The present invention is directed to certain compounds of general structural formula (I), wherein R₁, R₁b, R₂, R₃a, R₄, R₅, R₆, R₇, A, W, and n are as defined herein. These compounds promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to treat physiological or medical conditions characterized by a deficiency in growth hormone secretion, such as short stature in growth hormone deficient children, and to treat medical conditions which are improved by the anabolic effects of growth hormone. Growth hormone releasing compositions containing such compounds as the active ingredient thereof are also disclosed.
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TITLE OF THE INVENTION
INDOLYL GROUP CONTAINING COMPOUNDS AND THE USE THEREOF TO PROMOTE
THE RELEASE OF GROWTH HORMONE(S)

BACKGROUND OF THE INVENTION

Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic processes of the body: (1) Increased rate of protein synthesis in all cells of the body; (2) Decreased rate of carbohydrate utilization in cells of the body; (3) Increased mobilization of free fatty acids and use of fatty acids for energy. A deficiency in growth hormone secretion can result in various medical disorders, such as dwarfism.

Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering GRF or a peptidal compound which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone. Recombinant growth hormone has become available which, while no longer carrying any
risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray.

Other compounds have been developed which stimulate the release of endogenous growth hormone such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent 4,411,890. These peptides, while considerably smaller than growth hormones still have low oral bioavailability. Non peptidal growth hormone secretagogues with a benzolactam structure are disclosed in U.S. Patents 5,206,235, 5,283,241, 5,284,841, 5,310,737 and 5,317,017.

The instant compounds are low molecular weight peptide analogs for promoting the release of growth hormone which have good stability in a variety of physiological environments and which may be administered parenterally, nasally or by the oral route.

**SUMMARY OF THE INVENTION**

The present invention is directed to certain compounds which have the ability to stimulate the release of natural or endogenous growth hormone. The compounds thus have the ability to be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food or wool production where the stimulation of growth hormone will result in a larger, more productive animal. Thus, it is an object of the instant invention to describe such compounds. It is a further object of this invention to describe procedures for the preparation of such compounds. A still further object is to describe the use of such compounds to increase the secretion of growth hormone in humans and animals. A still further object of this invention is to describe compositions containing the compounds and their analogs for the use of treating humans and animals so as to increase the level of growth hormone secretions. Further objects will become apparent from a reading of the following description.
DESCRIPTION OF THE INVENTION

The compounds of the present invention are best described in the following structural Formula I:

\[
\begin{align*}
R_1 & \quad H \\
N & \quad O \\
R_3 & \quad R_3a \\
N & \quad R_1a \quad R_1a \\
\text{C} & \quad \text{O} \\
R_5 & \quad R_4 \\
\end{align*}
\]

wherein:
R1 is selected from the group consisting of:
15 C1-C10 alkyl, aryl, aryl(C1-C6 alkyl)-, C3-C7 cycloalkyl(C1-C6 alkyl)-, (C1-C5 alkyl)-K-(C1-C5 alkyl)-, aryl(C0-C5 alkyl)-K-(C1-C5 alkyl)-, and (C3-C7 cycloalkyl)(C0-C5 alkyl)-K-(C1-C5 alkyl)-, where K is O, S(O)m, N(R2)C(O), C(O)N(R2), OC(O), C(O)O, -CR2=CR2-, or -C≡C-, where aryl is selected from: phenyl, naphthyl, indoly1, azaindolyl, pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl, and where R2 and alkyl may be further substituted by 1 to 9 halogen, S(O)mR2a, 1 to 3 of OR2a or C(O)OR2a, and aryl may be further substituted by 1 to 3 of C1-C6 alkyl, 1 to 3 of halogen, 1 to 2 of OR2, methylenedioxy, -N(R2)(R2), -S(O)mR2, 1 to 2 of -CF3, -OCF3,
20 -C(O)H, nitro, -N(R2)C(O)(R2), -C(O)OR2, -C(O)N(R2)(R2), -1H-tetrazol-5-yl, -SO2N(R2)(R2), -N(R2)SO2 phenyl, or -N(R2)SO2R2;
R1a is independently hydrogen, or C1-C6 alkyl;

R2 is selected from the group consisting of: hydrogen, C1-C6 alkyl, and C3-C7 cycloalkyl, and where two C1-C6 alkyl groups are present on one atom, they may be optionally joined to form a C3-C8 cyclic ring, optionally including oxygen, sulfur, SO2 or NR2a;
30 R2a is hydrogen, or C1-C6 alkyl optionally substituted by hydroxyl;
R₃ is independently selected from the group consisting of: hydrogen, -C₁-C₁₀ alkyl, -(CH₂)ᵣ phenyl, -(CH₂)ᵣ naphthyl, -(CH₂)ᵣ C(O)OR₈, -(CH₂)ᵣ C(O)N(R₂)(R₈), (C₁-C₆ alkyl)-K-(C₁-C₄ alkyl)-, aryl(C₀-C₅ alkyl)-K-(C₁-C₄ alkyl)-, -(CH₂)ᵣ-C₃-C₇ cycloalkyl, and -(CH₂)ᵣ heteroaryl, where K is O or S(O)ₘ, and where heteroaryl is selected from: pyridyl, indolyl, imidazolyl, quinolinyl, benzothiopheneyl, benzofuranyl, indanyl, thiazolyl, benzimidazolyl, and azaindolyl, and where the phenyl, naphthyl and heteroaryl may be substituted by:

C₁-C₆ alkyl, 1 to 2 of halogen, 1 to 2 of -OR₉, -NHSO₂CF₃,-C(O)H, -(CH₂)ᵣ N(R₂)(R₉), -(CH₂)ᵣ C(O)OR₉, -(CH₂)ᵣ N(R₂)C(O)R₉, -(CH₂)ᵣ C(O)N(R₂)(R₉), -(CH₂)ᵣ N(R₆)C(O)N(R₂)(R₉), or -(CH₂)ᵣ (R₉);

R₃a is hydrogen or C₁-C₆ alkyl;

R₄ and R₅ are independently selected from:
hydrogen, C₁-C₆ alkyl, and substituted C₁-C₆ alkyl where the substituents are selected from: 1 to 5 halogen, 1 to 3 of hydroxy, 1 to 3 of C₁-C₁₀ alkanoyloxy, 1 to 3 of C₁-C₆ alkoxy, phenyl, phenoxy, 2-furyl, C₁-C₆ alkoxy carbonyl, and S(O)ₘ(C₁-C₆ alkyl); or R₄ and R₅ can be taken together to form -(CH₂)ₜ L₋ₐ(CH₂)ₑ₋ where L₋ₐ is C(R₂)₂, O, S(O)ₘ or N(R₂₋ₐ), d and e are independently 1 to 3;

R₆ is hydrogen or C₁-C₄ alkyl;

R₇ and R₇ₐ are independently hydrogen, C₁-C₆ alkyl, trifluoromethyl, phenyl, substituted C₁-C₆ alkyl where the substituents are selected from: imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)ₘR₂, C(O)O(C₁-C₆ alkyl), C₃-C₇ cycloalkyl, N(R₂)(R₂), and C(O)N(R₂)(R₂); or R₇ and R₇ₐ can independently be joined to one or both of R₄ and R₅ groups to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R₇ or R₇ₐ groups, wherein the bridge contains 1 to 5 carbons atoms; or R₇ and R₇ₐ can be joined to one another to form a C₃-C₇ cycloalkyl;
R8 is selected from the group consisting of:
hydrogen, C1-C6 alkyl, aryl, and aryl-C1-C2 alkyl, where the alkyl
5
groups may be substituted by a substituent selected from the group
consisting of: -OR2, -C(O)OR2, -CON(R2)(R2), -N(R2)C(O)N(R2)(R2),
and 1H-tetrazol-5-yl, and where aryl is selected from the group
consisting of: phenyl, naphthyl, indolyl, quinolinyl, benzothiophenethyl,
benzofuranyl, azaindolyl, benzimidazolyl, pyridyl, and thiazolyl, and
where the aryl may be substituted by: 1 to 2 of -OR2, 1 to 2 of halogen,
1 to 2 of C1-C3 alkyl, -C(O)OR2, -C(O)N(R2)(R2), or -1H-tetrazol-5-yl;

R9 is hydrogen, C1-C6 alkyl, or (CH2)yaryl, wherein the alkyl and
(CH2)y groups may be optionally substituted by 1 to 2 of -O(R2),
-S(O)mR2, -N(R2)(R2), 1H-tetrazol-5-yl, -C(O)OR2, -C(O)N(R2)(R2),
15
-SO2N(R2)(R2), or -N(R2)C(O)N(R2)(R2), and where aryl is selected
from: phenyl, pyridyl, 1H-tetrazol-5-yl, triazolyl, imidazolyl, thiazolyl,
oxadiazolyl, pyrazolyl, thiadiazolyl, imidazolone-1-yl, and benzimidazol-
2-yl, triazolinone-yl, and where the aryl is optionally substituted with
C1-C6 alkyl, C3-C6 cycloalkyl, amino, hydroxyl, or -C(O)O(R2);

20

A is:

\[
\begin{align*}
\text{R7} & \quad \text{or} \quad \text{R7} \\
\text{R7a} & \\
-(CH2)x-C-(CH2)y & \quad \text{or} \quad -Z-(CH2)x-C-(CH2)y \\
\text{R7a} & 
\end{align*}
\]

where \(x\) and \(y\) are independently 0, 1, 2 or 3;

W is selected from the group consisting of: hydrogen, -C(O)OR8,
-C(O)N(R2)(R2), -C(O)NH-SO2(R2), -C(O)N(R2)(R8),
25
-CH2N(R2)C(O)R8, -CH2N(R2)C(O)(R8), -(CH2)yOR2,
-CH(OH)R2, -CH2SO2R2, -CH2SO2N(R2)(R2), 1H-tetrazol-5-yl,
-5-amino-1,2,4-oxadiazol-3-yl, 5-methyl-1,2,4-oxadiazol-3-yl,
30
3-amino-1,2,4-oxadiazol-5-yl, and 3-methyl-1,2,4-oxadiazol-5-yl;
m is 0, 1, or 2;
n is 0 or 1;
r is 0, 1, 2, or 3;
v is 0, 1, or 2;

and pharmaceutically acceptable salts and individual diastereomers thereof.

In the above structural formula and throughout the instant specification, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkyl groups are methyl (Me), ethyl (Et), propyl (Pr), isopropyl (i-Pr), butyl (Bu), sec-butyl (s-Bu), tertiary butyl (t-Bu), pentyl, isopentyl, hexyl, isohexyl, allyl, propinyl, butadienyl, hexenyl and the like.

The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropanoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopent oxy, hexoxy, isohexoxy, allyloxy, propinyloxy, isobutenyloxy, hexenyloxy and the like.

The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

The term "aryl" within the present invention, unless otherwise specified, is intended to include aromatic rings, such as carbocyclic and heterocyclic aromatic rings selected the group consisting of: phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiopheneyl, quinolinyl, pyrazinyl, or isothiazolyl, which may be optionally substituted by 1 to 3 of C1-C6 alkyl, 1 to 3 of halogen, 1 to 2 of -OR2, -N(R2)(R2), methylenedioxy, -S(O)mR2, 1 to 2 of -CF3, -OCF3, nitro, -N(R2)C(O)(R2), -C(O)OR2, -C(O)N(R2)(R2), -1H-
tetrazol-5-yl, -SO₂N(R₂)(R₂), -N(R₂)SO₂ phenyl, or -N(R₂)SO₂R₂, wherein R₂ is as defined herein.

Certain of the above defined terms may occur more than once in the above formula or definitions and upon such occurrence, each term shall be defined independently of the other.

Preferred compounds of the instant invention include those of Formula Ia:

```
  O
 H     N   C   A   N
 R₁      R₄
        C=O
 R₆
     N   R₂a
 R₃    W
      R₃a
```

wherein:

- R₁ is selected from the group consisting of:
  C₁-C₁₀ alkyl, aryl, aryl(C₁-C₄ alkyl)-, C₃-C₆ cycloalkyl(C₁-C₄ alkyl)-,
  (C₁-C₄ alkyl)-K-(C₁-C₂ alkyl)-, aryl(C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-,
  and (C₃-C₇ cycloalkyl)(C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-, where K is O,
  S(O)ₓ, OC(O), or C(O)O, where the alkyl groups may be further substituted by 1 to 7 halogen, S(O)ₓR₂, 1 to 3 of OR₂a or C(O)OR₂a,
  and where aryl is selected from: phenyl, naphthyl, indolyl, pyridyl,
  benzimidazolyl, azaindolyl, benzothienyl, and benzofuranyl, and where the aryl may be further substituted by 1 to 2 of C₁-C₄ alkyl, 1 to 2 of halogen, -C(O)H, 1 to 2 of -OR₂, -S(O)ₓR₂, or -C(O)OR₂;
  R₂a is independently hydrogen or C₁-C₃ alkyl;

- R₂ is selected from the group consisting of: hydrogen, C₁-C₆ alkyl, and C₃-C₇ cycloalkyl, and where two C₁-C₆ alkyl groups are present on one atom they may be optionally joined to form a C₄-C₇ cyclic ring optionally including oxygen, sulfur or NR₂a;
  R₂a is hydrogen or C₁-C₄ alkyl;
R3 is independently selected from the group consisting of: hydrogen, -C1-C8 alkyl, -(CH2)r phenyl, -(CH2)r naphthyl, and -(CH2)r heteroaryl, where heteroaryl is selected from: pyridyl, indolyl, quinolinyl, benzothiophenyl, benzofuranyl, thiazolyl, benzimidazolyl, and azaindolyl, and where the phenyl, naphthyl and heteroaryl may be substituted by: C1-C4 alkyl, 1 to 2 of halogen, 1 to 2 of -OR2, -NHSO2CF3, -(CH2)r C(O)OR2, -(CH2)r C(O)N(R2)(R2), -(CH2)r N(R6)C(O)N(R2)(R2), or -(CH2)r (R9);

R3a is hydrogen or C1-C6 alkyl;

R4 and R5 are independently selected from: hydrogen, C1-C6 alkyl, and substituted C1-C6 alkyl where the substituents are selected from: 1 to 5 of halogen, 1 to 3 of hydroxyl, S(O)m (C1-C6 alkyl), and phenyl;

R6 is hydrogen or C1-C4 alkyl;

R7 and R7a are independently hydrogen, C1-C6 alkyl, trifluoromethyl, phenyl, substituted C1-C6 alkyl where the substituents are selected from: imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR2, S(O)mR2, C(O)O(C1-C6 alkyl), C3-C7 cycloalkyl, N(R2)(R2), and C(O)N(R2)(R2); or R7 and R7a can independently be joined to one or both of R4 and R5 groups to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R7 or R7a groups, wherein the bridge contains 1 to 5 carbons atoms; or R7 and R7a can be joined to another to form a C3-C7 cycloalkyl;

R8 is selected from the group consisting of: hydrogen, C1-C4 alkyl, aryl, and aryl-C1-C2 alkyl, where the alkyl groups may be substituted by a substituent selected from the group consisting of: -OR2, -C(O)OR2, -CON(R2)(R2), -N(R2)C(O)N(R2)(R2), and 1H-tetrazol-5-yl, and where aryl is selected from the group consisting of: phenyl, indolyl, azaindolyl, pyridyl, and thiazolyl, and where the aryl may be substituted by: 1 to 2 of -OR2, 1 to 2 of halogen, or 1 to 2 of
C₁-C₃ alkyl;

R₉ is (CH₂)ₙaryl, where aryl is selected from: phenyl, pyridyl, 1H-tetrazol-5-yl, or oxadiazolyl, and where the aryl is optionally substituted with C₁-C₆ alkyl, amino, hydroxyl, or -C(O)O(R₂);

A is:

```
\begin{align*}
\text{R}_7 & \quad \text{or} \quad \text{R}_7 \\
\text{R}_{7a} & \quad \text{R}_{7a}
\end{align*}
```

where x and y are independently 0, 1, 2 or 3;

W is selected from the group consisting of: hydrogen, -C(O)OR₈, -C(O)N(R₂)(R₂), -C(O)N(R₂)(R₈), 1H-tetrazol-5-yl, 3-amino-1,2,4-oxadiazol-5-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 5-amino-1,2,4-oxadiazol-3-yl, and 5-methyl-1,2,4-oxadiazol-3-yl;

m is 0, 1, or 2;

n is 0 or 1;

r is 0, 1, 2, or 3;

v is 0, 1, or 2;

and pharmaceutically acceptable salts and individual diastereomers thereof.
More preferred compounds of the instant invention include those of Formula Ib:

\[
\begin{align*}
\text{R}_1 & \text{N-C=O} \text{R}_4 \\
\text{R}_2 & \text{N-C-A-N} \\
\text{C} & \text{O} \\
\text{R}_3 & \text{N} \text{R}_{1a} \\
\text{R}_6 & \text{N} \text{R}_{1a} \\
\text{W} & \text{R}_{3a} \\
\text{R}_5 & 
\end{align*}
\]

wherein:
R1 is selected from the group consisting of: C1-C10 alkyl, aryl (C1-C3 alkyl)-, C3-C7 cycloalkyl(C1-C3 alkyl)-, and aryl (C0-C1 alkyl)-K-(C1-C2 alkyl)-, where K is O or S(O)_m and aryl is selected from: phenyl, pyridyl, naphthyl, indolyl, azaindolyl, and benzofuranyl and where the aryl may be further substituted by 1 to 2 of C1-C4 alkyl, 1 to 2 of halogen, 1 to 2 of -OR2, -S(O)_m R2, or -C(O)OR2;

