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AMINOALKYLAMINOCARBONYL AMINODIOL AMINO ACID DERIVATIVES AS ANTI-HYPERTENSIVE AGENTS

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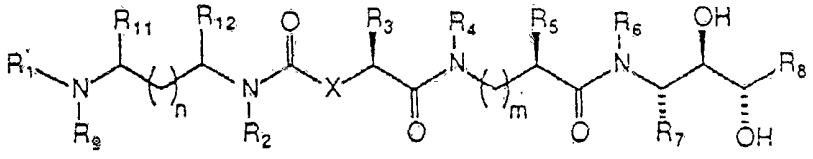
(56) Prior Art Documents
EP 229667
WO 87/04347

(57) Renin-inhibiting compounds are known for control of hypertension. Of particular interest herein are non-peptidyl compounds useful as renin inhibiting agents.

CLAIM

1. A compound of the formula



wherein X is selected from oxygen atom, methylene and $>NR_{10}$ with R_{10} selected from hydrido, alkyl and benzyl; wherein each of R_1 and R_9 is a group independently selected from hydrido, alkyl, cycloalkyl, alkoxyacyl, alkoxycarbonyl, benzyloxycarbonyl, loweralkanoyl, haloalkylacyl, phenyl, benzyl, heterocyclicalkyl, naphthyl and naphthylmethyl, any one of which groups having a substitutable position may be optionally

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substituted with one or more radicals selected from alkyl, alkoxy, alkenyl, alkynyl, halo, haloalkyl, cyano and phenyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having one or two hetero atoms selected from nitrogen, oxygen and sulfur, which heterocyclic group has 4 to 10 ring members and contains as a ring member the nitrogen atom to which R_1 and R_9 are attached within said formula; wherein R_2 is selected from hydrido, alkyl, dialkylaminoalkyl, alkylacylaminoalkyl, benzyl and cycloalkyl; wherein R_3 is selected from alkyl, cycloalkylalkyl, acylaminoalkyl, phenylalkyl, naphthylmethyl, aryl and heterocyclicalkyl, wherein the aromatic portion of any of said phenylalkyl, naphthylmethyl, aryl and heterocyclicalkyl may be substituted by one or more halo or alkyl or by both; wherein each of R_4 and R_6 is independently selected from hydrido, alkyl, benzyl and cycloalkyl; wherein R_7 is selected from substituted or unsubstituted cycloalkyl, phenyl, cycloalkylalkyl and phenylalkyl, any one of which may be substituted with one or more groups selected from alkyl, alkoxy, halo, haloalkyl, alkenyl, alkynyl and cyano; wherein R_8 is selected from hydrido, alkyl, haloalkyl, alkylcycloalkyl, alkylcycloalkenyl and alkoxycarbonyl; wherein each of R_{11} and R_{12} is independently selected from hydrido, alkyl, dialkylaminoalkyl and phenyl; and wherein m is zero or one and n is a number selected from zero through five;

with the proviso that where m is zero, then R_5 is selected from hydrido, alkyl, benzyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, alkylthioalkyl, heterocyclicalkyl, sulfonylheterocyclicalkyl and acylheterocyclicalkyl; and

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with the further proviso that when m is one, then R_5 is selected from hydrido, alkyl, benzyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylthioalkyl and imidazolemethyl.

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Complete Specification for the invention entitled:

"AMINOALKYLAMINOCARBONYL AMINODIOL AMINO ACID DERIVATIVES AS ANTI-HYPERTENSIVE AGENTS"

The following statement is a full description of this invention including the best method of performing it known to us.

FIELD OF THE INVENTION

Renin-inhibiting compounds are known for control of hypertension. Of particular interest herein are non-peptidyl compounds useful as renin inhibiting agents.

BACKGROUND OF THE INVENTION

Renin is a proteolytic enzyme produced and secreted into the bloodstream by the juxtaglomerular cells of the kidney. In the bloodstream, renin cleaves a peptide bond in the serum protein angiotensinogen to produce a decapeptide known as angiotensin I. A second enzyme known as angiotensin converting enzyme, cleaves angiotensin I to produce the octapeptide known as angiotensin II. Angiotensin II is a potent pressor agent responsible for vasoconstriction and elevation of cardiovascular pressure. Attempts have been made to control hypertension by blocking the action of renin or by blocking the formation of angiotensin II in the body with inhibitors of angiotensin I converting enzyme.

Classes of compounds published as inhibitors of the action of renin on angiotensinogen include renin antibodies, pepstatin and its analogs, phospholipids, angiotensinogen analogs, pro-renin related analogs and peptide aldehydes.

A peptide isolated from actinomyces has been reported as an inhibitor of aspartyl proteases such as pepsin, cathepsin D and renin [Umezawa et al, in J. Antibiot. (Tokyo), 23, 259-262 (1970)]. This peptide, known as pepstatin, was found to reduce blood pressure in vivo after the the injection of hog renin into nephrectomized rats [Gross et al, Science, 175, 656 (1971)]. Pepstatin has the disadvantages of low solubility and of inhibiting acid proteases in addition to renin. Modified pepstatins have been synthesized in an attempt to increase the specificity for human renin over other physiologically important enzymes. While some degree of specificity has been achieved, this approach has led to rather high molecular weight hepta- and octapeptides [Boger et al, Nature, 303, 81 (1983)]; high molecular weight peptides are generally considered undesirable as drugs because gastrointestinal absorption is impaired and plasma stability is compromised.

Short peptide aldehydes have been reported as renin inhibitors [Kokubu et al, Biochim. Biophys. Res. Commun., 118, 929 (1984); Castro et al, FEBS Lett., 167, 273 (1984)]. Such compounds have a reactive C-terminal aldehyde group and would likely be unstable in vivo.

Other peptidyl compounds have been described as renin inhibitors. EP Appl. #128,762, published 18 December 1984, describes dipeptide and tripeptide glycol-containing compounds as renin inhibitors [also see Hanson et al, Biochm. Biophys. Res. Comm., 132, 155-161 (1985), 146, 959-963 (1987)]. EP Appl. #181,110, published 14 May 1986, describes dipeptide

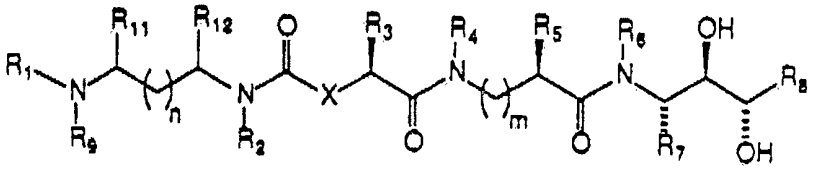
histidine derivatives as renin inhibitors. EP Appl. #189,203, published 30 July 1986, describes peptidyl-aminodiols as renin inhibitors. EP Appl. #200,406, published 10 December 1986, describes alkylnaphthyl-methylpropionyl-histidyl aminohydroxy alkanoates as renin inhibitors. EP Appl. #216,539, published 1 April 1987, describes alkylnaphthylmethylpropionyl aminoacyl aminoalkanoate compounds as renin inhibitors orally administered for treatment of renin-associated hypertension. EP Appl. #229,667, published 22 July 1987, describes acyl α-aminoacyl aminodiol compounds having a piperazinylcarbonyl or an alkylaminoalkylcarbonyl terminal group at the N-amino acid terminus, such as 2(S)-{[(1-piperazinyl)carbonyl]-oxy]-3-phenylpropionyl}-Phe-His amide of 2(S)-amino-1-cyclohexyl-3(R),4(S)-dihydroxy-6-methylheptane. PCT Application No. WO 87/04349, published 30 July 1987, describes aminocarbonyl aminoacyl hydroxyether derivatives having an alkylamino-containing terminal substituent and which are described as having renin-inhibiting activity for use in treating hypertension. EP Appl. #300,189 published 25 January 1989 describes amino acid monohydric derivatives having an alkylamino-alkylamino N-terminus mentioned as useful in treating hypertension.

For other articles describing previous efforts to devise renin inhibitors, see Marshall, Federation Proc., 35, 2494-2501 (1976); Burton et al, Proc. Natl. Acad. Sci. USA, 77, 5476-5479 (1980); Suketa et al, Biochemistry, 14, 3188 (1975); Swales, Pharmac. Ther., 7, 173-201 (1979); Kokubu et al, Nature, 217, 456-457 (1986); Matsushita et al, J. Antibiotics, 28, 1016-1018 (1975); Lazar et al,

Biochem. Pharma., 23, 2776-2778 (1974); Miller et al., Biochem. Pharma., 21, 2941-2944 (1972); Haber, Clinical Science, 59, 7s-19s (1980); Rich et al, J. Org. Chem., 43: 3624 (1978); J. Med. Chem., 23, 27 (1980); especially Haber, Clin. and Exper. Hyper., A5(7&8), 1193 (1983); and European Patent Applications #172,346 and #172,347 published 26 February 1986.

DESCRIPTION OF THE INVENTION

Non-peptidyl aminoalkylaminocarbonyl aminodiol amino acid derivatives having utility as renin inhibitors for treatment of hypertension in mammals constitute a family of compounds of general Formula I:



(I)

wherein X is selected from oxygen atom, methylene and $\geq NR_{10}$ with R_{10} selected from hydrido, alkyl and benzyl; wherein each of R_1 and R_9 is a group independently selected from hydrido, alkyl, alkoxycarbonyl, benzyloxycarbonyl, loweralkanoyl, cycloalkyl, alkoxyacyl, haloalkylacyl, phenyl, benzyl, heterocyclicalkyl, naphthyl and naphthylmethyl, any one of which groups having a substitutable position may be optionally substituted with one or more radicals selected from alkyl, alkoxy, alkenyl, alkynyl, halo, haloalkyl, cyano and phenyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocylic group having one or

two hetero atoms selected from nitrogen, oxygen and sulfur, which heterocyclic group has 4 to 10 ring members and contains as a ring member the nitrogen atom to which R_1 and R_9 are attached within said Formula I; wherein R_2 is selected from hydrido, alkyl, dialkylaminoalkyl, alkylacylaminoalkyl, benzyl and cycloalkyl; wherein R_3 is selected from alkyl, cycloalkylalkyl, acylaminoalkyl, phenylalkyl, naphthylmethyl, aryl and heterocyclicalkyl, wherein the aromatic portion of any of said phenylalkyl, naphthylmethyl, aryl and heterocyclicalkyl may be substituted by one or more halo or alkyl or by both; wherein each of R_4 and R_6 is independently selected from hydrido, alkyl, benzyl and cycloalkyl; wherein R_7 is selected from substituted or unsubstituted cycloalkyl, phenyl, cycloalkylalkyl and phenylalkyl, any one of which may be substituted with one or more groups selected from alkyl, alkoxy, halo, haloalkyl, alkenyl, alkynyl and cyano; wherein R_8 is selected from hydrido, alkyl, haloalkyl, alkylcycloalkyl, alkylcycloalkenyl and alkoxycarbonyl; wherein each of R_{11} and R_{12} is independently selected from hydrido, alkyl, dialkylaminoalkyl and phenyl; and wherein m is zero or one and n is a number selected from zero through five;

with the proviso that where m is zero, then R_5 is selected from hydrido, alkyl, benzyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, alkylthioalkyl, heterocyclicalkyl, sulfonylheterocyclicalkyl and acylheterocyclicalkyl; and

with the further proviso that when m is one, then R_5 is selected from hydrido, alkyl, benzyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylthioalkyl and imidazolemethyl.

Two distinct families of renin-inhibiting compounds are specified within Formula I, namely, those families being defined by the values of m. A first family of compounds consists of those α-amino acid derivatives defined by the condition where m is zero. A second family of compounds consists of those β-amino acid derivatives defined by the condition where m is one.

A preferred family of compounds consists of those compounds of Formula I wherein X is selected from oxygen atom, methylene and $>NR_{10}$ with R_{10} selected from hydrido, alkyl and benzyl; wherein each of R_1 and R_8 is independently selected from hydrido, lower alkyl, cycloalkyl, alkoxycarbonyl, benzyloxycarbonyl, loweralkanoyl, alkoxyacyl, heterocyclicalkyl, phenyl and benzyl; wherein R_1 and R_8 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and one or two nitrogen atoms as ring atoms; wherein each of R_2, R_4 and R_6 is independently selected from hydrido and alkyl; wherein R_3 is selected from phenylalkyl, naphthylmethyl, pyridylmethyl, cyclohexylalkyl, pyridylethyl and pyridylpropyl; wherein R_7 is selected from substituted or unsubstituted cyclohexylmethyl and benzyl, either one of which may be substituted with one or more groups selected from alkyl, alkoxy, halo and haloalkyl; wherein R_8 is selected from hydrido, ethyl, n-propyl, n-butyl, isobutyl and fluoroalkyl; wherein each of R_{11} and R_{12} is independently selected from hydrido and lower alkyl; wherein m is zero or one and n is a number selected from zero through five; or a pharmaceutically-acceptable salt thereof;

with the proviso that where m is zero, then R_5 is selected from hydrido, alkyl, benzyl, cycloalkyl, cycloalkylalkyl, imidazolemethyl, imidazoleethyl, thiazolemethyl, pyridylmethyl, sulfonylimidazolemethyl acylimidazolemethyl; and

with the further proviso that when m is one, then R_5 is selected from hydrido, alkyl and imidazolemethyl.

A further preferred family of compounds consists of those compounds of Formula I wherein X is selected from oxygen atom, methylene and $>NR_{10}$ with R_{10} selected from hydrido, alkyl and benzyl; wherein each of R_1 and R_9 is independently selected from hydrido, alkyl, alkoxyacyl, heterocyclicalkyl, benzyl and alkoxycarbonyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and having one or two nitrogen atoms as ring atoms; wherein each of R_2, R_4 and R_6 is independently selected from hydrido and alkyl; wherein R_3 is selected from benzyl, phenethyl, phenpropyl, cyclohexylmethyl, pyridylmethyl and 2-pyridylethyl; each of R_4 and R_6 is independently selected from hydrido and methyl; wherein R_7 is cyclohexylmethyl; wherein R_8 is selected from ethyl, n-propyl, isobutyl and perfluoropropyl; wherein each of R_{11} and R_{12} is independently selected from hydrido and methyl; wherein m is zero or one and n is a number selected from zero through five; or a pharmaceutically-acceptable salt thereof;

with the proviso that where m is zero, then R_5 is selected from imidazolemethyl, thiazolemethyl and isobutyl; and

with the further proviso that when m is one, then R_5 is methyl or ethyl.

