LOW MOLECULAR WEIGHT 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 (eg. ADP TXA 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. From this analysis, it is apparent that inhibition of thrombin activity constitutes a viable therapeutic approach towards the attenuation of proliferative events associated with thrombosis.

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 exerts clinical efficacy in 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. Adverse side effects such as thrombocytopenia, osteoporosis and triglyceridemia have been observed following prolonged treatment with heparin.

Hirudin, derived from the glandular secretions of the leech *hirido medicinalis* is one of the high molecular weight natural anticoagulant protein inhibitors of thrombin activity (Markwardt F. Cardiovascular Drug Reviews, 10, 211, 1992). It is a biopharmaceutical that has demonstrated efficacy in experimental and clinical thrombosis. A potential drawback to the use of Hirudin as a therapeutic agent is likely antigenicity and lack of an effective method of neutralization, especially in view of its extremely tight binding characteristics toward thrombin. The exceedingly high affinity for thrombin is

unique and is attributed to a simultaneous interaction with the catalytic site as well as a distal "anion binding exosite" on the enzyme.

Thrombin activity can also be abrogated by Hirudin-like molecules such as hirulog (Maraganore, J.M. et al., Biochemistry, 29, 7095, 1990) or hirutonin peptides (DiMaio, J. et al., J. Med. Chem., 35, 3331, 1992).

Thrombin activity can also be inhibited by low molecular weight 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. Thus, Blomback et al. first designed a thrombin inhibitor that was modeled upon the partial sequence of the fibrinogen A(Bβ)α 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).

Bajusz et al. have also reported related compounds such as (D)Phe-Pro-Arg-(CO)H (GYKI-14166) and (D)MePhe-Pro-Arg-(CO)H (GYKI-14766) (Peptides-Synthesis, Structure and Function: Proceedings of the Seventh American Peptide Symposium, Rich, D.H. & Gross, E. eds., Pierce Chemical Company , 1981, pp. 417). These tripeptidyl aldehydes are effective thrombin inhibitors both *in vitro* and *in vivo*. In the case of both GYKI-14166 and GYKI-14766, the aldehyde group is presumed to contribute strongly to inhibitory activity in view of its chemical reactivity toward thrombin's catalytic Ser_{195} residue, generating a hemiacetal intermediate.

Related work in the area of thrombin inhibitory activity has exploited the basic recognition binding motif engendered by the tripeptide (D)Phe-Pro-Arg while incorporating various functional or reactive groups in the locus corresponding to the putative scissile bond (i.e. P_1-P_1').

In U.S. Patent 4,318,904, Shaw reports chloromethyl-ketones (PPACK) that are reactive towards Ser_{195} and His_{57}. These two residues comprise part of thrombin's catalytic triad (Bode, W. et al., EMBO Journal 8, 3467, 1989).

Other examples of thrombin inhibitors bearing the (D)Phe-Pro-Arg general motif are those incorporating COOH-terminal boroarginine variants such as boronic acids or boronates (Kettner, C. et al., J. Biol. Chem., 268, 4734, 1993).

Still other congeners of this motif are those bearing phosphonates (Wang, C-L J., Tetrahedron Letters, 33, 7667,

1992) and α-Keto esters (Iwanowicz, E.J. et al.,Bioorganic and Medicinal Chemistry Letters, 12, 1607, 1992).

Neises, B. et al. have described a trichloromethyl ketone thrombin inhibitor (MDL-73756) and Attenburger, J.M. et al. have revealed a related difluoro alkyl amide ketone (Tetrahedron Letters, 32, 7255, 1991).

Maraganore et al. (European 0,333,356; WO 91/02750; U.S. 5,196,404) disclose a series of thrombin inhibitors that incorporate the D-Phe-Pro- moiety and hypothesize that this preferred structure fits well within the groove adjacent to the active site of thrombin. Variations on these inhibitors are essentially linear or cyclic peptides built upon the D-Phe-Pro moiety.

Another series of patents and patent applications have described attempts to develop effective inhibitors against thrombosis by using alpha-ketoamides and peptide aldehyde analogs (EP 0333356;WO 93/15756; WO 93/22344; WO 94/08941; WO 94/17817).

Still others have focused their attention on peptides, peptide derivatives, peptidic alcohols, or cyclic peptides as anti-thrombotic agents (WO 93/22344, EP 0276014; EP 0341607; EP 0291982). Others have examined amidine sulfonic acid moieties to achieve this same end (U.S. 4,781,866), while yet others have examined para or meta substituted phenlyalanine derivatives (WO 92/08709; WO 92/6549).

A series of Mitsubishi patents and patent applications have disclosed apparently effective argininamide compounds for use as antithrombotic agents. The chemical structures described in these documents represent variations of side groups on the argininamide compound (U.S. 4,173,630; U.S.

4,097,591; CA 1,131,621; U.S. 4,096,255; U.S. 4,046,876; U.S. 4,097,472; CA 2,114,153).

Canadian patent applications 2,076,311 and 2,055,850 disclose cyclic imino derivatives that exhibit inhibitory effects on cellular aggregation.

Many of the examples cited above are convergent by maintaining at least a linear acyclic tripeptidyl motif consisting of an arginyl unit whose basic side chain is required for interaction with a carboxylate group located at the base of the P_1 specificity cleft in thrombin. Two adjacent hydrophobic groups provide additional binding through favourable Van der Waals interactions within a contiguous hydrophobic cleft on the enzyme surface designated the P_3-P_2 site.

One object of the present invention is to provide thrombin inhibitors that display inhibitory activity towards the target enzyme, thrombin.

A further object of the present invention is to provide thrombin inhibitors that display inhibitory activity towards the target enzyme thrombin and are provided for in a pharmacologically acceptable state.

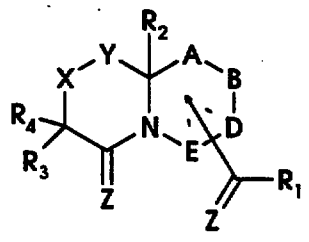
Still a further object of the present invention is to provide for the use of heterocyclic thrombin inhibitors and formulations thereof as anticoagulant and thrombin inhibitory agents.

Yet a further object of the present invention is to provide for the use of heterocyclic thrombin inhibitors and formulations thereof for therapeutic treatment of various thrombotic maladies.

A further object of the present invention is a process for the synthesis of these low molecular weight thrombin inhibitors. The enzyme inhibitors of the present invention are encompassed by the structure of general Formula I.

SUMMARY OF THE INVENTION

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



(I)

wherein:

A is selected from $(CH\text{-}R_8)_{n=1}$, S, SO, SO_2, O and NR_9 wherein R_8 is hydrogen, C_{1-6} alkyl optionally interupted with 1 or 2 heteroatoms; C_{6-10} aryl, C_{3-7} 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_{1-6} alkyl provided that when A is S, SO, SO_2, O, or NR_9, then B is CR_6R_7;

D is selected from $(CH\text{-}R_5)_{n=1}$ wherein R_5 is hydrogen, C_{1-6} alkyl or $-C(O)R_4$; 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 $-C(O)R_4$, provided that only one of D and E is substituted with 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, $N\text{-}R_5$ and $CH\text{-}R_5$ provided that when X is $N\text{-}R_5$ then Y is $CH\text{-}R_5$ or O, and when X is O then Y is $CH\text{-}R_5$;

Z is selected from O, S and H_2;

R_1 is a polar amino acid residuearginyl moiety or an analog or derivative thereof optionally substituted with an amino acid, a peptide or a heterocycle;

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

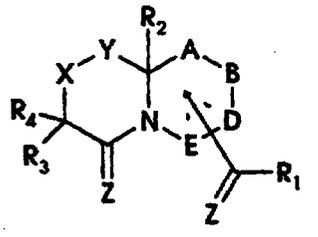
R_3 is selected from H, NR_6R_7 and C_{1-6} alkyl; and

R_4 and R_5 are independently selected from H; NR_6R_7; C_{6-10} aryl or C_{3-7} cycloalkyl optionally substituted with C_{1-6} alkyl; C_{1-6} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_6R_7 or a C_{6-10} 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.

As will be appreciated from the disclosure to follow, the molecules, compositions and methods of this invention are useful as anti-coagulants, or in the treatment and prevention of various diseases attributed to the undesirable effects of thrombin, as well as for diagnostic purposes.

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_5 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_{1-6} alkyl, C_{2-6} alkenyl (e.g. vinyl, allyl) or C_{2-6} alkynyl (e.g. propargyl) optionally interrupted by a carbonyl group, (e.g. forming an acyl group); C_{6-10} aryl, C_{3-7} cycloalkyl, C_{7-12} aralkyl, C_{3-7} cycloalkyl substituted C_{1-6} 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 "arginyl moiety" represents an arginine amino acid residue or an analogue or derivative thereof. For example, an analogue or derivative of the natural residue may incorporate a longer or shorter methylene chain from the alpha carbon (i.e. ethylene or butylene chain); replacement of the guanidino group with a hydrogen bond donating or accepting group (i.e. amino, amidino or methoxy); replacement of the methylene chain with a constrained group (i.e. an aryl, cycloalkyl or heterocyclic ring); elimination of the terminal carboxyl (i.e. des-carboxy) or hydroxyl (i.e. an aldehyde); or a combination thereof.

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_1R_2) 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_1R_2) halogen or C_{1-4} 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_1R_2) halogen or C_{1-4} 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. Preferrably, 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_1R_2), halogen, CF_3, oxo or C_{1-4} 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, 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_{1-4} alkyl. More preferably R_2 is H, methyl or ethyl and most preferably R_2 is H.

Preferably, R_3 is H or C_{1-4} 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_{1-4} alkyl optionally substituted by NR_6R_7 or

carboxy. The hydrophobic moiety may be linked via a spacer such as a C_{1-15} alkyl chain optionally interrupted with 1 or more (i.e. 1-4) heteroatoms, carbonyl or sulfonyl (SO_2) groups. More preferably, one of R_1 and R_2 is phenyl, cyclohexyl, indole, thienyl, quinoline, tetrahydroisoquinoline, naphthyl or benzodioxolane linked via C_{1-3} alkyl optionally interupted 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.

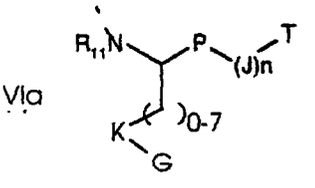
Preferably, **E** is CH substituted with $-C(O)R_3$ wherein R_3 is as previously defined.

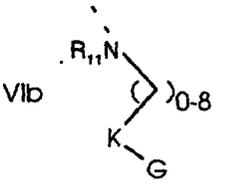
Preferably, **X** is $CH-R_5$ or $N-R_5$.

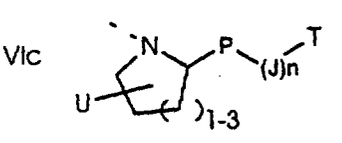
Preferably, **Y** is $CH-R_4$ or S.

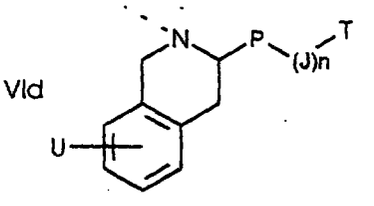
Preferably, **Z** is O.

In a preferred embodiment, $\mathbf{R_1}$ is represented by one of formula VIa to VId:









wherein:

$\mathbf{R_{11}}$ is hydrogen or C_{1-4} alkyl;

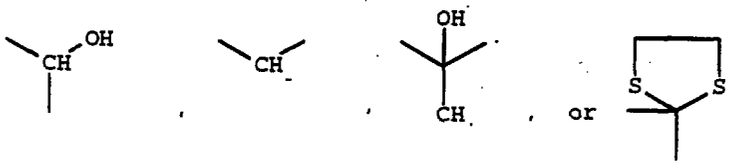
K is a bond or -NH-;

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;

P is a bond, -C(O)- or a bivalent group:



J is C_{1-6} alkylene optionally substituted with OH, NH_2 and C_{1-6} alkyl and optionally interrupted by a heteroatom selected from O, S and N;

n is 0 or 1; and

T is H, OH, amino, a peptide chain, C_{1-12} alkyl, C_{1-12} alkoxy, C_{7-12} aralkyl, or heterocycle optionally substituted.

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

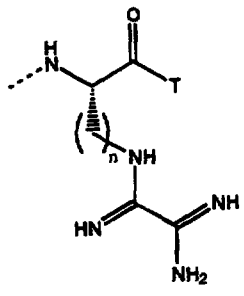
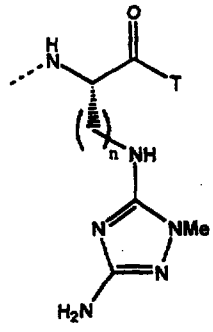
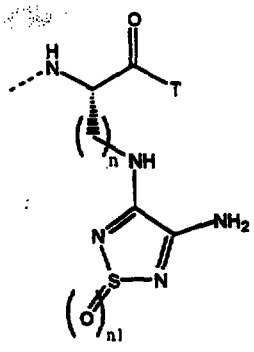
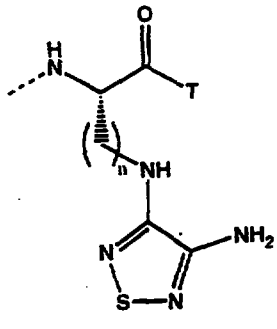
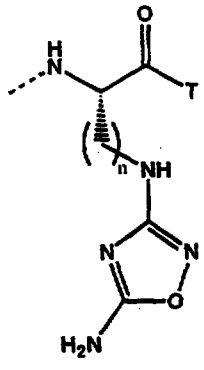
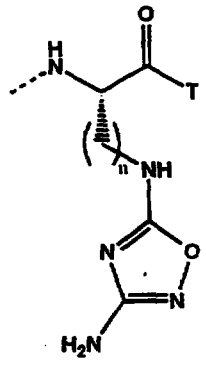
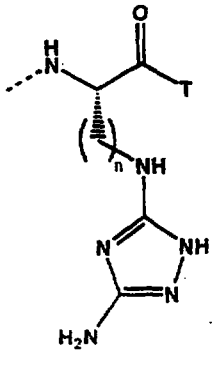
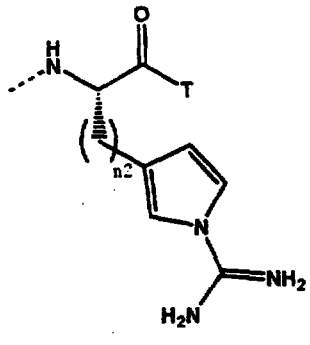
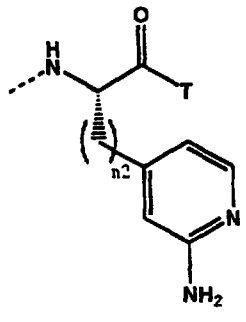
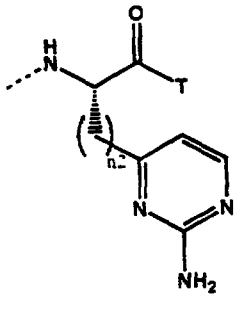
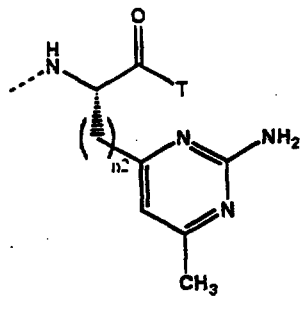
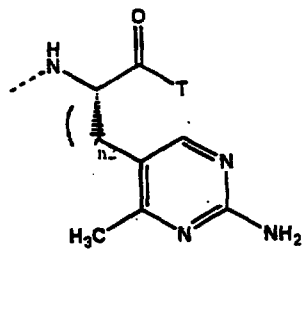
Preferably **K** is a bond.

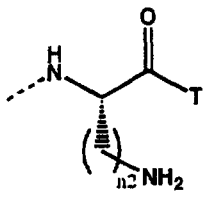
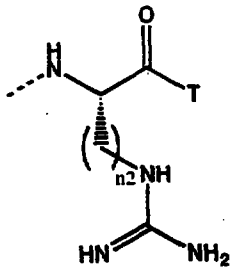
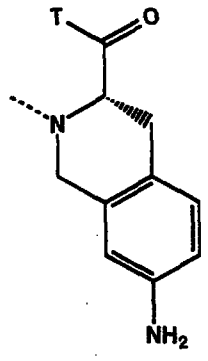
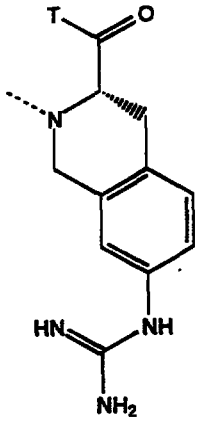
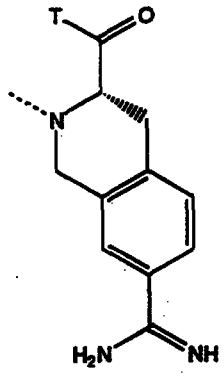
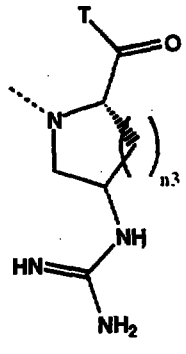
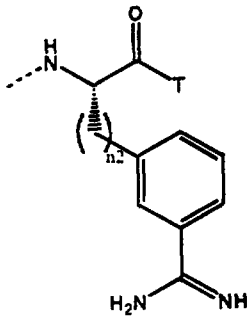
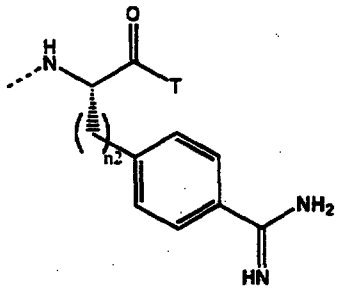
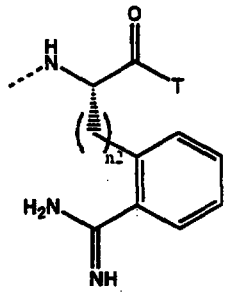
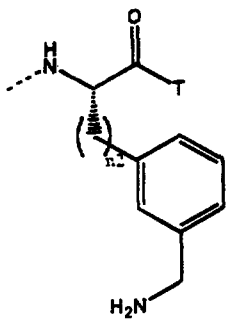
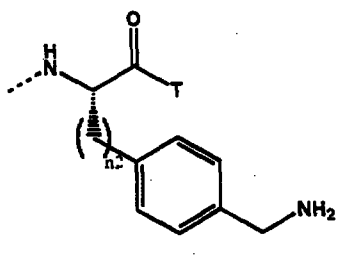
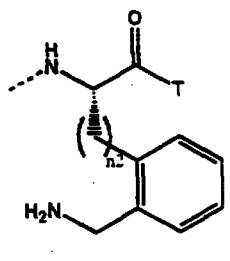
Preferably **G** is -NH-C(NH)-NH_2 attached via a methylene chain of 3-7 carbons or phenyl substituted with -C(NH)-NH_2 attached via a methylene chain of 0 to 3 carbons. More preferably G -NH-C(NH)-NH_2 attached via a methylene chain of 3 atoms.

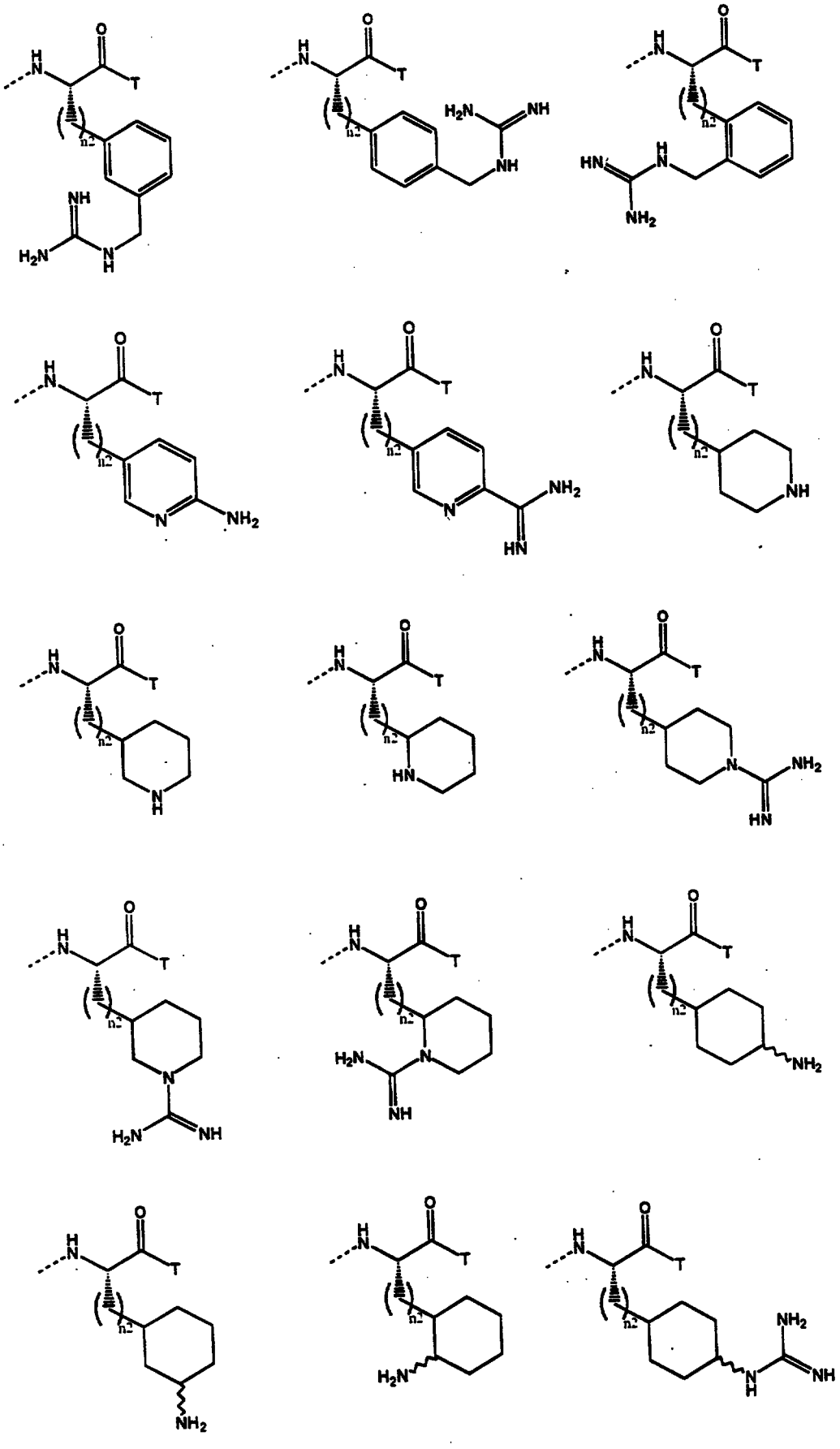
Preferably **P** is -C(O)-.

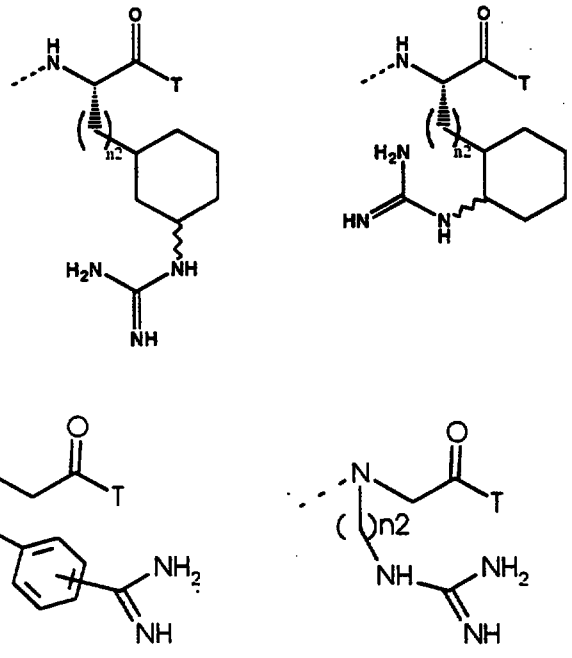
Preferably **J** is selected from: -CH_2-S-CH_2-CH_2-; -CH_2-O-CH_2-CH_2-; -CH_2-NH-CH_2-CH_2-; and a bond when n is 0. More preferably, J is a bond while n is 0.

In particular embodiments of the invention, R is selected from the following amino acid derivatives prepared according to the procedures described in Bioorg. Med. Chem., 1995, 3:1145 :

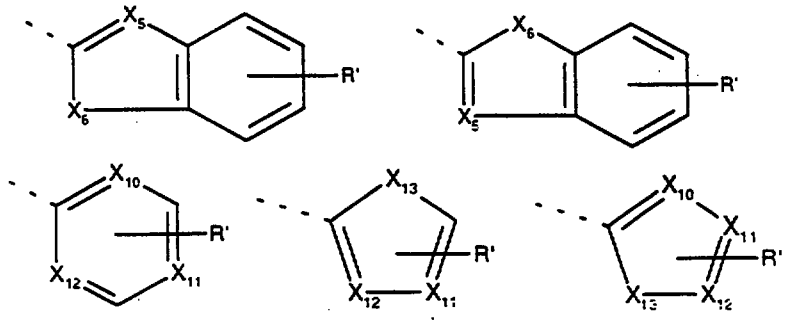

















wherein n=1-6, n1=1-2, n2=0-7 and T is as previously defined.

In a preferred embodiment, **T** is a peptide of 1 to 4 amino acid residues in length and preferably fibrinogen's A or B chain or fragment or derivative thereof. In another preferred embodiment, T is a heterocycle selected from the group consisting of:



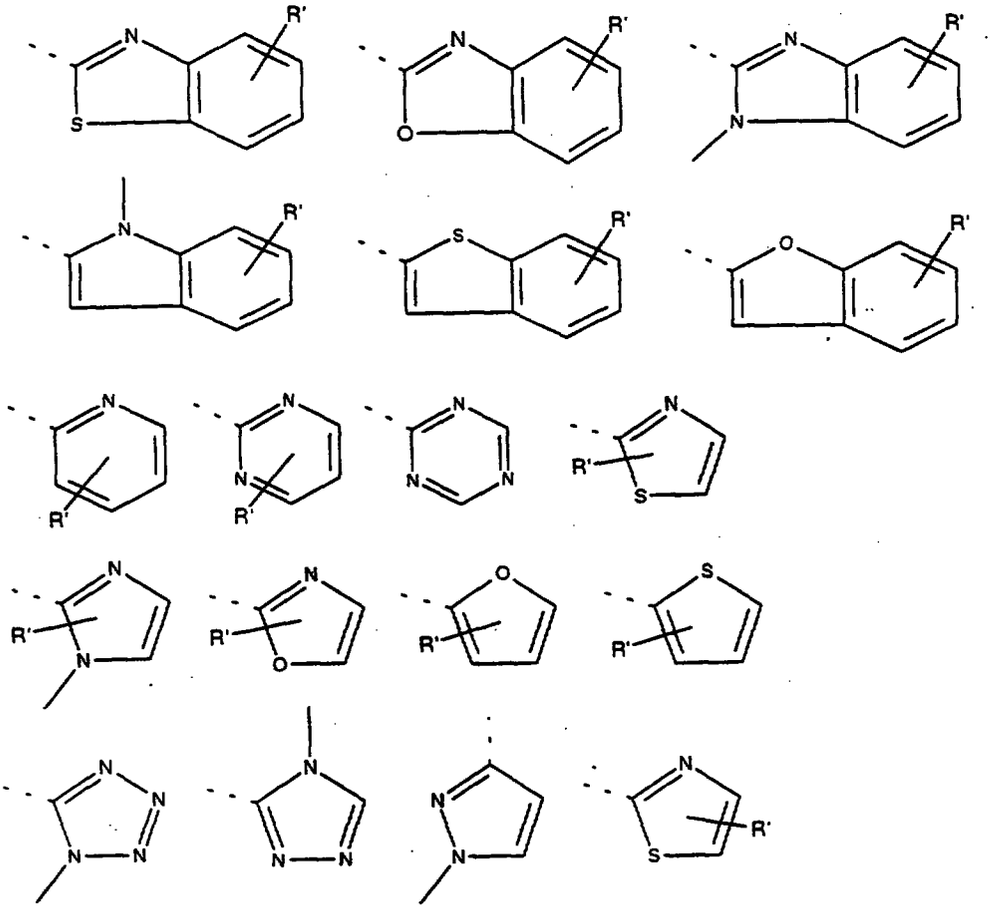
wherein

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

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

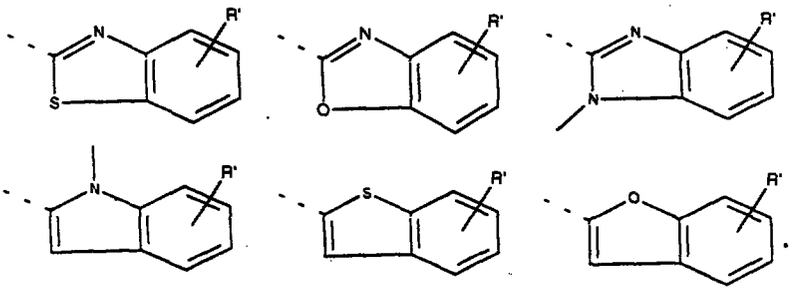
R' is hydrogen, C_{1-10} alkyl optionally carboxyl substituted, carboxyl, -C_{1-10} alkyl-CO-C_{1-10} alkyl, C_{7-9} aralkyl, C_{3-7} cycloalkyl, aryl or an aromatic heterocycle.

Preferably T is selected from the group consisting of:



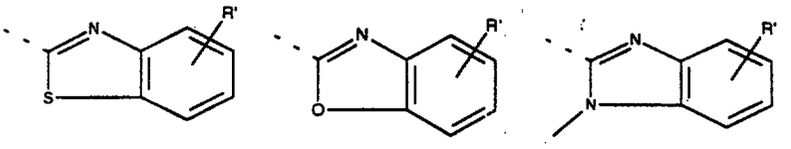
wherein R' is as defined above.

More preferably T is selected from the group consisting of:



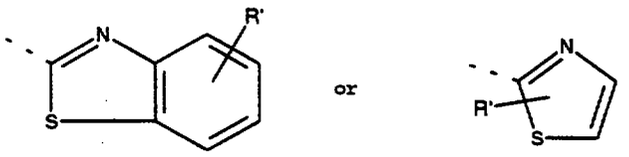
wherein R' is as defined above.

More preferably T is selected from the group consisting of:



wherein R' is as defined above.

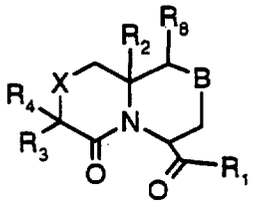
Most preferably T is



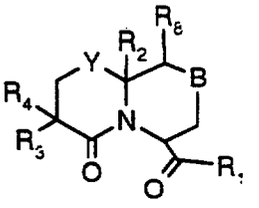
wherein R' is H or C_{1-4} alkyl such as methyl, ethyl, propyl or butyl and most preferably wherein R' is hydrogen,. In another embodiment, T is a 1,2 thiazole optionally substituted with R' and\or is attached to J at the 2, 3, 4 or 5 position of the ring.

In particular embodiments, compounds of the invention are represented by formulas II, III, IV and V, wherein X, Y, B, R to R_4 and R_5 are as previously defined.

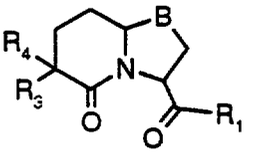
(II)



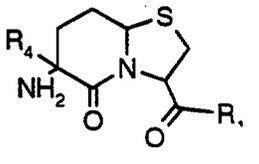
(III)



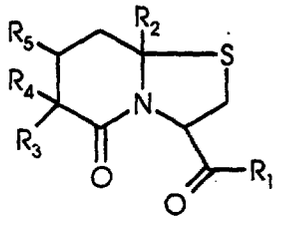
(IV)

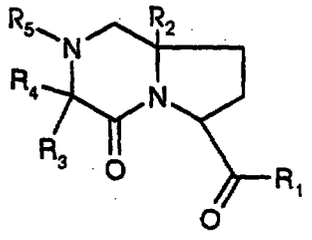


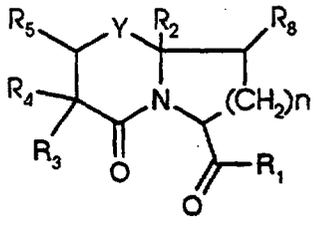
(V)

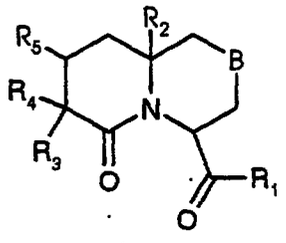


In a particularly preferred embodiment, compounds of the invention are represented by one of formulas VII, VIII, IX and X:

(VII) 

(VIII) 

(IX) 

(X) 

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 an arginyl moiety or an analog or derivative thereof optionally substituted with an amino acid, a peptide or a heterocycle;

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; C_{6-10} aryl or C_{3-7} cycloalkyl optionally substituted with C_{1-6} alkyl; C_{1-10} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_6R_7 or a C_{6-10} 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;

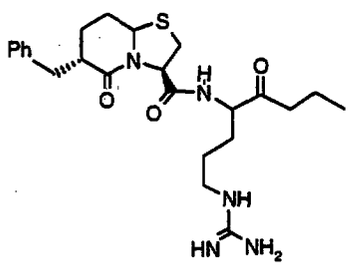
R_8 is hydrogen, C_{1-6} alkyl optionally interupted with 1 or 2 heteroatoms; C_{6-10} aryl, C_{3-7} cycloalkyl or heterocyclic ring or a hydrophobic group; and

n is 1 or 2.

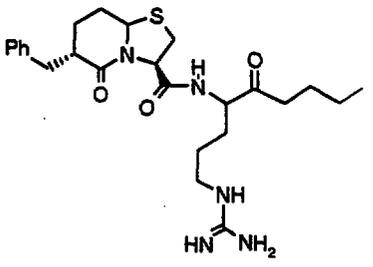
Preferred compounds according to formula VII include:

SUBSTITUTE SHEET

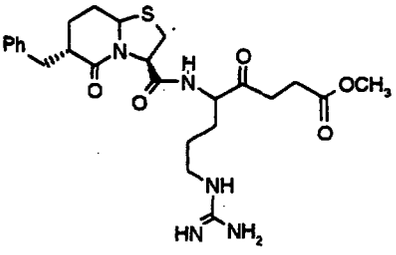
0005 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a] pyridine-3R-carboxamido (propyl ketoarginine)



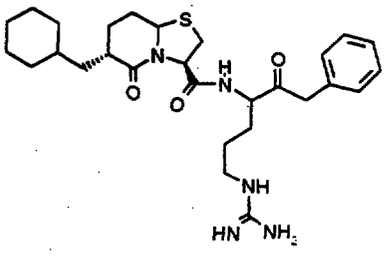
0010 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a] pyridine-3R-carboxamido (butyl ketoarginine)



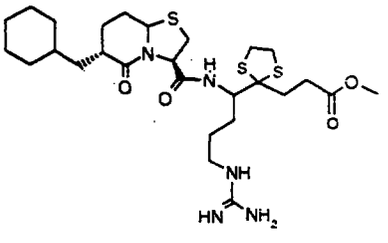
0015 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a] pyridine-3R-carboxamido(propylcarbmethoxy ketoarginine)



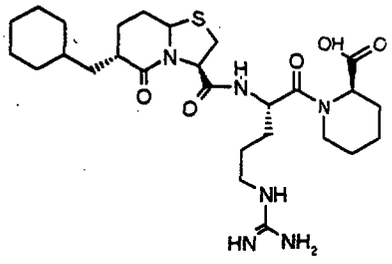
0020 6S-cyclohexylmethyl hexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(benzylketo arginine)



0025 6S-cyclohexyl methyl hexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine -3R-carboxamido(carbmethoxy propyl cyclodithioketalarginine)

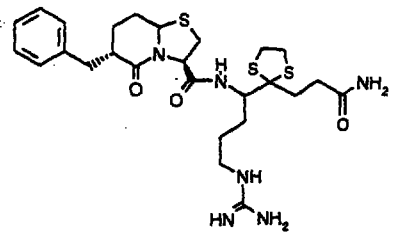


0030 6S-cyclohexylmethyl hexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((S)-Arg-(R)-pipecolilic acid)

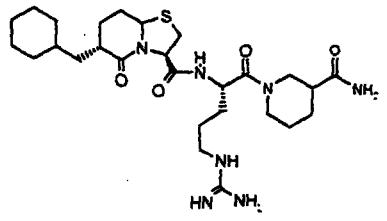


SUBSTITUTE SHEET

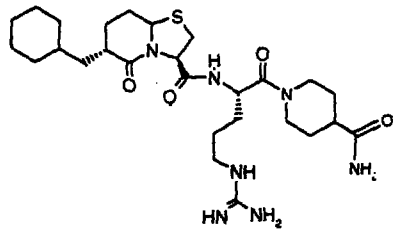
0035 6S-benzylhexa hydro-5-oxo-5H-thiazolo [3,2-a]pyridine-3R-carboxamido(carboxamidopropyl cyclodithioketal arginine)



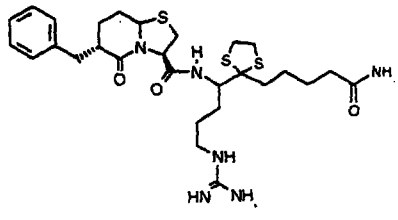
0040 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((S)-Arg nipecotamide)



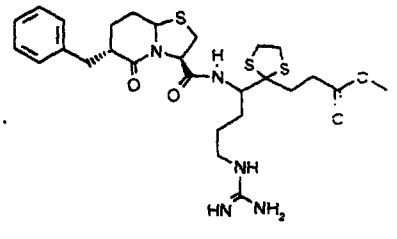
0045 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((S)Arg isonipecotamide)



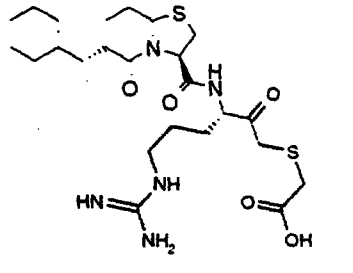
0050 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(carboxamidopentyl cyclodithioketal arginine)



0055 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(carbmethoxy propyl cyclodithioketal arginine)

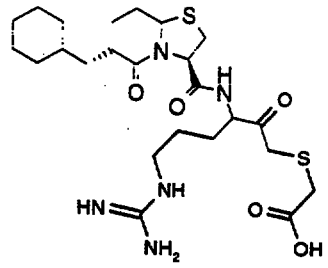


0060 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(1-carboxy-3-thiobutyl ketoarginine)

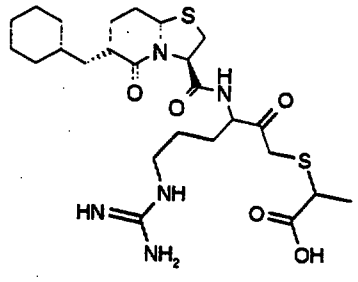


SUBSTITUTE SHEET

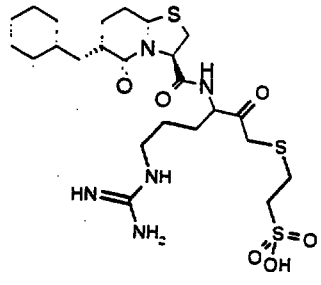
0065 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(1-carboxy-3-thiobutyl ketoarginine)



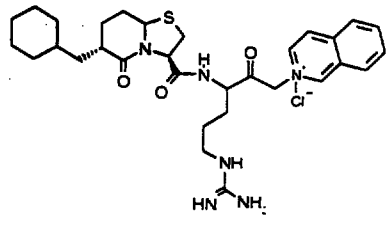
0070 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(1-carboxy-2-methyl-3-thiobutyl ketoarginine)



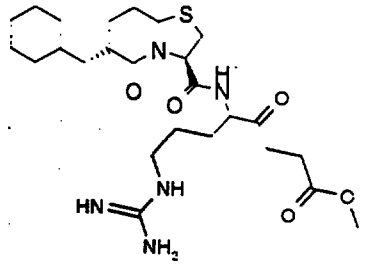
0075 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((3-thiobutyl sulfonic acid) ketoarginine)



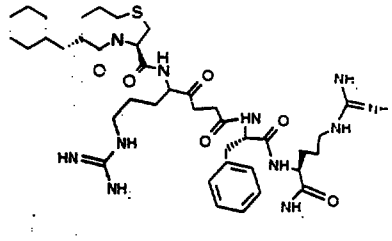
0080 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(iso-quinolinium methyl ketoarginine)



0085 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(propylcarbmethoxy ketoarginine)

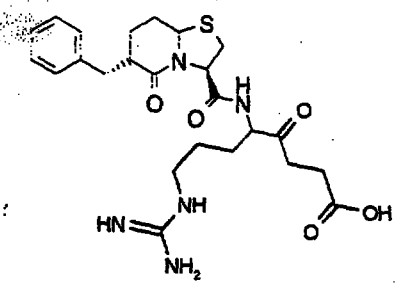


0090 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((propylketo)Arg-Phe-Arg-NH_2)

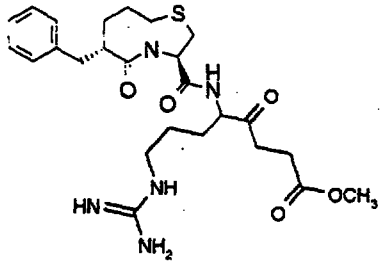


SUBSTITUTE SHEET

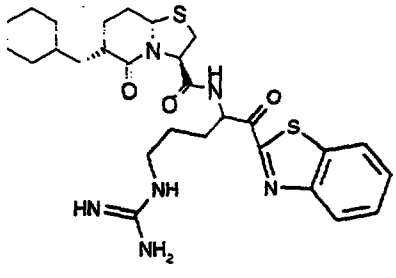
0095 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((propanoic acid) ketoarginine)



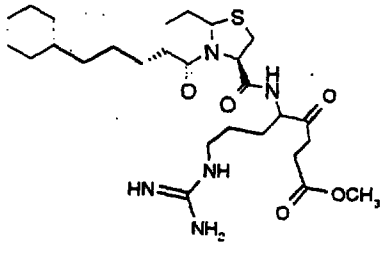
0100 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(propyl carbmethoxy ketoarginine)



0105 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo [3,2-a]pyridine-3R-carboxamido (α-benzothiazolo keto arginine); and

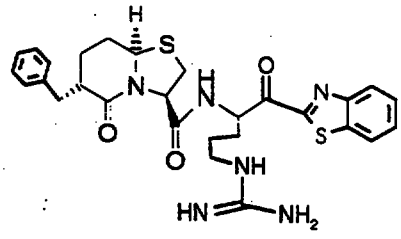


0110 6S-cyclohexylpropylhexahydro-5-oxo-5H-thiazolo [3,2-a]pyridine-3R-carboxamido(propylcarbmethoxy ketoarginine)

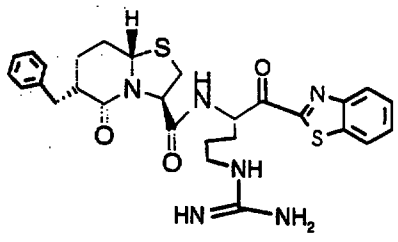


SUBSTITUTE SHEET

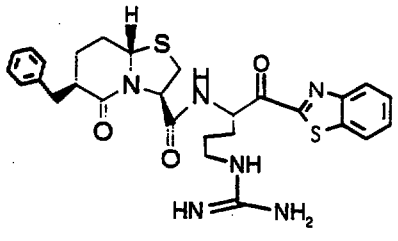
0205 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



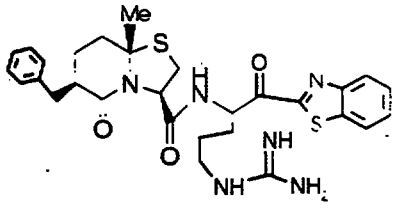
0210 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



0215 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide

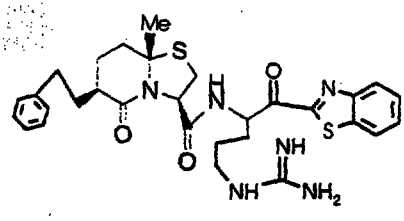


0220 6-Benzyl-8a-methyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide

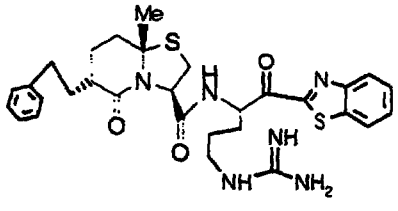


SUBSTITUTE SHEET

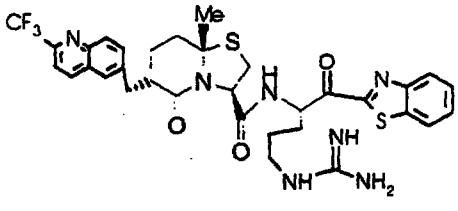
0225 8a-Methyl-5-oxo-6-phenethyl-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



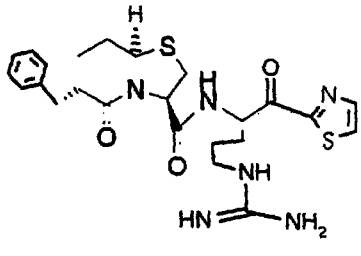
0230 8a-Methyl-5-oxo-6-phenethyl-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



0240 8a-Methyl-5-oxo-6-(2-trifluoro methyl-quinolin-6-ylmethyl)-hexahydro-thiazolo[3,2-a] pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide

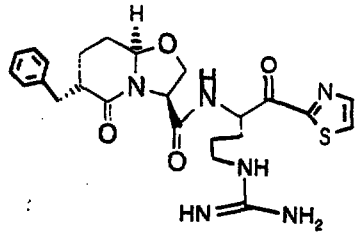


0245 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide

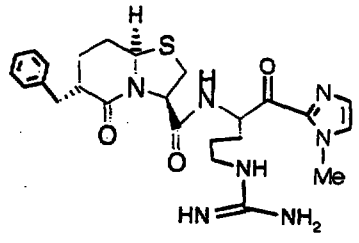


SUBSTITUTE SHEET

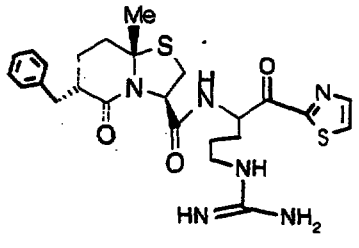
0250 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide



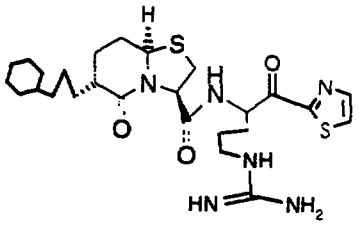
0255 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(1-methyl-1H imidazole-2-carbonyl)butyl]-amide



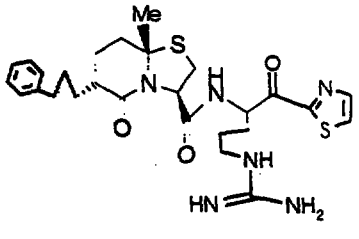
0260 6-Benzyl-8a-methyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



0265 5-Oxo-6-(3-cyclohexyl-propyl)-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide

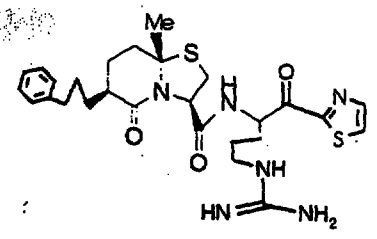


0275 8a-Methyl-5-oxo-6-(3-phenyl-propyl)-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

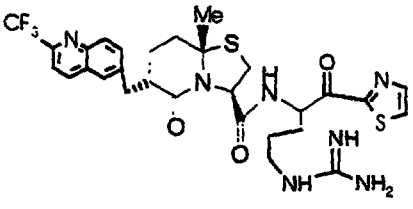


SUBSTITUTE SHEET

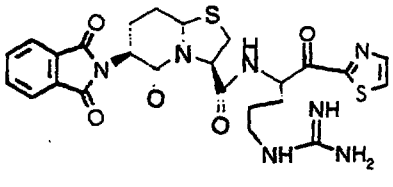
0280 8a-Methyl-5-oxo-6-(3-phenyl-propyl)-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



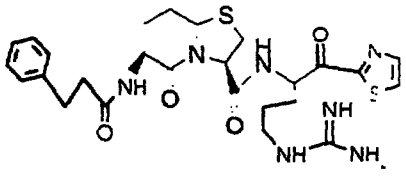
0285 8a-Methyl-5-oxo-6-(2-trifluoromethyl-quinolin-6-ylmethyl)-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



0295 6-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

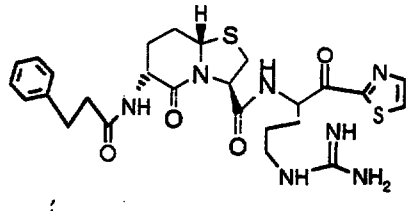


0305 5-Oxo-6-(3-phenyl-propionyl amino)-hexahydro thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



SUBSTITUTE SHEET

0315 5-Oxo-6-(3-phenyl-propionyl amino)-hexahydro thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



More preferred compounds according to formula (VII) include:

0085 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(propylcarbo methoxyketoarginine);

0090 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((propylketo)Arg-Phe-Arg-NH_2);

0095 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((propanoic acid) ketoarginine);

0105 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo [3,2-a]pyridine-3R-carboxamido (α-benzothiozolo keto arginine);

0210 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide;

0220 6-Benzyl-8a-methyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide;0240 8a-Methyl-5-oxo-6-(2-trifluoromethyl-quinolin-6-ylmethyl)-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide;

0245 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide;

This Sheet Has Been Replaced

SUBSTITUTE SHEET

0260 6-Benzyl-8a-methyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide;

0265 5-Oxo-6-(3-cyclohexyl-propyl)-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide;

0285 8a-Methyl-5-oxo-6-(2-trifluoromethyl-quinolin-6-ylmethyl)-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide; and

0315 5-Oxo-6-(3-phenyl-propionylamino)-hexahydro thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide.

