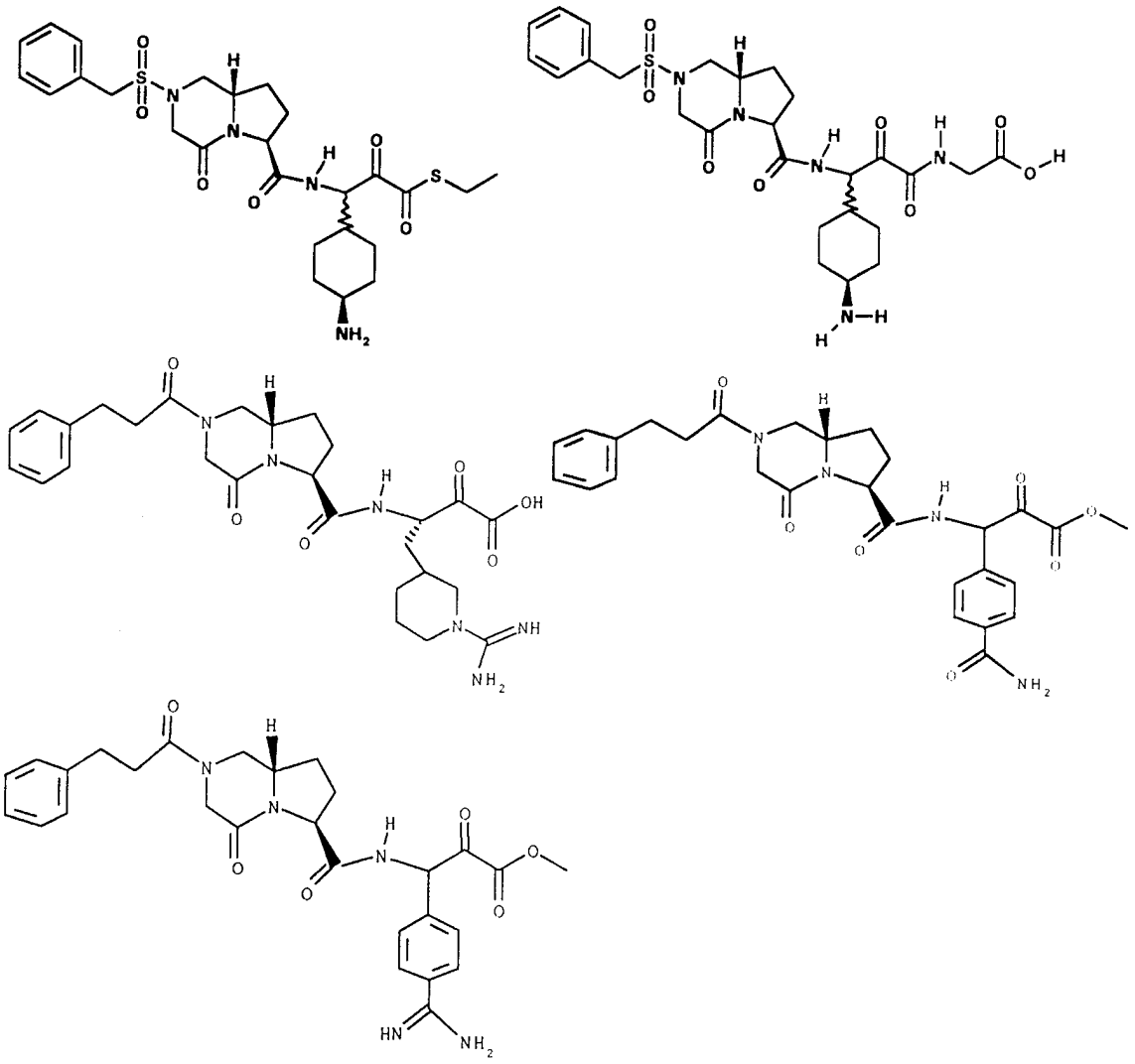












and stereoisomers thereof.