A more preferred family of compounds consists of those compounds of Formula I wherein X is selected from oxygen atom, methylene and $>NR_{10}$ with R_{10} selected from hydrido and methyl; wherein each of R_1 and R_9 is independently selected from hydrido, lower alkyl, alkoxycarbonyl, alkoxyacyl, heterocyclicalkyl and benzyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and having one or two nitrogen atoms as ring atoms; wherein R_2 is selected from hydrido, methyl, ethyl and isopropyl; wherein R_3 is selected from benzyl, cyclohexylmethyl, phenethyl, pyridylmethyl and 2-pyridylethyl; wherein each of R_4 and R_6 is independently selected from hydrido and methyl; wherein R_7 is cyclohexylmethyl; wherein R_8 is independently selected from ethyl, n-propyl and isobutyl; wherein each of R_{11} and R_{12} is hydrido; wherein m is zero or one and n is a number selected from zero through five; or a pharmaceutically-acceptable salt thereof; with the proviso that where m is zero, then R_5 is selected from imidazolemethyl, thiazolemethyl and isobutyl; and with the further proviso that when m is one, then R_5 is methyl or ethyl.

A particularly preferred family of compounds consists of those compounds of Formula I wherein X is selected from oxygen atom and methylene; wherein each of R_1 and R_9 is independently selected from hydrido, methyl, ethyl, 2-(1H-imidazole-4-yl)ethyl, t-butyloxycarbonyl and methoxymethylcarbonyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and having one or two nitrogen atoms as ring atoms; wherein R_2 is selected from hydrido, methyl, ethyl and isopropyl; wherein R_3 is selected from benzyl, phenethyl, pyridylmethyl

cyclohexylmethyl and 2-pyridylethyl; wherein each of R_4 and R_6 is independently selected from hydrido and methyl; wherein R_7 is cyclohexylmethyl; wherein R_8 is isobutyl; wherein each of R_{11} and R_{12} is hydrido; wherein m is zero or one and n is a number selected from zero through five; or a pharmaceutically-acceptable salt thereof; with the proviso that where m is zero, then R_5 is selected from imidazolemethyl, thiazolemethyl and isobutyl; and with the further proviso that when m is one, then R_5 is methyl or ethyl.

A more particularly preferred family of compounds consists of those compounds of Formula I wherein X is selected from oxygen atom and methylene; wherein each of R_1 and R_9 is a group independently selected from hydrido, methyl, ethyl, 2-(1H-imidazole-4-yl)ethyl, t-butyloxycarbonyl and methoxymethylcarbonyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and having one or two nitrogen atoms as ring atoms; wherein R_2 is selected from hydrido, methyl, ethyl and isopropyl; wherein R_3 is selected from benzyl, phenethyl, pyridylmethyl and 2-pyridylethyl; wherein each of R_4 and R_6 is independently selected from hydrido and methyl; wherein R_7 is cyclohexylmethyl; wherein R_8 is isobutyl; wherein each of R_{11} and R_{12} is hydrido; wherein m is zero or one and n is a number selected from zero through three; or a pharmaceutically-acceptable salt thereof; with the proviso that where m is zero, then R_5 is selected from imidazolemethyl and isobutyl; and with the further proviso that when m is one, then R_5 is methyl or ethyl.

A most preferred family of compounds of Formula I consists of the following compounds:

O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

O-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

O-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

3-{N-[4-(N-methyl-N-boc-amino)butyl-N-methyl-aminocarbonyl}-2-(R)-phenethyl propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylaminocarbonyl}-3-L-benzyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylaminocarbonyl}-3-L-benzyllactyl-α-(R)-ethyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

3-{N-[2-(N,N-dimethylamino)ethyl]-N-methylaminocarbonyl}-2-(R)-(2-phenylethyl)-propionyl-α-(R)-ethyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

3-{N-[2-(N-piperidino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

3-{N-[2-(N-piperidino)ethyl]-N-methylaminocarbonyl}-2-(R)-(2-phenylethyl)-propionyl-α-(R)-ethyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

3-{N-[2-(N,N-dimethylamino)ethyl]-N-methylaminocarbonyl}-2-R-benzyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

O-{N-[2-(N,N-dimethylamino)ethyl]-N-isopropyl-aminocarbonyl}-3-L-phenyllactyl-L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

3-{N-[4-(N-methylamino)butyl]-N-methyl-aminocarbonyl}-2-R-phenethyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

O-{N-[2-N-methyl-N-boc-amino)ethyl)butyl]-N-methyl-aminocarbonyl}-3-L-phenyllactyl-L-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

O-{N-[2-(N,N-dimethylamino)ethyl]-N-methyl-aminocarbonyl}-3-L-benzyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

3-{N-[2-(N-methyl-N-boc-amino)ethyl]-N-methylaminocarbonyl}-2-R-phenethyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R.4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

O-{N-[2-(N-methyl-N-boc-amino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane;

O-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane; and

3-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-2-R-phenethylpropionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane trifluoroacetate salt.

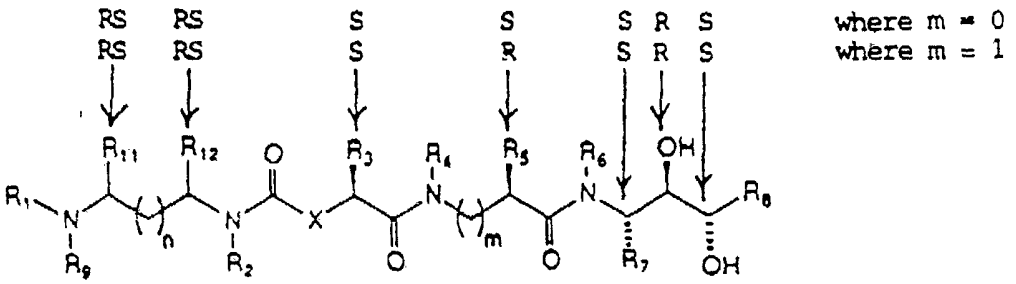
Unless otherwise described, the chemical groups recited herein shall have meanings as follows: "Alkyl" includes linear and branched radicals; "lower alkyl" means alkyl radicals containing one to about 10 carbon atoms in a linear or branched configuration, examples of which include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl, 1-methylhexyl, n-heptyl, 2-ethylheptyl, n-octyl, 3-propyloctyl, n-nonyl, 4-butylnonyl, n-decyl and the like. "Haloalkyl" means alkyl radicals substituted at one or more substitutable positions with one or more halo groups. Preferred haloalkyl group are those provided by lower alkyl radicals substituted at least at one position with one, two or three halo groups such as fluoro or chloro, a specific example of which is trifluoromethyl. "Alkylcycloalkyl" means a cyclized alkyl having from four to about nine ring carbon atoms, any one or more of the substitutable ring carbon atoms being substituted with an alkyl group, preferably a lower alkyl group. "Alkoxycarbonyl" means an oxycarbonyl radical having an alkyl, preferably lower alkyl, group attached to the oxygen atom. "Aryl" means an aromatic hydrocarbon radical provided by a homocyclic or heterocyclic ring system, such as phenyl, naphthyl, and pyridyl. "Acyl"

means a carbonyl moiety attached to a hydrocarbon moiety, typically an alkyl or lower alkyl group. "Heterocyclicalkyl" means a cyclized group having three to about ten ring members, of which one to about three of such ring members is a hetero atom selected from oxygen, nitrogen and sulfur, with the remaining ring members being carbon atoms and such cyclized group being fully unsaturated, or partially saturated, or fully saturated, and having an alkyl group attached to any ring member, except a ring nitrogen atom, through which alkyl group the heterocyclic ring is attached to the Formula I backbone. Examples of heterocyclicalkyl are (1H-imidazole-4-yl)methyl, 2-(1H-imidazole-4-yl)ethyl, (1H-pyrimid-4-yl)methyl, 2-(1H-pyrimid-4-yl)ethyl, (1H-pyridin-4-yl)methyl and 2-(1H-pyridin-4-yl)ethyl.

Based upon the foregoing, the meanings of the following terms should be readily discernible, namely, "acylaminoalkyl", "cycloalkyl", "alkoxyacyl", "cycloalkylalkyl", "phenylalkyl" and "alkoxy".

Compounds of Formula I have at least five asymmetric carbons. Such compounds whether in their pure form or as diastereomeric mixtures are embraced in the Formula I compounds of the invention. Many of the more active renin inhibitors are provided by compounds having a specific arrangement of stereogenic carbons. Within Formula I, reading from the N

terminus to the C terminus (terminating with the diol moiety), the preferred configurations for the asymmetric carbons are as follows:



Compounds of Formula I have been found to inhibit renin and thus limit the production of angiotensin I which, in turn, limits the production of angiotensin II in mammals. Angiotensin II is a potent vasoconstrictor and participates in the formation of aldosterone which regulates sodium and water balance in mammals. Thus, compounds of Formula I are therapeutically useful in methods for treating hypertension by administering to a hypertensive patient a therapeutically-effective amount of a compound of Formula I. The phrase "hypertensive patient" means, in this context, a mammalian subject suffering from the effects of hypertension or susceptible to a hypertensive condition if not treated to prevent or control such hypertension.

These compounds can be formulated into pharmaceutically-acceptable dosage forms by any of a number of well-known carriers or diluents. The compounds can be formulated using pharmacologically-acceptable acid addition salts and can be used in a suitable hydrated form. The formulated compounds can be administered in oral dosage forms such as tablets,

capsules, pills, powders, or granules. The compounds can also be administered intramuscularly, using forms known to the pharmaceutical art. In general, the preferred form of administration is oral. A therapeutically effective but non-toxic quantity of the compound is employed in treatment of high blood pressure in mammals. The dosage regimen for preventing or treating hypertension with the compounds of Formula I is selected upon consideration of a variety of factors, including the type, age, weight, sex, and medical condition of the patient, the severity of the hypertension, the route of administration, and the particular compound employed. Dosages of the compounds are ordinarily in the range from about 0.5 to about 100. mg/kg (active compound-to-body weight), and preferably from about 1.0 to about 20 mg/kg given orally or by injection.

Compounds of Formula I are also useful as diagnostic agents for identification of hypertension due to renin excess.

Compounds of Formula I can be administered as prodrugs. Preferably, esterification of one or more of the hydroxyl groups of the compounds of Formula I is accomplished with amino acids to make aminoesters, succinates to make succinic acid esters, alkanoic acids to make carboxylic acid esters such as valerates, or phosphates to make phosphoric acid esters. Aminoesters and valerates of the Formula I compounds are more preferred.

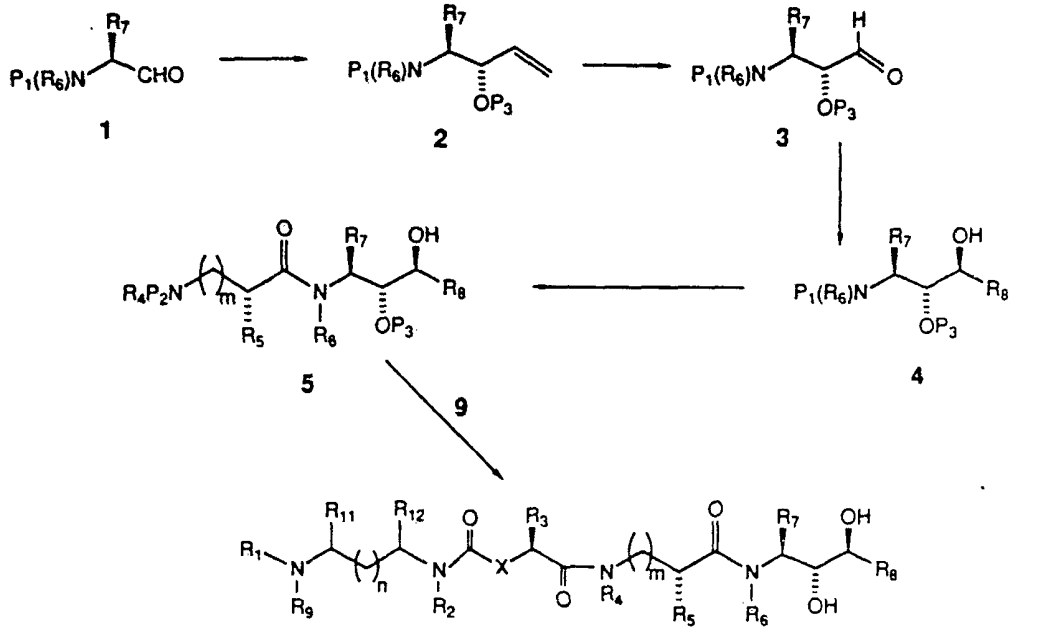
Procedures for preparation of compounds of Formula I are set forth in the schemes and descriptions under General Synthetic Schemes I & II taken with the

specific procedures described in Examples 1-30 which follow thereafter. The substituents X and R_1 through R_{12} are as described above for the Formula I substituents.

GENERAL SYNTHETIC SCHEMES I & II

A suitably protected amino aldehyde 1 (Scheme I) is treated with a Grignard reagent, preferably vinylmagnesium bromide to obtain vinyl carbinol 2. This material, suitably protected, is oxidized, preferably with ozone, followed by dimethyl sulfide treatment to give 3. This aldehyde is reacted with an organometallic reagent such as isobutylmagnesium chloride to give compound 4. This intermediate is deprotected then coupled, using standard amide/peptide coupling methodology, to either alpha or beta amino acid derivatives, suitably protected, to give compound 5. This intermediate is deprotected then coupled, using standard amide/peptide coupling methodology, to intermediate 9 (shown in Scheme II) to give renin inhibitor 6 (Formula I). Synthetic Scheme II shows synthetic routes to intermediate 9, using the reaction of intermediates 7 and 8 followed by deprotection. The synthesis of various types of intermediates 8 (shown more explicitly as intermediates 11, 13 and 15) is depicted, depending on whether X is O, CH_2 or NHR_{10}. If X = O, a suitably protected lactic acid derivative is treated with phosgene or carbonyl diimidazole to give intermediate 11. If X = CH_2, a suitably protected succinic acid derivative is activated by treatment with base/isobutylchloroformate or other standard activating agent to give intermediate 13. If X = NHR_{10}, a suitably protected amino acid derivative is activated by treatment with phosgene or other activating agent to give intermediate 15.