R1a is independently hydrogen or C1-C2 alkyl;

R2 is selected from the group consisting of: hydrogen, C1-C6 alkyl, and C3-C7 cycloalkyl, and where two C1-C6 alkyl groups are present on one atom they may be optionally joined to form a C5-C7 cyclic ring optionally including oxygen, sulfur or NR2a;

R2a is hydrogen or C1-C3 alkyl;

R3 is independently selected from the group consisting of:
hydrogen, -C1-C6 alkyl, -(CH2)_r phenyl, and -(CH2)_r heteroaryl, where heteroaryl is selected from: pyridyl, thiazolyl, indolyl, quinolinyl, benzofuranyl, and azaindolyl, and where the phenyl and heteroaryl may be substituted by: C1-C3 alkyl, 1 to 2 of halogen, 1 to 2 of -OR2,
-(CH₂)ᵣC(O)OR₂, -(CH₂)ᵣC(O)N(R₂)(R₂),
-(CH₂)ᵣN(R₆)C(O)N(R₂)(R₂), or -(CH₂)ᵣ (R₉);

R₃a is hydrogen or C₁ alkyl;

R₄ and R₅ are independently hydrogen, C₁-C₄ alkyl, or substituted
C₁-C₃ alkyl where the substituents are selected from: 1 to 5 of halogen,
1 to 3 of hydroxyl, S(O)ₓm (C₁-C₆ alkyl), and phenyl;

R₆ is hydrogen or C₁-C₃ alkyl;

R₇ and R₇a are independently hydrogen, C₁-C₂ alkyl, phenyl, substituted
C₁-C₆ alkyl where the substituents are selected from: imidazolyl,
phenyl, indolyl, p-hydroxyphenyl, -OR₂, and -S(O)ₓmR₂, or R₇ and R₇a
can independently be joined to one of R₄ and R₅ groups to form an
alkylene bridge between the terminal nitrogen and the alkyl portion of the
R₇ or R₇a groups to form a 5 or 6 membered ring; or R₇ and R₇a can be
joined to one another to form a C₃ cycloalkyl;

R₈ is selected from the group consisting of:
hydrogen, C₁-C₄ alkyl, and aryl-C₁-C₂ alkyl, where the alkyl groups
may be substituted by a substituent selected from the group consisting
of: -OR₂, -C(O)OR₂, -CON(R₂)(R₂), -N(R₂)C(O)N(R₂)(R₂), and
1H-tetrazol-5-yl, and where aryl is selected from the group consisting of:
phenyl, indolyl, 7-azaindolyl, pyridyl, and thiazolyl, and where the aryl
may be substituted by: 1 to 2 of -OR₂, 1 to 2 of halogen, or 1 to 2 of
C₁-C₃ alkyl;

R₉ i (CH₂)ᵣaryl, where aryl is selected from: 1H-tetrazol-5-yl, and
oxadiazolyl, and where the aryl is optionally substituted with C₁-C₆
alkyl, amino, or hydroxyl;
A is:

\[
\begin{align*}
&\text{R}_7 \\
&\text{R}_{7a} \\
&\text{R}_{7a} \\
&\text{R}_7 \\
&\text{R}_{7a} \\
\end{align*}
\]

\[(\text{CH}_2)_x \text{O} \text{C} \text{O} \text{H} \text{C} \text{O} \text{H} \text{C} \text{O} \text{H} \text{C} \text{O} \text{H}
\]

where \(x\) and \(y\) are independently 0 or 1;

\(W\) is selected from the group consisting of: hydrogen, -\(\text{C}(\text{O})\text{OR}_8\), -\(\text{C}(\text{O})\text{N(}\text{R}_2\text{)}\text{(}\text{R}_2\text{)}\), -\(\text{C}(\text{O})\text{N(}\text{R}_8\text{)}\text{(}\text{R}_8\text{)}\), 1H-tetrazol-5-yl, 3-amino-1,2,4-oxadiazol-5-yl, and 3-methyl-1,2,4-oxadiazol-5-yl;

\(m\) is 0, 1, or 2;
\(n\) is 0 or 1;
\(r\) is 0, 1, 2, or 3;
\(v\) is 0, 1, or 2;

and pharmaceutically acceptable salts and individual diastereomers thereof.

The most preferred growth hormone releasing compounds of the present invention include the following:
and their pharmaceutically acceptable salts and individual diasteromers thereof, where not otherwise specified.

Throughout the instant application, the following abbreviations are used with the following meanings:
The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in the structural Formula I above.

Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers, racemic mixtures or diastereomeric mixtures thereof, be included within the ambit of the instant invention. Compounds which are more active as growth hormone secretagogues and, therefore are preferred, are those in
which the nitrogen substituent is above and the hydrogen atom is
below the plane of the structure as represented in Formula II. An
equivalent representation places R\textsuperscript{1} and the N-substituent in the plane
of the structure with the C=O group above the plane of the structure.

\[ \text{Formula Ia} \]

where R\textsubscript{1}, R\textsubscript{3}, R\textsubscript{3a}, R\textsubscript{4}, R\textsubscript{5}, R\textsubscript{6}, A, W and n are as defined above.

The configuration at the carbon atom bearing R\textsubscript{1}
corresponds to that present in a D-amino acid. In most cases, this is also
designated as an R-configuration although this will vary according to the
value of R\textsubscript{1} used in making the R- or S- stereochemical assignments.

Both absolute configurations at the carbon atom bearing W are consistent
with activity when n is 2 and this is also true when n is 0, although the
configuration corresponding to as (D)- amino acid is then preferred. The
absolute stereochemistry of the compounds of this invention may be
determined by the X-ray crystallography of crystalline products or
crystalline intermediates which are derivatized, if necessary, containing
an asymmetric center of known configuration.

The instant compounds are generally isolated in the form of
their pharmaceutically acceptable acid addition salts, such as the salts
derived from using inorganic and organic acids. Examples of such acids
are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoro-
acetic, propionic, maleic, succinic, malonic, methane sulfonic and the
like. In addition, certain compounds containing an acidic function such
as a carboxy can be isolated in the form of their inorganic salt in which
the counterion can be selected from sodium, potassium, lithium, calcium,
magnesium and the like, as well as from organic bases.
The preparation of compounds of Formula I of the present invention can be carried out in sequential or convergent synthetic routes. Syntheses detailing the preparation of the compounds of Formula I in a sequential manner are presented in the following reaction schemes.

The phrase "standard peptide coupling reaction conditions" is used repeatedly here, and it means coupling a carboxylic acid with an amine using an acid activating agent such as EDC, DCC, and BOP in an inert solvent such as dichloromethane in the presence of a catalyst such as HOBT. The uses of protective groups for amine and carboxylic acid to facilitate the desired reaction and minimize undesired reactions are well documented. Conditions required to remove protecting groups which may be present are found in Greene, T; Wuts, P. G. M. Protective Groups in Organic Synthesis, John Wiley & Sons, Inc., New York, NY (1991). CBZ and BOC were used extensively in the syntheses of this invention, and their removal conditions are known to those skilled in the art. Removal of CBZ groups can be achieved by a number of methods, for example, catalytic hydrogenation with hydrogen in the presence of palladium catalyst in a protic solvent such as ethanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, removal of CBZ groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid, or by treatment with a mixture of TFA and dimethylsulfide. Removal of BOC protecting groups is carried out in a solvent such as methylene chloride or methanol, with a strong acid, such as trifluoroacetic acid (TFA) or hydrochloric acid (HCl).

The protected amino acid derivatives 1 are, in many cases, commercially available, where the protecting group L is, for example, BOC or CBZ groups. Other protected amino acid derivatives 1 can be prepared by literature methods (Williams, R. M. Synthesis of Optically Active α-Amino Acids, Pergamon Press: Oxford, 1989). The skills required in carrying out the reaction and purification of the resulting reaction products are known to those skilled in the art. Purification procedures include crystallization, normal phase or reverse phase chromatography.
Intermediates of formula 3 can be synthesized as described in Scheme 1. Coupling of amine of formula 2, whose preparations are described later if they are not commercially available, to protected amino acids of formula 1, wherein L is a suitable protecting group, is conveniently carried out under standard peptide coupling conditions.

Conversion of 3 to intermediates 4 can be carried out as illustrated in Scheme 2 by removal of the protecting group L (CBZ, BOC, etc.)
Intermediates of formula 5, wherein A is connected to the carbonyl by a carbon atom and thus A is -(CH₂)ₓ-C(R₇)(R₇ₐ)-(CH₂)ᵧ-can be coupled as shown in Scheme 3 to intermediates of formula 4 under the standard peptide coupling reaction conditions. The amino acids 5, as amino acids 1, are either commercially available or can be synthesized. Also if R₄ or R₅ is a hydrogen then the protected amino acids 6 are employed in the coupling reaction, wherein L is a protecting group as defined above. Removal of L in 7 affords I, where R₄ = H, can be carried out under conditions known in the art.
Compounds of formula I wherein R4 and/or R5 is a hydrogen can be further elaborated to new compounds I (with preferred side chains R4 = CH2-CH(OH)-CH2X, wherein X = H or OH) which are substituted on the amino group as depicted in Scheme 4. Reductive alkylation of I with an aldehyde is carried out under conditions known in the art; for example, by catalytic hydrogenation with hydrogen in the presence of platinum, palladium, or nickel catalysts or with chemical reducing agents such as sodium cyanoborohydride in an protic solvent such as methanol or ethanol in the present of catalytic amount of acid. Alternatively, a similar transformation can be accomplished via an epoxide opening reaction.
Compounds of formula I, wherein A is \( \text{Z-(CH}_2\text{)}_x\text{-}
\text{C(R}_7\text{)(R}_7\text{a)-(CH}_2\text{)}_y \) and \( \text{Z is N-R}_2\text{ or O can be prepared as shown in}
Scheme 5 by reacting 4 with reagents 8, wherein X is a good leaving
group such as Cl, Br, I, or imidazole. Alternatively, 4 can be reacted with
an isocyanate of formula 9 in an inert solvent such as 1,2-dichloroethane
results in compound of formula I where Z is NH.

The compounds of general formula I of the present invention
can also be prepared in a convergent manner as described in reaction
Schemes 6, 7 and 8.

**SCHEME 6**

![Scheme 6 Diagram]

The carboxylic acid protected amino acid derivatives 10 are,
in many cases, commercially available where M = methyl, ethyl, or
benzyl esters. Other ester protected amino acids can be prepared by
classical methods familiar to those skilled in the art. Some of these
methods include the reaction of the amino acid with an alcohol in the
presence of an acid such as hydrochloric acid or p-toluenesulfonic acid
and azeotropic removal of water. Other reactions includes the reaction of
a protected amino acid with a diazoalkane, or with an alcohol and an acid
activating agent such as EDC, DCC in the presence of a catalyst such as
DMAP and removal of the protecting group L.

Intermediates of formula 11 or 11a, can be prepared as
shown in Scheme 6 by coupling of amino acid ester 10 to amino acids of
formula 5 or 6. When a urea or urethan linkage is present in 11 or 11a, it can be introduced as illustrated in Scheme 5.

**SCHEME 7**

5

\[
\begin{align*}
\text{R}_1 \text{N-C-A-N-R}_5 & \quad \text{COOH} \\
\text{H} & \text{H} & \text{O} & \text{R}_4 \\
\text{R}_1 \text{N-C-A-N-R}_5 & \quad \text{COOH}
\end{align*}
\]

11 → 12

10

\[
\begin{align*}
\text{R}_1 \text{N-C-A-N-R}_5 & \quad \text{COOH} \\
\text{H} & \text{H} & \text{O} & \text{L} & \text{R}_4 \\
\text{R}_1 \text{N-C-A-N-R}_5 & \quad \text{COOH}
\end{align*}
\]

11a → 12a

Conversion of the ester 11 or 11a to intermediate acids 12 or 12a can be achieved by a number of methods known in the art as described in Scheme 7; for example, methyl and ethyl esters can be hydrolyzed with lithium hydroxide in a protic solvent like aqueous methanol. In addition, removal of benzyl group can be accomplished by a number of reductive methods including hydrogenation in the presence of palladium catalyst in a protic solvent such as methanol. An allyl ester can be cleaved with tetrakis-triphenylphosphine palladium catalyst in the presence of 2-ethylhexanoic acid in a variety of solvents including ethyl acetate and dichloromethane (see J. Org. Chem. 1982, 42, 587).

**SCHEME 8**

30

\[
\begin{align*}
\text{R}_1 \text{N-C-A-N-R}_5 & \quad \text{COOH} \\
\text{H} & \text{H} & \text{O} & \text{R}_4 \\
\text{R}_1 \text{N-C-A-N-R}_5 & \quad \text{COOH}
\end{align*}
\]

12 + 12a

\[\text{Removal of L, } \text{R}_4 = \text{H}\]

2
Acid 12 or 12a can then be elaborated to I or compound 7 as described in Scheme 8. Coupling amines of formula 2 to acids of formula 12 or 12a, wherein L is a suitable protecting group, is conveniently carried out under the standard peptide coupling reaction conditions. Transformation of 7 to I is achieved by removal of the protecting group L. When R4 and/or R5 is H, substituted alkyl groups may be optionally added to the nitrogen atom as described in Scheme 4.

Alternatively, the compounds of this invention can be synthesized by solid phase peptide synthesis.

Compounds of formula 2:

\[
\begin{align*}
N & \quad R_6 \quad R_1a \\
\quad R_3 & \quad R_3a \\
\end{align*}
\]

where W is carboxylic acid or derivative, are amino acids or derivatives, most of which are commercially available or known in the literature or they are simple conversion products thereof and can be prepared analogously to the known compounds. Some of the methods of synthesizing \(\alpha\)-amino acids are noted above. The methods for the synthesis of \(\beta\)-amino acids are also well documented and these methods include the hydrolysis of substituted \(\beta\)-lactams to afford \(\beta\)-amino acids.

**SCHEME 9**

\[
\begin{align*}
H_2N & \quad R_1a \\
\quad R_3 & \quad W \\
\end{align*} \xrightarrow{\text{Reductive alkylation}} \xrightarrow{\text{or direct alkylation}} 
\begin{align*}
N & \quad R_6 \\
\quad R_3 & \quad R_3a \\
\end{align*}
\]

In cases where \(R_6\) is not hydrogen, it can be introduced by direct alkylation with an alkylation reagent such as alkyl halide or by reductive alkylation with an aldehyde in a protic solvent such as methanol in the presence of a reducing agent such as sodium cyanoborohydride or under hydrogenation conditions in the presence of a
noble metal catalyst such as palladium or its oxide. Alternatively R₆ can also be introduced by direct alkylation with alkyl halide of a N-protected amino acid by groups such t-BOC using a strong base such as sodium hydride in an inert solvent such as THF. The t-Boc protecting group can be conveniently removed after the alkylation.

**SCHEME 10**

\[
\begin{align*}
R_6^\equiv & - \text{NH}_2 + X &\quad \xrightarrow{-HX} \quad R_6^\equiv \text{NH} \\
R_3 & \quad \text{W} & R_3 & \quad \text{W}
\end{align*}
\]

Alternatively, compounds of formula 2 where n=0 can be prepared by reacting the amine R₆NH₂ with an α-halo carboxylic acid derivative in an inert solvent such as dichloromethane in the presence of a base such as diisopropylethyl amine. The amino acids or their derivatives generated by this synthetic protocols may be racemic. However, procedures for resolving RS-α-amino acid by various methods are known in the literature (Toone, E. J. and Jones, J. B. *Can. J. Chem.* 1987, 65, 2722; Okamoto, S.; Hijikato, A. *Biochem. Biophys. Res. Commun.* 1981, 101, 440; Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Wiley: New York, 1961, Vol. 1, 715-760). Therefore, the separated R- and S- isomers can be prepared by this methodology. Alternatively, the racemic derivatives can be converted directly to growth hormone secretagogues or their intermediates, and the resulting diastereomeric mixtures can be separated at the appropriate stage by chromatography to yield the enantiomerically pure compounds.

**SCHEME 11**
R₃ and R₃a can be sequentially introduced by alkylation of the corresponding N-protected amino acid derivative where W is electron withdrawing group such as ester, amide, sulphone etc. and as shown in Scheme 11. The reaction can be carried out using LiHMDS as base in an inert solvent such as THF and HMPA and alkyl bromide.

