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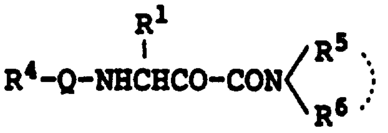

$$R^4\text{-Q-NH}\overset{R^1}{\text{C}}\text{HCO-CON}\begin{cases}R^5\\R^6\end{cases}$$

(Ia)

(57) Abstract

The present invention relates to a cathepsin L inhibitor comprising a compound of general formula (Ia), wherein Q represents a direct bond or 1 or 2 amino acid residues that may be substituted; R^1 represents a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted; R^4 represents an acyl group or a carboxyl group that may be esterified and R^5 and R^6 independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted or R^5 and R^6 may bind together to form a ring; or a salt thereof, which has strong bone resorption-suppressing action and is useful for preventing or treating osteoporosis.

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DESCRIPTION

ALPHA-KETOAMIDE DERIVATIVES AS CATHEPSIN L INHIBITOR

Technical Field

This invention relates to a cathepsin L inhibitor comprising an α-ketoamide derivative or a salt thereof as an active ingredient, and use thereof.

Background Art

Osteoporosis is a pathologic state or disease involving some symptom or risk due to quantitative bone reduction exceeding a certain degree. Major symptoms are spinal kyphosis, fractures of dorsolumbar bones, vertebral centra, femoral necks, lower end of radius, ribs, upper end of humerus, and others. In normal bone tissue, bone destruction occurs continuously, but there is good balance between bone formation and resorption; osteoblasts and osteoclasts play key roles in bone formation and bone resorption, respectively. Upon deterioration of this balance, bone resorption surpasses bone formation, resulting in quantitative bone reduction. Drugs suppressing bone resorption are therefore expected to serve well in preventing and treating osteoporosis. Traditionally, bone resorption-suppressing agents, such as estrogens and calcitonin have been used to treat osteoporosis. However, these therapeutic agents fail to achieve satisfactory effect in some cases, due to subject limitations or uncertain efficacy. There is therefore need of a new prophylactic/therapeutic method for accentuated bone resorption.

It has recently been shown that cathepsin L, a protease secreted by osteoclasts in the process of bone resorption, is integrally involved in the decomposition of collagen, a bone-supporting protein (FEBS Lett., Vol. 321, p. 247, 1993). Presumably therefore, bone collagen decomposition due to bone resorption can be prevented by inhibiting cathepsin L activity, a means useful in the prevention and treatment of osteoporosis. Leupeptin, antipain and epoxysuccinic acid derivatives (Japanese Patent Unexamined Publication Nos. 304074/1990, 304075/1990 and 304085/1990) are known to exhibit cathepsin L inhibitory action.

Traditionally, naturally occurring postostain has been known as an α-ketoamide derivative possessing protease inhibitory activity, and various compounds have been synthesized as α-ketoamide derivatives from amino acids. For example, PCT Int. Appl. WO 94/00095 discloses α-ketoamide derivatives as calpain inhibitors, and PCT Int. Appl. WO 92/12140 (Japanese Publication of translations of International patent application No. 504547/1994) discloses α-ketoamide derivatives as calpain, papain and cathepsin B inhibitors.

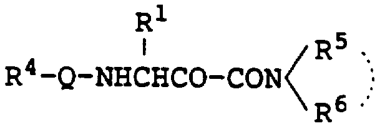
However, no α-ketoamide derivatives have been reported as inhibiting cathepsin L. In addition, most synthetic α-ketoamide derivatives have been racemates at their ketone α-position, because they are synthesized by converting the corresponding amino acids to α-keto esters by the Dakin-West reaction of the carboxyl group of each amino acid.

Disclosure of Invention

The present inventors sought to develop a more commonly applicable drug showing selective inhibition of cathepsin L and direct action on the bone to suppress bone resorption, and found that an α-ketoamide derivative shows potent cathepsin L inhibition and direct action on the bone to excellently suppress bone resorption, and that it serves well as a prophylactic/therapeutic agent for bone disease. The inventors made further investigations based on this finding, and developed the present invention.

Accordingly, the present invention relates to:

(1) A cathepsin L inhibitor comprising a compound of the formula (Ia):

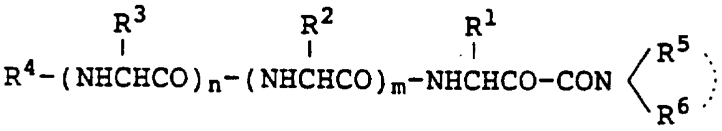


(Ia)

$$R^4\text{-Q-NH}\overset{\overset{\displaystyle R^1}{|}}{\text{C}}\text{HCO-CON}\left\langle\begin{matrix}R^5\\R^6\end{matrix}\right.$$

wherein Q represents a direct bond or 1 or 2 amino acid residues that may be substituted; R^1 represents a hydrogen atom or a hydrocarbon or heterocyclic group that may be substituted; R^4 represents an acyl group or a carboxyl group that may be esterified and R^5 and R^6 independently represent a hydrogen atom or a hydrocarbon or heterocyclic group that may be substituted or R^5 and R^6 may bind together to form a ring; or a salt thereof,

(2) A cathepsin L inhibitor of item (1), wherein the compound is one of the formula (I):



(I)