Most preferred compounds according to formula VII include:

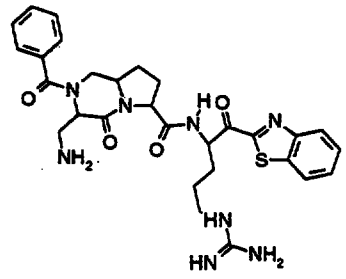
0085 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(propylcarbo methoxy ketoarginine); and

0105 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo [3,2-a]pyridine-3R-carboxamido (α-benzothiozolo keto arginine).

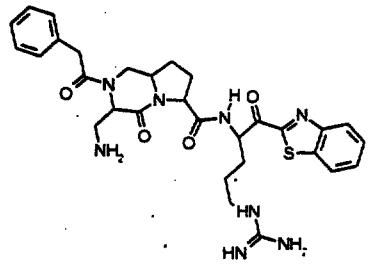
SUBSTITUTE SHEET

Preferred compounds according to formula VIII include:

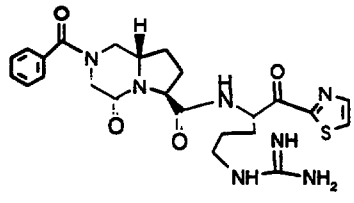
0325 3-Aminomethyl-2-benzoyl-4-oxo-octahydro-pyrrolo[1,2-a]pyridine-6-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



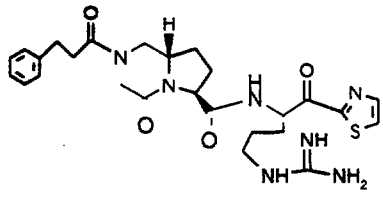
0330 3-Aminomethyl-4-oxo-2-phenylacetyl-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



0335 2-Benzoyl-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

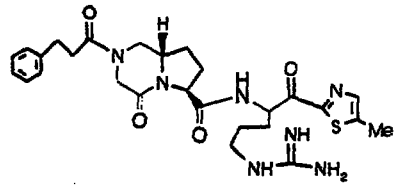


0340 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

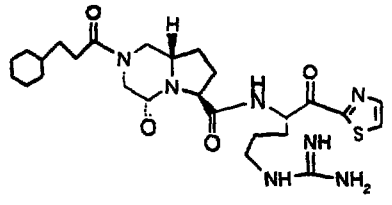


SUBSTITUTE SHEET

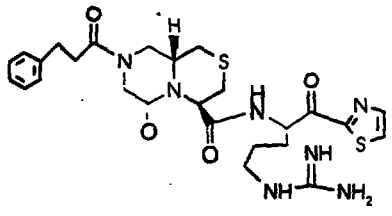
0345 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(5-methyl-thiazole-2-carbonyl)-butyl]-amide



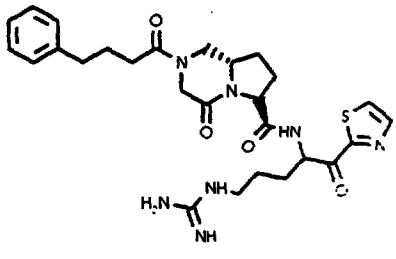
0350 2-(3-Cyclohexyl-propionyl)-4-oxo- octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(2-thiazole-carbonyl)-butyl]-amide



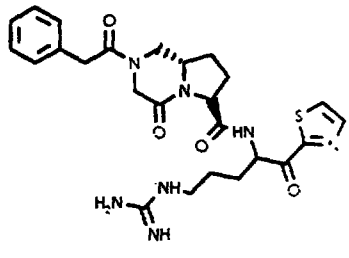
0355 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



0365 4-Oxo-2-(4-phenyl-butyryl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

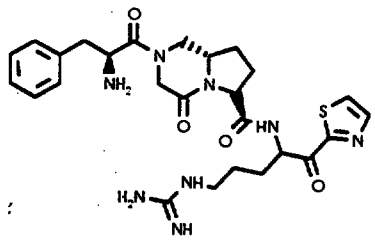


0370 4-Oxo-2-phenylacetyl-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

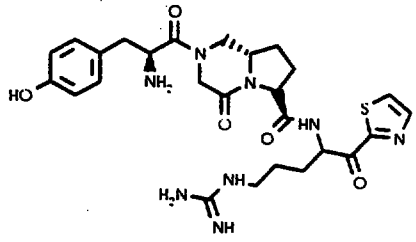


SUBSTITUTE SHEET

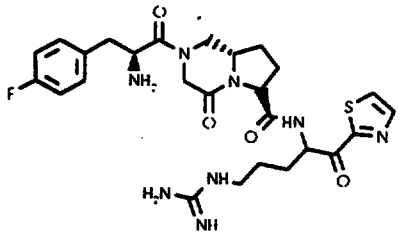
0375 2-(2-Amino-3-phenyl-propionyl)-4-oxo-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



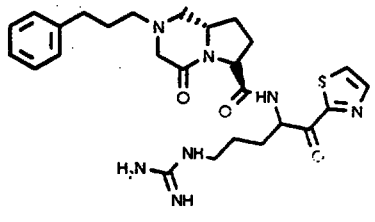
0380 2-[2-Amino-3-(4-hydroxy-phenyl)-propionyl]-4-oxo-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



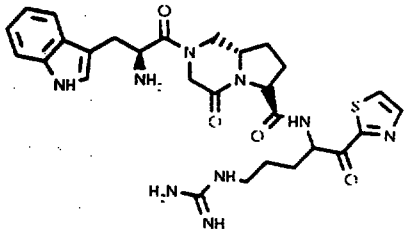
0385 2-[2-Amino-3-(4-fluoro-phenyl)-propionyl]-4-oxo-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



0390 4-Oxo-2-(3-phenyl-propyl)-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

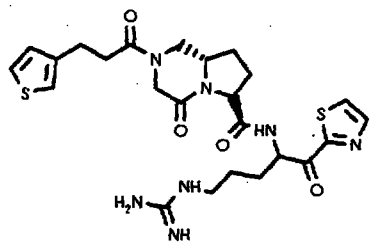


0395 2-[2-Amino-3-(1H-indol-3-yl)-propionyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

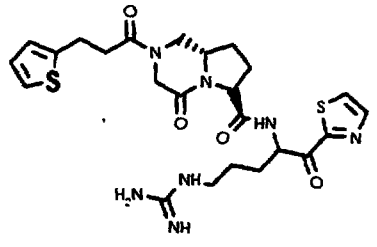


SUBSTITUTE SHEET

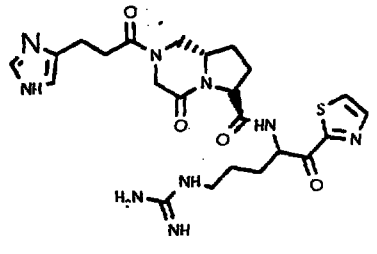
0400 4-Oxo-2-(3-thiophen-3-yl-propionyl)-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



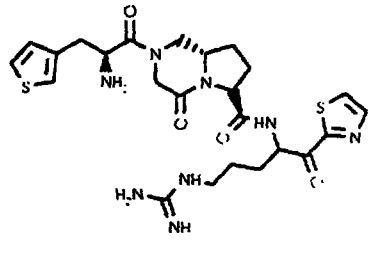
0405 4-Oxo-2-(3-thiophen-2-yl-propionyl)-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



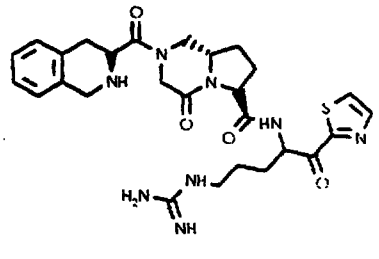
0410 2-(3-1 H-Imidazol-4-yl-propionyl)-4-oxo-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



0415 2-(2-Amino-3-thiophen-3-yl-propionyl)-4-oxo-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

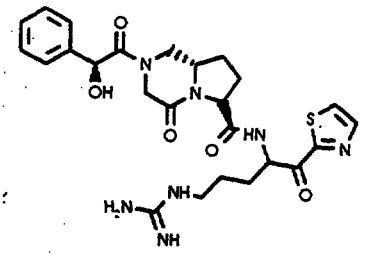


0420 4-Oxo-2-(1,2,3,4-tetrahydro-isoquinoline-3-carbonyl)-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

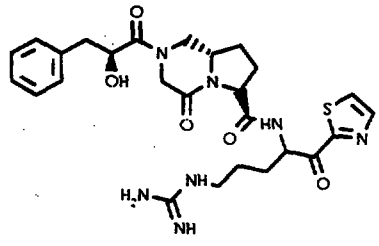


SUBSTITUTE SHEET

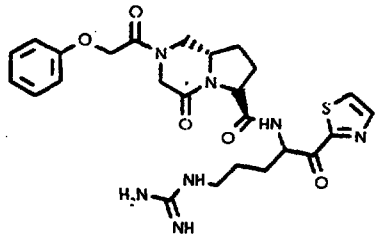
0425 2-(Hydroxy-phenyl-acetyl)-4-oxo-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



0430 2-(2-Hydroxy-3-phenyl-propionyl)-4-oxo-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

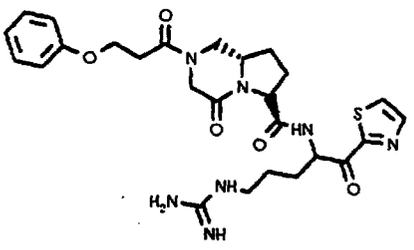


0435 4-Oxo-2-phenoxyacetyl-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

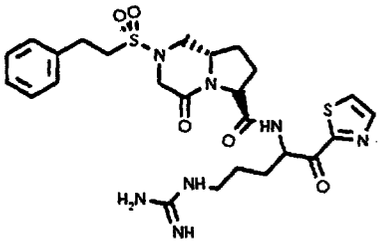


SUBSTITUTE SHEET

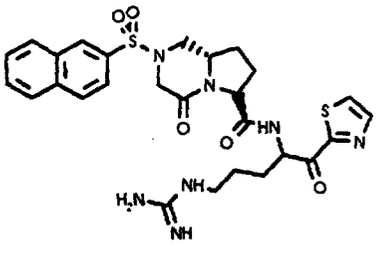
0440 4-Oxo-2-(3-phenoxy-propionyl)-ocatahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



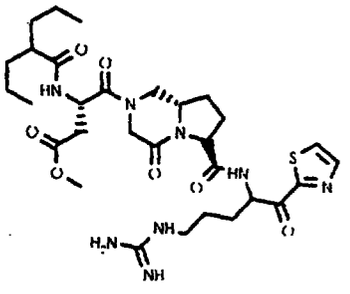
0445 4-Oxo-2-(2-phenyl-ethanesulfonyl)-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazle-2-carbonyl)-butyl]-amide



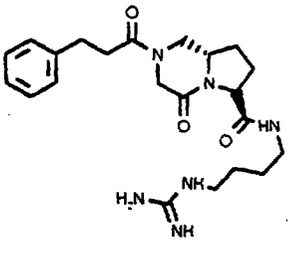
0450 2-(Naphthalene-2-sulfonyl)-4-oxo-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



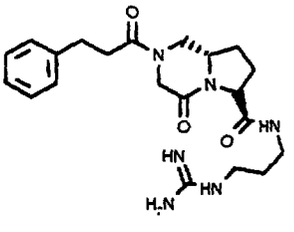
0455 4-(6-[4-Guanidino-1-(thiazole-2-carbonyl)-butylcarbamoyl]-4-oxo-hexahydro-pyrrolo[1,2-a] pyrazin-2yl)-4-oxo-3-(2 propyl -pentanoylamino)-butyric acid methyl ester



0460 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [4-guanidino-1)-butyl]-amide

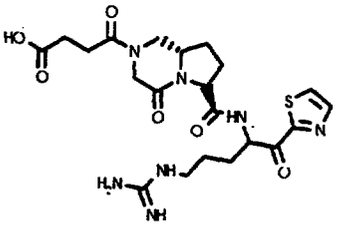


0465 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a] pyrazine-6-carboxylic acid [3-guanidino-propyl) -amide

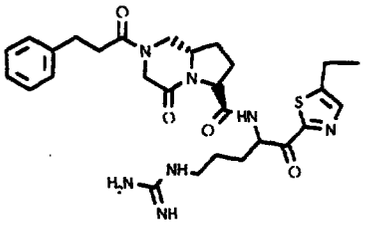


SUBSTITUTE SHEET

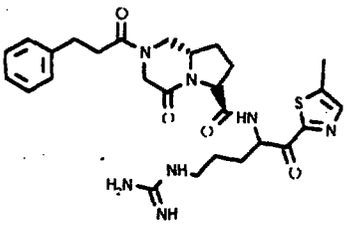
0470 4-(6-[4-Guanidino-1-(thiazole-2-carbonyl)-butylcarbamoyl]-4-oxo-hexahydro-pyrrolo[1,2-a]pyrazin 2-yl)-4-oxo-butyric acid



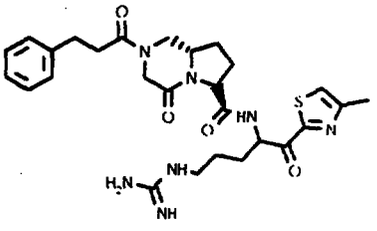
0475 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(5-ethyl-thiazole-2-carbonyl)-4-guanidino-butyl]-amide



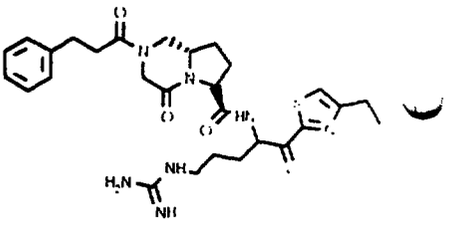
0480 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(5-methyl-thiazole-2-carbonyl)-butyl]-amide



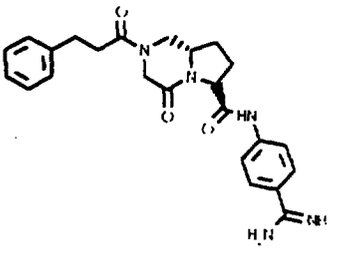
0485 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(4-methyl-thiazole-2-carbonyl)-butyl]-amide



0490 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid[1-(4-ethyl-thiazole-2-carbonyl)-4-guanidino-butyl]-amide

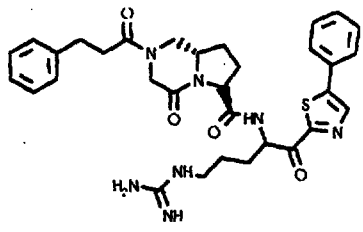


0495 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (4-carbamimidoyl-pheny)-amide

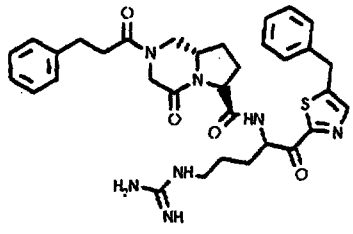


SUBSTITUTE SHEET

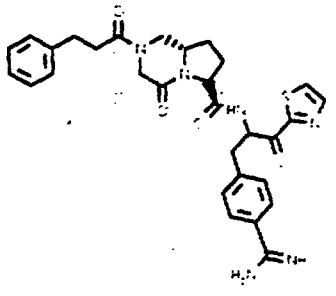
0500 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(5-phenyl-thiazole-2-carbonyl)-butyl]-amide



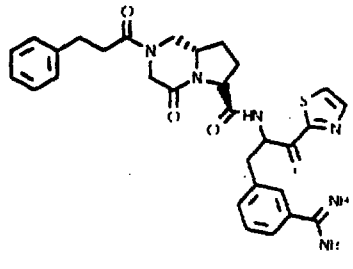
0505 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(5-benzyl-thiazole-2-carbonyl)-4-guanidino-butyl]-amide



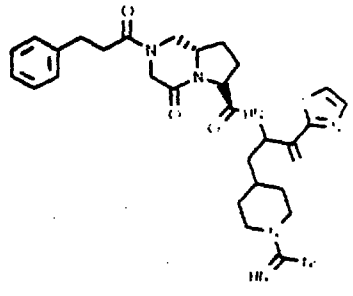
0510 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-carbarnimidoyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



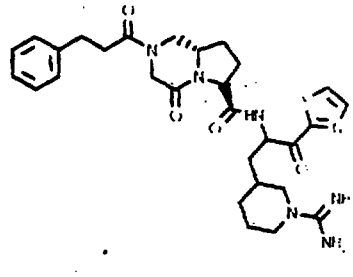
0515 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(3-carbamimidoyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



0520 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

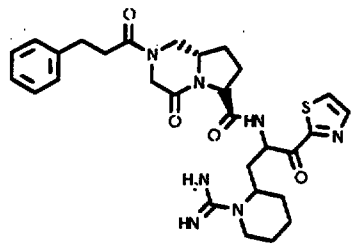


0525 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

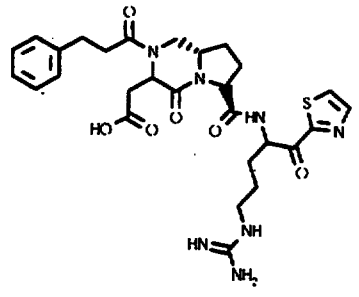


SUBSTITUTE SHEET

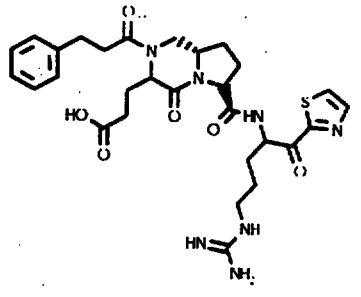
0530 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-2-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



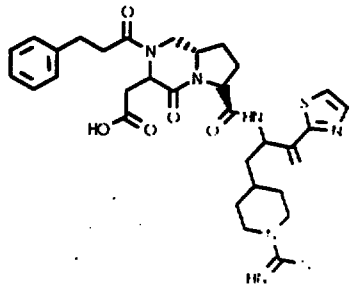
0535 [6-[4-Guanidino-1-(thiazole-2-carbonyl)-butylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-3-yl]-acetic acid



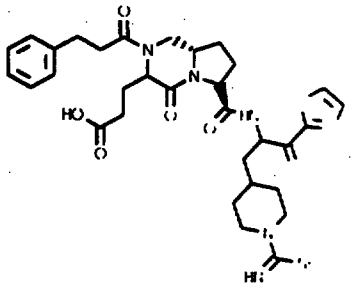
0540 3-[6-[4-Guanidino-1-(thiazole-2-carbonyl)-butylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl]-propionic acid



0545 [6-[1-(1-Carbamimidoyl-piperin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-acetic acid

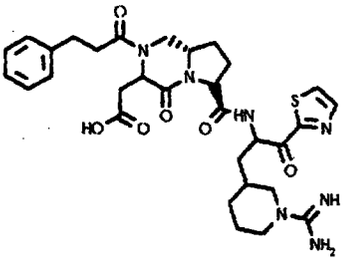


0550 3-[6-[1-(1-Carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-acetic acid

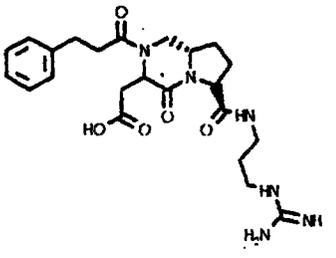


SUBSTITUTE SHEET

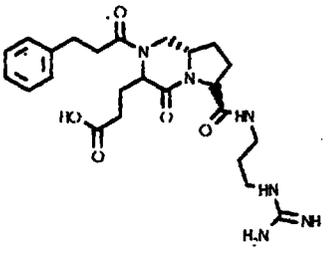
0555 [6-[1-(1-Carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-acetic acid



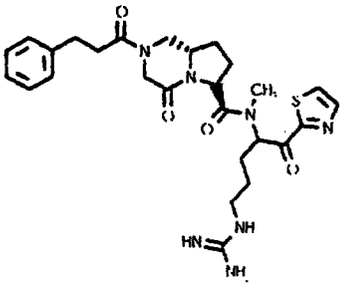
0560 [6-(3-Guanidino-propylcarbamoyl)-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-acetic acid



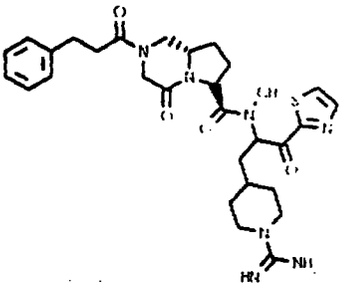
0565 3-[6-(3-Guanidino-propylcarbamoyl)-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-propionic acid



0570 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazolc-2-carbonyl)-butyl]-methyl-amide

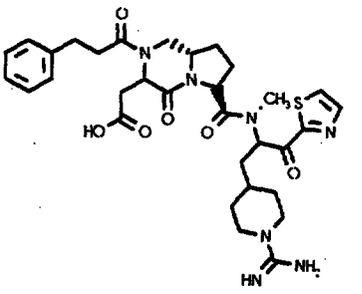


0575 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-methyl-amide

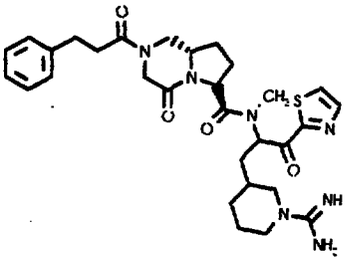


SUBSTITUTE SHEET

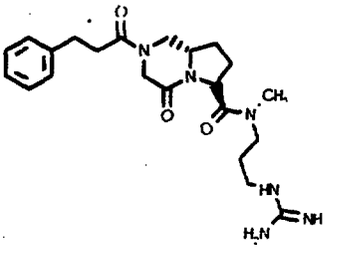
0580 [6-([1-Carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-methyl-carbamoyl)-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl]-acetic-acid



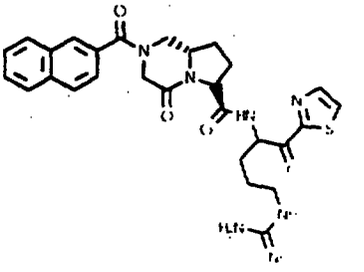
0585 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-methyl-amide



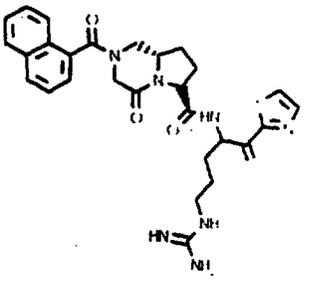
0590 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (3-guanidino-propyl)-methyl-amide



0595 2-(Naphthalene-2-carbonyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

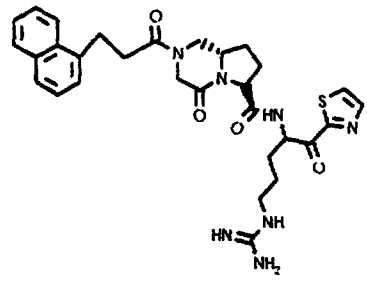


0600 2-(Naphthalene-1-carbonyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

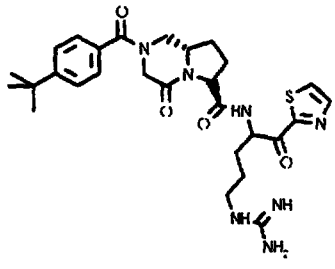


SUBSTITUTE SHEET

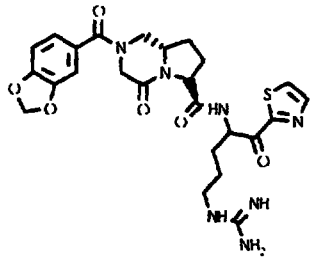
0605 2-(3-Naphthalen-1-yl-proplonyl)4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



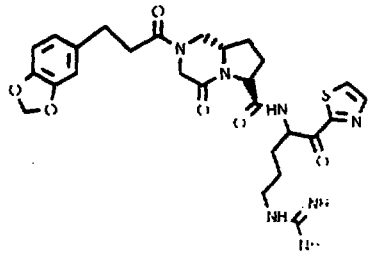
0610 2-(4-tert-Butyl-benzoyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



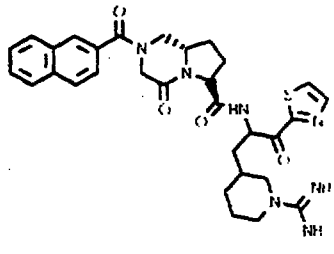
0615 2-(Benzo[1,3]dioxole-5-carbonyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



0620 2-(3-Benzo[1,3]dioxol-5-yl-propionyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

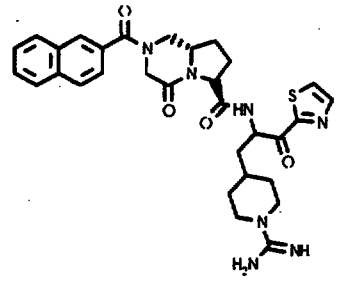


0625 2-[2-(2-Methyl-benzylidene)-but-3-enoyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

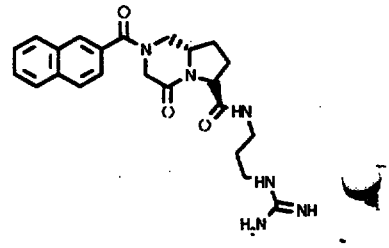


SUBSTITUTE SHEET

0630 2-[2-(2-Methyl-benzylidene)-but-3-enoyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

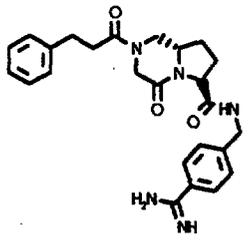


0635 2-(2-Benzylidene-pent-3-enoyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (3-guanidino-propyl)-amide

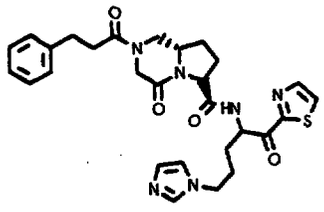


SUBSTITUTE SHEET

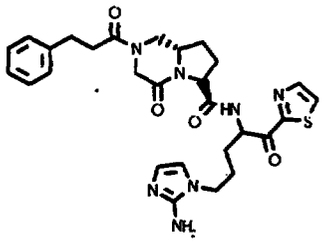
0640 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid 4-carbamimidoyl-benzylamide



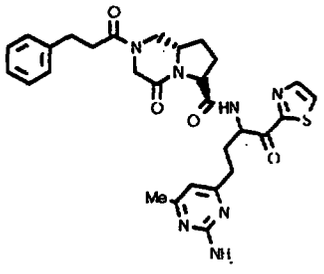
0645 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-imidazol-1-yl-1-(thiazole-2-carbonyl)-butyl]-amide



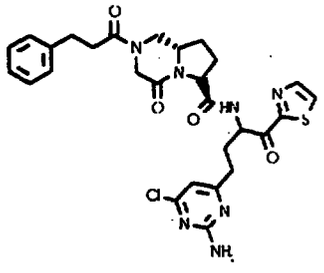
0650 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-(2-amino-imidazol-1-yl)-1-(thiazole-2-carbonyl)-butyl]-amide



0655 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [3-(2-amino-6-methyl-pyrimidin-4-yl)-1-(thiazole-2-carbonyl)-propyl]-amide

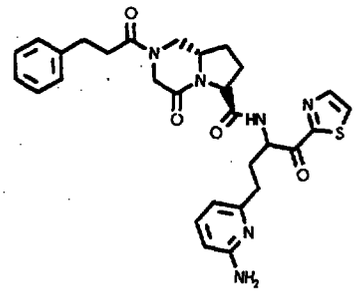


0670 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [3-(2-amino-6-chloro-pyrimidin-4-yl)-1-(thiazole-2-carbonyl)-propyl]-amide

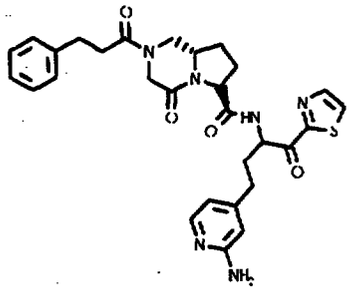


SUBSTITUTE SHEET

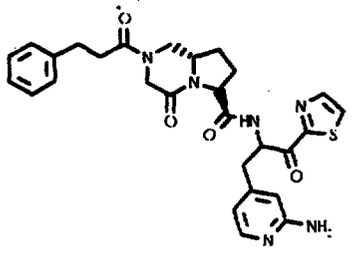
0675 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [3-(6-amino-pyridin-2-yl)-1-(thiazole-2-carbonyl)-propyl]-amide



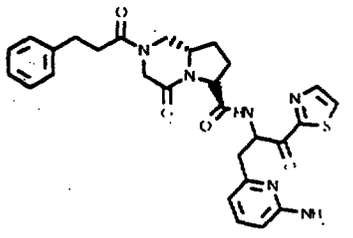
0680 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [3-(2-amino-pyridin-4-yl)-1-(thiazole-2-carbonyl)-propyl]-amide



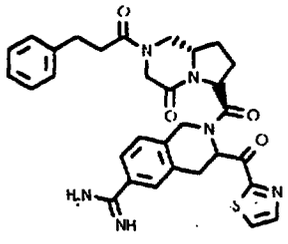
0685 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [2-(2-amino-pyridin-4-yl)-1-(thiazole-2-carbonyl)-ethyl]-amide



0690 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [2-(6-amino-pyridin-2-yl)-1-(thiazole-2-carbonyl)-ethyl]-amide

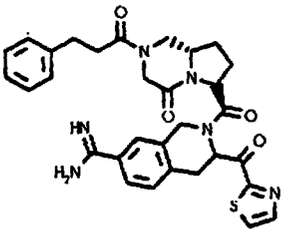


0695 2-[4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-3-(thiazole-2-carbonyl)-1,2,3,4-tetrahydro-isoquinoline-6-carboxamidine

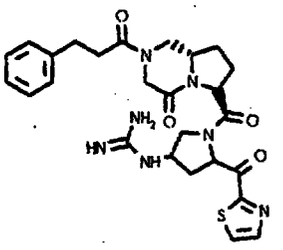


SUBSTITUTE SHEET

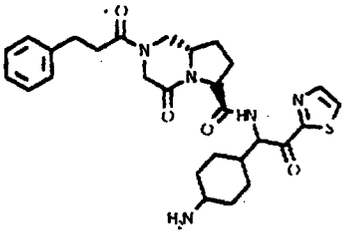
0700 2-[4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-3-(thiazole-2-carbonyl)-1,2,3,4-tetrahydro-isoquinoline-7-carboxamidine



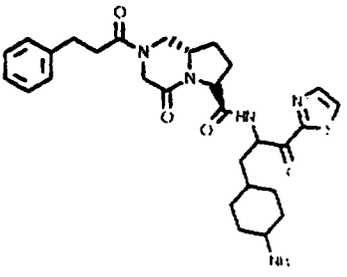
0705 N-[1-[4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-5-(thiazole-2-carbonyl)-pyrrolidin-3-yl]-guanidine



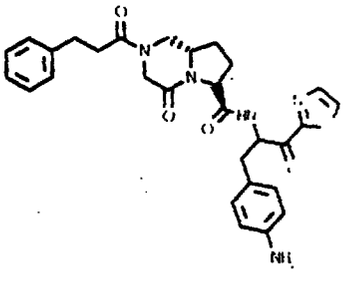
0710 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-amino-cyclohexyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



0715 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-amino-cyclohexylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

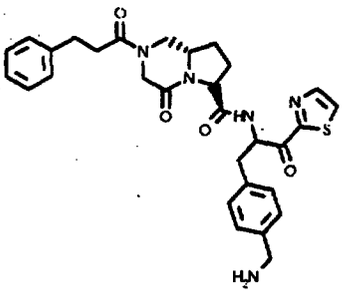


0720 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-amino-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

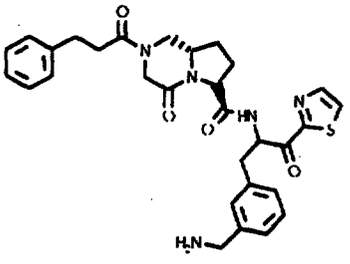


SUBSTITUTE SHEET

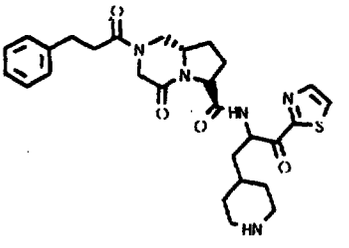
0725 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-aminomethyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



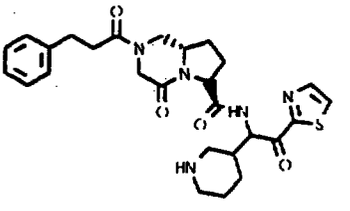
0730 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(3-aminomethyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



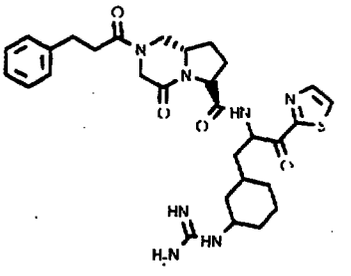
0735 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (2-oxo-1-piperidin-4-ylmethyl-2-thiazol-2-yl-ethyl)-amide



0740 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (2-oxo-1-piperidin-3-yl-2-thiazol-2-yl-ethyl)-amide

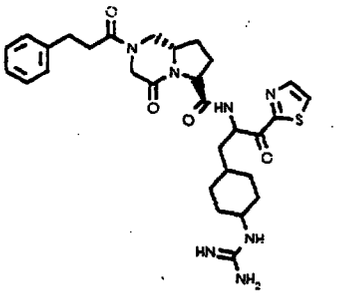


0745 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(3-guanidino-cyclohexylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

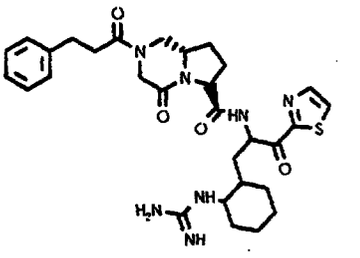


SUBSTITUTE SHEET

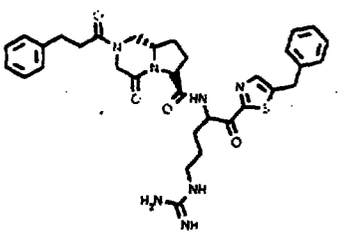
0750 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-guanidino-cyclohexylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



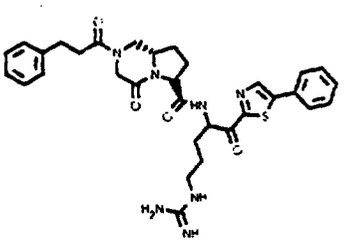
0755 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(2-guanidino-cyclohexylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



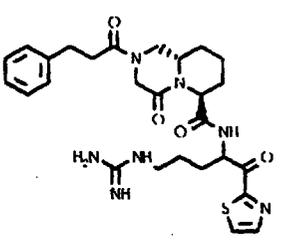
0760 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(5-benzyl-thiazole-2-carbonyl)-4-guanidino-butyl]-amide



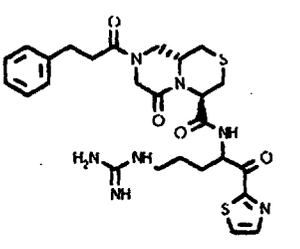
0765 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(5-phenyl-thiazole-2-carbonyl)-butyl]-amide



0770 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrido[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

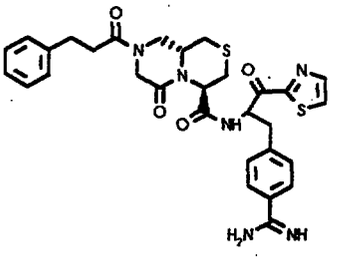


0775 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

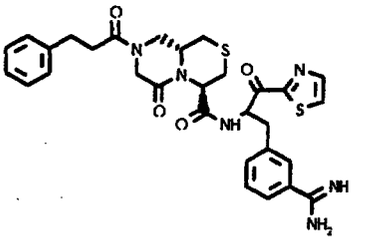


SUBSTITUTE SHEET

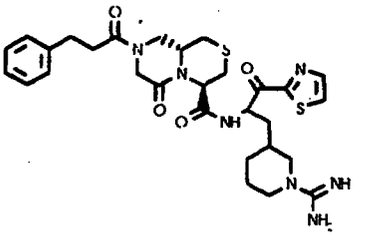
0780 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [1-(4-carbamimidoyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



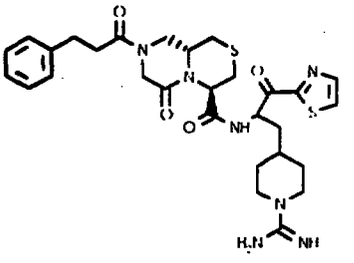
0785 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [1-(3-carbamimidoyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



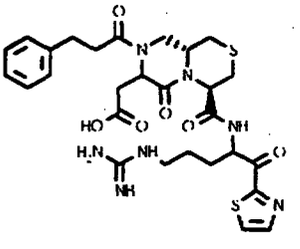
0790 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide



0795 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

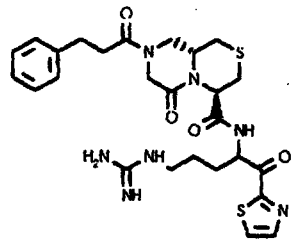


0800 [4-[4-Guanidino-1-(thiazole-2-carbonyl)-butylcarbamoyl]-5-oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalen-6-yl]-acetic acid

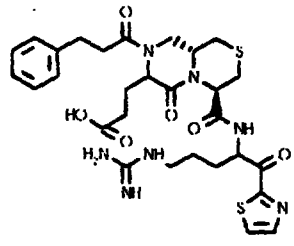


SUBSTITUTE SHEET

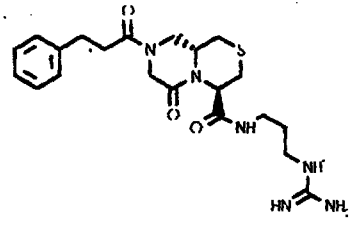
0805 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



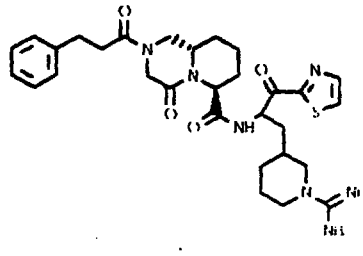
0810 3-[4-[4-Guanidino-1-(thiazole-2-carbonyl-butylcarbamoyl]-5-oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalen-6-yl]-propionic acid



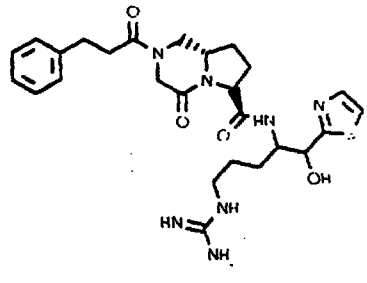
0815 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [3-guanidino-propyl]-amide



0820 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

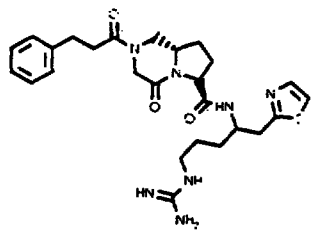


0825 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(hydroxy-thiazol-2-yl-methyl)-butyl]-amide

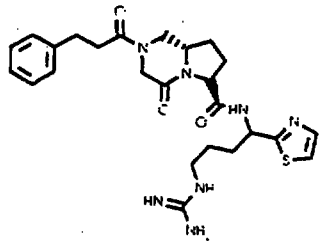


SUBSTITUTE SHEET

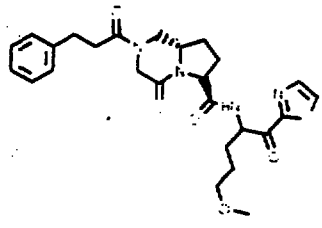
0830 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (4-guanidino-1-thiazol-2-ylmethyl-butyl)-amide



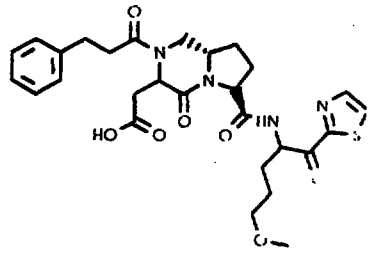
0835 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-thiazol-2-yl-butyl)-amide



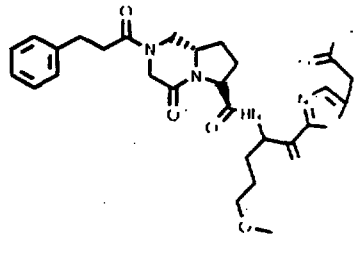
0840 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-methoxy-1-(thiazole-2-carbonyl)-butyl]-amide



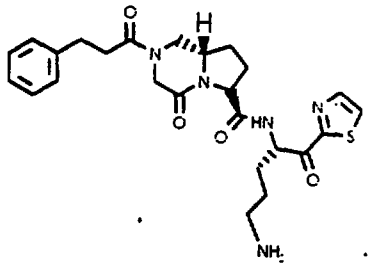
0845 [6-[4-Methoxy-1-(thiazole-2-carbonyl)-butylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl]-acetic acid



0850 [2-(5-Methoxy-2-([4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-amino)-pentanoyl)-thiazol-5-yl]-acetic acid



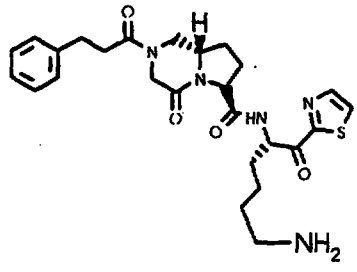
0855 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-amino-1-(thiazole-2-carbonyl)-butyl]-amide



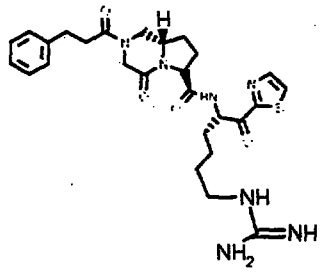
This Sheet Has Been Replaced

SUBSTITUTE SHEET

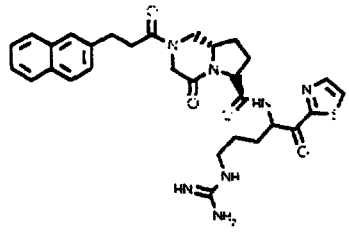
0860 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [5-amino-1-(thiazole-2-carbonyl)-pentyl]-amide



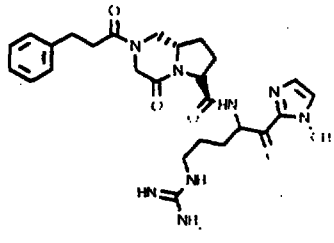
0865 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [5-guanidino-1-(thiazole-2-carbonyl)-pentyl]-amide