When W = CO₂H and it is desired to convert this group to ester, amide, acyl sulfonamide, and moieties as defined by W, these transformations can be made according to the conventional methods well documented in the literature and known to those skilled in the art (*The Practice of Peptide Synthesis*, by M. Bodanszky and A. Bodanszky, Springer-Verlag, 1984). For example, esters can be prepared by reacting the amino acid with an alcohol in the presence of an acid catalyst such as p-toluenesulfonic acid under azeotropic conditions. Alternatively, a removable protecting group L such as BOC or CBZ is put onto the NH to which R₆ is attached and the desired transformations are made of the carboxyl group. For example, a carboxyl group can be activated with reagents such as EDC, DCC and BOP in an inert solvent such as dichloromethane in the presence of a catalyst such as DMAP or HOBT and then reacted with alcohols or amines to provide esters and amides respectively.

The carboxylic acid can also be converted into its next higher homologue, or to a derivative of the homologous acid, such as amide or ester by an Arndt-Eistert reaction. Alternatively, the ester can be directly homologated by the protocol using ynolate anions described by C. J. Kowalski and R. E. Reddy in *J. Org. Chem.* 1992, 57, 7194-7208. The resulting acid and/or ester can be converted to the next higher homologue, and so on and so forth.
Reduction of a carboxyl group with a reducing agent such as borane or DIBALH as shown in Scheme 12 affords the corresponding alcohol which can be alkylated or esterified or converted to a reactive leaving group X using, for example, mesyl chloride. Displacement of the X group with amines or equivalents affords amino products or intermediates which may, in turn, be further reacted with sulfonyl chlorides, acyl chlorides or isocyanates to produce sulfonamides, amides or ureas as defined by W.
As illustrated in Scheme 13, displacement of the X group with thiols or thiocarboxylic acid affords thioether or thio ester products. Alternatively, the thioethers and thioesters can be prepared directly from the alcohol under the Mitsunobu reaction conditions (Volante, R.P. Tetrahedron Lett. 1981, 22, 3119-3122). Thioethers can be oxidized, for example, to sulfoxides with sodium periodate and to sulfones with OXONE®. Thioesters can be converted to thiols which can be oxidized by chlorine to afford sulfonyl chloride which can be converted to sulfonamide by reacting with amine.

Other functional group transformations which are required to generate the groups specified by W including homologation reactions and the formation of tetrazoles and oxadiazoles are well known in the art and, for example, are to be found in the annual volumes of Theilheimer’s Synthetic Methods of Organic Chemistry. When W is hydrogen in formula 2, most of the amines of formula 2 are known in the literature or they can be prepared by standard methods, for example, by the reduction of nitriles or carboxamides, the reductive amination of aldehydes or ketones or by the reaction of alkyl or arylalkyl halides with ammonia or with a primary or secondary amine.

The compounds of the present invention may be prepared from a variety of substituted natural and unnatural amino acids of
formulas 31. The preparation of many of these acids is described in e.g., U.S. Patent Nos 5,206,235, 5,283,241, 5,284,841, 5,310,737 and 5,317,017. The preparation of these intermediates in racemic form is accomplished by classical methods familiar to those skilled in the art (Williams, R. M. "Synthesis of Optically Active α-Amino Acids" Pergamon Press: Oxford, 1989; Vol. 7). Several methods exist to resolve (DL)-

\[
\begin{array}{c}
\text{H} \\
\text{R} \\
\text{N} \\
\text{R}_1 \\
\text{CO}_2\text{H}
\end{array}
\]

amino acids. One of the common methods is to resolve amino or carboxyl protected intermediates by crystallization of salts derived from optically active acids or amines. Alternatively, the amino group of carboxyl protected intermediates may be coupled to optically active acids by using chemistry described earlier. Separation of the individual diastereomers either by chromatographic techniques or by crystallization followed by hydrolysis of the chiral amide furnishes resolved amino acids. Similarly, amino protected intermediates may be converted to a mixture of chiral diastereomeric esters and amides. Separation of the mixture using methods described above and hydrolysis of the individual diastereomers provides (D) and (L) amino acids. Finally, an enzymatic method to resolve N-acetyl derivatives of (DL)-amino acids has been reported by Whitesides and coworkers in J. Am. Chem. Soc., 111, 6354-6364 (1989).


SCHEME 14

For example, alkylation of the enolate of diphenyloxazinone 32 (J. Am. Chem. Soc., 113, 9276 (1991)) with cinnamyl bromide in the presence of sodium bis(trimethylsilyl)amide proceeds smoothly to afford 33 which is converted into the desired (D)-2-amino-5-phenylpentanoic acid 34 by removing the N-t-butyloxy carbonyl group with trifluoroacetic acid and hydrogenation over a PdCl₂ catalyst (Scheme 14).

SCHEME 15

Intermediates of formula 31 which are O-benzyl-(D)-serine derivatives 36 are conveniently prepared from suitably substituted benzyl halides and N-protected-(D)-serine 35. The protecting group L is
conveniently a BOC or a CBZ group. Benzylaion of 35 can be achieved by a number of methods well known in the literature including deprotonation with two equivalents of sodium hydride in an inert solvent such as DMF followed by treatment with one equivalent of a variety of benzyl halides (Synthesis, 36 (1989)) as shown in Scheme 15.

The O-alkyl-(D)-serine derivatives may also be prepared using an alkylation protocol. Other methods that could be utilized to prepare (D)-serine derivatives of formula 36 include the acid catalyzed benzylaion of carboxyl protected intermediates derived from 35 with reagents of formula ArCH2OC(=NH)CCl3 (O. Yonemitsu et al., Chem. Pharm. Bull., 36, 4244 (1988)). Alternatively, alkylation of the chiral glycine enolates (J. Am. Chem. Soc., 113, 9276 (1991); J. Org. Chem., 54, 3916 (1989)) with ArCH2OCH2X where X is a leaving group affords 36. In addition D,L-O-aryl(alkyl)serines may be prepared and resolved by methods described above.

**SCHEME 16**

![Scheme 16](image)

The asymmetric synthesis of $\alpha,\alpha$-disubstituted amino acids can be achieved by the bislactim chemistry developed by Schollkopf and coworkers (Schollkopf, U., Tetrahedron, 39, 2085 (1983)) as illustrated in Scheme 16. Thus, the readily available optically active bislactim can be alkylated with an alkyl or arylalkyl halide to obtain the intermediate shown with high asymmetric induction due to the presence the other methyl group which directs the R3 group trans to it. Hydrolysis of this alkylated product yields the
α-methyl amino acid methyl ester. The resulting methyl ester can be converted to groups as defined by W through conventional chemistry as discussed before. Shown in the scheme was the preparation of one enantiomer of the α-methyl amino acid, the other enantiomer can be prepared in a similar way from starting material of the opposite stereochemistry.

Alternatively, the asymmetric synthesis of α,α-disubstituted amino acids can be achieved by the alkylation of the Schiff base of L-alanine methyl ester and chiral auxiliary 1,2,3,4-di-O-cyclohexylidene-α-D-galacto-hexo-1,5-dialdopyranose which was also developed by Schollkopf and coworkers (Synthesis, 789 (1983)). The chiral auxiliary is removed by acid hydrolysis to yield the desired α-methyl amino acids.

**SCHEME 17**

![Chemical diagram](attachment:image.png)
Another asymmetric synthesis of \( \alpha \)-methyl amino acids can be achieved by the methods developed by Seebach and coworkers which involves reproduction of chirality without using a chiral auxiliary (Naef, R., and Seebach, D., *Helv. Chim. Acta.*, 68, 135 (1985)) as shown in Scheme 17. The Schiff base of trimethylacetaldehyde and L-AlaNHMe can be converted to the two imidazolindinones as shown in the scheme under different reaction conditions. Alkylation and acid hydrolysis yields the amino acids. Thus both enantiomers of the amino acid can be prepared from the same intermediate.

The compounds of general formula 2 (n=1) of the present invention are either commercially available or known compounds which can be prepared by literature procedures. Illustrated here are some, but by no means all the methods available for their preparation. For example, the synthesis of \( \alpha \)-substituted \( \beta \)-amino acids and \( \alpha,\beta \)-disubstituted \( \beta \)-amino acids can be prepared from the nucleophilic addition of an excess of hydroxyamine to the corresponding \( \alpha \)- or \( \beta \)-substituted \( \alpha,\beta \)-unsaturated acids (*Organic Syntheses, Collect. Vol. III; Wiley: New York, 91 (1955)).

**SCHEME 18**

\[
\begin{align*}
\text{L} & \quad \text{CO}_2\text{Me} \\
\text{R}_3X & \quad \text{R}_6X \\
2\text{eq. base} & \\
\rightarrow & \\
\text{L} & \quad \text{CO}_2\text{Me} \\
\end{align*}
\]

In addition, the synthesis of \( \alpha \)-substituted-\( \beta \)-amino acids can be prepared from alkylation of a dianion of \( \beta \)-alanine as detailed in Scheme 18 involving stepwise alkylation first of the more reactive carbon anion. In these two procedures, the \( \beta \)-amino acids are obtained in racemic form. Several methods exist to resolve (D,L) amino acids. One of the most common methods is to resolve an amino or carboxyl protected intermediate by crystallization of salts derived from optically active acids or amines.
Alternatively, the asymmetric synthesis of enantiomerically pure β-amino acids is available. For example, E. Juaristi and J. Escalante (J. Org. Chem., 58, 2282 (1993)) have used 1-benzoyl-3,6-(S)-dimethylperhydropyrimidin-4-one as an intermediate to synthesize in enantiomerically pure form α,β-disubstituted-β-amino acids. Specifically, the synthesis of a signal enantiomer of α-substituted-b-amino acids can be achieved by 1,4-asymmetric induction in the alkylation of a titanium enolate (D. A. Evans et al., J. Am. Chem. Soc., 112, 8215 (1990)) as detailed in Scheme 19. Removal of the chiral template from the alkylation product can be carried out by a number of methods familiar to those skilled in the art, including the lithium benzoxide protocol detailed by D. A. Evans et al., J. Am. Chem. Soc., 104, 1737 (1982)).

**SCHEME 20**

β-Substituted-β-amino acids or β,β-disubstituted-β-amino acids can be obtained from the corresponding α-amino acids or α-substituted amino acids with full retention of configuration using the Arndt-Eistert method (Tetrahedron, 43, 3509, (1987)) depicted in
Scheme 20. The α-amino acids and α-substituted amino acids can be prepared by methods familiar to those skilled in the art, including the procedures described in Schemes 16 and 17. The protecting group L can be removed through conventional chemistry. The natural and unnatural amino acids of general formula 2 can be elaborated to compounds of formula I by using chemistry described above.

It is noted that in some situations the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

The utility of the compounds of the present invention as growth hormone secretagogues may be demonstrated by methodology known in the art, such as an assay described by Smith, et al., Science, 260, 1640-1643 (1993) (see text of Figure 2 therein). In particular, the intrinsic growth horomone secretagogue activities of the compounds of the present invention may be demonstrated in this assay.

The growth hormone releasing compounds of Formula I are useful in vitro as unique tools for understanding how growth hormone secretion is regulated at the pituitary level. This includes use in the evaluation of many factors thought or known to influence growth hormone secretion such as age, sex, nutritional factors, glucose, amino acids, fatty acids, as well as fasting and non-fasting states. In addition, the compounds of this invention can be used in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that somatostatin inhibits growth hormone release and that the growth hormone releasing factor (GRF) stimulates its release. Other hormones that are important and in need of study as to their effect on growth hormone release include the gonadal hormones, e.g., testosterone, estradiol, and progesterone; the adrenal hormones, e.g., cortisol and other corticoids, epinephrine and norepinephrine; the pancreatic and gastrointestinal hormones, e.g., insulin, glucagon, gastrin, secretin; the vasoactive peptides, e.g., bombesin, the neurokinins; and the thyroid hormones, e.g., thyroxine and triiodothyronine. The compounds of Formula I can also be employed
to investigate the possible negative or positive feedback effects of some of the pituitary hormones, e.g., growth hormone and endorphin peptides, on the pituitary to modify growth hormone release. Of particular scientific importance is the use of these compounds to elucidate the subcellular mechanisms mediating the release of growth hormone.

The compounds of Formula I can be administered to animals, including man, to release growth hormone in vivo. For example, the compounds can be administered to commercially important animals such as swine, cattle, sheep and the like to accelerate and increase their rate and extent of growth, to improve feed efficiency and to increase milk production in such animals. In addition, these compounds can be administered to humans in vivo as a diagnostic tool to directly determine whether the pituitary is capable of releasing growth hormone. For example, the compounds of Formula I can be administered in vivo to children. Serum samples taken before and after such administration can be assayed for growth hormone. Comparison of the amounts of growth hormone in each of these samples would be a means for directly determining the ability of the patient's pituitary to release growth hormone.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula I in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise an anabolic agent in addition to at least one of the compounds of Formula I or another composition which exhibits a different activity, e.g., an antibiotic growth permittant or an agent to treat osteoporosis or in combination with a corticosteroid to minimize the catabolic side effects or with other pharmaceutically active materials wherein the combination enhances efficacy and minimizes side effects.

Growth promoting and anabolic agents include, but are not limited to, TRH, diethylstilbesterol, estrogens, β-agonists, theophylline, anabolic steroids, enkephalins, E series prostaglandins,
compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Patent No. 4,411,890.

A still further use of the growth hormone secretagogues of this invention is in combination with other growth hormone secretagogues such as the growth hormone releasing peptides GHRP-6, GHRP-1 as described in U.S. Patent Nos. 4,411,890 and publications WO 89/07110, WO 89/07111 and B-HT920 as well as hexarelin and the newly discovered GHRP-2 as described in WO 93/04081 or growth hormone releasing hormone (GHRH, also designated GRF) and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2 or α- adrenergic agonists such as clonidine or serotonin 5HTID agonists such as sumatriptan or agents which inhibit somatostatin or its release such as physostigmine and pyridostigmine.

As is well known to those skilled in the art, the known and potential uses of growth hormone are varied and multitudinous. Thus, the administration of the compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself. These varied uses of growth hormone may be summarized as follows: treating growth hormone deficient adults; prevention of catabolic side effects of glucocorticoids; treatment of osteoporosis; stimulation of the immune system, acceleration of wound healing; accelerating bone fracture repair; treatment of growth retardation; treating acute or chronic renal failure or insufficiency; treatment of physiological short stature, including growth hormone deficient children; treating short stature associated with chronic illness; treatment of obesity and growth retardation associated with obesity; treating growth retardation associated with Prader-Willi syndrome and Turner's syndrome; accelerating the recovery and reducing hospitalization of burn patients or following major surgery such as gastrointestinal surgery; treatment of intrauterine growth retardation, and skeletal dysplasia, treatment of peripheral neuropathies; replacement of growth hormone in stressed patients; treatment of osteochondrodys-
splasias, Noonans syndrome, schizophrenia, depression, Alzheimers disease, delayed wound healing, and psychosocial deprivation; treatment of pulmonary dysfunction and ventilator dependency; attenuation of protein catabolic response after a major operation; treating malabsorption syndromes; reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; accelerating weight gain and protein accretion in patients on TPN (total parenteral nutrition); treatment of hyperinsulinemia including nesidioblastosis; adjuvant treatment for ovulation induction and to prevent and treat gastric and duodenal ulcers; to stimulate thymic development and prevent the age-related decline of thymic function; adjunctive therapy for patients on chronic hemodialysis; treatment of immunosuppressed patients and to enhance antibody response following vaccination; increasing the total lymphocyte count of a human, in particular, increasing the T4/T8-cell ratio in a human with a depressed T4/T8-cell ratio resulting, for example, from infection, such as bacterial or viral infection, especially infection with the human immunodeficiency virus; improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; stimulation of osteoblasts, bone remodelling, and cartilage growth; stimulation of the immune system in companion animals and treatment of disorders of aging in companion animals; growth promotant in livestock; and stimulation of wool growth in sheep. Further, the instant compounds are useful for increasing feed efficiency, promoting growth, increasing milk production and improving the carcass quality of livestock.

In particular, the instant compounds are useful in the prevention or treatment of a condition selected from the group consisting of: osteoporosis; catabolic illness; immune deficiency, including that in individuals with a depressed T4/T8 cell ratio; hip fracture; musculoskeletal impairment in the elderly; growth hormone deficiency in adults or in children; obesity; cachexia and protein loss due to chronic illness such as AIDS or cancer; and treating patients recovering from major surgery, wounds or burns, in a patient in need thereof.
It will be known to those skilled in the art that there are numerous compounds now being used in an effort to treat the diseases or therapeutic indications enumerated above. Combinations of these therapeutic agents some of which have also been mentioned above with the growth hormone secretagogues of this invention will bring additional, complementary, and often synergistic properties to enhance the growth promontant, anabolic and desirable properties of these various therapeutic agents. In these combinations, the therapeutic agents and the growth hormone secretagogues of this invention may be independently present in dose ranges from one one-hundredth to one times the dose levels which are effective when these compounds and secretagogues are used singly.

