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(54) Title: ENDOTHELIN ANTAGONISTS

(57) Abstract

Novel antagonists of endothelin are described, as well as methods for the preparation and pharmaceutical compositions of the same, which are useful in controlling hypertension, myocardial infarction, metabolic, endocrinological, and neurological disorders, congestive heart failure, endotoxic shock, subarachnoid hemorrhage, arrythmias, asthma, acute renal failure, preeclampsia, and diabetes.

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ENDOTHELIN ANTAGONISTS

BACKGROUND OF THE INVENTION

The present invention relates to novel antagonists of endothelin useful as pharmaceutical agents, to methods for their production, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment. More particularly, the novel compounds of the present invention are antagonists of endothelin useful in controlling hypertension, myocardial infarction, metabolic, endocrinological, and neurological disorders, congestive heart failure, endotoxic shock, subarachnoid hemorrhage, arrhythmias, asthma, acute renal failure, preeclampsia, and diabetes.

Endothelin-1 (ET-1), a potent vasoconstrictor, is a 21 amino acid bicyclic peptide that was first isolated from cultured porcine aortic endothelial cells. Endothelin-1, is one of a family of structurally similar bicyclic peptides which include; ET-2, ET-3, vasoactive intestinal contractor (VIC), and the sarafotoxins (SRTX's). The unique bicyclic structure and corresponding arrangement of the disulfide bridges of ET-1, which are the same for the endothelins, VIC, and the sarafotoxins, has led to significant speculation as to the importance of the resulting induced secondary structure to receptor binding and functional activity. ET-1 analogues with incorrect disulfide pairings exhibit at least 100-fold less vasoconstrictor activity. The flexible C-terminal hexapeptide of ET-1 has been shown to be

important for binding to the ET receptor and functional activity in selected tissues. Additionally, the C-terminal amino acid (Trp-21) has a critical role in binding and vasoconstrictor activity, since ET[1-20] exhibits approximately 1000-fold less functional activity.

Rovero, P., et al, British Journal of Pharmacology 101, pages 232-236 (1990) disclosed various analogs of the C-terminal hexapeptide of ET-1, none of which were reported to be antagonists of ET-1.

Doherty, A. M., et al, Abstract, Second International Conference on Endothelin, Tsukuba, Japan, December 9, 1990, and the published manuscript (J. Cardiovasc. Pharm. 17 (Suppl. 7), 1991, pp. 559-561) disclosed various analogs of the C-terminal hexapeptide of ET-1, none of which exhibited any functional activity.

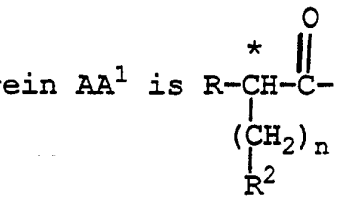
However, we have surprisingly and unexpectedly found that a series of C-terminal hexapeptide and related analogs of ET-1 are receptor antagonists of endothelin.

SUMMARY OF THE INVENTION

Accordingly, the present invention is a compound of Formula I

$$AA^1\text{-}AA^2\text{-}AA^3\text{-}AA^4\text{-}AA^5\text{-}AA^6$$

I

wherein AA^1 is 

wherein R is

hydrogen

alkyl,

alkenyl,

alkynyl,

cycloalkyl,

cycloalkylalkyl,

aryl,

heteroaryl,

fluorenylmethyl,

 wherein R^3 and R^4 are each the same or different and each is

hydrogen,

alkyl,

alkenyl,

alkynyl,

cycloalkyl,

cycloalkylalkyl,

aryl,

heteroaryl, or

fluorenylmethyl,

$-OR^3$ wherein R^3 is as defined above,

 wherein R^3 is as defined above,

 wherein R^3 and R^4 are each the same or different and each is as defined above,

 wherein R^3 and R^4 where R^4 is not hydrogen are each the same or different and each is as defined above,

 wherein R^3 is as defined above, or

$-CH_2OR^3$ wherein R^3 is as defined above,

n is zero or an integer of 1, 2, 3, 4, 5, or 6 and

R^2 is hydrogen,

alkyl,

 wherein R^3 and R^4 are each the same or different and each is as defined above,

 wherein R^5 is

hydrogen,

p-toluenesulfonyl,

nitro or

 wherein R^6 is

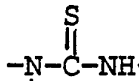
alkyl,

cycloalkyl,

aryl, or

heteroaryl,

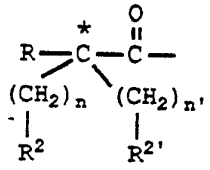
 wherein R^6 is as defined above,

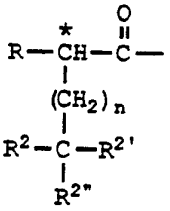

wherein R^3 and R^4 are each the same or different and each is as defined above,

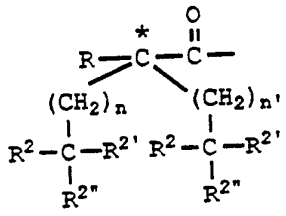
aryl,

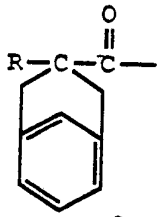
heteroaryl, or

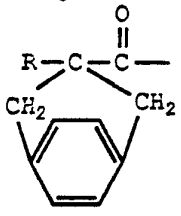
heterocycloalkyl,

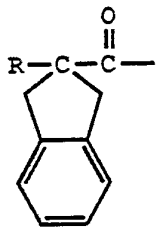

wherein n and n′ are each the same different and each is as defined above for n,
R^2 and $R^{2'}$ are each the same or different and each is as defined above for R^2, and R is as defined above,


wherein R^2, $R^{2'}$, and $R^{2''}$ are each the same or different and each is as defined above for R^2, R and n,

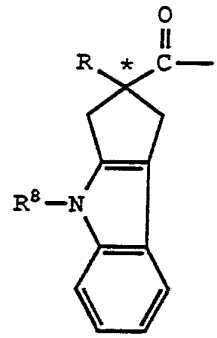

wherein n and n′ are each the same or different and each is as defined above for n,
R^2, $R^{2'}$, and $R^{2''}$ are each the same or different and each is as defined above for R^2 and R is as defined above,


wherein R is as defined above,

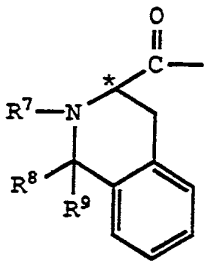

wherein R is as defined above,



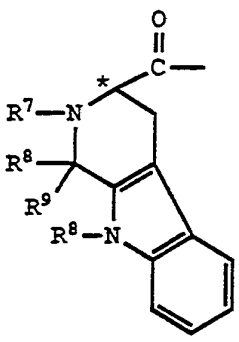
wherein R is as defined above,



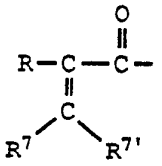
wherein R^8 is
hydrogen, or
alkyl,
and R is as defined above,



wherein R^7 is
hydrogen,
alkyl,
cycloalkyl,
aryl, or
heteroacyl,
R^8 and R^9 are each the same or different and each is as defined above for R^8

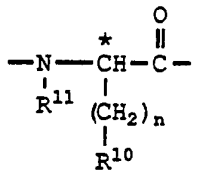


wherein R^7, R^8, and R^9 are as defined above or



wherein R^7 and $R^{7'}$ are each the same or different and each is as defined above for R^7, and R is as defined above;

AA^2, AA^3, AA^4, and AA^5 are each independently absent or each independently



wherein R^{10} is

hydrogen,

alkyl,

aryl,

cycloalkyl,

alkenyl,

alkynyl,

$-OR^3$ wherein R^3 is as defined above,

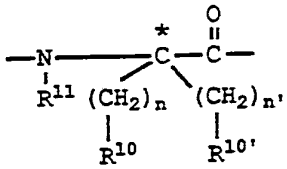
$-\underset{\underset{R^4}{|}}{N}-R^3$ wherein R^3 and R^4 are each the same or different and each is as defined above,

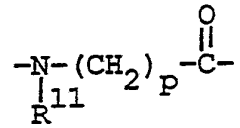
$-\overset{\overset{O}{\|}}{C}-\underset{\underset{R^4}{|}}{N}-R^3$ wherein R^3 and R^4 are each the same or different and each is as defined above,

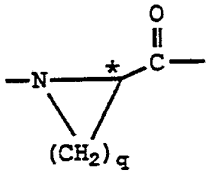
$-S(O)_m R^3$ wherein m is zero or an integer of 1 or 2, and R^3 is as defined above where R^3 is not hydrogen,

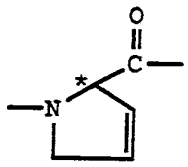
$-\overset{\overset{O}{\|}}{C}-R^3$ wherein R^3 is as defined above,

wherein R^3 is as defined above,
R^{11} is hydrogen, alkyl, or aryl, and
n is as defined above,


wherein n and n′ are each the same or different and each is as defined above for n, R^{10} and $R^{10'}$ are each the same or different and each is as defined above for R^{10}, and R^{11} is as defined above,


wherein p is an integer of 1, 2, 3, 4, 5, or 6 and R^{11} is as defined above,


wherein q is zero or an integer of 1, 2, 3, or 4,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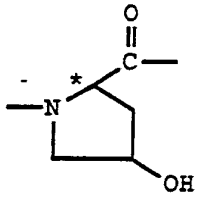
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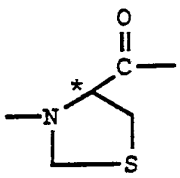
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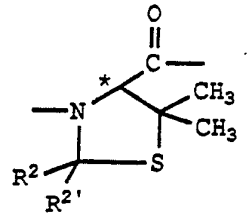
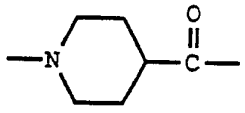
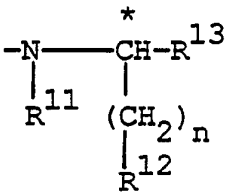


wherein R^2 and $R^{2'}$ are each the same or different and each is as defined above for R^2, and



;

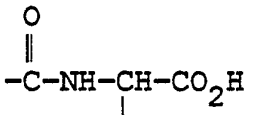
AA^6 is 

wherein R^{13} is

$-(CH_2)_n-CO_2H$ wherein n is as defined above,

$-(CH_2)_n-OH$ wherein n is as defined above,

or



wherein R^{14} is hydrogen or

$-CH_2-CO_2H$

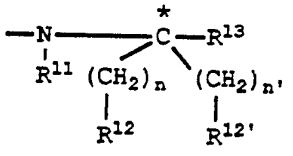
R^{12} is

aryl,

heteroaryl, or

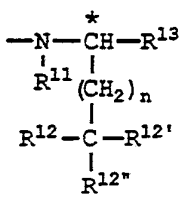
heterocycloalkyl, and

R^{11} and n are as defined above,

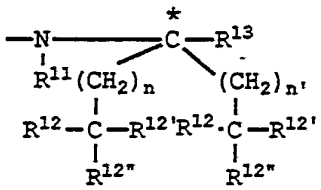


wherein n and n' are each the same or different and each is as defined above for n, and R^{12} and $R^{12'}$ are each the same or different and each is as defined

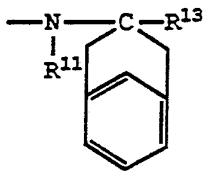
above for R^{12} and R^{11}, and R^{13} are as defined above,



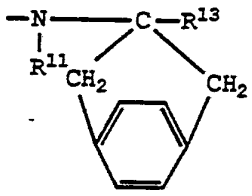
wherein R^{12}, $R^{12'}$, and $R^{12''}$ are each the same or different and each is as defined above for R^{12} and R^{11}, R^{13} and n are as defined above,



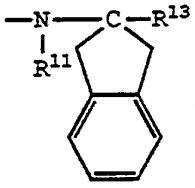
wherein n and n' are each the same or different and each is as defined above for n, R^{12}, $R^{12'}$, and $R^{12''}$ are each the same or different and each is as defined above for R^{12}, and R^{11} and R^{13} are as defined above,



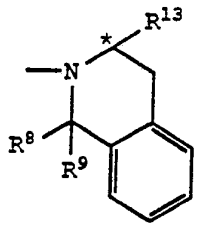
wherein R^{11} and R^{13} are as defined above,



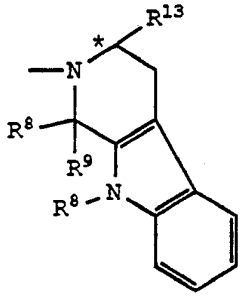
wherein R^{11} and R^{13} are as defined above,



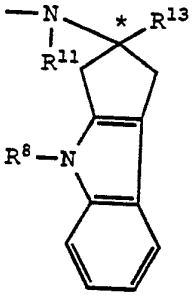
wherein R^{11} and R^{13} are as defined above,



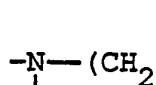
wherein R^8 and R^9 are each the same or different and each is as defined above for R^8 and R^9, and R^{13} is as defined above,



wherein R^8 and R^9 are each the same or different and each is as defined above for R^8 and R^9, and R^{13} is as defined above,



wherein R^8, R^{11}, and R^{13} are as defined above, and

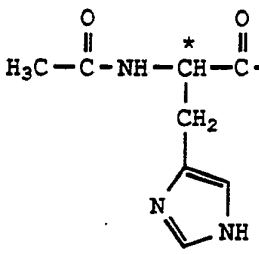


wherein R^{11} and p are as defined above;

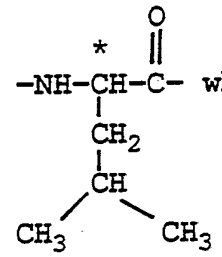
stereochemistry at in AA^1 is D,

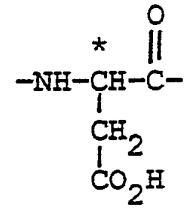
stereochemistry at  in AA^2, AA^3, AA^4, or AA^5 is D, L, or DL and

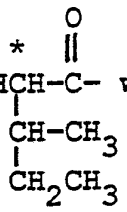
stereochemistry at  in AA^6 is L; and with the exclusion of the compound wherein AA^1 is

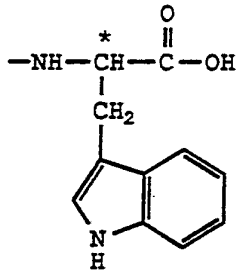


wherein is D stereochemistry,

AA^2 is  wherein CH is L stereochemistry,

AA^3 is  wherein CH is L stereochemistry,

AA^4 and AA^5 are each  wherein CH is L stereochemistry, and

AA^6 is  wherein CH is L stereochemistry; or a pharmaceutically acceptable salt thereof.

Elevated levels of endothelin have been postulated to be involved in a number of pathophysiological states including diseases associated with the cardiovascular system as well as various metabolic and endocrinological disorders. As antagonists of endothelin, the compounds of Formula I are useful in the treatment of hypertension, myocardial infarction, metabolic, endocrinological and neurological disorders, congestive heart failure, endotoxic shock, subarachnoid hemorrhage,

arrhythmias, asthma, acute renal failure, preeclampsia, and diabetes.

A still further embodiment of the present invention is a pharmaceutical composition for administering an effective amount of a compound of Formula I in unit dosage form in the treatment methods mentioned above.

Finally, the present invention is directed to methods for production of a compound of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

In the compounds of Formula I, the term "alkyl" means a straight or branched hydrocarbon radical having from 1 to 12 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, undecyl, dodecyl, and the like.

The term "alkenyl" means a straight or branched unsaturated hydrocarbon radical having from 2 to 12 carbon atoms and includes, for example, ethenyl, 2-propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 3-methyl-3-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 3-heptenyl, 1-octenyl, 1-nonenyl, 1-decenyl, 1-undecenyl, 1-dodecenyl, and the like.

The term "alkynyl" means a straight or branched triple bonded unsaturated hydrocarbon radical having from 2 to 12 carbon atoms and includes, for example, ethynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 3-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 3-heptynyl, 1-octynyl, 2-octynyl, 1-nonynyl, 2-nonynyl, 3-nonynyl, 4-nonynyl,

1-decynyl, 2-decynyl, 2-undecynyl, 3-undecynyl, 3-dodecynyl, and the like.

The term "cycloalkyl" means a saturated hydrocarbon ring which contains from 3 to 12 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, and the like.

The term "cycloalkylalkyl" means a saturated hydrocarbon ring attached to an alkyl group wherein alkyl is as defined above. The saturated hydrocarbon ring contains from 3 to 12 carbon atoms. Examples of such are cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, adamantylmethyl and the like.

The terms "alkoxy" and "thioalkoxy" are O-alkyl or S-alkyl as defined above for alkyl.

The term "aryl" means an aromatic radical which is a phenyl group, a benzyl group, a naphthyl group, a biphenyl group, a pyrenyl group, an anthracenyl group, or a fluorenyl group and the like, unsubstituted or substituted by 1 to 4 substituents selected from alkyl as defined above, alkoxy as defined above, thioalkoxy as defined above, hydroxy, thiol, nitro, halogen, amino, $-NH-\overset{O}{\overset{\|}{C}}-$alkyl wherein alkyl is as defined above, $-\overset{O}{\overset{\|}{C}}-O-$alkyl wherein alkyl is as defined above, $-\overset{O}{\overset{\|}{C}}-$alkyl wherein alkyl is as defined above, or aryl.