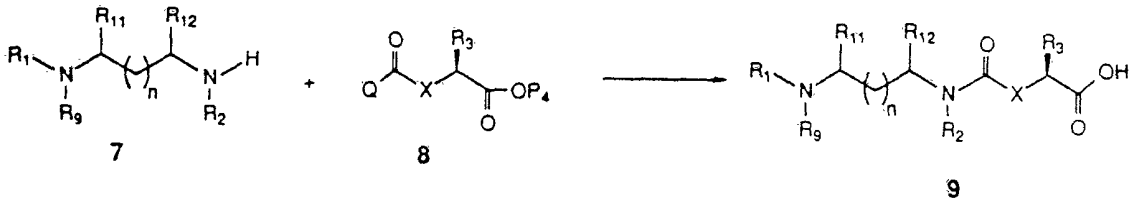
Synthetic Scheme I



P_1 is an N-protecting group
P_2 is H or N-protecting group
P_3 is H or oxygen protecting group

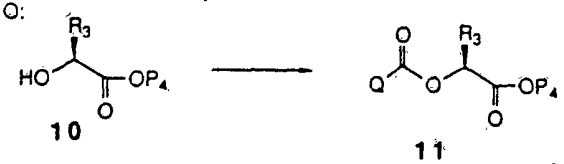
(Formula I)

Synthetic Scheme II



Synthesis of 8:

X = O:



X = CH_2:

X = $NR_{10}H$:

Q is an activating group such as Cl, imidazole
P_4 is alkyl, benzyl, oxygen protecting group

The following examples are provided to illustrate the present invention and are not intended to limit the scope thereof. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures expressed are in degrees Centigrade. Within the foregoing synthetic description and examples which follow, abbreviations have meanings as indicated below:

BOC	=	t-butyloxycarbonyl
i-Bu	=	isobutyl
Leu	=	leucine
Ac	=	acyl
Me	=	methyl
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
im	=	imidazole

Example 1

(3S,4S)-N-[(tert-Butyloxy)carbonyl]-4-amino-3-acetoxy-5-phenylpentene

The preparation of the above intermediate was carried out using the procedure described in Hanson, et al., (1985) J. Org. Chem. 50, 5399.

Example 2

(2R,3S)-N-[(tert-Butyloxy)carbonyl]-3-amino-2-acetoxy-4-phenylbutanal

The preparation of the above intermediate was carried out as described in Hanson, et al. above. Ozone/oxygen was bubbled at -70° into a solution of 2.55g (8.0 mmol) of the allylic acetate of Example 1 in 100mL of methylene chloride until a deep blue color persisted. Oxygen was introduced until the blue color completely faded, then 3.0 mL of Me_2S was added and the solution was allowed to warm to 0-5° and stand overnight. The solvent was removed at 0° under vacuum yielding the title compound as a thick yellow oil which was used in the following step without purification.

Example 3

(2S,3R,4S)-N-[(tert-Butyloxy)carbonyl]-2-amino-1-phenyl-3,4-dihydroxy-6-methylheptane

The oil prepared in Example 2 was dissolved under nitrogen in 100mL of dry THF and cooled to -70°. To this solution was added 13mL (26mmol) of a 2.0M solution of isobutylmagnesium chloride in ether and the stirred mixture was allowed to warm to room temperature and stir for 2 hrs. After decomposition with $MeOH/H_2O$ the mixture was diluted with ether, washed with saturated NH_4Cl solution twice, then dried and the solvents stripped off under vacuum. The residue was allowed to stand overnight in 80% MeOH-H_2O containing excess ammonium hydroxide. The MeOH was stripped off and the mixture was extracted with ether.

These extracts were combined, washed with water, dilute $KHSO_4$, then dried and evaporated to give 2.36g of a yellow glass which crystallized from 50mL of pentane on standing overnight. The yellow-white powder obtained was recrystallized from ether-hexane and furnished the title compound (0.41g) as white, hairy needles, mp 134-136°, Rf (ether): single spot, 0.6. By chromatography of the mother liquors and crystallization of the appropriate fractions, an additional 0.22g of product, mp 138-139°, was obtained.
Anal: Calc'd. for $C_{19}H_{31}NO_4$ (337.45): C, 67.62; H, 9.26; N, 4.15. Found: C, 67.51; H, 9.43; N, 4.24.

Example 4

(2S,3R,4S)-N-[(tert-Butyloxy)carbonyl]-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

The diol of Example 3, 0.27g, was reduced in MeOH with 60psi H_2 at 60° in 3 hrs using 5% Rh/C catalyst. After filtering, the solvent was stripped off and the white crystals were recrystallized from CH_2Cl_2-hexane to furnish tiny needles of the title compound, 0.19g, mp 126-128°; further recrystallization gave mp 128.5-129.5°. Rf (ether): single spot, 0.8.
Anal: Calc'd. for $C_{19}H_{37}NO_4$ (343.50): C, 66.43; H, 10.86; N, 4.08. Found: C, 66.43; H, 11.01; N, 4.03.

Example 5

L-Leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

The title compound of Example 4 was treated with trifluoroacetic acid (TFA) for 30 minutes at room temperature and the solvent evaporated. The residue was neutralized with aqueous potassium carbonate and the free amine was extracted with ethyl acetate. This amine was then coupled to Boc-L-leucine-OH following the general procedure given in Example 6. The resulting amide was treated with TFA for 30 minutes at room temperature and the solvent evaporated. The residue was neutralized with aqueous potassium carbonate and the mixture extracted with ethyl acetate. After evaporation, the title free base was obtained: Rf = 0.45 (single spot, 9:1 methylene chloride-MeOH, silica); 400 MHz ^{1}H NMR (DMSO) spectrum: consistent with structure. Anal: Calc'd. for $C_{20}H_{40}N_2O_3 + 0.5\ H_2O$: C, 65.70; H, 11.31; N, 7.67. Found: C, 65.62; H, 11.01; N, 7.49.

Example 6

Boc-(im-Tosyl)-L-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

To a stirred solution of N-Boc-(im-tosyl)-L-histidine (809mg, 1.6eq) in methylene chloride(5ml) cooled with an ice/salt bath was added N-methylpiperidine (0.240ml, 1.6eq) followed by isobutylchloroformate (0.224ml, 1.4eq). After 5 minutes, the free base (300mg, 1.23mmol), which had been previously formed by treating the title compound of Example 4 with trifluoro-

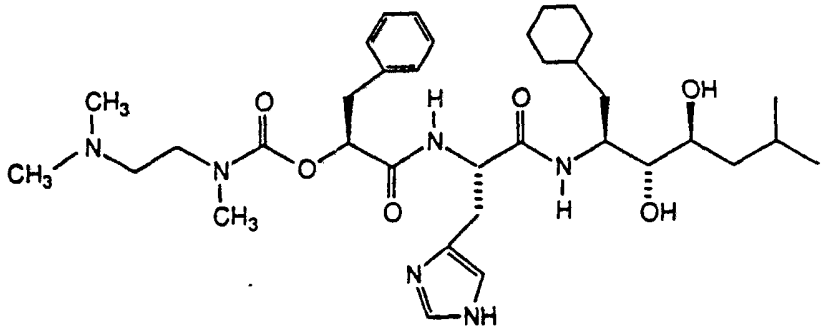
acetic acid followed by potassium carbonate as described in Example 5, dissolved in methylene chloride (5mL) was added and the reaction mixture was stirred at 0° overnight ca. 15h. The methylene chloride was evaporated in vacuo to afford an oily residue which was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer was separated and further washed with $KHSO_4$ solution (1M) followed by $NaHCO_3$ (1M). The ethyl acetate layer was dried ($MgSO_4$) and evaporated in vacuo to afford a white solid, which was recrystallized from methanol/diethyl ether. This gave the title compound; (560mg, 72% yield), 300 MHz ^1H NMR was fully consistent with the proposed structure. Anal: Calc'd. for $C_{32}H_{50}O_7N_4S$ +0.75 H_2O: C, 59.28; H, 8.01; N, 8.64. Found: C, 59.31; H, 7.98; N, 8.63.

Example 7

(im-Tosyl)-L-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

To a stirred solution of the title compound of Example 6 (3.78g, 5.96mmol) in methylene chloride (20mL) and methanol (5mL) was added trifluoroacetic acid (25mL). The reaction mixture was stirred at room temperature for 30min and then poured onto saturated sodium bicarbonate solution. The solution was adjusted to pH>12 by addition of potassium carbonate and then extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), and evaporated to afford a solid white residue. Recrystallization from methanol/diethyl ether gave the title compound; (2.8g, 88% yield); 300 MHz ^1H NMR spectrum: consistent with the proposed structure. Anal: Calc'd. for $C_{27}H_{42}N_4O_5S$ + 0.7 H_2O: C, 59.25; H, 7.99; N, 10.24. Found: C, 59.29; H, 7.75; N, 10.15.

Example 8



O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

To a stirred solution of O-(N-(dimethylaminoethyl)-N-methylaminocarbonyl)-3-L-phenyllactic acid (220mg,0.75 mmol) [the title compound of Example 14] in methylene chloride (5mL) in an ice/salt bath was added N-methylpiperidine (0.10ml, 0.82 1) followed by isobutylchloroformate (94mg, 0.69mmol). After 5 min, the title compound of Example 7 (390mg, 0.69 mmol) in methylene chloride (5ml) was added and the reaction mixture was stirred at 0° for ca 15h. The methylene chloride was evaporated in vacuo to afford an oily residue which was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was separated and dried ($MgSO_4$). After evaporation, the crude residue was dissolved in methanol (4mL) and potassium hydroxide solution (1mL, 1M) was added. The reaction mixture was stirred for 30 min, evaporated to dryness and the residue extracted into ethyl acetate. The organic extracts were washed with water, citric acid (1M) and saturated

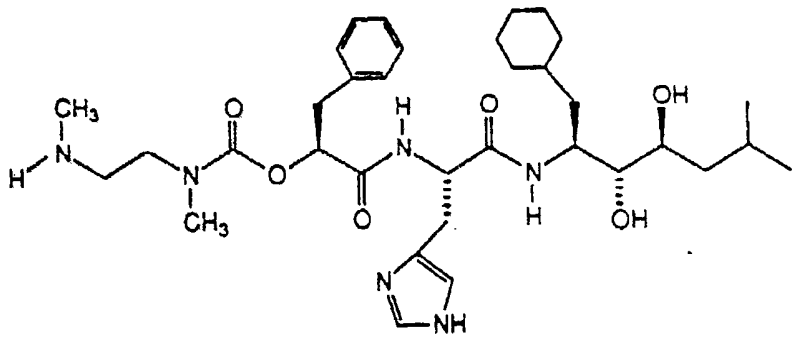
aqueous sodium bicarbonate solution and dried over $MgSO_4$. Evaporation of the solvent gave a yellow residue which was purified by chromatography on silica (eluting with; methylene chloride/methanol-NH_3 (15:85)) to afford the title compound; (60 mg, 14% yield). Anal: Calc'd. for $C_{35}H_{56}N_6O_6$ + 2.5 H_2O: C, 59.89; H, 8.76; N, 11.97. Found: C, 59.78; H, 8.43; N, 11.85. 300 MHz ^1H NMR was consistent with the proposed structure.

Example 9

O-(N-(N-methyl-N-Boc-aminoethyl)-N-methylamino-carbonyl)-3-L-phenyllactyl-L-(im-tosyl)-histidine-amide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

To a solution of O-(N-(N-methyl-N-Boc-amino-ethyl)-N-methylaminocarbonyl)-3-L-phenyllactic acid (355mg, 0.93mmol) in methylene chloride (2mL) was added N-methylpiperidine (101mg) in methylene chloride (1mL). This solution was cooled to 0° and isobutyl-chloroformate (132mg) in methylene chloride (1mL) was added. After 8.5 minutes, the title compound of Example 7 (500mg, 0.94mmol) was added as a solid in one portion. The mixture was allowed to stand at 0-4° for 50 hours and then evaporated. The residue was taken up in ethyl acetate and washed with water, followed by 0.5M citric acid (3x20mL), 5%$NaHCO_3$ (3x20mL), brine, dried (Na_2SO_4) and evaporated to give the title compound as an off-white foam: 612mg (73% yield). Anal: Calc'd. for $C_{46}H_{68}N_6O_{10}S$ + 0.25 H_2O: C, 61.27; H, 7.65; N, 9 .32. Found: C, 60.96; H, 7.61; N, 8.98. 200 MHz ^1H NMR was consistent with proposed structure.

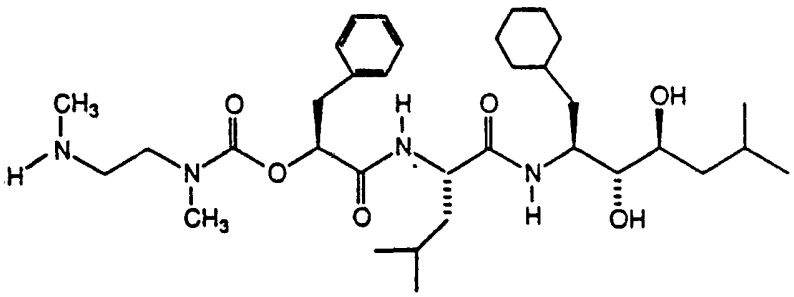
Example 10



O-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

The title compound of Example 9 (577mg) was dissolved in methylene chloride (2mL) and trifluoroacetic acid (8mL) was added. The solution was allowed to stand at room temperature for 25min, then evaporated to an oil. To this was added ethyl ether and the mixture evaporated to form a white, hygroscopic foam. A portion of this foam (300mg) was dissolved in methanol (2mL) and 1N aqueous KOH (1.5mL) was added. The solution was stirred at room temperature for 25min and the methanol was then evaporated. The mixture was extracted with methylene chloride and the extracts washed with water, dried (Na_2SO_4) and evaporated to yield a foam (140mg). A sample was chromatographed on silica gel (eluting with methylene chloride-methanol containing ammonia, 80/20) to give pure title compound: Anal: Calc'd. for $C_{34}H_{54}N_6O_6 + 2\ H_2O$: C, 60.15; H, 8.61; N, 12.37. Found: C, 60.15; H, 8.26; N, 12.24. 200 MHz ^1H NMR was consistent with proposed structure.

Example 11



O-{N-[2-(N-methylamino)ethyl[-N-methyl-aminocarbonyl}-3-L-phenyllactyl-L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

A solution of O-(N-(N-methyl-N-Boc-amino-ethyl)-N-methylaminocarbonyl)-3-L-phenyllactic acid [Example 13] (268mg) and N-methylpiperidine (69mg) in methylene chloride (2mL) was cooled to 0° and isobutyl-chloroformate (91mg) was added. This solution was stirred at 0° for 8 minutes, then a solution of the title compound of Example 5 (L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane, 238mg) in methylene chloride (2mL) containing methanol (0.25mL) was added. This mixture was stirred at 0° for 3 hours and room temperature for 8 hours, then evaporated. The residue was dissolved in methanol and treated with 1N KOH for 20 min at room temperature, then the methanol was evaporated. The residue was partitioned between water and methylene chloride. The organic layer was evaporated to give a foam (395mg). This foam with treated with trifluoroacetic acid for 30 minutes at room temperature and the solvent evaporated. The residue was neutralized with aqueous potassium carbonate and the free amine was extracted with ethyl acetate to

give the title compound (254mg). Anal: Calc'd. for $C_{34}H_{58}N_4O_6 + 3H_2O$: C, 60.68. Found: C, 60.63. 200 MHz ^1H NMR was consistent with proposed structure.