Combined therapy to inhibit bone resorption, prevent osteoporosis and enhance the healing of bone fractures can be illustrated by combinations of bisphosphonates and the growth hormone secretagogues of this invention. The use of bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N.A.T., Role of Bisphosphonates in Metabolic Bone Diseases. Trends in Endocrinol. Metab., 4, 19-25 (1993). Bisphosphonates with these utilities include alendronate, tiludronate, dimethyl - APD, risedronate, etidronate, YM-175, clodronate, pamidronate, and BM-210995. According to their potency, oral daily dosage levels of the bisphosphonate of between 0.1 mg and 5 g and daily dosage levels of the growth hormone secretagogues of this invention of between 0.01 mg/kg to 20 mg/kg of body weight are administered to patients to obtain effective treatment of osteoporosis.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated in dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than
inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 10 mg/kg. of body weight daily are
administered to patients and animals, e.g., mammals, to obtain effective release of growth hormone.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

**INTERMEDIATE 1**

![Chemical Structure Image]

**Step A:**

![Chemical Structure Image]

To 5.0 g (16.5 mmole) of the commercially available N-t-BOC-D-tryptophan in 100 mL of chloroform was added 1.80 mL (16.5 mmole) of benzyl alcohol, 0.20 g (1.65 mmole) of 4-N,N-dimethylamino pyridine (DMAP), and 3.20 g of EDC and stirred for 16h. The reaction mixture was poured into 100 mL of water and the organic layer was separated. The aqueous was further extracted with 2X100 mL of chloroform. The combined organic solution was washed with 50 mL of 10% aqueous citric acid, 100 mL of 10% aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered and concentrated to give a thick oil.

To a solution of this oil in 10 mL of dichloromethane was added 20 mL of trifluoroacetic acid and stirred for 1h. The reaction mixture was concentrated, basified carefully with saturated aqueous sodium bicarbonate solution, and extracted with chloroform (2X100 mL). The combined organic solution were washed with brine (100 mL), dried
over potassium carbonate, filtered, and concentrated to give 5.46 g of the amine as a brown oil which was used without purification.

To 5.46 g of the above product in 100 mL of chloroform was added 3.40 g (22.2 mmole) of HOBT, 4.60 g (22.2 mmole) of N-BOC-α-methyl alanine, and 5.32 g (28.0 mmole) of EDC and stirred for 16h. The reaction mixture was poured into 100 mL of water and the organic layer was separated. The aqueous was further extracted with 2X100 mL of chloroform. The combined organic solution were washed with 50 mL of 10% aqueous citric acid, 100 mL of 10% aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered and concentrated to give 6.94 g of the product as a thick oil. Flash chromatography (200 g SiO2; hexane-ethyl acetate as eluent) gave 4.75 g of the desired material as a colorless foam.

\[
\text{1H NMR (CDCl}_3, 200MHz) \ d \ 8.48 \ (bs, 1H), \ 7.54 \ (bd, 1H), \ 7.38-7.23 \ (m, 3H), \ 7.19 \ (bd, 2H), \ 7.15-7.00 \ (m, 1H), \ 6.90 \ (d, 1H), \ 6.86 \ (d, 1H), \ 5.06 \ (bs, 2H), \ 4.95 \ (ddd, 1H), \ 3.30 \ (2dd, 2H), \ 1.40 \ (s, 15H)
\]

**Step B:**

\[
\begin{align*}
\text{N} & \quad \text{NHBOc} \\
\text{H} & \quad \text{C=O} \\
\text{OH} & \quad \text{H}
\end{align*}
\]

To a solution of 4.75 g of the material from Step A in 100 mL of ethanol was added 1.0 g of 10% Pd/C and stirred at RT under a H2 balloon for 18h. The catalyst was filtered off through a pad of celite and washed with ethyl acetate. The filtrate was concentrated to give 2.96 g of the acid as a colorless foam.

\[
\text{1H NMR (CDCl}_3, 200MHz) \ d \ 8.60 \ (bs, 1H), \ 7.55 \ (d, 1H), \ 7.26-6.90 \ (m, 3H), \ 6.88 \ (bd, 1H), \ 4.80 \ (m, 1H), \ 3.32 \ (2dd, 2H), \ 1.37 \ (s, 3H), \ 1.35 \ (s, 12H)
\]
INTERMEDIATE 2

Step A:

Prepared from N-tBOC-O-benzyl-D-serine and allyl alcohol by the procedure described in Intermediate 1, Step A and subsequent coupling to N-BOC-α-methylalanine to give the desired compound.

$^1$H NMR (400MHz, CDCl$_3$) d 7.25 (s, 5H), 5.8 (m, 1H), 5.2 (dd, 2H), 5.0 (bs, 1H), 4.7 (m, 1H), 4.6 (m, 2H), 4.4 (dd, 2H), 3.9 (dd, 1H), 3.6 (dd, 1H), 1.45 (d, 6H), 1.39 (s, 9H).

Step B:

To a stirred solution of the crude intermediate obtained in Step A (6.7 g, 15.9 mmol), tetrakis (triphenylphosphine)-palladium (1.8 g, 0.1 eq) and, triphenyl phosphine (1.25 g, 0.3 eq) was added a solution of potassium-2-ethyl hexanoate (35 mL, 0.5M solution in EtOAc). The reaction mixture was stirred at room temperature under nitrogen atmosphere for 1h and then diluted with ether (100 mL) and poured into ice-water. The organic layer was seperated and the aqueous fraction was acidified with citric acid (20%), then extracted with EtOAc. The EtOAc extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated to give the title compound as a solid.
1H NMR (400Hz, CD3OD) δ 7.3 (s, 5H), 4.7 (m, 1H), 4.5 (s, 2H), 4.0 (m, 1H), 3.6 (m, 1H), 1.4 (d, 6H), 1.3 (s, 9H).

**INTERMEDIATE 3**

This intermediate was synthesized as described in Step A and B of Intermediate 1, but (2R)-N-t-BOC-5-phenylpentanoic acid (H. K. Chenault et al., *J. Am. Chem. Soc.*, 111, 6354-6364 (1989)) was used in place of N-t-BOC-(D)-Tryptophan.

1H NMR (CDCl3, 400MHz) 7.24-7.20 (m, 2H), 7.15-7.04 (m, 3H), 4.60-4.55 (m, 1H), 2.62-2.55 (m, 2H), 2.00-1.86 (m, 1H), 1.78-1.60 (m, 3H), 1.50 (s, 6H), 1.30 (s, 9H).

**EXAMPLE 1**

**Step A: L-HomoPhe ethyl ester hydrochloride**

Thionyl chloride (0.41 mL, 5.58 mmol) was added slowly into stirred ethanol (20 mL) at 0°, the mixture was stirred for 10 min., and to which was added L-HomoPheOH (1g, 5.58 mmol). The mixture was refluxed for 2 hours and then allowed to cool to room temperature. The material was then concentrated and taken to dryness in vacuo to give the title compound (1.35 g).
Step B:

To a solution of L-HomoPhe ethyl ester hydrochloride (75 mg, 0.255 mmol), Intermediate 1 (100 mg, 0.255 mmol), HOBT (34 mg), N-methylmorpholine (0.033 mL) in dichloromethane (15 mL) was added EDC (100 mg). The reaction mixture was stirred at room temperature overnight. The solution was diluted with ethyl acetate and washed subsequently with water, saturated sodium bicarbonate solution, and saturated sodium chloride solution, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 60% ethyl acetate in hexane provided the desired compound (120.6 mg). FAB-MS calc. for C32H42N4O6: 578; found: 579 (M+H).

Step C:

A solution of the intermediate from previous step (120 mg) in ethyl acetate (5 mL) was cooled to 0°C. While stirring, hydrogen chloride gas was bubbled into the mixture until saturation occurred. The reaction was stirred for 15 minutes, until TLC analysis indicated that the reaction was complete. The solution was then concentrated to remove the ethyl acetate. The residue was then redissolved in dichloromethane and
hexane was added followed by evaporation in vacuo to afford the product as a solid (100 mg).
FAB-MS calc. for C_{27}H_{34}N_{4}O_{4}: 478; found: 479 (M+H).
\(^1\)HNMR (400 MHz, CD_{3}OD): 8.29, 8.05 (2d, 1H), 7.64 (d, J=7.5 Hz, 1H), 7.30-7.00 (m, 9H), 4.85 (m, 1H), 4.23-4.17 (m, 1H), 4.11 (q, J=7.1 Hz, 2H), 3.34-3.10 (dd, J1=7.1 Hz, 1H), 3.16 (dd, J=8.2 Hz, 14.2 Hz, 1H), 2.34-2.29 (m, 2H), 1.95-1.89 (m, 1H), 1.79-1.74 (m, 1H), 1.56 (s, 3H), 1.39 (s, 3H), 1.22 (t, J=7 Hz, 3H).

**EXAMPLE 2**

![Diagram](image)

**Step A:**

![Diagram](image)

Prepared by the procedure described in Example 1, Step B from D-HomoPhe ethyl ester hydrochloride (75 mg, 0.255 mmol), Intermediate 1 (100 mg, 0.255 mmol), HOBT (34 mg.), N-methyl morpholine(0.033 mL; 0.255 mmol), and EDC (100 mg). Product: 108 mg. FAB-MS calc. for C_{32}H_{42}N_{4}O_{6}: 578; found: 579 (M+H).
Step B:

Prepared by the procedure described in Example 1, Step C from the intermediate from previous step (106 mg) and HCl gas in ethyl acetate (3 mL) at 0°C. Reaction time: 1 hour. Product: 94.5 mg.

FAB-MS calc. for C27H34N4O4: 478; found: 479 (M+H).

1HNMR (400 MHz, CD3OD): 8.54, 7.98 (2d, 1H), 7.67 (d, J=7.7 Hz, 1H), 7.32 (d, J=8.1 Hz, 1H), 7.27-7.14 (m, 6H), 7.08 (t, J=7.1 Hz, 1H), 7.01 (t, J=7.1 Hz, 1H), 4.85 (m, 1H), 4.38-4.33 (m, 1H), 4.13 (q, J=7.1 Hz, 2H), 3.36 (dd, J=5.4 Hz, 14.5 Hz, 1H), 3.16 (dd, J=9.5 Hz, 14.5 Hz, 1H), 2.73-2.59 (m, 2H), 2.13-2.07 (m, 1H), 2.03-1.96 (m, 1H), 1.54 (s, 3H), 1.31 (s, 3H), 1.24 (t, J=7.1 Hz, 3H).

The additional products shown in Table I were prepared according to Example 1 Steps A, B and C from the corresponding α-methyl amino acid instead of L-homoPheOH
TABLE I: ADDITIONAL EXAMPLES

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The additional products shown in Table IA were prepared according to Example 1 Steps B and C or Example 2 Steps A and B, using Intermediate 2 and Intermediate 3 and D or L-homophenylalanine ethyl ester.
TABLE IA: ADDITIONAL EXAMPLES

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EXAMPLE 2A

Step A: N-Me-D-homoPheOEt

To a suspension of sodium hydride (60%, 458 mg, washed with hexane) in THF (3 mL) at room temperature under Ar, was added D-Boc-homoPhOH (533 mg, 1.9 mmol) in THF (2mL) via a syringe. After stirring for 5 minutes, iodomethane (1.43 mL) was added and the resulting mixture was stirred at room temperature overnight. The reaction mixture was slowly added to 1 N sodium bisulfate solution then it was extracted with ethyl acetate twice. The combined organic solution was dried over magnesium sulfate,
evaporated to give a brown solid (700 mg, crude) which was used without further purification.
The solid obtained was dissolved in ethyl acetate (3mL). HCl gas was bubbled through the solution until it was saturated at 0°C. The reaction mixture was stirred for additional 15 minutes, and it was evaporated to dryness to give N-Me-D-homophenylalanine.
The resulting amino acid was dissolved in 20 mL of acidic ethanol and refluxed for two hours. The solution was evaporated to give the desired product.

Step B:

\[\text{Chemical Structure Image}\]

Prepared by the procedure described in Example 1, Step B from the intermediate from the previous step (200 mg), Intermediate 1 (200 mg, 0.514 mmol), HOBT (68 mg.), N-methyl morpholine(0.066 mL; 0.514 mmol), and EDC (200 mg). Product: 235.2 mg.
FAB-MS calc. for C33H44N4O6: 592; found: 593 (M+H).

Step C:

\[\text{Chemical Structure Image}\]
- 51 -

Prepared by the procedure described in Example 1, Step C from the intermediate from previous step (204 mg) and HCl gas in ethyl acetate (3 mL) at 0°C. Reaction time: 30 minutes. Product: 186 mg.

FAB-MS calc. for C<sub>28</sub>H<sub>36</sub>N<sub>4</sub>O<sub>4</sub>: 492; found: 493 (M+H).

**EXAMPLE 3**

![Chemical Structure](image)

**Step A:**

Prepared by the procedure described in Example 1, Step B from L-Phe ethyl ester hydrochloride (176 mg, 0.771 mmol), Intermediate 1 (200 mg, 0.514 mmol), HOBT (64), N-methyl morpholine(0.068 mL, 0.514 mmol), and EDC (200 mg, 1.03 mmol). Product: 246 mg. FAB-MS calc. for C<sub>31</sub>H<sub>40</sub>N<sub>4</sub>O<sub>4</sub>: 464; found: 465 (M+H). ¹HNMR (400 MHz, CD<sub>3</sub>OD) : 8.73 (br, s, 1 H), 7.57 (d, J=2.3 Hz, 1H), 7.40-7.00 (m, 9H), 6.97 (s, 1H), 6.71 (br, d, 1H), 4.86 (s, 1H), 4.68 (dd, J=6 Hz, 14 Hz, 1H), 4.59 (dd, J=7.3 Hz, 14.3 Hz, 1H), 4.0 (q, 2H), 3.36 (dd, J=5.5 Hz, 14.7 Hz, 1H), 3.20 (dd, J=5.5 Hz, 14.6 Hz, 1H), 2.97 (br. d., J=6.5 Hz, 1H), 1.38 (s, 3H), 1.29 (s, 9H), 1.18 (s, 3H), 1.08 (t, J=7 Hz, 3H).
Step B:

Prepared by the procedure described in Example 1, Step C from the intermediate from previous step (240 mg) and HCl gas in ethyl acetate (5 mL) at 0°C. Reaction time: 20 minutes. Product: 152.5 mg. FAB-MS calc. for C26H32N4O4: 464; found: 465 (M+H).

$^1$HNMR (400 MHz, CD$_3$OD): 8.24-6.94 (m, 11H), 4.79-4.74 (m, 1H), 4.64-4.59 (m, 1H), 4.10 (q, J=7.1 Hz, 2H), 3.11 (dd, J=6 Hz, 14.6 Hz, 1H), 3.01-2.92 (m, 2H), 2.81(dd, J=8.4 Hz, 13.8 Hz, 1H), 1.49 (s, 3H), 1.29 (s, 3H), 1.18 (t, J=7 Hz, 3H).

EXAMPLE 4

Step A:
Prepared by the procedure described in Example 1, Step B from D-phenylalanine ethyl ester hydrochloride (176 mg, 0.771 mmol), Intermediate 1 (200 mg, 0.514 mmol), HOBT (1 eq.), N-methyl morpholine (0.068 mL, 0.514 mmol), and EDC (200 mg, 1.03 mmol). Product: 287 mg. FAB-MS calc. for C$_{31}$H$_{40}$N$_4$O$_4$: 464; found: 465 (M+H).

Step B:

Prepared by the procedure described in Example 1, Step C from the intermediate from previous step (280 mg) and HCl gas in ethyl acetate (10 mL) at 0°C. Reaction time: 20 minutes. Product: 231.7 mg. FAB-MS calc. for C$_{26}$H$_{32}$N$_4$O$_4$: 464; found: 465 (M+H).

$^1$HNMR (400 MHz, CD$_3$OD): 8.29-6.94 (m, 11H), 4.79-4.75 (m, 1H), 4.64-4.59 (m, 1H), 4.10-4.05 (m, 2H), 3.27-2.96 (m, 4H), 1.49 (s, 3H), 1.28 (s, 3H), 1.19-1.15 (m, 3H).
The additional examples shown in Table II were prepared according to Example 1 Steps B and C, using Intermediate 1 and commercially available intermediates.

**TABLE II: ADDITIONAL EXAMPLES**

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</table>
EXAMPLE 5

Step A:

Prepared by the procedure described in Example 1, Step B from L-methionine ethyl ester hydrochloride (165 mg, 0.771 mmol), Intermediate 1 (200 mg, 0.514 mmol), HOBT (1 eq.), N-methyl morpholine (0.068 mL, 0.514 mmol), and EDC (200 mg, 1.03 mmol). Product: 262 mg. FAB-MS calc. for C_{27}H_{40}N_{4}O_{6}S: 548; found: 549 (M+H).