The term "heteroaryl" means a heteroaromatic radical which is 2-or 3-thienyl, 2- or 3-furanyl, 2- or 3-pyrrolyl, 2-, 4-, or 5-imidazolyl, 3-, 4-, or 5-pyrazolyl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 4-, or 5-oxazolyl, 3-, 4-, or 5-isoxazolyl, 3- or 5-1,2,4-triazolyl, 4- or

5-1,2,3-triazolyl, tetrazolyl, 2-, 3-, or 4-pyridinyl, 3-, 4-, or 5-pyridazinyl, 2-pyrazinyl, 2-, 4-, or 5-pyrimidinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl, or 2-, 4-, 5-, 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 4-, 5-, 6-, or 7-benzothiazolyl, unsubstituted or substituted by 1 to 2 substituents selected from alkyl as defined above, aryl as defined above, alkoxy as defined above, thioalkoxy as defined above, hydroxy, thiol, nitro, halogen, formyl, amino, -NH-C(=O)-alkyl wherein alkyl is as defined above, -C(=O)-O-alkyl wherein alkyl is as defined above, -C(=O)-alkyl wherein alkyl is as defined above or phenyl.

The term "heterocycloalkyl" means 2- or 3-tetrahydrothieno, 2- or 3-tetrahydrofurano, 2- or 3-pyrrolidino, 2-, 4-, or 5-thiazolidino, 2-, 4-, or 5-oxazolidino, 2-, 3-, or 4-piperidino, N-morpholinyl or N-thiamorpholinyl.

"Halogen" is fluorine, chlorine, bromine or iodine.

The following table provides a list of abbreviations and definitions thereof used in the present invention.

TABLE

Abbreviation*	Amino Acid
Ala	Alanine
Arg	Arginine
Asn	Asparagine
Asp	Aspartic acid
Cys	Cysteine
Glu	Glutamic acid
Gln	Glutamine
Gly	Glycine
His	Histidine
Ile	Isoleucine
Leu	Leucine
Lys	Lysine
Met	Methionine
Phe	Phenylalanine
Pro	Proline
Ser	Serine
Thr	Threonine
Trp	Tryptophan
Tyr	Tyrosine
Val	Valine

* If the optical activity of the amino acid is other than L(S), the amino acid or abbreviation is preceded by the appropriate configuration D(R) or DL(RS).

Abbreviation*	Modified and Unusual Amino Acid
Bip	(Paraphenyl)phenylalanine
Dip	3,3-Diphenylalanine**
3Hyp	3-Hydroxyproline
4Hyp	4-Hydroxyproline
N-MePhe	N-Methylphenylalanine
N-MeAsp	N-Methylaspartic acid
Nva	Norvaline
Nle	Norleucine
Orn	Ornithine
Abu	2-Aminobutyric acid
Alg	2-Amino-4-pentenoic acid (Allylglycine)
Arg(NO_2)	N^G-nitroarginine
Atm	2-Amino-3-(2-amino-5-thiazole)propanoic acid
Cpn	2-Amino-3-cyclopropanepropanoic acid (Cyclopropylalanine)
Chx	Cyclohexylalanine (Hexahydrophenylalanine)
Emg	2-Amino-4,5(RS)-epoxy-4-pentenoic acid
His(Dnp)	N^{im}-2,4-Dinitrophenylhistidine
HomoGlu	2-Aminoadipic acid
HomoPhe	2-Amino-5-phenylpentanoic acid (Homophenylalanine)
Met(O)	Methionine sulfoxide
Met(O_2)	Methionine sulfone

** Synthesis can be accomplished according to the procedure described by Josien, H., et al, Tetrahedron Letters, 1991, 32, 6547-50.

Abbreviation*	Modified and Unusual Amino Acid (cont)
1-Nal	3-(1'-Naphthyl)alanine
2-Nal	3-(2'-Naphthyl)alanine
Nia	2-Amino-3-cyanopropanoic acid (Cyanoalanine)
Pgl	Phenylglycine
Pgy	2-Aminopentanoic acid (Propylglycine)
Pha	2-Amino-6-(1-pyrrolo)-hexanoic acid
Pyr	2-Amino-3-(3-pyridyl)-propanoic acid (3-Pyridylalanine)
Tic	1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid
Tza	2-Amino-3-(4-thiazolyl)-propanoic acid
Tyr(Ot-Bu)	O-tertiary butyl-tyrosine
Tyr(OMe)	O-Methyl-tyrosine
Tyr(OEt)	O-Ethyl-tyrosine
Trp(For)	N^{in}-Formyltryptophan

Abbreviation	Protecting Group
Ac	Acetyl
Ada	1-Adamantyl acetic acid
Adoc	Adamantyloxycarbonyl
Bzl	Benzyl
MeBzl	4-Methylbenzyl
Z	Benzyloxycarbonyl
2-Br-Z	ortho-Bromobenzyloxycarbonyl
2-Cl-Z	ortho-Chlorobenzyloxycarbonyl
Bom	Benzyloxymethyl
Boc	tertiary Butyloxycarbonyl

Abbreviation*	Protecting Group (cont)
TBS	tertiary Butyldimethylsilyl
Dnp	2,4-Dinitrophenyl
For	Formyl
Fmoc	9-Fluorenylmethyloxycarbonyl
NO_2	Nitro
Tos	4-Toluenesulfonyl (tosyl)
Trt	Triphenylmethyl (trityl)

Abbreviation	Solvents and Reagents
HOAc	Acetic acid
CH_3CN	Acetonitrile
DCM	Dichloromethane
DCC	N,N'-Dicyclohexylcarbodiimide
DIEA	N,N-Diisopropylethylamine
DMF	Dimethylformamide
HCl	Hydrochloric acid
HF	Hydrofluoric acid
HOBt	1-Hydroxybenzotriazole
KOH	Potassium hydroxide
TFA	Trifluoroacetic acid
MBHA Resin	Methylbenzhydrylamine resin
PAM Resin	4-(Oxymethyl)-phenylacetamidomethyl resin

The compounds of Formula I are capable of further forming both pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention.

Pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from nontoxic inorganic acids such as hydrochloric,

nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge, S. M., et al, "Pharmaceutical Salts," Journal of Pharmaceutical Science, 66, pp. 1-19 (1977)).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. Preferably a peptide of Formula I can be converted to an acidic salt by treating with an aqueous solution of the desired base, such that the resulting pH is less than 4. The solution can be passed through a C18 cartridge to absorb the peptide, washed with copious amounts of water, the peptide eluted with a polar organic solvent such as, for example, methanol, acetonitrile, and the like, and isolated by

concentrating under reduced pressure followed by lyophilization. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge, S. M., et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science, 66, pp. 1-19 (1977)).

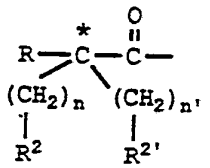
The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. Preferably, a peptide of Formula I can be converted to a base salt by treating with an aqueous solution of the desired base, such that the resulting pH is greater than 9. The solution can be passed through a C18 cartridge to absorb the peptide, washed with copious amounts of water, the peptide eluted with a polar organic solvent such as, for example, methanol, acetonitrile and the like, and isolated by concentrating under reduced pressure followed by lyophilization. The

free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R(D) or S(L) configuration. The present invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof.

A preferred compound of Formula I is one wherein AA^1 is



wherein R is

hydrogen

alkyl,

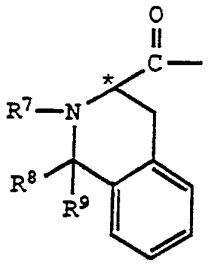
alkenyl,
alkynyl,
cycloalkyl,
cycloalkylalkyl,
aryl,
heteroaryl,
fluorenylmethyl,
$-N-R^3$ wherein R^3 and R^4 are
R^4 each the same or different and each is
hydrogen,
alkyl,
alkenyl,
alkynyl,
cycloalkyl,
cycloalkylalkyl,
aryl,
heteroaryl, or
fluorenylmethyl,

wherein R^3 and R^4 are each the same or different and each is as defined above or

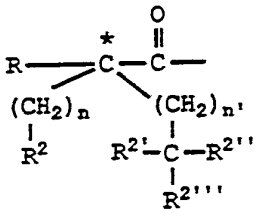
wherein R^3 and R^4 are each the same or different and each is as defined above,

n is zero,
R^2 is hydrogen or methyl,
n' is zero or an integer of 1, 2, or 3, and
$R^{2'}$ is hydrogen,
trityl,
aryl,
heteroaryl,
heterocycloalkyl,

$-N-R^3$ wherein R^3 and R^4 are each the same or different and each is as defined above or

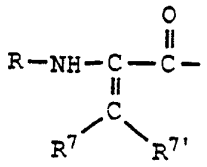


wherein R^7 is
hydrogen,
alkyl,
aryl, or
heteroaryl,
R^8 and R^9 are each the same or different and each is
hydrogen or
alkyl,



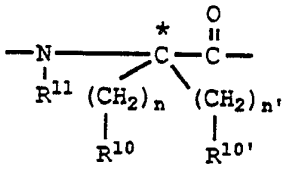
wherein $R^{2'}$, $R^{2''}$, and $R^{2'''}$ are each the same or different and each is hydrogen,
alkyl,
aryl, or
heteroaryl with the proviso that at least one of $R^{2'}$, $R^{2'''}$, and $R^{2'''}$ is aryl or heteroaryl

and R^2, n, and n′ are as defined above, or



wherein R^7 and $R^{7'}$ are each the same or different and each is hydrogen,
alkyl,
cycloalkyl,
aryl, or
heteroaryl.

AA^2, AA^3, AA^4, and AA^5 are each independently absent or each independently



wherein R^{11} is
hydrogen or methyl,
n is zero,
R^{10} is hydrogen or methyl,
n′ is zero or an integer of 1, 2, 3, or 4 and
$R^{10'}$ is hydrogen,
alkyl,
cycloalkyl,
alkenyl,
alkynyl,
$-OR^{3'}$ wherein $R^{3'}$ is
hydrogen,
alkyl,

alkenyl,
cycloalkyl,
aryl, or
heteroaryl,

$-N(R^{4'})-R^{3'}$ wherein $R^{3'}$ and $R^{4'}$ are each the same or different and each is as defined above for $R^{3'}$,

$-C(=O)-NR^{4'}R^{3'}$ wherein $R^{3'}$ and $R^{4'}$ are each the same or different and each is as defined above,

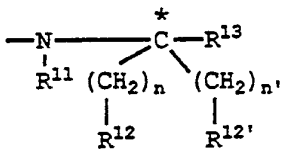
$-C(=O)-NHR^{3'}$ wherein $R^{3'}$ is as defined above,

$-C(=O)-R^{3'}$ wherein $R^{3'}$ is as defined above,

$-S(O)_mR^{3'}$ wherein m is zero or an integer of 1 of 2 and $R^{3'}$ is as defined above except that $R^{3'}$ is not hydrogen, or

$-C(=O)-OR^{4'}$ wherein $R^{4'}$ is as defined above,

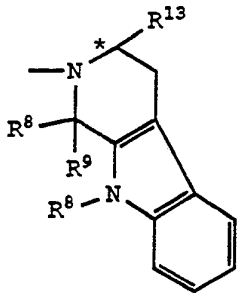
AA^6 is



wherein R^{11} is hydrogen or methyl,
n is zero,
R^{12} is hydrogen, or methyl,
n' is zero or an integer of 1, 2, or 3,
$R^{12'}$ is aryl or heteroaryl,
R^{13} is $-(CH_2)_n-CO_2H$ wherein n is as defined above,

$-(CH_2)_n-OH$ wherein n is as defined above, or

$-C(=O)-NH-CH(R^{14})-CO_2H$ wherein R^{14} is hydrogen or $-CH_2-CO_2H$, or

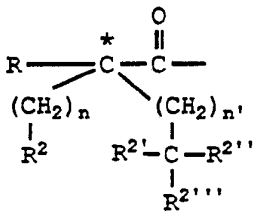


wherein R^8 and R^9 are each the same or different and each is as defined above for R^8 and R^9 and R^{13} is as defined above, and R^8 is hydrogen, formyl, acetyl, Z, Boc, Bzl, or alkyl;

stereochemistry at * C in AA^1 is D,

stereochemistry at * C in AA^2, AA^3, AA^4, or AA^5 is D, L, or DL, and stereochemistry at * C in AA^6 is L.

Most preferred compounds of Formula I are one wherein AA^1 is



wherein R is

hydrogen,

alkyl,

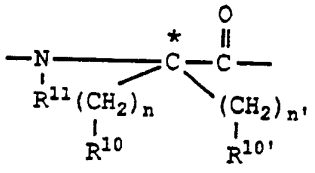
alkenyl,
alkynyl,
cycloalkyl,
cycloalkylalkyl,
aryl,
heteroaryl,
fluorenylmethyl,

$-\underset{\underset{R^4}{|}}{N}-R^3$ wherein R^3 and R^4 are each the same or different and each is
hydrogen,
alkyl,
alkenyl,
alkynyl,
cycloalkyl,
cycloalkylalkyl,
aryl,
heteroaryl, or
fluoroenylmethyl,

$-\underset{\underset{R^4}{|}}{N}-\overset{\overset{O}{\|}}{C}-OR^4$ wherein R^3 and R^4 are each the same or different and each is as defined above, and $R^{2'}$, $R^{2''}$, and $R^{2'''}$ are each the same or different and each is
hydrogen,
alkyl,
aryl, or
heteroaryl with the proviso that at least one of R^2, $R^{2'}$, and $R^{2''}$ is aryl or heteroaryl, and $R^{2'''}$ is hydrogen or methyl,

R^2 is hydrogen or methyl,
n is zero, and
n′ is zero or an integer of 1, 2, or 3, or

AA^2 is



wherein R^{11} is hydrogen or methyl,

n is zero,

R^{10} is hydrogen or methyl,

n' is zero or an integer of 1, 2, 3, or 4, and

R^{10} is alkyl,

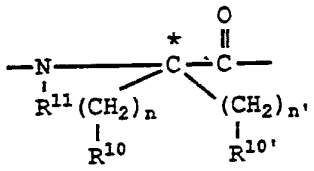
OH,

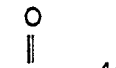
$-N(R^{3'})(R^{4'})$ wherein $R^{3'}$ and $R^{4'}$ are each the same or different and each is hydrogen, alkyl, or aryl,

$-C(=O)-NR^{3'}R^{4'}$ wherein $R^{3'}$ and $R^{4'}$ are as defined above,

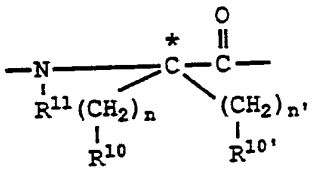
$-C(=O)-OR^{4'}$ wherein $R^{4'}$ is as defined above;

AA^3 is



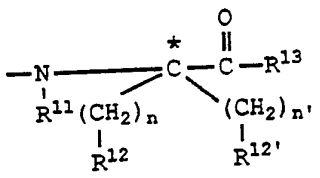
wherein R^{11} is hydrogen or methyl,
n is zero,
R^{10} is hydrogen or methyl,
n" is zero or an integer of 1, 2, or 3, and
$R^{11'}$ is alkyl,
aryl,
 wherein $R^{3'}$ and $R^{4'}$ are as defined above,
 wherein $R^{4'}$ is as defined above,

AA^4 and AA^5 are each



wherein R^{11} is hydrogen or methyl,
n is zero,
R^{10} is hydrogen or methyl,
n' is zero, and
$R^{10'}$ is alkyl,
or cycloalkyl,

AA^6 is



wherein R^{11} is hydrogen or methyl,

n is zero,

R^{12} is hydrogen, or methyl,

n' is zero or an integer of 1, 2, of 3,

$R^{12'}$ is aryl or heteroaryl,

R^{13} is $-(CH_2)_n-CO_2H$ wherein n is zero or an integer of 1, 2, 3, 4, 5, or 6,

$-(CH_2)_n-OH$ wherein n is zero or an integer of 1, 2, 3, 4, 5, or 6, or

$-C(=O)-NH-CH$ wherein R^{14} is hydrogen or $-CH_2CO_2H$,

stereochemistry at C^* in AA^1 is D,

stereochemistry at C^* in AA^2, AA^3, AA^4, or AA^5 is D or L and

stereochemistry at C^* in AA^6 is L.