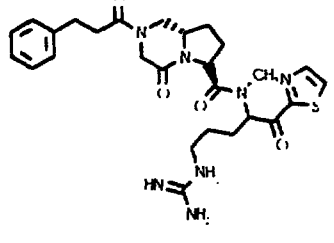
0870 2-(3-Naphthalen-2-yl-propionyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



0875 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(1-methyl-1H-imidazole-2-carbonyl)-butyl]-amide

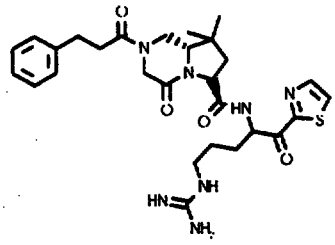


0880 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



SUBSTITUTE SHEET

0885 8,8-Dimethyl-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



SUBSTITUTE SHEET

Preferred compounds according to formula (VIII) include:

0325 3-Aminomethyl-2-benzoyl-4-oxo-octahydro-pyrrolo[1,2-a]pyridine-6-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide

0330 3-Aminomethyl-4-oxo-2-phenylacetyl-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide

0515 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(3-carbamimidoyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0530 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-2-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0545 [6-[1-(1-Carbamimidoyl-piperin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-acetic acid

0550 3-[6-[1-(1-Carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-acetic acid

0555 [6-[1-(1-Carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-acetic acid

SUBSTITUTE SHEET

0560 [6-(3-Guanidino-propylcarbamoyl)-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-acetic acid

0565 3-[6-(3-Guanidino-propylcarbamoyl)-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl)-propionic acid

0575 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-methyl-amide

0580 [6-([1-Carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-methyl-carbamoyl)-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl]-acetic-acid

0585 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-methyl-amide

0590 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (3-guanidino-propyl)-methyl-amide

0595 2-(Naphthalene-2-carbonyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

SUBSTITUTE SHEET

0625 2-[2-(2-Methyl-benzylidene)-but-3-enoyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0630 2-[2-(2-Methyl-benzylidene)-but-3-enoyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0635 2-(2-Benzylidene-pent-3-enoyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (3-guanidino-propyl)-amide

0625 2-[2-(2-Methyl-benzylidene)-but-3-enoyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0630 2-[2-(2-Methyl-benzylidene)-but-3-enoyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0635 2-(2-Benzylidene-pent-3-enoyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (3-guanidino-propyl)-amide

0645 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-imidazol-1-yl-1-(thiazole-2-carbonyl)-butyl]-amide

This Sheet Has Been Replaced

SUBSTITUTE SHEET

0670 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [3-(2-amino-6-chloro-pyrimidin-4-yl)-1-(thiazole-2-carbonyl)-propyl]-amide

0675 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [3-(6-amino-pyridin-2-yl)-1-(thiazole-2-carbonyl)-propyl]-amide

0680 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [3-(2-amino-pyridin-4-yl)-1-(thiazole-2-carbonyl)-propyl]-amide

0685 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [2-(2-amino-pyridin-4-yl)-1-(thiazole-2-carbonyl)-ethyl]-amide

0690 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [2-(6-amino-pyridin-2-yl)-1-(thiazole-2-carbonyl)-ethyl]-amide

0695 2-[4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-3-(thiazole-2-carbonyl)-1,2,3,4-tetrahydro-isoquinoline-6-carboxamidine

0700 2-[4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-3-(thiazole-2-carbonyl)-1,2,3,4-tetrahydro-isoquinoline-7-carboxamidine

0705 N-[1-[4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-5-(thiazole-2-carbonyl)-pyrrolidin-3-yl]-guanidine

SUBSTITUTE SHEET

0710 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-amino-cyclohexyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0730 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(3-aminomethyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0745 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(3-guanidino-cyclohexylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0755 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(2-guanidino-cyclohexylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0795 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0800 [4-[4-Guanidino-1-(thiazole-2-carbonyl)-butylcarbamoyl]-5-oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalen-6-yl]-acetic acid

0810 3-[4-[4-Guanidino-1-(thiazole-2-carbonyl-butylcarbamoyl]-5-oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalen-6-yl]-propionic acid

SUBSTITUTE SHEET

0815 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [3-guanidino-propyl]-amide

0820 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0830 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (4-guanidino-1-thiazol-2-ylmethyl-butyl)-amide

0835 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-thiazol-2-yl-butyl)-amide

More preferred compounds according to formula VIII include:

0335 2-Benzoyl-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

0650 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-(2-amino-imidazol-1-yl)-1-(thiazole-2-carbonyl)-butyl]-amide

0655 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [3-(2-amino-6-methyl-pyrimidin-4-yl)-1-(thiazole-2-carbonyl)-propyl]-amide

SUBSTITUTE SHEET

0715 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-amino-cyclohexylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0720 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-amino-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0725 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-aminomethyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0735 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (2-oxo-1-piperidin-4-ylmethyl-2-thiazol-2-yl-ethyl)-amide

0740 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (2-oxo-1-piperidin-3-yl-2-thiazol-2-yl-ethyl)-amide

0750 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(4-guanidino-cyclohexylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0760 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(5-benzyl-thiazole-2-carbonyl)-4-guanidino-butyl]-amide

0765 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(5-phenyl-thiazole-2-carbonyl)-butyl]-amide

SUBSTITUTE SHEET

0770 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrido[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

0775 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

0780 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [1-(4-carbamimidoyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0785 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [1-(3-carbamimidoyl-benzyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0790 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0805 5-Oxo-7-(3-phenyl-propionyl)-octahydro-2-thia-4a,7-diaza-naphthalene-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

0825 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(hydroxy-thiazol-2-yl-methyl)-butyl]-amide

SUBSTITUTE SHEET

0840 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-methoxy-1-(thiazole-2-carbonyl)-butyl]-amide

0845 [6-[4-Methoxy-1-(thiazole-2-carbonyl)-butylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl]-acetic acid

0850 [2-(5-Methoxy-2-([4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-amino)-pentanoyl)-thiazol-5-yl]-acetic acid

0855 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-amino-1-(thiazole-2-carbonyl)-butyl]-amide

0860 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [5-amino-1-(thiazole-2-carbonyl)-pentyl]-amide

0865 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [5-guanidino-1-(thiazole-2-carbonyl)-pentyl]-amide

Most preferred compounds according to formula VIII include:

0345 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(5-methyl-thiazole-2-carbonyl)-butyl]-amide; and0340 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-

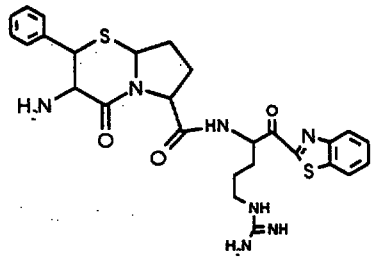
This Sheet Has Been Replaced

SUBSTITUTE SHEET

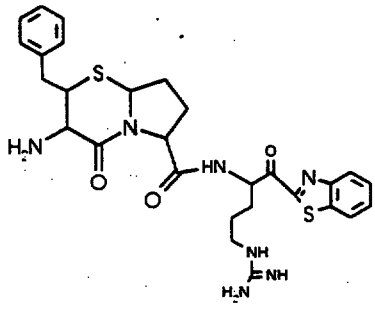
6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide.

Preferred compounds according to formula IX include:

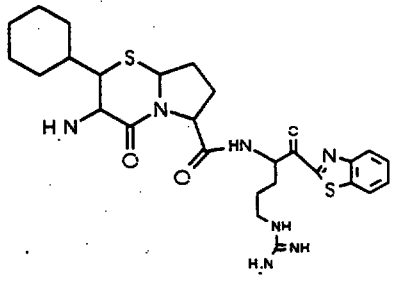
0890 3-Amino-4-oxo-2-phenyl-hexahydro-pyrrolo[2,1-b][1,3]thiazine-6-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



0895 3-Amino-2-benzyl-4-oxo--hexahydro-pyrrolo[2,1-b][1,3]thiazine-6-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



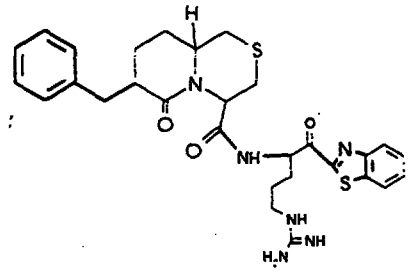
0900 3-Amino-2-cyclohexyl-4-oxo-hexahydro-pyrrolo[2,1-b][1,3]thiazine-6-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



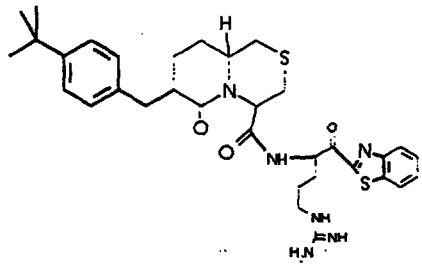
SUBSTITUTE SHEET

Preferred compounds according to formula X include:

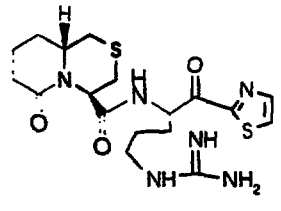
0905 7-Benzyl-6-oxo-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



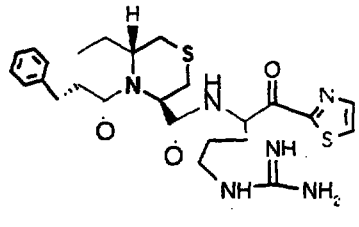
0910 7-(4-tert-Butyl-benzyl)-6-oxo-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide



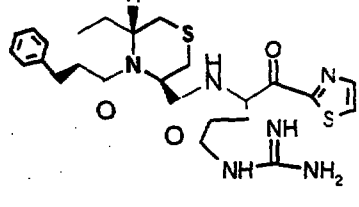
0915 6-Oxo-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



0925 7-Benzyl-6-oxo-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide

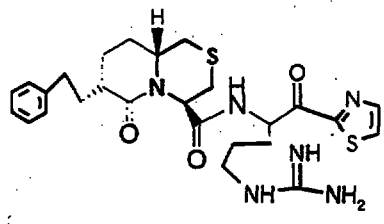


0935 7-Benzyl-6-oxo-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide

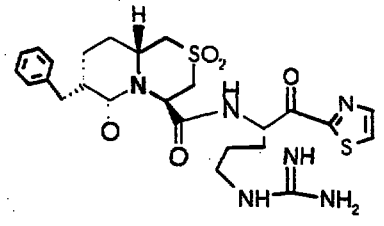


SUBSTITUTE SHEET

0940 6-Oxo-7-phenethyl-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



0950 7-Benzyl-2,2,6-trioxo-octahydro-21>6_pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

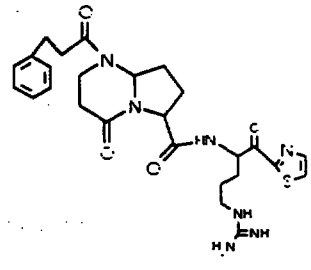


More preferred compounds according to formula X include:

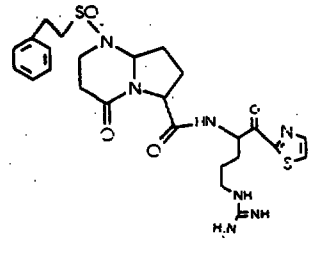
925 7-Benzyl-6-oxo-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide; and940 6-Oxo-7-phenethyl-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide.

Preferred compounds according to formula III include:

0960 4-oxo-1-(3-phenyl-propionyl)-octahydropyrrolo[1,2]pyrimidine-6-carboxylic acid[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



0965 4-oxo-1-(phenethylsulfonyl)-octahydropyrrolo[1,2]pyrimidine-6-carboxylic acid[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



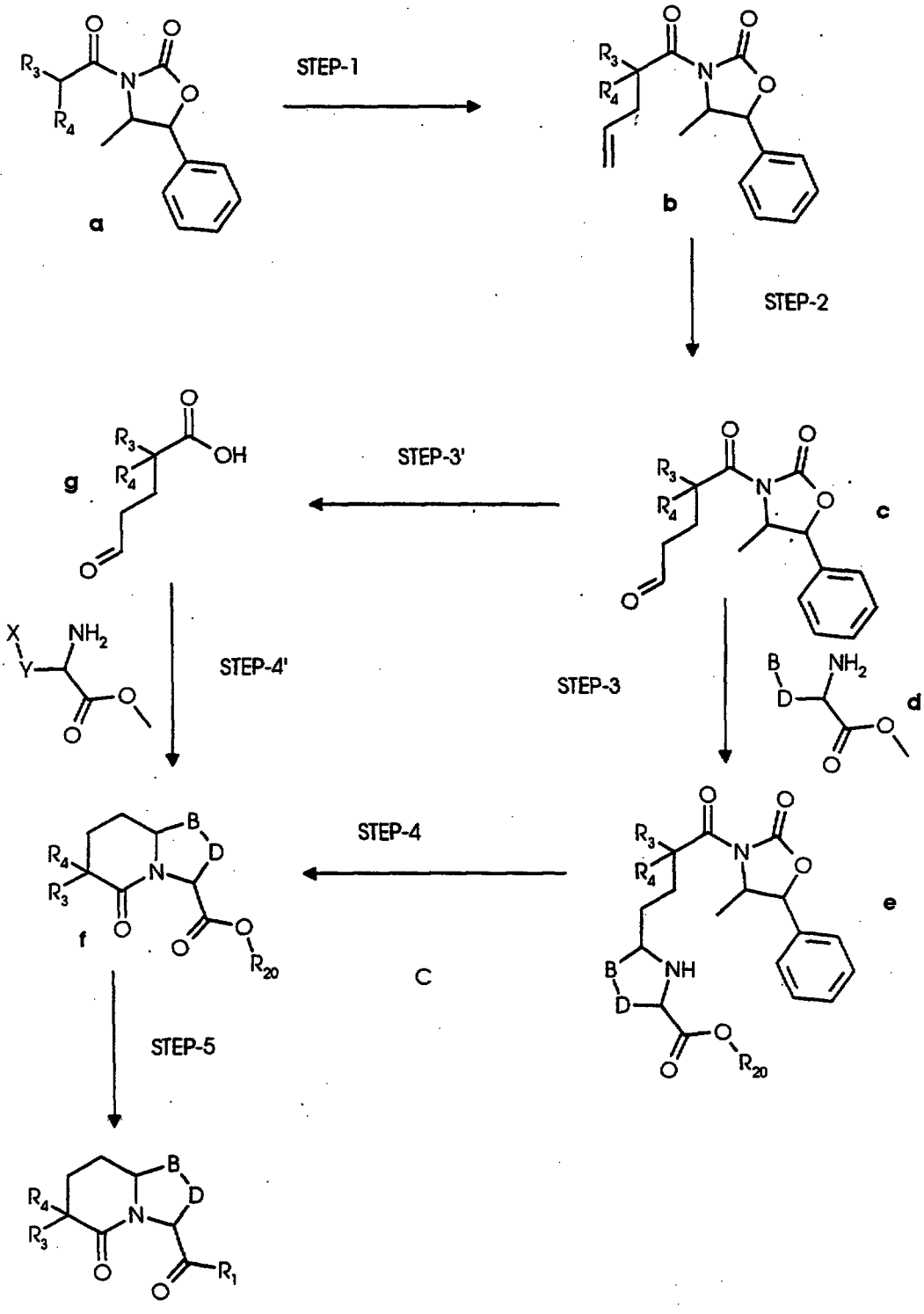
This Sheet Has Been Replaced

SUBSTITUTE SHEET

For preparation of the compounds of formula (VII) various methods can be employed depending upon the particular starting materials and/or intermediates involved. The following scheme is one particular method of

SUBSTITUTE SHEET

SCHEME 1



Step 1:
The alkylation of a is done with appropriate bases according to the procedures described in Evans et al (J. Am. Chem. Soc., 1981, 103, 2127; ibid, 1982, 104, 1737; Aldrichimica Acta, 1982, 15, 23) to give b.

Step 2:
Compound b upon hydroboration and oxidation following conditions available in the literature (Synthesis, 1980, 151) results in the aldehyde c.

Step 3:
The formation of adduct e from aldehyde c with d is done by stirring the reactant in aromatic solvents e.g. benzene or toluene in presence of catalytic amount of suitable acid e.g, p-toluenesulfonic acid.

Step 3':
The inter conversion of aldehyde c to aldehyde g is readily achieved by appropriate protection deprotection protocals found in T. Greene, Protective Groups In Organic Synthesis, (John Wiley & Sons, 1981).

Step 4:
The cylization of adduct e to f may readily be achieved by appropriate Lewis acids e.g, trimethyl aluminum in suitable solvents e.g. dichloromethane, the methodology found in T. Greene, supra.

Step 4':
Alternatively, the compound f can be derived from the treatment of aldehyde g with d in presence of suitable aromatic solvents e.g, benzene.

Step 5:
The ester function (-C(O)O-R_1) of the bicyclic intermediate of formula f is then subjected to

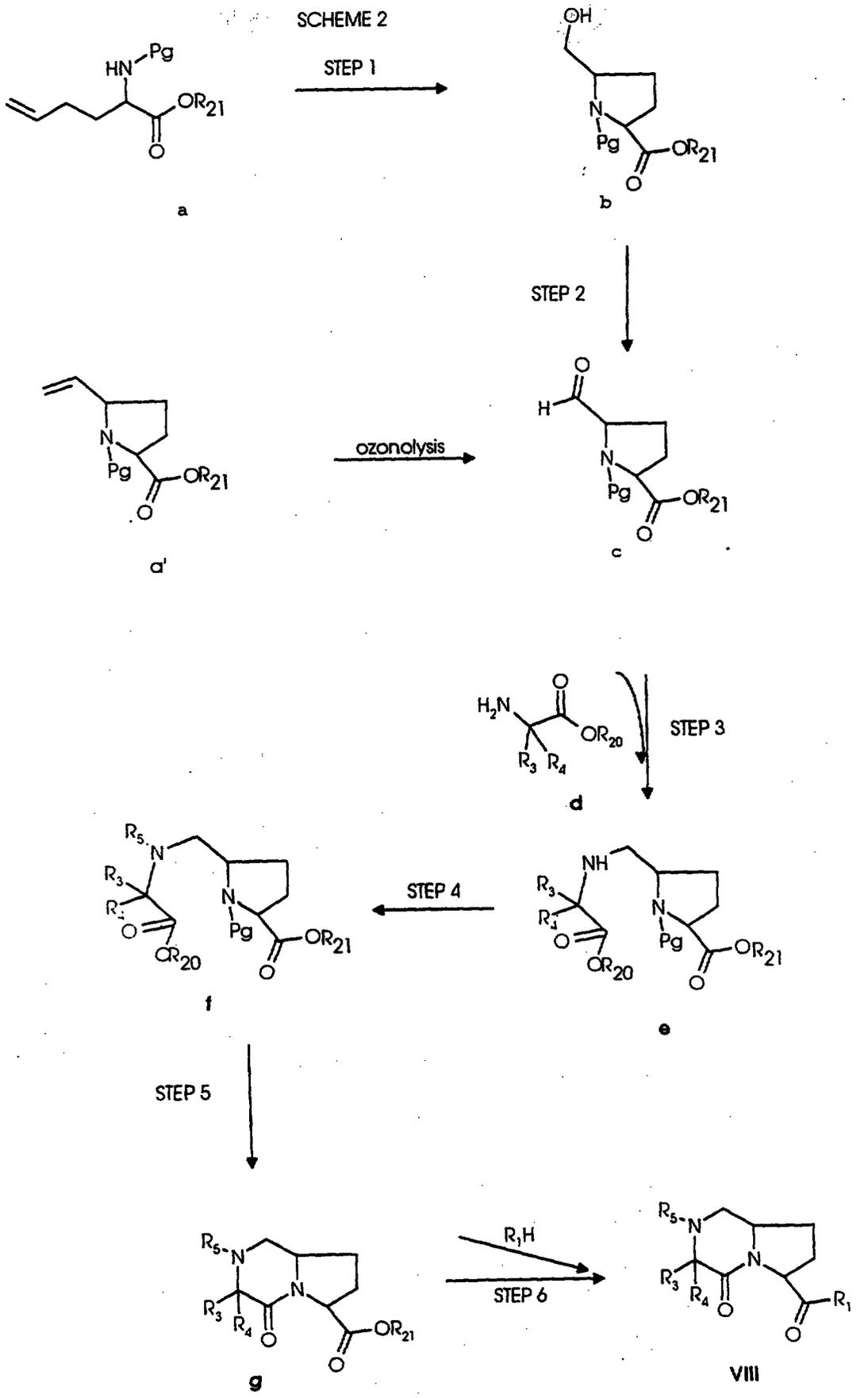
SUBSTITUTE SHEET

hydrolysation using an appropriate agent such as HCl in an appropriate solvent such as ethyl ether to yield to the free carboxylic acid. The resulting compound is then coupled to R_1H with a peptide coupling agent such as BOP in an appropriate solvent such as DMF to yield to a bicyclic coupled compound of formula (VIII). Suitable conditions for peptide bond formation are well known in th art of peptide chemistry. For example see Principles of Peptide Synthesis, Bodanszky M., Springer-Verlag, Berlin, Heidelberg, New York, Tokyo 1984; and The Peptides, Analysis, Synthesis, Biology, Vol. 1,edited by Gross E., and Meienhofer J., Academic Press , New York, San Francisco, London, 1979.

For preparation of the compounds of formula (VIII) various methods can be employed depending upon the particular starting materials and/or intermediates involved. The following scheme is one particular method of preparation.

SUBSTITUTE SHEET

SCHEME 2



SUBSTITUTE SHEET

wherein;

Pg is a nitrogen protecting group;

each of R_{20} and R_{21} is independently a C_{1-4} alkyl; and **X**, R_1, R_3, R_4 and R_5 are as previously defined.

The process in scheme 2 is briefly described as follows:

STEP 1:

The amino and carboxylic functions of the unsaturated compound of formula **(a)** are protected with appropriate protecting groups. A variety of protecting groups known for reactive functional groups and suitable protection and deprotection protocols may be found in T. Greene, Protective Groups In Organic Synthesis, (John Wiley & Sons, 1981). The appropriate protecting group to use in a particular synthetic scheme will depend on many factors, including the presence of other reactive functional groups and the reaction conditions desired for removal. The unsaturated compound of formula is easily obtained by methods and protocols known to chemist skill on the art. The protected unsaturated compound of formula (a) is subjected to appropriate conditions to allow cyclisation using an appropriate reagent such as mercuric acetate in an inert solvent such as tetrahydrofuran (THF) to yield to a protected amino alcohol of formula **(b)**.

STEP 2

The protected amino alcohol of formula (b) is oxidized using an appropriate oxidizing agent such as sulfur trioxide pyridine complex in an appropriate solvent such as diclhoromethane or dimethylformamide to yield to a protected amino aldehyde of formula **(c)**. Alternatively, intermediate (C) can be made by the ozonolysis of a compound of formula (a') prepared according to Collado et al, J. Org. Chem.,1995, 60:5011.

SUBSTITUTE SHEET

STEP 3

The protected amino aldehyde of formula (c) is coupled with an amino acid alkyl ester of formula (d) by first forming the imine followed by contacting the obtained imine with an appropriate reagent such as sodium triacetoxy borohydride $NaBH(OAc)_3$ to yield to a cyclic intermediate of formula (e).

STEP 4

The cyclic intermediate of formula (e) is functionalized at the amino position to yield to the amino substituted cyclic intermediate of formula (f). Conditions appropriate for such reactions are well known in the art and will depend on the nature of the R_5 substituent.

STEP 5

The amino protecting group of the cyclic intermediate of formula **(f)** is removed under appropriate conditions and the resulting compound is then subjected to appropriate condition for internal ring closure such as low heat in an inert solvent or as a raw compound to yield to a bicyclic intermediate of formula (g). The bicyclic intermediate of formula (g) can also be obtained by hydrolysing the ester function ($-C(O)O-R_{20}$) of the cyclic intermediate of formula **(g)** to the free carboxylic acid followed by standard peptide coupling using an appropriate coupling reagent such as benzotriazole-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP) in an inert solvent such as dimethyl formamide (DMF).

STEP 6

The ester function ($-C(O)O-R_{21}$) of the bicyclic intermediate of formula (g) is then subjected to hydrolysation using an appropriate agent such as HCl in an appropriate solvent such as ethyl ether to yield to the

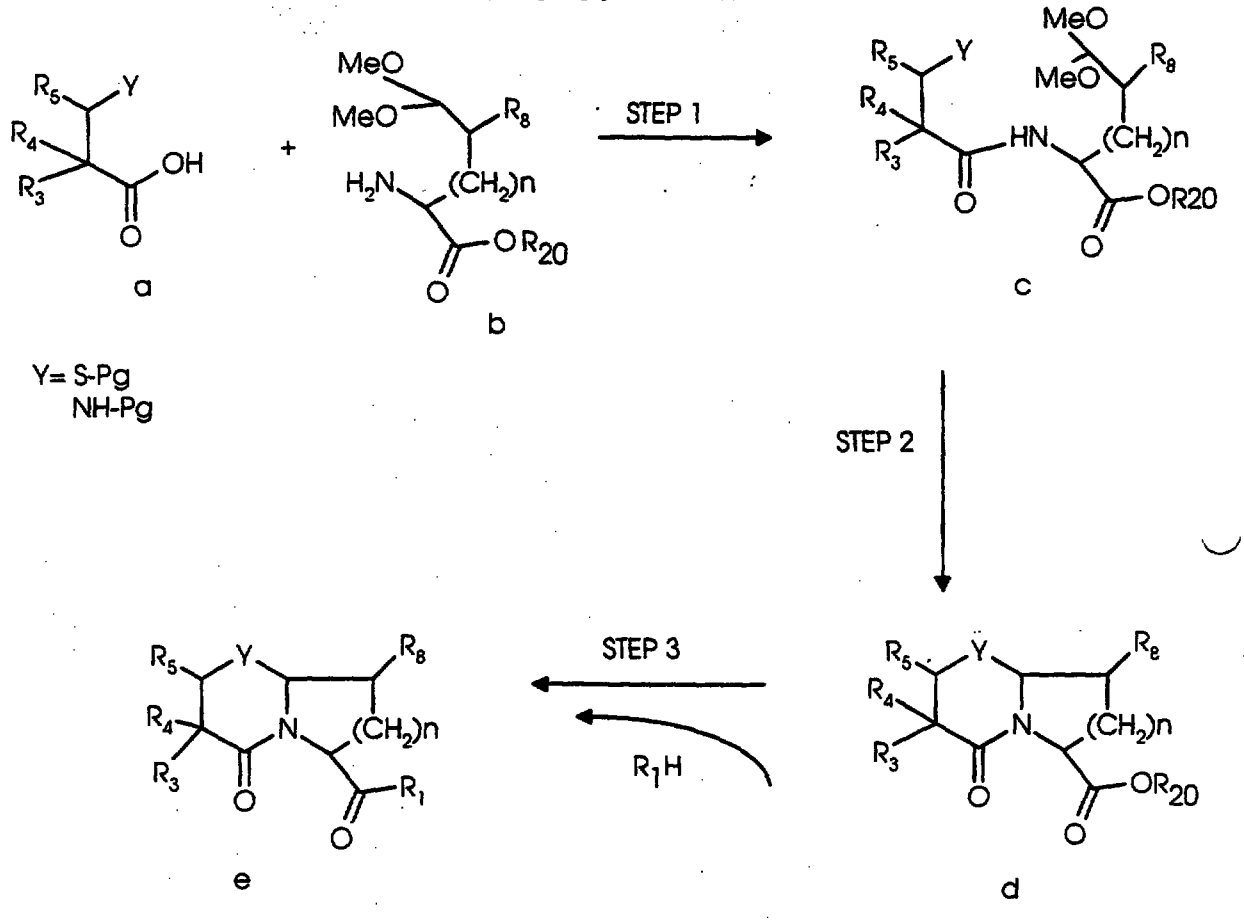
SUBSTITUTE SHEET

free carboxylic acid. The resulting compound is then coupled to R_1H with a peptide coupling agent such as BOP in an appropriate solvent such as DMF to yield to a bicyclic coupled compound of formula (VIII). Suitable conditions for peptide bond formation are well known in th art of peptide chemistry. For example see Principles of Peptide Synthesis, Bodanszky M., Springer-Verlag, Berlin, Heidelberg, New York, Tokyo 1984; and The Peptides, Analysis, Synthesis, Biology, Vol. 1.edited by Gross E., and Meienhofer J., Academic Press , New York, San Francisco, London, 1979.

For preparation of the compounds of formula (IX) various methods can be employed depending upon the particular starting materials and/or intermediates involved. The following scheme is one particular method of preparation.

SUBSTITUTE SHEET

SCHEME 3



wherein:

Pg is a sulfur or amino protecting group;

L is a leaving group;

each of R_{20}; and R_{21} is independently a C_{1-6} alkyl; and R_1, R_3, R_4 and R_5 are as previously defined.

The process depicted in scheme 3 is briefly described as follows:

STEP 1:

The carboxylic acid compound (a) is coupled to the cyclic amine compound (b) with a peptide coupling agent such as benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) in the presence of a base such as *n*-methylmorpholine in an appropriate solvent such as dimethylformamide (DMF) or dichloromethane (DCM) to yield to an amido compound of formula (c). Suitable

SUBSTITUTE SHEET

conditions for peptide bond formation are well known in th art of peptide chemistry. For example see Principles of Peptide Synthesis, Bodanszky M., Springer-Verlag, Berlin, Heidelberg, New York, Tokyo 1984; and The Peptides, Analysis, Synthesis, Biology, Vol. 1 edited by Gross E., and Meienhofer J., Academic Press , New York, San Francisco, London, 1979.

STEP 2

The compound of formula (c) is subjected to appropriate conditions to allow internal cyclisation to yield to a bicyclic intermediate of formula (d). For example, acid mediated cyclisation using p-toluenesulfonic acid or TFA in an appropriate solvent such as dichloroethane.

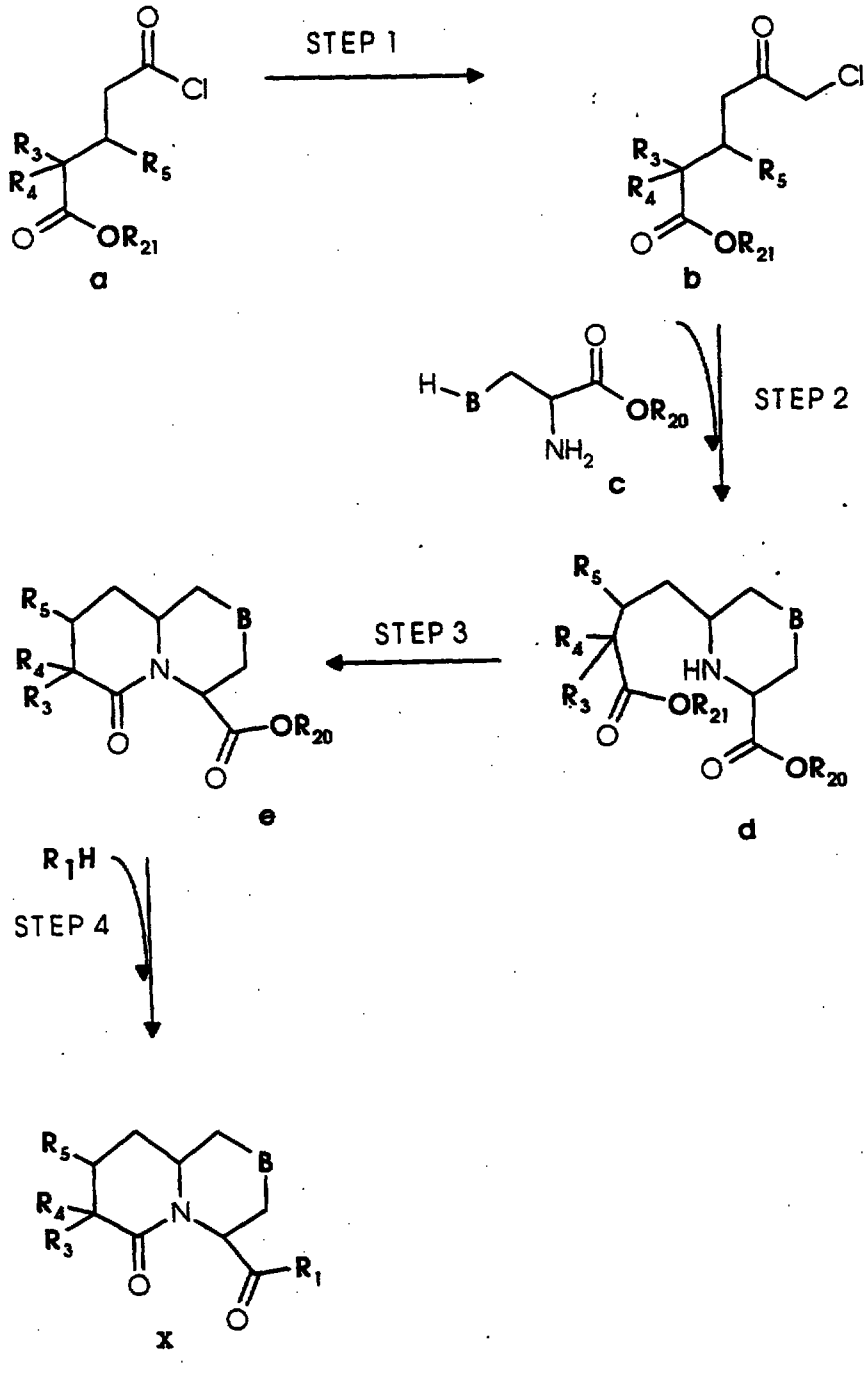
STEP 3

The ester function (-C(O)O-R_a) of the bicyclic intermediate of formula (d) is subjected to hydrolysis using an appropriate agent such as lithium hydroxide (LiOH) in an appropriate solvent such as tetrahydrofuran (THF) to yield to the free carboxylic acid. The resulting compound is then coupled to R.H with a peptide coupling agent such as BOP in an appropriate solvent such as DMF to give compound (e). Suitable conditions for peptide bond formation are well known in the art of peptide chemistry. For example see Principles of Peptide Synthesis, Bodanszky M., Springer-Verlag, Berlin, Heidelberg, New York, Tokyo 1984; and The Peptides, Analysis, Synthesis, Biology, Vol. 1 edited by Gross E., and Meienhofer J., Academic Press , New York, San Francisco, London, 1979.

For preparation of the compounds of formula (X) various methods can be employed depending upon the particular starting materials and/or intermediates involved. The following scheme 4 is one particular method of preparation.

SUBSTITUTE SHEET

SCHEME 4



wherein:

each of R_{20} and R_{21} is independently a C_{1-4} alkyl; and B, R_1, R_3, R_4, and R_5 are as previously defined.

SUBSTITUTE SHEET

The process depicted in scheme 4 is briefly described as follows:

STEP 1:

The halogenated compound of formula (a) is converted to a halomethyl ketone of formula (b) using an appropriate reagent, such as diazomethane in an inert solvent such as diethyl ether at a temperature of about -25°C to about 0°C. The resulting mixture is then treated under acidic conditions to yield to the halomethyl ketone of formula (b).

STEP 2

The halomethyl ketone of formula **(b)** is coupled with an amino acid alkyl ester of formula **(c)** with an appropriate base such as sodium cyanoborohydride in an organic solvent such as methanol (MeOH) to yield to a cyclic intermediate of formula (d).

STEP 3

The cyclic intermediate of formula **(d)** is treated under acidic conditions using an appropriate acid such as camphorsulfonic acid in an appropriate solvent such as toluene to yield to a bicyclic intermediate of formula (e).

STEP 4

The ester function (-C(O)O-$\mathbf{R}_{20}$) of the bicyclic intermediate of formula (e) is subjected to hydrolysation using an appropriate reagent such as LiOH to yield to the free carboxylic acid. The resulting compound is then coupled to $\mathbf{R}_1$H with a peptide coupling agent such as BOP in an appropriate solvent such as dimethylformamide to yield to a coupled bicyclic compound of formula **(X)**. Suitable conditions for peptide bond formation are well known in th art of peptide chemistry. For example see

SUBSTITUTE SHEET

Principles of Peptide Synthesis, Bodanszky M., Springer-Verlag, Berlin, Heidelberg, New York, Tokyo 1984; and The Peptides, Analysis, Synthesis, Biology, Vol. 1 edited by Gross E., and Meienhofer J., Academic Press , New York, San Francisco, London, 1979.

Compounds of the present invention are further characterized by their ability to inhibit the catalytic activity of thrombin, which is demonstrated in the assay 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.

The compounds of the present invention may 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.

The therapeutic agents of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers. The proportion of each carrier is determined by the solubility and chemical nature of the compound, the route of administration, and standard pharmaceutical practice. For example, the compounds may

SUBSTITUTE SHEET

be injected parenterally; this being 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, flavouring 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 colouring and/or flavouring agents.

Physicians will determine the dosage of the present therapeutic agents which will be most suitable. Dosages may vary with the mode of administration and the particular compound chosen. In addition, the dosage may vary with the particular patient under treatment.

When the composition is administered orally, a larger quantity of the active agent will typically be required to produce the same effect as caused with a smaller quantity given parenterally.

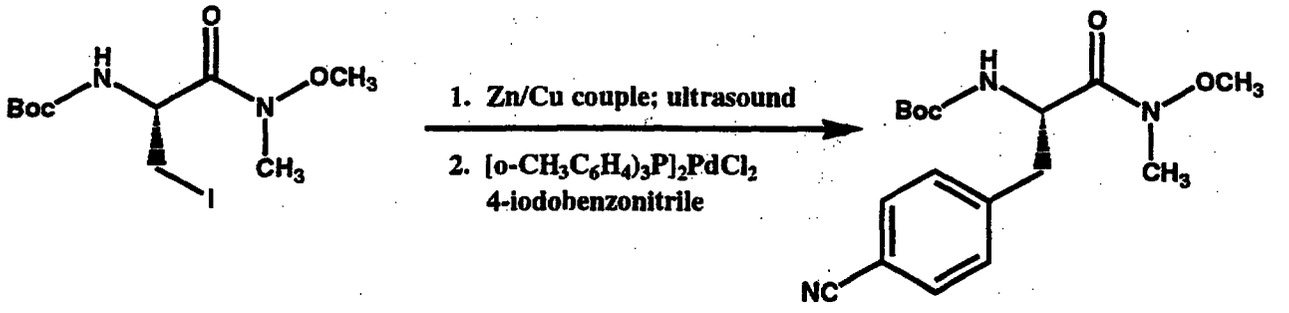
To further assist in understanding the present invention, the following non-limiting examples of such thrombin inhibitory compounds are provided. The following examples, of course, should not be construed as specifically limiting the present invention, variations presently known or later developed, which would be within the purview of one skilled in the art and considered to fall within the scope of the present invention as described herein. The preferred compounds as of the

SUBSTITUTE SHEET

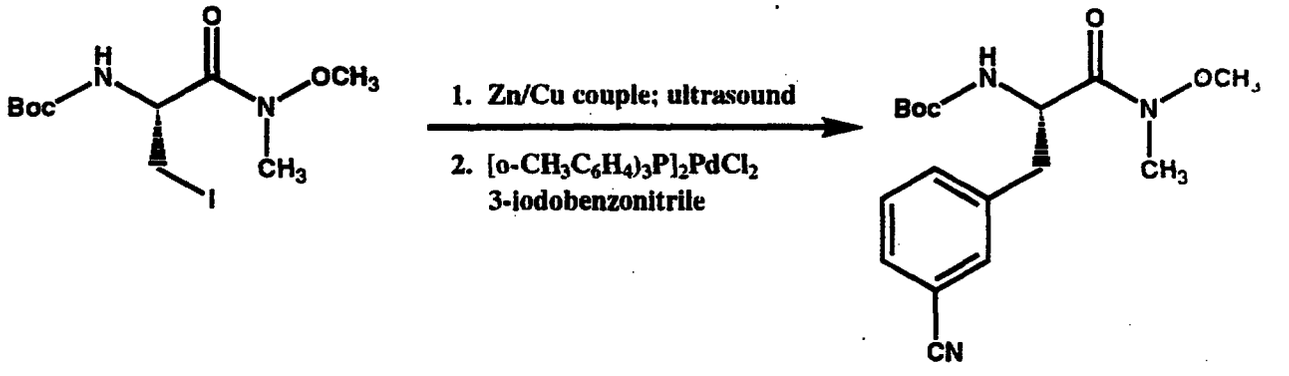
present invention are synthesized using conventional preparative steps and recovery methods known to those skilled in the art of organic and bio-organic synthesis, while providing a new a unique combination for the overall synthesis of each compound. Preferred synthetic routes for intermediates involved in the synthesis as well as the resulting anti-thrombotic compounds of the present invention follow.

SUBSTITUTE SHEET

EXAMPLE 1



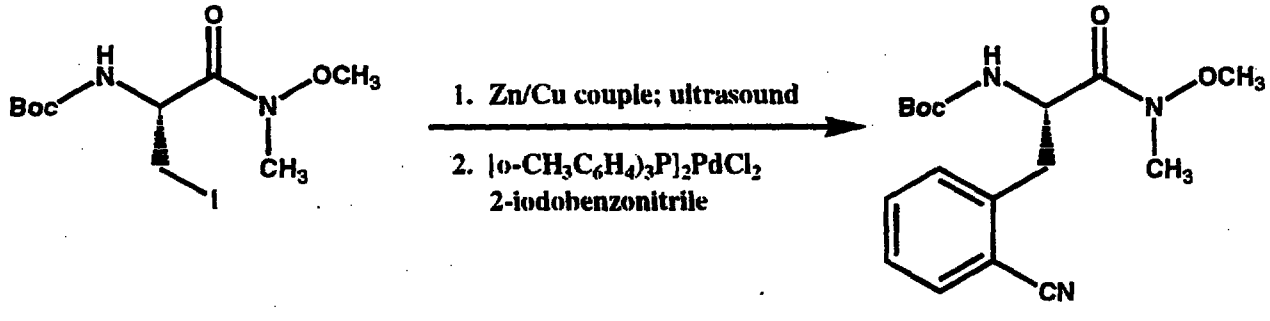
A solution of *tert*-butyloxycarbonyl-iodo-alanine-N,O-dimethylamide (2.68 g, 7.5 mmol) (J. Org. Chem. **1992,** 57, *3397-3404)* in dry benzene (30 mL), and dry N,N-dimethylacetamide (2.0 mL) was added to a dry nitrogen-purged round bottom flask charged with zinc-copper couple (0.90 g). The resulting mixture was sonicated under nitrogen until no starting material remained (as judged by TLC). Bis(tri-o-tolylphosphine)palladium dichloride (0.35 g, 0.40 mmol) was added followed by 4-iodobenzonitrile (1.72 g, 7.5 mmol). The resulting mixture was stirred under a nitrogen atmosphere with heating, allowed to cool, ethyl acetate (100 mL) was added, and the mixture filtered into a separatory funnel. Sequential washing with aqueous HCl (50 mL; 0.1N), distilled H_2O (3 x 50 mL), drying over Na_2SO_4, filtration, and concentration under reduced pressure yielded the crude product. Flash chromatography over silica gel (light petroleum-ethyl acetate gradient) afforded the purified compound.



A solution of *tert*-butyloxycarbonyl-iodo-alanine-N,O-

SUBSTITUTE SHEET

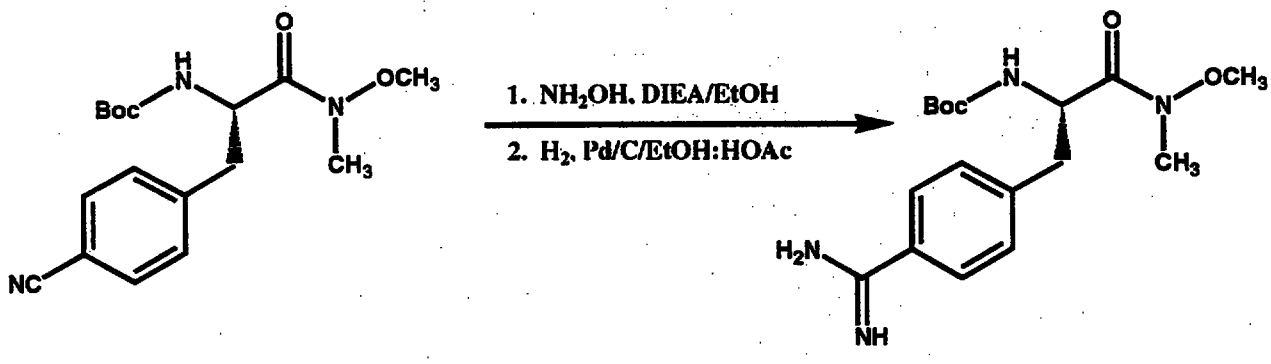
dimethylamide (2.68 g, 7.5 mmol) (J. Org. Chem. **1992,** 57, *3397-3404)* in dry benzene (30 mL), and dry N,N-dimethylacetamide (2.0 mL) was added to a dry nitrogen-purged round bottom flask charged with zinc-copper couple (0.90 g). The resulting mixture was sonicated under nitrogen until no starting material remained (as judged by TLC). Bis(tri-o-tolylphosphine)palladium dichloride (0.35 g, 0.40 mmol) was added followed by 3-iodobenzonitrile (1.72 g, 7.5 mmol). The resulting mixture was stirred under a nitrogen atmosphere with heating, allowed to cool, ethyl acetate (100 mL) was added, and the mixture filtered into a separatory funnel. Sequential washing with aqueous HCl (50 mL; 0.1N), distilled H_2O (3 x 50 mL), drying over Na_2SO_4, filtration, and concentration under reduced pressure yielded the crude product. Flash chromatography over silica gel (light petroleum-ethyl acetate gradient) afforded the purified compound.