Step B:

Prepared by the procedure described in Example 1, Step C from the intermediate from previous step (250 mg) and HCl gas in ethyl acetate (10 mL) at 0°C. Reaction time: 20 minutes. Product: 209.4 mg.
FAB-MS calc. for C_{22}H_{32}N_{4}O_{4}S: 448; found: 449 (M+H).
{H}NMR (400 MHz, CD_{3}OD): 8.26-6.99(m, 6H), 4.82-4.78 (m, 1H),
4.42-4.37 (m, 1 H), 4.14 (q, J=7 Hz, 2H), 3.31-3.26(dd, 2H), 3.14 (dd,
J=8.0 Hz, 2H), 2.20-2.10 (m, 2H), 1.98 (s, 3H), 1.96-1.87 (m, 1H), 1.81-
1.73 (m, 1H), 1.56 (s, 3H), 1.39 (s, 3H), 1.24 (t, J=7 Hz, 3H).

**EXAMPLE 6**

![Chemical Structure](image)

**Step A:**

![Chemical Structure](image)

Prepared by the procedure described in Example 1, Step B
from D-methionine ethyl ester hydrochloride (165 mg, 0.771 mmol),
Intermediate 1 (200 mg, 0.514 mmol), HOBT (1 eq.), N-methyl
morpholine (0.068 mL, 0.514 mmol), and EDC (200 mg, 1.03 mmol).
Product: 243 mg. FAB-MS calc. for C_{27}H_{40}N_{4}O_{6}S: 548; found: 549
(M+H).
**Step B:**

Prepared by the procedure described in Example 1, Step C from the intermediate from previous step (240 mg) and HCl gas in ethyl acetate (10 mL) at 0°C. Reaction time: 20 minutes. Product: 200 mg. FAB-MS calc. for C_{22}H_{32}N_{4}O_{4}S: 448; found: 449 (M+H).

^1^HNMR (400 MHz, CD_{3}OD): 8.48, 8.00 (2d, 1H), 7.65 (d, J=7.8 Hz, 1H), 7.32 (d, J=8.0 Hz, 1H), 7.15 (s, 1H) 7.07 (t, 1H), 7.00 (t, 1H), 4.80-4.78 (m, 1H), 4.59-4.54 (m, 1H), 4.15 (q, J=7.1 Hz, 2H), 3.34 (dd, J=5.4 Hz, 14.9 Hz, 1H), 3.15 (dd, J=9.5 Hz, 14.7 Hz, 1H), 2.59-2.44 (m, 2H), 2.14-2.08 (m, 1H), 2.06 (s, 3H), 2.02-1.94 (m, 3H), 1.54 (s, 3H), 1.31 (s, 3H), 1.25 (t, J=7.1 Hz, 3H).

**EXAMPLE 7**

<table>
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<td>25</td>
<td>30</td>
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</table>
Step A:

Prepared by the procedure described in Example 1, Step B from N-methyl-DL-phenylalanine ethyl ester hydrochloride (125 mg, 0.514 mmol), Intermediate 1 (200 mg, 0.514 mmol), HOBT (1 eq.), N-methyl morpholine (0.068 mL, 0.514 mmol), and EDC (200 mg, 1.03 mmol). Product: 141 mg. FAB-MS calc. for C_{32}H_{42}N_{4}O_{6}: 578; found: 579 (M+H).

Step B:

Prepared by the procedure described in Example 1, Step C. The intermediate from previous step (90 mg) and HCl gas in ethyl acetate (5 mL) at 0°C. Product: 78 mg. FAB-MS calc. for C_{27}H_{34}N_{4}O_{4}: 478; found: 479 (M+H).
EXAMPLE 8

Step A:

Prepared by the procedure described in Example 1, Step B from L-2-amino-5-phenylpentanoic acid ethyl ester hydrochloride (Chenault et al, J. Am. Chem. Soc., 111, 6354-6364 (1989)) (200 mg, 0.776 mmol), Intermediate 1 (200 mg, 0.514 mmol), HOBT (1 eq.), N-methyl morpholine(0.068 mL, 0.514 mmol), and EDC (200 mg, 1.02 mmol). Product: 265.4 mg. FAB-MS calc. for C_{33}H_{44}N_{4}O_{6}: 592; found: 593 (M+H).

Step B:

Prepared by the procedure described in Example 1, Step C from the intermediate from previous step (235 mg) and HCl gas in ethyl
acetate (5 mL) at 0°C. Product: 210 mg. FAB-MS calc. for C_{28}H_{36}N_{4}O_{4}: 492; found: 493 (M+H). ¹H NMR (400 MHz, CD_{3}OD): 7.61 (d, J=8.7 Hz, 1H), 7.29-6.99 (m, 9H), 4.79 (t, J=7.5 Hz, 1H), 4.23 (dd, J=5 Hz, 8.3 Hz, 1H), 4.13-4.08 (m, 2H), 3.27 (dd, J=7 Hz, 14 Hz, 1H), 3.12 (dd, J=8 Hz, 14 Hz, 1H), 2.51-2.46 (m, 2H), 1.63-1.54 (m, 1H), 1.54 (s, 3H), 1.50-1.40 (m, 1H), 1.37 (s, 3H), 1.40-1.20 (m, 2H), 1.20 (t, J=7.1 Hz, 3H).

EXAMPLE 9

\[ \text{Formula Image} \]

Step A:

\[ \text{Formula Image 2} \]

Prepared by the procedure described in Example 1, Step B from D-2-amino-5-phenylpentanoic acid ethyl ester hydrochloride (Chenault et al, J. Am. Chem. Soc., 111, 6354-6364 (1989)) (200 mg, 0.776 mmol), Intermediate 1 (200 mg, 0.514 mmol), HOBT (1 eq.), N-methyl morpholine(0.068 mL, 0.514 mmol), and EDC (200 mg, 1.02 mmol). Product: 260.0 mg. FAB-MS calc. for C_{33}H_{44}N_{4}O_{6}: 592; found: 593 (M+H).
Step B:

\[
\text{\begin{center}
\includegraphics[width=0.4\textwidth]{structure.png}
\end{center}}
\]

Prepared by the procedure described in Example 1, Step C.

The intermediate from previous step (230 mg) and HCl gas in ethyl acetate (5 mL) at 0°C. Reaction time: 30 minutes. Yield: 201 mg FAB-MS calc. for C_{28}H_{36}N_{4}O_{4}: 492; found: 493 (M+H).

\[^1\text{HNMR (400 MHz, CD3OD): 7.65 (d, J=7.8 Hz, 1H), 7.32-6.98 (m, 9H), 4.84-4.80 (m, 1H), 4.39 (dd, J=5 Hz, 8 Hz, 1H), 4.13 (q, J=7.1 Hz, 2H), 3.33 (dd, J=5.4 Hz, 15 Hz, 1H), 3.12 (dd, J=9.6 Hz, 14.5 Hz, 1H), 2.70-2.60 (m, 2H), 1.90-1.80 (m, 1H), 1.75-1.60 (m, 3H), 1.50 (s, 3H), 1.27 (s, 3H), 1.23 (t, J=7.1 Hz, 3H).}\]

EXAMPLE 10

\[
\text{\begin{center}
\includegraphics[width=0.4\textwidth]{structure.png}
\end{center}}
\]
Step A:

To a solution of 0.10g of Intermediate 1 in 5 mL of CH₂Cl₂ was added 0.10g of D-TRP methyl ester, 64 mg of HOBT, 0.052 mL of NMM, and 0.10g of EDC and stirred at RT for 18h. The reaction mixture was diluted with 10 mL of CH₂Cl₂ and washed with 0.10N HCl (10 mL), saturated NaHCO₃ (10 mL), dried over MgSO₄ and concentrated. Flash chromatography of the residue with CH₂Cl₂-acetone (1:1) as the eluent gave 0.134g of the desired material.

To a solution of this above intermediate in 5 mL of ethyl acetate at 0°C was bubbled in HCl gas for 30 seconds. The flask was capped and stirred for 30 minutes. Ether was added and the precipitate was filtered under an N₂ atmosphere. This gave 89 mg of the title compound as a yellow solid.

¹H NMR (CD₃OD, 400 MHz) δ 7.60 (d, 1H), 7.42 (d, 1H), 7.33 (s, 1H), 7.30 (s, 1H), 6.97-7.10 (m, 6H), 4.78 (dd, 1H), 4.70 (dd, 1H), 3.68 (s, 3H), 3.30-3.10 (m, 4H), 1.40 9s, 3H), 1.28 (s, 3H).
EXAMPLE 10A

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Step A:

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The above intermediate was synthesized as described in Example 10 but D-Tryptophan benzyl ester was used in place of the methyl ester.

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Step B:

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A solution of 0.075g of the intermediate synthesized in Step A in ethyl acetate was treated with HCl (gas) at 0°C for a few seconds. After 30 min. ether was added and the precipitate was filtered under a nitrogen atmosphere and dried to give 0.060g of the title compound as a pale yellow solid.

$^1$H NMR (400MHz; CD$_3$OD) 8.15, 7.83, 7.60, 7.47 (4 doublets, 2H), 7.38-6.90 (m, 13H), 5.00 (ABq, 2H), 4.80-4.65 (m, 2H), 3.30-3.06 (m, 4H), 1.40 (s, 3H), 1.22 (s, 3H).

**EXAMPLE 10B**

![Chemical Structure](image)

**Step A:**

![Chemical Structure](image)

A solution of 0.70g of the compound prepared in Step A of Example 10A was hydrogenated with 10% Pd/C in methanol for 3h. The catalyst was filtered off through a pad of celite. The filtrate was concentrated to give the desired acid as a white foam.
Step B:

The intermediate prepared in Step A was deprotected with the HCl/EtOAc protocol as described above to give the title compound as an off-white solid.

$^1$H NMR (400MHz; CD$_3$OD) 7.92, 7.74, 7.60, 7.30 (4 doublets, 2H), 7.30 (d, 2H), 7.16-6.90 (m, 8H), 4.81-4.65 (m, 2H), 3.34-3.06 (m, 4H), 1.38 (s, 3H), 1.22 (s, 3H).

EXAMPLE 10C

A solution of 0.10g of the intermediate prepared in Step A of Example 10B in isopropanol was treated with HCl(gas) at 0°C for 10 seconds. The reaction mixture was allowed to warm up to room temperature and stirred overnight. The solvent was removed under reduced pressure and the crude precipitate was washed with EtOAc-CH$_2$Cl$_2$-MeOH-ether (2:1:0.10:2) and the remaining solid was collected and dried to give the title compound.
\[ \text{H NMR (400MHz; CD}_3\text{OD)} 8.15, 7.80, 7.62, 7.45 (4 doublets, 2H), 7.30 (d, 2H), 7.16-6.95 (m, 8H), 4.90 (m, 1H), 4.80-4.60 (m, 2H), 3.30-3.06 (m, 4H), 1.40 (s, 3H), 1.25 (s, 3H), 1.20 and 1.05 (2 doublets, 6H). \]

**EXAMPLE 10D**

![Chemical Structure 10D](image)

**Step A:**

![Chemical Structure 10B](image)

To a solution of 0.10g of N-tBOC-D-Tryptophan in 10mL of chloroform was added 0.090g of the monomethylamine derivative of amitriptyline, 0.055g of HOBT and 0.086g of EDC and stirred at RT for 2h. The reaction was diluted with 15mL of ether and washed with water (5mL), 10% aqueous citric acid (10mL), and saturated aqueous NaHCO3 (5mL), dried over anhydrous MgSO4 and concentrated to provide a crude product that was used without purification.

A solution of crude product from above was treated with 3mL of TFA and 4 drops of anisole for 1h at RT. The reaction mixture was evaporated to dryness and azeotroped with toluene. The residue was
dissolved in 5mL of chloroform and reacted with 0.076g of N-BOC-a-methylalanine in the presence of 0.055g of HOBT, 0.15mL of N-methylmorpholine, and 0.086g of EDC for 2h. The reaction mixture was worked-up as described above and the crude product was separated by flash chromatography (10g silica gel; hexane-EtOAc (2:1) as eluent) gave 0.069g of the desired product.

**Step B:**

![Chemical structure](image)

The compound prepared in Step A (0.069g) was treated with 1.0mL of TFA for 1h. The reaction mixture was evaporated to dryness to give 0.052g of the desired product after trituration with ether.

**EXAMPLE 11**

![Chemical structure](image)
Step A:

This compound was made in a similar manner to the compound reported in Example 10 but L-TRP methyl ester was used in place of D-TRP methyl ester.

$^{1}H$ NMR (CD$_3$OD, 400 MHz) $\delta$ 7.60 (d, 1H), 7.42 (d, 1H), 7.33 (s, 1H), 7.30 (s, 1H), 6.97-7.10 (m, 6H), 4.78 (dd, 1H), 4.70 (dd, 1H), 3.68 (s, 3H), 3.30-3.10 (m, 4H), 1.40 (s, 3H), 1.28 (s, 3H).

EXAMPLE 12
Step A:

To 0.40g of commercially available (DL)-7-aza-TRP in 10 mL of dry ethanol at 0°C was bubbled in HCl gas for 15 seconds. The reaction mixture was heated to reflux for 18h. The reaction mixture was neutralized with aqueous Na₂CO₃ solution, and extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried over K₂CO₃, and concentrated.

To 0.10g of the above ethyl ester in 4 mL of CH₂Cl₂ was added 0.10g of Intermediate 1, 0.069g of HOBT, 0.12g of EDC and stirred at RT for 2 days. The reaction mixture was poured in saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated. Flash chromatography of the residue with CH₂Cl₂-acetone-ether (3:2:1) as the eluent gave 75 mg of the title compound.

To 75 mg of the above intermediate in 2 mL of ethyl acetate was bubbled in HCl gas for 15 seconds. The flask was capped and stirred for 30 minutes. Ether was added and the precipitate was filtered under an N₂ atmosphere to give the title compound as a yellow solid.

$^1$H NMR (CD₃OD, 400 MHz) δ 8.75 (d, 1H), 8.40 (d, 1H), 7.70-7.55 (m, 3H), 7.30 (d, 1H), 7.15-6.93 (m, 3H), 4.80-4.66 (m, 2H), 4.10 (2q, 2H), 3.30-3.10 (m, 4H), 1.52 (s, 3H), 1.36 (s, 3H), 1.18 (2t, 3H).
EXAMPLE 13

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Step A:

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This compound was made as described in Step A of Example 11 but (DL)-1-methyl TRP was used in place of (DL)-7-aza TRP.

The compound exists as a mixture of rotamers.

$^1$H NMR (CD$_3$OD, 400 MHz) $\delta$ 8.10-8.00 (2d, 1H), 7.60 (d, 1H), 7.45 (d, 1H), 7.33 (d, 1H), 7.31 (d, 1H), 7.18-7.05 (m, 3H), 7.03-6.95 (m, 3H), 4.80-4.70 (m, 1H), 4.70-4.60 (m, 1H), 4.05 (2q, 2H), 3.70 (s, 3H), 3.28-3.00 (m, 4H), 1.44 (s, 3H), 1.26 (s, 3H), 1.13 (t, 3H).
EXAMPLE 14

Step A:

This compound was made as described in Step A of Example 11 but (DL)-α-methyl TRP was used in place of (DL)-7-aza TRP.

The compound exists as a mixture of rotamers.

$^1$H NMR (CD$_3$OD, 400 MHz) δ 8.05 (s, 1/2H), 7.98 (d, 1/2H), 7.90 (d, 1/2H), 7.85 (s, 1/2H), 7.63 (t, 1H), 7.48 (t, 1H), 7.33 (d, 2H), 7.13-6.98 (m, 4H), 4.82-4.70 (m, 1H), 4.10 (2q, 2H), 3.43-2.20 (m, 3H), 3.15-3.00 (m, 1H), 1.50 and 1.49 (2s, 6H), 1.41 (s, 1H), 1.30-1.14 (m, 5H).
EXAMPLE 15

Step A:

This compound was made as described in Step A of Example 11 but (D)-2-naphthyl alanine was used in place of (DL)-7-aza TRP.

The compound exists as a mixture of rotamers.

$^1$H NMR (CD$_3$OD, 400 MHz) $\delta$ 8.33 (d, 1H), 7.80 7.75 (m, 3H), 7.66 (s, 1H), 7.60 (d, 1H), 7.48-7.39 (m, 2H), 7.35 (dd, 1H), 7.31 (d, 1H), 7.08 (t, 1H), 6.98 (t, 1H), 5.50 (s, 1H), 4.80-4.70 (m, 1H), 4.10 (q, 1H), 3.15-3.08 (m, 4H), 1.40 (s, 1H), 1.28 (s, 3H), 1.15 (t, 3H).
EXAMPLE 16

Step A:

To a suspension of 0.55g of 60% sodium hydride in mineral oil in 40 mL of dry DMF at 0°C was added a solution of 1.0g of N-t-BOC-D-TRP in 10 mL of DMF and stirred for 30 min. Methyl iodide (1 mL) was added and stirred at RT for 1h. The reaction mixture was poured into ice-water and extracted with CHCl3. The combined organic extracts were washed with brine, dried over Na2SO4, filtered and concentrated. This material was dissolved in 5 mL of methanol and 0.50 mL of concentrated HCl was added and heated at reflux for 24h. The reaction mixture was concentrated. The residue was dissolved in CH2Cl2 and washed with aqueous NaHCO3. The aqueous layers were back extracted with CH2Cl2. The combined organic extracts were washed with brine, dried over K2CO3, and concentrated.