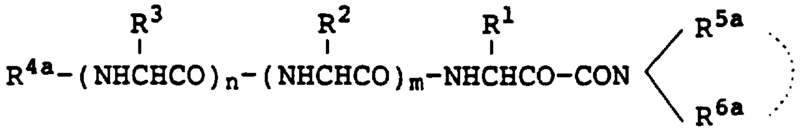
$$R^4\text{-}(\text{NH}\overset{\overset{\displaystyle R^3}{|}}{\text{C}}\text{HCO})_n\text{-}(\text{NH}\overset{\overset{\displaystyle R^2}{|}}{\text{C}}\text{HCO})_m\text{-NH}\overset{\overset{\displaystyle R^1}{|}}{\text{C}}\text{HCO-CON}\left\langle\begin{matrix}R^5\\R^6\end{matrix}\right.$$

wherein R^1, R^2 and R^3 independently represent a hydrogen atom or a hydrocarbon or heterocyclic group that may be substituted; R^4 represents an acyl group or a carboxyl group that may be esterified and R^5 and R^6 independently represent a hydrogen atom or a hydrocarbon or heterocyclic group that may be substituted or R^5 and R^6 may bind together to form a ring; m and n independently represent 0 or 1; or a salt thereof,

(3) A method for inhibiting a cathepsin L activity of a mammal which comprises administering to said mammal a pharmaceutically effective amount of a compound of the formula (Ia) in item (1),

(4) Use of a compound of the formula (Ia) in item (1) for the manufacture of a medicament to be used as a cathepsin L inhibitor,

(5) A compound of the formula (I')



$$R^{4a}\text{-}(\mathrm{NH}\overset{R^3}{\mathrm{C}}\mathrm{HCO})_n\text{-}(\mathrm{NH}\overset{R^2}{\mathrm{C}}\mathrm{HCO})_m\text{-}\mathrm{NH}\overset{R^1}{\mathrm{C}}\mathrm{HCO\text{-}CON}\left\langle\begin{matrix}R^{5a}\\ R^{6a}\end{matrix}\right. \quad (I')$$

wherein R^1, R^2 and R^3 independently represent a hydrogen atom or a hydrocarbon or heterocyclic group that may be substituted; R^{4a} is a group represented by the formula $-COR^a$ or $-SO_2R^b$ wherein R^a and R^b are independently an optionally substituted aryl or aromatic heterocyclic group; R^{5a} and R^{6a} independently represent a straight-chain or branched C_{1-6} alkyl group which may be substituted with an optionally substituted aryl or aromatic heterocyclic group or an optionally esterified carboxyl group and m and n independently represent 0 or 1; provided that where R^a is an optionally substituted aromatic heterocyclic group, R^{5a} and R^{6a} independently represent a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl or aromatic heterocyclic group or an optionally esterified carboxyl group; or a salt thereof,

(6) A compound of item (5), wherein the aryl group for R^a and R^b is naphthyl,

(7) A compound of item (5), wherein the aromatic heterocyclic group for R^a and R^b is quinolyl,

(8) A compound of item (5), wherein one of R^{5a} and R^{6a} is a hydrogen atom and the other is benzyl,

(9) A compound of item (5), wherein R' is a straight-chain or branched C_{1-6} alkyl group which is substituted with a phenyl gorup,

(10) A compound of item (5), wherein R^2 and R^3 are independently a straight-chain or branched C_{1-6} alkyl gorup,

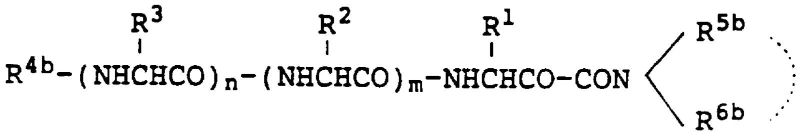
(11) A compound of N-(quinoline-2-carbonyl)-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide, or a salt thereof.

(12) A compound of N-[N-(6-oxo-1,4,5,6-tetrahydropyridazine-3-carbonyl)-L-leucyl]-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide, or a salt thereof,

(13) A compound of N-benzyloxycarbonyl-L-leucyl-L-leucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide, or a salt thereof,

(14) A compound of N-(quinoline-2-carbonyl)-L-leucyl-L-leucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide, or a salt thereof,

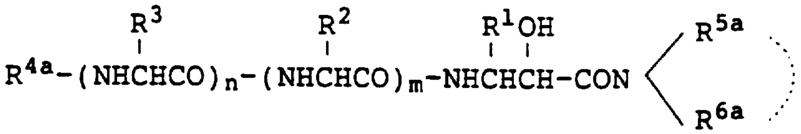
(15) A compound of the formula (I")



$$R^{4b}\text{-}(NH\overset{R^3}{C}HCO)_n\text{-}(NH\overset{R^2}{C}HCO)_m\text{-}NH\overset{R^1}{C}HCO\text{-}CON\left\langle\begin{matrix}R^{5b}\\ \\ R^{6b}\end{matrix}\right. \qquad (I")$$

wherein R^1, R^2 and R^3, whether identical or not, independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted; R^{4b} is represented by the formula $-COR^c$ wherein R^c is a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl or aromatic heterocyclic group; R^{5b} and R^{6b} independently represent a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl group or an esterified carboxyl group; and m and n independently represent 0 or 1, or a salt thereof,