A solution of tert-butyloxycarbonyl-iodo-alanine-N,O-dimethylamide (2.68 g, 7.5 mmol) (J. Org. Chem. **1992,** 57, *3397-3404)* in dry benzene (30 mL), and dry N,N-dimethylacetamide (2.0 mL) was added to a dry nitrogen-purged round bottom flask charged with zinc-copper couple (0.90 g). The resulting mixture was sonicated under nitrogen until no starting material remained (as judged by TLC). Bis(tri-o-tolylphosphine)palladium dichloride (0.35 g, 0.40 mmol) was added followed by 2-iodobenzonitrile (1.72 g, 7.5 mmol). The resulting mixture was stirred under a nitrogen atmosphere with heating, allowed to cool, ethyl acetate (100 mL) was added, and the mixture filtered into a separatory funnel. Sequential

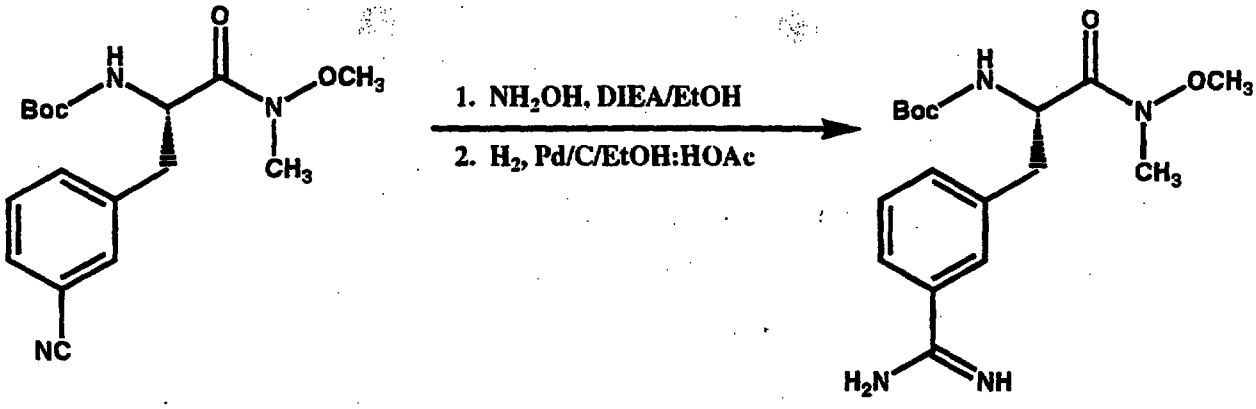
SUBSTITUTE SHEET

washing with aqueous HCl (50 mL; 0.1N), distilled H_2O (3 x 50 mL), drying over Na_2SO_4, filtration, and concentration under reduced pressure yielded the crude product. Flash chromatography over silica gel (light petroleum-ethyl acetate gradient) afforded the purified compound.

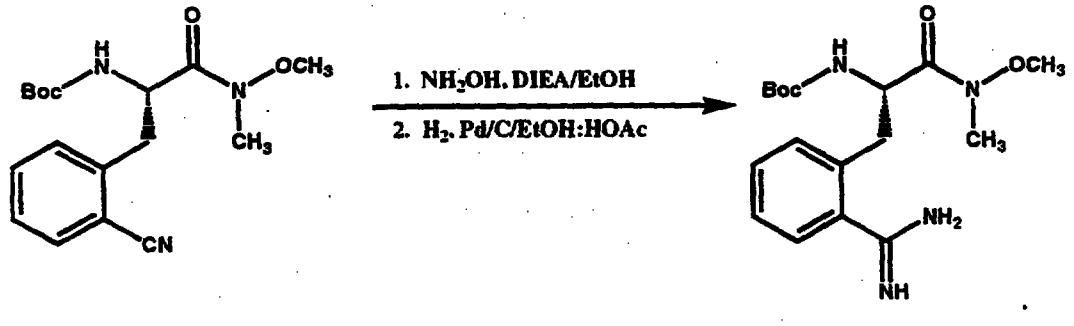


To a solution of *tert*-butyloxycarbonyl-*para*-cyano-phenylalanine-N,O-dimethylamide (1.33 g, 4.0 mmol) in dry ethanol (20 mL) was added hydroxlyamine hydrochloride (0.416 g, 6.0 mmol), and diisopropylethylamine (1.02 mL, 6.0 mmol). The mixture was refluxed and then cooled. The precipitate was filtered, washed with cold ethanol, diisopropylether, dried with $MgSO_4$, concentrated under reduced pressure, and used directly in the next step. The semi-solid was suspended in a mixture of acetic acid (20 mL), and dry ethanol (40 mL) with warming. Subsequently, Pd/C catalyst (0.30 g, 10% Pd) was added, and hydrogen was bubbled through the mixture with warming. The hydrogenation was continued until no starting material could be detected as judged by TLC. The catalyst was removed by filtration, the solution was concentrated under reduced pressure (50 mL), HCl (50 mL, 1 N) was added, and the mixture was concentrated once again to 50 mL. The solution was chilled overnight yielding the title compound.

SUBSTITUTE SHEET

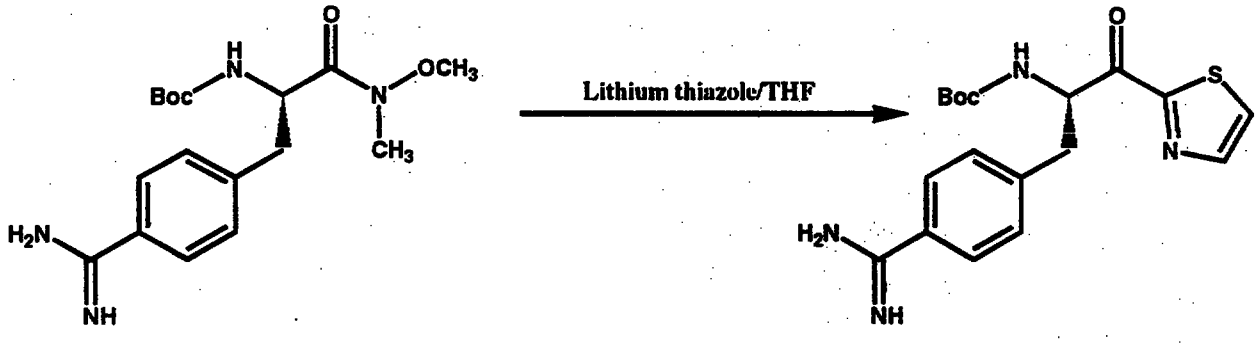


To a solution of *tert*-butyloxycarbonyl-*meta*-cyano-phenylalanine-N,O-dimethylamide (1.33 g, 4.0 mmol) in dry ethanol (20 mL) was added hydroxlyamine hydrochloride (0.416 g, 6.0 mmol), and diisopropylethylamine (1.02 mL, 6.0 mmol). The mixture was refluxed and then cooled. The precipitate was filtered, washed with cold ethanol, diisopropylether, dried with $MgSO_4$, concentrated under reduced pressure, and used directly in the next step. The semi-solid was suspended in a mixture of acetic acid (20 mL), and dry ethanol (40 mL) with warming. Subsequently, Pd/C catalyst (0.30 g, 10% Pd) was added, and hydrogen was bubbled through the mixture with warming. The hydrogenation was continued until no starting material could be detected as judged by TLC. The catalyst was removed by filtration, the solution was concentrated under reduced pressure (50 mL), HCl (50 mL, 1 N) was added, and the mixture was concentrated once again to 50 mL. The solution was chilled overnight yielding the title compound.



SUBSTITUTE SHEET

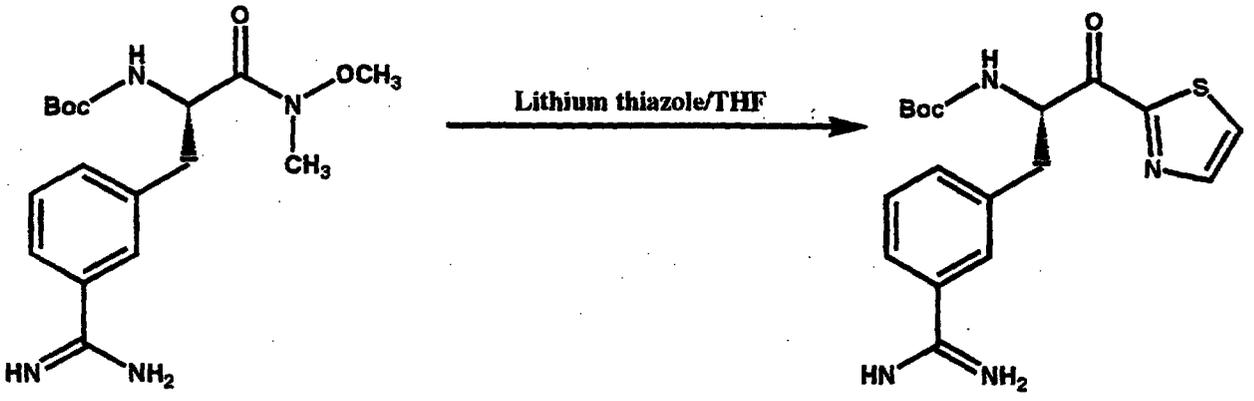
To a solution of *tert*-butyloxycarbonyl-*ortho*-cyano-phenylalanine-N,O-dimethylamide (1.33 g, 4.0 mmol) in dry ethanol (20 mL) was added hydroxlyamine hydrochloride (0.416 g, 6.0 mmol), and diisopropylethylamine (1.02 mL, 6.0 mmol). The mixture was refluxed and then cooled. The precipitate was filtered, washed with cold ethanol, diisopropylether, dried with $MgSO_4$, concentrated under reduced pressure, and used directly in the next step. The semi-solid was suspended in a mixture of acetic acid (20 mL), and dry ethanol (40 mL) with warming. Subsequently, Pd/C catalyst (0.30 g, 10% Pd) was added, and hydrogen was bubbled through the mixture with warming. The hydrogenation was continued until no starting material could be detected as judged by TLC. The catalyst was removed by filtration, the solution was concentrated under reduced pressure (50 mL), HCl (50 mL, 1 N) was added, and the mixture was concentrated once again to 50 mL. The solution was chilled overnight yielding the title compound.



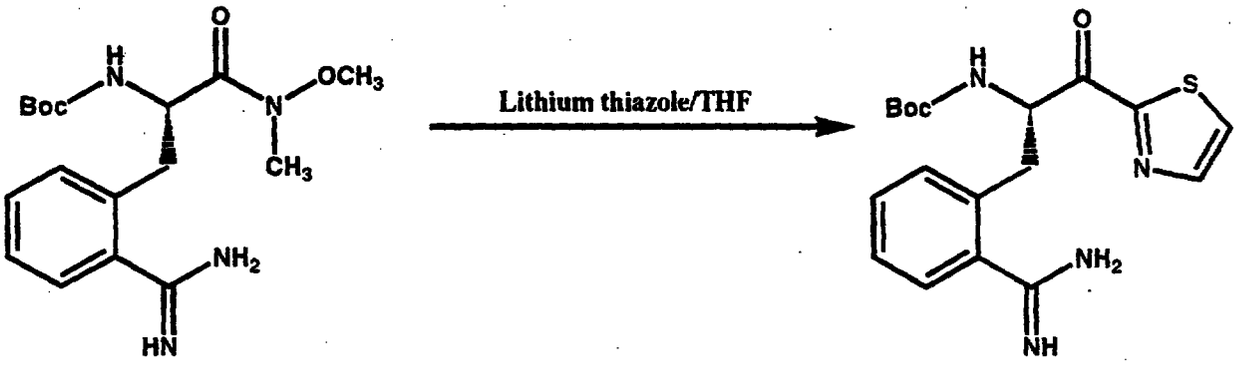
To a solution of thiazole (1.28 g, 15.0 mmol) in anhydrous THF (30 mL) was added *n*-BuLi (1.6 M/hexane, 8.9 mL, 13.9 mmol) dropwise at -78° C, and the solution stirred. *tert*-Butyloxycarbonyl-*para*-amidino-phenylalanine-N,O-dimethylamide (1.15 g, 3.3 mmol) in THF (15 mL) was then added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel

SUBSTITUTE SHEET

(ethyl acetate/hexane), and concentrated under reduced pressure.



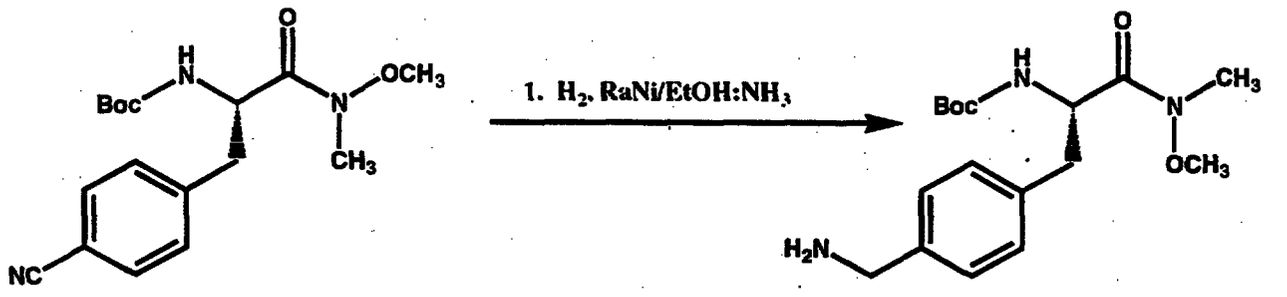
To a solution of thiazole (1.28 g, 15.0 mmol) in anhydrous THF (30 mL) was added *n*-BuLi (1.6 M/hexane, 8.9 mL, 13.9 mmol) dropwise at -78° C, and the solution stirred. *tert*-Butyloxycarbonyl-*meta*-amidino-phenylalanine-N,O-dimethylamide (1.15 g, 3.3 mmol) in THF (15 mL) was then added dropwise and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.



To a solution of thiazole (1.28 g, 15.0 mmol) in anhydrous THF (30 mL) was added *n*-BuLi (1.6 M/hexane, 8.9 mL, 13.9 mmol)

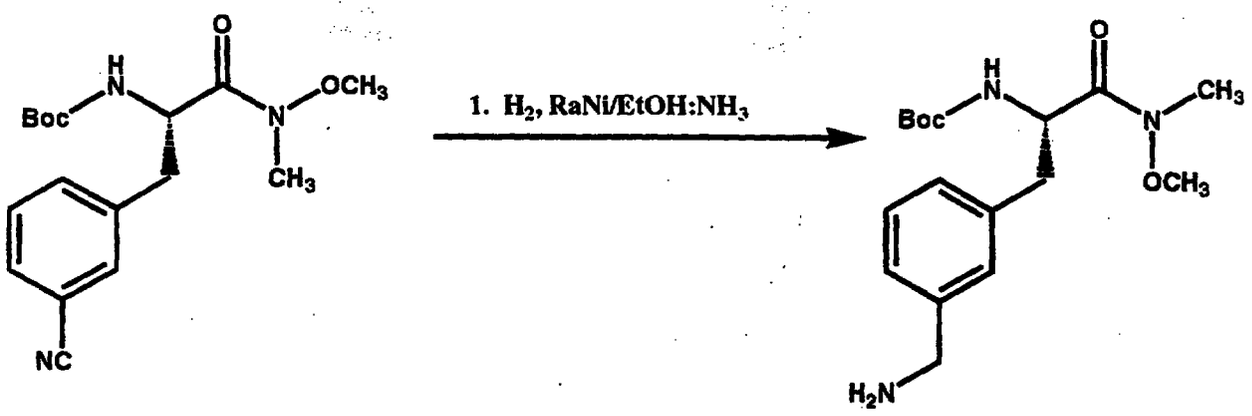
SUBSTITUTE SHEET

dropwise at -78° C, and the solution stirred. *tert*-Butyloxycarbonyl-*ortho*-amidino-phenylalanine-N,O-dimethylamide (1.15 g, 3.3 mmol) in THF (15 mL) was then added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL) and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.

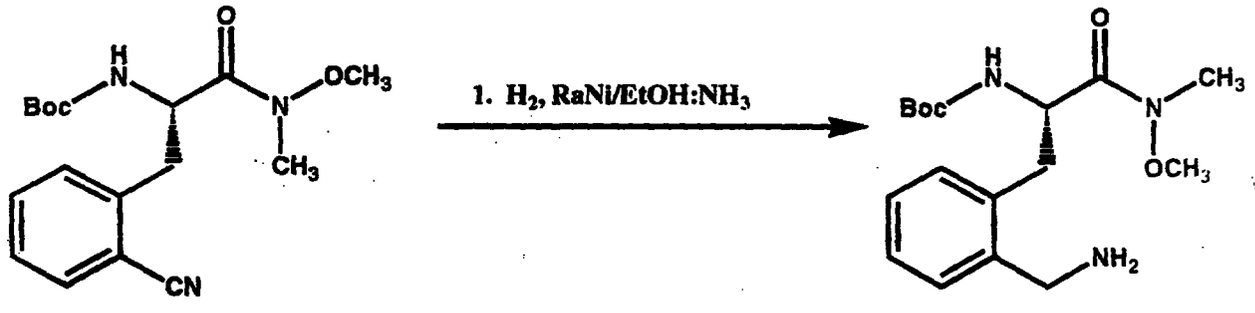


tert-Butyloxycarbonyl-*para*-cyano-phenylalanine-N,O-dimethylamide (1.33 g, 4.0 mmol) was dissolved in ethanol saturated with ammonia (30 mL), and sponge Raney Ni (100 mg) added. The solution was shaken under H_2 at room temperature (40 psi). The solution was filtered through celite, and concentrated under reduced pressure to yield a clear residue. The residue was dissolved in ethyl acetate (250 mL), and washed with 1 N NaOH (2 x 50 mL), and brine (2 x 50 mL). The solution was dried with $MgSO_4$, filtered, and concentrated under reduced pressure.

SUBSTITUTE SHEET



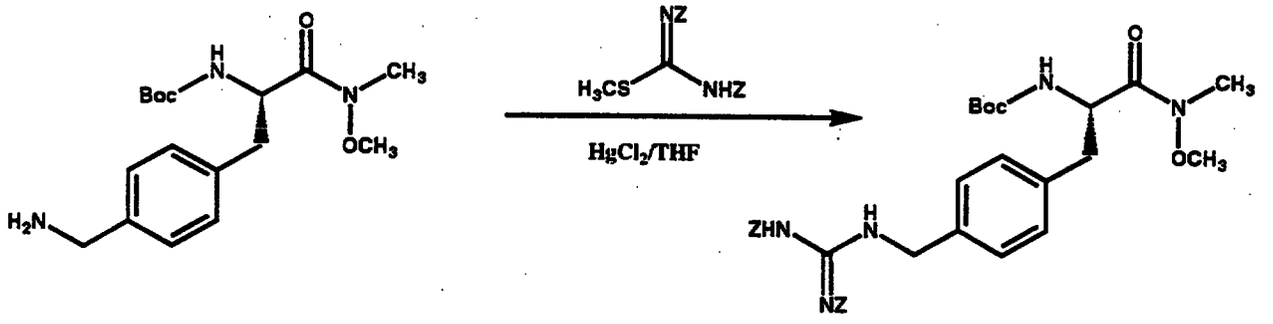
tert-Butyloxycarbonyl-*meta*-cyano-phenylalanine-N,O-dimethylamide (1.33 g, 4.0 mmol) was dissolved in ethanol saturated with ammonia (30 mL), and sponge Raney Ni (100 mg) added. The solution was shaken under H_2 at room temperature (40 psi). The solution was filtered through celite, and concentrated under reduced pressure to yield a clear residue. The residue was dissolved in ethyl acetate (250 mL), and washed with 1 N NaOH (2 x 50 mL), and brine (2 x 50 mL). The solution was dried with $MgSO_4$, filtered, and concentrated under reduced pressure.



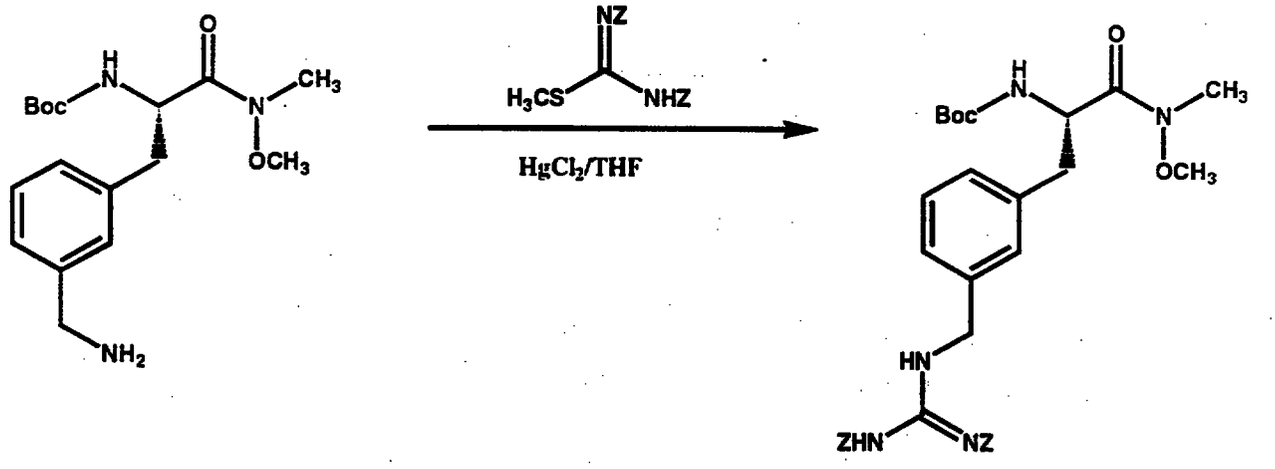
tert-Butyloxycarbonyl-*ortho*-cyano-phenylalanine-N,O-dimethylamide (1.33 g, 4.0 mmol) was dissolved in ethanol saturated with ammonia (30 mL), and sponge Raney Ni (100 mg) added. The solution was shaken under H_2 at room temperature (40 psi). The solution was filtered through celite, and concentrated under reduced pressure to yield a clear residue. The residue was dissolved in ethyl acetate (250 mL), and washed with 1 N NaOH (2 x 50 mL), and brine (2 x 50 mL). The solution was dried with $MgSO_4$, filtered, and concentrated under

SUBSTITUTE SHEET

reduced pressure.



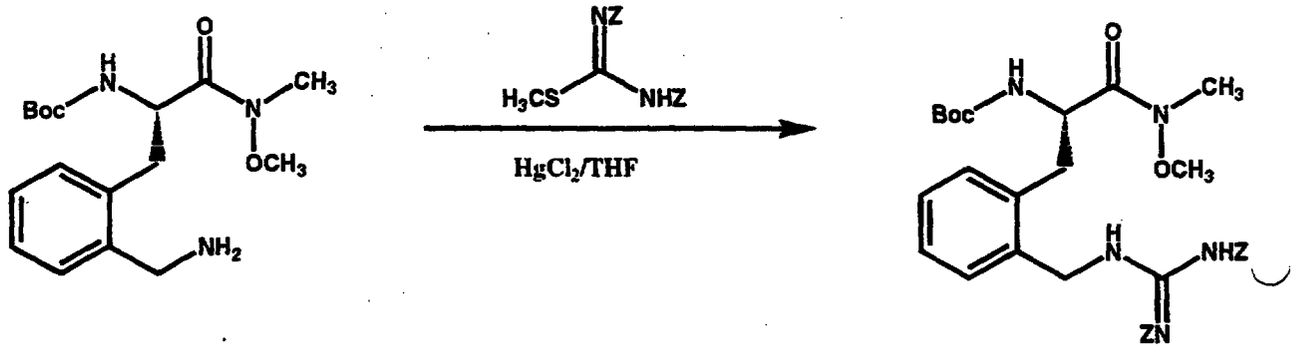
tert-Butyloxycarbonyl-*para*-aminomethyl-phenylalanine-N,O-dimethylamide (1.00 g, 3.1 mmol) was dissolved in dry THF (10 mL) under nitrogen with stirring. The solution was cooled, N,N'-bis-(benzyloxycarbonyl)-S-methyl-isothiourea (1.14 g, 3.2 mmol), and $HgCl_2$ (0.95 g, 3.5 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (200 mL), and filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the purified compound.



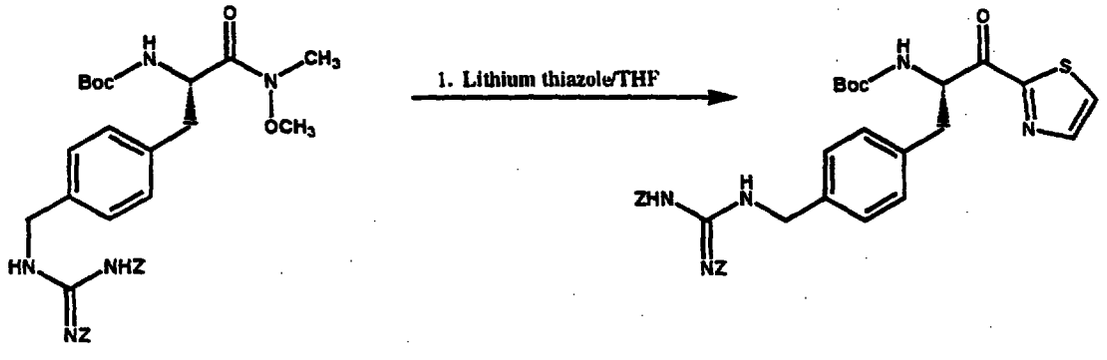
tert-Butyloxycarbonyl-*meta*-aminomethyl-phenylalanine-N,O-dimethylamide (1.00 g, 3.1 mmol) was dissolved in dry THF (10 mL) under nitrogen with stirring. The solution was cooled, N,N'-bis-(benzyloxycarbonyl)-S-methyl-isothiourea (1.14 g, 3.2

SUBSTITUTE SHEET

mmol), and $HgCl_2$ (0.95 g, 3.5 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (200 mL), and filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the purified compound.



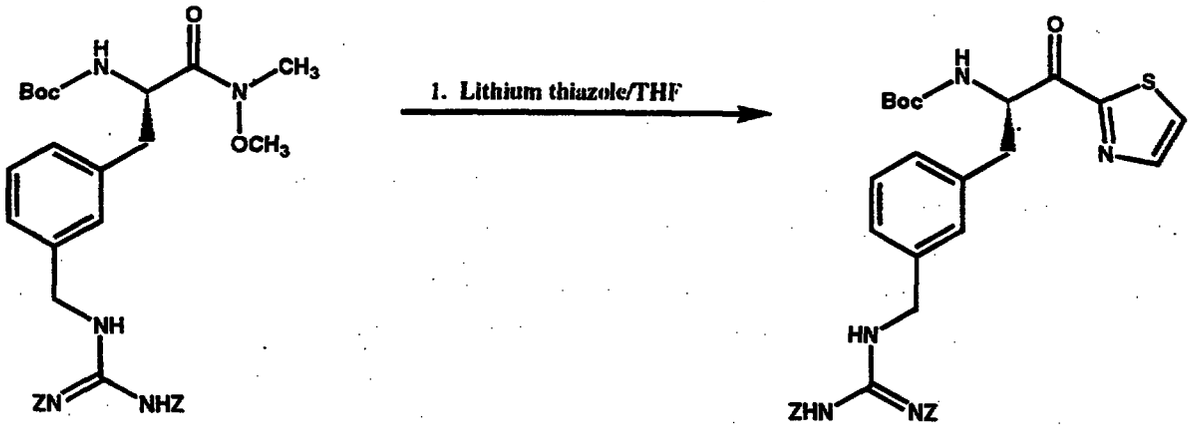
tert-Butyloxycarbonyl-*ortho*-aminomethyl-phenylalanine-N,O-dimethylamide (1.00 g, 3.1 mmol) was dissolved in dry THF (10 mL) under nitrogen with stirring. The solution was cooled, N,N'-bis-(benzyloxycarbonyl)-S-methyl-isothiourea (1.14 g, 3.2 mmol), and $HgCl_2$ (0.95 g, 3.5 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (200 mL), and filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the purified compound.



To a solution of thiazole (1.28 g, 15.0 mmol) in anhydrous THF

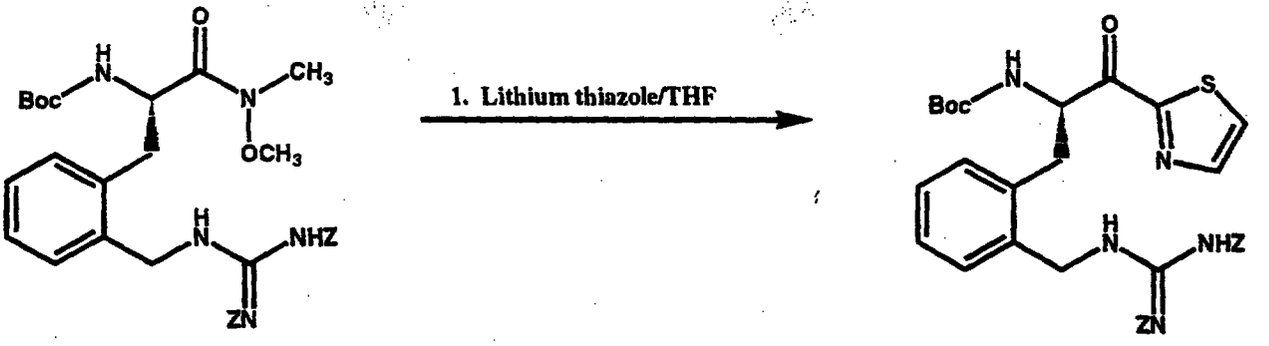
SUBSTITUTE SHEET

(30 mL) was added *n*-BuLi (1.6 M/hexane, 8.9 mL, 13.9 mmol) dropwise at -78° C, and the solution stirred. The protected amino acid (1.36 g, 3.3 mmol) in THF (15 mL) was then added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.

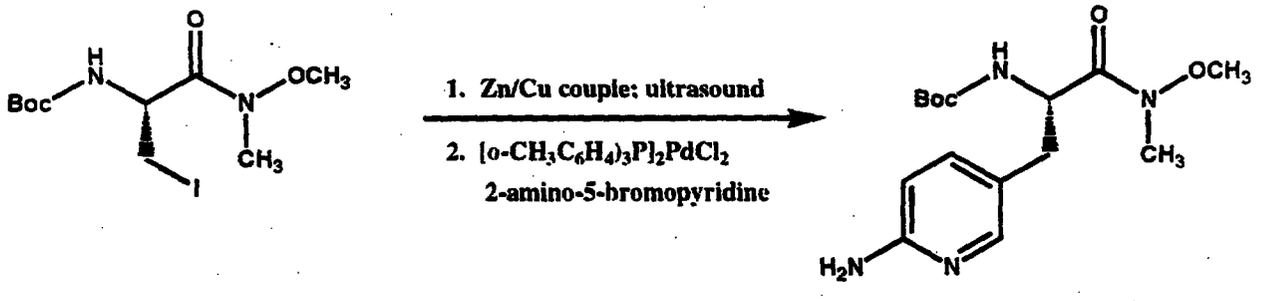


To a solution of thiazole (1.28 g, 15.0 mmol) in anhydrous THF (30 mL) was added *n*-BuLi (1.6 M/hexane, 8.9 mL, 13.9 mmol) dropwise at -78° C, and the solution stirred. The protected amino acid (1.36 g, 3.3 mmol) in THF (15 mL) was then added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.

SUBSTITUTE SHEET



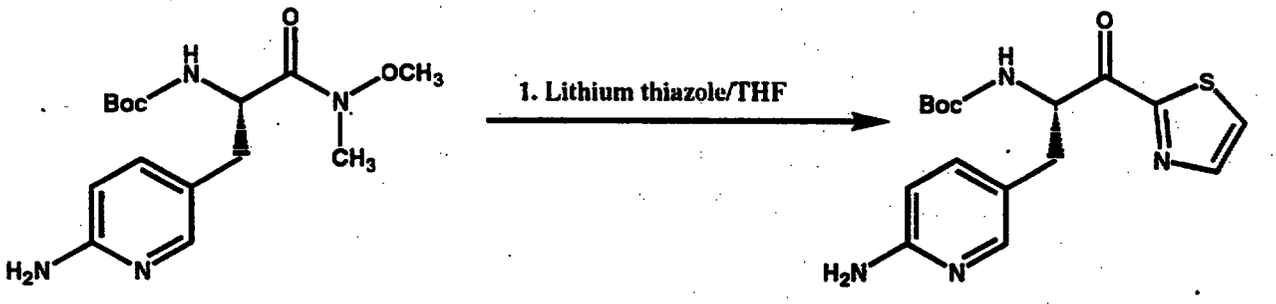
To a solution of thiazole (1.28 g, 15.0 mmol) in anhydrous THF (30 mL) was added *n*-BuLi (1.6 M/hexane, 8.9 mL, 13.9 mmol) dropwise at -78° C, and the solution stirred. The protected amino acid (1.36 g, 3.3 mmol) in THF (15 mL) was then added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.



A solution of tert-butyloxycarbonyl-iodo-alanine-N,O-dimethylamide (2.68 g, 7.5 mmol) (J. Org. Chem. **1992,** 57, *3397-3404)* in dry benzene (30 mL), and dry N,N-dimethylacetamide (2.0 mL) was added to a dry nitrogen-purged round bottom flask charged with zinc-copper couple (0.90 g). The resulting mixture was sonicated under nitrogen until no

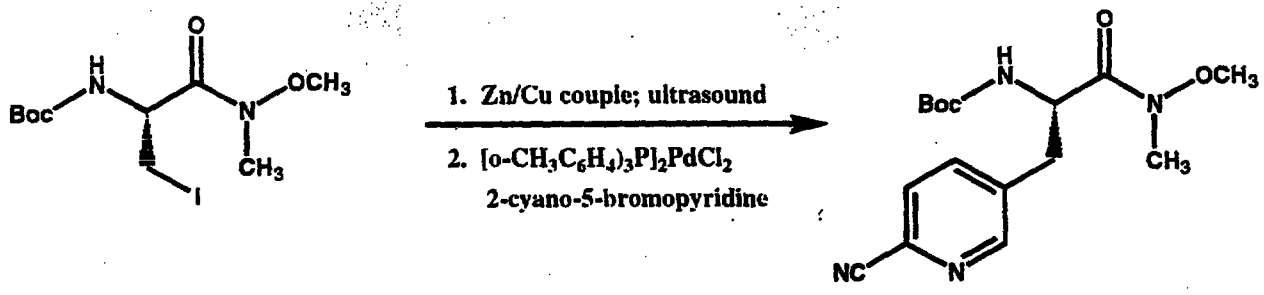
SUBSTITUTE SHEET

starting material remained (as judged by TLC). Bis(tri-o-tolylphosphine)palladium dichloride (0.35 g, 0.40 mmol) was added followed by 2-iodobenzonitrile (1.72 g, 7.5 mmol). The resulting mixture was stirred under a nitrogen atmosphere with heating, allowed to cool, ethyl acetate (100 mL) was added, and the mixture filtered into a separatory funnel. Sequential washing with aqueous HCl (50 mL; 0.1N), distilled H_2O (3 x 50 mL), drying over Na_2SO_4, filtration, and concentration under reduced pressure yielded the crude product. Flash chromatography over silica gel (light petroleum/ethyl acetate gradient) afforded the purified compound.

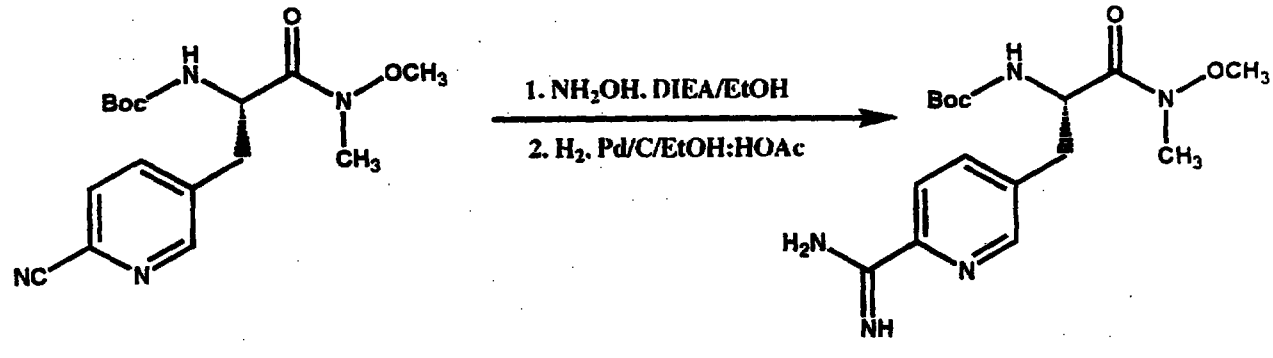


To a solution of thiazole (1.28 g, 15.0 mmol) in anhydrous THF (30 mL) was added *n*-BuLi (1.6 M/hexane, 8.9 mL, 13.9 mmol) dropwise at -78° C, and the solution stirred. The amino acid-N,O-dimethylamide (1.07 g, 3.3 mmol) in anhydrous THF (15 mL) was then added dropwise and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.

SUBSTITUTE SHEET



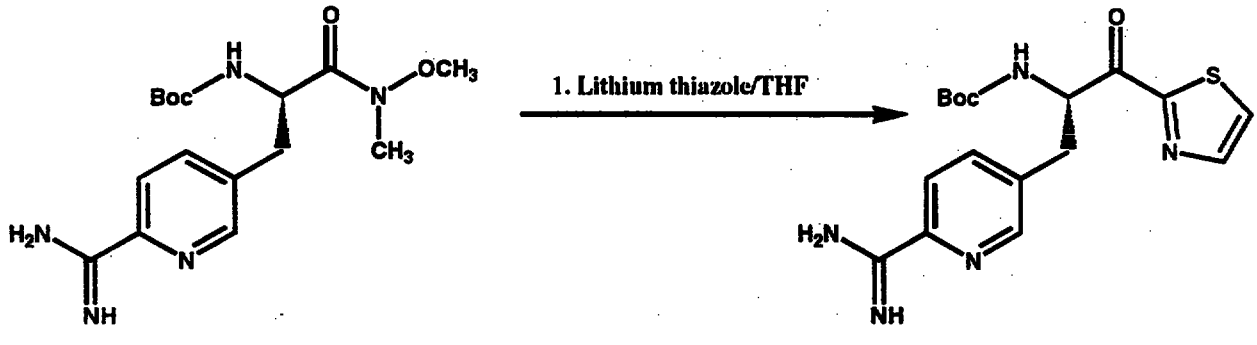
A solution of *tert*-butyloxycarbonyl-iodo-alanine-N,O-dimethylamide (2.68 g, 7.5 mmol) (J. Org. Chem. **1992,** 57, *3397-3404)* in dry benzene (30 mL), and dry N,N-dimethylacetamide (2.0 mL) was added to a dry nitrogen-purged round bottom flask charged with zinc-copper couple (0.90 g). The resulting mixture was sonicated under nitrogen until no starting material remained (as judged by TLC). Bis(tri-o-tolylphosphine)palladium dichloride (0.35 g, 0.40 mmol) was added followed by 2-iodobenzonitrile (1.72 g, 7.5 mmol). The resulting mixture was stirred under a nitrogen atmosphere with heating, allowed to cool, ethyl acetate (100 mL) was added, and the mixture filtered into a separatory funnel. Sequential washing with aqueous HCl (50 mL; 0.1N), distilled H_2O (3 x 50 mL), drying over Na_2SO_4, filtration, and concentration under reduced pressure yielded the crude product. Flash chromatography over silica gel (light petroleum/ethyl acetate gradient) afforded the purified compound.



To a solution of *tert*-butyloxycarbonyl-(4-cyano)3-pyridylalanine-N,O-dimethylamide (1.34 g, 4.0 mmol) in dry

SUBSTITUTE SHEET

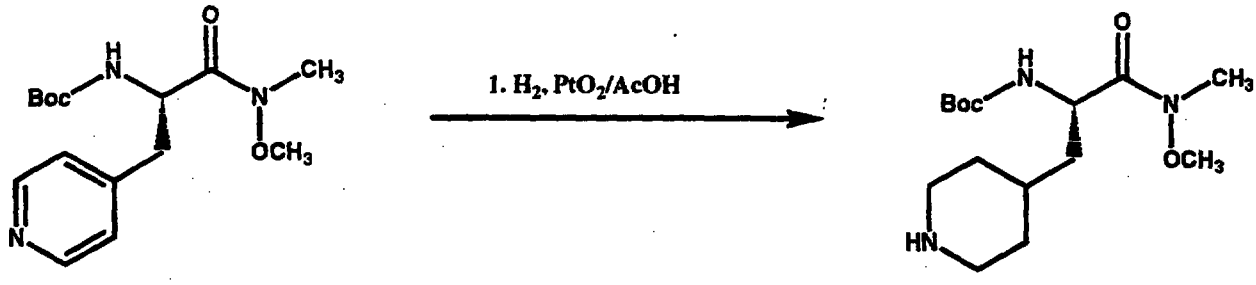
ethanol (20 mL) was added N,O-hydroxlyamine hydrochloride (0.416 g, 6.0 mmol), and diisopropylethylamine (1.02 mL, 6.0 mmol). The mixture was refluxed and then cooled. The precipitate was filtered, washed with cold ethanol, diisopropylether, dried with $MgSO_4$, concentrated under reduced pressure, and used directly in the next step. The semi-solid was suspended in a mixture of acetic acid (20 mL), and dry ethanol (40 mL) with warming. Subsequently, Pd/C catalyst (0.30 g, 10% Pd) was added, and hydrogen was bubbled through the mixture with warming. The hydrogenation was continued until no starting material could be detected as judged by TLC. The catalyst was removed by filtration, and the solution was concentrated under reduced pressure (50 mL), HCl (50 mL, 1 N) was added, and the mixture was concentrated once again to 50 mL. The solution was chilled overnight yielding the title compound.



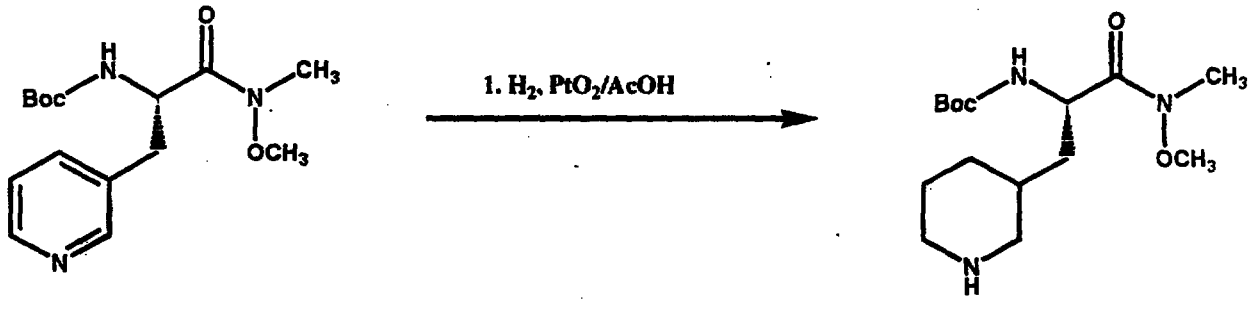
To a solution of thiazole (1.28 g, 15.0 mmol) in anhydrous THF (30 mL) was added *n*-BuLi (1.6 M/hexane, 8.9 mL, 13.9 mmol) dropwise at -78° C, and the solution stirred. The amino acid-N,O-dimethylamide (1.16 g, 3.3 mmol) in anhydrous THF (15 mL) was then added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel ethyl acetate/hexane), and

SUBSTITUTE SHEET

concentrated under reduced pressure.



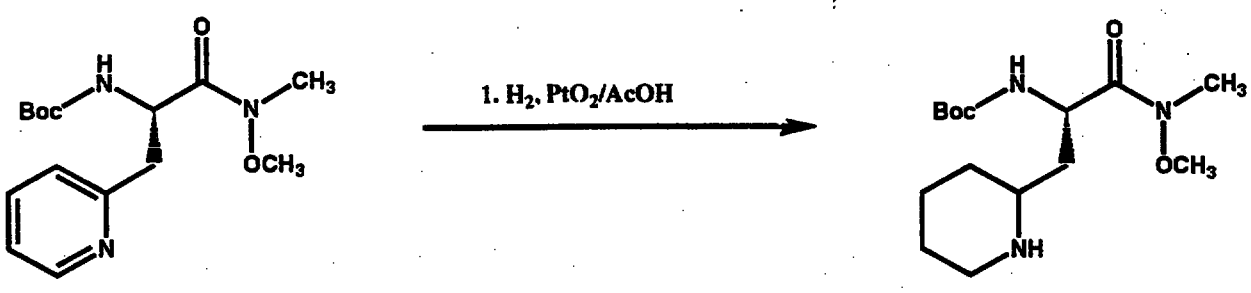
tert-Butyloxycarbonyl-3-(4-pyridyl)alanine-N,O-dimethylamide (4.50 g, 14.4 mmol) was dissolved in acetic acid (100 mL), and PtO_2 (100 mg) added. The solution was shaken under H_2 until gas uptake ceased. The solution was filtered through celite, and concentrated under reduced pressure yielding *tert*-butyloxycarbonyl-3-(4-piperidyl)alanine-N,O-dimethylamide. The residue was dissolved in ethyl acetate (250 mL), washed with 1 N NaOH (2 x 50 mL), brine (2 x 50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to yield the title compound.



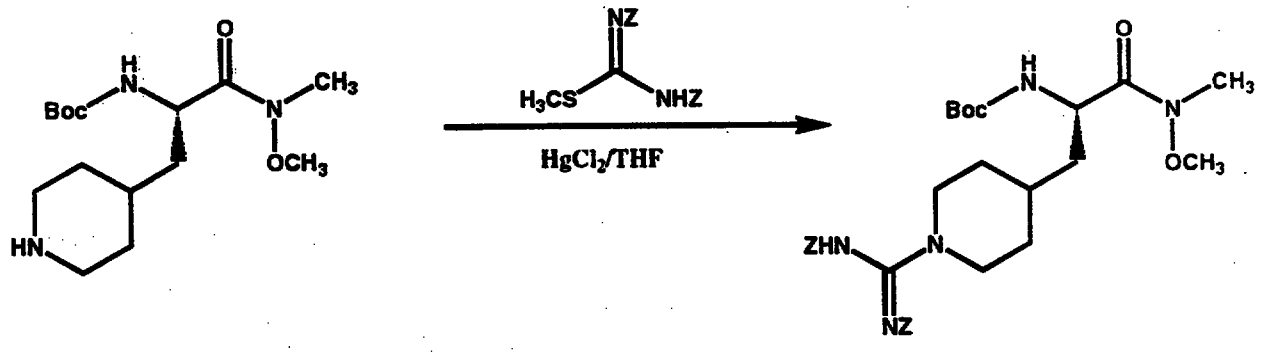
tert-Butyloxycarbonyl-3-(3-pyridyl)alanine-N,O-dimethylamide (4.50 g, 14.4 mmol) was dissolved in acetic acid (100 mL), and PtO_2 (100 mg) added. The solution was shaken under H_2 until gas uptake ceased. The solution was filtered through celite, and concentrated under reduced pressure yielding *tert*-butyloxycarbonyl-3-(3-piperidyl)alanine-N,O-dimethylamide. The residue was dissolved in ethyl acetate (250 mL), washed

SUBSTITUTE SHEET

with 1 N NaOH (2 x 50 mL), brine (2 x 50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to yield the title compound.