1H NMR (CDCl3, 400 MHz) δ 7.60 (d, 1H), 7.28 (d, 1H), 7.22 (t, 1H), 7.10 (t, 1H), 6.89 (s, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 3.53 (t, 1H), 3.16 (dd, 1H), 3.09 (dd, 1H), 2.37 (s, 3H).
Step B:

The above intermediate was transformed to the title compound as described in Step A of Example RN-3 but the intermediate from Step A was used in place of (DL)-7-aza TRP.

$^1$H NMR (CD$_3$OD, 400 MHz) $\delta$ 7.58 (d, 1H), 7.35 (d, 1H), 7.32-7.25 (m, 2H), 7.15 (t, 1H), 7.10-6.95 (m, 4H), 6.88 (s, 1H), 5.34 (dd, 1H), 5.03 (t, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.38 (dd, 1H), 3.22-3.10 (m, 2H), 2.96 (s, 3H), 2.58 (bd, 1H), 1.50 (s, 3H), 1.28 (s, 3H).

EXAMPLE 17

Step A:
To 1.0g of indene in 10 mL of dry THF at -78°C was added 10.3 mL of 1.6M n-BuLi in hexane and stirred for 45 minutes. A solution of 2.50g of 2-t-butyldimethylsilyloxy-1-bromoethane in 10 mL of THF was added and allowed to warm up to 0°C and stir for 6h. The reaction mixture was poured into 50 mL of water and extracted with ether (3X50 mL). The combined organic extracts were washed with brine, dried over MgSO4, and concentrated to 8.6g of a product. This material was stirred overnight in 50 mL of THF and 50 mL of 5% aqueous HCl. The reaction was extracted with ether (2X50 mL). The combined organic extracts were washed with brine (50 mL), dried over MgSO4 and concentrated to yield 4.6g of the crude product. Flash chromatography of this residue with hexane-ether (1:1) as eluent gave 4.6g of product.

This material was dissolved in 25 mL of ethanol and 1.0g of 10% Pd/C was added and hydrogenated for 3h. The catalyst was filtered off through a pad of celite and washed with ether, and concentrated to give a colorless oil. This material was used without purification.

**Step B:**

![Diagram](image)

To 0.471g of the above intermediate in 10 mL of THF at 0°C was added 0.61 mL of triethylamine and 0.27 mL of mesyl chloride and stirred for 1h. The reaction mixture was poured into 10 mL of saturated aqueous NaHCO3 and extracted with ether (2X10 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO4, and concentrated. To this crude product in 5 mL of DMSO was added 0.50 g of sodium azide and stirred at 60°C overnight. The reaction mixture was poured into 15 mL of water and extracted with ether (2X15 mL). The combined organic extracts were washed with brine (10 mL),
dried over MgSO\textsubscript{4}, and concentrated to give a the azido-material as a brown oil.

Nickel/aluminum alloy was added to a solution of the above intermediate in 10 mL of ethanol and 10 mL of 20\% aqueous NaOH solution and stirred at 60°C for 1h. The reaction mixture was cooled to RT, the solids were filtered and washed with CHCl\textsubscript{3}. The filtrate was concentrated, and then diluted with 10 mL of brine, and extracted with CHCl\textsubscript{3} (2X10 mL). The combined organic extracts were washed with brine (10 mL), dried over K\textsubscript{2}CO\textsubscript{3}, and concentrated. This gave 0.150g of the amine.

**Step C:**

![Chemical Structure Diagram]

To a solution of 0.150g of the amine intermediate from Step B in 10 mL of CHCl\textsubscript{3} was added 0.28g of N-t-BOC-D-TRP, 0.142g of HOBT, and 0.220g of EDC and stirred at RT for 3h. The reaction mixture was poured into 10 mL of water and extracted with ether (2X15 mL). The combined organic extracts were extracted with 20\% aqueous citric acid (10 mL), saturated NaHCO\textsubscript{3} (10 mL), dried over MgSO\textsubscript{4}, and concentrated. The residue was treated with 3 mL of CH\textsubscript{2}Cl\textsubscript{2}, 3 mL of TFA, and 0.10 mL of anisole for 1h. The reaction mixture was evaporated to dryness and the residue was azeotroped with toluene, dried under vacuum, and used without purification. To a solution of this material in 10 mL of CHCl\textsubscript{3} was added 0.70 mL of NMM, 0.142g of HOBT, 0.212g of N-t-BOC-α-methylalanine, and stirred at RT for 3h. The reaction was worked-up as described above. Flash chromatography
of the residue with hexane-ethyl acetate (1:1) as the eluent gave 86 mg of
the desired product.

Deprotection of the intermediate with TFA (2 mL), in
CH₂Cl₂ (2 mL), with 0.020 mL of anisole, gave the title compound as a
solid. This material is a mixture of diastereomers.

¹H NMR (CD₃OD, 400 MHz) δ 7.60 (d, 1H), 7.55-7.50 (m, 1H), 7.29
(dd, 1H), 7.18-6.95 (m, 6H), 4.60 (t, 1H), 3.30-3.10 (m, 4H), 2.95-2.70
(m, 3H), 2.20 (q, 1H), 1.81 (q, 1H), 1.66-1.53 (m, 1H), 1.50 (s, 3H), 1.42-
1.30 (m, 1H), 1.33 (s, 3H).

EXAMPLE 18

Step A:

To 80 mg of the amine intermediate prepared in Step B of
Example 17 in 5 mL of CH₂Cl₂ and 0.10 mL of triethylamine was added
0.104g of di-t-butyl dicarbonate and stirred for 2 h. The reaction mixture
poured into 5 mL of 20% aqueous citric acid and extracted with ether
(2X10 mL). The combined organic extracts were washed with saturated
aqueous NaHCO₃, brine (10 mL), dried over MgSO₄, and concentrated. This gave 0.123g of the desired product.

To a solution of the above intermediate in 5 mL of THF was added 1.50 mL of 1M solution of sodium bis(trimethylsilyl)amide in THF at 0°C, and stirred for 30 minutes. Methyl iodide (0.10 mL) was added and stirred at RT overnight. The reaction mixture was poured into water (10 mL), and extracted with ether (3X10 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, and concentrated to give 0.108g of the methylated product.

1H NMR (CDCl₃, 400 MHz) δ 7.30-7.05 (m, 4H), 3.45-3.20 (m, 2H), 3.20-3.00 (m, 1H), 3.00-2.75 (m, 1H), 2.88 (s, 1H), 2.33 (q, 1H), 2.10 (q, 1H), 1.80-1.55 (m, 2H), 1.48 (s, 9H), 1.50-1.35 (m, 1H).

Step B:

The intermediate was deprotected with TFA and then transformed to the title compound as described in Step C of Example 17. This compound is a mixture of diastereomers.

1H NMR (CD3OD, 400 MHz) δ 7.65-7.50 (m, 1H), 7.40-7.20 (m, 1H), 7.20-6.5 (m, 7H), 5.20-5.05 (m, 1H), 3.40-3.00 (m, 4H), 3.00-2.60 (m, 5H), 2.25 (q, 1/2H), 2.10-1.95 (m, 1/2H), 1.90-1.78 (m, 1H), 1.75-1.30 (m, 10H).
EXAMPLE 19

Step A:

The indoline ethanol was converted to the indoline ethyl amine as described in Step B of Example 17. The amine derivative thereby synthesized was converted to the title compound as described in Step C of Example 17 with one minor modification. The final deprotection was carried out in methanol with concentrated HCl to give the dihydrochloride salt.

$^{1}$H NMR (CD$_3$OD, 400 MHz) δ 8.20 (d, 1H), 7.60 (d, 1H), 7.55-7.40 (m, 4H), 7.28 (d, 1H), 7.17 (s, 1H), 7.00-6.90 (m, 2H), 4.70-4.60 (m, 1H), 3.95-3.85 (m, 1H), 3.82-3.70 (m, 1H), 3.60-3.45 (m, 2H), 4.40-3.15 (m, 4H), 1.60 (m, 3H), 1.36 (m, 3H).
EXAMPLE 20

Step A:

The title compound was prepared from commercially available N-\textit{t}-BOC-D-tryptophan and tryptamine as described in Step C of Example 17. The title compound was isolated as a free base after NaHCO$_3$ work-up of the final trifluoroacetic acid salt.

$^1$H NMR (CD$_3$OD, 400 MHz) $\delta$ 7.60 (d, 1H), 7.40 (d, 1H), 7.32 (d, 1H), 7.27 (d, 1H), 7.10-6.90 (m, 6H), 4.52 (t, 1H), 3.50-3.30 (m, 2H), 3.18 (t, 2H), 2.70 (t, 3H), 1.13 (s, 6H).
EXAMPLE 21

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\[ \text{Structure diagram} \]

10 Step A:

\[ \text{Structure diagram} \]

20 The title compound was synthesized from 1-(benzimidazol-yl)-2-propylamine and N-\text{-}t\text{-}BOC\text{-}D\text{-}TRP as described in Step C Example 17. This compound is a mixture of diastereomers.

\[ ^1\text{H NMR (CD}_3\text{OD, 400 MHz)} \delta \text{7.609.22 and 9.15 (2s, 1H), 8.30 and} \]

8.10 (2d, 1H), 8.00-7.80 (m, 2H), 7.70-7.60 (m, 2H), 7.50 (dd, 1H), 7.31

7.15-6.93 (m, 4H), 4.60-4.10 (m, 3H), 3.10 (d, 1H), 2.88 (d, 1H), 2.83-2.67 (m, 1H), 1.55 (s, 3H), 1.48 (s, 3H), 1.30 and 0.75 (2d, 3H).
EXAMPLE 22

\[ \text{N-CBZ-\( \beta \)-alanine methyl ester} \]

Prepared by the procedure described in Example 1, Step A from N-CBZ-\( \beta \)-alanine (5g, 22.4 mmole), methanol and thionyl chloride to give the title compound.

Step B:

To a stirred solution of the intermediate (330 mg) from the previous step in THF (3 mL) was added potassium bis(trimethylsilyl)amide (3 mL, 0.5 M in toluene) at -78°C followed by the addition of hexamethylyphosphoramide (5 mL). This mixture was warmed to room temperature to give a clear solution and then re-cooled to -78°C. To this solution was added another portion of potassium bis(trimethylsilyl)amide (3 mL, 0.5N in toluene). After 1 hour at -78°C, benzyl bromide (193 \( \mu \)L) was added to reaction mixture. The solution was stirred at -78°C for 3 hours and poured into 0.5N HCl, extracted with ether three times. The combined organic layers were washed with water (five times), brine,
dried over magnesium sulfate, and concentrated. The residue was purified by Pre-TLC (hexanes/ethyl acetate=4/1) to give the desired compound (164 mg, 35% yield).

**Step C:**

![Chemical structure](image)

To a solution of the intermediate (154 mg) obtained from the previous step in methanol was added Pd(OH)$_2$ and hydrogenated under H$_2$ balloon for 1/2 hour. The mixture was filtered through Celite. The filtrate was concentrated. The residue was coupled to the Intermediate 1 by the procedure described in Example 1, Step B (without NMM) to give desired compound (240 mg, 87%).

**Step D:**

![Chemical structure](image)

Prepared from the intermediate obtained from the previous step (31 mg) HCl gas in ethyl acetate at 0°C by the procedure described in Example 1, Step C to give the title compound (27 mg).

$^1$H NMR (400 MHz, CD$_3$OD, mixture of two diastereomers): 7.61 (m, 1 H), 7.32-6.99 (m, 9 H), 4.70 (m, 1 H), 3.56 (s, 3/2 H), 3.54 (s, 3/2 H),
3.37 (m, 1 H), 3.26 (m, 2 H), 3.10 (m, 1 H), 2.74 (m, 3 H), 1.54 (s, 3 H), 1.34 (s, 3/2 H), 1.32 (s, 3/2 H).

EXAMPLE 23

Step A:

To a stirred solution of the intermediate from Example 22, Step C (66 mg) in 1 mL of methanol was added lithium hydroxide (25 mg) in 1 mL of water. The reaction was stirred at room temperature for 16 hours and evaporated in vacuo. The residue was diluted with water and acidified with 1N hydrochloric acid and then exacted with ether. The organic layer was dried over sodium sulfate, filtered and concentrated to give the desired compound (44 mg).
Step B:

Prepared from the intermediate obtained from the previous step (7 mg) and HCl gas in ethyl acetate at 0°C by the procedure described in Example 1, Step C to give the desired compound (5 mg).

$^1$H NMR (400 MHz, CD$_3$OD, mixture of two diastereomers): 7.62 (d, 8 Hz, 1 H), 7.31-6.99 (m, 9 H), 4.71 (m, 1 H), 3.37 (m, 1 H), 3.28 (m, 2 H), 3.12 (m, 1 H), 2.77 (m, 3 H), 1.53 (s, 3 H), 1.30 (s, 3 H).

FAB-MS: 451.2 (M+1).

EXAMPLE 24
Step A:

Prepared from the intermediate from Example 23, Step A (37 mg) and ethylamine hydrochloride (16 mg) by the procedure described in Example 1, Step C using triethylamine instead of NMM to give the coupling product.

Step B:

Prepared from the intermediate from the previous step and HCl gas at 0°C by the procedure described in Example 1, Step C to give the desired compound (24 mg).

$^1$H NMR (400 MHz, CD$_3$OD, mixture of two diastereomers): 7.62 (d, 8 Hz, 1 H), 7.31-6.99 (m, 9 H), 4.68 (m, 1 H), 3.37-3.23 (m, 3 H), 3.15-2.91 (m, 3 H), 2.65 (m, 3 H), 1.55 (s, 3 H), 1.32 (s, 3 H), 0.90 (m, 3 H).

FAB-MS: 478.3 (M+1).
EXAMPLE 25

To a solution of the intermediate obtained from Example 22, Step A (1.15 g) in 10 mL of THF was added potassium bis(trimethylsilyl)amide (10.7 mL, 0.5N in toluene) at -78°C and then warmed to room temperature. To this reaction mixture was added hexamethylphosphoramide (10 mL) to give a clear solution and then re-cooled to -78°C. This solution was added another portion of potassium bis(trimethylsilyl)amide (10.7 mL, 0.5N in toluene). After 1 hour at -78°C, benzyl bromide (577 μL) was added to reaction mixture. The solution was stirred at -78°C for 4 hours and quenched with 1 mL of methyl iodide. The mixture was poured into 1N HCl, extracted with ether three times. The combined organic layers were washed with water (five times), brine, dried over magnesium sulfate, and concentrated. The residue was purified on silica gel to give the desired compound (1.43 g, 90%).
Step B:

Prepared from the intermediate from the previous step (757 mg) by the procedure described in Example 22, Step C to give the coupling product (806 mg, 60%).

Step C:

Prepared from the intermediate from the previous step (30 mg) by the procedure described in Example 1, Step C to give the desired compound 24 mg.

$^1$H NMR (400 MHz, CD$_3$OD, mixture of two diastereomers): 7.56 (m, 1 H), 7.32-6.89 (m, 9 H), 5.12 (m, 1 H), 3.53 (s, 3/2 H), 3.48 (s, 3/2 H), 3.42 (m, 1 H), 3.18 (m, 2 H), 2.99 (m, 1 H), 2.85 (s, 3 H), 2.70 (m, 3 H), 1.55 (s, 3 H), 1.45 (s, 3/2 H), 1.42(s, 3/2 H).

FAB-MS: 479.3 (M+1).
EXAMPLE 26

Step A:

To a solution of the intermediate obtained from Example 25, Step A (304 mg) in 2 ml of methanol was added 2 ml 6N sodium hydroxide. The reaction was stirred at room temperature for 2 hours. This basic mixture was washed with ether three times. The ether layer was then washed with 1N sodium hydroxide three times. The combined basic aqueous layers were cooled to 0°C and acidified with conc. HCl until a precipitate formed. Litmus paper turns blue to red. This solution was extracted with ethyl acetate three times. The combined organic layers were dried over sodium sulfate, filtered and concentrated to give the desired compound (225 mg, 75%).

Step B:

Prepared from the intermediate from the previous step (32 mg) and ethyl amine hydrochloride by the procedure described in Example 1, Step B using triethyl amine instead of NMM to give the coupling product (24 mg, 67%).
Step C:

Prepared from the intermediate from the previous step (24 mg) by the procedure described in Example 22, Step C to give the coupling product. The residue was purified (chromatotron, methylene chloride/methanol=20/1) to give the desired compound (17 mg, 48%). Diastereomers separated during purification where applicable.