29. A compounds according to claim 8 selected from the group consisting of 3-(4-Amino-cyclohexyl)-2-oxo-3-[(4-oxo-2-phenylmethanesulfonyl-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl)-amino]-propionic acid methyl ester;

{3-(4-Amino-cyclohexyl)-2-oxo-3-[(4-oxo-2-phenylmethanesulfonyl-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl)-amino]-propionylamino}-acetic acid;

3-(4-Amino-cyclohexyl)-2-oxo-3-[(4-oxo-2-phenylmethanesulfonyl-octahydro-pyrrolo[1,2-a] pyrazine-6-carbonyl)-amino]-propionic acid;

4-Oxo-2-phenylmethanesulfonyl-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-amino-cyclohexyl)-2-methylcarbamoyl-2-oxo-ethyl]-amide;

3-(4-Amino-cyclohexyl)-2-oxo-3-[(4-oxo-2-phenylmethanesulfonyl-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl)-amino]-propionic acid butyl ester;

3-(4-Amino-cyclohexyl)-2-oxo-3-[(4-oxo-2-phenylmethanesulfonyl-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl)-amino]-thiopropionic acid *S*-ethyl ester;

3-(4-Carbamoyl-phenyl)-2-oxo-3-{[4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-amino}-propionic acid methyl ester;

3-(4-Carbamimidoyl-phenyl)-2-oxo-3-{[4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-amino}-propionic acid methyl ester;

4-(1-Carbamimidoyl-piperidin-3-yl)-2-oxo-3-{[4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-amino}-butyric acid;

and pharmaceutically acceptable salts thereof.

30. A method for the treatment or prophylaxis of thrombotic disorders in a mammal, comprising administering to said mammal an effective amount of a compound according to claim 1.

31. A method according to claim 30, wherein said thrombotic disorder is venous thrombosis.

32. A method according to claim 30, wherein said thrombotic disorder is a pulmonary embolism.

33. A method according to claim 30, wherein said thrombotic disorder is arterial thrombosis.

34. A method according to claim 30, wherein said thrombotic disorder is myocardial infarction.

35. A method according to claim 30, wherein said thrombotic disorder is cerebral infarction.

36. Use of a compound according to claim 1 in the manufacture of a medicament for the treatment or prophylaxis of thrombotic disorders in a mammal.

37. A use according to claim 36, wherein said thrombotic disorder is venous thrombosis.

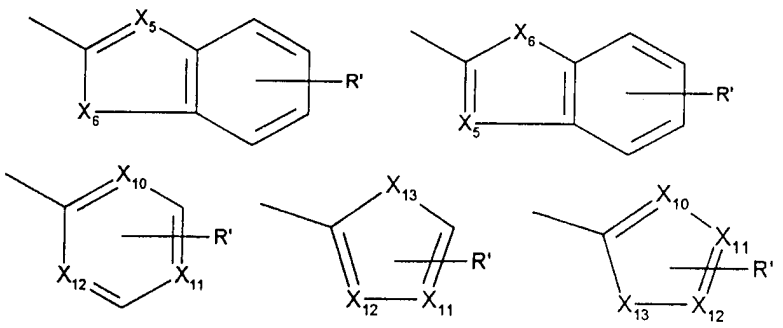
38. A use according to claim 36, wherein said thrombotic disorder is a pulmonary embolism.