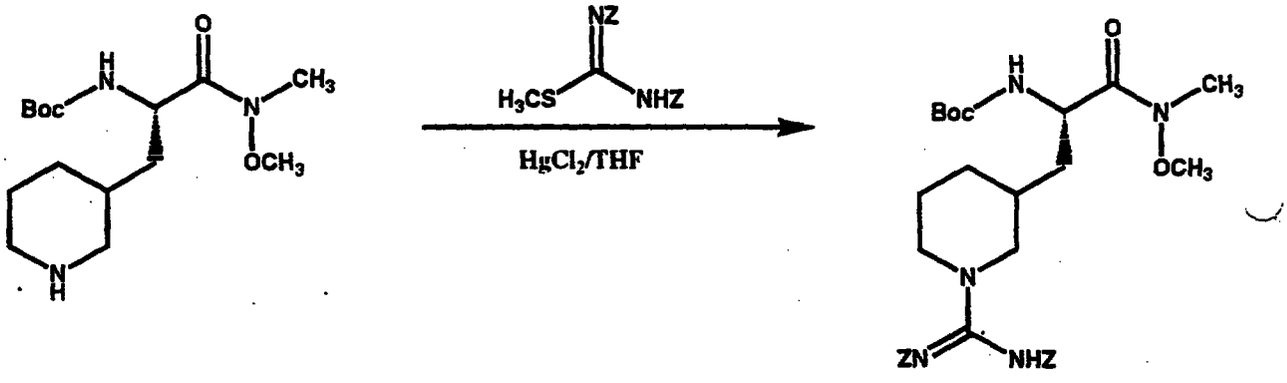
tert-Butyloxycarbonyl-3-(2-pyridyl)alanine-N,O-dimethylamide (4.50 g, 14.4 mmol) was dissolved in acetic acid (100 mL), and PtO_2 (100 mg) added. The solution was shaken under H_2 until gas uptake ceased. The solution was filtered through celite, and concentrated under reduced pressure yielding *tert*-butyloxycarbonyl-3-(2-piperidyl)alanine-N,O-dimethylamide. The residue was dissolved in ethyl acetate (250 mL), washed with 1 N NaOH (2 x 50 mL), brine (2 x 50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to yield the title compound.



tert-Butyloxycarbonyl-3-(4-piperidyl)alanine-N,O-dimethylamide (1.00 g, 3.2 mmol) was dissolved in dry THF (10 mL) under nitrogen with stirring. The solution was cooled, N,N'-bis-(benzyloxycarbonyl)-S-methyl-isothiourea (1.14 g, 3.2 mmol),

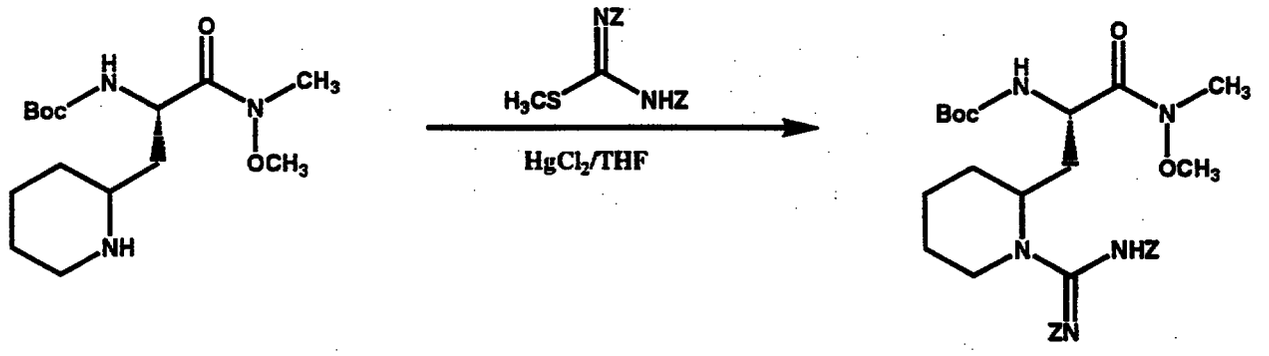
SUBSTITUTE SHEET

and $HgCl_2$ (0.95 g, 3.5 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (200 mL), and filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the title compound.

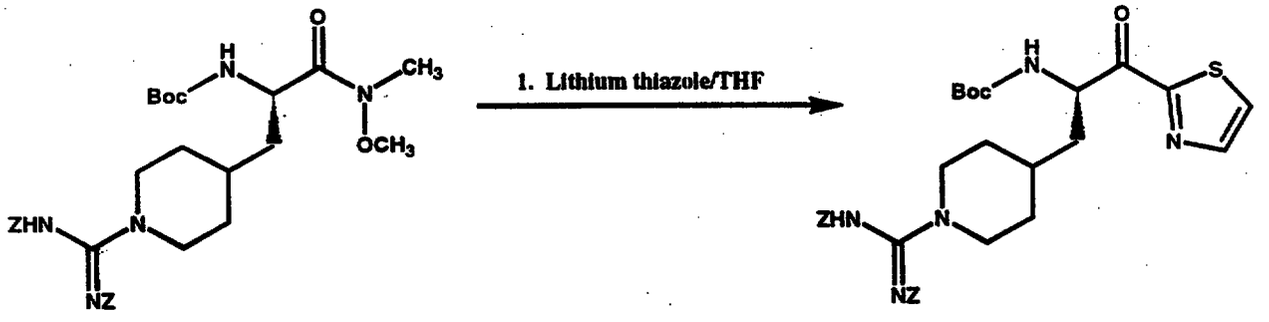


tert-Butyloxycarbonyl-3-(3-piperidyl)alanine-N,O-dimethylamide (1.00 g, 3.2 mmol) was dissolved in dry THF (10 mL) under nitrogen with stirring. The solution was cooled, N,N'-bis-(benzyloxycarbonyl)-S-methyl-isothiourea (1.14 g, 3.2 mmol), and $HgCl_2$ (0.95 g, 3.5 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (200 mL), and filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the title compound.

SUBSTITUTE SHEET



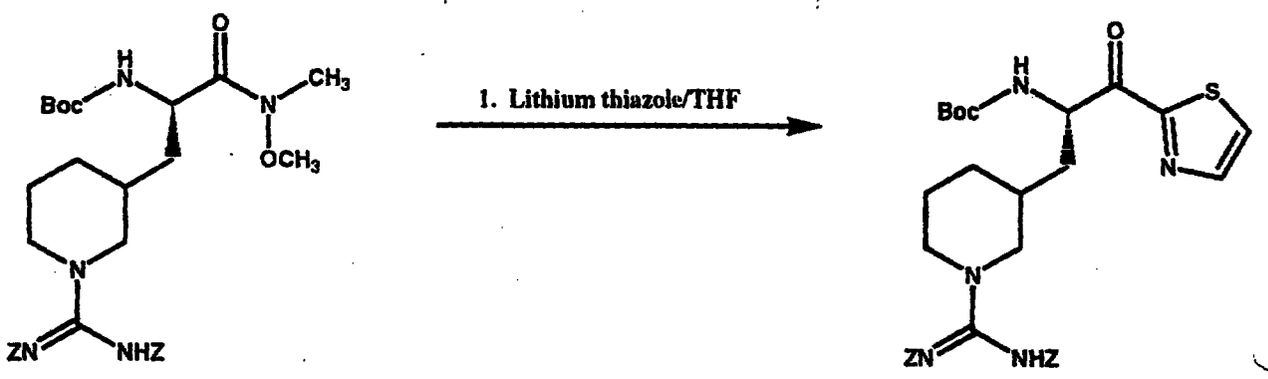
tert-Butyloxycarbonyl-3-(2-piperidyl)alanine-N,O-dimethylamide (1.00 g, 3.2 mmol) was dissolved in dry THF (10 mL) under nitrogen with stirring. The solution was cooled, N,N'-bis-(benzyloxycarbonyl)-S-methyl-isothiourea (1.14 g, 3.2 mmol), and $HgCl_2$ (0.95 g, 3.5 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (200 mL), and filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the title compound.



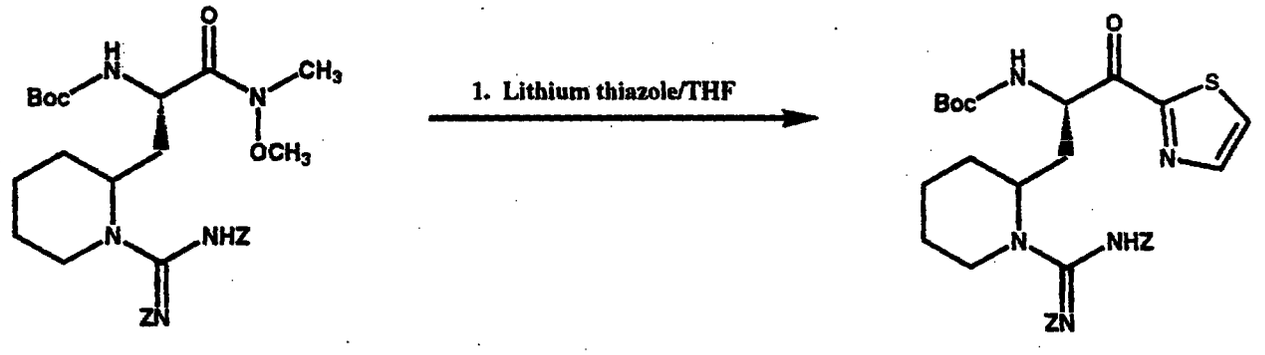
To a solution of thiazole in anhydrous THF (1.23 g, 14.4 mmol) was added *n*-BuLi (1.6 M/hexane, 8.4 mL, 13.4 mmol) dropwise at -78 C and the solution stirred. The guanidylated 4-piperidylalanine derivative (2.00 g, 3.2 mmol) in anhydrous THF (15 mL) was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate

SUBSTITUTE SHEET

(150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure.



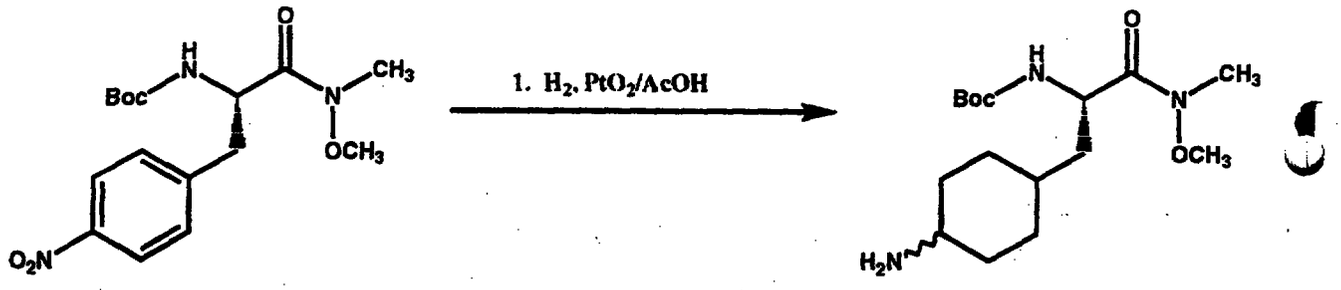
To a solution of thiazole in anhydrous THF (1.23 g, 14.4 mmol) was added *n*-BuLi (1.6 M/hexane, 8.4 mL, 13.4 mmol) dropwise at -78° C with stirring. The mixture was stirred at -78° C for 1 h. The guanidylated 3-piperidylalanine derivative (2.00 g, 3.2 mmol) in THF (15 mL) was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure.



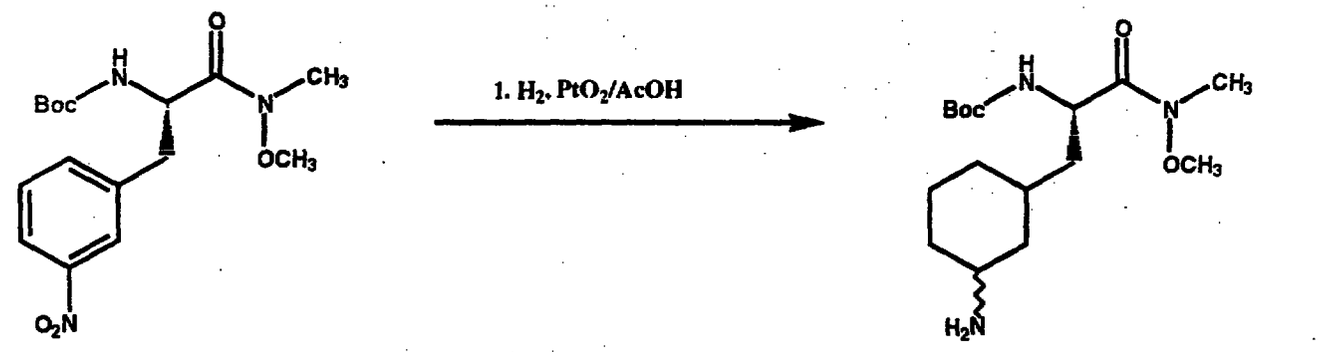
To a solution of thiazole in anhydrous THF (1.23 g, 14.4 mmol) was added *n*-BuLi (1.6 M/hexane, 8.4 mL, 13.4 mmol) dropwise at

SUBSTITUTE SHEET

-78° C with stirring. The mixture was stirred at -78° C for 1 h. The guanidylated 2-piperidylalanine derivative (2.00 g, 3.2 mmol) in THF (15 mL) was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure.

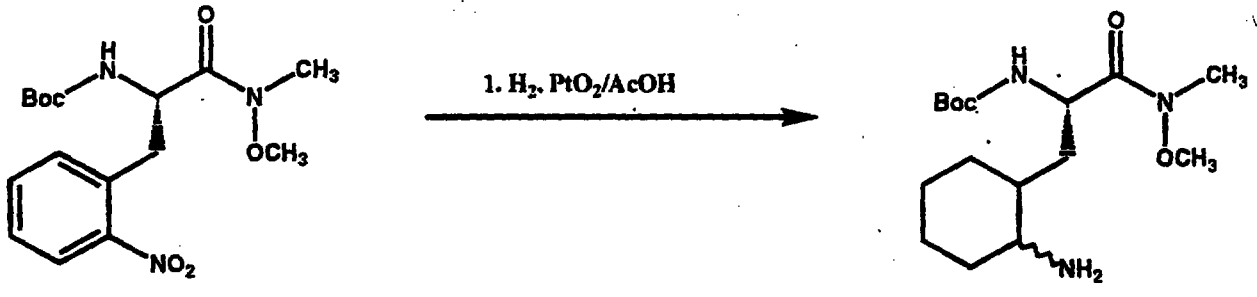


tert-Butyloxycarbonyl-para-nitro-phenylalanine-N,O-dimethylamide (13.88 g, 39.3 mmol) was dissolved in acetic acid (100 mL), and PtO_2 (100 mg) added. The solution was shaken under H_2 until gas uptake ceased. The solution was filtered through celite, concentrated under reduced pressure, taken up in H_2O (150 mL), and lyophilized. The semi-solid was dissolved in ethyl acetate (350 mL), washed with 1 N NaOH (3 x 50 mL), and brine (3 x 50 mL). The solution was dried with $MgSO_4$, filtered, and concentrated under reduced pressure yielding the title compound.

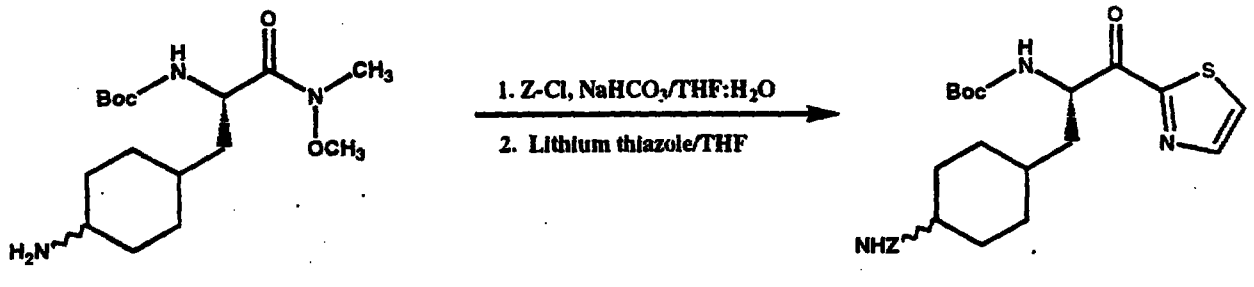


SUBSTITUTE SHEET

tert-Butyloxycarbonyl-*meta*-nitro-phenylalanine-N,O-dimethylamide (13.88 g, 39.3 mmol) was dissolved in acetic acid (100 mL), and PtO_2 (100 mg) added. The solution was shaken under H_2 until gas uptake ceased. The solution was filtered through celite, concentrated under reduced pressure, taken up in H_2O (150 mL), and lyophilized. The semi-solid was dissolved in ethyl acetate (350 mL), washed with 1 N NaOH (3 x 50 mL), and brine (3 x 50 mL). The solution was dried with $MgSO_4$, filtered, and concentrated under reduced pressure yielding the title compound.



tert-Butyloxycarbonyl-*ortho*-nitro-phenylalanine-N,O-dimethylamide (13.88 g, 39.3 mmol) was dissolved in acetic acid (100 mL), and PtO_2 (100 mg) added. The solution was shaken under H_2 until gas uptake ceased. The solution was filtered through celite, concentrated under reduced pressure, taken up in H_2O (150 mL), and lyophilized. The semi-solid was dissolved in ethyl acetate (350 mL), washed with 1 N NaOH (3 x 50 mL), and brine (3 x 50 mL). The solution was dried with $MgSO_4$, filtered, and concentrated under reduced pressure yielding the title compound.

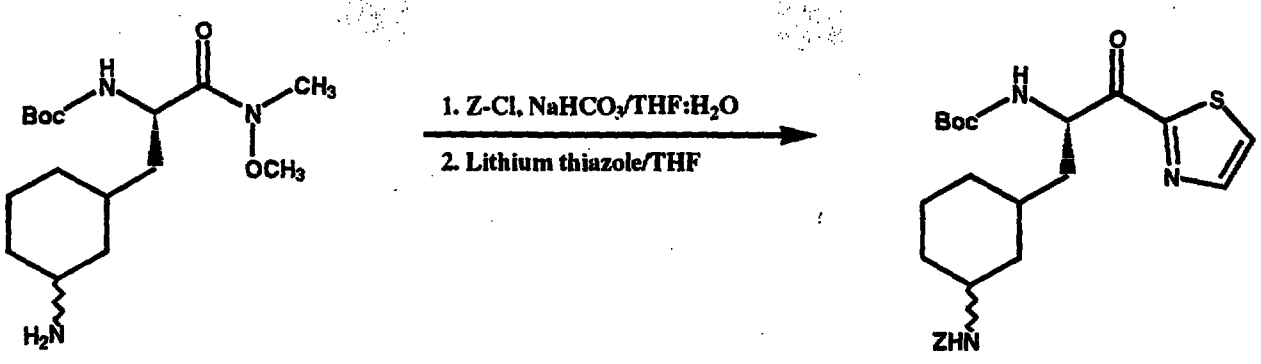


SUBSTITUTE SHEET

1. *tert*-Butyloxycarbonyl-3-(*cis/trans*-4-aminocyclohexyl)alanine-N,O-dimethylamide (1.00 g, 3.0 mmol) was dissolved in saturated aqueous sodium bicarbonate, and THF [60 mL, (1:1)] with stirring. The solution was cooled and a solution of benzyl chloroformate (0.43 mL, 3.0 mmol) in THF (10 mL) was added dropwise. Excess solid sodium bicarbonate was added, the THF was removed under reduced pressure, and the remaining aqueous phase was poured into ethyl acetate (250 mL), and mixed thoroughly. The aqueous phase was discarded and the remaining solution was washed with saturated aqueous sodium bicarbonate (2 x 50 mL), 4 N aqueous sodium bisulfate (2 x 50 mL), and brine (2 x 50 mL). The solution was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The semi-solid was chromatographed on silica gel (ethyl acetate/ hexane).

2. To a solution of thiazole (1.16 g, 13.7 mmol) in anhydrous THF was added *n*-BuLi (1.6 M/hexane, 8.0 mL, 12.8 mmol) dropwise at -78° C and the solution stirred. The above protected amino acid amide (1.41 g, 3.0 mmol) in THF (15 mL) was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.

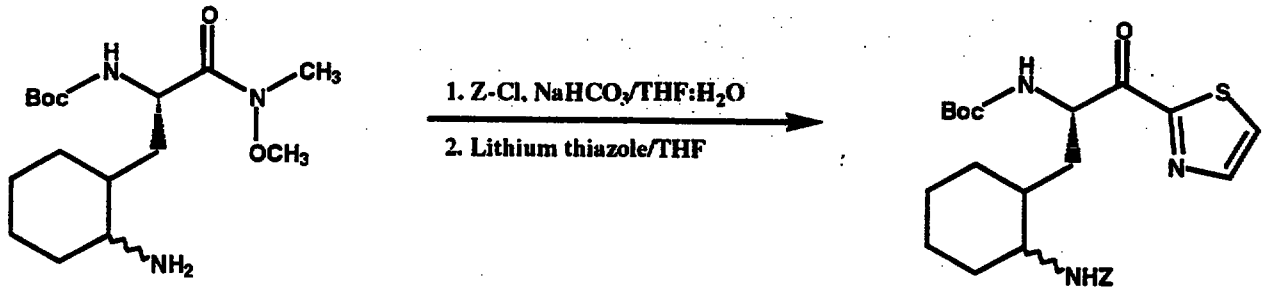
SUBSTITUTE SHEET



1. *tert*-Butyloxycarbonyl-3-(*cis/trans*-3-aminocyclohexyl)alanine-N,O-dimethylamide (1.00 g, 3.0 mmol) was dissolved in saturated aqueous sodium bicarbonate, and THF [60 mL, (1:1)] with stirring. The solution was cooled and a solution of benzyl chloroformate (0.43 mL, 3.0 mmol) in THF (10 mL) was added dropwise. Excess solid sodium bicarbonate was added, the THF was removed under reduced pressure, and the remaining aqueous phase was poured into ethyl acetate (250 mL), and mixed thoroughly. The aqueous phase was discarded and the remaining solution was washed with saturated aqueous sodium bicarbonate (2 x 50 mL), 4 N aqueous sodium bisulfate (2 x 50 mL), and brine (2 x 50 mL). The solution was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The semi-solid was chromatographed on silica gel (ethyl acetate/ hexane).

2. To a solution of thiazole (1.16 g, 13.7 mmol) in anhydrous THF was added *n*-BuLi (1.6 M/hexane, 8.0 mL, 12.8 mmol) dropwise at -78° C and the solution stirred. The above protected amino acid amide (1.41 g, 3.0 mmol) in THF (15 mL) was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.

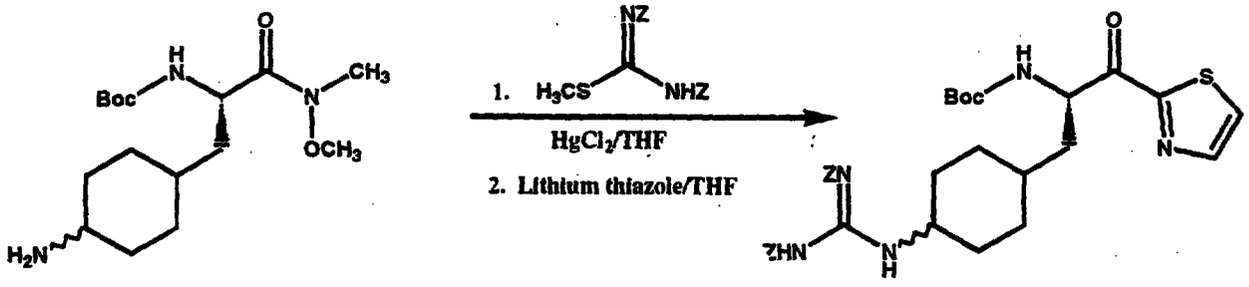
SUBSTITUTE SHEET



1. *tert*-Butyloxycarbonyl-3-(*cis*/*trans*-2-aminocyclohexyl)alanine-N,O-dimethylamide (1.00 g, 3.0 mmol) was dissolved in saturated aqueous sodium bicarbonate, and THF [60 mL, (1:1)] with stirring. The solution was cooled and a solution of benzyl chloroformate (0.43 mL, 3.0 mmol) in THF (10 mL) was added dropwise. Excess solid sodium bicarbonate was added, the THF was removed under reduced pressure, and the remaining aqueous phase was poured into ethyl acetate (250 mL), and mixed thoroughly. The aqueous phase was discarded and the remaining solution was washed with saturated aqueous sodium bicarbonate (2 x 50 mL), 4 N aqueous sodium bisulfate (2 x 50 mL), and brine (2 x 50 mL). The solution was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The semi-solid was chromatographed on silica gel (ethyl acetate/ hexane).

2. To a solution of thiazole (1.16 g, 13.7 mmol) in anhydrous THF was added *n*-BuLi (1.6 M/hexane, 8.0 mL, 12.8 mmol) dropwise at -78° C and the solution stirred. The above protected amino acid amide (1.41 g, 3.0 mmol) in THF (15 mL) was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.

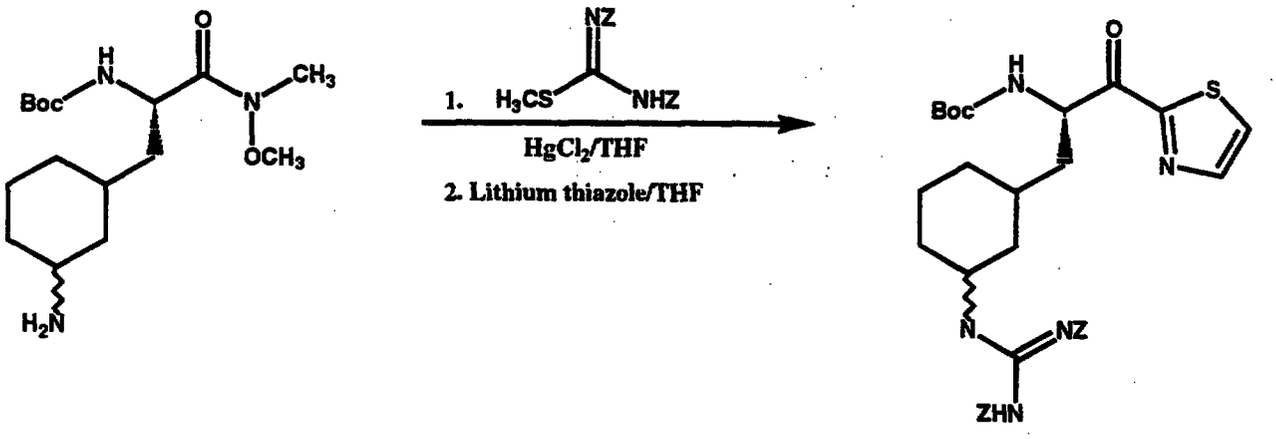
SUBSTITUTE SHEET



1. *tert*-Butyloxycarbonyl-3-(*cis/trans*-4-aminocyclohexyl)alanine-N,O-dimethylamide (2.0 g, 6.1 mmol) was dissolved in dry THF (20 mL) under nitrogen with stirring. The solution was cooled to 0° C, N,N'-bis-(benzyloxycarbonyl)-S-methyl-isothiourea (2.18 g, 6.1 mmol), and $HgCl_2$ (1.81 g, 6.7 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (300 mL), and filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the purified product.

2. To a solution of thiazole (2.32 g, 27.3 mmol) in anhydrous THF was added *n*-BuLi (1.6 M/hexane, 15.9 mL, 25.4 mmol) dropwise at -78° C and the solution stirred. The above guanidylated amino acid (3.88 g, 6.1 mmol) in THF (15 mL) was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.

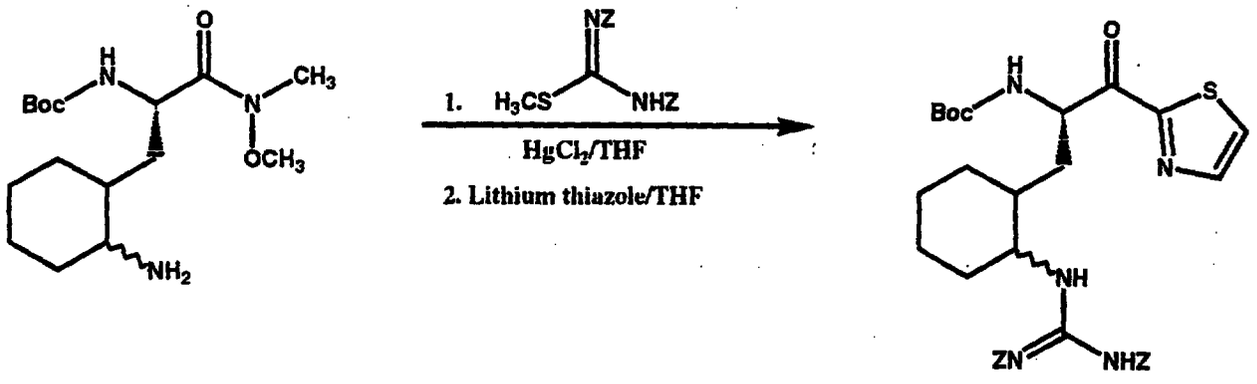
SUBSTITUTE SHEET



1. *tert*-Butyloxycarbonyl-3-(*cis*/*trans*-3-aminocyclohexyl)alanine-N,O-dimethylamide (2.0 g, 6.1 mmol) was dissolved in dry THF (20 mL) under nitrogen with stirring. The solution was cooled to 0° C, N,N'-bis-(benzyloxycarbonyl)-S-methyl-isothiourea (2.18 g, 6.1 mmol), and $HgCl_2$ (1.81 g, 6.7 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (300 mL), and filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the purified product.

2. To a solution of thiazole (2.32 g, 27.3 mmol) in anhydrous THF was added *n*-BuLi (1.6 M/hexane, 15.9 mL, 25.4 mmol) dropwise at -78° C and the solution stirred. The above guanidylated amino acid (3.88 g, 6.1 mmol) in THF (15 mL) was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.

SUBSTITUTE SHEET



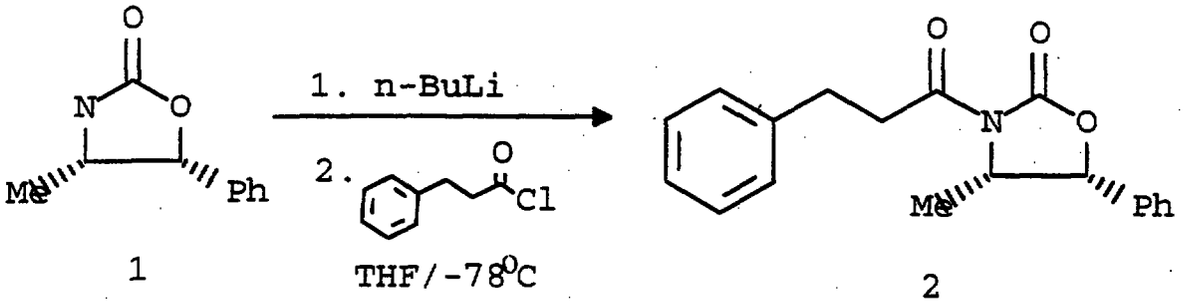
1. *tert*-Butyloxycarbonyl-3-(*cis/trans*-2-aminocyclohexyl)alanine-N,O-dimethylamide (2.0 g, 6.1 mmol) was dissolved in dry THF (20 mL) under nitrogen with stirring. The solution was cooled to 0 C, N,N'-bis-(benzyloxycarbonyl)-S-methyl-isothiourea (2.18 g, 6.1 mmol), and $HgCl_2$ (1.81 g, 6.7 mmol) added. The solution was concentrated under reduced pressure, the remaining residue was suspended in ethyl acetate (300 mL), and filtered through celite. The filtrate was concentrated under reduced pressure. Flash chromatography over silica gel (hexane/ethyl acetate gradient) afforded the purified product.

2. To a solution of thiazole (2.32 g, 27.3 mmol) in anhydrous THF was added *n*-BuLi (1.6 M/hexane, 15.9 mL, 25.4 mmol) dropwise at -78 C and the solution stirred. The above guanidylated amino acid (3.88 g, 6.1 mmol) in THF (15 mL) was added dropwise, and the resulting mixture stirred. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ethyl acetate (150 mL), and the organic layer washed with saturated aqueous ammonium chloride (2 x 50 mL), brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (ethyl acetate/hexane), and concentrated under reduced pressure.

SUBSTITUTE SHEET

Example 2

Synthesis of Intermediates



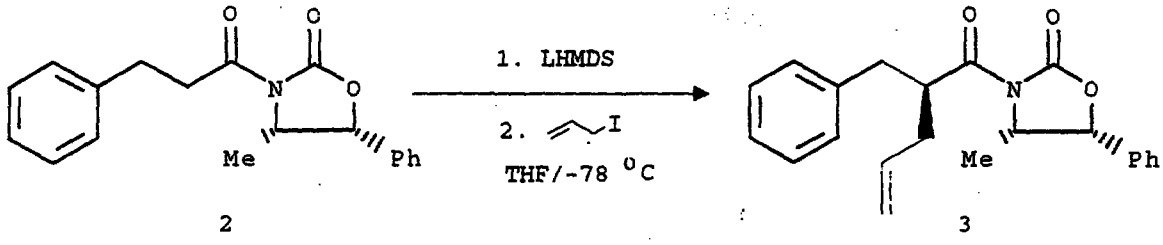
1 2

(4S,5R)-3-(1-oxo-3-phenylpropyl)-4-(phenyl)-5-(methyl)-2-oxazolidone **(2)**. A solution of 10.0 g (1.0 equiv., 56.4 mmol) of (4S, 5R)-4-phenyl-5-methyl-2-oxazolidone **(1)** in 250 mL of dry THF, stirred at -78°C under argon, was treated dropwise with n-butyllithium (1.6 M in Hexane, 1.1 eq., 38.8 mL). After stirring for 30 min., 8.4 mL (1.0 equiv., 56.4 mmol) of hydrocinnamoyl chloride was introduced dropwise over a 10 minute period. The resulting mixture was warmed to 0°C, stirred for an additional hour, and quenched with saturated ammonium chloride. The solvent was removed *in vacuo* and the resulting white solid dissolved in ethyl acetate and ddH_2O. The aqueous phase was removed and extracted with two additional portions of ethyl acetate. The extracts were combined, washed with saturated sodium chloride, dried over sodium sulfate, and the solvent was removed *in vacuo* to afford a white crystalline solid **(2)**(in 91% yield).

m.p.95-96.5; $[\alpha]_D$-35.8 (c=1, CH_2Cl_2); $[\alpha]_D$-26.6 (c=1.018. CH_2Cl_2).

^{1}HNMR ($CDCl_3$) δ 0.89(d, 3H, CH_3, J=6.6 Hz), 3.00-3.05 (m, 2H), 3.26-3.34 (m, 2H), 4.73-4.78 (m, 1H), 5.64, d, 1H, J=7.4 Hz), 7.22-7.46 (m, 10H).

SUBSTITUTE SHEET



2 3

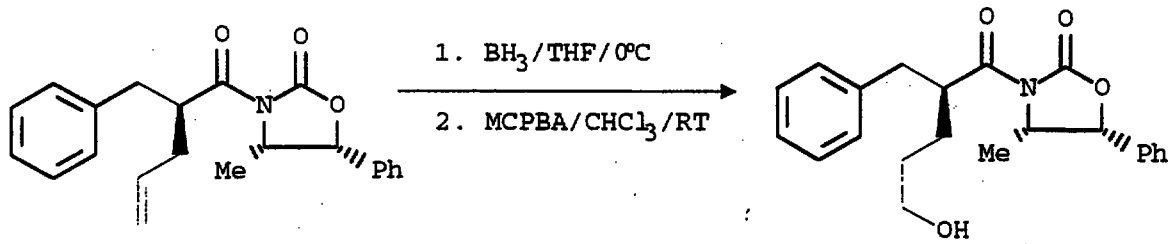
A solution of 5.0 g (1.00 equiv., 16.2 mmol) of **(2)** in 100 mL of dry THF, was cooled to -78°C. Enolization was achieved with 17.8 mL (1.1 equiv., 17.8 mmol) of lithium bis-trimethylsilylamide, which was added dropwise via syringe. The solution was stirred for 30 min. before 4.45 mL (3.0 equiv., 48.5 mmol) of allyl iodide was introduced and the reaction warmed to -15°C. After 1 h the reaction was quenched with saturated ammonium chloride and extracted (3X) with ethyl acetate.. The organic phase was washed with sodium metabisulfite, dried over sodium sulfate and the solvent removed *in vacuo* to afford an off-colour oil. Purification was achieved by flash chromatography on silica gel using a stepwise gradient (15:1, 12:1, 10:1) to yield **(3)**, a colourless oil (95%).

$[\alpha]_D$ 47.5 (c=3.12, CH_2Cl_2).

^{1}HNMR ($CDCl_3$) δ 0.82 (d, 3H, CH_3, J=6.6), 2.31-2.40 (m, 1H, RCH=$CHCH_2$), 2.49-2.57 (m, 1H, RCH=$CHCH_2$), 2.84-3.00 (m, 2H, Ph-CH_2), 4.32-4.37 (m, 1H, CH-(N)CO), 4.53-4.58 (m, 1H, CH_3-CH-), 5.03-5.13 (m, 2H, ABX, $CH=CH_2$), 5.21 (d, 1H, Ph-CH, J=7.1 Hz), 5.81-5.89 (m, 1H, $CH=CH_2$), 7.20-7.42 (m, 10H, ArH);

^{13}C ($CDCl_3$) δ 14.4, 36.2, 38.2, 43.9, 54.7, 78.4, 117.1, 125.4, 126.3, 128.2, 128.5, 129.0, 133.1, 134.8, 138.9, 152.4, 174.9.

SUBSTITUTE SHEET



3 4

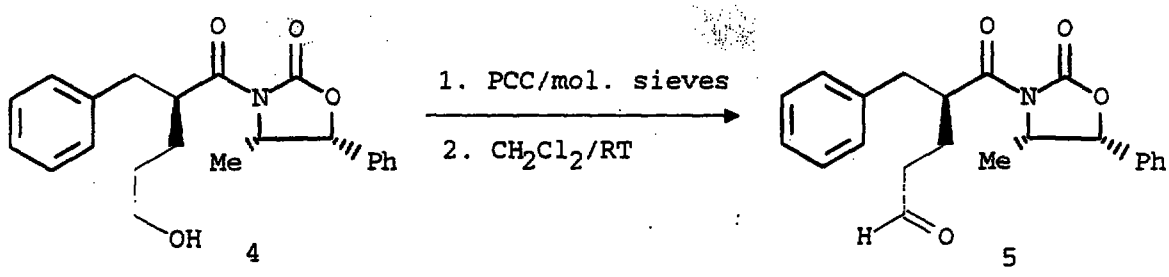
A sample of the allyl compound, **(3)**, (4.75 g, 13.6 mmol) in THF (100 mL) was treated with 13.6 mL (1.0 equiv., 13.6 mmol) of a 1.0 M solution of borane-tetrahydrofuran complex at 0°C and stirred for 2h. The solvent was evaporated and chloroform (100 mL) added via syringe. Oxidation of the organoborane was achieved by the addition of 4.7 g (2.0 equiv., 27.2 mmol) of 3-chloroperoxybenzoic acid at 0°C, with warming to ambient temperature and stirring for an additional hour. The organic phase was washed with 5% Na_2CO_3, , ddH_2O, and dried over sodium sulfate. Due to the instability of the alcohol, a quick column was performed to remove the extreme polar and nonpolar material which originated from the 3-chloroperoxybenzoic acid. The alcohol **(4)** was obtained in a yield of 65%.

$[\alpha]_D$ 39.3 (c=1.038, CH_2Cl_2).

^{1}HNMR ($CDCl_3$) δ 1.07 (d, 3H, CH_3-CH, J=6.5 Hz), 1.81-1.93 (m, 3H, CH_2-CH-H), 2.10-2.19 (m, 1H, CH_2-CH-H), 3.10-3.17 (m, 2H, Ph-CH_2), 3.873.90 (m, 2H, CH_2OH), 4.43-4.49 (m, 1H, CH-CO), 4.70-4.75 (m, 1H, CH_3-CH), 5.36 (d, 1H, Ph-CH, J=7.1 Hz), 7.41-7.63 (m, 10H, ArH);

This Sheet Has Been Replaced

SUBSTITUTE SHEET

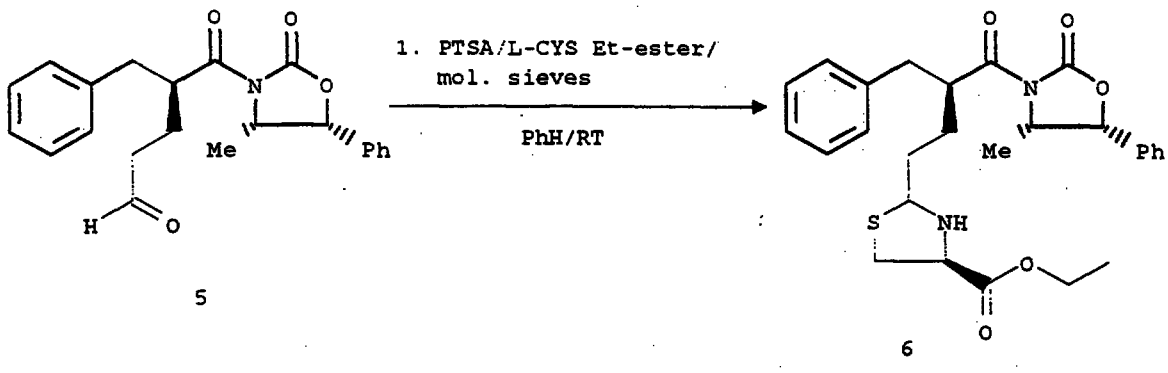


To a solution of the alcohol **(4)** (1.0 g, 2.7 mmol), dissolved in dichloromethane (27 mL), 876 mg (1.5 equiv., 4.1 mmol) of pyridinium chlorochromate and 1.0 g of 4 angstrom molecular sieves were introduced and the mixture changed from bright orange to a black colour. The reaction was monitored by TLC and after 30 min., if starting material remained, additional molecular sieves were added. The solution was filtered through celite and the solvent was evaporated. The residue was dissolved in ethyl acetate and washed with saturated sodium chloride. If the orange colour persisted in the organic phase, additional filterings through celite pads were performed. The aldehyde was obtained in a quantitative yield as a transparent, colourless oil **(5)**.

^{1}HNMR ($CDCl_3$) δ 0.84 (d, 3H, CH_3-CH, J=6.6Hz), 1.87-1.94 (m, 1H, CH_2-C<u>H</u>(H)-CHO), 2.04-2.13 (m, 1H, CH_2-C<u>H</u>(H)-CHO), 2.45-2.50 (m, 2H, Ph-C<u>H</u>$_2$), 2.79-2.85 (dd, 1H, C<u>H</u>$_2$-CHO, J=13.3 & J=6.6), 2.92-2.99 (dd, 1H, C<u>H</u>$_2$-CHO, J=13.2 & J=8.8), 4.19-4.22 (m, 1H, C<u>H</u>-CO), 4.46-4.51 (m, 1H, CH_3-C<u>H</u>), 5.13-5.25 (m, 1H, Ph-C<u>H</u>), 7.20-7.39 (m, 10H, Ar<u>H</u>), 9.69 (s, 1H, C<u>H</u>O);

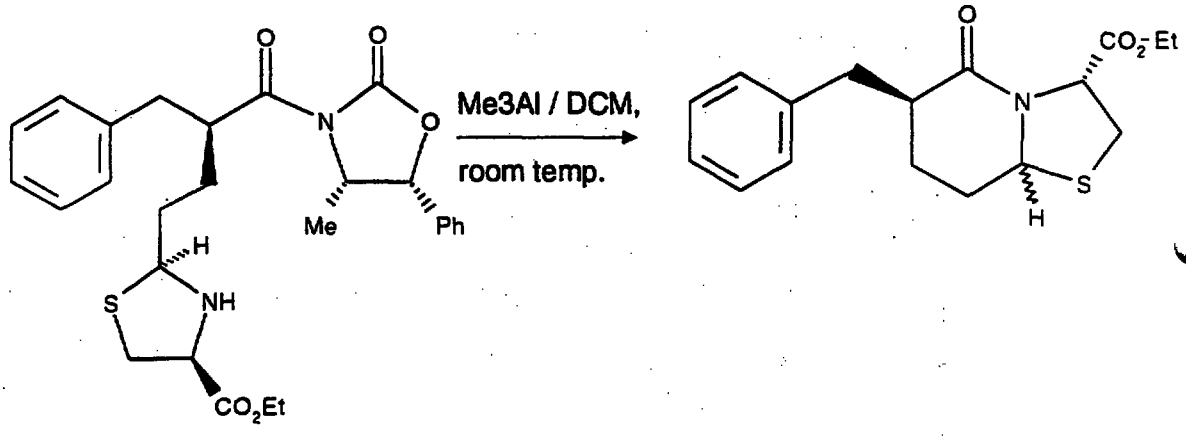
^{13}C ($CDCl_3$) δ 14.2, 23.8, 39.0, 41.2, 43.8, 54.9, 78.6, 125.3, 126.4, 128.2, 128.4, 128.5, 128.9, 132.8, 138.4, 152.4, 174.9, 201.1.

SUBSTITUTE SHEET



5 6

The aldehyde, **(5)**, (2.6 g, 7.10 mmol) was dissolved in benzene (70 mL) and a catalytic amount of p-toluenesulfonic acid was added, followed by 1.58 g (1.2 equiv., 8.52 mmol) of L-cysteine ethyl ester and 4 Å molecular sieves. The reaction was allowed to stir overnight at ambient temperature followed be removal of solvent *in vacuo*. The residue was dissolved in chloroform, washed with saturated sodium chloride, ddH_2O, and dried over sodium sulfate. The solvent was removed *in vacuo* to afford a gummy solid **(6)**.