Example 12

N-Boc-N,N'-dimethylethylene diamine

N,N'-dimethyl ethylenediamine (8.8g) was dissolved in 200 ml tetrahydrofuran and to this was added over a 10min period di-t-butyldicarbonate (4.36g) in 30 mL tetrahydrofuran. 72 hours later, the solvent was evaporated and the residue partitioned between ether and $KHCO_3$ and the organic layer was dried ($MgSO_4$) and evaporated to give 11.6g title compound (58% yield). 300 MHz ^1H NMR was consistent with proposed structure.

Example 13

O-(N-(N-methyl-N-Boc-aminoethyl)-N-methylamino-carbonyl)-3-L-phenyllactic acid

At room temperature methyl L-3-phenyllactate (5.7g) was dissolved in tetrahydrofuran (202mL) and to this was added carbonyl diimidazole (5.5g). The mixture was stirred for 4 hours, then the title amine of Example 12 (7.14g) was added and the mixture was stirred overnight. The solvent was evaporated and the residue taken up in ether, washing with dilute HCl, water, drying over $MgSO_4$ and evaporating to give an oily ester (12.37g). This ester was dissolved in methanol (32 mL) and 1.5N NaOH (32mL) was added and stirred for 15 min. at room temperature. The solution

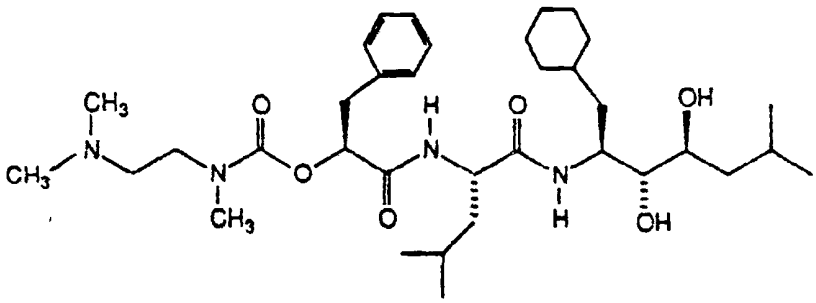
volume was reduced by 50% and water was added followed by washing with ether. The aqueous phase was acidified with 6N HCl, extracted with ethyl acetate and organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give a pale yellow oil (10.3g). 300 MHz ^1H NMR was consistent with proposed structure.

Example 14

O-(N-(dimethylaminoethyl)-N-methyl-aminocarbonyl)-3-L-phenyllactic acid

Benzyl L-3-phenyllactate (14.28g) was dissolved in tetrahydrofuran (357mL) and to this was added carbonyl diimidazole (9.78g) and the mixture was stirred at room temperature for 4 hours. N,N,N'-trimethylethylene diamine (6.8g) was added and the mixture stirred for 8 hours. The solvent was evaporated and the residue taken up in ether and washed with water, dried ($MgSO_4$) and evaporated to give a yellow oil (13g, 61% yield); 300 MHz ^1H NMR consistent with proposed structure. This ester was hydrogenated over 4% Pd-C @ 50psi and room temperature for 3.5 hours in tetrahydrofuran. The title compound was obtained as a white solid (10g) and recrystallized from methanol. Anal: Calc'd. for $C_{15}H_{22}N_2O_4 + H_2O$: C, 57.68; H, 7.75; N, 8.98. Found: C, 57.60; H, 7.82; N, 8.94.

Example 15



O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-3-L-phenyllactyl-L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

O-(N-(dimethylaminoethyl)-N-methyl-amino-carbonyl)-3-L-phenyllactic acid (200mg) was dissolved in methylene chloride (2mL), cooled to 0° and treated with isobutylchloroformate (90mg). The resulting solution was stirred at 0° for 10 minutes, whereupon the title amine of Example 5 (210mg) was added. The mixture was stirred at 0° for 3 hours and at room temperature for 8 hours. The solvent was evaporated, the residue dissolved in methanol (5mL) and treated with 1N KOH (0.5mL) for 10 minutes at room temperature. The methanol was evaporated and the residue extracted with methylene chloride. The organic phase was dried and evaporated to give the title compound as a foam (322mg, 86% yield). Anal: Calc'd. for $C_{35}H_{60}N_4O_6$ + 0.25 H_2O: C, 65.95; H, 9.56; N, 8.79. Found: C, 65.72; H, 9.76; N, 8.57. 200 MHz ^1H NMR was consistent with proposed structure.

Example 16

N-Boc-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

To a solution of N-Boc-α-(R,S)-methyl-β-alanine (137mg, 0.67mmol) in methylene chloride (4mL) at -10°C was added N-methylpiperidine (61mg, 0.61mmol) followed by isobutylchloroformate (75mg, 0.55mmol). After stirring for 5min, a solution of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane (101mg, 0.41mmol) [prepared from the title compound of Example 4 by treatment with trifluoroacetic acid, followed by aqueous potassium carbonate] in methylene chloride (2mL) was added. The resulting solution was stirred for 3 hours at -10°C, followed by 2 hours at room temperature at which time a white solid was isolated by filtration (60mg, 34% yield): Rf = 0.3 (5% MeOH/methylene chloride, silica gel); mp 197-200°; ^{1}H NMR ($CDCl_3$): consistent with proposed structure. Anal: Calc'd. for $C_{23}H_{44}N_2O_5$ + 0.25 H_2O: C, 63.77; H, 10.35; N, 6.46. Found: C, 63.84; H, 10.50; N, 6.45.

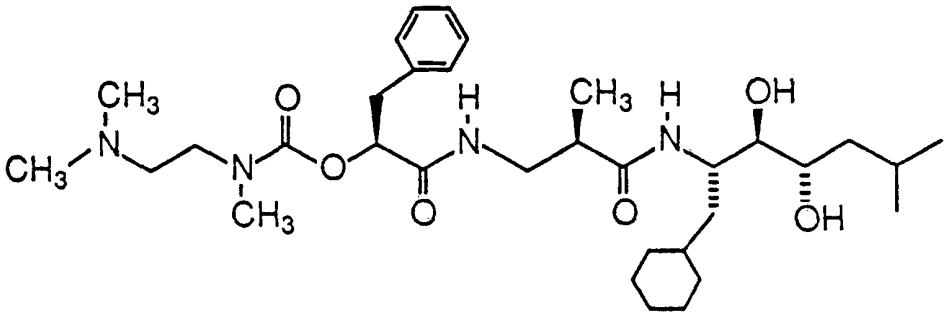
Example 17

α-(R)-Methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

The title compound of Example 16 (53mg, 0.12mmol) was stirred with a mixture of trifluoroacetic acid and methanol (9:1, 5mL). The resulting solution was allowed to stand at room temperature for 20 minutes, then the solvent was evaporated. The resulting oil was stirred for 2 hours with aqueous potassium carbonate (5%, 10mL). This mixture was then extracted with ethyl

acetate which was dried, filtered and evaporated to give the title compound (40mg, 100%): Rf: 0.10 (5% MeOH/methylene chloride, silica gel). This material was used without further purification.

Example 18

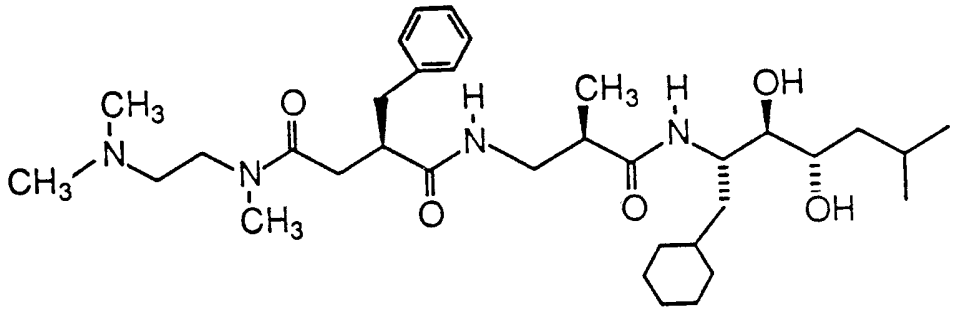


O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-3-L-phenyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

O-(N-(dimethylaminoethyl)-N-methylamino-carbonyl)-3-L-phenyllactic acid (the title compound of Example 14) (130mg, 0.44mmol) and N-methylpiperidine (49mg, 0.49 mmol) were dissolved in CH_2Cl_2 (3.0mL) and cooled to -10°C in a salt/ice bath. To this solution was added isobutyl chloroformate (60mg, 0.44 mmol) in CH_2Cl_2 (2.0mL) and the resulting solution was stirred at -10°C for 5 minutes. Next, a solution of α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane (the title compound of Example 17) (136mg, 0.41 mmol) in 2.5 mL CH_2Cl_2 was added via pipette, and this solution was stirred at -10°C for 2 hours followed by 17 hours at 5°C. The solvent was then removed in vacuo and the residue dissolved in ethyl acetate/water. After partitioning, the organic layer was washed twice with

0.5M citric acid, twice with saturated $NaHCO_3$ and once with brine. The organics were dried over $MgSO_4$, filtered and the solvent removed in vacuo to yield 174mg of a yellow oil. Chromatography on silica gel (eluting with 5% CH_3OH/CH_2Cl_2-NH_3) afforded 20mg of a white solid. The NMR is consistent with the assigned structure. Anal: Calc'd. for $C_{33}H_{56}N_4O_6$+ 0.50 H_2O: C: 64.57, H: 9.36, N: 9.12; found C: 64.72, H: 9.33, N: 8.91.

Example 19



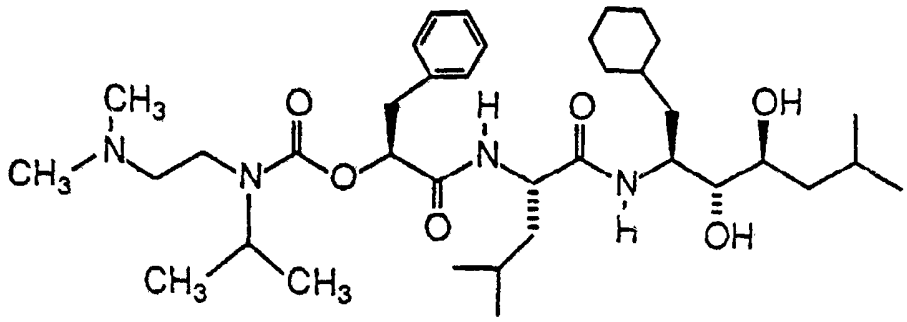
3-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-2-R-benzyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

Following the procedure of Example 18, the title compound of Example 30 (970 mg, 3.33 mmol) was employed as the acid component. The crude product (1.2 g) was purified by flash chromatography on silica gel, eluting with 20:1:1 CH_2Cl_2:MeOH:Et_3N to give pure title compound (530 mg, 33% yield). ^1H NMR: 300 MHz spectrum consistent with proposed structure.

Anal.: $C_{34}H_{58}N_4O_5$ + 0.5 H_2O

Calc.:	C	66.74	Found:	C 66.67
	H	9.72		H 9.67
	N	9.16		N 9.06

Example 20



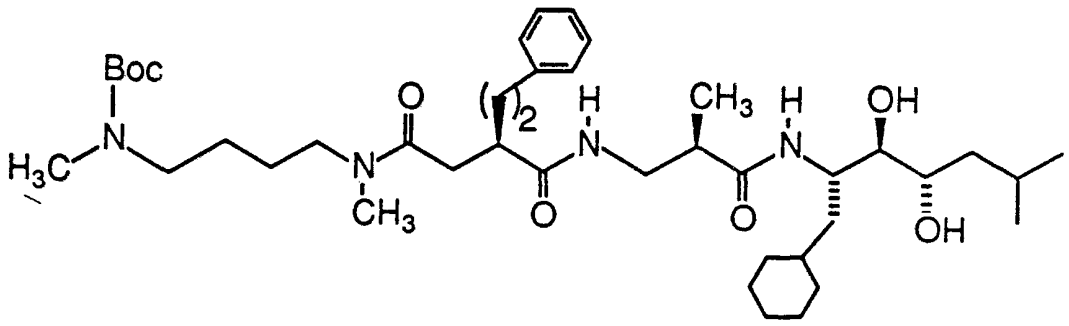
O-{N-[2-(N,N-dimethylamino)ethyl]-N-isopropyl-aminocarbonyl}-3-L-phenyllactyl-L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

The procedure of Example 15 was followed, substituting O-{N-[2-(N,N-dimethylamino)ethyl]-N-isopropyl-aminocarbonyl}-3-L-phenyllactic acid (the title compound of Example 29) for the acid component. The crude product was chromatographed on silica gel, eluting with 9:1 methylene chloride-methanol to give the title compound (40% yield).

Anal. calc. for $C_{37}H_{64}N_4O_6 + 0.5\ H_2O$

Calc.:	C	66.33	Found:	C 66.29
	H	9.77		H 9.65
	N	8.36		N 8.15

Example 21



3-{N-[4-(N-methyl-N-Boc-amino)butyl]-N-methyl-aminocarbonyl}-2-R-phenethyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

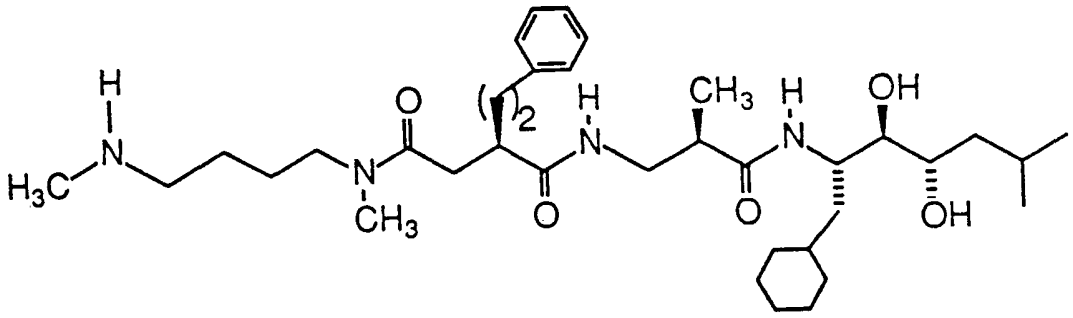
To a solution of N,N'-dimethyl-1,4-butane diamine (84 mmol) in tetrahydrofuran (35 mL) was added $(Box)_2O$ in tetrahydrofuran (35 mL); this mixture was stirred at room temperature overnight. Solvent was evaporated and the residue was taken up in water. This aqueous mixture was acidified to pH 1, washed with ethyl acetate, basified to pH 11, extracted with methylene chloride and the extracts were dried, filtered and evaporated to yield an oil (1.78 g, 40% yield). This amine was coupled to (3R)-3-(2-phenylethyl)-3-carbomethoxy-propionic acid following the coupling procedure of Example 6 to give a methyl ester (60% yield). This ester was hydrolyzed with 1N KOH-methanol to give an acid (91% yield). Following the procedure of Example 18, using the above acid, crude title compound was obtained; it was purified by silica chromatography (eluting with 9:1 methylene chloride-methanol) to give pure title

compound (oil, 30% yield): 200 MHz ^{1}H NMR: consistent with proposed structure.