39. A use according to claim 36, wherein said thrombotic disorder is arterial thrombosis.

40. A use according to claim 36, wherein said thrombotic disorder is myocardial infarction.

41. A use according to claim 36, wherein said thrombotic disorder is cerebral infarction.

42. A compound according to claim 14 where in T is a heterocycle selected from the group consisting of:



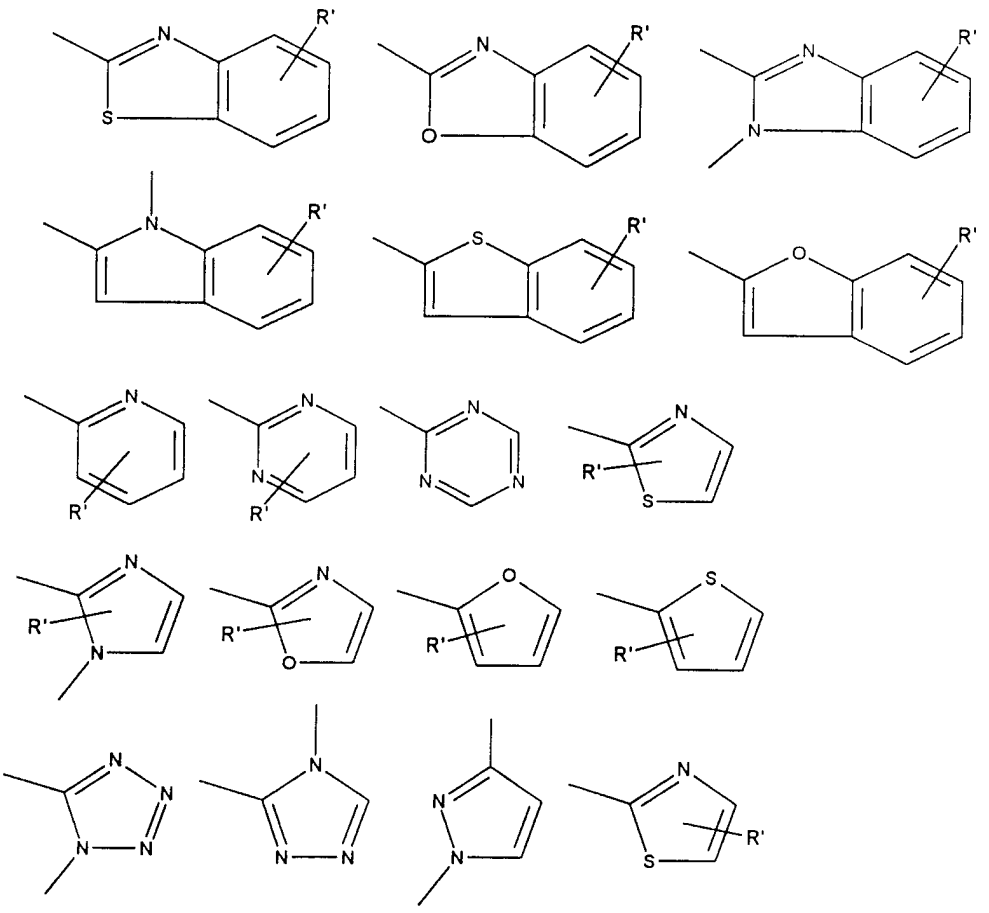
wherein

X_6, X_{10}, X_{11} and X_{12} are each independently selected from the group consisting of N, or C-X_7 where X_7 is hydrogen, C_{1-4} alkyl, or C_{6-16} aryl;

X_8 and X_{13} are each independently selected from the group consisting of C, O, N, S, N-X_7, or CH-X_7;

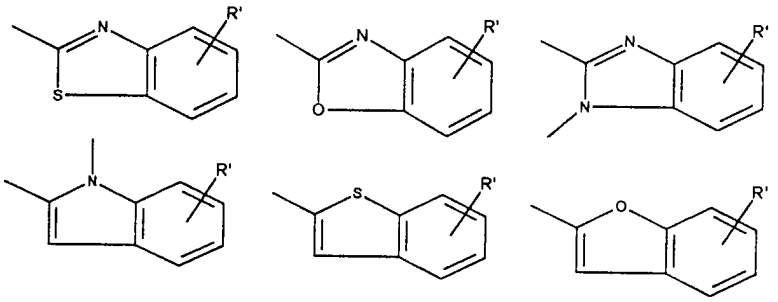
R' is selected from the group consisting of hydrogen, C_{1-16} alkyl optionally carboxyl substituted, carboxyl, -C_{0-16} alkyl-CO_2-C_{1-16} alkyl, C_{6-20} aralkyl, C_{3-7} cycloalkyl, C_{6-16} aryl or an aromatic heterocycle.

43. A compound according to claim 42 wherein T is selected from the group consisting of:



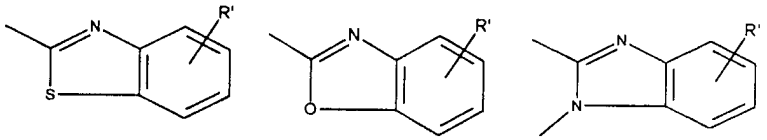
wherein R' is selected from the group consisting of hydrogen, C_{1-16} alkyl optionally carboxyl substituted, carboxyl, -C_{0-16} alkyl-CO_2-C_{1-16} alkyl, C_{6-20} aralkyl, C_{3-7} cycloalkyl, C_{6-16} aryl or an aromatic heterocycle.

44. A compound according to claim 43 wherein T is selected from the group consisting of:



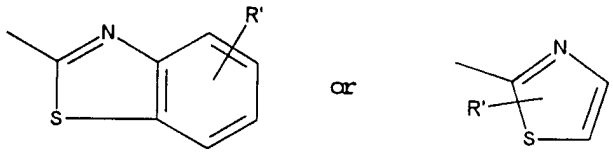
wherein **R'** is selected from the group consisting of hydrogen, C_{1-16} alkyl optionally carboxyl substituted, carboxyl, -C_{0-16} alkyl-CO_2-C_{1-16} alkyl, C_{6-20} aralkyl, C_{3-7} cycloalkyl, C_{6-16} aryl or an aromatic heterocycle.