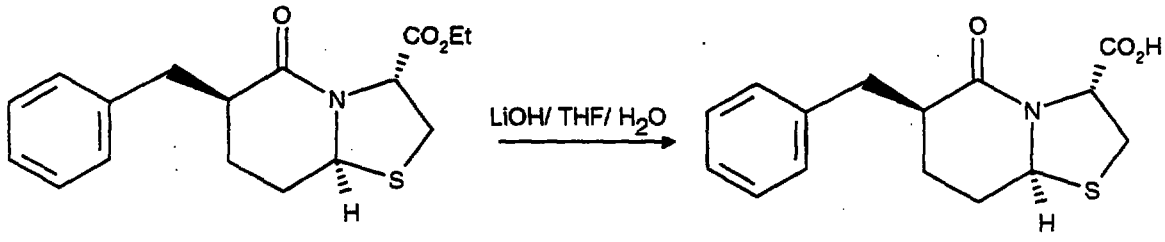
6 **7**

2.0M trimethylaluminum in hexane (2.4mL, 4.8mmol, 3 equivalents) was added slowly to starting material **(6)** (800mg, 1.61mmol) stirring in anhydrous dichloromethane under argon, using ovendried equipment. After stirring overnight, HPLC indicated that the reaction had gone to completion.

SUBSTITUTE SHEET

The mixture was quenched with excess methanol, then filtered on a short silica gel column (washing through with excess 10% methanol in ethylacetate. Evaporation gave 784 mg of crude material that was purified using 2:1 hexane:EtOAc on a silica gel column affording 258mg (0.81mmol being a 50% yield) of pure compound **(7)**,a 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-ethyl ester as a white/yellow solid.

^{1}H NMR (CDCl3) d 1.28-1.31 (m, 3H), 1.72-1.81 (m, 3H), 2.10-2.13 (m, 1H), 2.66 (dd, 1H, J= 11.5 and 6.0 Hz), 3.29-3.34 (m, 2H), 4.19-4.29 (m, 2H), 4.88 (dd, 1H, J= 9.0 and 5.0 Hz), 5.22 (dd, 1H, J= 8.0 and 6.0 Hz), 7.18-7.23 (m, 3H), 7.28-7.31 (m, 2H).



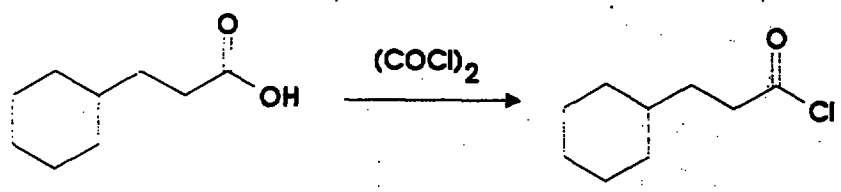
7 **8**

LiOH.H2O (48mg, 1.12mmol) in 10mL of water was added to starting material **(7)** (240mg, 0.76mmol) dissolved in 10mL of dioxane. After 1 hour, TLC in 1:1 Hexane:EtOAc showed no starting material. The reaction was quenched with 10% citric acid, then extracted twice with dichloromethane. Drying and evaporating the combined organic layers gave 354mg of crude product. This was redissolved in dichloromethane, then precipitated by adding excess hexane. The product was filtered to give 200mg (0.68mmol being a 90% yield)) of an off-white solid, **(8)**, also known as 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxylic acid.

^{1}H NMR (CD3OD) d 1.71-1.82 (m, 3H), 2.12-2.17 (m, 1H), 2.67 (dd, 1H, J= 14 and 11 Hz), 2.77-2.81 (m, 1H), 3.30-3.40

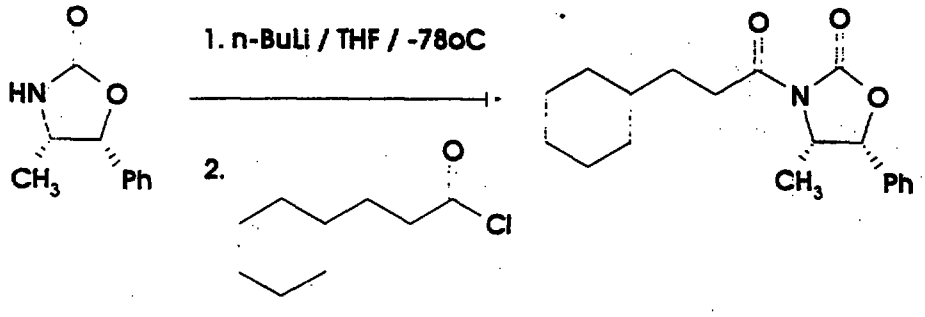
SUBSTITUTE SHEET
This Sheet Has Been Replaced

(m, 3H), 4.81 (dd, 1H, J= 8.5 and 4.9 Hz), 5.16 (t, 1H, J= 7.5 Hz), 7.18-7.31 (m, 5H).



9 10

Oxalyl chloride **(9)** (25 g, 0.197 mol) was cooled to 0°C and cyclohexane propionic acid (20 ml, 0.14 mol) was added. This was left to stir overnight. The resultant mixture was distilled to give an 84% yield of the colorless liquid **(10)**, cyclohexyl propionic acid chloride.



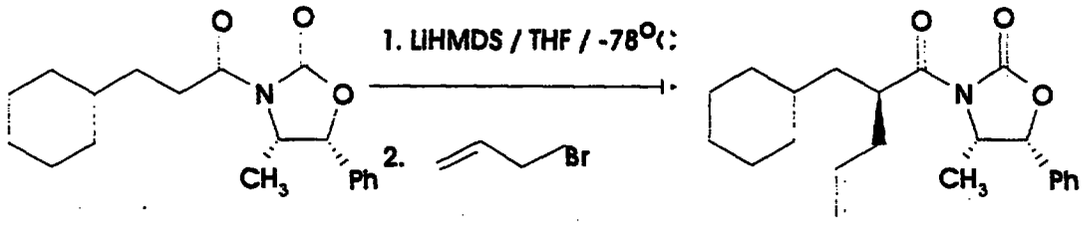
11 **10** **12**

The chiral auxiliary **(11)** (13.6g, 76.7 mmol, 1 eq) was dissolved in dry THF and cooled to -78°C. Then n-BuLi (52.8 mL, 84.4 mmol, 1.2 equiv.) was added and left for 30 mins (dark orange solution). The acid chloride **(10)** (13.4 g, 76.6 mmol, 1 eq) was then added and left to stir overnight. Work-up was done by quenching with saturated NH_4Cl extracting with ethyl acetate, washing the extracts with water and brine, drying over sodium sulphate and concentration. A fast column, with dry loading, (6:1 hexane ethyl acetate) was run to purify the product. This afforded in a white solid **(12)** which was recrystallized

from ether and hexane to give the title compound in 78% yield.

[α]D=-20.1(c=1,EtOH); MP/BP mp=90.5-91.5oC

1H NMR (CDCl3) d 0.86-1.10 (m, 5H), 1.18-1.30 (m, 4H), 1.54-1.75 (m, 7H), 2.86-2.97 (m, 2H0, 4.70-4.76 (m, 1H), 5.65 (d, 1H, J= 7.2 Hz), 7.28-7.42 (m, 5H).



12 13

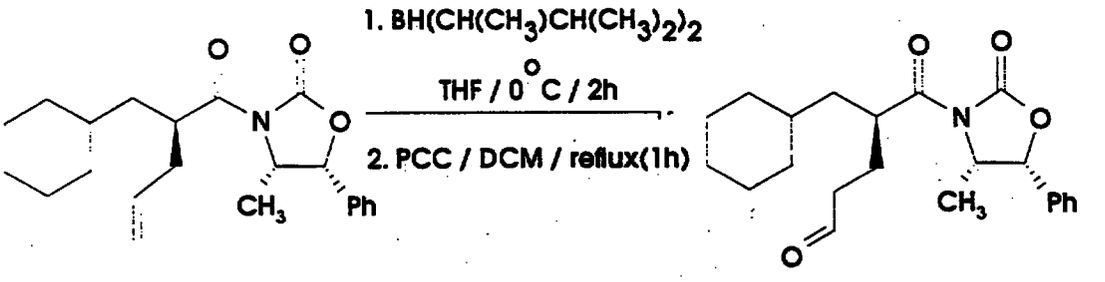
The starting material **(12)** (9.13g, 29 mmol, 1eq) was dissolved in dry THF and cooled to -78°C, after which LiHMDS (31.9 mL, 31.9 mmol, 1.1 eq) was added dropwise over 40 mins. Then, 30 minutes later, allyl bromide (7.5 mL, 86.9 mmol, 3 eq) was added slowly over 10 mins. The mixture was left to warm overnight. Work-up included quenching with sat. ammonium chloride, extraction with ethyl acetate, washing with 10% sodium thiosulphate, decolourising with charcoal, drying over sodium sulphate and concentration *in vacuo*. The product was obtained as a yellow oil **(13)** in 96% yield.

[α]D=+9.5(c=1.0,EtOH)

H NMR (CDCl3) d 0.92-1.10 (m, 5H), 1.10-1.39 (m, 5H), 1.63-1.75 (m, 6H), 2.27-2.42 (m, 2H), 4.01-4.14 (m, 1H), 4.76-4.85 (m, 1H), 5.00-5.07 (m, 2H0, 5.65 (d, 1H, J= 7 Hz), 5.64-5.88 (m, 1H0, 7.27-7.46 (m, 5H).

This Sheet Has Been Replaced

SUBSTITUTE SHEET



13 14

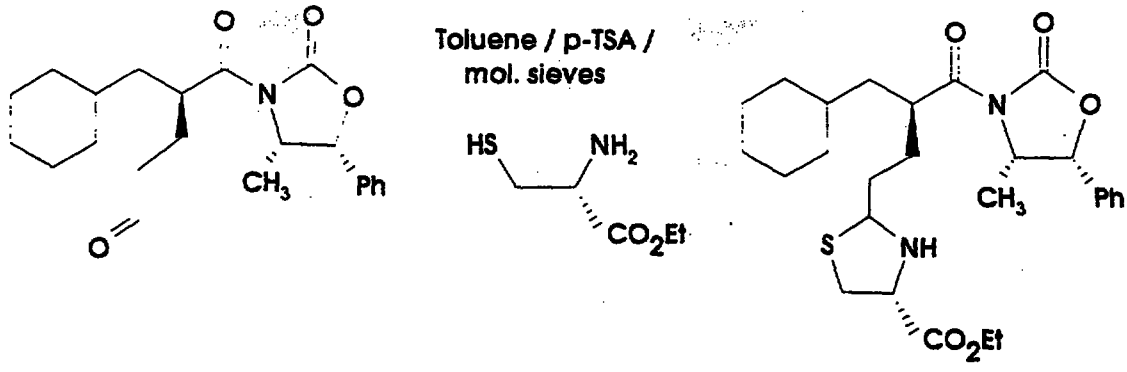
2-methyl-2-butene was added dropwise to borane dimethylsulphide complex at -12°C. The reaction was maintained at this temperature for 15 minutes and then it was warmed to 0°C, after which it was stirred for 2 hours. The disiamyl borane was then added to a mixture of the starting material **13** in THF using a double-ended needle at 0 C. The mixture was then stirred for 2 hours after which the solvents were removed and the residue dissolved in dichloromethane. It was carefully added to a suspension of pyridinium chlorochromate in dichloromethane contained in a flask equipped with a reflux condenser. After the initial exothermic reaction had subsided, the mixture was refluxed at 50°C for 1 hour. The dark brown liquid was dissolved in ethyl acetate and filtered through Florisil. The black residue of PCC was extracted with ethyl acetate and also filtered through the same Florisil pad. Concentration of the filtrates resulted in a 78% yield of a yellow gummy product **(14)**.

[α]D=-17.8(c=1.245,EtOH)

H NMR (CDCl3) d 0.89-1.18 (m, 5H), 1.20-1.47 (m, 8H), 1.60-1.74 (m, 6H), 1.83-2.00 (m, 1H), 2.48-2.53 (m, 2H), 3.90-4.10 (m, 1H0, 4.12-4.16 (m, 1H), 4.76-4.80 (m, 1H0, 5.67 (d, 1H, J= 7Hz), 7.27-7.46 (m, 5H), 9.77 (s, 1H).

This Sheet Has Been Replaced

SUBSTITUTE SHEET

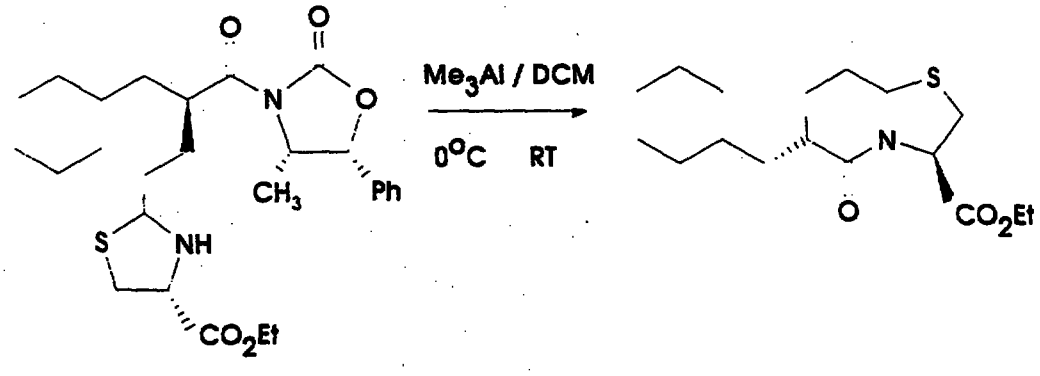


14 15

The resulting aldehyde **(14)** (7.7g crude, 20.8 mmol 1 equiv.) was dissolved in 75 mL of toluene. To the solution was added a catalytic amount of p-toluenesulphonic acid (50 mg), 10 g of 4Å molecular sieves, and L-cysteine ethyl ester (3.87 g, 20:8 mmol, 1 equiv.). The mixture was stirred overnight, filtered and concentrated. The residue was then purified by silica gel chromatography (6:1 hexane:ethyl acetate) afforded 6.36 g of the product **(15)** in 61% yield.

[α]D=-48.3(c=1.095,EtOH)

H NMR (CDCl3) d 0.84-0.98 (m, 4H), 1.11-1.38 (m, 7H), 1.50-1.90 (m, 10H), 2.80-2.99 (m, 1H), 3.24-3.34 (m, 1H), 3.77-4.29 (m, 4H), 4.46-4.81 (m, 2H), 5.66 (d, 1H, J= 7Hz), 7.27-7.46 (m, 5H).



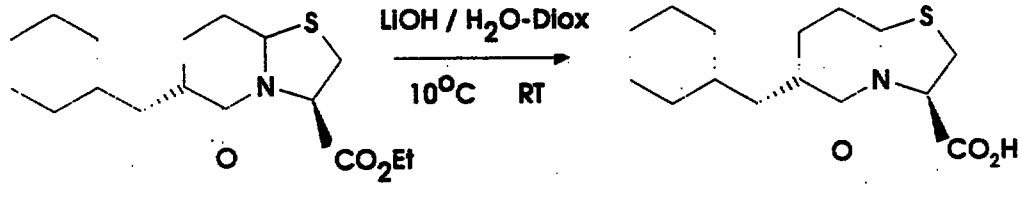
15 16

This Sheet Has Been Replaced

SUBSTITUTE SHEET

The starting material **(15)** (1.97 g, 3.9 mmol, 1 equiv.) was dissolved in 20 mL of dry dichloromethane and cooled to 0°C. Trimethylaluminum (5.9 mL, 11.8 mmol, 3 equiv.), was added dropwise and the mixture was left stirring overnight. After complete reaction as evidenced by HPLC, methanol was added until a yellow solid mass was formed. Dichloromethane was added to dissolve the solid and the whole mixture was stirred for 15-30 minutes and then filtered. The residue after concentration *in vacuo* was run through a quick column (6:1 hexane:ethyl acetate), to remove auxilary and as many of the polar decomposition products as possible, affording in a 50% yield of a yellow oil **(16)**.

^{1}H NMR (CDCl3) d 0.83-0.98 (m, 2H), 1.09-1.38 (m, 10H), 1.57-2.00 (m, 11H), 2.12-2.18 (m, 1H), 2.49-2.54 (m, 1H), 3.10 (dd, 1H, J= 11 and 6 Hz), 3.27 (dd, 1H, J= 11.5 and 8.0 Hz), 4.11-4.25 (m, 2H), 4.88 (dd, 1H, J= 11.0 and 5.o Hz), 5.14 (dd, 1H, J= 10 and 6 Hz).



16 **17**

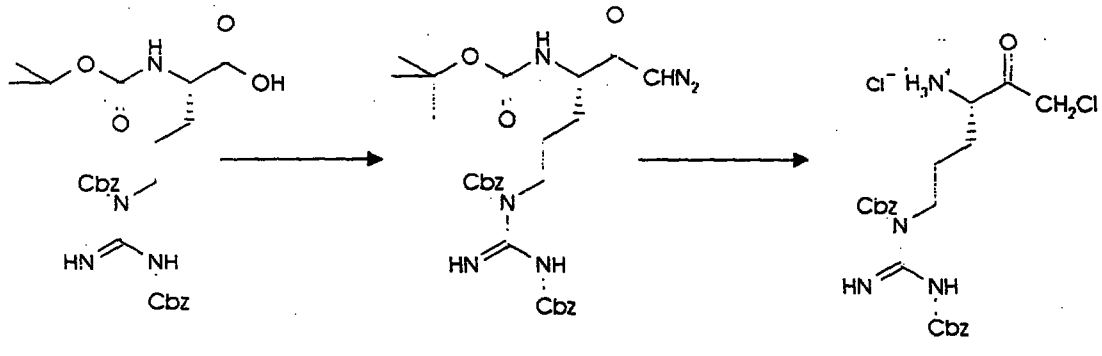
The starting material **(16)** (0.95 g, 2.9 mmol, 1 equiv.) was dissolved in 10 mL of dioxane. The solution was cooled to 10 C, and to it was added LiOH·H$_2$O(0.123 g, 2.9 mmol, 1 eq.) dissolved in 10 mL of water. The bath was removed and the mixture was stirred at room temperature for 1 hour. TLC showed complete reaction and the solvent was evaporated under vacuum. The remaining aqueous layer was washed with ether (2X), acidified with 10% citric acid, and extracted with dichloromethane (3X). The

This Sheet Has Been Replaced

SUBSTITUTE SHEET

combined extracts were dried over sodium sulphate and concentrated to give a white solid which was recrystallized from ether. Concentration of the filtrate and purification by silica gel column chromatography (2:1 hexane: ethyl acetate) resulted in more product **(17)** with a m.p. of 198.2-199°C.

^{1}H NMR (DMSO-d6) d 0.78-0,93 (m, 2H), 1.11-1.27 (m, 5H), 1.34-1.36 (m, 1H), 1.51-1.56 (m, 1H), 1.60-1.75 (m, 1H), 1.82-1.87 (m, 1H), 2.15-2.18 (m, 1H), 2.37-2.41 (m, 1H), 3.03 (dd, 1H, J= 11.5 and 5.5 Hz), 3.35-3.38 (m, 2H), 4.83 (dd, 1H, J= 9 and 4 Hz), 4.95 (dd, 1H, J= 8 and 5.5 Hz).



18 **19** **20**

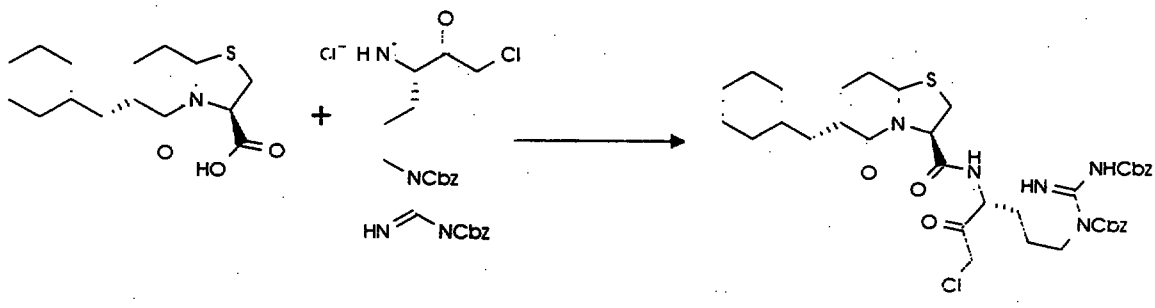
BOC-DiCbz Arg **(18)** (7.6 g, 14.0 mmol) was dissolved in anhydrous THF (40 mL) and cooled to 0°C. Triethylamine (2.2 mL) was added followed by 14.5 mmol of a 1M toluene solution of isopropyl chloroformate via a syringe. The reaction was allowed to stir at 0°C for 30 minutes then quickly filtered. The white solid was discarded. To the filtrate was bubbled freshly prepared diazomethane until the color of the solution turned yellow. The reaction mixture was allowed to stand overnight in a well ventilated fumehood which facilitated the discharge of excess diazomethane. Dry ether was added to precipitate the diazoketone. The product was filtered and dried under vacuum to give light yellow fluffy solid (4.6 g, 58%).

SUBSTITUTE SHEET

Diazoketone **(19)** (1g, 1.77 mmol) was dissolved in THF (20 mL) and to this solution was added 1M HCl in ether (20 mL) at 0°C. The reaction was allowed to stir at ambient temperature overnight during which time a white precipitate was formed. Further precipitation was achieved by adding ether. Filtration and drying the solid afforded the product **(20)** (1.02 g , 100%).

^{1}H NMR (DMSO-d6) d 1.65-1.77 (m, 3H), 2.06-2.50 (m, 1H), 3.86-3.90 (m, 2H), 4.29 (m, 1H), 4.76 (d, 1H, J= 18Hz), 4.95 (d, 1H, J= 18 Hz), 7.35 (s, 2H), 7.36 (s, 2H), 7.35-7.41 (m, 10H), 8.71 (br s, 3H), 10.1 (br s, 2H).

^{13}C NMR (DMSO-d6) d 23.7, 26.4, 47.2, 47.9, 56.2, 68.0, 69.3, 128.6, 128.7, 128.8, 128.9, 135.2, 135.9, 153.4, 157.4, 198.9.



17 **20** **21**

To mimetic **(17)** (0.422 g, 1.42 mmol) in THF (50 mL) at 0 C and in presence of N-methyl morpholine (0.19 mL), was slowly added 1M toluene solution of isopropylchloroformate (1.71 mL). The reaction was allowed to stir at 0 C for 30 minutes then treated with aminochloromethylketone **(20)** in small portions. Once the addition was complete the reaction was further stirred for 15 minutes followed by addition of N-methyl morpholine (0.19 mL). The reaction was stirred at ambient temperature for 3 hours, then extracted with ethyl acetate followed by washing with brine and 10% aqueous citric acid. Removal of organic solvent gave a white foam

SUBSTITUTE SHEET

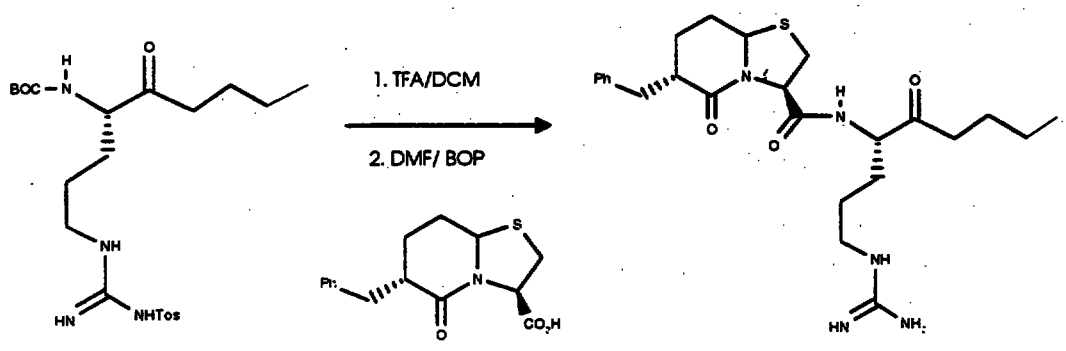
(21) (1.03 g, 96%) which was used further without purification.

^{1}H NMR (CDCl3) d 0.07-0.97 (m, 1H), 1.15-1.41 (m, 7H), 1.62-1.91 (m, 10H), 2.10-2.16 (m, 1H), 2.43-2.48 (m, 1H), 2.74-2.80 (m, 1H), 3.01-3.07 (m, 1H), 3.87-3.94 (m, 1H), 4.11-4.19 (m, 2H), 4.60-4.66 (m, 1H), 4.74-4.86 (m, 2H), 5.09-5.24 (m, 4H), 7.30-7.39 (m, 10H), 7.95 (d, 1H, J= 8 Hz), 9.4 (br s, 1H), 9.56 (br s, 1H).

This Sheet Has Been Replaced

SUBSTITUTE SHEET

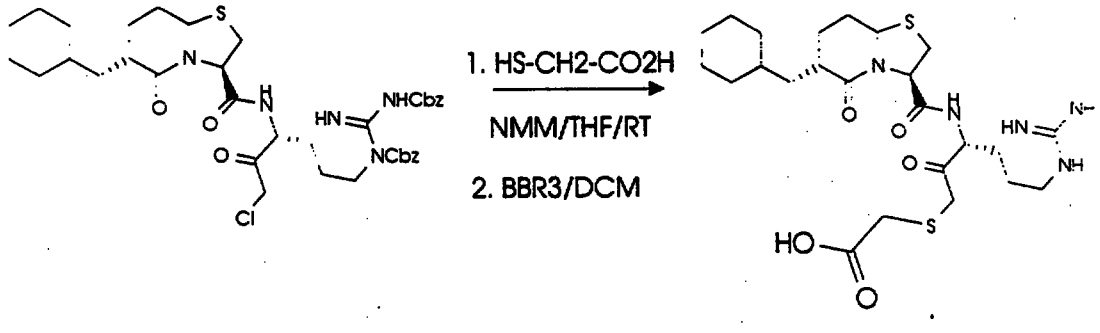
EXAMPLE 3



8

(N-t-BOC-N-tosyl)butyrylketoarginine (240mg, 0.515 mmol), was deprotected using 30% TFA in dichloromethane. The deprotected arginine derivative, was coupled with the mimetic **(8)** (100 mg, 0.343 mmol) in DMF under basic conditions (Et_3N, pH = 8-9), using BOP reagent (228 mg, 0.52 mmol) as the dehydrating agent. The reaction was typically complete within 2-4 hours. Extraction with ethyl acetate followed by successive washing with brine and 10% aqueous citric acid yielded the crude product. The crude product was purified by column chromatography affording 180 mg (76%) of pure product. This product was then treated with HF to remove the tosyl group. Purification of the isolated deprotected product by HPLC afforded **BCH-2737**.

EXAMPLE 4



21

SUBSTITUTE SHEET

Chloromethylketone **(21)** (0.188 g, 0.245 mmol) was dissolved in THF (10 mL) treated with NMM (0.036 mL) followed by mercapto acetic acid (0.02 mL, 0.299 mmol). The reaction was stirred at ambient temperature overnight. Extraction of the reaction mixture with ethyl acetate followed by successive washing with brine and 10 % aqueous citric acid and evaporation of organic solvent gave the crude product which was purified by column chromatography to give foamy solid as the product (0.125 g, 62%).

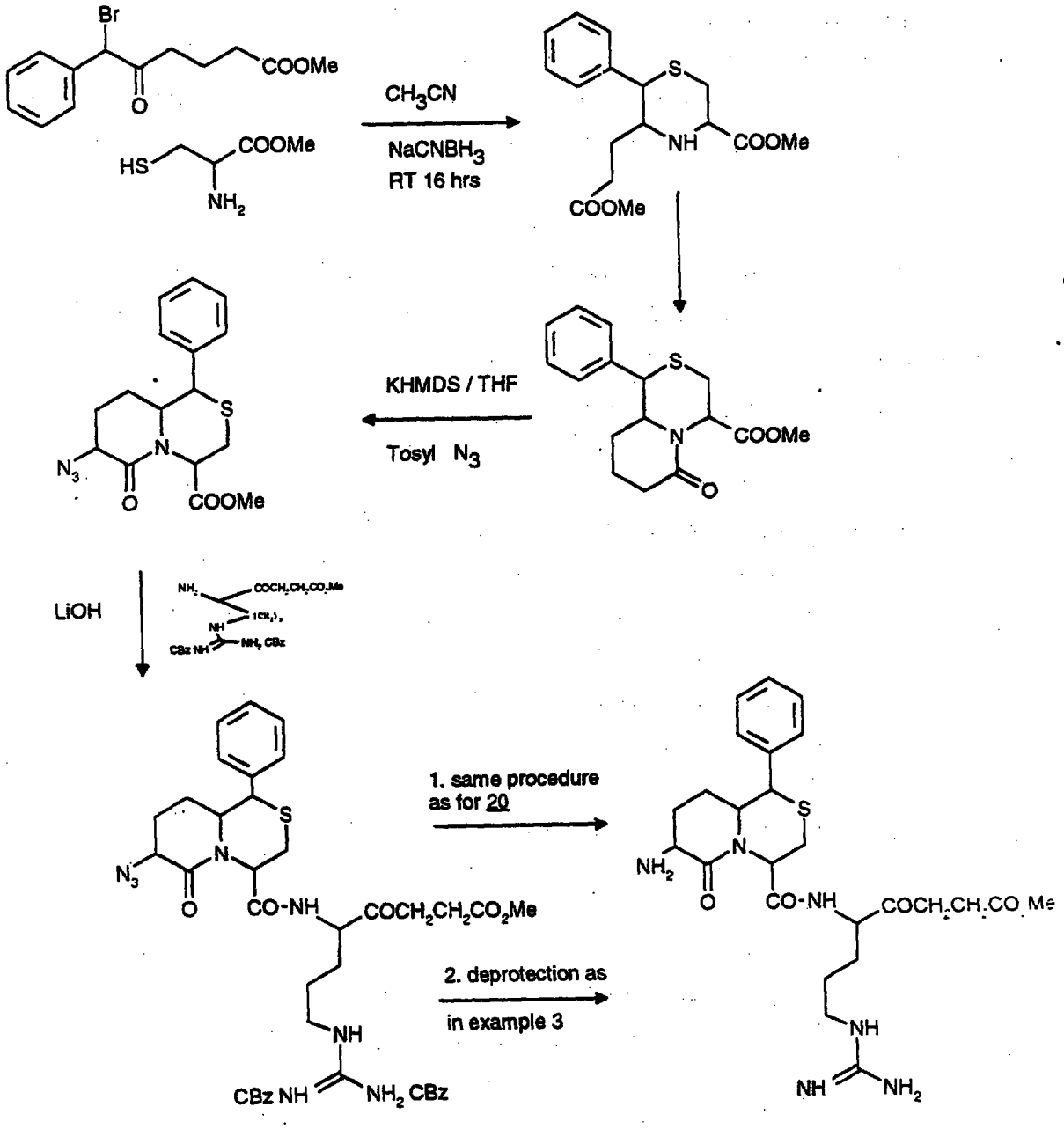
This protected precursor (0.125 g, 0.154 mmol) was dissolved in DCM (5 mL) and cooled to -78°C. A 1M DCM solution of BBr (1.54 mL, 1.54 mmol) was slowly added. The reaction was stirred at ambient temperature for 5 hours, then cooled to -78°C again and treated with anhydrous methanol (2mL). The reaction was brought to room temperature and stirred for 2 additional hours. The solvents were removed under reduced pressure and the residue was partitioned between ether and water. The water layer was collected, lyophilized and the final product **(23)** obtained as a powder after HPLC purification and lyophilization.

The products of the reactions described above can be isolated in the free form or in the form of salts. In addition, the products can be obtained as pharmaceutically acceptable acid addition salts by reacting one of the free bases with an acid. In a similar manner, the product can be obtained as pharmaceutically acceptable salts by reacting one of the free carboxylic acids with a base. Likewise, treatment of the salts with a base or acid results in a regeneration of the free amide.

SUBSTITUTE SHEET

EXAMPLE 5

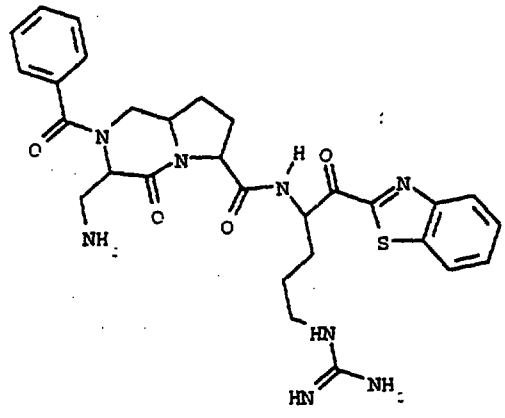
A general method of synthesizing compound of formula II or III:



SUBSTITUTE SHEET

EXAMPLE 6

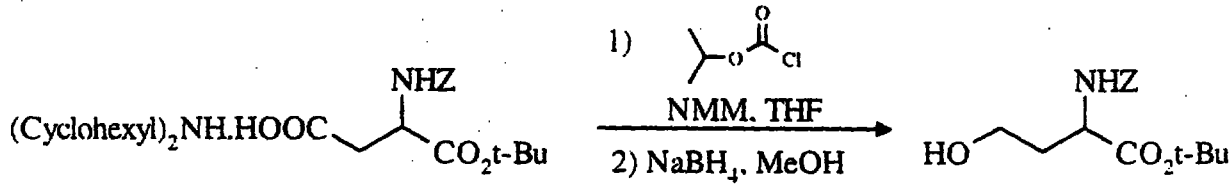
Synthesis of :



(16)

STEP 1

Synthesis of 2-Benzyloxycarbonylamino-4-hydroxybutyric acid tert-butyl ester



(1) (2)

To a solution of the protected aspartic acid (1)(Bachem, 2.50 g, 4.95 mmols) in 50 mL of dry tetrahydrofuran (THF), at -10°C, under N_2, was added N-methylmorpholine (109 µL, 0.2 eq) and isopropyl chloroformate (1.0 M/toluene : 384 µL, 1.1 eq). The soluion was stirred at -10°C for 60 min. In another flask, $NaBH_4$ (375 mg, 2 eq) was suspended in a dry 5:1 mixture of THF/MeOH (50 mL), at -78°C, under N_2. This suspension was stirred at -78°C for 30 min. The mixted anhydride solution was then added to the $NaBH_4$ suspension dropwise *via canula*, and the final solution was stirred at -78°C for 3 hr. Acetic acid (2.8 mL, 10 eq) was then added and the solution was

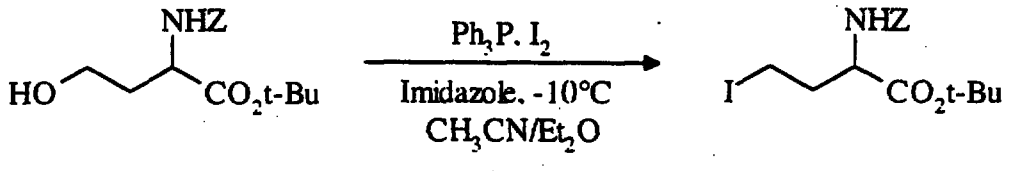
SUBSTITUTE SHEET

warmed to r.t. (30 min). The solvents were evaporated, the residue taken up in EtOAc and washed with sat.aq. $NaHCO_3$ (2x) and brine. The organic layer was dried over $MgSO_4$, the solids were filtered and the solvent evaporated to give 1.53 g (4.95 mmols; 100%) of the alcohol (2) as a clear oil.

^1H NMR ($CDCl_3$, 400 MHz) : δ 7.40-7.31 (m, 5H, ArH), 5.63 (d, 1H, J=7.3, NH), 5.13 (AB system, 2H, J=12.2, CH_2Ph), 4.43 (m, 1H, H-2), 3.69 (m, 2H, H-4), 2.17 (m, 1H, H-3), 1.63 (m, 1H, H-3), 1.48 (s, 9H, t-Bu).

STEP 2

2-Benzyloxycarbonylamino-4-iodobutyric acid tert-butyl ester



(2) (3)

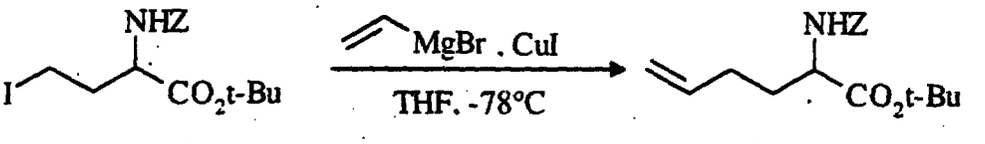
To a solution of the alcohol (2) (1.53 g, 4.95 mmols) in a 1:1 mixture of CH_3CN/Et_2O (50 mL), at -10°C, under N_2, were added successively imidazole (607 mg, 1.8 eq) and Ph_3P (2.21 g, 1.7 eq). Iodine (2.14 g, 1.7 eq) was then added in small portions over a period of 15 min. After the addition was completed, a white precipitate formed and the solution was brown. It was stirred at -10°C for 45 min. It was then poured in Et_2O and the organic phase was washed with sat.aq. Na_2SO_3, sat.aq. $CuSO_4$, H_2O and dried over $MgSO_4$. The solids were filtered and the solvent evaporated to give a yellow oil that was purified by flash chromatography (silica gel, 5% to 20% EtOAc/ Hex). The iodide (3) was obtained in 83% yield (1.71 g) as a clear oil.

SUBSTITUTE SHEET

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.41-7.31 (m, 5H, ArH), 5.35 (bd, 1H, J=7.3, NH), 5.13 (s, 2H, CH_2Ph), 4.30 (m, 1H, H-2), 3.22-3.12 (m, 2H, H-4), 2.42 (m, 1H, H-3), 2.20 (m, 1H, H-3), 1.48 (s, 9H, t-Bu).

STEP 3

Synthesis of 2-Benzyloxycarbonylamino-4-hexenoic acid tert-butyl ester



(3) (4)

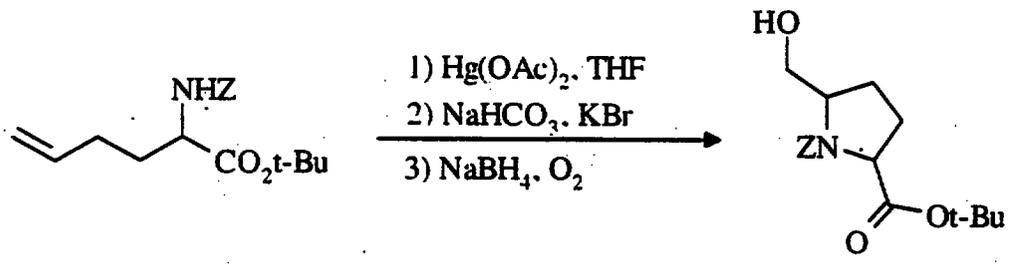
To a suspension of CuI (2.27 g, 5 eq) in dry THF (20 mL), at -78°C, under N_2, was added slowly a 1.0M solution in THF of vinyl magnesium bromide (23.4 mL, 9.8 eq). The solution was then warmed up to -10°C for 30 min (it turned then black) and cooled back to -78°C. A solution of the iodide (3) (1.00g, 2.39 mmols) in dry THF (3.5 mL) was then added slowly to the cuprate solution. The reaction mixture was stirred at -78°C for 2.5 hr. Sat.aq. NH_4Cl (50 mL) was added and the mixture was brought back to room temp. with vigorous stirring. It was then poured in Et_2O and stirred for 5 min. The dark suspension was filtered through a cintered funnel and the phases were separated. The aqueous phase was extracted with Et_2O (2x) and the combined organic extracts were dried over $MgSO_4$. The solids were filtered, the solvents evaporated and the crude oil purified by flash chromatography (silica gel, 5% AcOEt/Hex) to give 0.51 g (67%) of the pure alkene (4).

SUBSTITUTE SHEET

^1H NMR ($CDCl_3$, 400 MHz) : δ 7.37-7.31 (m, 5H, ArH), 5.80 (m, 1H, H-5), 5.33 (d, 1H, J=7.8, NH), 5.12 (s, 2H, CH_2Ph), 5.05 (d, 1H, J=17.2, H-6), 5.01 (d, 1H, J=10.4, H-6), 4.30 (q, 1H, J=7.4, H-2), 2.16-2.08 (m, 2H, H-4), 1.92 (m, 1H, H-3), 1.74 (m, 1H, H-3), 1.48 (s, 9H, t-Bu).

STEP 4

Synthesis of 1-Benzyloxycarbonyl-5-hydroxymethyl-2-pyrrolidinecarboxylic acid tert-butyl ester



(4) (5)

To a solution of the alkene (4)(50 mg, 0.157 mmol) in dry THF (3.1 mL), at r.t., under N_2, was added mercuric acetate (75 mg, 1.5 eq). The solution was stirred at r.t. for 18 hr after which it was cooled down to 0°C. Sat.aq. $NaHCO_3$ (2 mL) was then added and the mixture was stirred at 0°C for 30 min. KBr (0.11g, 6 eq) was added and the mixture was stirred at r.t. for 2 hr. It was then poured in H_2O/Et_2O and the phases were separated. The aqueous phase was extracted with Et_2O (2x) and the combined organic extracts were dried over $MgSO_4$. The solids were filtered and the solvents evaporated. Oxygen (O_2) was bubbled into a suspension of $NaBH_4$ (3.3 mg, 0.55 eq) in dry DMF (0.4 mL) for 1 hr, and to this was added dropwise (syringe pump, 3 mL/hr) a solution of the organomercurial bromide in DMF (3.1 mL) with continuous introduction of O_2. The bubbling was continued for 1 hr and Et_2O (5 mL) was added. The grey suspension was

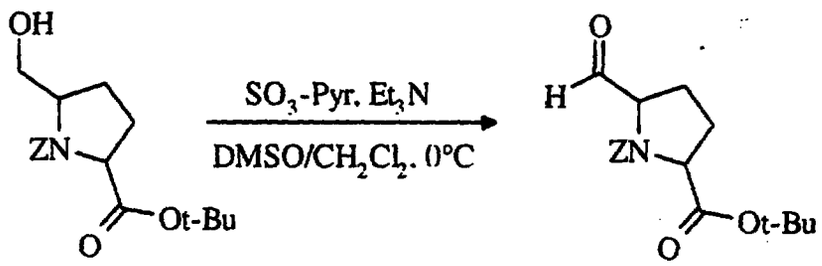
SUBSTITUTE SHEET

filtered through Celite and the filtrate was evaporated. The residue was chromatographed (silica gel, 6:4 Hex/EtOAc) to give the pyrrolidinol (5) (30 mg, 57%) as a clear oil.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.37-7.28 (m, 5H, ArH), 5.22-5.09 (m, 2H, CH_2Ph), 4.30 (dd, 1H, J=1.4, 8.3, H-2), 4.24 (m, 1H, H-5), 3.70-3.57 (m, 3H, CH_2-OH), 2.25 (m, 1H), 2.13 (m, 1H), 1.92 (m, 1H), 1.70 (m, 1H), 1.34 (s, 9H, t-Bu).

STEP 5

Synthesis of 1-Benzyloxycarbonyl-5-carboxy-2-pyrrolidinecarboxylic acid tert-butyl ester



(5) (6)

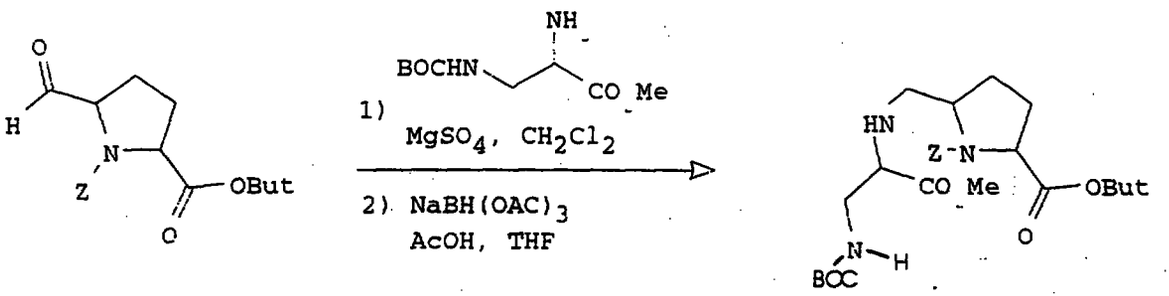
To a solution of the alcohol (5) (50 mg, 0.149 mmol) and Et_3N (62µL, 3 eq) in dry CH_2Cl_2 (0.8 mL) is added slowly, under N_2, at 0°C, a solution of SO_3-Pyridine complex (71 mg, 3 eq) in dry DMSO. The solution was stirred at 0°C for 30 min and 10% citric acid (2 mL) is added. The pH is brought to 4 with 1M NaOH and the aqueous phase is extracted with Et_2O (3x). The combined organic extracts were dried over $MgSO_4$. The solids were filtered and the solvents evaporated to give a crude oil which was purified by flash chromatography (silica gel, 7:3 Hex/EtOAc). The pure aldehyde (6) was obtained as a clear oil (45 mg, 90%).

SUBSTITUTE SHEET

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 9.68 + 9.56 (ds, 1H, CHO), 7.36-7.29 (m, 5H, ArH), 5.23-5.11 (m, 2H, CH_2Ph), 4.57-4.39 (m, 2H, H-2, H-5), 2.30-1.97 (m, 4H, H-3, H-4), 1.47 + 1.36 (2s, 9H, t-Bu).

STEP 6

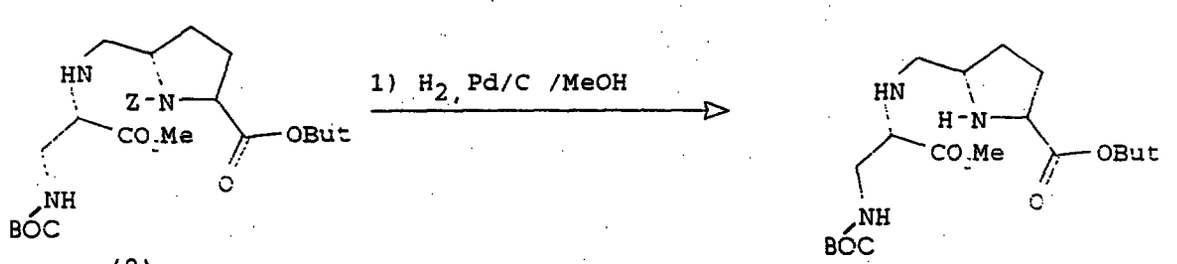
(7)



(6) (8)

The pyrrolidine-aldehyde (6) is coupled with the protected diamino-propionic acid (7) by first forming the imine (8) ($MgSO_4$, CH_2Cl_2). Isolation of the imine (8) is done by filtration of the $MgSO_4$ and evaporation of the solvent. The crude imine is then treated with NaBH(OAc) and actic acid (AcOH) in THF for 15 hours to obtain the amine (8) after extrative work-up.