Anal. calc'd. for $C_{41}H_{70}N_4O_7$

Calc'd.:	C	67.36	Found:	C 63.16
	H	9.65		H 9.20
	N	7.66		N 7.07

Example 22



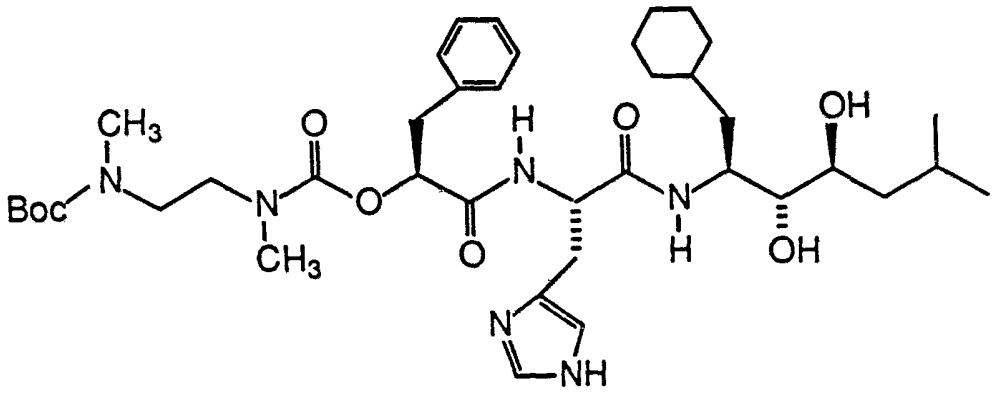
3-{N-[4-(N-methylamino)butyl]-N-methyl-aminocarbonyl}-2-R-phenethyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

The title compound of Example 21 was treated with trifluoroacetic acid at room temperature for 30 minutes and evaporated. The residue was treated with aqueous potassium carbonate to give the title compound: 200 MHz ^{1}H NMR: consistent with proposed structure.

Anal. calc'd. for $C_{36}H_{62}N_4O_5$

Calc'd.:	C	68.54	Found:	C 67.57
	H	9.90		H 9.56
	N	8.88		N 8.48

Example 23



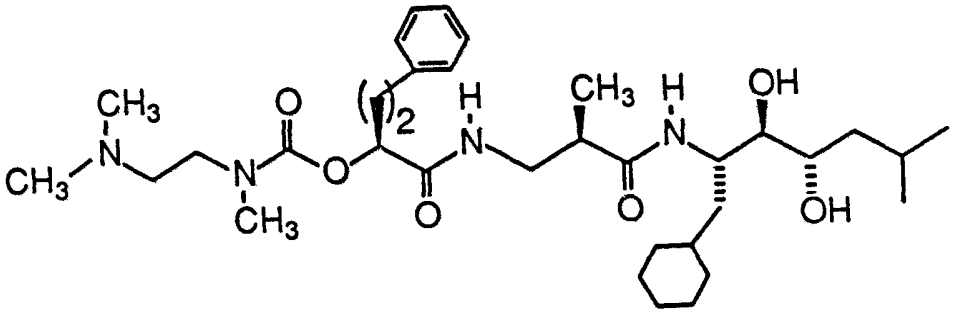
O-{N-[2-(N-methyl-N-Boc-amino)ethyl]-N-methyl-amino-carbonyl}-3-L-phenyllactyl-L-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

The title compound of Example 9 was dissolved in methanol and to this was added 1N aqueous KOH. After 45 minutes, the solvent was evaporated, the residue extracted with ethyl acetate and this organic layer washed with 5% aqueous potassium carbonate to give the title compound as a colorless foam (75% yield).

Anal. calc'd. for $C_{39}H_{62}N_6O_8 + 1.5\ H_2O$

Calc'd.:	C	60.83	Found: C	60.50
	H	8.50	H	8.03

Example 24



O-{N-[2-N,N-dimethylamino)ethyl]-N-methyl-aminocarbonyl}-3-L-benzyllactyl-α-(R)-methyl-β-alanine-amide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

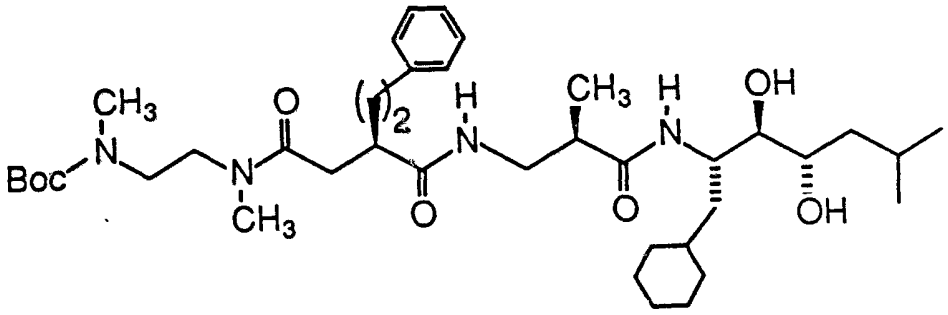
(+)-α-Amino-4-phenylbutyric acid (5 g) was partially dissolved in 27.7 ml of 1N HCl, 7.1 ml water and 284 ml 1N sulfuric acid, then cooled in an ice bath. 19.45 g of sodium nitrite in 85 ml water was added over 1 hour then stirred at zero degrees for an additional 4 hours. Solid NaCl was added to saturation followed by extraction with ether. The ether extracts were combined, washed with brine, dried over magnesium sulfate and stripped dry to give a pale yellow solid which was allowed to air dry (1.7 g pale yellow solid, 34% yield). 1.6 g of the above acid was dissolved in 10 ml DMF followed by the addition of 2.94 g of cesium carbonate. The mixture was stirred 10 minutes at room temperature 1.6 g of benzyl bromide was added and the mixture was stirred overnight at room temperature. Water was added followed by extraction with ether. The ether extract was dried and the solvent removed under vacuum. The residue was chromatographed to obtain 551 mg of product (22% yield). 300 MHz ^{1}H NMR: consistent with expected structure. This ester was dissolved in

14 ml dry THF and to the resulting solution was added 365 mg of 1,1"-carbonyldiimidazole followed by stirring for 2 hours. 208 mg of N,N,N'-trimethyl ethylene diamine was added and stirred for 18 hours at room temperature. The solvent was removed in vacuo and to the residue was added water followed by extraction with ether. The ether extract was washed with water, dried and evaporated, leaving 714 mg of the carbamate as a yellow oil (89% yield). The oil was hydrogenated, the solvent was evaporated and the solid residue was recrystallized twice from ethyl acetate to yield 214 mg (39% yield) of an acid as a white solid. This acid was used as the acid component, following the procedure of Example 18 to give the title compound (88%): 400 MHz ^{1}H NMR: consistent with proposed structure.

Anal. Calc'd. (+0.25 H_2O):

Calc'd.:	C	65.23	Found:	C	65.61
	H	9.47		H	9.7
	N	8.95		N	8.52

Example 25

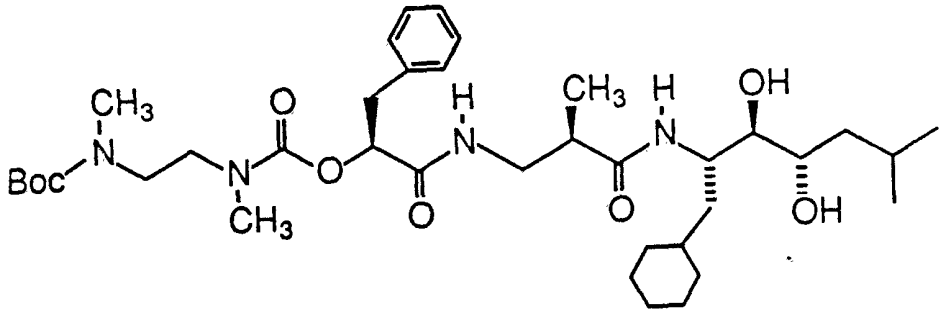


3-{N-[2-(N-methyl-N-Boc-amino)ethyl]-N-methylamino-carbonyl}-2-R-phenethyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

The procedure of Example 18 was followed, using 3-(N-(2-methyl-N-Boc-amino)ethyl)-N-methylamino-carbonyl)-2-R-phenethyl-propionic acid as the acid component, to give the title compound (55% yield): 400 MHz ^{1}H NMR was consistent with proposed structure.

Anal. Calc'd.:	C	66.63	Found:	C	66.20
	H	9.46		H	9.46
	N	7.97		N	7.80

Example 26

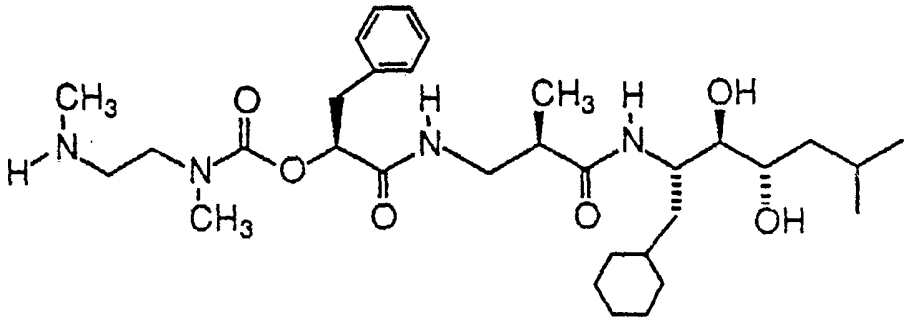


O-{N-[2-(N-methyl-N-Boc-amino)ethyl]-N-methylamino-carbonyl}-3-L-phenyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

The procedure of Example 18 was followed, using O-(N-(2-(N-methyl-N-Boc-amino)ethyl)-N-methyl-aminocarbonyl)-3-L-phenyllactic acid as the acid component, to give the title compound (42% yield): 400 MHz ^{1}H NMR was consistent with proposed structure.

Anal. Calc'd.:	C	63.49	Found:	C	63.24
	H	9.07		H	8.96
	N	8.00		N	7.89

Example 27

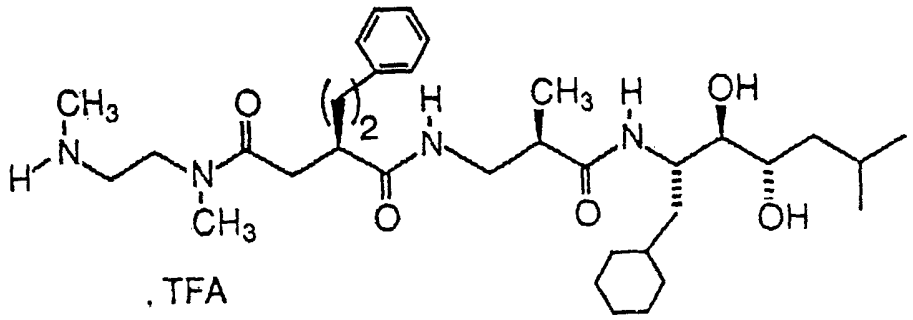


O-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

The title compound of Example 26 was treated with trifluoroacetic acid at room temperature for 30 minutes and then evaporated. The residue was stirred with 5% potassium carbonate and extracted with methylene chloride. Evaporation of the organic layer gave the title compound: 400 MHz ^{1}H NMR was consistent with proposed structure.

Anal. Calc'd.:	C	63.12	Found:	C	62.99
	H	9.27		H	9.10
	N	9.20		N	8.86

Example 28



3-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-2-R-phenethylpropionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane trifluoroacetate salt

The procedure of Example 27 was followed, employing the title compound of Example 25 as the substrate, omitting the potassium carbonate treatment, to give the title compound. 400 MHz ^{1}H NMR was consistent with proposed structure.

Example 29

O-{N-[2-(N,N-dimethylamino)ethyl]-N-isopropyl-amino-carbonyl}-3-L-phenyllactic acid

25 g of N,N-dimethylethylenediamine was stirred with excess acetone over 5% Pt/C, 60 psi at room temperature for one hour. The solvent was removed in vacuo and the residue was used without further purification. 4 g of benzyl 3-L-phenyllactate was dissolved in 121 ml of 20% solution of phosgene in toluene and cooled in an ice bath. 3.15 g of triethylamine was added over 5 minutes and the mixture was stirred for 18 hours. The solvent was removed in vacuo and the residue was taken up in ether and then filtered. To the filtrate was added 6.05 g of the above amine and stirred for 18 hours again at room temperature. Ether was added to the mixture followed by washing with potassium bicarbonate thn drying over magnesium sulfate. The solution was stripped dry and chromatographed on silica to give 1.6 g of product as a yellow oil (25% yield). The yellow oil was hydrogenated, and the product recrystallized from methanol to give 840 mg of the title compound as a white solid (yield 86.7%).

Example 30

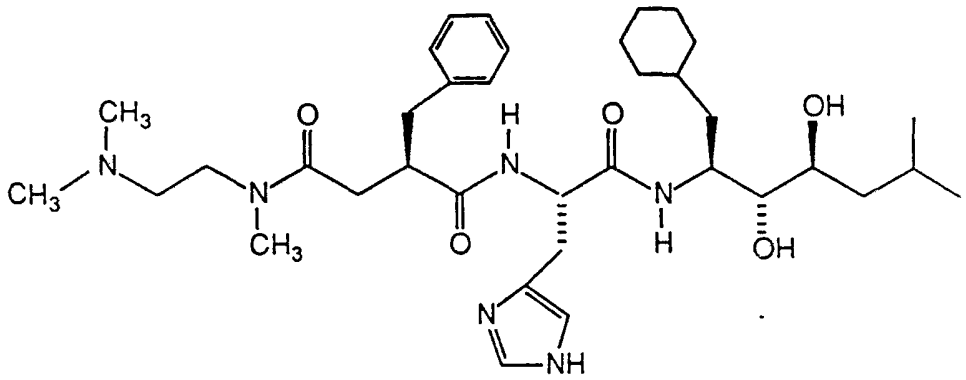
3-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-2-R-benzylpropionic acid hydrochloride salt

N-methylpiperidine (0.65 mL, 5.35 mmol) was added to a stirred solution of methyl 2-(R)-benzyl-3-carboxy-propionate (1.2 g, 5.35 mmol) in methylene chloride (100 mL). After the reaction flask was cooled to -10°C, isobutylchloroformate (0.7 mL, 5.35 mmol) was added, and the reaction was stirred for 5 minutes at -10°C at which time N,N,N'-trimethylethylenediamine (0.7 mL, 6 mmol) was introduced. The solution was allowed to warm to 0°C over a 30 minute period and was maintained at 0°C for 15 hours. The reaction mixture was washed successively with saturated sodium bicarbonate and brine. The solution was dried (Na_2SO_4) and evaporated. The residue was dissolved in a mixture of methanol (16 mL) and 1N KOH (8 mL), and stirred at r.t. overnight. After evaporation of the solvent, the residue was dissolved in water (30 mL). The aqueous solution was washed with ethyl acetate, then acidified to pH 6.5 with 1N CHl. The solvent was evaporated and the residue was extracted with methylene chloride and the organic solvent evaporated to give the title compound (970 mg, 62% yield). ^1H NMR: 300 MHz spectrum was consistent with the proposed structure.