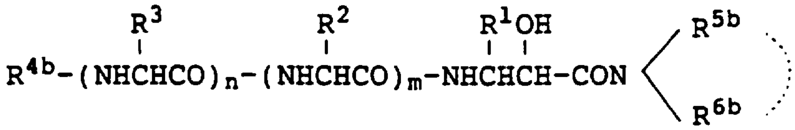
(16) A method of producing a compound of item (5) which comprises subjecting a compound of the formula (II')



$$R^{4a}\text{-}(NH\overset{R^3}{C}HCO)_n\text{-}(NH\overset{R^2}{C}HCO)_m\text{-}NH\overset{R^1}{C}H\overset{OH}{C}H\text{-}CON\left\langle\begin{matrix}R^{5a}\\ \\ R^{6a}\end{matrix}\right. \qquad (II')$$

wherein R^1, R^2 and R^3 independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted; R^{4a} is a group represented by the formula $-COR^a$ or $-SO_2R^b$ wherein R^a and R^b are independently an optionally substituted aryl or aromatic heterocyclic group and R^{5a} and R^{6a} independently represent a straight-chain or branched C_{1-6} alkyl group which may be substituted with an optionally substituted aryl or aromatic heterocyclic group or an optionally esterified carboxyl group; provided that where R^a is an optionally substituted aromatic heterocyclic group and R^{5a} and R^{6a} independently represent a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl or aromatic heterocyclic group or an optionally esterified carboxyl group; or a salt thereof, to an oxidation reaction,

(17) A method of producing a compound of item (15) which comprises subjecting a compound of the formula (II")



$$R^{4b}-(\overset{R^3}{\overset{|}{NHCHCO}})_n-(\overset{R^2}{\overset{|}{NHCHCO}})_m-\overset{R^1\,OH}{\overset{|\;\;|}{NHCHCH}}-CON\left\langle\begin{matrix}R^{5b}\\R^{6b}\end{matrix}\right. \qquad (II'')$$

wherein R^1, R^2 and R^3 independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted; R^{4b} is a group represented by the formula $-COR^c$ wherein R^c is a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl or aromatic heterocyclic group and R^{5b} and R^{6b} independently represent a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl group or an esterified carboxyl group; or a salt thereof, to an oxidation reaction,

(18) A composition which comprises a compound of item (5), and

(19) A composition which comprises a compound of item (15).

The α-ketoamide derivative for the present invention, synthesized by oxidizing a corresponding optically active α-hydroxyamide derivative under easy DMSO oxidization conditions, is an optically active isomer with the S-configuration at β position.

With respect to the above formula (Ia), the amino acid residue for the "1 or 2 amino acid residues that may be substituted," shown by Q, is exemplified by α-amino acids, β-amino acids and γ-amino acids, which are represented by the respective formulas $RCH(NH_2)COOH$, $H_2NCH_2CHRCO_2H$ and $H_2NCH_2CH_2CHRCO_2H$ (R represents a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted), with preference given to α-amino acids. When Q is a dipeptide residue resulting from the binding of 2 amino acids and the 2 amino acids may be of the same type or not, but the residue preferably consists of 2 α-amino acids. When the dipeptide residue consists of 2 amino acids of the same type (e.g., amino acid residue consisting of 2 α-amino acids), the 2 amino acids may be identical or not.

The "hydrocarbon group that may be substituted," shown by R, is exemplified by the same hydrocarbon groups as those exemplifying the "hydrocarbon group that may be substituted," shown by R^1, R^2 or R^3 below.

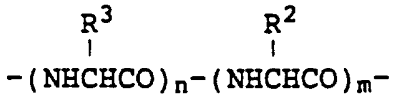
The "heterocyclic group that may be substituted," shown by R, is exemplified by the same heterocyclic groups as those exemplifying the "heterocyclic group that may be substituted," shown by R^1, R^2 or R^3 below.

The substituent for the "hydrocarbon group or heterocyclic group that may be substituted," shown by R, is exemplified by the same substituents as those for the "hydrocarbon group or heterocyclic group that may be substituted," shown by R^1, R^2 or R^3 below.

The above-described α-amino acid residue is exemplified by glycine and natural or non-natural L- or D-α-amino acids. Such amino acids include glycine, and α-L-amino acids or α-D-amino acids (e.g., α-L- or α-D-alanine, valine, leucine, isoleucine, serine, threonine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, cysteine, methionine, phenylalanine, tyrosine, tryptophan, histidine, proline), with preference given to glycine and α-L-alanine, valine, leucine, isoleucine, methionine, phenylalanine, tyrosine, tryptophan etc.

The "1 or 2 amino acid residues that may be substituted," shown by Q, may have 1 to 3 substituents at any possible positions. Such substituents are exemplified by the same substituents for the "hydrocarbon group or heterocyclic group that may be substituted," shown by R^1, R^2 or R^3 below.

Q is preferably a group represented by formula (Ia-Q):



$$-(\mathrm{NH}\overset{\overset{R^3}{|}}{\mathrm{C}}\mathrm{HCO})_n-(\mathrm{NH}\overset{\overset{R^2}{|}}{\mathrm{C}}\mathrm{HCO})_m- \qquad \text{(Ia-Q)}$$

wherein R^2 and R^3, whether identical or not, independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted; m and n, whether identical or not, independently represent 0 or 1.