STEP 7

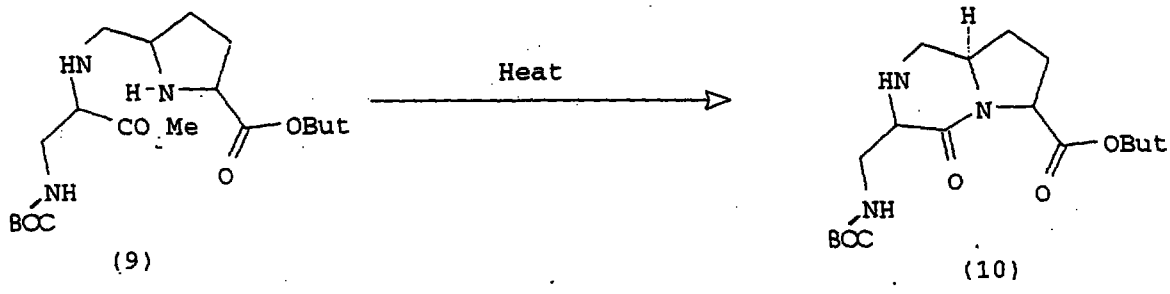


(8) (9)

SUBSTITUTE SHEET

The CB7 (7) protecting group of the amine (8) is removed by hydrogenation with palladium on charcoal 10% as a catalyst in methanol (MeOH). The catalyst is filtered and the MeOH evaporated to give the crude diamine (9) that can be used without any purification.

STEP 8

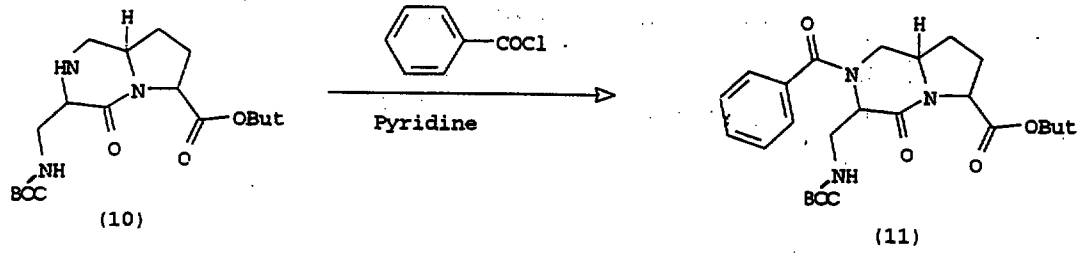


(9) (10)

The cyclisation is done by heating the crude oil (9) from step 7, neat slightly above the boiling point of methanol. The bicyclic lactam (10) is purified by flash chromatography.

SUBSTITUTE SHEET

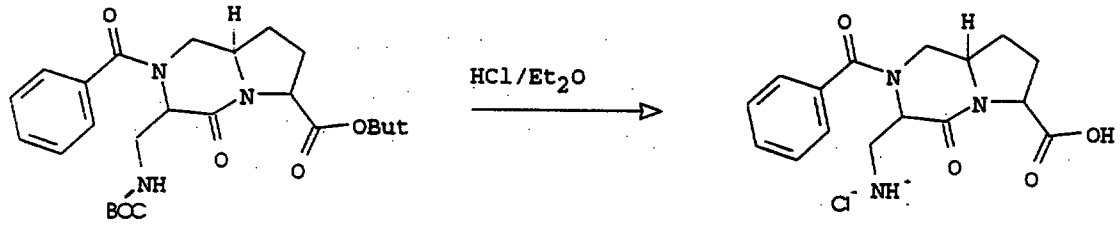
STEP 9



(10) (11)

The secondary amine of the bicyclic lactam (10) is protected as an amide using benzoyl chloride in pyridine. Evaporation of the pyridine and extractive work-up give the bicyclic lactam-amide (11).

STEP 10

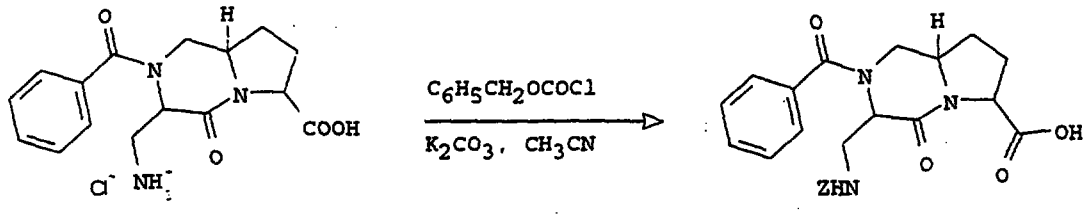


(11) (12)

The BOC and t-butyl ester protecting groups of bicyclic lactam amide (11) are removed under acidic conditions (HCl in ethyl ether (Et_2O)). The amine salt (12) precipitates out of solution and is collected by filtration.

SUBSTITUTE SHEET

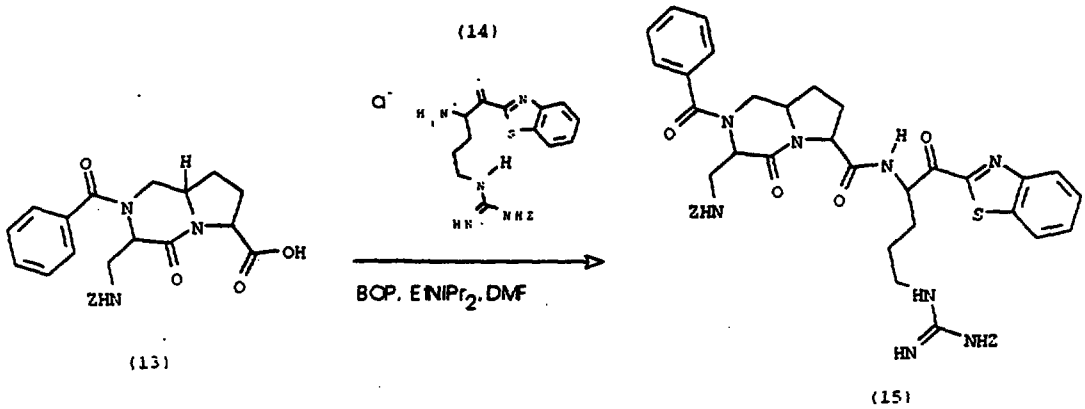
STEP 11



(12) (13)

The primary amine of compound (12) is protected with a CBZ group by reacting it with benzyl chloroformate in acetonitrile (CH_3CN) with K_2CO_3 as a base. Extrative work-up gives fully protected carboxylic acid (13) which can be use for step 12 without further purification..

STEP 12

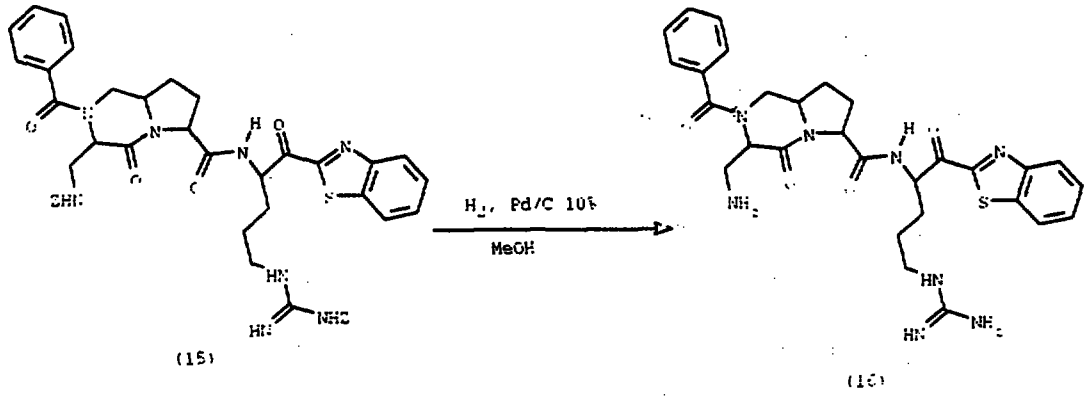


(13) (15)

The carboxylic acid (13) is coupled with benzothiazole ketoarginine (14) in DMF using BOP as the coupling agent in the presence of diisopropylethylamine ($EtNiPr_2$). Extraction with ethyl acetate (EtOAC) gives compound (15) as a solid which is purified by chromatography.

SUBSTITUTE SHEET

STEP 13



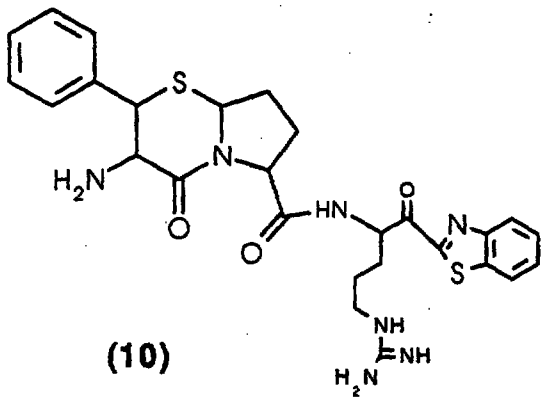
(15) (16)

The two CBZ(Z) protecting groups of compound (15) are removed by catalytic hydrogenation with Pd/C 10% as a catalyst. The catalyst is filtered and the solvent is evaporated to give the amino-guanidine (16).

SUBSTITUTE SHEET

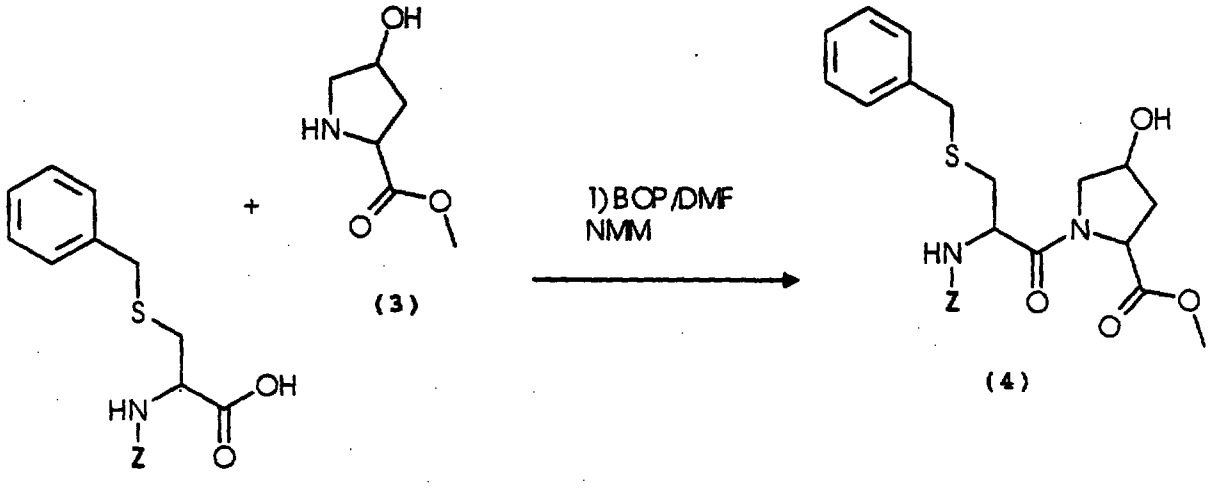
EXAMPLE 7

SYNTHESIS OF COMPOUND (10)



(10)

STEP 1

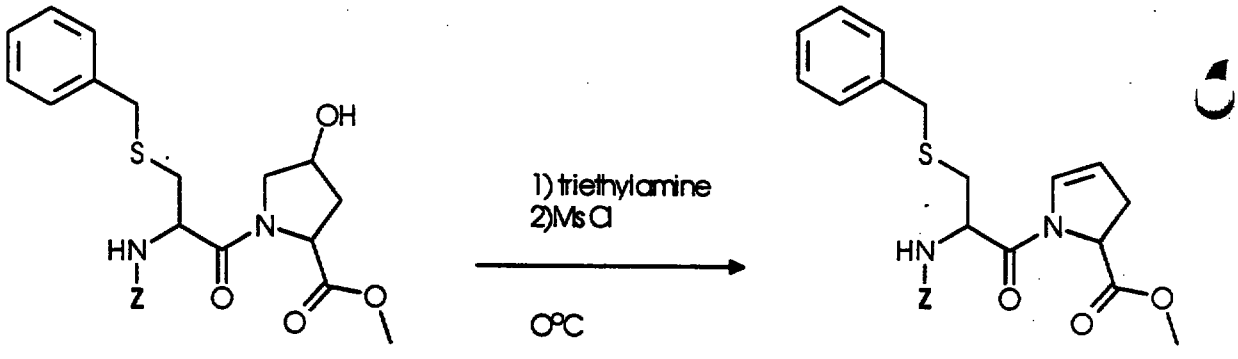


4-methylmorpholine (NMM) was added to a solution of the carboxylic acid **(2)** (1.7g, 4.9mmol, 1.0eq), 4-hydroxyproline **(3)** (5.39mmol, 1.1eq), and BOP reagent (2.17g, 4.9mmol, 1.0eq) in anhydrous DMF (10mL) at room temperature. The reaction mixture was stirred at room tenperature over night, quenched with brine (50mL) and ethyl acetate (100mL). The organic layer washed with

SUBSTITUTE SHEET

aqueous citric acid (10%, 2x50mL), sodium bicarbonate (10%, 2x50mL) and brine (50mL). The resulting organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent evaporated. The crude residue was purified by flash chromatography (5:4:1, ethyl acetate-hexane-methanol). 1.1g of pure product **(4)** was recovered 48% yield.

STEP 2

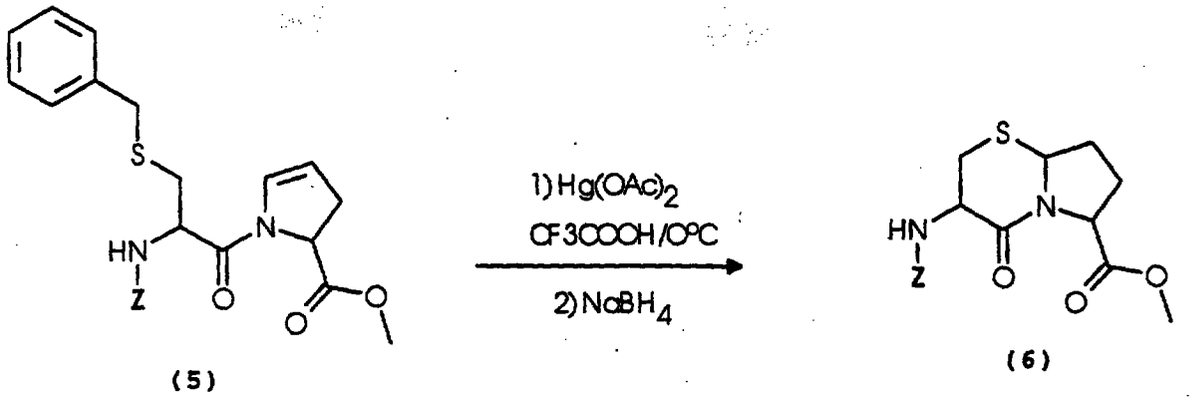


(4) **(5)**

To a solution of 4-hydroxyproline derivative **(4)** (115mg, 240umol, 1.0eq) in dichloromethane (10 mL, anhydrous) at 0°C is added triethylamine (72mg, 720umol, 3.0eq) and methanesulfonyl chloride (28mg, 240umol, 1.0eq) and the reaction mixture is stirred at room temperature. The mixture is then quenched with an aqueous solution of ammonium chloride and extracted with ethyl acetate. The organic layer is washed with 10% citric acid and brine, dried, filtered and the solvent is evaporated to dryness yielding compound **(5)**.

STEP 3

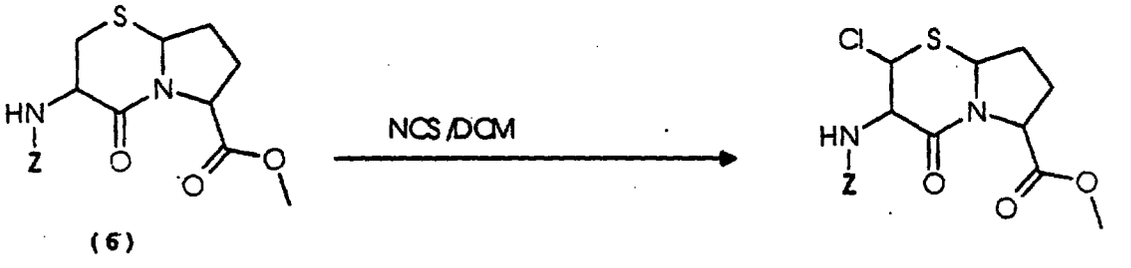
SUBSTITUTE SHEET



(5) (6)

The enamine (5) (1.0eq) is treated with mercuric acetate (1.1 eq) in THF. The solvent is evaporated to dryness and the residue dissolved in methanol. The resulting organo-mercurial is reductivly cleaved with sodium borohydride (1.3eq). The resulting crude lactam thioether is purified by flash chromatography on silica gel affording compound **(6)**.

STEP 4

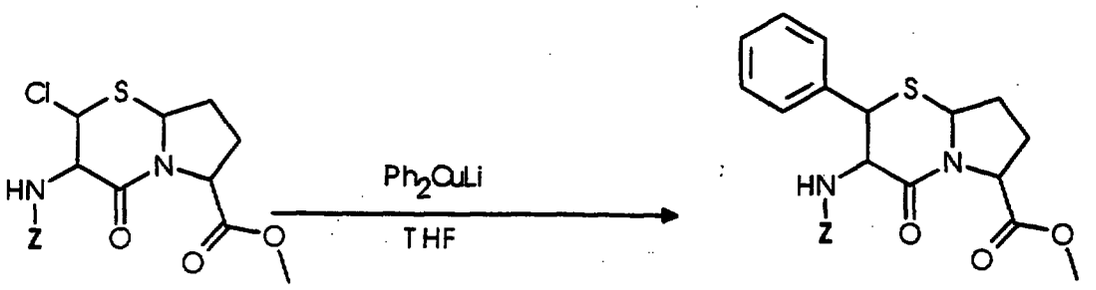


(6) (7)

To a solution of the lactam thioether **(6)** (1.0eq) in dry dichloromethane N-chlorosuccinimide (1.0eq) is added at 0°C. The reaction mixture is warmed to room temperature. When the reaction shows no more starting material the solid is filtered and the solvent evaporated to dryness. The crude material **(7)** is use without any further purification for step 5.

SUBSTITUTE SHEET

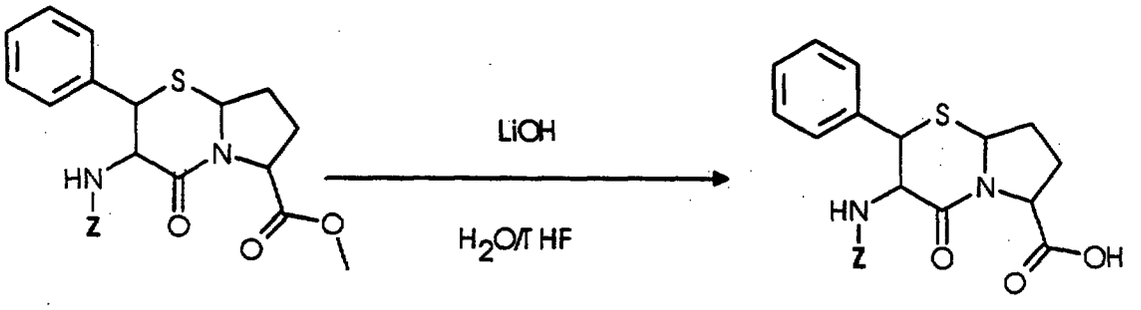
STEP 5



(7) (8)

To a solution of the alpha-chlorothioether **(7)** (1.0eq) in THF (anhydrous) a solution of phenylcuprate (1.0eq) (prepared according to litterature procedure) is added at low temperature. When the reaction mixture shows no starting chlorothioether, brine and ethyl acetate is added. The organic layer is dried, filtered and evaporated to dryness to afford the desired product **(8)**.

STEP 6

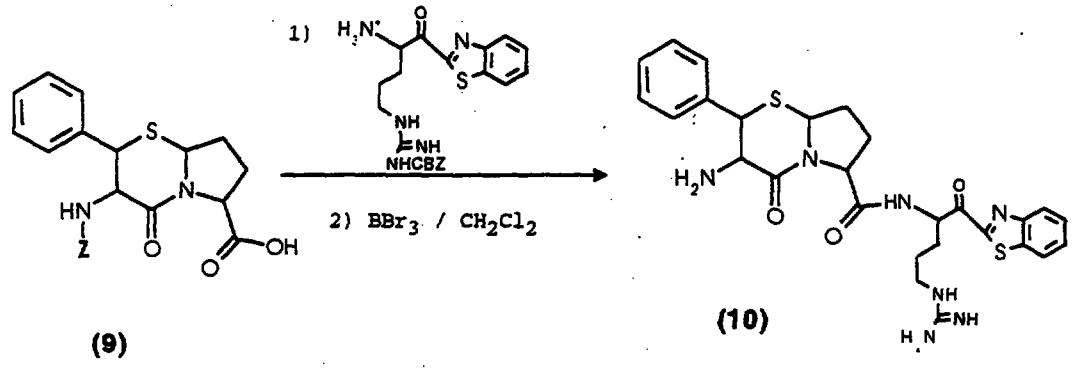


(8) (9)

The isolated bicyclic lactam **(8)** is hydrolysed with one equivalent of lithium hydroxyde in a 1:1 mixture of THF and water. The mixture is stirred at room temperature for 1 hour. The crude mixture is extracted with ether and the resulting solution is poured into 10% citric acic aqueous solution and extracted with dichloromethane to yield the corresponding carboxylic acid **(9)**.

SUBSTITUTE SHEET

STEP 6

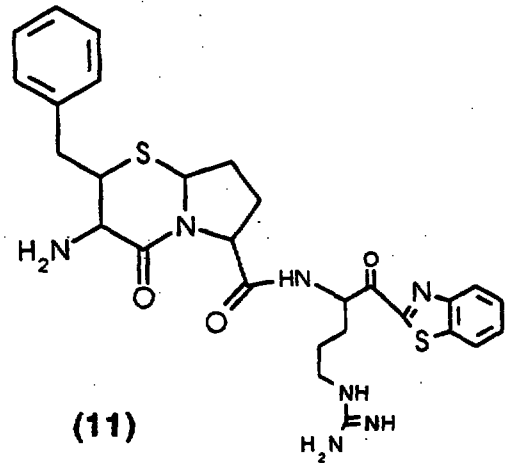


(9) (10)

The crude carboxylic acid (9) is coupled with benzythiazole keto arginine in DMF using BOP as the coupling reagent in the presence of diisopropylethylamine. Extraction with EtOAc gives a solid that is purified on silica gel to give the protected amide. The CBZ protecting group is removed with BBr_3 in dichloromethane at room temperature finally gives the bicyclic benzothiazole keto arginine inhibitors (10).

The following compounds are produced accordingly with the execption that the appropriate substitution of products were made in order to obtain the final compounds.

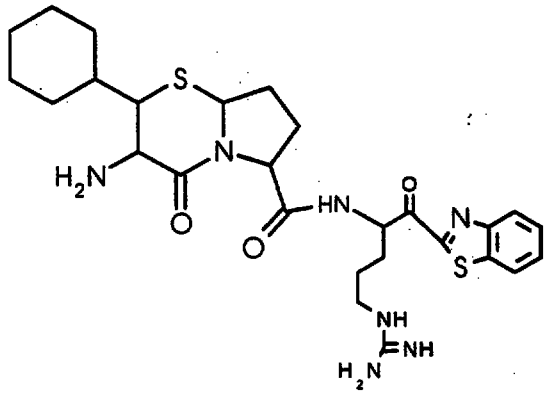
COMPOUND #11



(11)

SUBSTITUTE SHEET

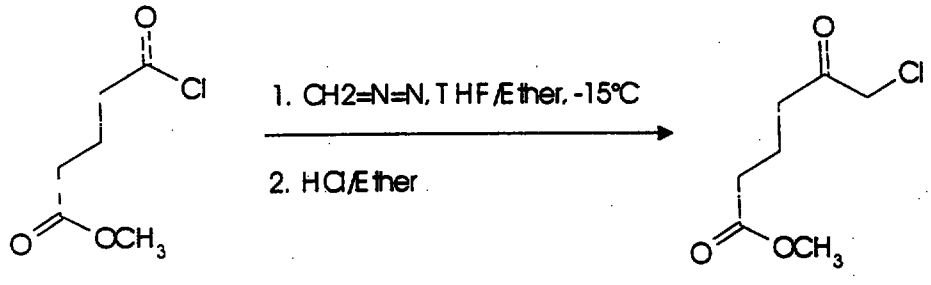
COMPOUND #12



(12)

EXAMPLE 8

STEP 1



1 2

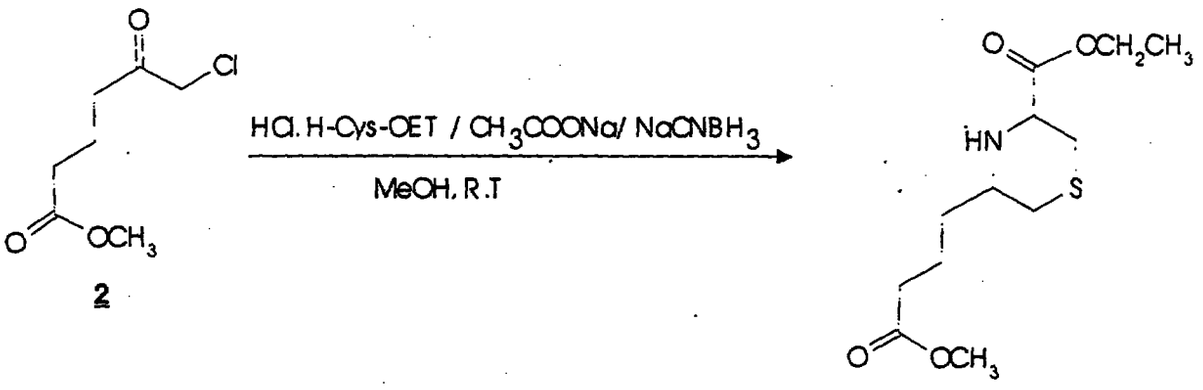
Commercially available glutaric acid monomethyl ester chloride (1) (20 ml, 0.144 mol) was disolved in 40 ml of dry tetrahydrofuran (THF) and cooled to -15°C. Excess diazomethane freshly prepared in 300 ml of Ether was introduced via cannula at -15°C to the solution. The mixture was left to warm up to room temperature overnight. Excess diazomethane was evacuated from the flask with a current of argon. To bring the reaction to completion, 75 ml of 1 N HCl in Ether was added at 0°C and left to warm up to room temperature for 5 hours. The volume of the solvent was reduced and then washed with 2x 5% $NaHCO_3$

SUBSTITUTE SHEET

dried over Na_2CO_3 and evaporated to give crude chloromethylketone (20.46 g , 79%) wich was used in the next step without further purification.

^1H NMR ($CDCL_3$, 400 MHz) d 1.16-1.2 (t,1H), 1.83-1.9 (m,2H), 2.27-2.35 (m,2H), 2.6-2.64(t,1H), 3.6 (s,3H), 4.04 (s,2H).

STEP 2



2 3

Crude chloromethylketone (2)(10.04 g, 56.15 mmol) was disolved in 300 ml of dry MeOH. Sodium acetate (2 eq, 9.21 g, 112.3 mmol) was added followed by L-Cysteine ethyl ester hydrochloride salt (1.3 eq, 13.55g, 72.98 mmol) and sodium cyanoborohydride (1.4 eq, 4.9 g, 78.59 mmol). The heterogeneous mixture was left to stir at room temperature for 2h30 min. 200 ml of methanol (MeOH) was then added to disolve all the solid and the pH was brought to 2 with 1N HCl .The mixture was then basified with saturated $NaHCO_3$ until pH= 8. MeOH was evaporated and the remaining aqueous solvent was washed with ethyl acetate and dichloromethane. Solvents were combined, dried over Na_2SO_4 and evaporated. The crude residue was purified by silica gel flash column chromatography using a gradient.of eluents ethyl acetate / hexane in the

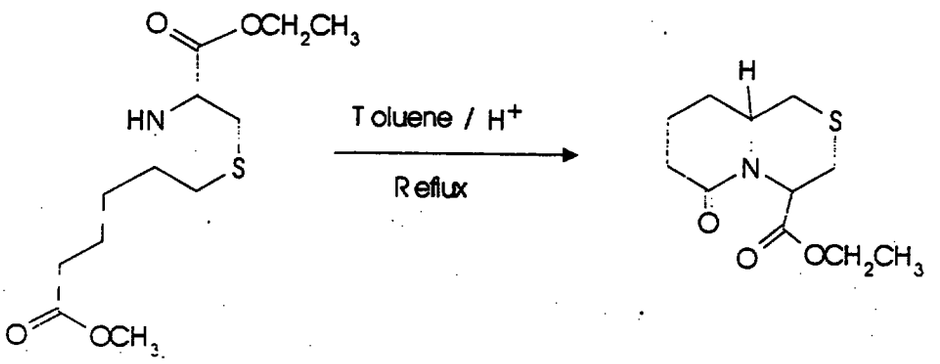
SUBSTITUTE SHEET

following ratios: (3:7, 5:5, 6:4, 7:3) giving cyclic compound (3).

^{1}H NMR ($CDCl_3$, 400MHz) of compound (3) d 1.21-1.27 (t, 3H, J=7.06 Hz), 1.41-1.48 (m, 2H), 1.65-1.73 (m, 2H), 2.28-2.39 (m, 4H), 2.57-2.63 (t, 1H, J=10.9), 2.72-2.76 (dd, 1H, J=10.7 Hz), 2.8-2.86 (m, 1H), 3.6-3.64 (d, 4H, .J=2.55 Hz), 3.63 (s, 3H), 4.13-4.2 (m, 2H)

^{13}C NMR ($CDCl_3$, 400 MHz) 13.078, 19.888, 28.326, 31.133, 32.741, 35.277, 50.462, 56.394, 59.149, 60.188, 69.713, 170.182, 172.52

STEP 4



3 4

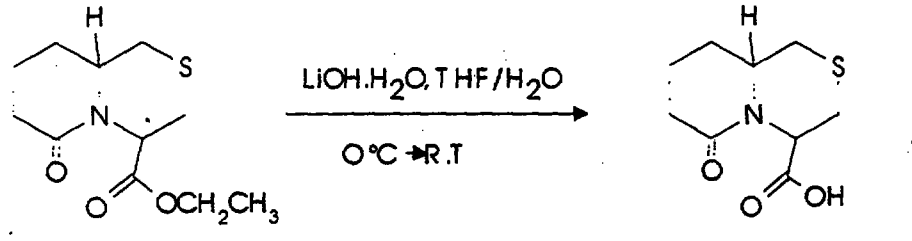
Cyclic compound (3) (913mg, 3.32 mmol) was disolved in 50 ml of dry Toluene. (1S)-(+)-10-Camphorsulfonic acid (92 mg, 0.39 mmol) was added and the mixture was left to reflux for 4 days. When all starting material was shown to be consumed (by TLC), the mixture was worked up by evaporation of solvent, dissolving residue in ethyl acetate and washing with 2 x 5 % $NaHCO_3$. The Ethyl acetate layer was dried over Na_2SO_4 and evaporated. The crude residue was purified by silica gel flash column chromatography using 60 % ETOAC / 40 %Hexane followed by

SUBSTITUTE SHEET

70 % ETOAC / 30 % Hexane giving 62.5% of Bicyclic compound (4).

^1H NMR ($CDCl_3$, 400MHz) of compound (4) d 1.27-1.31 (t, 3H, J=7 Hz), 1.5-1.6 (m, 1H), 1.72-1.87 (m, 2H), 2.02-2.1 (m, 1H), 2.33-2.46 (m, 2H), 2.52-2.59 (m, 2H), 2.83-2.88 (dd, 1H, J=14 , 4 Hz), 3.14-3.18 (d, 1H), 3.78-3.85 (m, 1H), 4.2-4.27 (q, 2H, J= 3.9 Hz), 5.9-5.92(t, 1H, J=3.4 Hz).

STEP 5



4 5

Bicyclic (4) (366mg, 1.5 mmol) was dissolved in 25 ml of THF and 5 ml H_2O Lihium hydroxide. monohydrate (1.1 eq, 7.05 mg, 1.68 mmol) was added in 2.3 ml of H_2O, at 0°C and the mixture was left to stirr at 0°C for 1 hr and at room temperature for 3 hrs. THF was then evaporated and the remaining aqueous mixture was acidified by addition of Citric acid until pH=2. Extraction of aqueous mixture with 2 x CH_2CL_2 and 2 x ETOAC, drying of combined organic layers with Na_2SO_4 and evaporation gave a crude residue wich was purified by silica gel flash column chromatography using 70 % ETOAC / 30 %Hexane followed by 4.7 % HOAC / Ethyl acetate giving the pure acid (5) in 54 % yield . 16 % of starting material(4) was recovered.

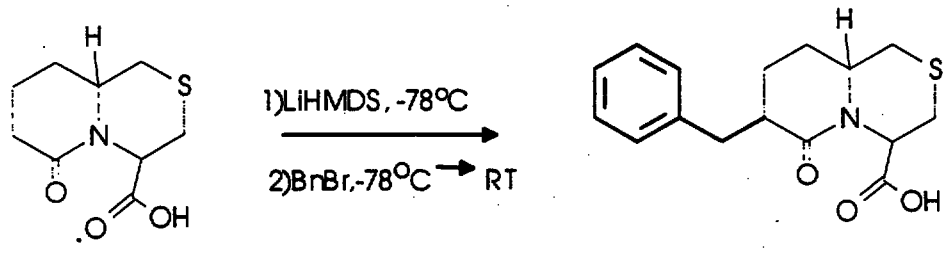
^1H NMR (MeOD, 400 MHz) of compound (5) d 1.57-1.69 (m, 1H), 1.70-1.80 (m, 1H), 1.81-1.89 (m, 1H), 2.05-2.12 (m, 1H), 2.35-2.5 (m, 2H), 2.51-2.66 (m, 2H), 2.86-

SUBSTITUTE SHEET

2.91 (dd, 1H, J=13.8, 4 Hz), 3.12-3.17 (d, 1H), 3.3-3.32 (m, 1H), 3.78-3.84 (m, 1H), 5.76-5.78(t, 1H, J=3.53 Hz).

^{13}C NMR (MeOD, 400 MHz) d 17.052, 27.07, 28.928, 31.382, 32.096, 51.016, 55.138, 170,088, 171.24

STEP 6

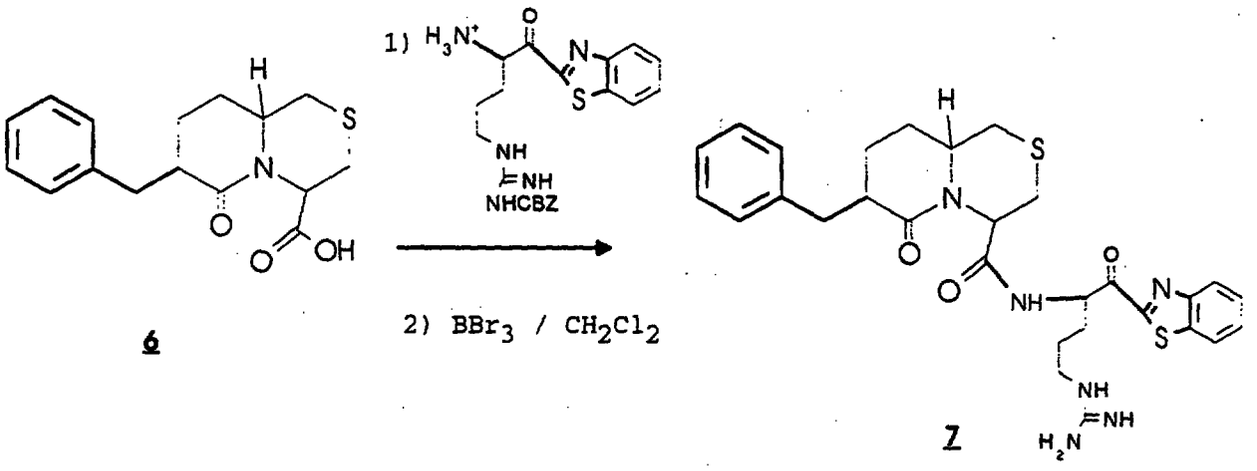


5 6

To a solution of lithium bis (trimethylsilyl) amide (5ml of 1M THF solution, 5mmol) in THF (10 ml) is added at -78°C a solution of the carboxylic acid (5) (500mg, 2.32 mmol). the resulting solution is stirred at -78°C for 1 hour. Benzyl bromide (0.26 ml, 2.22 mmol) is then added and the mixture is allowed to reach room temperature and stirred for 15 hours. The mixture is then poured into 10% HCl (50 ml) and extracted wiht diclhoromethane (4x 60ml). The combined organic phases are dried over $MgSO_4$ and the solvent remove by evaporation to yield to the crude alkylated amide (6).

SUBSTITUTE SHEET

STEP 7

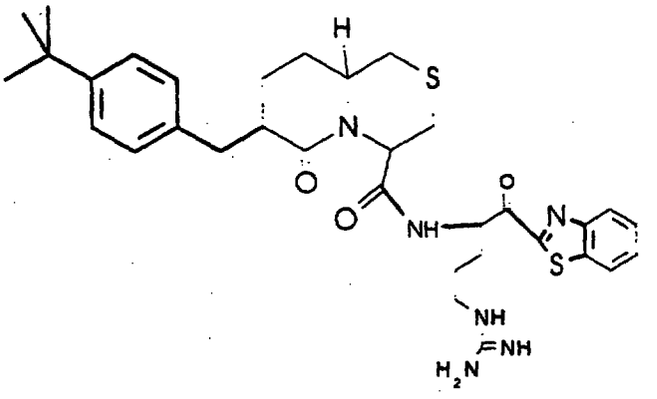


6 Z

The crude aklylated amide (6) is coupled with benzythiazole keto arginine in DMF using BOP as the coupling reagent in the presence of diisopropylethylamine. Extraction with EtOAc gives a solid that is purified on silica gel to give the protected amide. The CBZ protecting group is removed with BBr_3 in dichloromethane at room temperature finally gives the bicyclic benzothiazole keto arginine inhibitors (7).

The following compound is produced accordingly with the exeption that the appropriate substitution of products were made in order to obtain the final compounds.

COMPOUND #8



8

SUBSTITUTE SHEET

EXAMPLE 9

Determination of K_i Values for Heterocyclics

The affinity of inhibitors for thrombin was measured according to the procedures described in (DiMaio et al, J. Bio. Chem., 1990, 265:21698) Inhibition of amidolytic activity of human thrombin was 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 was 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 was calibrated using AMC. The reaction reached a steady-state within 3 minutes after mixing thrombin with the substrate and an inhibitor. The steady-state velocity was then measured for a few minutes. The compounds of this invention were also pre-incubated with thrombin for 20 minutes at room temperature before adding the substrate. The steady-state was 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 was 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™ , was used to estimate the kinetic parameters (K_i, V_{max} and K_i).

dTT assay

SUBSTITUTE SHEET

The fibrin clotting assay was performed in 50 mM Tris HCl buffer (pH 7.52 at 37 °C) containing 0.1 M NaCl and 0.1% poly(ethylene glycol) 8000 with 9.0 x 10-10 M (0.1 NIH unit/mL) and 0.03 % (w/v) of the final concentrations of human thrombin and bovine fibrinogen, respectively, as reported elsewhere (Szewczuk et al.,supra). The clotting time was plotted against the inhibitor concentrations and the IC_{5r} was estimated as the inhibitor concentration required to double the clotting time relative to the control. Results are summarized in Tables 1 and 2 below.

Fibrin Clot Assay

The fibrin clot assay was performed essentially as described by Krtenansky et al, FEBS, 1987, 211:10. A serial dilution of the inhibitor was prepared in 50 mM tris HCl buffer (pH7.8 at 23 °C) containing 0.1M NaCl and 0.1% (w/v) polyethylene glycol 8000. Human plasma (60µL, collected in 3.8% sodium citrate, blood/anticoagulant 9:1) was added to microtiter wells (microtiter plate, Falcon) containing 100µL of various inhibitor dilutions. The solution was mixed after which 50µL of human thrombin (1nM final conc.) was added and mixed for 15 seconds. The turbidity of the clot was immediately monitored by microplate autoreader (Dynateck MR 5000) at 405nm and recorded every 3 min. The maximal turbidity in the absence of inhibitors was reached within a 60 min. IC_i values were calculated at 30 minutes as the inhibitor concentration that gave half the optical density of the control.

Platelet Aggregation and Secretion

Rat blood was collected into ACD (6/1 v/v) by cardiac puncture. Suspensions of washed platelets were prepared as described by Ardlie et al, (Br. J. Haematol. 1970, 19:7

SUBSTITUTE SHEET

and Proc. Soc. Exp. Biol. Med., 1971, 136:1021). The final suspending medium was a modified Tyrode solution (NaCl 138mM, KCl 2.9mM, HEPES 20mM, NaH_2PO_4 0.42mM, $NaHCO_3$ 12mM, $CaCl_2$ 1mM, $MgCl_2$ 2mM, 0.1% glucose, 0.35% albumin, apyrase 1µL/mL pH 7.4). Platelet counts were adjusted to 5000,000/µL.

To permit measurement of the extent of release of the contents of the dense granules, the platelets were labelled in the first washing solution with ^{14}C-serotonin (5-HT) (1µCi/10mL of washing fluid) and release of ^{14}C-serotonin was determined as described in Holmsen et al, (Enzymology, 1989, 169:206). Inipramine (5µM final conc.) was added to present the reuptake of released serotonin.

Platelet aggregation was recorded at 37°C in an aggregometer (BioData PAP-4) at a stirring speed of 1,100 rpm by measuring the variations of light transmission. Percentage of aggregation was determined 3 min. after the addition of the stimulating agent (human thrombin 0.1IU/mL final conc.). Inhibitors were preincubated 1 minute at 37°C before addition of stimulating agent. IC_{50} values represent the concentration that was necessary to inhibit platelet aggregation or secretion to 50% of the control.

Arterial Thrombosis Model

$FeCl_2$ Induced Carotid Arterial Injury Model

The $FeCl_2$ induced injury to the carotid artery in rats was induced according to the method described by Kurz, K.D., Main, R.W., Sandusky, G.E., Thrombosis Research 60; 269-280, 1990 and Schumacher, W.A. et al. J. Pharmacology and Experimental Therapeutics 267; 1237-1242, 1993.

Male, Sprague-Dawley rats (375-410 g) were anesthetized with urethane (1500 mg\kg ip). Animals were laid on a

SUBSTITUTE SHEET

37°C heating pad. The carotid artery was exposed through a midline cervical incision. Careful blunt dissection was used to isolate the vessel from the carotid sheath. Using forceps, the artery was lifted to provide sufficient clearance to insert two small pieces of polyethylene tubing (PE-205) underneath it. A temperature probe (Physitemp MT23/3) was placed between one of the pieces of tubing and the artery. Injury was induced by topical application on the carotid artery above the temperature probe of a small disc (3 mm dia.) of Whatman No.1 filter paper previously dipped in a 35% solution of $FeCl_3$. The incision area was covered with aluminum foil in order to protect the $FeCl_3$ from degradation by light. The vessel temperature was monitored for 60 minutes after application of $FeCl_3$ as an indication of blood flow. Vessel temperature changes were recorded on a thermister (Cole-Palmer Model 08533-41).

The time between the $FeCl_3$ application and the time at which the vessel temperature decreased abruptly (>2.4°C) was recorded as the time to occlusion of the vessel. Inhibitor compounds were given as an iv bolus (mg/kg) followed immediately by an iv infusion (µg/kg/min. via femoral vein). The dose of inhibitor needed to double the time to occlusion in comparison to control animals in which injury was induced in the absence of inhibitor was determined.