A more preferred compound of Formula I is one wherein AA^1 is

D-Dip,

D-Bip,

D-His,

D-His(Dnp),
D-2-Nal,
D-1-Nal,
D-Phe,
D-Pgl,
D-Tyr,
D-Tyr(OMe),
D-Tyr(OEt),
D-Tyr(OtBu),
D-Trp,
D-Trp(For),
D-Tic,
D-Tza,
D-Pyr,
Ac-D-Dip,
Ac-D-Bip,
Ac-D-His,
Ac-D-His(Dnp),
Ac-D-2-Nal,
Ac-D-1-Nal,
Ac-D-Phe,
Ac-D-Pgl,
Ac-D-Tyr,
Ac-D-Tyr(OMe),
Ac-D-Tyr(OEt),
Ac-D-Tyr(OtBu),
Ac-D-Trp,
Ac-D-Trp(For),
Ac-D-Tic,
Ac-D-Tza,
Ac-D-Pyr,
Ada-D-Dip,
Ada-D-Bip,
Ada-D-His,

Ada-D-His(Dnp),
Ada-D-2-Nal,
Ada-D-1-Nal,
Ada-D-Phe,
Ada-D-Pgl,
Ada-D-Tyr,
Ada-D-Tyr(OMe),
Ada-D-Tyr(OEt),
Ada-D-Tyr(OtBu),
Ada-D-Trp,
Ada-D-Trp(For),
Ada-D-Tic,
Ada-D-Tza,
Ada-D-Pyr,
Adoc-D-Dip,
Adoc-D-Bip,
Adoc-D-His,
Adoc-D-His(Dnp),
Adoc-D-2-Nal,
Adoc-D-1-Nal,
Adoc-D-Phe,
Adoc-D-Pgl,
Adoc-D-Tyr,
Adoc-D-Tyr(OMe),
Adoc-D-Tyr(OEt),
Adoc-D-Tyr(OtBu),
Adoc-D-Trp,
Adoc-D-Trp(For),
Adoc-D-Tic,
Adoc-D-Tza,
Adoc-D-Pyr,
Boc-D-Dip,
Boc-D-Bip,
Boc-D-His,

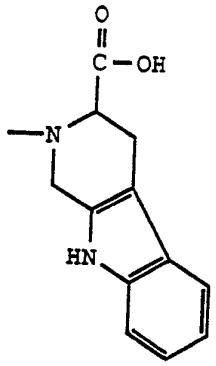
Boc-D-His(Dnp),
Boc-D-2-Nal,
Boc-D-1-Nal,
Boc-D-Phe,
Boc-D-Pgl,
Boc-D-Tyr,
Boc-D-Tyr(OMe),
Boc-D-Tyr(OEt),
Boc-D-Tyr(OtBu),
Boc-D-Trp,
Boc-D-Trp(For),
Boc-D-Tic,
Boc-D-Tza,
Boc-D-Pyr,
Z-D-Dip,
Z-D-Bip,
Z-D-His,
Z-D-His(Dnp),
Z-D-2-Nal,
Z-D-1-Nal,
Z-D-Phe,
Z-D-Pgl,
Z-D-Tyr,
Z-D-Tyr(OMe),
Z-D-Tyr(OEt),
Z-D-Tyr(OtBu),
Z-D-Trp,
Z-D-Trp(For),
Z-D-Tic,
Z-D-Tza,
Z-D-Pyr,
Fmoc-D-Dip,
Fmoc-D-Bip,
Fmoc-D-His,

Fmoc-D-His(Dnp),
Fmoc-D-2-Nal,
Fmoc-D-1-Nal,
Fmoc-D-Phe,
Fmoc-D-Pgl,
Fmoc-D-Tyr,
Fmoc-D-Tyr(OMe),
Fmoc-D-Tyr(OEt),
Fmoc-D-Tyr(OtBu),
Fmoc-D-Trp,
Fmoc-D-Trp(For),
Fmoc-D-Tic,
Fmoc-D-Tza,
Fmoc-D-Pyr, or

AA^2 is Ala,
Alg,
Arg
Asn,
Asp,
Dab,
Glu,
Gln,
Gly,
homoArg,
homoGlu,
homoLys,
Ile,
Leu,
D-Leu,
Lys,
Met,
Met(O),
Met(O_2),
Nva,

Nle,
Orn,
Phe,
Tyr,
Val, or
AA^2 is absent;
AA^3 is Asn,
Asp,
D-Asp,
N-MeAsp,
Glu,
Gln,
homoPhe,
Phe,
Tyr, or
AA^3 is absent;
AA^4 is Ala,
Chx,
Gly,
Glu,
Ile,
D-Ile,
Leu,
Nleu,
Nval,
Val, or
AA^4 is absent;
AA^5 is Ala,
Chx,
Gly,
Ile,
D-Ile,
Leu,
Nleu,

Nval,
Val, or
AA^5 is absent; and
AA^6 is 2-Nal,
1-Nal,
Pyr,
Trp,
Tyr(OMe),
Tyr(OEt),
Tyr(Ot-Bu),
Tyr,
Trp-Gly,
Trp-Asp,
Trp(For),
Dip,
Phe,
Bza,



Particularly valuable are:
D-Phe-Leu-Asp-Ile-Ile-Trp;
D-His(Dnp)-Leu-Asp-Ile-Ile-Trp;
D-Trp-Leu-Asp-Ile-Ile-Trp;
D-Tyr-Leu-Asp-Ile-Ile-Trp;
D-Tyr(OMe)-Leu-Asp-Ile-Ile-Trp;
D-Tyr(OEt)-Leu-Asp-Ile-Ile-Trp;
D-2-Nal-Leu-Asp-Ile-Ile-Trp;
D-1-Nal-Leu-Asp-Ile-Ile-Trp;
D-Pgl-Leu-Asp-Ile-Ile-Trp;
D-Pyr-Leu-Asp-Ile-Ile-Trp;
D-Tic-Leu-Asp-Ile-Ile-Trp;

D-Dip-Leu-Asp-Ile-Ile-Trp;
D-Bip-Leu-Asp-Ile-Ile-Trp;
Ac-D-Phe-Leu-Asp-Ile-Ile-Trp;
Ac-D-His(Dnp)-Leu-Asp-Ile-Ile-Trp;
Ac-D-Trp-Leu-Asp-Ile-Ile-Trp;
Ac-D-Tyr-Leu-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Leu-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Leu-Asp-Ile-Ile-Trp;
Ac-D-2-Nal-Leu-Asp-Ile-Ile-Trp;
Ac-D-1-Nal-Leu-Asp-Ile-Ile-Trp;
Ac-D-Pgl-Leu-Asp-Ile-Ile-Trp;
Ac-D-Pyr-Leu-Asp-Ile-Ile-Trp;
Ac-D-Tic-Leu-Asp-Ile-Ile-Trp;
Ac-D-Dip-Leu-Asp-Ile-Ile-Trp;
Ac-D-Bip-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-Phe-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-His-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-Trp-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-Tyr-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-Tyr(OMe)-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-Tyr(OEt)-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-2-Nal-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-1-Nal-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-Dip-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-Bip-Leu-Asp-Ile-Ile-Trp;
Ada-D-Phe-Leu-Asp-Ile-Ile-Trp;
Ada-D-His-Leu-Asp-Ile-Ile-Trp;
Ada-D-Trp-Leu-Asp-Ile-Ile-Trp;
Ada-D-Tyr-Leu-Asp-Ile-Ile-Trp;
Ada-D-Tyr(OMe)-Leu-Asp-Ile-Ile-Trp;
Ada-D-Tyr(OEt)-Leu-Asp-Ile-Ile-Trp;
Ada-D-2-Nal-Leu-Asp-Ile-Ile-Trp;
Ada-D-1-Nal-Leu-Asp-Ile-Ile-Trp;
Ada-D-Dip-Leu-Asp-Ile-Ile-Trp;

Ada-D-Bip-Leu-Asp-Ile-Ile-Trp;
Ac-D-Phe-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-His-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-Trp-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-Tyr-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-2-Nal-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-1-Nal-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-Dip-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-Bip-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-Phe-Ile-Asp-Ile-Ile-Trp;
Ac-D-His-Ile-Asp-Ile-Ile-Trp;
Ac-D-Trp-Ile-Asp-Ile-Ile-Trp;
Ac-D-Tyr-Ile-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Ile-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Ile-Asp-Ile-Ile-Trp;
Ac-D-2-Nal-Ile-Asp-Ile-Ile-Trp;
Ac-D-1-Nal-Ile-Asp-Ile-Ile-Trp;
Ac-D-Dip-Ile-Asp-Ile-Ile-Trp;
Ac-D-Bip-Ile-Asp-Ile-Ile-Trp;
Ac-D-Phe-Val-Asp-Ile-Ile-Trp;
Ac-D-His-Val-Asp-Ile-Ile-Trp;
Ac-D-Trp-Val-Asp-Ile-Ile-Trp;
Ac-D-Tyr-Val-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Val-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Val-Asp-Ile-Ile-Trp;
Ac-D-2-Nal-Val-Asp-Ile-Ile-Trp;
Ac-D-1-Nal-Val-Asp-Ile-Ile-Trp;
Ac-D-Dip-Val-Asp-Ile-Ile-Trp;
Ac-D-Bip-Val-Asp-Ile-Ile-Trp;
Ac-DPhe-Dab-Asp-Ile-Ile-Trp;
Ac-DHis-Dab-Asp-Ile-Ile-Trp;
Ac-DTrp-Dab-Asp-Ile-Ile-Trp;

Ac-DTyr(OMe)-Dab-Asp-Ile-Ile-Trp;
Ac-DTyr(OEt)-Dab-Asp-Ile-Ile-Trp;
Ac-D2Nal-Dab-Asp-Ile-Ile-Trp;
Ac-D3Nal-Dab-Asp-Ile-Ile-Trp;
Ac-DDip-Dab-Asp-Ile-Ile-Trp;
Ac-DBip-Dab-Asp-Ile-Ile-Trp;
Ac-DPhe-Arg-Asp-Ile-Ile-Trp;
Ac-DHis-Arg-Asp-Ile-Ile-Trp;
Ac-DTrp-Arg-Asp-Ile-Ile-Trp;
Ac-DTyr(OMe)-Arg-Asp-Ile-Ile-Trp;
Ac-DTyr(OEt)-Arg-Asp-Ile-Ile-Trp;
Ac-D2Nal-Arg-Asp-Ile-Ile-Trp;
Ac-D3Nal-Arg-Asp-Ile-Ile-Trp;
Ac-DDip-Arg-Asp-Ile-Ile-Trp;
Ac-DBip-Arg-Asp-Ile-Ile-Trp;
Ac-DPhe-hLys-Asp-Ile-Ile-Trp;
Ac-DHis-hLys-Asp-Ile-Ile-Trp;
Ac-DTrp-hLys-Asp-Ile-Ile-Trp;
Ac-DTyr(OMe)-hLys-Asp-Ile-Ile-Trp;
Ac-DTyr(OEt)-hLys-Asp-Ile-Ile-Trp;
Ac-D2Nal-hLys-Asp-Ile-Ile-Trp;
Ac-D3Nal-hLys-Asp-Ile-Ile-Trp;
Ac-DDip-hLys-Asp-Ile-Ile-Trp;
Ac-DBip-hLys-Asp-Ile-Ile-Trp;
Ac-DPhe-hGlu-Asp-Ile-Ile-Trp;
Ac-DHis-Glu-Asp-Ile-Ile-Trp;
Ac-DTrp-Glu-Asp-Ile-Ile-Trp;
Ac-DTyr(OMe)-Glu-Asp-Ile-Ile-Trp;
Ac-DTyr(OEt)-Glu-Asp-Ile-Ile-Trp;
Ac-D2Nal-Glu-Asp-Ile-Ile-Trp;
Ac-D3Nal-Glu-Asp-Ile-Ile-Trp;
Ac-DDip-Glu-Asp-Ile-Ile-Trp;
Ac-DBip-Glu-Asp-Ile-Ile-Trp;
Ac-DPhe-hGlu-Asp-Ile-Ile-Trp;

Ac-DHis-hGlu-Asp-Ile-Ile-Trp;
Ac-DTrp-hGlu-Asp-Ile-Ile-Trp;
Ac-DTyr(OMe)-hGlu-Asp-Ile-Ile-Trp;
Ac-DTyr(OEt)-hGlu-Asp-Ile-Ile-Trp;
Ac-D2Nal-hGlu-Asp-Ile-Ile-Trp;
Ac-D3Nal-hGlu-Asp-Ile-Ile-Trp;
Ac-DDip-hGlu-Asp-Ile-Ile-Trp;
Ac-DBip-hGlu-Asp-Ile-Ile-Trp;
Ac-DPhe-Asp-Asp-Ile-Ile-Trp;
Ac-DHis-Asp-Asp-Ile-Ile-Trp;
Ac-DTrp-Asp-Asp-Ile-Ile-Trp;
Ac-DTyr(OMe)-Asp-Asp-Ile-Ile-Trp;
Ac-DTyr(OEt)-Asp-Asp-Ile-Ile-Trp;
Ac-D2Nal-Asp-Asp-Ile-Ile-Trp;
Ac-D3Nal-Asp-Asp-Ile-Ile-Trp;
Ac-DDip-Asp-Asp-Ile-Ile-Trp;
Ac-DBip-Asp-Asp-Ile-Ile-Trp;
Ac-D-Phe-Lys-Asp-Ile-Ile-Trp;
Ac-D-His-Lys-Asp-Ile-Ile-Trp;
Ac-D-Trp-Lys-Asp-Ile-Ile-Trp;
Ac-D-Tyr-Lys-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Lys-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Lys-Asp-Ile-Ile-Trp;
Ac-D-2-Nal-Lys-Asp-Ile-Ile-Trp;
Ac-D-1-Nal-Lys-Asp-Ile-Ile-Trp;
Ac-D-Phe-Orn-Asp-Ile-Ile-Trp;
Ac-D-His-Orn-Asp-Ile-Ile-Trp;
Ac-D-Trp-Orn-Asp-Ile-Ile-Trp;
Ac-D-Tyr-Orn-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Orn-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Orn-Asp-Ile-Ile-Trp;
Ac-D-2-Nal-Orn-Asp-Ile-Ile-Trp;
Ac-D-1-Nal-Orn-Asp-Ile-Ile-Trp;
Ac-D-Phe-Gln-Asp-Ile-Ile-Trp;

Ac-D-His-Gln-Asp-Ile-Ile-Trp;
Ac-D-Trp-Gln-Asp-Ile-Ile-Trp;
Ac-D-Tyr-Gln-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Gln-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Gln-Asp-Ile-Ile-Trp;
Ac-D-2-Nal-Gln-Asp-Ile-Ile-Trp;
Ac-D-1-Nal-Gln-Asp-Ile-Ile-Trp;
Ac-D-Phe-Leu-Glu-Ile-Ile-Trp;
Ac-D-His-Leu-Glu-Ile-Ile-Trp;
Ac-D-Trp-Leu-Glu-Ile-Ile-Trp;
Ac-D-Tyr-Leu-Glu-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Leu-Glu-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Leu-Glu-Ile-Ile-Trp;
Ac-D-2-Nal-Leu-Glu-Ile-Ile-Trp;
Ac-D-1-Nal-Leu-Glu-Ile-Ile-Trp;
Ac-D-Phe-Leu-Asn-Ile-Ile-Trp;
Ac-D-His-Leu-Asn-Ile-Ile-Trp;
Ac-D-Trp-Leu-Asn-Ile-Ile-Trp;
Ac-D-Tyr-Leu-Asn-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Leu-Asn-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Leu-Asn-Ile-Ile-Trp;
Ac-D-2-Nal-Leu-Asn-Ile-Ile-Trp;
Ac-D-1-Nal-Leu-Asn-Ile-Ile-Trp;
Ac-D-Dip-Leu-Asn-Ile-Ile-Trp;
Ac-D-Bip-Leu-Asn-Ile-Ile-Trp;
Ac-DPhe-Leu-Phe-Ile-Ile-Trp;
Ac-DHis-Leu-Phe-Ile-Ile-Trp;
Ac-DTrp-Leu-Phe-Ile-Ile-Trp;
Ac-DTyr(OMe)-Leu-Phe-Ile-Ile-Trp;
Ac-DTyr(OEt)-Leu-Phe-Ile-Ile-Trp;
Ac-D2Nal-Leu-Phe-Ile-Ile-Trp;
Ac-D3Nal-Leu-Phe-Ile-Ile-Trp;
Ac-DDip-Leu-Phe-Ile-Ile-Trp;
Ac-DBip-Leu-Phe-Ile-Ile-Trp;

Ac-D-Phe-Glu-Asp-Ile-Ile-Trp;
Ac-D-Phe-Leu-Asp-Val-Ile-Trp;
Ac-D-His-Leu-Asp-Val-Ile-Trp;
Ac-D-Trp-Leu-Asp-Val-Ile-Trp;
Ac-D-Tyr-Leu-Asp-Val-Ile-Trp;
Ac-D-Tyr(OMe)-Leu-Asp-Val-Ile-Trp;
Ac-D-Tyr(OEt)-Leu-Asp-Val-Ile-Trp;
Ac-D-2-Nal-Leu-Asp-Val-Ile-Trp;
Ac-D-1-Nal-Leu-Asp-Val-Ile-Trp;
Ac-D-Dip-Leu-Asp-Val-Ile-Trp;
Ac-D-Bip-Leu-Asp-Val-Ile-Trp;
Ac-D-Phe-Leu-Asp-Chx-Ile-Trp;
Ac-D-His-Leu-Asp-Chx-Ile-Trp;
Ac-D-Trp-Leu-Asp-Chx-Ile-Trp;
Ac-D-Tyr-Leu-Asp-Chx-Ile-Trp;
Ac-D-Tyr(OMe)-Leu-Asp-Chx-Ile-Trp;
Ac-D-Tyr(OEt)-Leu-Asp-Chx-Ile-Trp;
Ac-D-2-Nal-Leu-Asp-Chx-Ile-Trp;
Ac-D-1-Nal-Leu-Asp-Chx-Ile-Trp;
Ac-D-Dip-Leu-Asp-Chx-Ile-Trp;
Ac-D-Bip-Leu-Asp-Chx-Ile-Trp;
Ac-D-Phe-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-His-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-Trp-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-Tyr-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-2-Nal-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-1-Nal-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-Dip-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-Bip-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-Phe-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-His-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-Trp-Leu-Asp-Ile-D-Ile-Trp;