With respect to the above formulas (I) and (Ia-Q), the "hydrocarbon group that may be substituted," shown by R^1, R^2 or R^3, is exemplified by saturated or unsaturated aliphatic hydrocarbon chain groups, saturated or unsaturated alicyclic hydrocarbon groups and aryl groups.

Such saturated aliphatic hydrocarbon groups include straight or branched saturated aliphatic hydrocarbon groups having 1 to 10 carbon atoms (e.g., C_{1-10} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, tert.-pentyl, hexyl, isohexyl, heptyl and octyl), with preference given to straight or branched saturated aliphatic hydrocarbon groups having 1 to 6 carbon atoms.

Such unsaturated aliphatic hydrocarbon groups include straight or branched unsaturated aliphatic hydrocarbon groups having 2 to 10 carbon atoms (e.g., C_{2-10} alkenyl groups such as ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl and 1-octenyl; C_{2-10} alkinyl groups such as ethynyl, 1-propinyl, 2-propinyl, 1-butinyl, 2-butinyl, 3-butinyl, 1-pentinyl, 2-pentinyl, 3-pentinyl, 4-pentinyl, 1-hexinyl, 3-hexinyl, 2,4-hexadinyl, 5-hexinyl, 1-heptinyl and 1-octinyl), with preference given to straight or branched unsaturated aliphatic hydrocarbon groups having 2 to 6 carbon atoms.

Such saturated alicyclic hydrocarbon groups include saturated alicyclic hydrocarbon groups having 3 to 12 carbon atoms (e.g., C_{3-12} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl and bicyclo[4.3.1]decyl), with preference given to saturated alicyclic hydrocarbon groups having 3 to 6 carbon atoms.

Such unsaturated alicyclic hydrocarbon groups include unsaturated alicyclic hydrocarbon groups having 5 to 12 carbon atoms (e.g., C_{5-12} cycloalkenyl groups such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2,4-cycloheptadienyl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl; C_{5-12} cycloalkadienyl groups such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl).

The "hydrocarbon group that may be substituted," shown by R^1, R^2 or R^3, may be a saturated aliphatic hydrocarbon group having 1 to 8 carbon atoms and substituted with one of the above saturated or unsaturated alicyclic hydrocarbon groups (e.g., C_{3-7} cycloalkyl-C_{1-8} alkyls or C_{5-7}

cycloalkenyl-C_{1-8} alkyls, such as cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl), or the like.

Aryl groups include monocyclic or condensed polycyclic aromatic hydrocarbon ring groups having 6 to 14 carbon atoms. Such aromatic hydrocarbon ring groups include phenyl, tolyl, xylyl, biphenyl, 1- or 2-naphthyl, 1-, 2- or 9-anthryl, 1-, 2-, 3-, 4- or 9-phenanthryl, 1-, 2-, 4-, 5- or 6-azulenyl and acenaphthylenyl, with preference given to C_{6-10} aryl such as phenyl, 1-naphthyl, 2-naphthyl etc.

The "hydrocarbon group that may be substituted," shown by R^1, R^2 or R^3, may have 1 to 3 optionally chosen substituents at any possible positions. Such substituents include aryl groups that may be substituted, cycloalkyl or cycloalkenyl groups that may be substituted, heterocyclic groups that may be substituted, carboxyl groups that may be esterified, carbamoyl groups that may be substituted, amino groups that may be substituted, hydroxyl groups that may be substituted, thiol groups that may be substituted, halogens (e.g., fluorine, chlorine, bromine, iodine) and phosphono groups that may be substituted.

The "aryl group that may be substituted" is exemplified by C_{6-14} aryl such as phenyl, naphthyl, anthryl, phenanthryl and acenaphthylenyl, with preference given to phenyl, 1-naphthyl and 2-naphthyl. Said aryl may have 1 to 2 optionally chosen substituents at any possible positions, these substituents including hydroxy, alkoxy groups that may be substituted (e.g., C_{1-3} alkoxys such as methoxy, ethoxy and propoxy), halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and alkyl groups that may be substituted (e.g., C_{1-3} alkyls such as methyl, ethyl and propyl). These alkoxy groups and alkyl groups may have 1 or 2 optionally chosen substituents at any possible positions, these substituents including phosphono groups that may be substituted (e.g., dimethoxyphosphoryl, diethoxyphosphoryl).

The "cycloalkyl group that may be substituted" is exemplified by C_{3-7} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The kinds and number of substituents for the cycloalkyl group that may be substituted are the same as those of the substituents for the above-described aryl group that may be substituted.

The "cycloalkenyl group that may be substituted" is exemplified by C_{3-6} cycloalkenyl groups such as cyclopropenyl, cyclobutenyl, cyclopentenyl and cyclohexenyl. The kinds and number of substituents for the cycloalkenyl group that may be substituted are the same as those of the substituents for the above-described aryl group that may be substituted.