Anal. Calc'd.: $C_{16}H_{24}N_2O_3$ + 1 HCl + 1.5 H_2O

Calc'd.:	C	54.00	Found: C	53.88
	H	7.93	H	8.21
	N	7.87	N	7.61

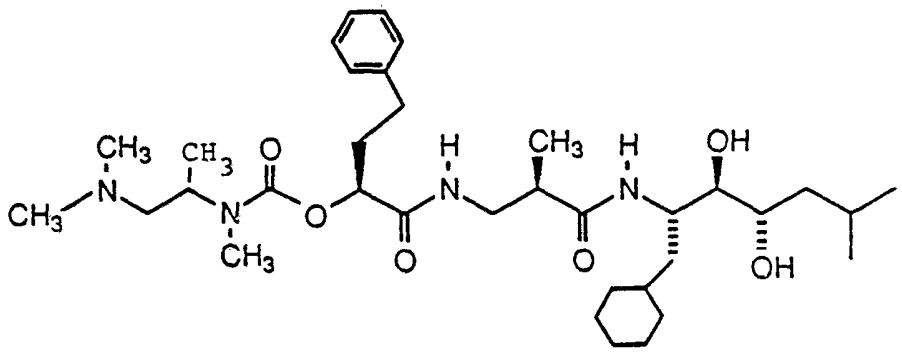
Example 31



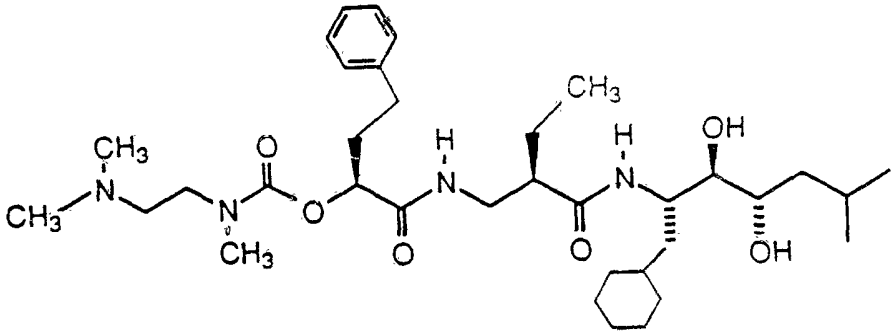
3-{N-[2-(N,N-dimethylamino)ethyl]-N-methylaminocarbonyl}-2-R-benzylpropionyl-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

The coupling procedure of Example 8 was followed, using the title compound of Example 30 (970 mg, 3.33 mmol) as the acid component in place of the title compound of Example 14, to give the title compound: Rf = 0.28 (chloroform-ethanol-ammonium hydroxide 84:15:1); ^{1}H NMR: 300 MHz spectrum consistent with proposed structure.

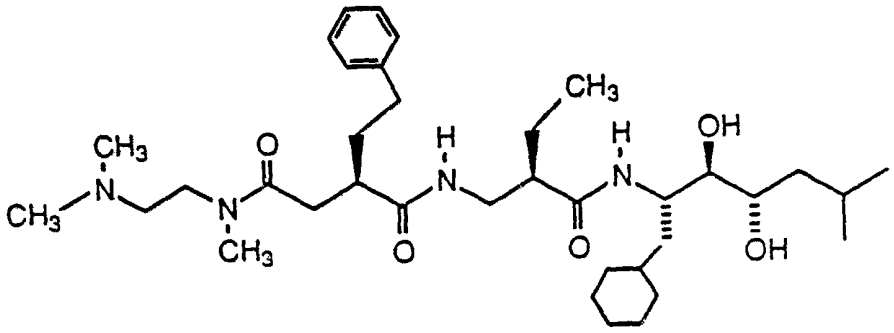
Other compounds of Formula I which can be prepared in accordance with the above-described general and specific procedures are as follows:



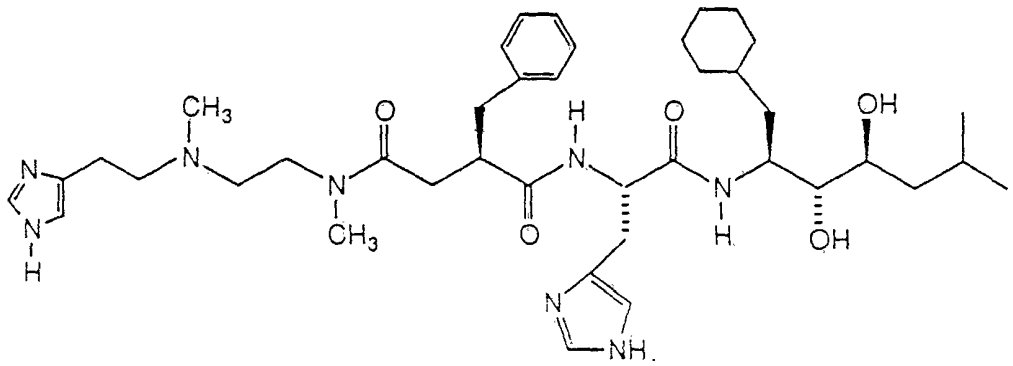
O-{N-[2-(N,N-dimethylamino)-1-(R,S)-methylethyl]-N-methylaminocarbonyl}-3-L-homophenyllactyl-α-(R)-methyl-β-alanineamide of (2S, 3R, 4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane



O-{N-[2-(N,N-dimethylamino)ethyl]-N-methyl-aminocarbonyl}-3-L-homophenyllactyl-α-(R)-ethyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane



3-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-2-(R)-(2-phenylethyl)-propionyl-α-(R)-ethyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclo-hexyl-3,4-dihydroxy-6-methylheptane



3-{N-[2-(N-methyl-N-2-(4-imidazole)ethylamino)ethyl]-N-methylaminocarbonyl}-2-R-benzylpropionyl-histidine-amide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

BIOLOGICAL EVALUATION

Compounds of Formula I were evaluated as inhibitors of human renin in an in vitro assay, as follows: This human renin inhibition test has been previously described in detail [Papaioannou et al., Clinical and Experimental Hypertension, A7(9), 1243-1257 (1985)]. Human renin was obtained from the National Institute for Biological Standards, London. An incubation mixture was prepared containing in a total volume of 0.25mL 100 mM Tris-acetate buffer at pH 7.4, 25 x 10^{-6} Goldblatt units of renin, 0.05mL of plasma from human volunteers taking oral contraceptives, 6.0 mM sodium EDTA, 2.4 mM phenylmethyl sulfonyl fluoride, 1.5 mM 8-hydroxyquinoline, 0.4 mg/mL BSA, and 0.024 mg/mL neomycin sulfate. This mixture was incubated for two hours at 37°C in the presence or absence of renin inhibitors. The produced angiotensin I was determined by radioimmunoassay (New England Nuclear kit). Test compounds to be assayed were solubilized in DMSO and diluted with 100mM Tris-acetate buffer at pH 7.4 containing 0.5% bovine serum albumin (BSA) to the appropriate concentration. The final concentration of organic solvent in the reaction mixture was less than 1%. Control incubations at 37°C were used to correct for effects of organic solvent on renin activity.

Biological Results:

TABLE I

In Vitro Effect of Compounds on Renin Activity

Compound	Human Renin IC_{50}
Example 8	1 nM
Example 10	1.5 nM
Example 11	7.7 nM
Example 15	5.4 nM
Example 18	170 nM
Example 19	48 nM
Example 20	19 nM
Example 21	1350 nM
Example 22	67 nM
Example 23	0.45 nM
Example 24	230 nM
Example 25	10 nM
Example 26	8.3 nM
Example 27	100 nM
Example 28	96 nM

The oral activity of compounds of Formula I was determined in vivo in Marmoset monkeys in accordance with the following procedure: Common marmosets (Callithrix jacchus, Charles River) were placed on a modified high protein low sodium diet (Purina, St. Louis, MO) for 1 to 2 weeks. On the day of the test

an animal was anesthetized with isoflurane and cannulated in the femoral artery and vein for blood pressure monitoring, intravenous saralasin infusion and blood sampling. After allowing the animal to recover from surgery for 2 hr, saralasin was infused at 1 microgram/min for 15 minutes to confirm that the animal's blood pressure was dependent on angiotensin II levels. The marmoset was allowed to stabilize for 30 min after the saralasin infusion. The test compound was administered orally and blood pressure was monitored for 2 hr. Blood samples were taken in K-EDTA for plasma renin activity before, 30 min, and 1 hr after compound administration. Results are shown in Table II.

Table II

Oral Effect of Compounds on Plasma Renin Activity in Sodium Depleted Marmoset

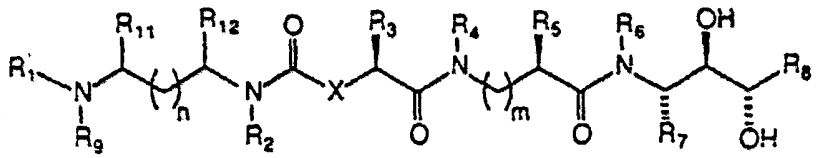
Compound Tested	% Reduction of Plasma Renin Activity @ 1h (3 mg/kg dose)
Example 8	100%
Example 10	100%
Example 11	100%
Example 15	79%

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

The matter contained in each of the following claims is to be read as part of the general description of the present invention.

The claims defining the invention are as follows:

1. A compound of the formula



wherein X is selected from oxygen atom, methylene and $>NR_{10}$ with R_{10} selected from hydrido, alkyl and benzyl; wherein each of R_1 and R_9 is a group independently selected from hydrido, alkyl, cycloalkyl, alkoxyacyl, alkoxycarbonyl, benzyloxycarbonyl, loweralkanoyl, haloalkylacyl, phenyl, benzyl, heterocyclicalkyl, naphthyl and naphthylmethyl, any one of which groups having a substitutable position may be optionally substituted with one or more radicals selected from alkyl, alkoxy, alkenyl, alkynyl, halo, haloalkyl, cyano and phenyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having one or two hetero atoms selected from nitrogen, oxygen and sulfur, which heterocyclic group has 4 to 10 ring members and contains as a ring member the nitrogen atom to which R_1 and R_9 are attached within said formula; wherein R_2 is selected from hydrido, alkyl, dialkylaminoalkyl, alkylacylaminoalkyl, benzyl and cycloalkyl; wherein R_3 is selected from alkyl, cycloalkylalkyl, acylaminoalkyl, phenylalkyl, naphthylmethyl, aryl and heterocyclicalkyl, wherein the aromatic portion of any of said phenylalkyl, naphthylmethyl, aryl and heterocyclicalkyl may be substituted by one or more halo or alkyl or by both; wherein each of R_4 and R_6 is independently selected from hydrido, alkyl, benzyl and cycloalkyl; wherein R_7 is selected from substituted or unsubstituted cycloalkyl, phenyl, cycloalkylalkyl and

phenylalkyl, any one of which may be substituted with one or more groups selected from alkyl, alkoxy, halo, haloalkyl, alkenyl, alkynyl and cyano; wherein R_8 is selected from hydrido, alkyl, haloalkyl, alkylcycloalkyl, alkylcycloalkenyl and alkoxycarbonyl; wherein each of R_{11} and R_{12} is independently selected from hydrido, alkyl, dialkylaminoalkyl and phenyl; and wherein m is zero or one and n is a number selected from zero through five;

with the proviso that where m is zero, then R_5 is selected from hydrido, alkyl, benzyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, alkylthioalkyl, heterocyclicalkyl, sulfonylheterocyclicalkyl and acylheterocyclicalkyl; and

with the further proviso that when m is one, then R_5 is selected from hydrido, alkyl, benzyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylthioalkyl and imidazolemethyl.

2. Compound of Claim 1 wherein X is selected from oxygen atom, methylene and $>NR_{10}$ with R_{10} selected from hydrido, alkyl and benzyl; wherein each of R_1 and R_9 is independently selected from hydrido, lower alkyl, cycloalkyl, alkoxycarbonyl, benzyloxycarbonyl, loweralkanoyl, alkoxyacyl, heterocyclicalkyl, phenyl and benzyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and one or two nitrogen atoms as ring atoms; wherein each of R_2, R_4 and R_6 is independently selected from hydrido and alkyl; wherein R_3 is selected from phenylalkyl, naphthylmethyl, cyclohexylalkyl, pyridylmethyl, cyclohexylalkyl, pyridylethyl and pyridylpropyl; wherein R_7 is selected from substituted or unsubstituted cyclohexylmethyl and

benzyl, either one of which may be substituted with one or more groups selected from alkyl, alkoxy, halo and haloalkyl; wherein R_8 is selected from hydrido, ethyl, n-propyl, n-butyl, isobutyl and fluoroalkyl; wherein each of R_{11} and R_{12} is independently selected from hydrido and lower alkyl; wherein m is zero or one and n is a number selected from zero through five; or a pharmaceutically-acceptable salt thereof;

with the proviso that where m is zero, then R_5 is selected from hydrido, alkyl, benzyl, cycloalkyl, cycloalkylalkyl, imidazolemethyl, imidazoleethyl, thiazolemethyl, pyridylmethyl, sulfonylimidazolemethyl and acylimidazolemethyl; and

with the further proviso that when m is one, then R_5 is selected from hydrido, alkyl and imidazolemethyl.

3. Compound of Claim 2 wherein X is selected from oxygen atom, methylene and $>NR_{10}$ with R_{10} selected from hydrido, alkyl and benzyl; wherein each of R_1 and R_9 is independently selected from hydrido, alkyl, alkoxyacyl, alkoxycarbonyl, heterocyclicalkyl and benzyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and having one or two nitrogen atoms as ring atoms; wherein each of R_2, R_4, and R_6 is independently selected from hydrido and alkyl; wherein R_3 is selected from benzyl, phenethyl, cyclohexylmethyl, phenpropyl, pyridylmethyl and 2-pyridylethyl; wherein R_7 is cyclohexylmethyl; wherein R_8 is selected from ethyl, n-propyl, isobutyl and perfluoropropyl; wherein each of R_{11} and R_{12} is independently selected from hydrido and methyl; wherein m is zero or one and n is a number selected from zero through five; or a pharmaceutically-acceptable salt thereof;

with the proviso that where m is zero, then R_5 is selected from imidazolemethyl, thiazolemethyl and isobutyl; and

with the further proviso that when m is one, then R_5 is methyl or ethyl.