Ac-D-Tyr-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-Tyr(OMe)-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-Tyr(OEt)-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-2-Nal-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-1-Nal-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-Dip-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-Bip-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-Phe-Leu-Asp-Ile-Val-Trp;
Ac-D-His-Leu-Asp-Ile-Val-Trp;
Ac-D-Trp-Leu-Asp-Ile-Val-Trp;
Ac-D-Tyr-Leu-Asp-Ile-Val-Trp;
Ac-D-Tyr(OMe)-Leu-Asp-Ile-Val-Trp;
Ac-D-Tyr(OEt)-Leu-Asp-Ile-Val-Trp;
Ac-D-2-Nal-Leu-Asp-Ile-Val-Trp;
Ac-D-1-Nal-Leu-Asp-Ile-Val-Trp;
Ac-D-Dip-Leu-Asp-Ile-Val-Trp;
Ac-D-Bip-Leu-Asp-Ile-Val-Trp;
Ac-D-Phe-Leu-Asp-Ile-Chx-Trp;
Ac-D-His-Leu-Asp-Ile-Chx-Trp;
Ac-D-Trp-Leu-Asp-Ile-Chx-Trp;
Ac-D-Tyr-Leu-Asp-Ile-Chx-Trp;
Ac-D-Tyr(OMe)-Leu-Asp-Ile-Chx-Trp;
Ac-D-Tyr(OEt)-Leu-Asp-Ile-Chx-Trp;
Ac-D-2-Nal-Leu-Asp-Ile-Chx-Trp;
Ac-D-1-Nal-Leu-Asp-Ile-Chx-Trp;
Ac-D-Dip-Leu-Asp-Ile-Chx-Trp;
Ac-D-Bip-Leu-Asp-Ile-Chx-Trp;
Ac-D-Phe-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-His-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-Trp-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-Tyr-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-Tyr(OMe)-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-Tyr(OEt)-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-2-Nal-Leu-Asp-Ile-Ile-2-Nal;

Ac-D-1-Nal-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-Dip-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-Bip-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-Phe-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-His-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-Trp-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-Tyr-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-Tyr(OMe)-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-Tyr(OEt)-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-2-Nal-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-1-Nal-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-Dip-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-Bip-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-His-Leu-D-Asp-Ile-D-Ile-Trp;
Ac-D-Phe-Leu-D-Asp-Ile-D-Ile-Trp;
Ac-D-Bip-Leu-D-Asp-Ile-D-Ile-Trp;
Ac-D-Dip-Leu-D-Asp-Ile-D-Ile-Trp;
Ac-D-2-Nal-Leu-D-Asp-Ile-D-Ile-Trp;
Ac-D-1-Nal-Leu-D-Asp-Ile-D-Ile-Trp;
Ac-D-Trp-Leu-D-Asp-Ile-D-Ile-Trp;
Ac-D-Dip-Asn-Ile-Ile-Trp;
Ac-D-Dip-Phe-Ile-Ile-Trp;
Ac-D-Dip-Ile-Ile-Trp;
Ac-D-Dip-Asp-Ile-Ile-Trp;
Ac-D(NMe)-Dip-Leu-Asp-Ile-Ile-Trp;
Ac-D-Dip-Leu-Asp-Ile-Ile-(NMe)Trp;
Ac-D-Dip-Leu-Asp-Ile-(NMe)Ile-Trp;
Ac-D-Dip-Leu-Asp-(NMe)Ile-Ile-Trp;
Ac-D-Dip-Leu-(NMe)Asp-Ile-Ile-Trp;
Ac-D-Dip-(NMe)Leu-Asp-Ile-Ile-Trp;
Ac-D-Phe-Asp-Ile-Ile-Trp;
Ac-D-His-Asp-Ile-Ile-Trp;
Ac-D-Trp-Asp-Ile-Ile-Trp;
Ac-D-Tyr-Asp-Ile-Ile-Trp;

Ac-D-Tyr(OMe)-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Asp-Ile-Ile-Trp;
Ac-D-2-Nal-Asp-Ile-Ile-Trp;
Ac-D-1-Nal-Asp-Ile-Ile-Trp;
Ada-D-Phe-Asp-Ile-Ile-Trp;
Ada-D-His-Asp-Ile-Ile-Trp;
Ada-D-Trp-Asp-Ile-Ile-Trp;
Ada-D-Tyr-Asp-Ile-Ile-Trp;
Ada-D-Tyr(OMe)-Asp-Ile-Ile-Trp;
Ada-D-Tyr(OEt)-Asp-Ile-Ile-Trp;
Ada-D-2-Nal-Asp-Ile-Ile-Trp;
Ada-D-1-Nal-Asp-Ile-Ile-Trp;
Ada-D-Dip-Asp-Ile-Ile-Trp;
Ada-D-Bip-Asp-Ile-Ile-Trp;
Ac-D-Phe-Asp-Ile-Ile-2-Nal;
Ac-D-Phe-Asp-Ile-Ile-1-Nal;
Ac-D-His-Asp-Ile-Ile-2-Nal;
Ac-D-His-Asp-Ile-Ile-1-Nal;
Ac-D-Tyr-Asp-Ile-Ile-2-Nal;
Ac-D-Tyr-Asp-Ile-Ile-1-Nal;
Ac-D-Trp-Asp-Ile-Ile-2-Nal;
Ac-D-Trp-Asp-Ile-Ile-1-Nal;
Ac-D-Dip-Asp-Ile-Ile-2-Nal;
Ac-D-Dip-Asp-Ile-Ile-1-Nal;
Ac-D-Bip-Asp-Ile-Ile-2-Nal;
Ac-D-Bip-Asp-Ile-Ile-1-Nal;
Ac-D-Phe-Leu-Asp-Ile-Trp;
Ac-D-His-Leu-Asp-Ile-Trp;
Ac-D-Tyr-Leu-Asp-Ile-Trp;
Ac-D-Dip-Leu-Asp-Ile-Trp;
Ac-D-Trp-Leu-Asp-Ile-Trp;
Ac-DPhe-Leu-Asp-Ile-Ile-Trp-Gly;
Ac-DHis-Leu-Asp-Ile-Ile-Trp-Gly;
Ac-DTrp-Leu-Asp-Ile-Ile-Trp-Gly;

Ac-DTyr(OMe)-Leu-Asp-Ile-Ile-Trp-Gly;
Ac-DTyr(OEt)-Leu-Asp-Ile-Ile-Trp-Gly;
Ac-D2Nal-Leu-Asp-Ile-Ile-Trp-Gly;
Ac-D3Nal-Leu-Asp-Ile-Ile-Trp-Gly;
Ac-DDip-Leu-Asp-Ile-Ile-Trp-Gly;
Ac-DBip-Leu-Asp-Ile-Ile-Trp-Gly;
Ac-DPhe-Leu-Asp-Ile-Ile-Trp-Asp;
Ac-DHis-Leu-Asp-Ile-Ile-Trp-Asp;
Ac-DTrp-Leu-Asp-Ile-Ile-Trp-Asp;
Ac-DTyr(OMe)-Leu-Asp-Ile-Ile-Trp-Asp;
Ac-DTyr(OEt)-Leu-Asp-Ile-Ile-Trp-Asp;
Ac-D2Nal-Leu-Asp-Ile-Ile-Trp-Asp;
Ac-D3Nal-Leu-Asp-Ile-Ile-Trp-Asp;
Ac-DDip-Leu-Asp-Ile-Ile-Trp-Asp; and
Ac-DBip-Leu-Asp-Ile-Ile-Trp-Asp-Asp;

or a pharmaceutically acceptable acid or base addition salt thereof.

The compounds of Formula I are valuable antagonists of endothelin. The tests employed indicate that compounds of Formula I possess endothelin antagonist activity. Thus, the compounds of Formula I were tested for their ability to inhibit [^{125}I]-ET-1([^{125}I]-Endothelin-1) binding in a receptor assay. The binding of the compounds of Formula I is determined by incubation (37°C, 2 hours) of a compound of Formula I with [^{125}I]-ET-1 and the tissue (rat heart ventricle (10 µg)) in 50 mM Tris(hydroxymethyl)aminomethane hydrochloride (Tris-HCl) (pH 7.4), 5 mM ethylenediamine tetraacetic acid (EDTA), 2 mM ethylene glycol bis(ß-aminoethyl ether)N,N,N',N'-tetraacetic acid (EGTA), 100 µM phenylmethylsulfonyl fluoride (PMSF), and 100 µM bacitracin containing protease inhibitors (total volume of 0.5 mL). IC_{50} values are calculated by

weighing nonlinear regression curve-fitting to the mass-action (Langmuir) equation. The functional activity of compounds of Formula I is determined in Rat-1 cells by measuring intracellular levels of second messengers. Thus, cells were prelabeled with [^{3}H]-inositol and endothelin-stimulated accumulation of total [^{3}H]-inositol phosphates in the presence of Li^+ is monitored using anion exchange chromatography as described by Muldoon, L. L., et al, Journal of Biological Chemistry, Volume 264, pages 8529-8536 (1989) and Dudley, D. T., et al, Molecular Pharmacology, Volume 38, pages 370-377 (1990). Antagonist activity is assessed as the ability of added compounds to reduce endothelin-stimulated inositol phosphate accumulation. Antagonist activity was also measured by the ability of added compounds to reduce endothelin-stimulated arachidonic acid release in cultured vascular smooth muscle cells as (AAR) described in Reynolds, E., Mok, L., Faseb J., 1991, 5, A1066. The data in the table show the endothelin antagonist activity of representative compounds of Formula I.

TABLE 1. Biological Activity of Compounds of Formula I
(Page 1 of 2)

Example Number	Compound	Binding Assay in Rat Heart Ventricle IC_{50} (μM) or % Inhibition	IP (Inositol Phosphate) Accumulation, IC_{50} (μM) or % Inhibition	AAR IC_{50} (μM)
1	Ac-D-Phe-Leu-Asp-Ile-Ile-Trp	0.72	0.86	
4	D-1-Nal-Leu-Asp-Ile-Ile-Trp	8.98	53% @ 50 μM	
5	Ac-D-1-Nal-Leu-Asp-Ile-Ile-Trp	1.63	0.63	1.9
6	Ac-D-Phe-Leu-Asp-Ile-Trp	24.5		
7	Ac-D-His-Leu-D-Asp-Ile-D-Ile-Trp	6.03		
8	Ac-D-Phe-Orn-Asp-Ile-Ile-Trp	0.68	0.43	
9	Ac-D-Phe-Glu-Asp-Ile-Ile-Trp	0.74		0.60
10	Ac-D-Tyr-Leu-Asp-Ile-Ile-Trp	0.70	0.43	0.25
11	Ac-D-Phe-Asp-Ile-Ile-Trp	2.15		
12	Fmoc-D-Phe-Leu-Asp-Ile-Ile-Trp	0.43		
13	Ac-D-Dip-Leu-Asp-Ile-Ile-Trp	0.015		0.07
16	Ac-D-Dip-Leu-Phe-Ile-Ile-Trp	0.047		1.8
17	Ac-D-Dip-Leu-Asp-Ile-Lys-Trp	24.6% @ 10 μM		
18	Ac-D-Dip-Leu-Asp-Ile-Glu-Trp	37.0% @ 10 μM		
19	Ac-D-Dip-Leu-Asp-Glu-Ile-Trp	0.015		

TABLE 1. Biological Activity of Compounds of Formula I
(Page 2 of 2)

Example Number	Compound	Binding Assay in Rat Heart Ventricle IC_{50} (μM) or % Inhibition	IP (Inositol Phosphate) Accumulation, IC_{50} (μM) or % Inhibition	AAR IC_{50} (μM)
20	Ac-D-Dip-Glu-Asp-Ile-Ile-Trp	0.085		
21	Ac-D-Dip-Orn-Asp-Ile-Ile-Trp	79% @ 0.05 μM		0.02
23	Ac-D-Dip-D-Leu-Asp-Ile-Ile-Trp	41.3% @ 10 μM		

General Method for Preparing Compounds of Formula I

The compounds of Formula I may be prepared by solid phase peptide synthesis on a peptide synthesizer, for example, an Applied Biosystems 430A peptide synthesizer using activated esters or anhydrides of N-alpha-Boc protected amino acids, on PAM or MBHA resins. Additionally, the compounds of Formula I may also be prepared by conventional solution peptide synthesis. Amino acid side chains are protected as follows: Bzl(Asp, Glu, Ser), 2-Cl-Z(Lys), 2-Br-Z(Tyr), Bom(His), For(Trp), and MeBzl(Cys). Each peptide resin (1.0 g) is cleaved with 9 mL of HF and 1 mL of anisole or p-cresol as a scavenger (60 minutes, 0°C). The peptide resin is washed with cyclohexane, extracted with 30% aqueous HOAc, followed by glacial HOAc, concentrated under reduced pressure, and lyophilized. (A peptide containing For(Trp) is dissolved in 0°C, the pH is adjusted to 12.5 with 1N KOH (2 minutes), neutralized with glacial HOAc, desalted on C_{18} (as described below), and lyophilized. The crude peptide is purified by preparative reversed phase high performance liquid chromatography (RP-HPLC) on a C_{18} column (2.2 x 25.0 cm, 15.0 mL/min) with a linear gradient of 0.1% TFA in water to 0.1% TFA in acetonitrile and lyophilized. The homogeneity and composition of the resulting peptide is verified by RP-HPLC, capillary electrophoresis, thin layer chromatography (TLC), proton nuclear magnetic resonance spectrometry (NMR), and fast atom bombardment mass spectrometry (FAB-MS).

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of

the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin,

dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsules, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 100 mg preferably 0.5 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as antagonist of endothelin, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 mg to about 20 mg per kilogram daily. A daily dose range of about 0.01 mg to about 10 mg per kilogram is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the

condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

EXAMPLE 1

Ac-D-Phe-Leu-Asp-Ile-Ile-Trp

The linear hexapeptide is prepared by standard solid phase synthetic peptide methodology utilizing a Boc/benzyl strategy (Stewart, J. M. and Young, J. D., Solid Phase Peptide Synthesis, Pierce Chemical Co., Rockford, IL, 1984). All protected amino acids and reagents are obtained from commercial sources and are not further purified. The protected peptide resin is prepared on an Applied Biosystems 430A Peptide Synthesizer, utilizing protocols supplied for a dicyclohexylcarbodiimide mediated coupling scheme (Standard 1.0, Version 1.40). Starting with 0.560 g of N-α-Boc-Trp(For)-PAM resin (0.88 meq/g, 0.43 meq of Boc-Trp(For) total) the protected peptide is prepared by the stepwise coupling of the following amino acids (in order of addition): N-α-Boc-D-Phe, N-α-Boc-Leu·H_2O, N-α-Boc-Asp(Bzl), and N-α-Boc-Ile·0.5 H_2O. A typical cycle for the

coupling of an individual amino acid residue is illustrated below (reproduced from the ABI manual):

All the single couple RV cycles conform to the following pattern:

1) 33% TFA in DCM for 80 seconds
2) 50% TFA in DCM for 18.5 minutes
3) Three DCM washes
4) 10% DIEA in DMF for 1 minute
5) 10% DIEA in DMF for 1 minute
6) Five DMF washes
7) Coupling period
8) five DCM washes

After the coupling of N-α-Boc-D-Phe, the Boc group is removed with the end-NH_2 cycle and the free amine is acetylated with N-acetylimidazole (1.0 g, 120 minutes) in 20 mL of dichloromethane (DCM). The resin is washed with DCM (3 x 20 mL) and dried under reduced pressure (0.878 g).