Step D:

Prepared from the intermediate from the previous step (17 mg) and HCl gas in ethyl acetate at 0°C by the procedure described in Example 1, Step C to give the desired compound (15 mg).

FAB-MS: 492.0 (M+1)
The additional final products shown in table were prepared to the above established procedure (with different amines) as exemplified in Example 26.

<table>
<thead>
<tr>
<th>R</th>
<th>FAB-MS (M+1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>d1+d2</td>
<td>morpholine</td>
</tr>
<tr>
<td>d1</td>
<td>N-methyl piperazine</td>
</tr>
<tr>
<td>d2</td>
<td>N-methyl piperazine</td>
</tr>
<tr>
<td>d1+d2</td>
<td>dimethyl amine</td>
</tr>
</tbody>
</table>

**EXAMPLE 27**

**Step A:**
To a stirred solution of the intermediate from Example 25, Step B (110 mg) in 5 mL of methanol was added 5 mL of 6N sodium hydroxide. This reaction was stirred at room temperature for 16 hours and evaporated in vacuo. The residue was diluted with water and acidified with 1N hydrochloric acid and then extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and concentrated to give the desired compound (64 mg, 60%).

**Step B:**

Prepared from the intermediate obtained from the previous step (20 mg) and HCl gas in ethyl acetate at 0°C by the procedure described in Example 1, Step C to give the desired compound (13mg). FAB-MS: 465.0 (M+1)

**EXAMPLE 28**

**Step A:**
To a solution of (4S)-benzyl oxazolidinone (1.77 g) in THF (40 ml) was added n-butyllithium (1.6 M, 8 ml) at -78°C. After 30 minutes, to the reaction mixture was added hydrocinnamoyl chloride (1 eq) and the mixture was warmed to room temperature for 5 minutes. The mixture was poured into water and extracted with ether. The organic layer was washed with brine, dried over MgSO₄, and concentrated. The residue was purified by chromatotron (hexanes/ethyl acetate=5/1) to give the desired product 2.06g.

**Step B:**

![Chemical Structure](image1)

A solution of the intermediate (1.24 g) obtained from Step A in methylene chloride (20 ml) was cooled to 0°C and treated dropwise with TiCl₄ (0.46 ml). After 5 minutes, diisopropylethylamine (0.74 ml) was added slowly and the resultant deep red solution was stirred at 0°C for 1 hour. To this deep red solution was added trioxane (400 mg) in methylene chloride (4 ml) and the resulting mixture was stirred for additional 5 minutes. Then, another portion of TiCl₄ (0.46 ml) was added. After stirring 2.5 hour at 0°C, this clear solution was quenched with saturated aqueous ammonium chloride. This mixture was extracted with methylene chloride, washed with sodium bicarbonate, brine and dried over sodium sulfate. Concentration and purification (hexanes/ethyl acetate=4/1) gave the desired product 0.79 g.

**Step C:**

![Chemical Structure](image2)
To a solution of the intermediate (0.7 g) obtained from Step B in THF (20 ml) was added triphenylphosphine (0.595 g) and diethylazodicarboxylate (0.357 ml) and then added diphenylphosphorylazide (0.488 ml) was added slowly. After stirring for 60 hours, the mixture was concentrated. The resulting residue was filtered through a plug of silica gel (100% ether) and concentrated. The material was purified by chromatron (hexanes/ethyl acetate=10/1) to give the desired product (189 mg) and unreacted starting material (463 mg).

$^1$H NMR (400 MHz, CDCl₃): 7.21 (m, 10 H), 4.50 (m, 1 H), 4.35 (m, 1 H), 4.06 (dd, 9 Hz, 3 Hz, 1H), 3.92 (t, 8 Hz, 1 H), 3.68 (dd, 12 Hz, 8 Hz, 1 H), 3.42 (dd, 12 Hz, 5 Hz, 1 H), 3.22 (dd, 13 Hz, 3 Hz, 1H), 2.95 (dd, 13 Hz, 7 Hz, 1H), 2.78 (t, 9 Hz, 1H), 2.74 (t, 9 Hz, 1H). FAB-MS: 365.2 (M+1).

Step D:

![Structure](image)

To a solution of benzyl alcohol (0.16 ml) in THF (5 ml) was added n-butyllithium (0.65 ml, 1.6 M) at 0°C. After stirring 10 minutes, the intermediate (189 mg) obtained from Step C in THF (2 ml) was added to the reaction mixture. The resulting solution was stirred for an hour at 0°C and quenched with 1 N HCl. The mixture was extracted with ether, washed with brine and dried over MgSO₄. Concentration and purification (PLC, hexanes/ethyl acetate=20/1) to give the desired product (87 mg).

Step E:
To a solution of the intermediate (87 mg) obtained from Step D in methanol was added Raney nickel and under 1 atmosphere of hydrogen for 2 hours. The mixture was filtered through Celite and the filtrate was concentrated. The residue was coupled to the Intermediate 1 by the procedure described in Example 1, Step B (without NMM) to give desired compound (101 mg).

**Step F:**

To a solution of the intermediate (101 mg) obtained from Step E in methanol was added Pd(OH)2 and hydrogenated under hydrogen (1 atmosphere) for an hour. The mixture was filtered through Celite. The filtrate was concentrated to give corresponding acid (88 mg). The acid (17 mg) in ether was added diazomethane (prepared from N-methyl N-nitroso urea) at 0°C until the solution turned yellow. The yellowish solution was stirred for a couple of hours at room temperature and concentrated. The residue was purified by PLC (hexanes/ethyl acetate=1/2) to give the desired product (11 mg).
Step G:

Prepared from the intermediate obtained from Step F and HCl gas in ethyl acetate at 0°C by the procedure described in Example 1, Step C to give the desired compound (9 mg).

$^1$H NMR (400 MHz, CD3OD): 7.62 (d, 8 Hz, 1 H), 7.31 (d, 8 Hz, 1 H), 7.26-7.06 (m, 7 H), 7.01 (t, 7 Hz), 4.70 (dd, 9 Hz, 2 Hz, 1 H), 3.56 (s, 3 H), 3.39-3.24 (m, 3 H), 3.10 (dd, 14 Hz, 9 Hz, 1 H), 2.85 (m, 1 H), 2.74 (m, 2 H), 1.54 (s, 3 H), 1.32 (s, 3 H).

FAB-MS: 465.1 (M+1).

EXAMPLE 29

Step A: N-(3-phenyl-1-propyl)glycine ethyl ester

To a stirred solution of 3-phenyl-1-propylamine (5 mL, 35.2 mmol) in THF (20 mL), was added ethyl bromoacetate (3.9 mL, 35.2 mmol) and diisopropyl ethyl amine (6.13 mL). The reaction was stirred at room temperature overnight. The solid formed was filtered off and the solution was evaporated and purified by flash column to yield the desired material (2 g).

$^1$HNMR (400 MHz, CD3OD): $\delta$ (ppM) 7.28-7.13 (m, 5 H), 4.13 (q, J=7.2 Hz, 3 H), 3.37 (s, 2 H), 2.68-2.60 (m, 4 H), 1.88-1.76 (m, 2 H), 1.25 (t, J=7.2 Hz, 3 H).
Step B:

Prepared by the procedure described in Example 1, Step B from the intermediate from the previous step (170 mg), Intermediate 1 (200 mg, 0.514 mmol), HOBT (68 mg.), and EDC (200 mg). Product: 254.8 mg. FAB-MS calc. for C$_{33}$H$_{44}$N$_4$O$_6$: 592; found: 593 (M+H).

Step C:

Prepared by the procedure described in Example 1, Step C from the intermediate from previous step (228.8 mg) and HCl gas in ethyl acetate (3 mL) at 0°C. Reaction time: 30 minutes. Product: 210 mg. FAB-MS calc. for C$_{28}$H$_{36}$N$_4$O$_4$: 492; found: 493 (M+H).
EXAMPLE 30

Step A:

Prepared by the procedure described in Example 1, Step B from D-HomoPhe benzyl ester (1.38 g, 5.13 mmol), Intermediate 1 (2 g, 5.13 mmol), HOBT (694 mg), and EDC (1.53 g). Product: 2.90 g (88%).

FAB-MS calc. for C_{37}H_{44}N_{4}O_{6}: 640; found: 641 (M+H).

Step B:

Prepared by the procedure described in Example 1, Step C from the intermediate from previous step (106 mg) and HCl gas in ethyl acetate (3 mL) at 0°C. Reaction time: 1 hour. Product: 94.5 mg.

FAB-MS calc. for C_{32}H_{36}N_{4}O_{4}: 540; found: 541 (M+H).
EXAMPLE 31

Step A:

A solution of the material from Step A (2.74 g) of the previous example in 20 mL of ethanol was stirred at RT under a H₂ balloon for 20 minutes in the presence of 10% palladium on carbon (150 mg). The catalyst was filtered off through a pad of celite and washed with ethyl acetate. The filtrate was concentrated to give the acid as a foam (2.19 g, 93%).

FAB-MS calc. for C₃₀H₃₈N₄O₆: 550 ; Found 551 (M+H)

Step B:
Prepared by the procedure described in Example 1, Step C from the intermediate from previous step (150 mg) and HCl gas in ethyl acetate (3 mL) at 0°C. Reaction time: 15 minutes. Product: 128 mg (96.5%).

FAB-MS calc. for C_{25}H_{30}N_{4}O_{4}: 450; Found 451 (M+H)

^{1}HNMR (400 MHz, CD3OD): δ (ppM) 8.50 (d, J=8 Hz, 1 H), 7.69 (d, J=8 Hz, 1 H), 7.31-7.00 (m, 8 H), 4.89-4.85 (m, 1 H), 4.39-4.35 (m, 1 H), 3.38 (dd, J=4, 14 Hz, 1 H), 3.16 (dd, J=10, 14 Hz, 1 H), 2.72-2.64 (m, 2 H), 2.21-2.12 (m, 1 H), 2.08-1.98 (m, 1 H), 1.53 (s, 3 H), 1.27 (s, 3 H).

**EXAMPLE 32**

![Chemical Structure](image)

20 **Step A:**

![Chemical Structure](image)

Prepared by the procedure described in Example 1, Step B from the intermediate from Step A of the previous example (150 mg, 0.272mmol), ethyl amine hydrochloride (25 mg, 0.544 mmol), HOBT (37 mg), N-methyl morpholine(0.06 mL; 0.544 mmol), and EDC (100 mg). Product: 139 mg. FAB-MS calc. for C_{32}H_{43}N_{5}O_{5}: 577; Found 578 (M+H)
Step B:

Prepared by the procedure described in Example 1, Step B from the intermediate from previous step (125 mg) and HCl gas in ethyl acetate (3 mL) at 0°C. Reaction time: 15 minutes. Product: 90.9 mg (82%).

FAB-MS calc. for C_{27}H_{35}N_{5}O_{3}: 477; Found 478 (M+H)

$^1$HNMR (400 MHz, CD3OD): $\delta$ (ppM) 8.19 (d, J=7.5 Hz, 1 H), 7.66-7.00 (m, 10 H), 4.85-4.79 (m, 1 H), 4.29-4.26 (m, 1 H), 3.57 (dd, J=6, 14 Hz, 1 H), 3.16 (dd, J=9, 14 Hz, 1 H), 3.15-3.08 (m, 2 H), 2.68-2.55 (2 m, 2 H), 2.10-1.98 (m, 1 H), 1.95-1.86 (m, 1 H), 1.55 (s, 3 H), 1.34 (s, 3 H), 1.05 (t, J=7.2 Hz).
While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.
WHAT IS CLAIMED IS:

1. A compound of the formula

\[
\begin{align*}
\text{H} & \quad \text{N} \quad \text{C} \quad \text{A} \quad \text{N} \\
& \quad \text{C}=\text{O} \\
\text{R}_1 & \quad \text{N} \quad \text{R}_{1a} \\
& \quad \text{R}_5 \\
\text{R}_3 & \quad \text{W} \\
\text{R}_4 & \quad \text{R}_5 \\
\end{align*}
\]

Formula I

wherein:
R1 is selected from the group consisting of:

C1-C10 alkyl, aryl, aryl(C1-C6 alkyl)-, C3-C7 cycloalkyl(C1-C6 alkyl)-,
(C1-C5 alkyl)-K-(C1-C5 alkyl)-, aryl(C0-C5 alkyl)-K-(C1-C5 alkyl)-,
and (C3-C7 cycloalkyl)(C0-C5 alkyl)-K-(C1-C5 alkyl)-, where K is O,
S(O)m, N(R2)C(O), C(O)N(R2), OC(O), C(O)O, -CR2=CR2-, or -C≡C-,
where aryl is selected from: phenyl, naphthyl, indolyl, azaindolyl,
pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl, and
where R2 and alkyl may be further substituted by 1 to 9 halogen,
S(O)mR2a, 1 to 3 of OR2a or C(O)OR2a, and aryl may be further
substituted by 1 to 3 of C1-C6 alkyl, 1 to 3 of halogen, 1 to 2 of OR2,
methylenedioxy, -N(R2)(R2), -S(O)mR2, 1 to 2 of -CF3, -OCF3,
-C(O)H, nitro, -N(R2)C(O)(R2), -C(O)OR2, -C(O)N(R2)(R2), -1H-
tetrazol-5-yl, -SO2N(R2)(R2), -N(R2)SO2 phenyl, or -N(R2)SO2R2;
R1a is independently hydrogen, or C1-C6 alkyl;

R2 is selected from the group consisting of: hydrogen, C1-C6 alkyl, and
C3-C7 cycloalkyl, and where two C1-C6 alkyl groups are present on one
atom, they may be optionally joined to form a C3-C8 cyclic ring,
optionally including oxygen, sulfur, SO2 or NR2a;
R2a is hydrogen, or C1-C6 alkyl optionally substituted by hydroxyl;
R3 is independently selected from the group consisting of:
hydrogen, -C1-C10 alkyl, -(CH2)rphenyl, -(CH2)rnapthyl,
-(CH2)rC(O)OR8, -(CH2)rC(O)N(R2)(R8),
(C1-C6 alkyl)-K-(C1-C4 alkyl)-, aryl(C0-C5 alkyl)-K-(C1-C4 alkyl)-,
-(CH2)r-C3-C7 cycloalkyl, and -(CH2)r heteroaryl,
where K is O or S(O)m, and where heteroaryl is selected from: pyridyl,
indolyl, imidazolyl, quinolinyl, benzothiopheneyl, benzofuranyl, indanyl,
thiazolyl, benzimidazolyl, and azaindolyl, and
where the phenyl, napthyl and heteroaryl may be substituted by:
C1-C6 alkyl, 1 to 2 of halogen, 1 to 2 of -OR9, -NHSO2CF3,-C(O)H,
-(CH2)rN(R2)(R9), -(CH2)rC(O)OR9, -(CH2)rN(R2)C(O)R9,
-(CH2)rC(O)N(R2)(R9), -(CH2)rN(R6)C(O)N(R2)(R9), or -(CH2)r (R9);

R3a is hydrogen or C1-C6 alkyl;

R4 and R5 are independently selected from:
hydrogen, C1-C6 alkyl, and substituted C1-C6 alkyl where the
substituents are selected from: 1 to 5 halogen, 1 to 3 of hydroxy, 1 to 3
of C1-C10 alkanoyloxy, 1 to 3 of C1-C6 alkoxy, phenyl, phenoxy,
2-furyl, C1-C6 alkoxycarbonyl, and S(O)m(C1-C6 alkyl); or R4 and
R5 can be taken together to form -(CH2)dLa(CH2)e- where La is
C(R2)2, O, S(O)m or N(R2a), d and e are independently 1 to 3;

R6 is hydrogen or C1-C4 alkyl;

R7 and R7a are independently hydrogen, C1-C6 alkyl, trifluoromethyl,
phenyl, substituted C1-C6 alkyl where the substituents are selected from:
imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR2, S(O)mR2,
C(O)O(C1-C6 alkyl), C3-C7 cycloalkyl, N(R2)(R2), and
C(O)N(R2)(R2); or R7 and R7a can independently be joined to one or
both of R4 and R5 groups to form an alkylene bridge between the
terminal nitrogen and the alkyl portion of the R7 or R7a groups, wherein
the bridge contains 1 to 5 carbons atoms; or R7 and R7a can be joined to
one another to form a C3-C7 cycloalkyl;
R8 is selected from the group consisting of: hydrogen, C1-C6 alkyl, aryl, and aryl-C1-C2 alkyl, where the alkyl groups may be substituted by a substituent selected from the group consisting of: -OR2, -C(O)OR2, -CON(R2)(R2), -N(R2)C(O)N(R2)(R2), and 1H-tetrazol-5-yl, and where aryl is selected from the group consisting of: phenyl, naphthyl, indolyl, quinolinyl, benzo thiophenyl, benzofuranyl, azaindolyl, benzimidazolyl, pyridyl, and thiazolyl, and where the aryl may be substituted by: 1 to 2 of -OR2, 1 to 2 of halogen, 1 to 2 of C1-C3 alkyl, -C(O)OR2, -C(O)N(R2)(R2), or -1H-tetrazol-5-yl;

R9 is selected from hydrogen, C1-C6 alkyl, or (CH2)νaryl, wherein the alkyl and (CH2)ν groups may be optionally substituted by 1 to 2 of -O(R2), -S(O)mR2, -N(R2)(R2), 1H-tetrazol-5-yl, -C(O)OR2, -C(O)N(R2)(R2), -SO2N(R2)(R2), or -N(R2)C(O)N(R2)(R2), and where aryl is selected from: phenyl, pyridyl, 1H-tetrazol-5-yl, triazolyl, imidazolyl, thiazolyl, oxadiazolyl, pyrazolyl, thiazolyl, imidazolone-1-yl, and benzimidazolo 2-yl, triazolinone-yl, and where the aryl is optionally substituted with C1-C6 alkyl, C3-C6 cycloalkyl, amino, hydroxyl, or -C(O)OR2;

A is:

\[
\begin{align*}
R_7 & \quad -(CH_2)_x-C-(CH_2)_y \quad \text{or} \quad -(CH_2)_x-C-(CH_2)_y \\
R_{7a} & \quad R_{7a}
\end{align*}
\]

where x and y are independently 0, 1, 2 or 3;

W is selected from the group consisting of: hydrogen, -C(O)OR8, -C(O)N(R2)(R2), -C(O)NH-SO2(R2), -C(O)N(R2)(R8), -CH2N(R2)C(O)R8, -CH2N(R2)C(O)(R8), -(CH2)νOR2, -CH(OH)R2, -CH2SO2R2, -CH2SO2N(R2)(R2), 1H-tetrazol-5-yl, 5-amino-1,2,4-oxadiazol-3-yl, 5-methyl-1,2,4-oxadiazol-3-yl, 3-amino-1,2,4-oxadiazol-5-yl, and 3-methyl-1,2,4-oxadiazol-5-yl;
m is 0, 1, or 2;
n is 0 or 1;
r is 0, 1, 2, or 3;
v is 0, 1, or 2;

and pharmaceutically acceptable salts and individual diastereomers thereof.