4. Compound of Claim 3 wherein X is selected from oxygen atom, methylene and $>NR_{10}$ with R_{10} selected from hydrido and methyl; wherein each of R_1 and R_9 is independently selected from hydrido, lower alkyl, alkoxyacyl, alkoxycarbonyl, heterocyclicalkyl and benzyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and having one or two nitrogen atoms as ring atoms; wherein R_2 is selected from hydrido, methyl, ethyl and isopropyl; wherein R_3 is selected from benzyl, phenethyl, pyridylmethyl, cyclohexylmethyl and 2-pyridylethyl; wherein each of R_4 and R_6 is independently selected from hydrido and methyl; wherein R_7 is cyclohexylmethyl; wherein R_8 is independently selected from ethyl, n-propyl and isobutyl; wherein each of R_{11} and R_{12} is hydrido; wherein m is zero or one and n is a number selected from zero through five; or a pharmaceutically-acceptable salt thereof; with the proviso that where m is zero, then R_5 is selected from imidazolemethyl, thiazolemethyl and isobutyl; and with the further proviso that when m is one, then R_5 is methyl or ethyl.

5. Compound of Claim 4 wherein X is selected from oxygen atom and methylene; wherein each of R_1 and R_9 is independently selected from hydrido, methyl, ethyl, 2-(1H-imidazole-4-yl)ethyl, t-butyloxycarbonyl and methoxymethylcarbonyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and having one or two nitrogen atoms

as ring atoms; wherein R_2 is selected from hydrido, methyl, ethyl and isopropyl; wherein R_3 is selected from benzyl, cyclohexylmethyl, phenethyl, pyridylmethyl and 2-pyridylethyl; wherein R_7 is cyclohexylmethyl; wherein each of R_4 and R_6 is independently selected from hydrido and methyl; wherein R_8 is isobutyl; wherein each of R_{11} and R_{12} is hydrido; wherein m is zero or one and n is a number selected from zero through five; or a pharmaceutically-acceptable salt thereof; with the proviso that where m is zero, then R_5 is selected from imidazolemethyl, thiazolemethyl and isobutyl; and with the further proviso that when m is one, then R_5 is methyl or ethyl.

6. Compound of Claim 5 wherein X is selected from oxygen atom and methylene; wherein each of R_1 and R_9 is a group independently selected from hydrido, methyl, ethyl, 2-(1H-imidazole-4-yl)ethyl, t-butyloxycarbonyl and methoxymethylcarbonyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and having one or two nitrogen atoms as ring atoms; wherein R_2 is selected from hydrido, methyl, ethyl and isopropyl; wherein R_3 is selected from benzyl, phenethyl, pyridylmethyl and 2-pyridylethyl; wherein R_7 is cyclohexylmethyl; wherein each of R_4 and R_6 is independently selected from hydrido and methyl; wherein R_8 is isobutyl; wherein each of R_{11} and R_{12} is hydrido; wherein m is zero or one and n is a number selected from zero through three; or a pharmaceutically-acceptable salt thereof; with the proviso that where m is zero, then R_5 is selected from imidazolemethyl and isobutyl; and with the further proviso that when m is one, then R_5 is methyl or ethyl.

7. Compound of Claim 6 which is O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

8. Compound of Claim 6 which is O-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

9. Compound of Claim 6 which is O-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

10. Compound of Claim 6 which is O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

11. Compound of Claim 6 which is O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

12. Compound of Claim 6 which is 3-{N-[4-(N-methyl-N-Boc-amino)butyl-N-methyl-aminocarbonyl}-2-(R)-phenethyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

13. Compound of Claim 6 which is O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylaminocarbonyl}-3-L-benzyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

14. Compound of Claim 6 which is O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-3-L-benzyllactyl-α-(R)-ethyl-β-alanine-amide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

15. Compound of Claim 6 which is 3-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-2-(R)-(2-phenylethyl)-propionyl-α-(R)-ethyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

16. Compound of Claim 6 which is 3-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-2-R-benzyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

17. Compound of Claim 6 which is O-{N-[2-(N,N-dimethylamino)ethyl]-N-isopropyl-aminocarbonyl}-3-L-phenyllactyl-L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

18. Compound of Claim 6 which is 3-{N-[4-(N-methylamino)butyl]-N-methyl-aminocarbonyl}-2-R-phenethyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

19. Compound of Claim 6 which is O-{N-[2-(N-methyl-N-Boc-amino)ethyl]-N-methyl-aminocarbonyl}-3-L-phenyllactyl-L-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

20. Compound of Claim 6 which is O-{N-[2-N,N-diethylamino)ethyl]-N-methyl-amino-carbonyl}-3-L-benzyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

21. Compound of Claim 6 which is 3-{N-[2-(N-methyl-N-Boc-amino)ethyl]-N-methylamino-carbonyl}-2-R-phenethyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

22. Compound of Claim 6 which is O-{N-[2-(N-methyl-N-Boc-amino)ethyl]-N-methylamino-carbonyl}-3-L-phenyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

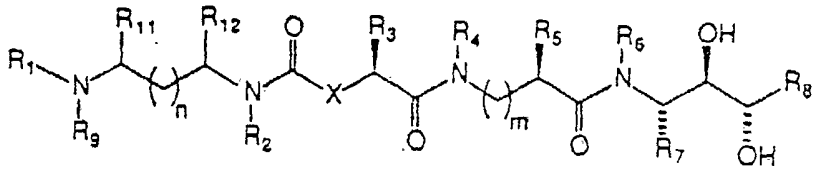
23. Compound of Claim 6 which is O-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

24. Compound of Claim 6 which is 3-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-2-R-phenethylpropionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane trifluoroacetate salt.

25. Compound of Claim 6 which is 3-{N-[2-(N,N-dimethylamino)ethyl]-N-methylaminocarbonyl}-2-R-benzylpropionyl-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

26. Compound of Claim 6 which is 3-{N-[2-(N-methyl-N-2-(4-imidazole)ethylamino)ethyl]-N-methylaminocarbonyl}-2-R-benzylpropionyl-histidine-amide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

27. A pharmaceutical composition comprising a therapeutically-effective amount of a renin-inhibiting compound and a pharmaceutically-acceptable carrier or diluent, said renin-inhibiting compound selected from a family of compounds of the formula



(I)

wherein X is selected from oxygen atom, methylene and $>NR_{10}$ with R_{10} selected from hydrido, alkyl and benzyl; wherein each of R_1 and R_9 is a group independently selected from hydrido, alkyl, cycloalkyl, alkoxyacyl, alkoxycarbonyl, benzyloxycarbonyl, loweralkanoyl, haloalkylacyl, phenyl, benzyl, heterocyclicalkyl, naphthyl and naphthylmethyl, any one of which groups having a substitutable position may be optionally substituted with one or more radicals selected from alkyl, alkoxy, alkenyl, alkynyl, halo, haloalkyl, cyano and phenyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having one or two heteroatoms selected from nitrogen, oxygen and sulfur, which heterocyclic group has 4 to 10 ring members and contains as a ring member the nitrogen atom to which R_1 and R_9 are attached within said formula; wherein R_2 is selected from hydrido, alkyl, dialkylaminoalkyl,

alkylacylaminoalkyl, benzyl and cycloalkylalkyl; wherein R_3 is selected from alkyl, acylaminoalkyl, phenylalkyl, naphthylmethyl, aryl and heterocyclicalkyl, wherein the aromatic portion of any of said phenylalkyl, naphthylmethyl, aryl and heterocyclicalkyl may be substituted by one or more halo or alkyl or by both; wherein each of R_4 and R_6 is independently selected from hydrido, alkyl, benzyl and cycloalkyl; wherein R_7 is selected from substituted or unsubstituted cycloalkyl, phenyl, cycloalkylalkyl and phenylalkyl, any one of which may be substituted with one or more groups selected from alkyl, alkoxy, halo, haloalkyl, alkenyl, alkynyl and cyano; wherein R_8 is selected from hydrido, alkyl, haloalkyl, alkylcycloalkyl, alkylcycloalkenyl and alkoxycarbonyl; wherein each of R_{11} and R_{12} is independently selected from hydrido, alkyl, dialkylaminoalkyl and phenyl; and wherein m is zero or one and n is a number selected from zero through five;

with the proviso that where m is zero, then R_5 is selected from hydrido, alkyl, benzyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, alkylthioalkyl, heterocyclicalkyl, sulfonylheterocyclicalkyl and acylheterocyclicalkyl; and

with the further proviso that when m is one, then R_5 is selected from hydrido, alkyl, benzyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylthioalkyl and imidazolemethyl.

28. The composition of Claim 27 wherein X is selected from oxygen atom, methylene and $>NR_{10}$ with R_{10} selected from hydrido, alkyl and benzyl; wherein each of R_1 and R_9 is independently selected from hydrido, lower alkyl, cycloalkyl, alkoxycarbonyl, benzyloxycarbonyl, loweralkanoyl, alkoxyacyl,

heterocyclicalkyl, phenyl and benzyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and one or two nitrogen atoms as ring atoms; wherein each of R_2, R_4 and R_6 is independently selected from hydrido and alkyl; wherein R_3 is selected from phenylalkyl, naphthylmethyl, cyclohexylalkyl, pyridylmethyl, pyridylethyl and pyridylpropyl; wherein R_7 is selected from substituted or unsubstituted cyclohexylmethyl and benzyl, either one of which may be substituted with one or more groups selected from alkyl, alkoxy, halo and haloalkyl; wherein R_8 is selected from hydrido, ethyl, n-propyl, n-butyl, isobutyl and fluoroalkyl; wherein each of R_{11} and R_{12} is independently is selected from hydrido and lower alkyl; wherein m is zero or one and n is a number selected from zero through five; or a pharmaceutically-acceptable salt thereof;

with the proviso that where m is zero, then R_5 is selected from hydrido, alkyl, benzyl, cycloalkyl, cycloalkylalkyl, imidazolemethyl, imidazoleethyl, thiazolemethyl, pyridylmethyl, sulfonylimidazolemethyl and acylimidazolemethyl; and

with the further proviso that when m is one, then R_5 is selected from hydrido, alkyl and imidazolemethyl.

29. The composition of Claim 28 wherein X is selected from oxygen atom, methylene and $>NR_{10}$ with R_{10} selected from hydrido, alkyl and benzyl; wherein each of R_1 and R_9 is independently selected from hydrido, alkyl, alkoxyacyl, alkoxycarbonyl, heterocyclicalkyl and benzyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring

members and having one or two nitrogen atoms as ring atoms; wherein each of R_2, R_4 and R_6 is independently selected from hydrido and alkyl; wherein R_3 is selected from benzyl, phenethyl, phenpropyl, pyridylmethyl, 2-pyridylethyl and cyclohexylmethyl; wherein R_7 is cyclohexylmethyl; wherein R_8 is selected from ethyl, n-propyl, isobutyl and perfluoropropyl; wherein each of R_{11} and R_{12} is independently is selected from hydrido and methyl; wherein m is zero or one and n is a number selected from zero through five; or a pharmaceutically-acceptable salt thereof;

with the proviso that where m is zero, then R_5 is selected from imidazolemethyl, thiazolemethyl and isobutyl; and

with the further proviso that when m is one, then R_5 is methyl or ethyl.

30. The composition of Claim 29 wherein X is selected from oxygen atom, methylene and $>NR_{10}$ with R_{10} selected from hydrido and methyl; wherein each of R_1 and R_9 is independently selected from hydrido, lower alkyl, alkoxyacyl, alkoxycarbonyl, heterocyclic-alkyl and benzyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and having one or two nitrogen atoms as ring atoms; wherein R_2 is selected from hydrido, methyl, ethyl and isopropyl; wherein R_3 is selected from benzyl, phenethyl, pyridylmethyl, 2-pyridylethyl and cyclohexylmethyl; wherein each of R_4 and R_6 is independently selected from hydrido and methyl; wherein R_7 is cyclohexylmethyl; wherein R_8 is independently selected from ethyl, n-propyl and isobutyl; wherein each of R_{11} and R_{12} is hydrido; wherein m is zero or one and n is a number selected from zero through five;

or a pharmaceutically-acceptable salt thereof; with the proviso that where m is zero, then R_5 is selected from imidazolemethyl, thiazolemethyl and isobutyl; and with the further proviso that when m is one, then R_5 is methyl or ethyl.

31. The composition of Claim 30 wherein X is selected from oxygen atom and methylene; wherein each of R_1 and R_9 is independently selected from hydrido, methyl, ethyl, 2-(1H-imidazole-4-yl)ethyl, t-butyloxy-carbonyl and methoxymethylcarbonyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and having one or two nitrogen atoms as ring atoms; wherein R_2 is selected from hydrido, methyl, ethyl and isopropyl; wherein R_3 is selected from benzyl, phenethyl, pyridylmethyl, cyclohexylmethyl and 2-pyridylethyl wherein R_7 is cyclohexylmethyl; wherein each of R_4 and R_6 is independently selected from hydrido and methyl; wherein R_8 is isobutyl; wherein R_{11} and R_{12} is hydrido; wherein m is zero or one and n is a number selected from zero through five; or a pharmaceutically-acceptable salt thereof; with the proviso that where m is zero, then R_5 is selected from imidazolemethyl, thiazolemethyl and isobutyl; and with the further proviso that when m is one, then R_5 is methyl or ethyl.

32. The composition of Claim 31 wherein X is selected from oxygen atom and methylene; wherein each of R_1 and R_9 is a group independently selected from hydrido, methyl, ethyl, 2-(1H-imidazole-4-yl)ethyl, t-butyloxycarbonyl and methoxymethylcarbonyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic

group having 5 to 7 ring members and having one or two nitrogen atoms as ring atoms; wherein R_2 is selected from hydrido, methyl, ethyl and isopropyl; wherein R_3 is selected from benzyl, phenethyl, pyridylmethyl and 2-pyridylethyl; wherein each of R_4 and R_6 is independently selected from hydrido and methyl; wherein R_7 is cyclohexylmethyl; wherein R_8 is isobutyl; wherein each of R_{11} and R_{12} is hydrido; wherein m is zero or one and n is a number selected from zero through three; or a pharmaceutically-acceptable salt thereof; with the proviso that where m is zero, then R_5 is selected from imidazolemethyl and isobutyl; and with the further proviso that when m is one, then R_5 is methyl or ethyl.