The "heterocyclic group that may be substituted" is exemplified by aromatic heterocyclic groups having at least 1 hetero atom selected from atoms of oxygen, sulfur and nitrogen as a ring-constituting atom (ring atom), and saturated or unsaturated non-aromatic heterocyclic groups (aliphatic heterocyclic groups), with preference given to aromatic heterocyclic groups. The aromatic heterocyclic group is exemplified by 5- to 7-membered aromatic heterocyclic groups containing 1 atom of sulfur, nitrogen or oxygen, 5- to 6-membered aromatic heterocyclic groups containing 2 to 4 atoms of nitrogen and 5- or 6-membered aromatic heterocyclic groups containing 1 or 2 atoms of nitrogen and 1 atom of sulfur or oxygen. These aromatic heterocyclic groups may have condensed with a 6-membered ring containing 2 or fewer atoms of nitrogen, a benzene ring or a 5-membered ring containing 1 atom of sulfur. Such aromatic heterocyclic groups include aromatic monocyclic heterocyclic groups (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl) and aromatic condensed heterocyclic groups (e.g., benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl), with preference given to quinolyl, isoquinolyl, furyl, thienyl, indolyl, isoindolyl, imidazolyl, pyrazinyl, pyridyl, pyrimidinyl etc. The non-aromatic heterocyclic group is exemplified by 5- to 7-membered non-aromatic heterocyclic groups containing 1 atom of sulfur, nitrogen or oxygen, and 4- to 7-membered non-aromatic heterocyclic groups containing 1 atom of nitrogen and 3 or fewer atoms selected from nitrogen, oxygen and sulfur. Such non-aromatic heterocyclic groups include oxylanyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperizyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl and piperazinyl. The substituent for said heterocyclic group that may be substituted is exemplified by alkyl groups having 1 to 3 carbon atoms (e.g., methyl, ethyl, propyl).

The carboxyl groups that may be esterified include -COOH, (lower(C_{1-6})alkoxy)carbonyls (e.g., methoxycarbonyl,

ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.-butoxycarbonyl, sec.-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, neopentyloxycarbonyl, tert.-pentyloxycarbonyl) and (C_{6-10} aryloxy)carbonyls (e.g., phenoxycarbonyl, 1-naphthoxycarbonyl), (C_{7-13} aralkyloxy)carbonyls (e.g., benzyloxycarbonyl), with preference given to the carboxyl group, methoxycarbonyl and ethoxycarbonyl.

The substituent for said carbamoyl group that may be substituted is exemplified by lower (C_{1-6}) alkyls (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl), C_{3-6} cycloalkyl groups (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), C_{6-10} aryl groups (e.g., phenyl, 1-naphthyl, 2-naphthyl) and C_{7-13} aralkyl groups (e.g., benzyl, phenethyl); 1 or 2 of these substituents, whether identical or not, may be present.

The substituent for said amino group that may be substituted is exemplified by lower (C_{1-6}) alkyls (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl), C_{3-6} cycloalkyl groups (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), C_{6-10} aryl groups (e.g., phenyl, 1-naphthyl, 2-naphthyl) and C_{7-13} aralkyl groups (e.g., benzyl, phenethyl); 1 or 2 of these substituents, whether identical or not, may be present.

The substituent for said hydroxyl group that may be substituted is exemplified by lower (C_{1-6}) alkyls (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl), C_{3-6} cycloalkyl groups (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), C_{6-10} aryl groups (e.g., phenyl, 1-naphthyl, 2-naphthyl) and C_{7-13} aralkyl groups (e.g., benzyl, phenethyl).

The substituent for said thiol group that may be substituted is exemplified by lower (C_{1-6}) alkyls (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl), C_{3-6} cycloalkyl groups (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), C_{6-10} aryl groups (e.g., phenyl, 1-naphthyl, 2-naphthyl) and C_{7-13} aralkyl groups (e.g., benzyl, phenethyl).

The substituent for said phosphono group that may be substituted is exemplified by lower (C_{1-6}) alkyls (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl), lower (C_{1-6}) alkoxys (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, tert.-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, isohexyloxy). Said phosphons groups include phosphoryl, dimethoxyphosphoryl, diethoxyphosphoryl, dipropoxyphosphoryl, diisopropoxyphosphoryl, ethylenedioxyphosphoryl, trimethylenedioxyphosphoryl and tetramethylenedioxyphosphoryl.

When the "hydrocarbon group that may be substituted," shown by R^1, R^2 or R^3, is an alicyclic hydrocarbon group or an aryl group, the substituent may be an aliphatic hydrocarbon group that may be substituted. Such aliphatic hydrocarbon groups include the same saturated or unsaturated (preferably saturated) aliphatic hydrocarbon groups as those exemplifying the "hydrocarbon group that may be substituted," shown by R^1, R^2 or R^3 above, with preference given to alkyl groups (e.g., C_{1-3} alkyls such as methyl, ethyl and propyl). The aliphatic hydrocarbon group may have 1 or 2 optionally chosen substituents at any possible positions, these substituents including phosphono groups that may be substituted (e.g., phosphoryl, dimethoxyphosphoryl, diethoxyphosphoryl).

The "heterocyclic group that may be substituted," shown by R^1, R^2 or R^3, is exemplified by aromatic heterocyclic groups having at least 1 hetero atom selected from atoms of oxygen, sulfur and nitrogen as a ring-constituting atom (ring atom), and saturated or unsaturated non-aromatic heterocyclic groups (aliphatic heterocyclic groups), with preference given to aromatic heterocyclic groups.