The peptide is liberated from the solid support, and the carboxylate of aspartic acid deprotected by treatment with anhydrous hydrogen fluoride (9.0 mL), anisole (1.0 mL), and dimethyl sulfide (0.5 mL) (60 minutes, 0°C). After removing the hydrogen fluoride under a stream of nitrogen, the resin is washed with diethyl ether (3 x 30 mL) and extracted with 20% HOAc in water (3 x 30 mL) and glacial HOAc (2 x 30 mL). The aqueous extractions are combined, concentrated under reduced pressure, and lyophilized (320 mg). To remove the formyl protecting group, the crude peptide is suspended in 50 mL of aqueous 0.1 N KOH at 0°C for 2 minutes. The pH of the solution is adjusted to less than 4.0 with 10% HCl/H_2O and passed through a C 18 (60 cc) cartridge. The cartridge is

washed with H_2O (50 mL), eluted with 0.1% TFA, 70% CH_3CN in H_2O, the eluants combined, concentrated under reduced pressure (10 mL), diluted with H_2O, and lyophilized to yield 153 mg of a white powder. The crude peptide is dissolved in 4.0 mL of 50% TFA/H_2O, filtered through a 0.4 μM syringe filter, and chromatographed on a Vydac 218TP 1022 column (2.2 x 25.0 cm, 15.0 mL/min, A: 0.1% TFA/H_2O, B: 0.1% TFA/CH_3CN, Gradient; 0% B for 10 minutes, 10% to 50% B over 120 minutes). Individual fractions are collected and combined based upon analysis by analytical HPLC. The combined fractions are concentrated under reduced pressure (10 mL), diluted with H_2O (50 mL), and lyophilized (14.8 mg). The homogeneity and structure of the resulting peptide is confirmed by analytical HPLC, capillary zone electrophoresis, Proton Nuclear Magnetic Resonance Spectroscopy (H^1-NMR) and Fast Atom Bombardment Mass Spectroscopy (FAB-MS), MH^+ 848.4.

In a process analogous to Example 1 using the appropriate amino acids, the corresponding compounds of Formula I are prepared as follows:

EXAMPLE 2

D-2-Nal-Leu-Asp-Ile-Ile-Trp; FAB-MS, MH^+ 856.3.

EXAMPLE 3

Ac-D-2-Nal-Leu-Asp-Ile-Ile-Trp; FAB-MS, MH^+ 898.5.

EXAMPLE 4

D-1-Nal-Leu-Asp-Ile-Ile-Trp; MH^+ 856.3, MNa^+ 878.2.

EXAMPLE 5

Ac-D-1-Nal-Leu-Asp-Ile-Ile-Trp; MH^+ 898.5, MNa^+ 920.5.

EXAMPLE 6

Ac-D-Phe-Leu-Asp-Ile-Trp; MH^+ 735.5, MNa^+ 757.8.

EXAMPLE 7

Ac-D-His-Leu-D-Asp-Ile-D-Ile-Trp; MH^+ 838.5, MNa^+ 860.40.

EXAMPLE 8

Ac-D-Phe-Orn-Asp-Ile-Ile-Trp; MH^+ 849.1, MNa^+ 871.0.

EXAMPLE 9

Ac-D-Phe-Glu-Asp-Ile-Ile-Trp; MH^+ 864.1, MNa^+ 886.0.

EXAMPLE 10

Ac-D-Tyr-Leu-Asp-Ile-Ile-Trp; MH^+ 864.0, MNa^+ 886.3.

EXAMPLE 11

Ac-D-Phe-Asp-Ile-Ile-Trp; MH^+ 735.1, MNa^+ 757.3.

EXAMPLE 12

Fmoc-D-Phe-Leu-Asp-Ile-Ile-Trp; MH^+ 1028.1, MNa^+ 1050.3.

EXAMPLE 13

Ac-D-Dip-Leu-Asp-Ile-Ile-Trp; FAB-MS, MNa^+ 946.6.

EXAMPLE 14

Ac-D-Dip-Ile-Ile-Trp; FAB-MS, MH^+ 696.5, MNa^+ 718.5.

EXAMPLE 15

Ac-D-Dip-Asp-Ile-Ile-Trp; FAB-MS, MH^+ 810.4, MNa^+ 833.5.

EXAMPLE 16

Ac-D-Dip-Leu-Phe-Ile-Ile-Trp; FAB-MS, MNa^+ 978.3.

EXAMPLE 17

Ac-D-Dip-Leu-Asp-Ile-Lys-Trp; FAB-MS, MH^+ 939.6.

EXAMPLE 18

Ac-D-Dip-Leu-Asp-Ile-Glu-Trp; FAB-MS, MH^+ 940.9, MNa^+ 963.3.

EXAMPLE 19

Ac-D-Dip-Leu-Asp-Glu-Ile-Trp; FAB-MS, MH^+ 938.2.

EXAMPLE 20

Ac-D-Dip-Glu-Asp-Ile-Ile-Trp; FAB-MS, MH^+ 940.5.

EXAMPLE 21

Ac-D-Dip-Orn-Asp-Ile-Ile-Trp; FAB-MS, MH^+ 925.1.

EXAMPLE 22

Ac-D-Dip-Leu-Asp(NMe)-Ile-Ile-Trp; FAB-MS, MNa^+ 960.7.

EXAMPLE 23

Ac-D-Dip-D-Leu-Asp-Ile-Ile-Trp; FAB-MS, MH^+ 924.12, M^+Na 946.0.

EXAMPLE 24

N-Methyl-glucamine salt of Ac-D-Phe-Leu-Asp-Ile-Ile-Trp

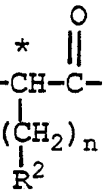
A saturated solution of N-methyl-glucamine in water is prepared, diluted with water (1:10), chilled to 0°C, and 10 mL of the solution is added to 20.45 mg of Ac-D-Phe-Leu-Asp-Ile-Ile-Trp (Example 1) with stirring. The pH of the solution is greater than 9. After 10 minutes, the solution is passed through a C18 cartridge, washed with water (100 mL), and the absorbed peptide is eluted with methanol (50 mL), concentrated under reduced pressure, resuspended in water (50 mL), and lyophilized (three times) to give the title compound.

CLAIMS

1. A compound of Formula I

$$AA^1\text{-}AA^2\text{-}AA^3\text{-}AA^4\text{-}AA^5\text{-}AA^6$$

I

wherein AA^1 is 

wherein R is

hydrogen

alkyl,

alkenyl,

alkynyl,

cycloalkyl,

cycloalkylalkyl,

aryl,

heteroaryl,

fluorenylmethyl,

 wherein R^3 and R^4 are each the same or different and each is

hydrogen,

alkyl,

alkenyl,

alkynyl,

cycloalkyl,

cycloalkylalkyl,

aryl,

heteroaryl, or

fluorenylmethyl,

$-OR^3$ wherein R^3 is as defined above,

$-\overset{O}{\overset{\|}{C}}-OR^3$ wherein R^3 is as defined above,

$-N(R^3)-\overset{O}{\overset{\|}{C}}-R^4$ wherein R^3 and R^4 are each the same or different and each is as defined above,

$-N(R^3)-\overset{O}{\overset{\|}{C}}-OR^4$ wherein R^3 and R^4 where R^4 is not hydrogen are each the same or different and each is as defined above,

$-\overset{O}{\overset{\|}{C}}-R^3$ wherein R^3 is as defined above, or

$-CH_2OR^3$ wherein R^3 is as defined above,

n is zero or an integer of 1, 2, 3, 4, 5, or 6 and

R^2 is hydrogen,

alkyl,

$-N(R^4)-R^3$ wherein R^3 and R^4 are each the same or different and each is as defined above,

$-NH-\overset{NH}{\overset{\|}{C}}-NH-R^5$ wherein R^5 is

hydrogen,

p-toluenesulfonyl,

nitro or

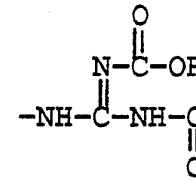
$-\overset{O}{\overset{\|}{C}}-OR^6$ wherein R^6 is

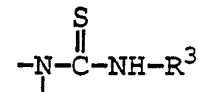
alkyl,

cycloalkyl,

aryl, or

heteroaryl,

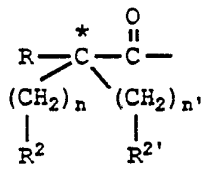

wherein R^6 is as defined above,


wherein R^3 and R^4 are each the same or different and each is as defined above,

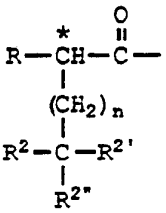
aryl,

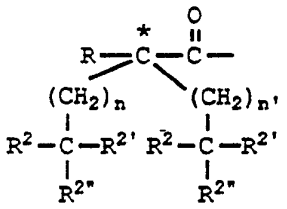
heteroaryl, or

heterocycloalkyl,

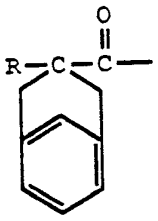

wherein n and n′ are each the same different and each is as defined above for n,

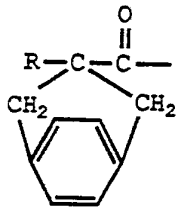
R^2 and $R^{2'}$ are each the same or different and each is as defined above for R^2, and R is as defined above,


wherein R^2, $R^{2'}$, and $R^{2''}$ are each the same or different and each is as defined above for R^2, R and n,

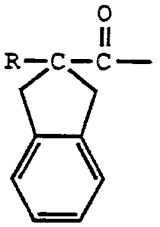

wherein n and n′ are each the same or different and each is as defined above for n,

R^2, $R^{2'}$, and $R^{2''}$ are each the same or different and each is as defined above for R^2 and R is as defined above,

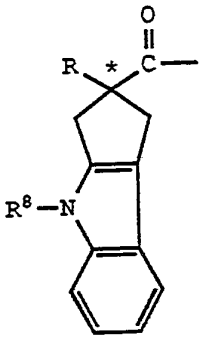

wherein R is as defined above,



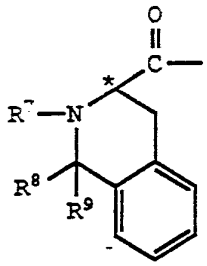
wherein R is as defined above,



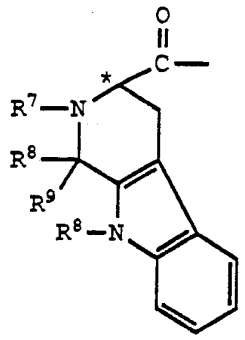
wherein R is as defined above,



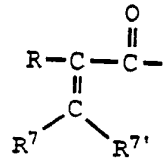
wherein R^8 is
hydrogen, or
alkyl,
and R is as defined above,



wherein R^7 is
hydrogen,
alkyl,
cycloalkyl,
aryl, or
heteroacyl,
R^8 and R^9 are each the same or different and each is as defined above for R^8

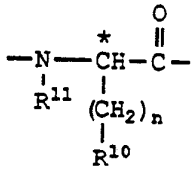


wherein R^7, R^8, and R^9 are as defined above or



wherein R^7 and $R^{7'}$ are each the same or different and each is as defined above for R^7, and R is as defined above;

AA^2, AA^3, AA^4, and AA^5 are each independently absent or each independently



wherein R^{10} is

hydrogen,

alkyl,

aryl,

cycloalkyl,

alkenyl,

alkynyl,

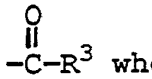
$-OR^3$ wherein R^3 is as defined above,

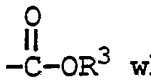
$-N(R^4)-R^3$ wherein R^3 and R^4 are each the same or different and each is as defined above,

$-C(=O)-N(R^4)-R^3$ wherein R^3 and R^4 are each the same or different and each is as defined above,

$-S(O)_mR^3$ wherein m is zero or an integer of

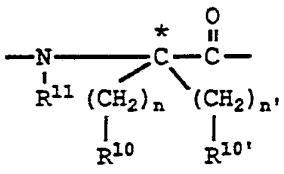
1 or 2, and R^3 is as defined above where R^3 is not hydrogen,

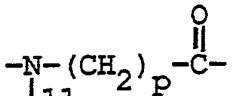

wherein R^3 is as defined above,

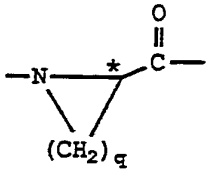

wherein R^3 is as defined above,

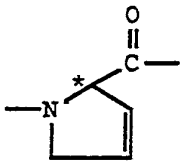
R^{11} is hydrogen, alkyl, or aryl, and

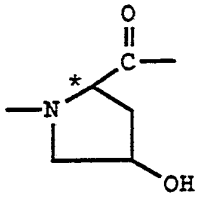
n is as defined above,

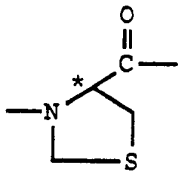

wherein n and n′ are each the same or different and each is as defined above for n, R^{10} and $R^{10'}$ are each the same or different and each is as defined above for R^{10}, and R^{11} is as defined above,


wherein p is an integer of 1, 2, 3, 4, 5, or 6 and R^{11} is as defined above,

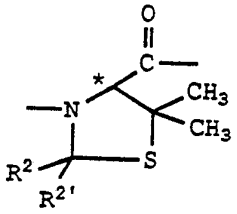

wherein q is zero or an integer of 1, 2, 3, or 4,



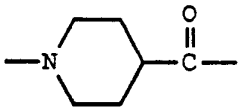




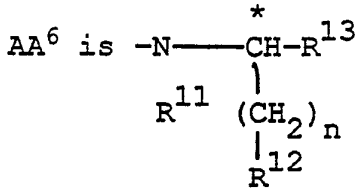
,



wherein R^2 and $R^{2'}$ are each the same or different and each is as defined above for R^2, and



;

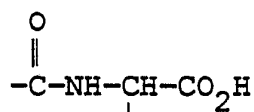
AA^6 is 

wherein R^{13} is

$-(CH_2)_n-CO_2H$ wherein n is as defined above,

$-(CH_2)_n-OH$ wherein n is as defined above,

or



wherein R^{14} is hydrogen or

$-CH_2-CO_2H$

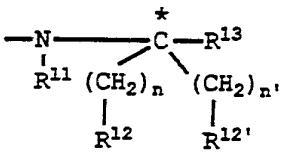
R^{12} is

aryl,

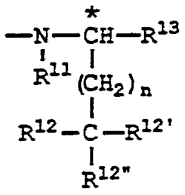
heteroaryl, or

heterocycloalkyl, and

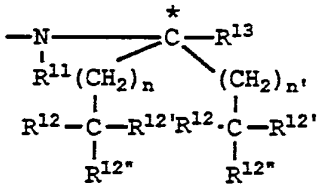
R^{11} and n are as defined above,



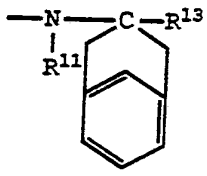
wherein n and n′ are each the same or different and each is as defined above for n, and R^{12} and $R^{12'}$ are each the same or different and each is as defined above for R^{12} and R^{11}, and R^{13} are as defined above,



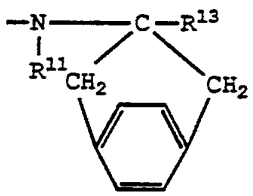
wherein R^{12}, $R^{12'}$, and $R^{12''}$ are each the same or different and each is as defined above for R^{12} and R^{11}, R^{13} and n are as defined above,



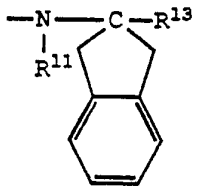
wherein n and n′ are each the same or different and each is as defined above for n, R^{12}, $R^{12'}$, and $R^{12''}$ are each the same or different and each is as defined above for R^{12}, and R^{11} and R^{13} are as defined above,



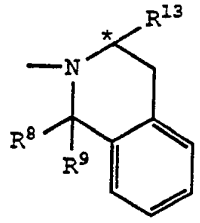
wherein R^{11} and R^{13} are as defined above,



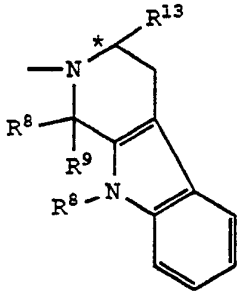
wherein R^{11} and R^{13} are as defined above,



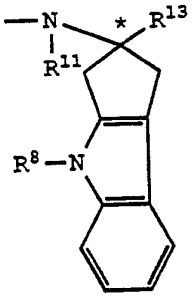
wherein R^{11} and R^{13} are as defined above,



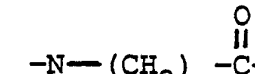
wherein R^8 and R^9 are each the same or different and each is as defined above for R^8 and R^9, and R^{13} is as defined above,



wherein R^8 and R^9 are each the same or different and each is as defined above for R^8 and R^9, and R^{13} is as defined above,



wherein R^8, R^{11}, and R^{13} are as defined above, and

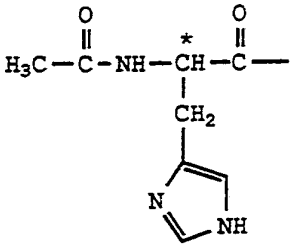


wherein R^{11} and p are as defined above;

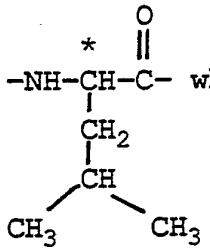
stereochemistry at * CH or * C in AA^1 is D,

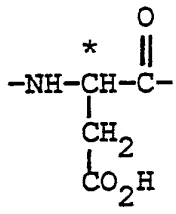
stereochemistry at * CH or * C in AA^2, AA^3, AA^4, or AA^5 is D, L, or DL and

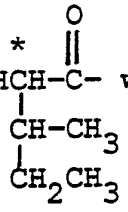
stereochemistry at CH or C in AA^6 is L; and with the exclusion of the compound wherein AA^1 is