45. A compound according to claim 44 wherein T is selected from the group consisting of:



wherein R' is selected from the group consisting of hydrogen, C_{1-16} alkyl optionally carboxyl substituted, carboxyl, -C_{0-16} alkyl-CO_2-C_{1-16} alkyl, C_{6-20} aralkyl, C_{3-7} cycloalkyl, C_{6-16} aryl or an aromatic heterocycle.

46. A compound according to claim 45 wherein T is



wherein R' is selected from the group consisting of H and C_{1-4} alkyl.

47. A compound according to claim 46 wherein R' is hydrogen.

48. A compound according to claim 46 wherein T is a 1,2 thiazole optionally substituted with R' and/or is attached to J at the 2, 3, 4 or 5 position of the ring.

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/US 97/22985

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/02 C07D513/04 A61K31/435 C07D487/04 A61K31/495

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)
IPC 6 C07K A61K

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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 19483 A (IAF BIOCHEM INT ;DIMAIO JOHN (CA); SIDDIQUI M ARSHAD (CA); GILLARD) 27 June 1996 see the whole document *0445* see page 37 *0965* see page 66 see page 11, line 19 - line 21 see page 18, line 9 - line 14 see page 15-17 see claim 20	1-27, 30-48
Y	--- -/--	9-12,28, 29

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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 but 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

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Date of the actual completion of the international search	Date of mailing of the international search report
16 April 1998	20. 05. 1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cervigni, S

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

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 97/22985

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 11697 A (MERCK & CO INC ;VEBER DANIEL F (US); LEWIS S DALE (US); SHAFER JUL) 25 April 1996 see the whole document see page 7 - page 9; tables 1,2	1-27, 30-48
Y	WO 96 40744 A (COR THERAPEUTICS INC ;MARLOWE CHARLES K (US); SCARBOROUGH ROBERT M) 19 December 1996 see claims 1,6	9-12,28, 29
A	WO 96 37497 A (IAF BIOCHEM INT ;DIMAIO JOHN (CA); GILLARD JOHN W (CA); SIDDIQUI M) 28 November 1996 see the whole document	1-48
A	WO 96 19491 A (IAF BIOCHEM INT ;GILLARD JOHN (CA); DIMAIO JOHN (CA); SIDDIQUI M A) 27 June 1996 see the whole document	1-48
A	COSTANZO M J ET AL: "POTENT THROMBIN INHIBITORS THAT PROBE THE S1' SUBSITE: TRIPEPTIDE TRANSITION STATE ANALOGUES BASED ON A HETEROCYCLE-ACTIVATED CARBONYL GROUP" JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 16, 2 August 1996, pages 3039-3043, XP002024065 see the whole document	

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INTERNATIONAL SEARCH REPORT

Ir ıational application No.
PCT/US 97/22985

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 30-35 are directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr[illegible]nal Application No
PCT/US 97/22985

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9619483 A	27-06-96	AU 4062795 A	27-06-96
		AU 4062895 A	04-07-96
		AU 4250596 A	10-07-96
		AU 4250896 A	10-07-96
		CA 2208772 A	27-06-96
		CA 2208773 A	27-06-96
		WO 9619491 A	27-06-96
		EP 0802916 A	29-10-97
		EP 0799240 A	08-10-97
		FI 972466 A	19-08-97
		NO 972892 A	20-08-97
		PL 320965 A	24-11-97
		ZA 9510960 A	09-07-96
		ZA 9510961 A	09-07-96
WO 9611697 A	25-04-96	US 5672582 A	30-09-97
		AU 3832895 A	06-05-96
WO 9640744 A	19-12-96	AU 6476196 A	30-12-96
		EP 0832102 A	01-04-98
WO 9637497 A	28-11-96	AU 5682596 A	11-12-96
WO 9619491 A	27-06-96	AU 4062795 A	27-06-96
		AU 4062895 A	04-07-96
		AU 4250596 A	10-07-96
		AU 4250896 A	10-07-96
		CA 2208772 A	27-06-96
		CA 2208773 A	27-06-96
		WO 9619483 A	27-06-96
		EP 0802916 A	29-10-97
		EP 0799240 A	08-10-97
		FI 972466 A	19-08-97
		NO 972892 A	20-08-97
		PL 320965 A	24-11-97
		ZA 9510960 A	09-07-96
		ZA 9510961 A	09-07-96