Such aromatic heterocyclic groups are exemplified by 5- to 7-membered heterocyclic groups containing 1 atom of sulfur, nitrogen or oxygen, 5- to 6-membered heterocyclic groups containing 2 to 4 atoms of nitrogen and 5- or 6-membered aromatic heterocyclic groups containing 1 or 2 atoms of nitrogen and 1 atom of sulfur or oxygen. These aromatic heterocyclic groups may have condensed with a 6-membered ring containing 2 or fewer atoms of nitrogen, a benzene ring or a 5-membered ring containing 1 atom of sulfur. Such aromatic heterocyclic groups include aromatic monocyclic heterocyclic groups (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4-, 5- or 6-pyrimidinyl, 2-pyrazinyl, triazinyl) and aromatic condensed heterocyclic groups (e.g., benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl), with preference given to quinolyl, isoquinolyl, furyl, thienyl, imidazolyl, indolyl, isoindolyl, pyrazinyl, pyridyl, pyrimidinyl etc.

Such non-aromatic heterocyclic groups are exemplified by 5- to 7-membered non-aromatic heterocyclic groups containing 1 atom of sulfur, nitrogen or oxygen, and 4- to 7-membered non-aromatic heterocyclic groups containing 1 atom of nitrogen and 3 or fewer atoms selected from nitrogen, oxygen and sulfur (e.g., oxylanyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, homopiperidyl, pyrrolinyl, imidazolidinyl). These non-aromatic heterocyclic groups may condense with a benzene ring, a 6-membered ring containing 2 or fewer atoms of nitrogen, or a 5-membered ring containing 1 atom of sulfur. Specifically, such condensed non-aromatic heterocyclic groups include chromanyl, isochromanyl, indolinyl, isoindolinyl, thiochromanyl and isothiochromanyl.

The "heterocyclic group that may be substituted," shown by R^1, R^2 or R^3, may have 1 to 3 optionally chosen substituents at any possible positions. Such substituents include aryl groups that may be substituted, cycloalkyl or cycloalkenyl groups that may be substituted, heterocyclic groups that may be substituted, carboxyl groups that may be esterified, carbamoyl groups that may be substituted, amino groups that may be substituted, hydroxyl groups that may be substituted, thiol groups that may be substituted, halogens (e.g., fluorine, chlorine, bromine, iodine), phosphono groups that may be substituted, and aliphatic hydrocarbon groups that may be substituted.

Said aryl groups that may be substituted, cycloalkyl or cycloalkenyl groups that may be substituted, heterocyclic groups that may be substituted, carboxyl groups that may be esterified, carbamoyl groups that may be substituted, amino groups that may be substituted, hydroxyl groups that may be substituted, thiol groups that may be substituted, halogens (e.g., fluorine, chlorine, bromine, iodine), phosphono groups that may be substituted, and aliphatic hydrocarbon groups that may be substituted are exemplified by the same substituents as those for the "hydrocarbon group that may be substituted," shown by R^1, R^2 or R^3 above.

The "hydrocarbon group that may be substituted," shown by R^1, R^2 or R^3 above, is exemplified by alkyl groups, preferably C_{1-10} alkyls, with greater preference given to linear or branched lower alkyls having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, tert.-pentyl, hexyl, isohexyl, 4-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl). Preferable substituents for the "hydrocarbon group that may be substituted" are aryls that may be substituted (preferably phenyl etc.) and heterocyclic groups that may be substituted.

R^1 is preferably an alkyl group substituted with an optionally substituted aryl or heterocyclic group.

More preferably, R^1 is an alkyl group substituted with an aryl or heterocyclic group. Said alkyl substituted with an aryl is exemplified by groups resulting from binding of a monocyclic or condensed polycyclic aromatic hydrocarbon group having 6 to 14 carbon atoms (e.g., phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl) and a lower alkyl having 1 to 6 carbon atoms (preferably C_{1-4} alkyl) (e.g., benzyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, 1-phenylpropyl, α-naphthylmethyl, α-naphthylethyl, β-naphthylmethyl, β-naphthylethyl). Said alkyl substituted with a heterocyclic group is exemplified by groups resulting from binding of an aromatic heterocyclic group and a lower alkyl having 1 to 6 carbon atoms (preferably C_{1-4} alkyl group). Such aromatic heterocyclic groups include 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-

pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazolyl, benz[b]furanyl, isobenzofuranyl, benz[b]thienyl, 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl and 1H-imidazo[4,5-b]pyrazin-2-yl, with preference given to 2-pyridyl, 3-pyridyl, 4-pyridyl, 4-imidazolyl, 2-thienyl, 2-furyl, indol-3-yl etc.

R^1 is more preferably a straight-chain or branched C_{1-6} alkyl group which is substituted with phenyl.

More preferably, R^2 and R^3 are independently a straight-chain or branched C_{1-6} alkyl.

R^1 is preferably indol-3-ylmethyl, benzyl, methyl, isopropyl, 1-naphthylmethyl, or the like.

R^2 and R^3, whether identical or not, are preferably sec.-butyl, benzyl, isobutyl, isopropyl, or the like.

With respect to the combination of R^1 and R^2, it is preferable that R^1 be indol-3-ylmethyl, benzyl, methyl, isopropyl or 1-naphthylmethyl and R^2 be sec.-butyl, benzyl, isobutyl or isopropyl.

With respect to the combination of R^1, R^2 and R^3, it is preferable that R^1 be indol-3-ylmethyl, benzyl, methyl, isopropyl or 1-naphthylmethyl, R^2 be sec.-butyl, benzyl, isobutyl or isopropyl, and R^3 be sec.-butyl, benzyl, isobutyl or isopropyl.