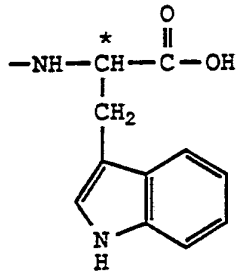


wherein CH is D stereochemistry,

AA^2 is  wherein CH is L stereochemistry,

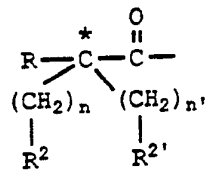
AA^3 is  wherein CH is L stereochemistry,

AA^4 and AA^5 are each  wherein CH is L stereochemistry, and

AA^6 is  wherein CH is L

stereochemistry; or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1, in which AA^1 is



wherein R is

hydrogen

alkyl,

alkenyl,

alkynyl,

cycloalkyl,

cycloalkylalkyl,

aryl,

heteroaryl,

fluorenylmethyl,

$-N(R^4)-R^3$ wherein R^3 and R^4 are each the same or different and each is

hydrogen,

alkyl,

alkenyl,

alkynyl,

cycloalkyl,

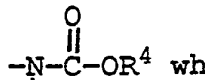
cycloalkylalkyl,

aryl,

heteroaryl, or

fluorenylmethyl,

$-N(R^4)-C(=O)-R^3$ wherein R^3 and R^4 are each the same or different and each is as defined above or


wherein R^3 and R^4 are each the same or different and each is as defined above,

n is zero,

R^2 is hydrogen or methyl,

n' is zero or an integer of 1, 2, or 3, and

$R^{2'}$ is hydrogen,

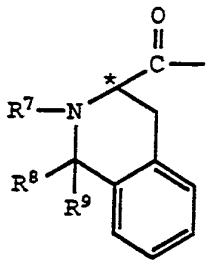
trityl,

aryl,

heteroaryl,

heterocycloalkyl,


wherein R^3 and R^4 are each the same or different and each is as defined above or



wherein R^7 is

hydrogen,

alkyl,

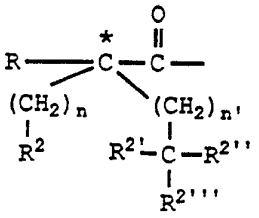
aryl, or

heteroaryl,

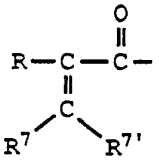
R^8 and R^9 are each the same or different and each is

hydrogen or

alkyl,

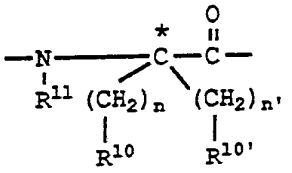


wherein $R^{2'}$, $R^{2''}$, and $R^{2'''}$ are each the same or different and each is hydrogen,
alkyl,
aryl, or
heteroaryl with the proviso that at least one of $R^{2'}$, $R^{2'''}$, and $R^{2'''}$ is aryl or heteroaryl and R^2, n, and n' are as defined above, or



wherein R^7 and $R^{7'}$ are each the same or different and each is hydrogen,
alkyl,
cycloalkyl,
aryl, or
heteroaryl.

AA^2, AA^3, AA^4, and AA^5 are each independently absent or each independently



wherein R^{11} is

hydrogen or methyl,

n is zero,

R^{10} is hydrogen or methyl,

n' is zero or an integer of 1, 2, 3, or 4 and

$R^{10'}$ is hydrogen,

alkyl,

cycloalkyl,

alkenyl,

alkynyl,

$-OR^{3'}$ wherein $R^{3'}$ is

hydrogen,

alkyl,

alkenyl,

cycloalkyl,

aryl, or

heteroaryl,

$-N(R^{4'})-R^{3'}$ wherein $R^{3'}$ and $R^{4'}$ are each the same or different and each is as defined above for $R^{3'}$,

$-C(=O)-N(R^{4'})R^{3'}$ wherein $R^{3'}$ and $R^{4'}$ are each the same or different and each is as defined above,

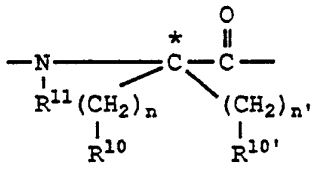
$-C(=O)-NHR^{3'}$ wherein $R^{3'}$ is as defined above,

$-C(=O)-R^{3'}$ wherein $R^{3'}$ is as defined above,

$-S(O)_mR^{3'}$ wherein m is zero or an integer of 1 of 2 and $R^{3'}$ is as defined above except that $R^{3'}$ is not hydrogen, or

$-\overset{O}{\overset{\|}{C}}-OR^{4'}$ wherein $R^{4'}$ is as defined above,

AA^6 is



wherein R^{11} is hydrogen or methyl,

n is zero,

R^{12} is hydrogen, or methyl,

n' is zero or an integer of 1, 2, or 3,

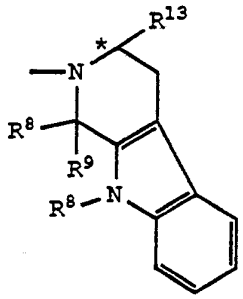
$R^{12'}$ is aryl or heteroaryl,

R^{13} is $-(CH_2)_n-CO_2H$ wherein n is as defined above,

$-(CH_2)_n-OH$ wherein n is as defined above, or

$-\overset{O}{\overset{\|}{C}}-NH-\underset{\underset{R^{14}}{|}}{CH}-CO_2H$ wherein R^{14} is hydrogen or

$-CH_2-CO_2H$, or



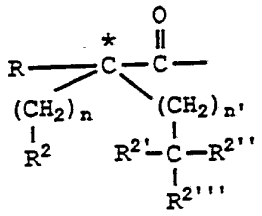
wherein R^8 and R^9 are each the same or different and each is as defined above for R^8 and R^9 and R^{13} is as defined above, and R^8

is hydrogen, formyl, acetyl, Z, Boc, Bzl, or alkyl;

stereochemistry at $\overset{*}{C}$ in AA^1 is D,

stereochemistry at $\overset{*}{C}$ in AA^2, AA^3, AA^4, or AA^5 is D, L, or DL, and stereochemistry at $\overset{*}{C}$ in AA^6 is L.

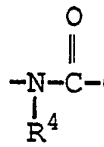
3. A compound according to Claim 2 in which AA^1 is



wherein R is

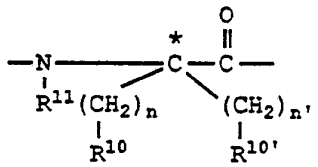
hydrogen,
alkyl,
alkenyl,
alkynyl,
cycloalkyl,
cycloalkylalkyl,
aryl,
heteroaryl,
fluorenylmethyl,
$-\underset{\underset{R^4}{|}}{N}-R^3$ wherein R^3 and R^4 are each the same or different and each is
hydrogen,
alkyl,
alkenyl,
alkynyl,
cycloalkyl,
cycloalkylalkyl,

aryl,
heteroaryl, or
fluoroenylmethyl,



wherein R^3 and R^4 are each the same or different and each is as defined above, and $R^{2'}$, $R^{2''}$, and $R^{2'''}$ are each the same or different and each is
hydrogen,
alkyl,
aryl, or
heteroaryl with the proviso that at least one of R^2, $R^{2'}$, and $R^{2''}$ is aryl or heteroaryl, and $R^{2'''}$ is hydrogen or
methyl,
R^2 is hydrogen or methyl,
n is zero, and
n' is zero or an integer of 1, 2, or 3, or

AA^2 is



wherein R^{11} is hydrogen or methyl,
n is zero,
R^{10} is hydrogen or methyl,
n' is zero or an integer of 1, 2, 3, or 4, and
R^{10} is alkyl,

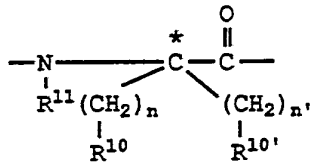
OH,

$-N-R^{3'}$ wherein $R^{3'}$ and $R^{4'}$ are each
$R^{4'}$ the same or different
and each is
hydrogen,
alkyl, or
aryl,

$-C-NR^{3'}$ wherein $R^{3'}$ and $R^{4'}$ are as
$R^{4'}$ defined above,

$-C-OR^{4'}$ wherein $R^{4'}$ is as defined above;

AA^3 is

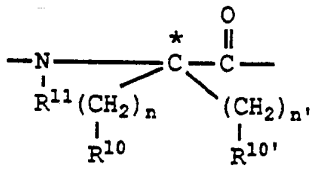


wherein R^{11} is hydrogen or methyl,
n is zero,
R^{10} is hydrogen or methyl,
n" is zero or an integer of 1, 2, or 3, and
$R^{11'}$ is alkyl,
aryl,

$-C-NR^{3'}$ wherein $R^{3'}$ and $R^{4'}$ are
$R^{4'}$ as defined above,

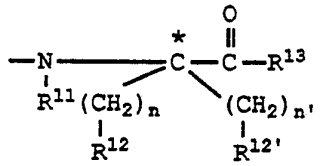
$-C-OR^{4'}$ wherein $R^{4'}$ is as
defined above,

AA^4 and AA^5 are each



wherein R^{11} is hydrogen or methyl,
n is zero,
R^{10} is hydrogen or methyl,
n' is zero, and
$R^{10'}$ is alkyl,
or cycloalkyl,

AA^6 is



wherein R^{11} is hydrogen or methyl,
n is zero,
R^{12} is hydrogen, or methyl,
n' is zero or an integer of 1, 2, of 3,
$R^{12'}$ is aryl or heteroaryl,
R^{13} is $-(CH_2)_n-CO_2H$ wherein n is zero or an integer of 1, 2, 3, 4, 5, or 6,
$-(CH_2)_n-OH$ wherein n is zero or an integer of 1, 2, 3, 4, 5, or 6, or

$-\overset{\overset{\displaystyle O}{\|}}{C}-NH-CH$ wherein R^{14} is hydrogen or $-CH_2CO_2H$,

stereochemistry at $\overset{*}{C}$ in AA^1 is D,

stereochemistry at $\overset{*}{C}$ in AA^2, AA^3, AA^4, or AA^5 is D or L and

stereochemistry at $\overset{*}{C}$ in AA^6 is L.

4. A compound according to Claim 3 in which AA^1 is

D-Dip,
D-Bip,
D-His,
D-His(Dnp),
D-2-Nal,
D-1-Nal,
D-Phe,
D-Pgl,
D-Tyr,
D-Tyr(OMe),
D-Tyr(OEt),
D-Tyr(OtBu),
D-Trp,
D-Trp(For),
D-Tic,
D-Tza,
D-Pyr,
Ac-D-Dip,
Ac-D-Bip,
Ac-D-His,
Ac-D-His(Dnp),

Ac-D-2-Nal,
Ac-D-1-Nal,
Ac-D-Phe,
Ac-D-Pgl,
Ac-D-Tyr,
Ac-D-Tyr(OMe),
Ac-D-Tyr(OEt),
Ac-D-Tyr(OtBu),
Ac-D-Trp,
Ac-D-Trp(For),
Ac-D-Tic,
Ac-D-Tza,
Ac-D-Pyr,
Ada-D-Dip,
Ada-D-Bip,
Ada-D-His,
Ada-D-His(Dnp),
Ada-D-2-Nal,
Ada-D-1-Nal,
Ada-D-Phe,
Ada-D-Pgl,
Ada-D-Tyr,
Ada-D-Tyr(OMe),
Ada-D-Tyr(OEt),
Ada-D-Tyr(OtBu),
Ada-D-Trp,
Ada-D-Trp(For),
Ada-D-Tic,
Ada-D-Tza,
Ada-D-Pyr,
Adoc-D-Dip,
Adoc-D-Bip,
Adoc-D-His,
Adoc-D-His(Dnp),

Adoc-D-2-Nal,
Adoc-D-1-Nal,
Adoc-D-Phe,
Adoc-D-Pgl,
Adoc-D-Tyr,
Adoc-D-Tyr(OMe),
Adoc-D-Tyr(OEt),
Adoc-D-Tyr(OtBu),
Adoc-D-Trp,
Adoc-D-Trp(For),
Adoc-D-Tic,
Adoc-D-Tza,
Adoc-D-Pyr,
Boc-D-Dip,
Boc-D-Bip,
Boc-D-His,
Boc-D-His(Dnp),
Boc-D-2-Nal,
Boc-D-1-Nal,
Boc-D-Phe,
Boc-D-Pgl,
Boc-D-Tyr,
Boc-D-Tyr(OMe),
Boc-D-Tyr(OEt),
Boc-D-Tyr(OtBu),
Boc-D-Trp,
Boc-D-Trp(For),
Boc-D-Tic,
Boc-D-Tza,
Boc-D-Pyr,
Z-D-Dip,
Z-D-Bip,
Z-D-His,
Z-D-His(Dnp),

Z-D-2-Nal,
Z-D-1-Nal,
Z-D-Phe,
Z-D-Pgl,
Z-D-Tyr,
Z-D-Tyr(OMe),
Z-D-Tyr(OEt),
Z-D-Tyr(OtBu),
Z-D-Trp,
Z-D-Trp(For),
Z-D-Tic,
Z-D-Tza,
Z-D-Pyr,
Fmoc-D-Dip,
Fmoc-D-Bip,
Fmoc-D-His,
Fmoc-D-His(Dnp),
Fmoc-D-2-Nal,
Fmoc-D-1-Nal,
Fmoc-D-Phe,
Fmoc-D-Pgl,
Fmoc-D-Tyr,
Fmoc-D-Tyr(OMe),
Fmoc-D-Tyr(OEt),
Fmoc-D-Tyr(OtBu),
Fmoc-D-Trp,
Fmoc-D-Trp(For),
Fmoc-D-Tic,
Fmoc-D-Tza,
Fmoc-D-Pyr, or

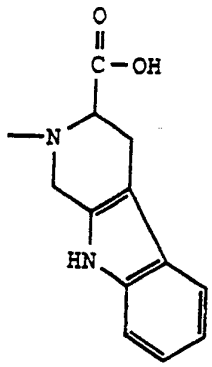
AA^2 is Ala,
Alg,
Arg
Asn,

Asp,
Dab,
Glu,
Gln,
Gly,
homoArg,
homoGlu,
homoLys,
Ile,
Leu,
D-Leu,
Lys,
Met,
Met(O),
Met(O_2),
Nva,
Nle,
Orn,
Phe,
Tyr,
Val, or
AA^2 is absent;

AA^3 is Asn,
Asp,
D-Asp,
N-MeAsp,
Glu,
Gln,
homoPhe,
Phe,
Tyr, or
AA^3 is absent;

AA^4 is Ala,
Chx,

Gly,
Glu,
Ile,
D-Ile,
Leu,
Nleu,
Nval,
Val, or
AA^4 is absent;
AA^5 is Ala,
Chx,
Gly,
Ile,
D-Ile,
Leu,
Nleu,
Nval,
Val, or
AA^5 is absent; and
AA^6 is 2-Nal,
1-Nal,
Pyr,
Trp,
Tyr(OMe),
Tyr(OEt),
Tyr(Ot-Bu),
Tyr,
Trp-Gly,
Trp-Asp,
Trp(For),
Dip,
Phe,
Bza, or



5. A compound according to Claim 4 selected from the groups consisting of:
D-Phe-Leu-Asp-Ile-Ile-Trp;
D-His(Dnp)-Leu-Asp-Ile-Ile-Trp;
D-Trp-Leu-Asp-Ile-Ile-Trp;
D-Tyr-Leu-Asp-Ile-Ile-Trp;
D-Tyr(OMe)-Leu-Asp-Ile-Ile-Trp;
D-Tyr(OEt)-Leu-Asp-Ile-Ile-Trp;
D-2-Nal-Leu-Asp-Ile-Ile-Trp;
D-1-Nal-Leu-Asp-Ile-Ile-Trp;
D-Pgl-Leu-Asp-Ile-Ile-Trp;
D-Pyr-Leu-Asp-Ile-Ile-Trp;
D-Tic-Leu-Asp-Ile-Ile-Trp;
D-Dip-Leu-Asp-Ile-Ile-Trp;
D-Bip-Leu-Asp-Ile-Ile-Trp;
Ac-D-Phe-Leu-Asp-Ile-Ile-Trp;
Ac-D-His(Dnp)-Leu-Asp-Ile-Ile-Trp;
Ac-D-Trp-Leu-Asp-Ile-Ile-Trp;
Ac-D-Tyr-Leu-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Leu-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Leu-Asp-Ile-Ile-Trp;
Ac-D-2-Nal-Leu-Asp-Ile-Ile-Trp;
Ac-D-1-Nal-Leu-Asp-Ile-Ile-Trp;
Ac-D-Pgl-Leu-Asp-Ile-Ile-Trp;
Ac-D-Pyr-Leu-Asp-Ile-Ile-Trp;
Ac-D-Tic-Leu-Asp-Ile-Ile-Trp;
Ac-D-Dip-Leu-Asp-Ile-Ile-Trp;
Ac-D-Bip-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-Phe-Leu-Asp-Ile-Ile-Trp;