2. The compound of Claim 1 wherein:

R₁ is selected from the group consisting of:
C₁-C₁₀ alkyl, aryl, aryl(C₁-C₄ alkyl)-, C₃-C₆ cycloalkyl(C₁-C₄ alkyl)-,
(C₁-C₄ alkyl)-K-(C₁-C₂ alkyl)-, aryl(C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-,
and (C₃-C₇ cycloalkyl)(C₀-C₂ alkyl)-K-(C₁-C₂ alkyl)-, where K is O,
S(O)ₓm, OC(O), or C(O)O, where the alkyl groups may be further
substituted by 1 to 7 halogen, S(O)ₓmR₂a, 1 to 3 of OR₂a or C(O)OR₂a,
and where aryl is selected from: phenyl, naphthyl, indolyl, pyridyl,
benzimidazolyl, azaindolyl, benzothienyl, and benzofuranyl, and where
the aryl may be further substituted by 1 to 2 of C₁-C₄ alkyl, 1 to 2 of
halogen, -C(O)H, 1 to 2 of -OR₂, -S(O)ₓmR₂, or -C(O)OR₂;
R₁a is independently hydrogen or C₁-C₃ alkyl;

R₂ is selected from the group consisting of: hydrogen, C₁-C₆ alkyl, and
C₃-C₇ cycloalkyl, and where two C₁-C₆ alkyl groups are present on one
atom they may be optionally joined to form a C₄-C₇ cyclic ring
optionally including oxygen, sulfur or NR₂a;
R₂a is hydrogen or C₁-C₄ alkyl;

R₃ is independently selected from the group consisting of:
hydrogen, -C₁-C₈ alkyl, -(CH₂)ₓphenyl, -(CH₂)ₓnaphthyl,
and -(CH₂)ₓheteroaryl, where heteroaryl is selected from: pyridyl,
indolyl, quinolinyl, benzothiopheneyl, benzofuranyl, thiazolyl,
benzimidazolyl, and azaindolyl, and where the phenyl, naphthyl and
heteroaryl may be substituted by: C₁-C₄ alkyl, 1 to 2 of halogen, 1 to 2
of -OR₂, -NHSO₂CF₃, -(CH₂)ₙC(O)OR₂, -(CH₂)ₙC(O)N(R₂)(R₂),
-(CH₂)ₙN(R₆)C(O)N(R₂)(R₂), or -(CH₂)ₙ(R₉);

R₃a is hydrogen or C₁-C₆ alkyl;

R₄ and R₅ are independently selected from: hydrogen, C₁-C₆ alkyl, and
substituted C₁-C₆ alkyl where the substituents are selected from: 1 to 5
of halogen, 1 to 3 of hydroxyl, S(O)ₙm (C₁-C₆ alkyl), and phenyl;

R₆ is hydrogen or C₁-C₄ alkyl;

R₇ and R₇a are independently hydrogen, C₁-C₆ alkyl, trifluoromethyl,
phenyl, substituted C₁-C₆ alkyl where the substituents are selected from:
imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR₂, S(O)ₙmR₂,
C(O)O(C₁-C₆ alkyl), C₃-C₇ cycloalkyl, N(R₂)(R₂), and
C(O)N(R₂)(R₂); or R₇ and R₇a can independently be joined to one or
both of R₄ and R₅ groups to form an alkylene bridge between the
terminal nitrogen and the alkyl portion of the R₇ or R₇a groups, wherein
the bridge contains 1 to 5 carbons atoms; or R₇ and R₇a can be joined to
one another to form a C₃-C₇ cycloalkyl;

R₈ is selected from the group consisting of:
hydrogen, C₁-C₄ alkyl, aryl, and aryl-C₁-C₂ alkyl, where the alkyl
groups may be substituted by a substituent selected from the group
consisting of: -OR₂, -C(O)OR₂, -CON(R₂)(R₂), -N(R₂)C(O)N(R₂)(R₂),
and 1H-tetrazol-5-yl, and where aryl is selected from the group consisting
of: phenyl, indolyl, azaindolyl, pyridyl, and thiazolyl, and where the aryl
may be substituted by: 1 to 2 of -OR₂, 1 to 2 of halogen, or 1 to 2 of
C₁-C₃ alkyl;

R₉ is (CH₂)ₙaryl, where aryl is selected from: phenyl, pyridyl,
1H-tetrazol-5-yl, or oxadiazolyl, and where the aryl is optionally
substituted with C₁-C₆ alkyl, amino, hydroxyl, or -C(O)O(R₂);
A is:

\[ R_7 \quad - (CH_2)_x - C - \quad \text{or} \quad - C - (CH_2)_y \quad R_7 \]

\[ R_{7a} \quad R_{7a} \]

where \( x \) and \( y \) are independently 0, 1, 2 or 3;

\( W \) is selected from the group consisting of: hydrogen, -C(O)OR_8, -C(O)N(R_2)(R_2), -C(O)N(R_2)(R_8), 1H-tetrazol-5-yl, 3-amino-1,2,4-oxadiazol-5-yl, 3-methyl-1,2,4-oxadiazol-5-yl, 5-amino-1,2,4-oxadiazol-3-yl, and 5-methyl-1,2,4-oxadiazol-3-yl;

\( m \) is 0, 1, or 2; 
\( n \) is 0 or 1; 
\( r \) is 0, 1, 2, or 3; 
\( v \) is 0, 1, or 2;

and pharmaceutically acceptable salts and individual diastereomers thereof.

3. The compound of Claim 1 wherein:

\( R_1 \) is selected from the group consisting of: C_1-C_10 alkyl, aryl (C_1-C_3 alkyl)-, C_3-C_7 cycloalkyl(C_1-C_3 alkyl)-, and aryl (C_0-C_1 alkyl)-K-(C_1-C_2 alkyl)-, where \( K \) is O or S(O)\(_m\) and aryl is selected from: phenyl, pyridyl, naphthyl, indolyl, azaindolyl, and benzofuranyl and where the aryl may be further substituted by 1 to 2 of C_1-C_4 alkyl, 1 to 2 of halogen, 1 to 2 of -OR\(_2\), -S(O)\(_m\) R\(_2\), or -C(O)OR\(_2\);

\( R_{1a} \) is independently hydrogen or C_1-C_2 alkyl;

\( R_2 \) is selected from the group consisting of: hydrogen, C_1-C_6 alkyl, and C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one
atom they may be optionally joined to form a C5-C7 cyclic ring
optionally including oxygen, sulfur or NR₂a;
R₂a is hydrogen or C₁-C₃ alkyl;

R₃ is independently selected from the group consisting of:
hydrogen, -C₁-C₆ alkyl, -(CH₂)ₗ phenyl, and -(CH₂)ₗ hetroaryl, where
heteroaryl is selected from: pyridyl, thiazolyl, indolyl, quinolinyl,
benzofuranyl, and azaindolyl, and where the phenyl and heteroaryl may
be substituted by: C₁-C₃ alkyl, 1 to 2 of halogen, 1 to 2 of -OR₂,
-(CH₂)ₗ C(O)OR₂, -(CH₂)ₗ C(O)N(R₂)(R₂),
-(CH₂)ₗ N(R₆)C(O)N(R₂)(R₂), or -(CH₂)ₗ (R₉);
R₃a is hydrogen or C₁ alkyl;

R₄ and R₅ are independently hydrogen, C₁-C₄ alkyl, or substituted
C₁-C₃ alkyl where the substituents are selected from: 1 to 5 of halogen,
1 to 3 of hydroxyl, S(O)m (C₁-C₆ alkyl), and phenyl;

R₆ is hydrogen or C₁-C₃ alkyl;

R₇ and R₇a are independently hydrogen, C₁-C₂ alkyl, phenyl, substituted
C₁-C₆ alkyl where the substituents are selected from: imidazolyl,
phenyl, indolyl, p-hydroxyphenyl, -OR₂, and -S(O)mR₂, or R₇ and R₇a
can independently be joined to one of R₄ and R₅ groups to form an
alkylene bridge between the terminal nitrogen and the alkyl portion of the
R₇ or R₇a groups to form a 5 or 6 membered ring; or R₇ and R₇a can be
joined to one another to form a C₃ cycloalkyl;

R₈ is selected from the group consisting of:
hydrogen, C₁-C₄ alkyl, and aryl-C₁-C₂ alkyl, where the alkyl groups
may be substituted by a substituent selected from the group consisting
of: -OR₂, -C(O)OR₂, -CON(R₂)(R₂), -N(R₂)C(O)N(R₂)(R₂), and
1H-tetrazol-5-yl, and where aryl is selected from the group consisting of: phenyl, indolyl, 7-azaindolyl, pyridyl, and thiazolyl, and where the aryl may be substituted by: 1 to 2 of -OR₂, 1 to 2 of halogen, or 1 to 2 of C₁-C₃ alkyl;

R₉ i (CH₂)ᵱaryl, where aryl is selected from: 1H-tetrazol-5-yl, and oxadiazolyl, and where the aryl is optionally substituted with C₁-C₆ alkyl, amino, or hydroxyl;

A is:

\[
\begin{align*}
\text{R}_7 & - (\text{CH}_2)_x - \text{C} - \frac{\text{R}_7}{\text{R}_7_a} \\
\text{or} & \\
\text{C} - (\text{CH}_2)_y - \frac{\text{R}_7}{\text{R}_7_a}
\end{align*}
\]

where x and y are independently 0 or 1;

W is selected from the group consisting of: hydrogen, -C(O)OR₈, -C(O)N(R₂)(R₂), -C(O)N(R₂)(R₈), 1H-tetrazol-5-yl, 3-amino-1,2,4-oxadiazol-5-yl, and 3-methyl-1,2,4-oxadiazol-5-yl;

m is 0, 1, or 2;

n is 0 or 1;

r is 0, 1, 2, or 3;

v is 0, 1, or 2;

and pharmaceutically acceptable salts and individual diastereomers thereof.
4. The stereospecifically defined compound of Claim 1 of the formula:

```
  H  H  O
 / \ /   \ R_4
 R_1-N-C-A-N\  C=O
   \  /       R_5
    R_6  \____/ R_1a
   /       R_1a
 R_3  R_3a  W
```

Formula Ia

where R_1, R_3, R_3a, R_4, R_5, R_6, A, W and n are as defined in Claim 1.

5. A compound which is selected from the group consisting of:

```
\(\text{[Chemical Structure]}\)
```

where [Chemical Structure] is defined in Claim 1.
and their pharmaceutically acceptable salts and individual diasteromers thereof, where not otherwise specified.
6. A process for the preparation of a compound of Claim 1 which comprises reacting a compound of the formula:

\[
\begin{align*}
\text{R}_1 & \text{N-H} \\
\text{C} & \text{=O} \\
\text{R}_6 & \text{N-} \text{R}_{1a} \\
\text{R}_3 & \text{R}_{3a} \\
\end{align*}
\]

with a compound of the formula:

\[
\begin{align*}
\text{HO-C-A-N}^{\text{R}^4} & \text{R}^5 \text{ or } \text{HO-C-A-N}^{\text{R}^4} & \text{R}^5
\end{align*}
\]

to give a compound of the formula:

\[
\begin{align*}
\text{R}_1 & \text{N-C-A-N} \text{R}_5 \\
\text{C} & \text{=O} \\
\text{R}_6 & \text{N-} \text{R}_{1a} \\
\text{R}_3 & \text{R}_{3a} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}_1 & \text{N-C-A-N} \text{R}_5 \\
\text{C} & \text{=O} \\
\text{R}_6 & \text{N-} \text{R}_{1a} \\
\text{R}_3 & \text{R}_{3a} \\
\end{align*}
\]

where \( R_1, R_3, R_{3a}, R_4, R_5, R_6, A, W, \) and \( n \) are as defined in Claim 1 and \( L \) is a protecting group which is subsequently removed if present and salts are formed if desired.
7. A process for the preparation of a compound of Claim 1 which comprises reacting a compound of the formula:

\[
\begin{align*}
R^1 & \quad N-C-A-N-R^5 \\
\text{COOH} & \quad \text{or} \quad \text{COOH}
\end{align*}
\]

with a compound of the formula:

\[
\begin{align*}
& \quad \quad \quad \quad \quad \quad R_6 \quad R_{1a} \\
& \quad \quad \quad \quad \quad \quad R_3 \quad R_{3a}
\end{align*}
\]

15
to give a compound of the formula:

\[
\begin{align*}
R_1^* & \quad N-C-A-N-R_5 \\
\text{C} & \quad \text{or} \quad \text{C}
\end{align*}
\]

20

where R1, R3, R3a, R4, R5, R6, A, W, and n are as defined in Claim 1 and L is a protecting group which is subsequently removed if present and salts are formed if desired.

30
8. A composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of a compound of Claim 1.

9. A composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of a compound of Claim 1 in combination with an additional growth hormone secretagogue.

10. The composition of Claim 9 wherein the additional growth hormone secretagogue is selected from the group consisting of: growth hormone releasing peptide GHRP-6; growth hormone releasing peptide GHRP-2; growth hormone releasing peptide GHRP-1; B-HT920; growth hormone releasing factor; an analog of growth hormone releasing factor; IGF-1 and IGF-2.

11. A composition useful for the treatment of osteoporosis which comprises a combination of a bisphosphonate compound and a compound of Claim 1.

12. The composition of Claim 11 wherein the bisphosphonate compound is alendronate.

13. A method for increasing levels of endogenous growth hormone in a human or an animal which comprises administering to such human or animal an effective amount of a compound of Claim 1.

14. A method for increasing feed efficiency, promoting growth, increasing milk production and improving the carcass quality of livestock which comprises administering to such livestock an effective amount of a compound of Claim 1.
15. A method of treating or preventing a condition selected from the group consisting of: osteoporosis; catabolic illness; immune deficiency, including that in individuals with a depressed T4/T8 cell ratio; hip fracture; musculoskeletal impairment in the elderly; growth hormone deficiency in adults or in children; obesity; cachexia and protein loss due to chronic illness such as AIDS or cancer; and treating patients recovering from major surgery, wounds or burns, in a patient in need thereof which comprises the administration to the patient of an effective amount of the compound of Claim 1.


17. The method of Claim 16 wherein the bisphosphonate compound is alendronate.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07D 209/20, 403/12; A61K 31/405
US CL. :548/455, 495; 514/414, 419
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 548/455, 495; 514/414, 419

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
CAS ONLINE DATABASE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>US, A, 4,658,038 (TAMIR ET AL) 14 April 1987, see entire document.</td>
<td>1-5</td>
</tr>
<tr>
<td>A</td>
<td>US, A, 4,522,824 (WAGNON ET AL) 11 June 1985, see entire document.</td>
<td>1-5</td>
</tr>
<tr>
<td>A,P</td>
<td>US, A, 5,324,737 (D'AMBRA ET AL) 28 June 1994, see entire document.</td>
<td>1-5</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search
15 MARCH 1995

Date of mailing of the international search report
28 MARCH 1995

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