With respect to formula (I), the "acyl group" shown by R^4 is exemplified by acyl groups derived from carbamic acids that may be substituted, thiocarbamic acids that may be substituted, carboxylic acids that may be substituted, sulfinic acids that may be substituted, sulfonic acids that may be substituted, etc., specifically those represented by the respective general formulas -CONHR^7, -CSNHR^8, -COR^9, -SOR^{10}, -SO$_2$R^{11} (R^7, R^8, R^9, R^{10} and R^{11}, whether identical or not, independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted) etc.

The "hydrocarbon group that may be substituted," shown by R^7, R^8, R^9, R^{10} or R^{11}, is exemplified by the same hydrocarbon groups as those exemplifying the "hydrocarbon group that may be substituted," shown by R^1, R^2 or R^3 above.

The "hydrocarbon group that may be substituted for," shown by R^7, R^8, R^9, R^{10} or R^{11}, may have 1 to 3 optionally chosen substituents at any possible positions, these substituents being exemplified by the same substituents as those defined for the "hydrocarbon group that may be substituted," shown by R^1, R^2 or R^3 above.

The "heterocyclic group that may be substituted," shown by R^7, R^8, R^9, R^{10} or R^{11}, is exemplified by the same heterocyclic groups as those for the "heterocyclic group that may be substituted," shown by R^1, R^2 or R^3 above.

The "heterocyclic group that may be substituted," shown by R^7, R^8, R^9, R^{10} or R^{11}, may have 1 to 3 optionally chosen substituents at any possible positions, these substituents being exemplified by the same substituents as those defined for the "heterocyclic group that may be substituted," shown by R^1, R^2 or R^3 above.

The "acyl group" shown by R^4 is exemplified by aliphatic acyl groups such as alkanoyl groups (e.g., (lower C$_{1-6}$ alkyl)carbonyl groups such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl and hexanoyl), alkenoyl groups (e.g., (lower C$_{2-6}$ alkenyl)carbonyl groups such as acryloyl, methacryloyl, crotonoyl and isocrotonoyl), cycloalkanecarbonyl groups (e.g., (C$_{3-6}$ cycloalkyl)carbonyl groups such as cyclopropanecarbonyl, cyclobutanecarbonyl, cyclopentanecarbonyl and cyclohexanecarbonyl), (C$_{3-7}$

cycloalkenyl)carbonyl groups (e.g., cyclopropenylcarbonyl, cyclobutenylcarbonyl, cyclopentenylcarbonyl, cyclohexenylcarbonyl) and alkanesulfonyl groups (e.g., (lower C_{1-6} alkyl)sulfonyl groups such as mesyl, ethanesulfonyl and propanesulfonyl); aromatic acyl groups such as aroyl groups (e.g., (C_{6-10} aryl)carbonyl groups such as benzoyl, p-toluoyl, 1-naphthoyl and 2-naphthoyl), arylalkanoyl groups (e.g., (C_{1-6} alkyl)carbonyl groups substituted with C_{6-10} aryl groups, such as phenylacetyl, phenylpropionyl, hydroatropoyl and phenylbutyryl), arylalkenoyl groups (e.g., (C_{2-6} alkenyl)carbonyl groups substituted with C_{6-10} aryl groups, such as cinnamoyl and atropoyl) and C_{6-10} arylsulfonyl groups (e.g., benzenesulfonyl group, p-toluenesulfonyl group); and aromatic acyl groups such as aromatic heterocyclic carbonyl groups (e.g., furoyl, thenoyl, nicotinoyl, isonicotinoyl, pyrrolcarbonyl, oxazolcarbonyl, imidazolcarbonyl and pyrazolcarbonyl), aromatic heterocyclic alkanoyl groups (e.g., (C_{1-6} alkyl)carbonyl groups substituted with aromatic heterocyclic groups, such as thienylacetyl, thienylpropanoyl, furylacetyl, thiazolylacetyl, 1,2,4-thiadiazolylacetyl and pyridylacetyl).

Of the above-mentioned acyl groups for R^4, those represented by the formula $-COR^9$ or $-SO_2R^{11}$ are preferable.

The groups of the formula $-COR^9$ are preferably represented by the formula $-COR^a$ (R^a is an optionally substituted aryl or aromatic heterocyclic group) or the formula $-COR^c$ (R^c is a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl or aromatic heterocyclic group).

The "optionally substituted aryl group" shown by R^a is exemplified by C_{6-10} aryl such as phenyl, 1-naphthyl, 2-naphthyl.

The "optionally substituted aromatic heterocyclic group" shown by R^a is exemplified by quinolyl, isoquinolyl, furyl, thienyl, indolyl, isoindolyl, pyrazinyl and pyridyl, with preference given to quinolyl, isoquinolyl.

The "optionally substituted aryl or aromatic heterocyclic group" shown by R^a may have one or more optionally chosen substituents at any possible position, these substituents being exemplified by C_{1-3} alkyls (e.g. methyl, ethyl, propyl), hydroxy, C_{1-3} alkoxys (e.g. methoxy, ethoxy, propoxy) and halogens (e.g. fluorine, chlorine, bromine).

The "straight-chain or branched C_{1-6} alkyl group" shown by R^c includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, tert.-pentyl, hexyl, isohexyl.