Fmoc-D-His-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-Trp-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-Tyr-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-Tyr(OMe)-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-Tyr(OEt)-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-2-Nal-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-1-Nal-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-Dip-Leu-Asp-Ile-Ile-Trp;
Fmoc-D-Bip-Leu-Asp-Ile-Ile-Trp;
Ada-D-Phe-Leu-Asp-Ile-Ile-Trp;
Ada-D-His-Leu-Asp-Ile-Ile-Trp;
Ada-D-Trp-Leu-Asp-Ile-Ile-Trp;
Ada-D-Tyr-Leu-Asp-Ile-Ile-Trp;
Ada-D-Tyr(OMe)-Leu-Asp-Ile-Ile-Trp;
Ada-D-Tyr(OEt)-Leu-Asp-Ile-Ile-Trp;
Ada-D-2-Nal-Leu-Asp-Ile-Ile-Trp;
Ada-D-1-Nal-Leu-Asp-Ile-Ile-Trp;
Ada-D-Dip-Leu-Asp-Ile-Ile-Trp;
Ada-D-Bip-Leu-Asp-Ile-Ile-Trp;
Ac-D-Phe-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-His-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-Trp-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-Tyr-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-2-Nal-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-1-Nal-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-Dip-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-Bip-D-Leu-Asp-Ile-Ile-Trp;
Ac-D-Phe-Ile-Asp-Ile-Ile-Trp;
Ac-D-His-Ile-Asp-Ile-Ile-Trp;
Ac-D-Trp-Ile-Asp-Ile-Ile-Trp;
Ac-D-Tyr-Ile-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Ile-Asp-Ile-Ile-Trp;

Ac-D-Tyr(OEt)-Ile-Asp-Ile-Ile-Trp;
Ac-D-2-Nal-Ile-Asp-Ile-Ile-Trp;
Ac-D-1-Nal-Ile-Asp-Ile-Ile-Trp;
Ac-D-Dip-Ile-Asp-Ile-Ile-Trp;
Ac-D-Bip-Ile-Asp-Ile-Ile-Trp;
Ac-D-Phe-Val-Asp-Ile-Ile-Trp;
Ac-D-His-Val-Asp-Ile-Ile-Trp;
Ac-D-Trp-Val-Asp-Ile-Ile-Trp;
Ac-D-Tyr-Val-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Val-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Val-Asp-Ile-Ile-Trp;
Ac-D-2-Nal-Val-Asp-Ile-Ile-Trp;
Ac-D-1-Nal-Val-Asp-Ile-Ile-Trp;
Ac-D-Dip-Val-Asp-Ile-Ile-Trp;
Ac-D-Bip-Val-Asp-Ile-Ile-Trp;
Ac-DPhe-Dab-Asp-Ile-Ile-Trp;
Ac-DHis-Dab-Asp-Ile-Ile-Trp;
Ac-DTrp-Dab-Asp-Ile-Ile-Trp;
Ac-DTyr(OMe)-Dab-Asp-Ile-Ile-Trp;
Ac-DTyr(OEt)-Dab-Asp-Ile-Ile-Trp;
Ac-D2Nal-Dab-Asp-Ile-Ile-Trp;
Ac-D3Nal-Dab-Asp-Ile-Ile-Trp;
Ac-DDip-Dab-Asp-Ile-Ile-Trp;
Ac-DBip-Dab-Asp-Ile-Ile-Trp;
Ac-DPhe-Arg-Asp-Ile-Ile-Trp;
Ac-DHis-Arg-Asp-Ile-Ile-Trp;
Ac-DTrp-Arg-Asp-Ile-Ile-Trp;
Ac-DTyr(OMe)-Arg-Asp-Ile-Ile-Trp;
Ac-DTyr(OEt)-Arg-Asp-Ile-Ile-Trp;
Ac-D2Nal-Arg-Asp-Ile-Ile-Trp;
Ac-D3Nal-Arg-Asp-Ile-Ile-Trp;
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Ac-DHis-Asp-Asp-Ile-Ile-Trp;
Ac-DTrp-Asp-Asp-Ile-Ile-Trp;
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Ac-DBip-Asp-Asp-Ile-Ile-Trp;
Ac-D-Phe-Lys-Asp-Ile-Ile-Trp;
Ac-D-His-Lys-Asp-Ile-Ile-Trp;
Ac-D-Trp-Lys-Asp-Ile-Ile-Trp;
Ac-D-Tyr-Lys-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Lys-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Lys-Asp-Ile-Ile-Trp;
Ac-D-2-Nal-Lys-Asp-Ile-Ile-Trp;
Ac-D-1-Nal-Lys-Asp-Ile-Ile-Trp;
Ac-D-Phe-Orn-Asp-Ile-Ile-Trp;
Ac-D-His-Orn-Asp-Ile-Ile-Trp;
Ac-D-Trp-Orn-Asp-Ile-Ile-Trp;
Ac-D-Tyr-Orn-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Orn-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Orn-Asp-Ile-Ile-Trp;
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Ac-D-Trp-Gln-Asp-Ile-Ile-Trp;
Ac-D-Tyr-Gln-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Gln-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Gln-Asp-Ile-Ile-Trp;
Ac-D-2-Nal-Gln-Asp-Ile-Ile-Trp;
Ac-D-1-Nal-Gln-Asp-Ile-Ile-Trp;
Ac-D-Phe-Leu-Glu-Ile-Ile-Trp;
Ac-D-His-Leu-Glu-Ile-Ile-Trp;
Ac-D-Trp-Leu-Glu-Ile-Ile-Trp;
Ac-D-Tyr-Leu-Glu-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Leu-Glu-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Leu-Glu-Ile-Ile-Trp;
Ac-D-2-Nal-Leu-Glu-Ile-Ile-Trp;
Ac-D-1-Nal-Leu-Glu-Ile-Ile-Trp;
Ac-D-Phe-Leu-Asn-Ile-Ile-Trp;

Ac-D-His-Leu-Asn-Ile-Ile-Trp;
Ac-D-Trp-Leu-Asn-Ile-Ile-Trp;
Ac-D-Tyr-Leu-Asn-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Leu-Asn-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Leu-Asn-Ile-Ile-Trp;
Ac-D-2-Nal-Leu-Asn-Ile-Ile-Trp;
Ac-D-1-Nal-Leu-Asn-Ile-Ile-Trp;
Ac-D-Dip-Leu-Asn-Ile-Ile-Trp;
Ac-D-Bip-Leu-Asn-Ile-Ile-Trp;
Ac-DPhe-Leu-Phe-Ile-Ile-Trp;
Ac-DHis-Leu-Phe-Ile-Ile-Trp;
Ac-DTrp-Leu-Phe-Ile-Ile-Trp;
Ac-DTyr(OMe)-Leu-Phe-Ile-Ile-Trp;
Ac-DTyr(OEt)-Leu-Phe-Ile-Ile-Trp;
Ac-D2Nal-Leu-Phe-Ile-Ile-Trp;
Ac-D3Nal-Leu-Phe-Ile-Ile-Trp;
Ac-DDip-Leu-Phe-Ile-Ile-Trp;
Ac-DBip-Leu-Phe-Ile-Ile-Trp;
Ac-D-Phe-Glu-Asp-Ile-Ile-Trp;
Ac-D-Phe-Leu-Asp-Val-Ile-Trp;
Ac-D-His-Leu-Asp-Val-Ile-Trp;
Ac-D-Trp-Leu-Asp-Val-Ile-Trp;
Ac-D-Tyr-Leu-Asp-Val-Ile-Trp;
Ac-D-Tyr(OMe)-Leu-Asp-Val-Ile-Trp;
Ac-D-Tyr(OEt)-Leu-Asp-Val-Ile-Trp;
Ac-D-2-Nal-Leu-Asp-Val-Ile-Trp;
Ac-D-1-Nal-Leu-Asp-Val-Ile-Trp;
Ac-D-Dip-Leu-Asp-Val-Ile-Trp;
Ac-D-Bip-Leu-Asp-Val-Ile-Trp;
Ac-D-Phe-Leu-Asp-Chx-Ile-Trp;
Ac-D-His-Leu-Asp-Chx-Ile-Trp;
Ac-D-Trp-Leu-Asp-Chx-Ile-Trp;
Ac-D-Tyr-Leu-Asp-Chx-Ile-Trp;
Ac-D-Tyr(OMe)-Leu-Asp-Chx-Ile-Trp;

Ac-D-Tyr(OEt)-Leu-Asp-Chx-Ile-Trp;
Ac-D-2-Nal-Leu-Asp-Chx-Ile-Trp;
Ac-D-1-Nal-Leu-Asp-Chx-Ile-Trp;
Ac-D-Dip-Leu-Asp-Chx-Ile-Trp;
Ac-D-Bip-Leu-Asp-Chx-Ile-Trp;
Ac-D-Phe-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-His-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-Trp-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-Tyr-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-2-Nal-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-1-Nal-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-Dip-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-Bip-Leu-Asp-D-Ile-Ile-Trp;
Ac-D-Phe-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-His-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-Trp-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-Tyr-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-Tyr(OMe)-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-Tyr(OEt)-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-2-Nal-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-1-Nal-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-Dip-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-Bip-Leu-Asp-Ile-D-Ile-Trp;
Ac-D-Phe-Leu-Asp-Ile-Val-Trp;
Ac-D-His-Leu-Asp-Ile-Val-Trp;
Ac-D-Trp-Leu-Asp-Ile-Val-Trp;
Ac-D-Tyr-Leu-Asp-Ile-Val-Trp;
Ac-D-Tyr(OMe)-Leu-Asp-Ile-Val-Trp;
Ac-D-Tyr(OEt)-Leu-Asp-Ile-Val-Trp;
Ac-D-2-Nal-Leu-Asp-Ile-Val-Trp;
Ac-D-1-Nal-Leu-Asp-Ile-Val-Trp;
Ac-D-Dip-Leu-Asp-Ile-Val-Trp;

Ac-D-Bip-Leu-Asp-Ile-Val-Trp;
Ac-D-Phe-Leu-Asp-Ile-Chx-Trp;
Ac-D-His-Leu-Asp-Ile-Chx-Trp;
Ac-D-Trp-Leu-Asp-Ile-Chx-Trp;
Ac-D-Tyr-Leu-Asp-Ile-Chx-Trp;
Ac-D-Tyr(OMe)-Leu-Asp-Ile-Chx-Trp;
Ac-D-Tyr(OEt)-Leu-Asp-Ile-Chx-Trp;
Ac-D-2-Nal-Leu-Asp-Ile-Chx-Trp;
Ac-D-1-Nal-Leu-Asp-Ile-Chx-Trp;
Ac-D-Dip-Leu-Asp-Ile-Chx-Trp;
Ac-D-Bip-Leu-Asp-Ile-Chx-Trp;
Ac-D-Phe-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-His-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-Trp-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-Tyr-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-Tyr(OMe)-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-Tyr(OEt)-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-2-Nal-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-1-Nal-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-Dip-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-Bip-Leu-Asp-Ile-Ile-2-Nal;
Ac-D-Phe-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-His-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-Trp-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-Tyr-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-Tyr(OMe)-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-Tyr(OEt)-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-2-Nal-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-1-Nal-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-Dip-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-Bip-Leu-Asp-Ile-Ile-1-Nal;
Ac-D-His-Leu-D-Asp-Ile-D-Ile-Trp;
Ac-D-Phe-Leu-D-Asp-Ile-D-Ile-Trp;
Ac-D-Bip-Leu-D-Asp-Ile-D-Ile-Trp;

Ac-D-Dip-Leu-D-Asp-Ile-D-Ile-Trp;
Ac-D-2-Nal-Leu-D-Asp-Ile-D-Ile-Trp;
Ac-D-1-Nal-Leu-D-Asp-Ile-D-Ile-Trp;
Ac-D-Trp-Leu-D-Asp-Ile-D-Ile-Trp;
Ac-D-Dip-Asn-Ile-Ile-Trp;
Ac-D-Dip-Phe-Ile-Ile-Trp;
Ac-D-Dip-Ile-Ile-Trp;
Ac-D-Dip-Asp-Ile-Ile-Trp;
Ac-D(NMe)-Dip-Leu-Asp-Ile-Ile-Trp;
Ac-D-Dip-Leu-Asp-Ile-Ile-(NMe)Trp;
Ac-D-Dip-Leu-Asp-Ile-(NMe)Ile-Trp;
Ac-D-Dip-Leu-Asp-(NMe)Ile-Ile-Trp;
Ac-D-Dip-Leu-(NMe)Asp-Ile-Ile-Trp;
Ac-D-Dip-(NMe)Leu-Asp-Ile-Ile-Trp;
Ac-D-Phe-Asp-Ile-Ile-Trp;
Ac-D-His-Asp-Ile-Ile-Trp;
Ac-D-Trp-Asp-Ile-Ile-Trp;
Ac-D-Tyr-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OMe)-Asp-Ile-Ile-Trp;
Ac-D-Tyr(OEt)-Asp-Ile-Ile-Trp;
Ac-D-2-Nal-Asp-Ile-Ile-Trp;
Ac-D-1-Nal-Asp-Ile-Ile-Trp;
Ada-D-Phe-Asp-Ile-Ile-Trp;
Ada-D-His-Asp-Ile-Ile-Trp;
Ada-D-Trp-Asp-Ile-Ile-Trp;
Ada-D-Tyr-Asp-Ile-Ile-Trp;
Ada-D-Tyr(OMe)-Asp-Ile-Ile-Trp;
Ada-D-Tyr(OEt)-Asp-Ile-Ile-Trp;
Ada-D-2-Nal-Asp-Ile-Ile-Trp;
Ada-D-1-Nal-Asp-Ile-Ile-Trp;
Ada-D-Dip-Asp-Ile-Ile-Trp;
Ada-D-Bip-Asp-Ile-Ile-Trp;
Ac-D-Phe-Asp-Ile-Ile-2-Nal;
Ac-D-Phe-Asp-Ile-Ile-1-Nal;

Ac-D-His-Asp-Ile-Ile-2-Nal;
Ac-D-His-Asp-Ile-Ile-1-Nal;
Ac-D-Tyr-Asp-Ile-Ile-2-Nal;
Ac-D-Tyr-Asp-Ile-Ile-1-Nal;
Ac-D-Trp-Asp-Ile-Ile-2-Nal;
Ac-D-Trp-Asp-Ile-Ile-1-Nal;
Ac-D-Dip-Asp-Ile-Ile-2-Nal;
Ac-D-Dip-Asp-Ile-Ile-1-Nal;
Ac-D-Bip-Asp-Ile-Ile-2-Nal;
Ac-D-Bip-Asp-Ile-Ile-1-Nal;
Ac-D-Phe-Leu-Asp-Ile-Trp;
Ac-D-His-Leu-Asp-Ile-Trp;
Ac-D-Tyr-Leu-Asp-Ile-Trp;
Ac-D-Dip-Leu-Asp-Ile-Trp;
Ac-D-Trp-Leu-Asp-Ile-Trp;
Ac-DPhe-Leu-Asp-Ile-Ile-Trp-Gly;
Ac-DHis-Leu-Asp-Ile-Ile-Trp-Gly;
Ac-DTrp-Leu-Asp-Ile-Ile-Trp-Gly;
Ac-DTyr(OMe)-Leu-Asp-Ile-Ile-Trp-Gly;
Ac-DTyr(OEt)-Leu-Asp-Ile-Ile-Trp-Gly;
Ac-D2Nal-Leu-Asp-Ile-Ile-Trp-Gly;
Ac-D3Nal-Leu-Asp-Ile-Ile-Trp-Gly;
Ac-DDip-Leu-Asp-Ile-Ile-Trp-Gly;
Ac-DBip-Leu-Asp-Ile-Ile-Trp-Gly;
Ac-DPhe-Leu-Asp-Ile-Ile-Trp-Asp;
Ac-DHis-Leu-Asp-Ile-Ile-Trp-Asp;
Ac-DTrp-Leu-Asp-Ile-Ile-Trp-Asp;
Ac-DTyr(OMe)-Leu-Asp-Ile-Ile-Trp-Asp;
Ac-DTyr(OEt)-Leu-Asp-Ile-Ile-Trp-Asp;
Ac-D2Nal-Leu-Asp-Ile-Ile-Trp-Asp;
Ac-D3Nal-Leu-Asp-Ile-Ile-Trp-Asp;
Ac-DDip-Leu-Asp-Ile-Ile-Trp-Asp; and
Ac-DBip-Leu-Asp-Ile-Ile-Trp-Asp-Asp.