SUBSTITUTE SHEET

Table 1

cmpd	Ki μM*	Antiplatelet activity μM		dTT IC_{50} μM	Plasma fibrin clot assay IC_{50} μM
		Aggregation	5-HT Secretion		
0005	4	ND	ND	47	>450
0010	4.6	21	19	89.5	>450
0015	16	>100	>100	162	>450
0020	2.2	18	14.2	22	>450
0025	53	>100	>100	>625	>450
0030	8.6	>100	>100	67	320
0035	34	>100	>100	319	>450
0040	19	>100	>100	207.5	>450
0045	74	ND	ND	415	>450
0050	62	ND	ND		>450
0065	32.7	47.5	52	42	200
0070	4.4	22	2.1	25	78
0080	0.048	0.4	0.38	0.375	ND
0090	0.031	ND	ND	0.33	ND

SUBSTITUTE SHEET

0095	26	ND	ND		
0100	19	ND	ND	165	ND

*suspension of washed platelets from rats

° Inhibitory dissociation constant for human α-thrombin

SUBSTITUTE SHEET

Table 2

Compound	ki (nM)	dTT (nM)	Route ivb+inf	M.O.T (min)+/-sem
0220	18			
0225	550 235		0.75-50	23+/-7
0245	5 8		0.5-30 0.75-50	27+/-3 22.6+/-2.6
0250	40	350	0.25-20 0.75-50	23+/-8 22+/-3
0295a	1500		0.75-50	20+/-1
0295b		5000 520	0.75-50	19+/-2.7
0240	18		0.75-50	17+/-2.6
0210	8		0.75-50	20.13+/-3.4
0255	500			
0260	16		0.75-50	14.83+/-0.2
0305a	220			
0305b	12000			
0265a	4		0.75-50	21.5+/-10
0265b	18		0.75-50	14.83+/-2.3
0285	10 150		0.75-50	11.33+/-1.34
0315a+b	45			
0315b	10		0.75-50	30.33+/-8.4
0335	25	138	0.75-50 0.5-30 0.25-20	45.8+/-14.2 41.5+/-7.27 27.5+/-11,3
0340	0.6		0.25-20 0.75-50	36+/-9,6 42.25+/-11,9
0345	2		0.75-50	50+/-5.86
0915	1600		0.75-50	15+/-1,3
0935	120			

SUBSTITUTE SHEET

Table 2 (continued)

Compound	Ki (nM)	dTT (nM)	Route ivb+inf	M.O.T (min)+/-sem
0925a+b	10		0.75-50	19.6+/-0.2
0925b	30			
0925a	7		0.75-50	20.3+/-3.5
0940a	16		0.75-50	15.2+/-0.82
0940b	160			
0950a	150			
0950b	1000			

a = early eluting on RP HPLC single isomer

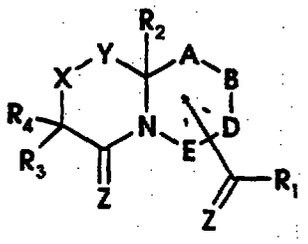
b = late eluting on RP HPLC single isomer

a + b = mixture

SUBSTITUTE SHEET

WE CLAIM:

1. A compound of formula (I):



(I)

wherein:

A is selected from $(CH\text{-}R_8)_{0-1}$, S, SO, SO_2, O and NR_8 wherein R_8 is hydrogen, C_{1-6} alkyl optionally interupted with 1 or 2 heteroatoms; C_{6-10} aryl, C_{3-7} 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_{1-6} alkyl provided that when A is S, SO, SO_2, O, or NR_8, then B is CR_6R_7;

D is selected from $(CH\text{-}R_9)_{0-2}$ wherein R_9 is hydrogen, C_{1-6} 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 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, $N\text{-}R_5$ and $CH\text{-}R_5$ provided that when X is $N\text{-}R_5$ then Y is $CH\text{-}R_5$ or O, and when X is O then Y is $CH\text{-}R_5$;

Z is selected from O, S and H_2;

R_1 is an arginyl moiety or an analog or derivative thereof optionally substituted with an amino acid, a peptide or a heterocycle;

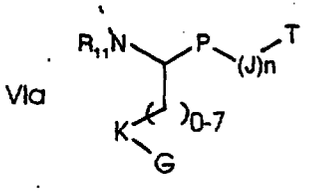
R_2 is selected from H and C_{1-6} alkyl optionally substituted with C_6 aryl, a 6 member heterocycle or a C_{3-7} cycloalkyl ring;

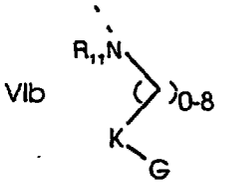
SUBSTITUTE SHEET

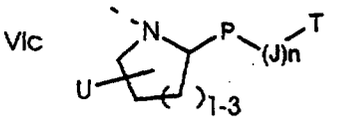
R_3 is selected from H, NR_6R_7 and C_{1-6} alkyl; and

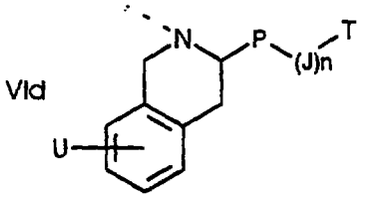
R_4 and R_5 are independently selected from H; NR_6R_7; C_{6-10} aryl or C_{3-7} cycloalkyl optionally substituted with C_{1-6} alkyl; C_{1-10} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_6R_7 or a C_{6-10} aryl, heterocycle or C_{3-7} cycloalkyl group optionally substituted with halogen, hydroxyl, C_{1-6} alkyl; an amino acid side chain; and a hydrophobic group.

2. A compound according to claim 1, wherein R_1 is one of formula VIa to VId:









wherein:

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

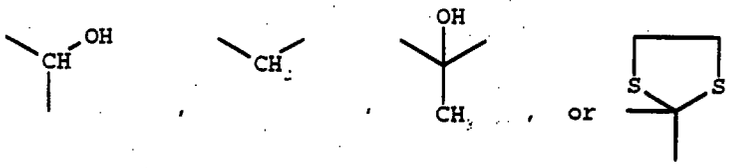
K is a bond or -NH-;

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_5 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 $-NH-C(NH)-NH_2$;

P is a bond, -C(O)- or a bivalent group:

SUBSTITUTE SHEET

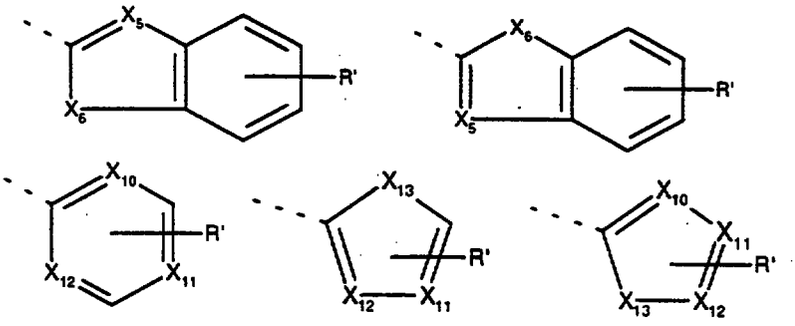


J is C_{1-6} alkylene optionally substituted with OH, NH_2 and C_{1-6} alkyl and optionally interrupted by a heteroatom selected from O, S and N;

n is 0 or 1; and

T is H, OH, amino, a peptide chain, C_{1-10} alkyl, C_{1-10} alkoxy, C_{7-9} aralkyl, or heterocycle optionally substituted.

3. A compound according to claim 2, wherein 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_{1-6} alkyl, or C_{5-7} aryl;

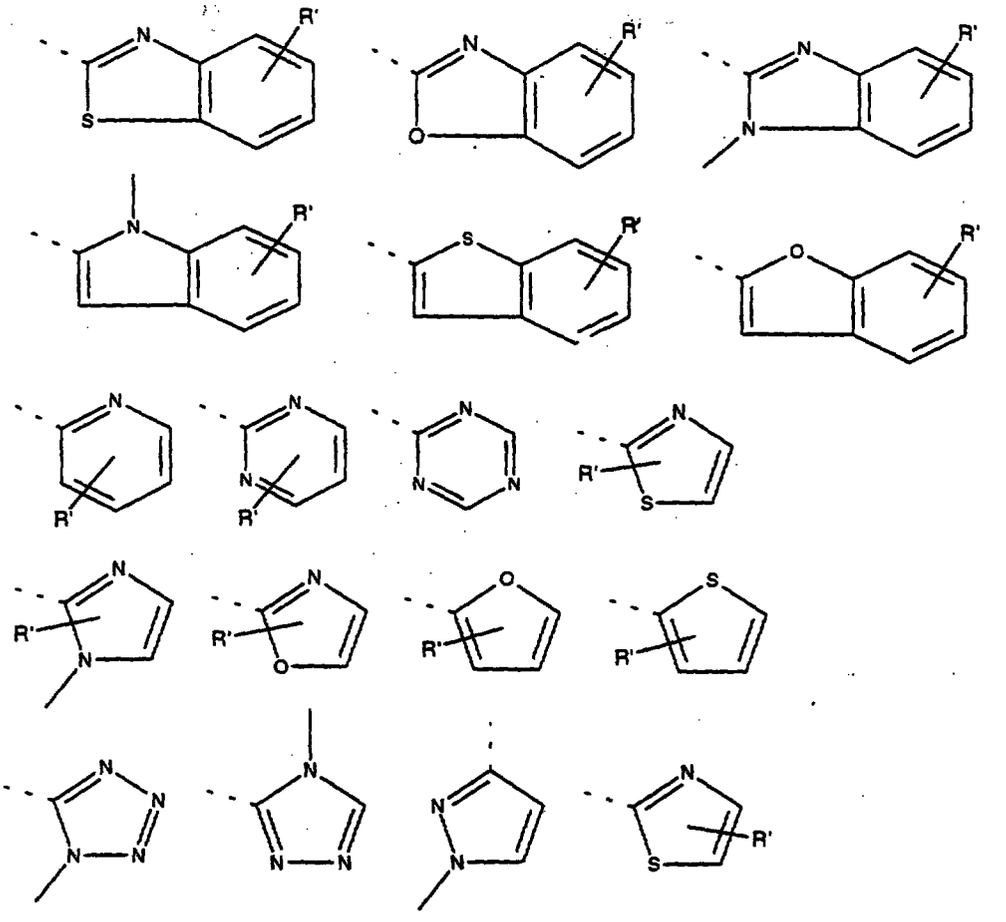
X_6 and X_{13} are each independently selected from the group consisting of C, O, N, S, N-X_7, or CH-X_7; and

R' is hydrogen, C_{1-10} alkyl optionally carboxyl substituted, carboxyl, -C_{1-10} alkyl-CO_2-C_{1-10} alkyl, C_{7-9} aralkyl, C_{3-7} cycloalkyl, aryl or an aromatic heterocycle.

4. A compound according to claim 3, wherein T is selected from the group consisting of:

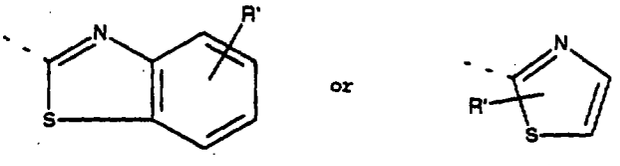
This Sheet Has Been Replaced

SUBSTITUTE SHEET



wherein R' is hydrogen, C_{1-16} alkyl optionally carboxyl substituted, carboxyl, -C_{0-16} alkyl-CO_2-C_{1-16} alkyl, C_{7-12} aralkyl, C_{3-8} cycloalkyl, aryl or an aromatic heterocycle.

5. A compound according to claim 4, wherein T is selected from:



wherein **R'** is hydrogen, C_{1-16} alkyl optionally carboxyl substituted, carboxyl, -C_{0-16} alkyl-CO_2-C_{1-16} alkyl, C_{7-12} aralkyl, C_{3-8} cycloalkyl, aryl or an aromatic heterocycle.

6. A compound according to claim 1, wherein one of R_4 and R_5 is a hydrophobic group selected from C_{7-22} alkyl, C_{7-22}

SUBSTITUTE SHEET

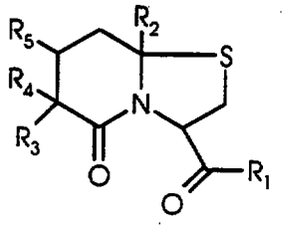
alkenyl or C_{2-20} alkynyl optionally interrupted by a carbonyl group, C_{6-14} aryl, C_{3-7} cycloalkyl, C_{6-20} aralkyl, C_{6-12} cycloalkyl substituted C_{1-20} alkyl, wherein the aliphatic portion is optionally interrupted by a carbonyl group and the ring portion is optionally substituted with C_{1-4} alkyl; and a hydrophobic amino acid side chain.

7. A compound according to claim 6, wherein R_3 is H.

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

9. A compound according to claim 1, wherein R_5 is H.

10. A compound of the formula (VII):



wherein

R_1 is an arginyl moiety or an analog or derivative thereof optionally substituted with an amino acid, a peptide or a heterocycle;

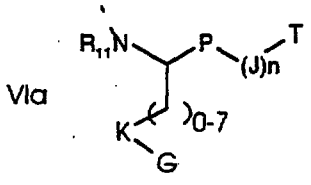
R_2 is H or C1-6 alkyl;

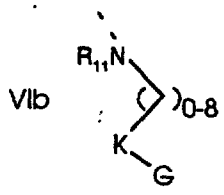
R_3 is selected from H, NR_6R_7 and C_{1-4} alkyl; and

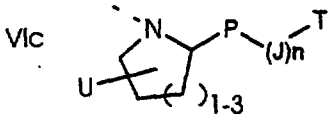
R_4 and R_5 are independently selected from H; NR_6R_7; C_{6-14} aryl or C_{3-7} cycloalkyl optionally substituted with C_{1-4} alkyl; C_{1-20} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_6R_7 or a C_{6-14} aryl, heterocycle or C_{3-7} cycloalkyl group optionally substituted with halogen, hydroxyl, C_{1-4} alkyl; an amino acid side chain; and a hydrophobic group.

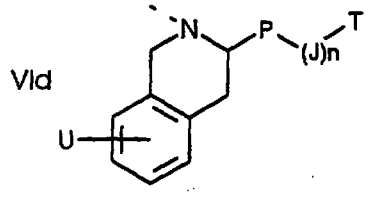
SUBSTITUTE SHEET

11. A compound according to claim 10, wherein R_1 is one of formula VIa to VId:









wherein:

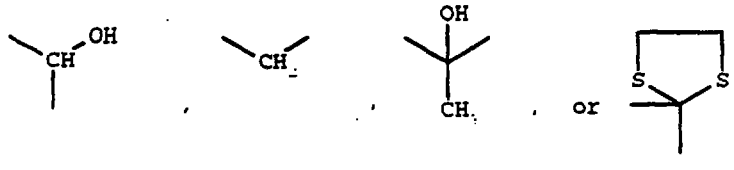
R_{11} is hydrogen or C_{1-6} alkyl;

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_{5-6} 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 $-NH-C(NH)-NH_2$;

P is a bond, -C(O)- or a bivalent group:



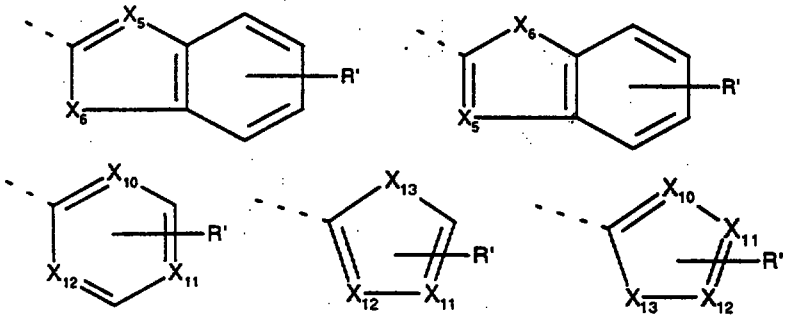
J is C_{1-6} alkylene optionally substituted with OH, NH_2 and C_{1-6} alkyl and optionally interrupted by a heteroatom selected from O, S and N;

n is 0 or 1; and

T is H, OH, amino, a peptide chain, C_{1-10} alkyl, C_{1-10} alkoxy, C_{7-12} aralkyl, or heterocycle optionally substituted.

SUBSTITUTE SHEET

12. A compound according to claim 11, wherein 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_{5-7} 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;

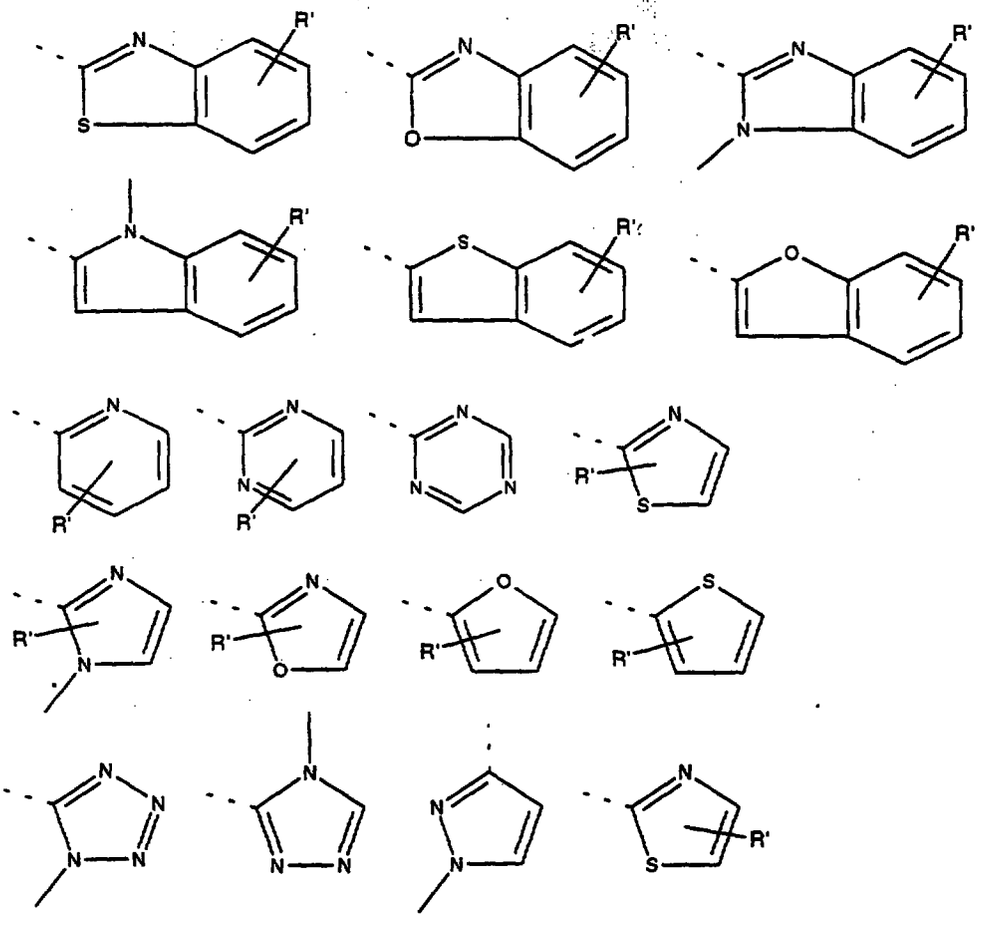
R' is hydrogen, C_{1-10} alkyl optionally carboxyl substituted, carboxyl, -C_{0-8} alkyl-CO_2-C_{1-10} alkyl, C_{6-20} aralkyl, C_{3-7} cycloalkyl, aryl or an aromatic heterocycle.

13. A compound according to claim 12, wherein T is selected from the group consisting of:

* C L M S *

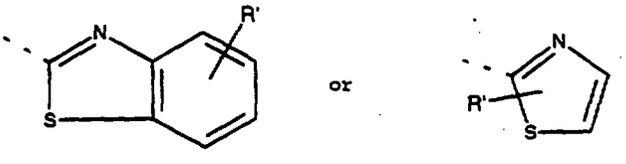
This Sheet Has Been Replaced

SUBSTITUTE SHEET



and **R'** is hydrogen, C_{1-10} alkyl optionally carboxyl substituted, carboxyl, $-C_{0-10}$ alkyl-CO_2-C_{1-10} alkyl, C_{7-} aralkyl, C_{3-} cycloalkyl, aryl or an aromatic heterocycle.

14. A compound according to claim 13, wherein T is selected from:



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

15. A compound according to claim 10, wherein R_2 and R_3 are H.

SUBSTITUTE SHEET

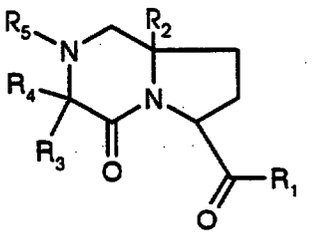
16. A compound according to claim 10, wherein R_4 is C_{1-1} alkyl optionally interupted with a heteroatom or a carbonyl, and optionally substituted with a C_{6-1} aromatic, C_{3-} cycloalkyl or heterocycle ring wherein the ring is optionally substituted with CF_3 or oxo.

17. A compound according to claim 10, wherein R_5 is H.

18. A compound according to claim 12, wherein:
R_2 is H;
R_4 is C_{1-1} alkyl optionally interupted with a heteroatom or a carbonyl, and optionally substituted with a C_{6-1} aromatic, C_{-} cycloalkyl or heterocycle ring wherein the ring is optionally substituted with CF_3 or oxo; and
R_5 is H.

19. A compound according to claim 10, selected from:
0085 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido (propylcarbo methoxy ketoarginine); and
0105 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo [3,2-a]pyridine-3R-carboxamido (α-benzothiozolo keto arginine).

20. A compound according to claim 1, of formula (VIII):



wherein

SUBSTITUTE SHEET

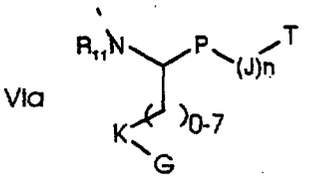
R_1 is an arginyl moiety or an analog or derivative thereof optionally substituted with an amino acid, a peptide or a heterocycle;

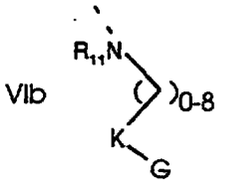
R_2 is H or C1-6 alkyl;

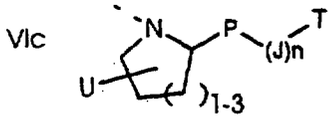
R_3 is selected from H, NR_6R_7 and C_{1-6} alkyl; and

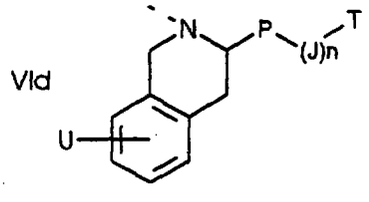
R_4 and R_5 are independently selected from H; NR_6R_7; C_{6-10} aryl or C_{3-7} cycloalkyl optionally substituted with C_{1-4} alkyl; C_{1-10} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_6R_7 or a C_{6-10} aryl, heterocycle or C_{3-7} cycloalkyl group optionally substituted with halogen, hydroxyl, C_{1-4} alkyl; an amino acid side chain; and a hydrophobic group.

21. A compound according to claim 20, wherein R_1 is one of formula VIa to VId:









wherein:

R_{11} is hydrogen or C_{1-4} alkyl;

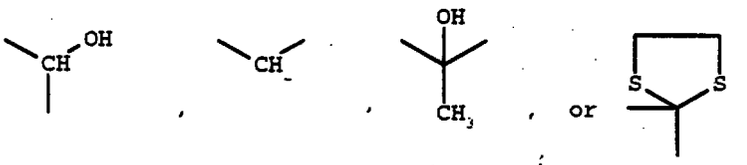
K is a bond or -NH-;

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_3 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;

SUBSTITUTE SHEET

P is a bond, -C(O)- or a bivalent group:

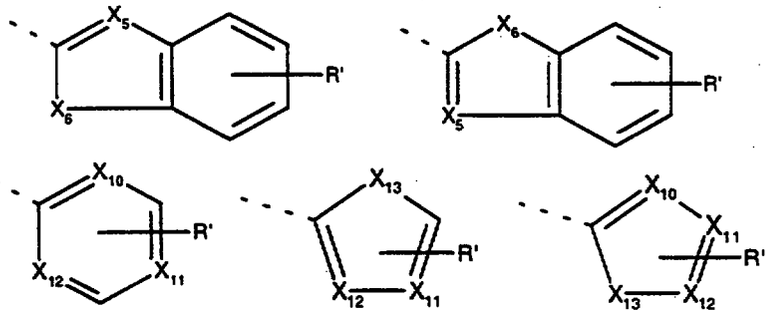


J is C_{1-6} alkylene optionally substituted with OH, NH_2 and C_{1-6} alkyl and optionally interrupted by a heteroatom selected from O, S and N;

n is 0 or 1; and

T is H, OH, amino, a peptide chain, C_{1-15} alkyl, C_{1-15} alkoxy, C_{7-12} aralkyl, or heterocycle optionally substituted.

22. A compound according to claim 21, wherein 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_{1-6} alkyl, or C_{5-6} aryl;

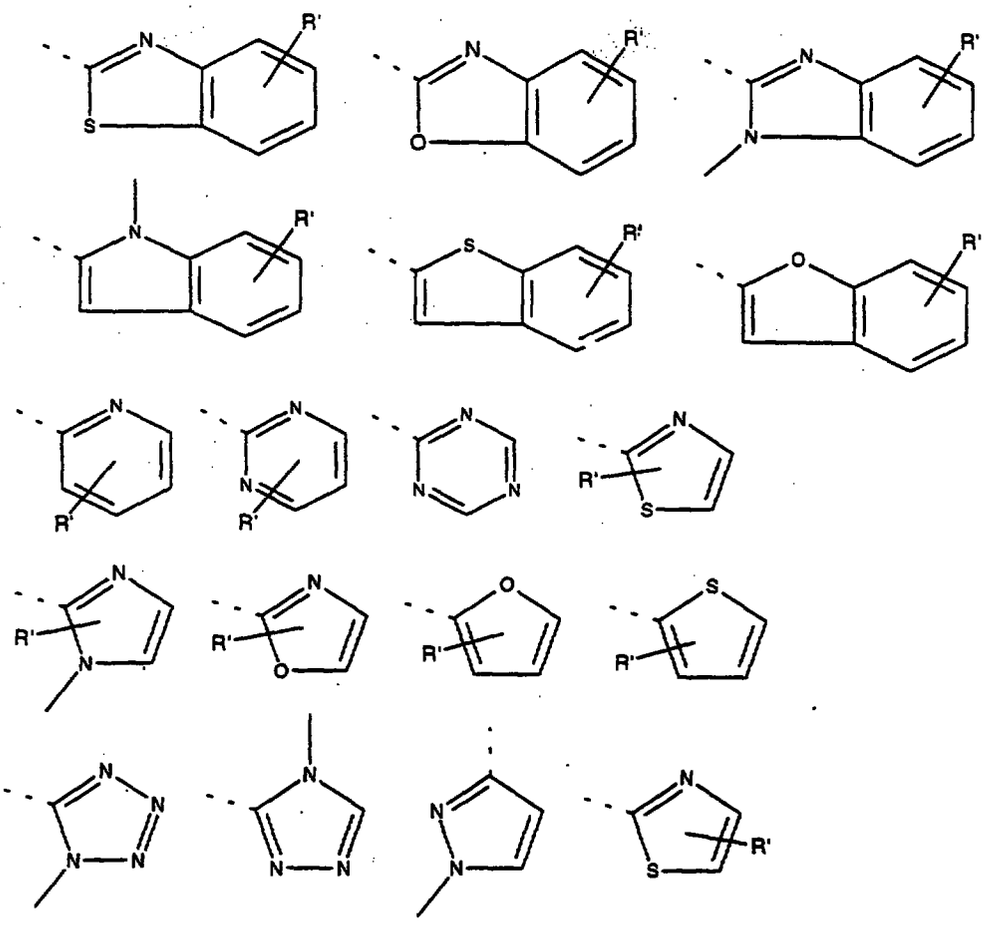
X_6 and X_{13} are each independently selected from the group consisting of C, O, N, S, N-X_7, or CH-X_7;

R' is hydrogen, C_{1-15} alkyl optionally carboxyl substituted, carboxyl, -C_{0-15} alkyl-CO_2-C_{1-6} alkyl, C_{7-12} aralkyl, C_{3-8} cycloalkyl, aryl or an aromatic heterocycle.

23. A compound according to claim 22, wherein T is selected from the group consisting of:

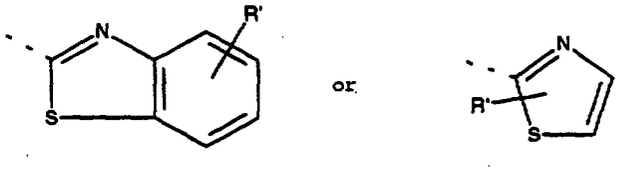
This Sheet Has Been Replaced

SUBSTITUTE SHEET



and **R'** is hydrogen, C_{1-10} alkyl optionally carboxyl substituted, carboxyl, $-C_{0-3}$ alkyl-CO_2-C_{1-3} alkyl, C_{7-9} aralkyl, C_{3-7} cycloalkyl, aryl or an aromatic heterocycle.

24. A compound according to claim 23, wherein T is selected from:



and **R'** is hydrogen, C_{1-10} alkyl optionally carboxyl substituted, carboxyl, $-C_{0-3}$ alkyl-CO_2-C_{1-3} alkyl, C_{7-9} aralkyl, C_{3-7} cycloalkyl, aryl or an aromatic heterocycle.

25. A compound according to claim 20, wherein R_2 and R_3 are both H.

SUBSTITUTE SHEET

26. A compound according to claim 20, wherein R_4 is H or C_{1-6} alkyl substituted with COOH.

27. A compound according to claim 20, wherein R_2, R_3 and R_4 are H and R_5 is C_{1-10} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_6R_7 or a C_{6-10} aryl, heterocycle or C_{3-7} cycloalkyl group optionally substituted with halogen, hydroxyl or C_{1-6} alkyl.

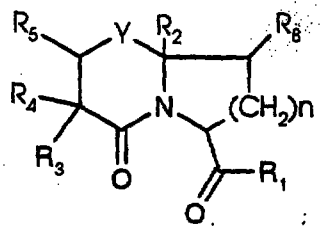
28. A compound according to claim 22, wherein:
R_2, R_3 and R_4 are H; and
R_5 is C_{1-10} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_6R_7 or a C_{6-10} aryl, heterocycle or C_{3-7} cycloalkyl group optionally substituted with halogen, hydroxyl or C_{1-6} alkyl.

29. A compound according to claim 20, selected from:
0345 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(5-methyl-thiazole-2-carbonyl)-butyl]-amide; and0340 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide.

30. A compound according to claim 1, of formula (IX):

This Sheet Has Been Replaced

SUBSTITUTE SHEET



wherein

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

R_1 is an arginyl moiety or an analog or derivative thereof optionally substituted with an amino acid, a peptide or a heterocycle;

R_2 is H or C1-6 alkyl;

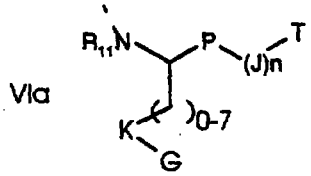
R_3 is selected from H, NR_6R_7 and C_{1-6} alkyl; and

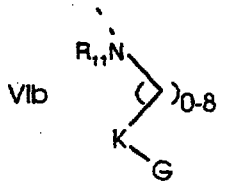
R_4 and R_5 are independently selected from H; NR_6R_7; C_{6-10} aryl or C_{3-7} cycloalkyl optionally substituted with C_{1-6} alkyl; C_{1-16} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_6R_7 or a C_{6-10} aryl, heterocycle or C_{3-7} cycloalkyl group optionally substituted with halogen, hydroxyl, C_{1-6} alkyl; an amino acid side chain; and a hydrophobic group;

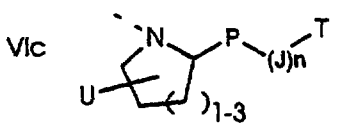
R_8 is hydrogen, C_{1-6} alkyl optionally interupted with 1 or 2 heteroatoms; C_{6-10} aryl, C_{3-7} cycloalkyl or heterocyclic ring or a hydrophobic group; and

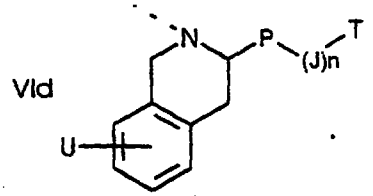
n is 1 or 2;

31. A compound according to claim 30, wherein R_1 is one of formula VIa to VId:









SUBSTITUTE SHEET

wherein:

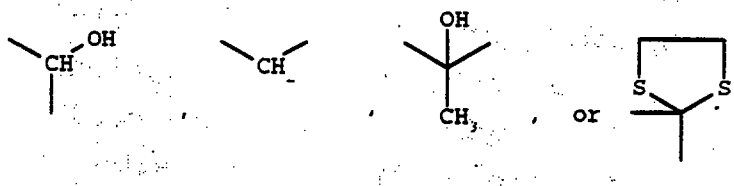
R_{11} is hydrogen or C_{1-6} alkyl;

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 $-NH-C(NH)-NH_2$;

P is a bond, -C(O)- or a bivalent group:

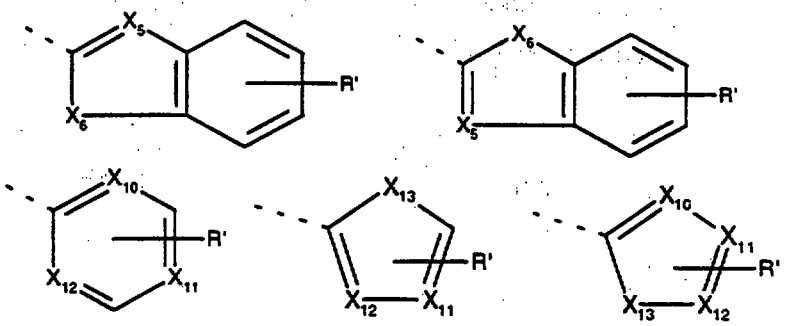


J is C_{1-6} alkylene optionally substituted with OH, NH_2 and C_{1-6} alkyl and optionally interrupted by a heteroatom selected from O, S and N;

n is 0 or 1; and

T is H, OH, amino, a peptide chain, C_{1-10} alkyl, C_{1-10} alkoxy, C_{6-20} aralkyl, or heterocycle optionally substituted.

32. A compound according to claim 31, wherein T is a heterocycle selected from the group consisting of:



wherein

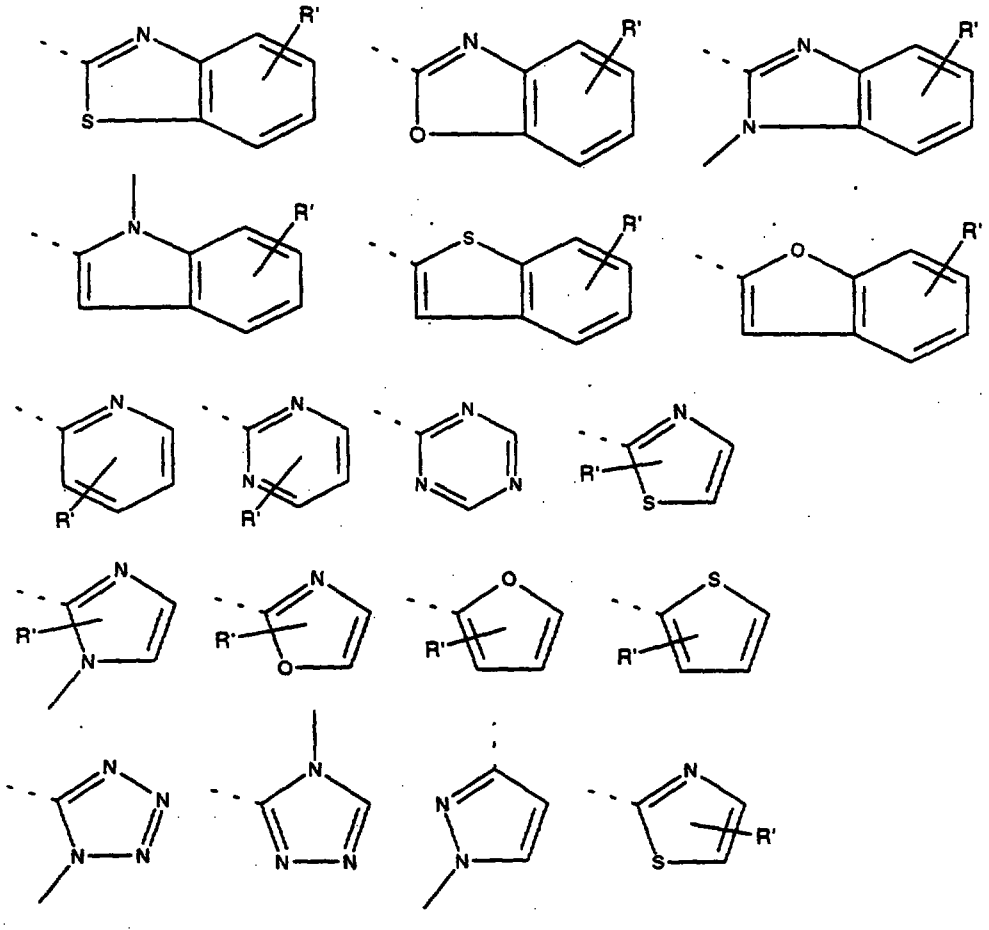
X_5, X_{10}, X_{11} and X_{12} are each independently selected from the group consisting of N, or C-X_7 where X_7 is hydrogen, C_{1-4} alkyl, or C_{5-6} aryl;

This Sheet Has Been Replaced

SUBSTITUTE SHEET

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.

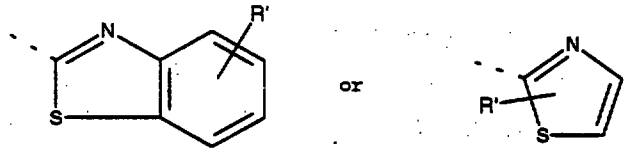
33. A compound according to claim 32, wherein T is selected from the group consisting of:



and **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.

34. A compound according to claim 33, wherein T is selected from:

SUBSTITUTE SHEET



and R' is hydrogen, C_{1-10} alkyl optionally carboxyl substituted, carboxyl, $-C_{0-10}$ alkyl-CO_2-C_{1-10} alkyl, C_{6-20} aralkyl, C_{3-7} cycloalkyl, aryl or an aromatic heterocycle.

35. A compound according to claim 30, wherein R_2 and R_3 are both H.

36. A compound according to claim 30, wherein R_4 is H, NR_6R_7 or C_{1-10} alkyl substituted COOH.

37. A compound according to claim 30, wherein R_5 is C_{6-10} aryl, C_{6-20} aralkyl, or C_{1-10} alkyl substituted with C_{3-7} cycloalkyl.

38. A compound according to claim 32, wherein
n is 1;
R_2, R_3 and R_4 are H; and
R_5 is C_{6-10} aryl, C_{6-20} aralkyl, or C_{1-10} alkyl substituted with C_{3-7} cycloalkyl.

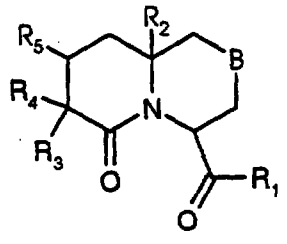
39. A compound according to claim 30, selected from:

0890 3-Amino-4-oxo-2-phenyl-hexahydro-pyrrolo[2,1-b][1,3]thiazine-6-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide;

0895 3-Amino-2-benzyl-4-oxo--hexahydro-pyrrolo[2,1-b][1,3]thiazine-6-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide; and

0900 3-Amino-2-cyclohexyl-4-oxo-hexahydro-pyrrolo[2,1-b][1,3]thiazine-6-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide.

40. A compound according to claim 1, of formula (X):



wherein

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

R_1 is an arginyl moiety or an analog or derivative thereof optionally substituted with an amino acid, a peptide or a heterocycle;

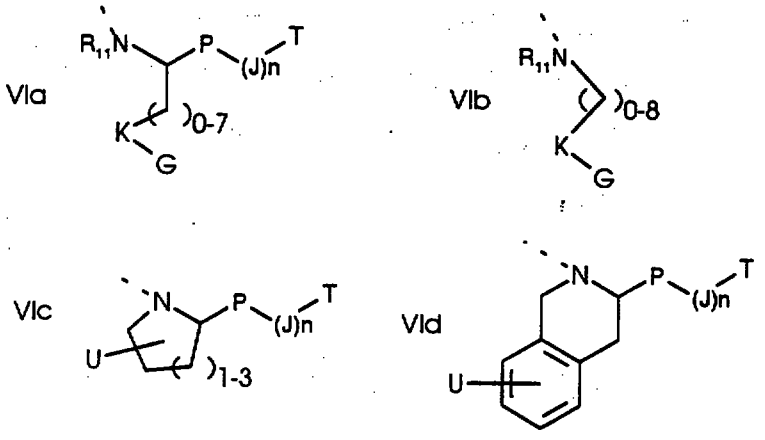
R_2 is H or C1-6 alkyl;

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; C_{6-10} aryl or C_{3-7} cycloalkyl optionally substituted with C_{1-6} alkyl; C_{1-10} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_6R_7 or a C_{6-10} 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.

41. A compound according to claim 40, wherein R_1 is one of formula VIa to VId:

SUBSTITUTE SHEET



wherein:

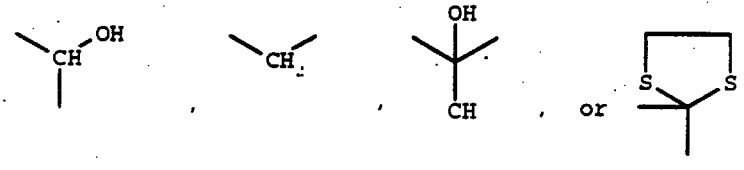
R_{11} is hydrogen or C_{1-4} alkyl;

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_5 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 $-NH-C(NH)-NH_2$;

P is a bond, -C(O)- or a bivalent group:



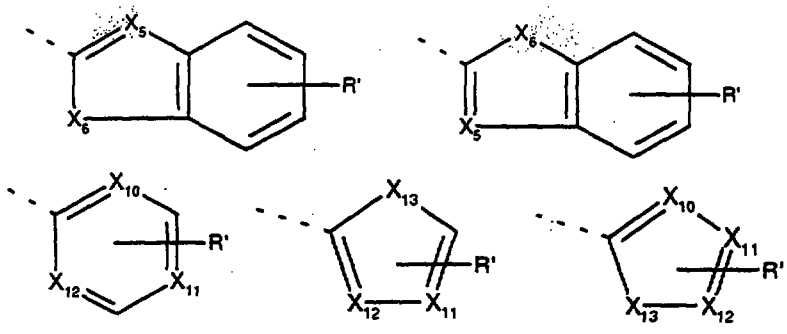
J is C_{1-4} alkylene optionally substituted with OH, NH_2 and C_{1-4} alkyl and optionally interrupted by a heteroatom selected from O, S and N;

n is 0 or 1; and

T is H, OH, amino, a peptide chain, C_{1-10} alkyl, C_{1-4} alkoxy, C_{7-9} aralkyl, or heterocycle optionally substituted.

42. A compound according to claim 41, wherein T is a heterocycle selected from the group consisting of:

SUBSTITUTE SHEET



wherein

X_5, X_{10}, X_{11} and X_{12} are each independently selected from the group consisting of N, or C-X_n where X_n is hydrogen, C_{1-6} alkyl, or C_{5-8} aryl;

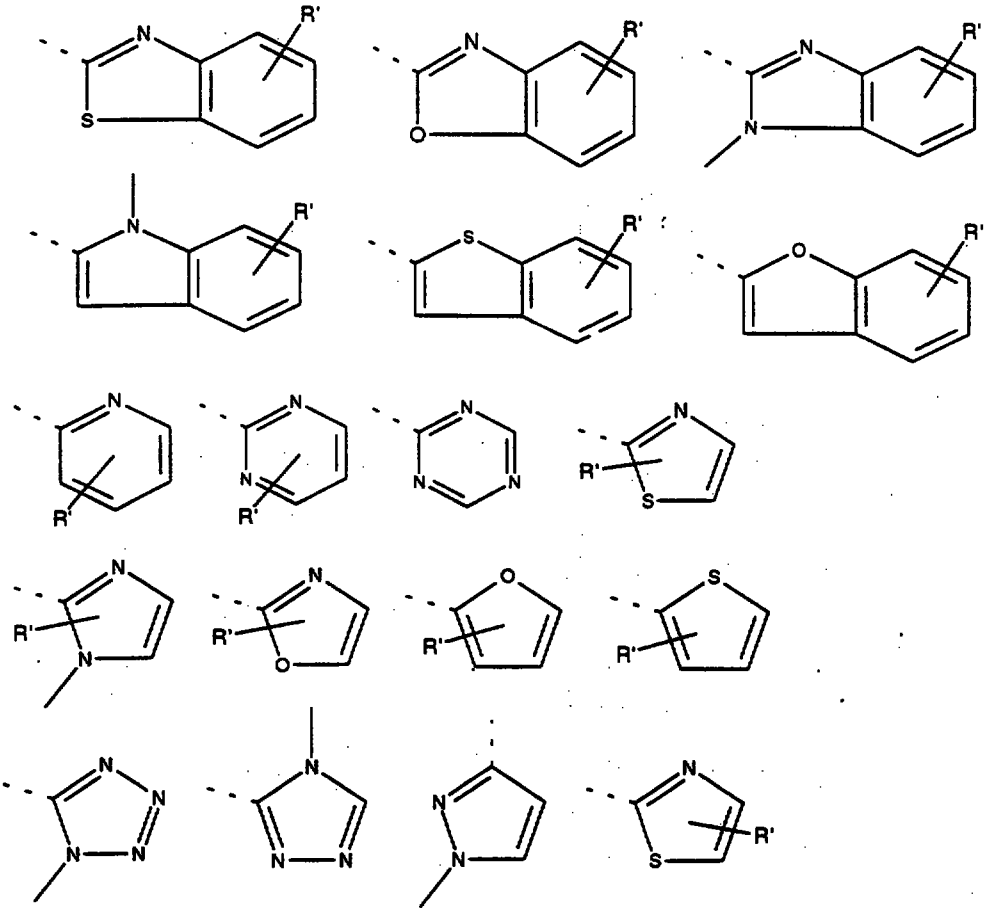
X_6 and X_{13} are each independently selected from the group consisting of C, O, N, S, N-X_n, or CH-X_n;

R' is hydrogen, C_{1-10} 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.

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

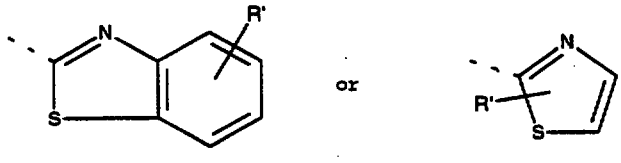
* C L M S *

This Sheet Has Been Replaced



and **R'** is hydrogen, C_{1-12} alkyl optionally carboxyl substituted, carboxyl, $-C_{0-12}$ alkyl-CO_2-C_{1-16} alkyl, C_{6-20} aralkyl, C_{3-8} cycloalkyl, aryl or an aromatic heterocycle.

44. A compound according to claim 43, wherein T is selected from:



and **R'** is hydrogen, C_{1-12} alkyl optionally carboxyl substituted, carboxyl, $-C_{0-12}$ alkyl-CO_2-C_{1-12} alkyl, C_{7-20} aralkyl, C_{3-8} cycloalkyl, aryl or an aromatic heterocycle.

45. A compound according to claim 40, wherein R_2 and R_3 are both H.

SUBSTITUTE SHEET

46. A compound according to claim 40, wherein R_4 is C_{1-10} alkyl substituted with C_{6-10} aryl optionally substituted with C_{1-10} alkyl.

47. A compound according to claim 40, wherein R_5 is H.

48. A compound according to claim 42, wherein
B is S;
R_2, R_3 and R_5 are H; and
R_4 is C_{1-10} alkyl substituted with C_{6-10} aryl optionally substituted with C_{1-10} alkyl.

49. A compound according to claim 40, selected from:
925 7-Benzyl-6-oxo-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide; and940 6-Oxo-7-phenethyl-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide.

50. 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.

51. A method according to claim 50, wherein said thrombotic disorder is venous thrombosis.

52. A method according to claim 50, wherein said thrombotic disorder is a pulmonary embolism.

53. A method according to claim 50, wherein said thrombotic disorder is arterial thrombosis.

* C L M S *

This Sheet Has Been Replaced

SUBSTITUTE SHEET

54. A method according to claim 50, wherein said thrombotic disorder is myocardial infarction.

55. A method according to claim 50, wherein said thrombotic disorder is cerebral infarction.

56. A process for producing a compound according to claim 1.

57. A process for producing a compound according to any one of claims 10, 20, 30 or 40.

SUBSTITUTE SHEET