33. The composition of Claim 32 wherein said renin-inhibiting compound is O-{N-[2-N,N-(dimethylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

34. The composition of Clair 32 wherein said renin-inhibiting compound is O-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

35. The composition of Claim 32 wherein said renin-inhibiting compound is O-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

36. The composition of Claim 32 wherein said renin-inhibiting compound is O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-3-L-phenyllactyl-L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

37. The composition of Claim 32 wherein said renin-inhibiting compound is O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-3-L-phenyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

38. The composition of Claim 32 wherein said renin-inhibiting compound is O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-3-L-homophenyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

39. The composition of Claim 32 wherein said renin-inhibiting compound is 3-{N-[4-(N-methyl-N-Boc-amino)butyl-N-methyl-aminocarbonyl}-2-(R)-phenethyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

40. The composition of Claim 32 wherein said renin-inhibiting compound is O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-3-L-benzyllactyl-α-(R)-ethyl-β-alanine-amide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

41. The composition of Claim 32 wherein said renin-inhibiting compound is 3-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-2-(R)-(2-phenylethyl)-propionyl-α-(R)-ethyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

42. The composition of Claim 32 wherein said renin-inhibiting compound is 3-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-2-R-benzyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

43. The composition of Claim 32 wherein said renin-inhibiting compound is O-{N-[2-(N,N-dimethylamino)ethyl]-N-isopropyl-aminocarbonyl}-3-L-phenyllactyl-L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

44. The composition of Claim 32 wherein said renin-inhibiting compound is 3-{N-[4-(N-methylamino)butyl]-N-methyl-aminocarbonyl}-2-R-phenethyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

45. The composition of Claim 32 wherein said renin-inhibiting compound is O-{N-[2-(N-methyl-N-boc-amino)ethyl]-N-methyl-aminocarbonyl}-3-L-phenyl-lactyl-L-histidineamide of (2S,3R,4S)-2-amino-1-cyclo-hexyl-3,4-dihydroxy-6-methylheptane.

46. The composition of Claim 32 wherein said renin-inhibiting compound is O-{N-[2-(N,N-dimethylamino)ethyl]-N-methyl-amino-carbonyl}-3-L-benzyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

47. The composition of Claim 32 wherein said renin-inhibiting compound is 3-{N-[2-(N-methyl-N-Boc-amino)ethyl]-N-methylamino-carbonyl}-2-R-phenethyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

48. The composition of Claim 32 wherein said renin-inhibiting compound is O-{N-[2-(N-methyl-N-Boc-amino)ethyl]-N-methylamino-carbonyl}-3-L-phenyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

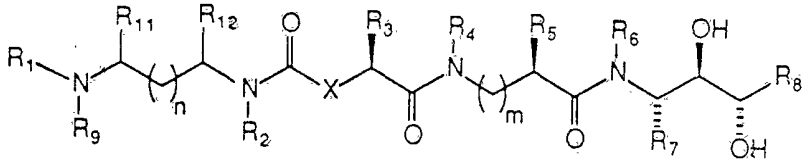
49. The composition of Claim 32 wherein said renin-inhibiting compound is O-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-α-(R)-methy-β- alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

50. The composition of Claim 32 wherein said renin-inhibiting compound is 3-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-2-R-phenethylpropionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane trifluoroacetate salt.

51. The composition of Claim 32 wherein said renin-inhibiting compound is 3-{N-[2-(N,N-dimethylamino)ethyl]-N-methylaminocarbonyl}-2-R-benzylpropionyl-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

52. The composition of Claim 32 wherein said renin-inhibiting compound is 3-{N-[2-(N-methyl-N-2-(4-imidazole)ethylamino)ethyl]-N-methylaminocarbonyl}-2-R-benzylpropionyl-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

53. A therapeutic method for treating hypertension, said method comprising administering to a hypertensive patient a therapeutically-effective amount of a compound of the formula



wherein X is selected from oxygen atom, methylene and $>NR_{10}$ with R_{10} selected from hydrido, alkyl and benzyl; wherein each of R_1 and R_9 is a group independently selected from hydrido, alkyl, cycloalkyl, phenyl, alkoxyacyl, alkoxycarbonyl, benzyloxycarbonyl, loweralkanoyl, haloalkylacyl, benzyl, heterocyclicalkyl, naphthyl and naphthylmethyl, any one of which groups having a substitutable position may be optionally substituted with one or more radicals selected from alkyl, alkoxy, alkenyl, alkynyl, halo, haloalkyl, cyano and phenyl; wherein R_1 and R_9 may be taken

together to form a saturated, unsaturated or partially unsaturated heterocyclic group having one or two hetero atoms selected from nitrogen, oxygen and sulfur, which heterocyclic group has 4 to 10 ring members and contains as a ring member the nitrogen atom to which R_1 and R_9 are attached within said formula; wherein R_2 is selected from hydrido, alkyl, dialkylaminoalkyl, alkylacylaminoalkyl, benzyl and cycloalkyl; wherein R_3 is selected from alkyl, cycloalkylalkyl, acylaminoalkyl, phenylalkyl, naphthylmethyl, aryl and heterocyclicalkyl, wherein the aromatic portion of any of said phenylalkyl, naphthylmethyl, aryl and heterocyclicalkyl may be substituted by one or more halo or alkyl or by both; wherein each of R_4 and R_6 is independently selected from hydrido, alkyl, benzyl and cycloalkyl; wherein R_7 is selected from substituted or unsubstituted cycloalkyl, phenyl, cycloalkylalkyl and phenylalkyl, any one of which may be substituted with one or more groups selected from alkyl, alkoxy, halo, haloalkyl, alkenyl, alkynyl and cyano; wherein R_8 is selected from hydrido, alkyl, haloalkyl, alkylcycloalkyl, alkylcycloalkenyl and alkoxycarbonyl; wherein each of R_{11} and R_{12} is independently selected from hydrido, alkyl, dialkylaminoalkyl and phenyl; and wherein m is zero or one and n is a number selected from zero through five;

with the proviso that where m is zero, then R_5 is selected from hydrido, alkyl, benzyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio-alkyl, heterocyclicalkyl sulfonylheterocyclicalkyl and acylheterocyclicalkyl; and

with the further proviso that when m is one, then R_5 is selected from hydrido, alkyl, benzyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylthioalkyl and imidazolemethyl.

54. The method of Claim 53 wherein X is selected from oxygen atom, methylene and $>NR_{10}$ with R_{10} selected from hydrido, alkyl and benzyl; wherein each of R_1 and R_9 is independently selected from hydrido, lower alkyl, cycloalkyl, alkoxycarbonyl, benzyloxycarbonyl, loweralkanoyl, alkoxyacyl, heterocyclicalkyl, phenyl and benzyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and one or two nitrogen atoms as ring atoms; wherein each of R_2, R_4 and R_6 is independently selected from hydrido and alkyl; wherein R_3 is selected from phenylalkyl, cyclohexylalkyl, naphthylmethyl, pyridylmethyl, pyridylethyl and pyridylpropyl; wherein R_7 is selected from substituted or unsubstituted cyclohexylmethyl and benzyl, either one of which may be substituted with one or more groups selected from alkyl, alkoxy, halo and haloalkyl; wherein R_8 is selected from hydrido, ethyl, n-propyl, n-butyl, isobutyl and fluoroalkyl; wherein each of R_{11} and R_{12} is independently is selected from hydrido and lower alkyl; wherein m is zero or one and n is a number selected from zero through five; or a pharmaceutically-acceptable salt thereof;

with the proviso that where m is zero, then R_5 is selected from hydrido, alkyl, benzyl, cycloalkyl, cycloalkylalkyl, imidazolemethyl, imidazoleethyl, thiazolemethyl and pyridylmethyl; and

with the further proviso that when m is one, then R_5 is selected from hydrido, alkyl and imidazolemethyl.

55. The method of Claim 54 wherein X is selected from oxygen atom, methylene and $>NR_{10}$ with R_{10} selected from hydrido, alkyl and benzyl; wherein each of R_1 and R_9 is independently selected from hydrido, alkyl, alkoxyacyl, heterocyclicalkyl, alkoxycarbonyl and benzyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and having one or two nitrogen atoms as ring atoms; wherein each of R_2, R_4 and R_6 is independently selected from hydrido and alkyl; wherein R_3 is selected from benzyl, phenethyl, phenpropyl, cyclohexylmethyl, pyridylmethyl and 2-pyridylethyl; wherein R_7 is cyclohexylmethyl; wherein R_8 is selected from ethyl, n-propyl, perfluoropropyl and isobutyl; wherein each of R_{11} and R_{12} is independently selected from hydrido and methyl;

wherein m is zero or one and n is a whole number selected from zero through five; or a pharmaceutically-acceptable salt thereof;

with the proviso that where m is zero, then R_5 is selected from imidazolemethyl, thiazolemethyl, sulfonylimidazolemethyl and acylimidazolemethyl, isobutyl; and

with the further proviso that when m is one, then R_5 is methyl or ethyl.

56. The method of Claim 55 wherein X is selected from oxygen atom, methylene and $>NR_{10}$ with R_{10} selected from hydrido and methyl; wherein each of R_1 and R_9 is independently selected from hydrido, lower alkyl, alkoxyacyl, heterocyclicalkyl, alkoxycarbonyl and benzyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and having one or two nitrogen atoms as ring atoms; wherein R_2 is selected from hydrido, methyl, ethyl and isopropyl; wherein R_3 is selected from benzyl, phenethyl, cyclohexylmethyl, pyridylmethyl and 2-pyridylethyl; wherein each of R_4 and R_6 is independently selected from hydrido and methyl; wherein R_7 is cyclohexylmethyl; wherein R_8 is independently selected from ethyl, n-propyl and isobutyl; wherein each of R_{11} and R_{12} is hydrido; wherein m is zero or one and n is a number selected from zero through five; or a pharmaceutically-acceptable salt thereof; with the proviso that where m is zero, then R_5 is selected from imidazolemethyl, thiazolemethyl and isobutyl; and with the further proviso that when m is one, then R_5 is methyl or ethyl.

57. The method of Claim 56 wherein X is selected from oxygen atom and methylene; wherein each of R_1 and R_9 is independently selected from hydrido, methyl, ethyl, 2-(1H-imidazole-4-yl)ethyl, t-butyloxy-carbonyl and methoxymethylcarbonyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and having one or two nitrogen atoms as ring atoms; wherein R_2 is selected from hydrido, methyl, ethyl and isopropyl; wherein R_3 is selected from benzyl, phenethyl, cyclohexylmethyl, pyridylmethyl and 2-pyridylethyl; wherein each of R_4 and R_6 is

independently selected from hydrido and methyl; wherein R_7 is cyclohexylmethyl; wherein R_8 is isobutyl; wherein each of R_{11} and R_{12} is hydrido; wherein m is zero or one and n is a number selected from zero through five; or a pharmaceutically-acceptable salt thereof; with the proviso that where m is zero, then R_5 is selected from imidazolemethyl, thiazolemethyl and isobutyl; and with the further proviso that when m is one, then R_5 is methyl or ethyl.

58. The method of Claim 57 wherein X is selected from oxygen atom and methylene; wherein each of R_1 and R_9 is a group independently selected from hydrido, methyl, ethyl, 2-(1H-imidazole-4-yl)ethyl, t-butyloxycarbonyl and methoxymethylcarbonyl; wherein R_1 and R_9 may be taken together to form a saturated, unsaturated or partially unsaturated heterocyclic group having 5 to 7 ring members and having one or two nitrogen atoms as ring atoms; wherein R_2 is selected from hydrido, methyl, ethyl and isopropyl; wherein R_3 is selected from benzyl, phenethyl, pyridylmethyl and 2-pyridylethyl; wherein each of R_4 and R_6 is independently selected from hydrido and methyl; wherein R_7 is cyclohexylmethyl; wherein R_8 is isobutyl; wherein each of R_{11} and R_{12} is hydrido; wherein m is zero or one and n is a number selected from zero through three; or a pharmaceutically-acceptable salt thereof; with the proviso that where m is zero, then R_5 is selected from imidazolemethyl and isobutyl; and with the further proviso that when m is one, then R_5 is methyl or ethyl.

59. The method of Claim 58 wherein said compound is O-{N-[2-N,N-(dimethylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

60. The method of Claim 58 wherein said compound is O-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

61. The method of Claim 58 wherein said compound is O-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

62. The method of Claim 58 wherein said compound is O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-3-L-phenyllactyl-L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

63. The method of Claim 58 wherein said compound is O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-3-L-phenyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

64. The method of Claim 58 wherein said compound is 3-{-[4-(N-methyl-N-Boc-amino)butyl-N-methyl-aminocar-bonyl]-2-(R)-phenethyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

65. The method of Claim 58 wherein said compound is O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-3-L-benzyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

66. The method of Claim 58 wherein said compound is O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-3-L-benzyllactyl-α-(R)-ethyl-β-alanine-amide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

67. The method of Claim 58 wherein said renin-inhibiting compound is 3-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-2-(R)-(2-phenylethyl)-propionyl-α-(R)-ethyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclo-hexyl-3,4-dihydroxy-6-methylheptane.

68. The method of Claim 58 wherein said compound is 3-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino-carbonyl}-2-R-benzyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

69. The method of Claim 58 wherein said compound is O-{N-[2-(N,N-dimethylamino)ethyl]-N-isopropyl-aminocarbonyl}-3-L-phenyllactyl-L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

70. The method of Claim 58 wherein said compound is 3-{N-[4-(N-methylamino)butyl]-N-methyl-aminocarbonyl}-2-R-phenethyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

71. The method of Claim 58 wherein said compound is O-{N-[2-(N-methyl-N-Boc-amino)ethyl]-N-methyl-aminocarbonyl}-3-L-phenyllactyl-L-histidineamide of (2S 3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

72. The method of Claim 58 wherein said compound is O-{N-[2-(N,N-dimethylamino)ethyl]-N-methyl-aminocarbonyl}-3-L-benzyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

73. The method of Claim 58 wherein said compound is 3-{N-[2-(N-methyl-N-Boc-amino)ethyl]-N-methylamino-carbonyl}-2-R-phenethyl-propionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

74. The method of Claim 58 wherein said compound is O-{N-[2-(N-methyl-N-Boc-amino)ethyl]-N-methylamino-carbonyl}-3-L-phenyllactyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

75. The method of Claim 58 wherein said compound is O-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-α-(R)-methy-β- alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

76. The method of Claim 58 wherein said compound is 3-{N-[2-(N-methylamino)ethyl]-N-methylaminocarbonyl}-2-R-phenethylpropionyl-α-(R)-methyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane trifluoroacetate salt.

77. The method of Claim 58 wherein said compound is 3-{N-[2-(N,N-dimethylamino)ethyl]-N-methylaminocarbonyl}-2-R-benzylpropionyl-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

78. The method of Claim 58 wherein said compound is 3-{N-[2-(N-methyl-N-2-(4-imidazole)ethylamino}ethyl]-N-methylaminocarbonyl}-2-R-benzylpropionyl-histidineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

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