6. A compound according to Claim 5 selected from the group consisting of:
Ac-D-Phe-Leu-Asp-Ile-Ile-Trp;
D-2-Nal-Leu-Asp-Ile-Ile-Trp;
Ac-D-2-Nal-Leu-Asp-Ile-Ile-Trp;
D-1-Nal-Leu-Asp-Ile-Ile-Trp;
Ac-D-Phe-Leu-Asp-Ile-Trp;
Ac-D-His-Leu-D-Asp-Ile-D-Ile-Trp;
Ac-D-Phe-Orn-Asp-Ile-Ile-Trp;
Ac-D-Phe-Glu-Asp-Ile-Ile-Trp;
Ac-D-Tyr-Leu-Asp-Ile-Ile-Trp;
Ac-D-Phe-Asp-Ile-Ile-Trp;
Fmoc-D-Phe-Leu-Asp-Ile-Ile-Trp;
Ac-D-Dip-Leu-Asp-Ile-Ile-Trp;
Ac-D-Dip-Ile-Ile-Trp;
Ac-D-Dip-Asp-Ile-Ile-Trp;
Ac-D-Dip-Leu-Phe-Ile-Ile-Trp;
Ac-D-Dip-Leu-Asp-Ile-Lys-Trp;
Ac-D-Dip-Leu-Asp-Ile-Glu-Trp;
Ac-D-Dip-Leu-Asp-Glu-Ile-Trp;
Ac-D-Dip-Glu-Asp-Ile-Ile-Trp;
Ac-D-Dip-Orn-Asp-Ile-Ile-Trp;
Ac-D-Dip-Leu-Asp(N-Me)-Ile-Ile-Trp; and
Ac-D-Dip-D-Leu-Asp-Ile-Ile-Trp.

7. A method of inhibiting elevated levels of endothelin comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

8. A pharmaceutical composition adapted for administration as an antagonist of endothelin comprising a therapeutically effective amount of

a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

9. A method of treating hypertension comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

10. A pharmaceutical composition adapted for administration as an antihypertensive agent comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

11. A method of treating metabolic and endocrine disorders comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

12. A pharmaceutical composition adapted for administration as an agent for treating metabolic and endocrine disorders comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

13. A method of treating congestive heart failure and myocardial infarction comprising administering to a host suffering therefrom a

therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

14. A pharmaceutical composition adapted for administration as an agent for treating congestive heart failure and myocardial infarction comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

15. A method of treating endotoxic shock comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

16. A pharmaceutical composition adapted for administration as an agent for treating endotoxic shock comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

17. A method of treating subarachnoid hemorrhage comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

18. A pharmaceutical composition adapted for administration as an agent for treating subarachnoid hemorrhage comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a

pharmaceutically acceptable excipient, diluent or carrier.

19. A method of treating arrhythmias comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

20. A pharmaceutical composition adapted for administration as an agent for treating arrhythmias comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

21. A method of treating asthma comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

22. A pharmaceutical composition adapted for administration as an agent for treating asthma comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

23. A method of treating acute renal failure comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

24. A pharmaceutical composition adapted for administration as an agent for treating acute renal failure comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

25. A method of treating preeclampsia comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

26. A pharmaceutical composition adapted for administration as an agent for treating preeclampsia comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

27. A method of treating diabetes comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

28. A pharmaceutical composition adapted for administration as an agent for treating diabetes comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

29. A method of treating neurological disorders comprising administering to a host suffering therefrom a therapeutically effective amount of

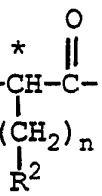
a compound according to Claim 1 in unit dosage form.

30. A pharmaceutical composition adapted for administration as an agent for treating neurological disorders comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

31. A method of preparing a compound of Formula I

$$AA^1\text{-}AA^2\text{-}AA^3\text{-}AA^4\text{-}AA^5\text{-}AA^6$$

I

wherein AA^1 is 

wherein R is

hydrogen
alkyl,
alkenyl,
alkynyl,
cycloalkyl,
cycloalkylalkyl,
aryl,
heteroaryl,
fluorenylmethyl,
 wherein R^3 and R^4 are each the same or different and each is
hydrogen,

alkyl,
alkenyl,
alkynyl,
cycloalkyl,
cycloalkylalkyl,
aryl,
heteroaryl, or
fluorenylmethyl,

$-OR^3$ wherein R^3 is as defined above,

$-\overset{O}{\overset{\|}{C}}-OR^3$ wherein R^3 is as defined above,

$-N(R^3)-\overset{O}{\overset{\|}{C}}-R^4$ wherein R^3 and R^4 are each the same or different and each is as defined above,

$-N(R^3)-\overset{O}{\overset{\|}{C}}-OR^4$ wherein R^3 and R^4 where R^4 is not hydrogen are each the same or different and each is as defined above,

$-\overset{O}{\overset{\|}{C}}-R^3$ wherein R^3 is as defined above, or

$-CH_2OR^3$ wherein R^3 is as defined above,

n is zero or an integer of 1, 2, 3, 4, 5, or 6 and

R^2 is hydrogen,
alkyl,

$-N(R^4)-R^3$ wherein R^3 and R^4 are each the same or different and each is as defined above,

$-NH-\overset{NH}{\overset{\|}{C}}-NH-R^5$ wherein R^5 is
hydrogen,
p-toluenesulfonyl,

nitro or



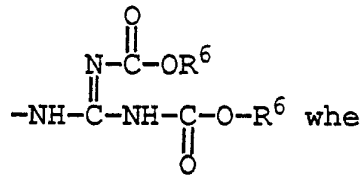
wherein R^6 is

alkyl,

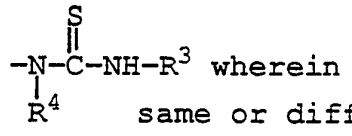
cycloalkyl,

aryl, or

heteroaryl,



wherein R^6 is as defined above,

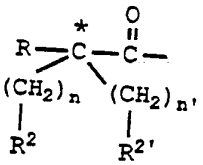


wherein R^3 and R^4 are each the same or different and each is as defined above,

aryl,

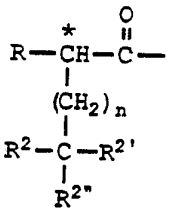
heteroaryl, or

heterocycloalkyl,

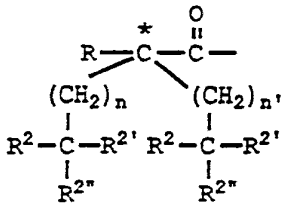


wherein n and n′ are each the same different and each is as defined above for n,

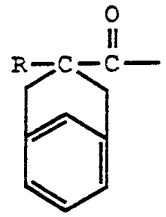
R^2 and $R^{2'}$ are each the same or different and each is as defined above for R^2, and R is as defined above,



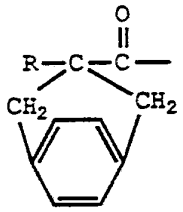
wherein R^2, $R^{2'}$, and $R^{2''}$ are each the same or different and each is as defined above for R^2, R and n,



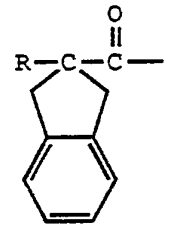
wherein n and n′ are each the same or different and each is as defined above for n,
R^2, $R^{2'}$, and $R^{2''}$ are each the same or different and each is as defined above for R^2 and R is as defined above,



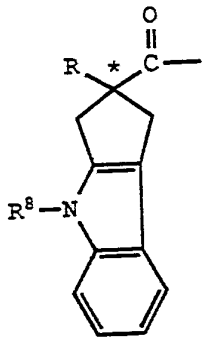
wherein R is as defined above,



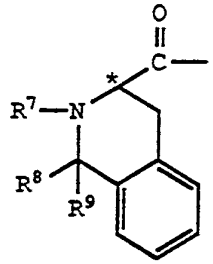
wherein R is as defined above,



wherein R is as defined above,

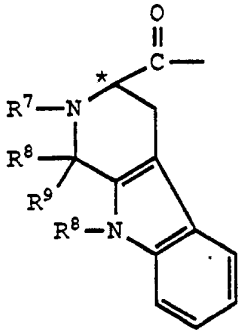


wherein R^8 is
hydrogen, or
alkyl,
and R is as defined above,

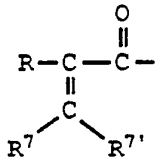


wherein R^7 is
hydrogen,

alkyl,
cycloalkyl,
aryl, or
heteroacyl,
R^8 and R^9 are each the same or different and each is as defined above for R^8

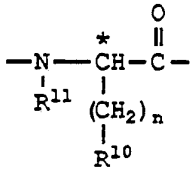


wherein R^7, R^8, and R^9 are as defined above or



wherein R^7 and $R^{7'}$ are each the same or different and each is as defined above for R^7, and R is as defined above;

AA^2, AA^3, AA^4, and AA^5 are each independently absent or each independently



wherein R^{10} is
hydrogen,
alkyl,
aryl,
cycloalkyl,
alkenyl,
alkynyl,

$-OR^3$ wherein R^3 is as defined above,

$-N(R^4)-R^3$ wherein R^3 and R^4 are each the same or different and each is as defined above,

$-C(=O)-N(R^4)-R^3$ wherein R^3 and R^4 are each the same or different and each is as defined above,

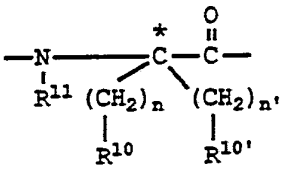
$-S(O)_m R^3$ wherein m is zero or an integer of 1 or 2, and R^3 is as defined above where R^3 is not hydrogen,

$-C(=O)-R^3$ wherein R^3 is as defined above,

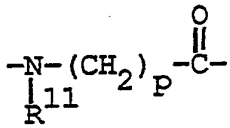
$-C(=O)-OR^3$ wherein R^3 is as defined above,

R^{11} is hydrogen, alkyl, or aryl, and

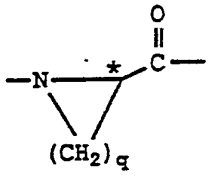
n is as defined above,



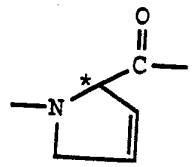
wherein n and n′ are each the same or different and each is as defined above for n, R^{10} and $R^{10'}$ are each the same or different and each is as defined above for R^{10}, and R^{11} is as defined above,



wherein p is an integer of 1, 2, 3, 4, 5, or 6 and R^{11} is as defined above,



wherein q is zero or an integer of 1, 2, 3, or 4,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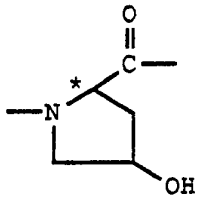
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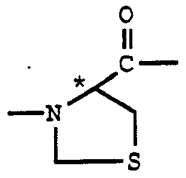
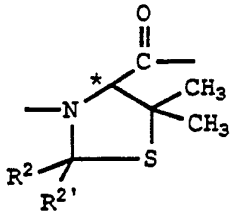
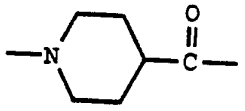
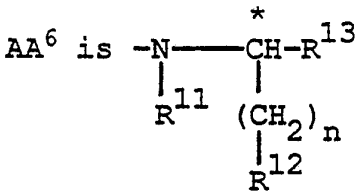

,



wherein R^2 and $R^{2'}$ are each the same or different and each is as defined above for R^2, and


;

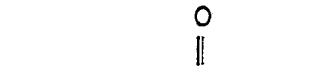
AA^6 is 

wherein R^{13} is

$-(CH_2)_n-CO_2H$ wherein n is as defined above,

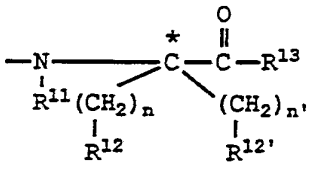
$-(CH_2)_n-OH$ wherein n is as defined above,

or

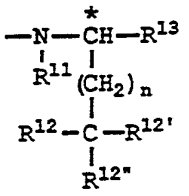


wherein R^{14} is hydrogen or $-CH_2-CO_2H$

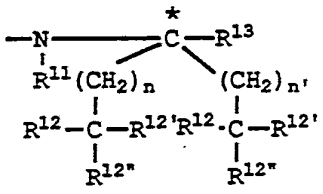
R^{12} is aryl, heteroaryl, or heterocycloalkyl, and R^{11} and n are as defined above,



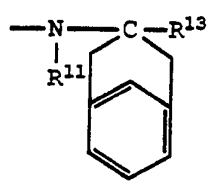
wherein n and n′ are each the same or different and each is as defined above for n, and R^{12} and $R^{12'}$ are each the same or different and each is as defined above for R^{12} and R^{11}, and R^{13} are as defined above,



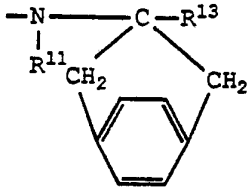
wherein R^{12}, $R^{12'}$, and $R^{12''}$ are each the same or different and each is as defined above for R^{12} and R^{11}, R^{13} and n are as defined above,



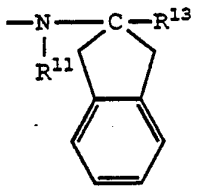
wherein n and n′ are each the same or different and each is as defined above for n, R^{12}, $R^{12'}$, and $R^{12''}$ are each the same or different and each is as defined above for R^{12}, and R^{11} and R^{13} are as defined above,



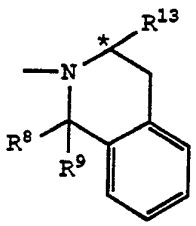
wherein R^{11} and R^{13} are as defined above,



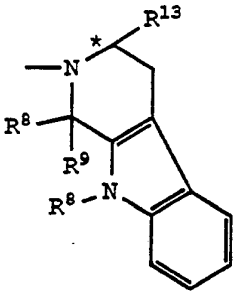
wherein R^{11} and R^{13} are as defined above,



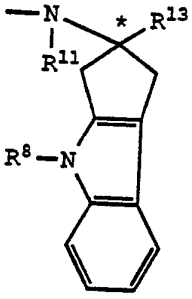
wherein R^{11} and R^{13} are as defined above,



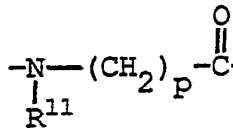
wherein R^8 and R^9 are each the same or different and each is as defined above for R^8 and R^9, and R^{13} is as defined above,



wherein R^8 and R^9 are each the same or different and each is as defined above for R^8 and R^9, and R^{13} is as defined above,



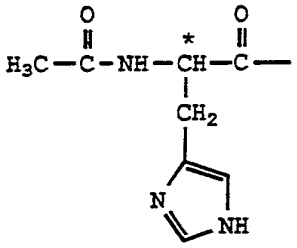
wherein R^8, R^{11}, and R^{13} are as defined above, and

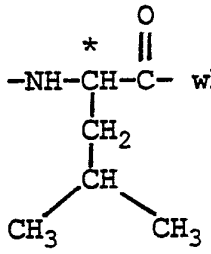

wherein R^{11} and p are as defined above;

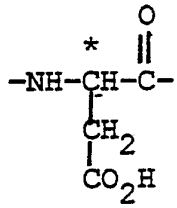
stereochemistry at * CH or * C in AA^1 is D,

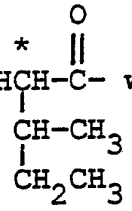
stereochemistry at * CH or * C in AA^2, AA^3, AA^4, or AA^5 is D, L, or DL and

stereochemistry at * CH or * C in AA^6 is L; and with the exclusion of the compound wherein AA^1 is

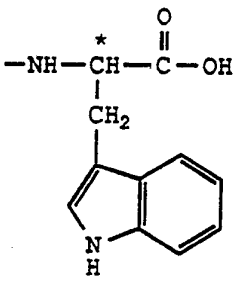

wherein * CH is D stereochemistry,

AA^2 is  wherein * CH is L stereochemistry,

AA^3 is  wherein * CH is L stereochemistry,

AA^4 and AA^5 are each  wherein * CH is L stereochemistry, and

*

AA6 is  wherein CH is L

stereochemistry; or a pharmaceutically acceptable salt thereof comprising sequential stepwise coupling of the amino acids selected from AA^1, AA^2, AA^3, AA^4, AA^5, or AA^6 to the preceding amino acid using conventional peptide synthesis methodology and after conventional deprotection to afford a compound of Formula I and, if desired, converting a compound of Formula I to a pharmaceutically acceptable salt of a compound of Formula I by conventional methodology and, if further desired, converting the obtained pharmaceutically acceptable salt of a compound of Formula I to a compound of Formula I by conventional methodology.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/03408

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 K 5/10 C 07 K 7/06 A 61 K 37/02

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 K A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X,O	Journal of Cardiovascular Pharmacology, (Endothelin II, Proceedings of the Second International Conference on Endothelin, Tsukaba, 9-12 December 1990), vol. 17, supplement 7, 1991, (New York, US), A.M. DOHERTY et al.: "Structure-activity studies of the C-terminal region of the endothelins and the sarafotoxins", pages S59-S61, see page S60, table 1 and the summary	1-4
X	G.R. PETTIT: "Synthetic Peptides", vol. 1, 1970, Van Nostrand Reinhold Co., New York, US, see page 149, peptides no. 6,16	1-2,4, 31

-/-

° Special categories of cited documents :[10]

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

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
13-08-1992	16. 09. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	KORSNER

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	Biochemical and Biophysical Research Communications, vol. 163, no. 1, 30 August 1989, (Duluth, US), K. NAKAJIMA et al.: "Structure-activity relationship of endothelin: importance of charged groups", pages 424-429, see page 428, peptide no. 10	1-31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/03408

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

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 7,9,11,13,15,17,19,21,23,25,27 and 29 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds

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

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

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

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

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

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

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

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

Remark on Protest

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

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