The "straight-chain or branched C_{1-6} alkyl group" shown by R^c has one or more (preferably one or two) substituents such as an optionally substituted aryl or aromatic heterocyclic group. Said optionally substituted aryl or aromatic heterocyclic group is exemplified by the same "optionally substituted aryl or aromatic heterocyclic group" as defined in R^a.

R^c is more preferably a straight-chain or branched C_{1-4} alkyl group which has one or two optionally substituted aryl (preferably phenyl) groups.

The group of the formula $-SO_2R^{11}$ is preferably represented by the formula $-SO_2R^b$ (R^b is an optionally substituted aryl or aromatic heterocyclic group).

The "optionally substituted aryl or aromatic heterocyclic group" shown by R^b is exemplified by the same "optionally substituted aryl or aromatic heterocyclic group" as defined in R^a.

R^b is more preferably an optionally substituted aryl group.

The "aryl group that may be substituted," shown by R^b, is exemplified by C_{6-14} aryl group such as phenyl, 1-naphthyl and 2-naphthyl. Said aryl group may have 1 or 2 optionally chosen substituents at any possible positions, these substituents including alkyl groups (e.g., C_{1-3} alkyls such as methyl, ethyl and propyl).

The "carboxyl group that may be esterified" shown by R^4 is exemplified by the groups represented by the general formula $-COOR^{12}$ (R^{12} represents a hydrogen atom, a C_{1-6} alkyl, a C_{2-6} alkenyl, a C_{6-10} aralkyl, or the like). For example, groups resulting from binding of a carboxyl group and an alkyl group having 1 to 6 carbon atoms include C_{1-6} alkoxycarbonyls (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec.-butoxycarbonyl, tert.-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl); groups resulting from binding of a carboxyl group and an alkenyl group having 2 to 6 carbon atoms include C_{2-6} alkenyloxycarbonyls (e.g., allyloxycarbonyl, crotyloxycarbonyl, 2-pentenyloxycarbonyl, 3-hexenyloxycarbonyl); the groups resulting from binding of a carboxyl group and an aralkyl group having 7 to 10 carbon atoms include C_{7-10} aralkyloxycarbonyls (e.g., benzyloxycarbonyl, phenethyloxycarbonyl).

With respect to the above formula (I), the "hydrocarbon group that may be substituted," shown by R^5 or R^6, is exemplified by saturated or unsaturated aliphatic chain hydrocarbon groups, saturated or unsaturated alicyclic hydrocarbon groups and aryl groups.

Such saturated aliphatic hydrocarbon groups include straight or branched saturated aliphatic hydrocarbon groups having 1 to 10 carbon atoms (e.g., C_{1-10} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, tert.-pentyl, hexyl, isohexyl, heptyl and octyl), with preference given to straight or branched saturated aliphatic hydrocarbon groups having 1 to 6 carbon atoms.

Such unsaturated aliphatic hydrocarbon groups include straight or branched unsaturated aliphatic hydrocarbon groups having 2 to 10 carbon atoms (e.g., C_{2-10} alkenyl groups such as ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl and 1-octenyl; C_{2-10} alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadynyl, 5-hexynyl, 1-heptynyl and 1-octynyl), with preference given to straight or branched unsaturated aliphatic hydrocarbon groups having 2 to 6 carbon atoms.

Such saturated alicyclic hydrocarbon groups include saturated alicyclic hydrocarbon groups having 3 to 12 carbon atoms (e.g., C_{3-12} cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl and bicyclo[4.3.1]decyl), with preference given to saturated alicyclic hydrocarbon groups having 3 to 6 carbon atoms.

Such unsaturated alicyclic hydrocarbon groups include unsaturated alicyclic hydrocarbon groups having 5 to 12 carbon atoms (e.g., C_{5-12} cycloalkenyl groups such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2,4-cycloheptadienyl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl; C_{5-12} cycloalkadienyl groups such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl).

The "hydrocarbon group that may be substituted," shown by R^5 or R^6, may be a saturated aliphatic hydrocarbon group having 1 to 8 carbon atoms and substituted with one of the above saturated or unsaturated alicyclic hydrocarbon groups (e.g., C_{3-7} cycloalkyl-C_{1-8} alkyls or C_{5-7} cycloalkenyl-C_{1-8}

alkyls, such as cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl), or the like.

Aryl groups include monocyclic or condensed polycyclic aromatic hydrocarbon ring groups having 6 to 14 carbon atoms. Such aromatic hydrocarbon ring groups include phenyl, tolyl, xylyl, biphenyl, 1- or 2-naphthyl, 1-, 2- or 9-anthryl, 1-, 2-, 3-, 4- or 9-phenanthryl, 1-, 2-, 4-, 5- or 6-azulenyl and acenaphthylenyl, with preference given to C_{6-10} aryl such as phenyl, 1-naphthyl and 2-naphthyl.

The "hydrocarbon group that may be substituted," shown by R^5 or R^6, may have 1 to 3 optionally chosen substituents at any possible positions. Such substituents include aryl groups that may be substituted, cycloalkyl or cycloalkenyl groups that may be substituted, heterocyclic groups that may be substituted, carboxyl groups that may be esterified, carbamoyl groups that may be substituted, amino groups that may be substituted, hydroxyl groups that may be substituted, thiol groups that may be substituted for, halogens (e.g., fluorine, chlorine, bromine, iodine) and phosphono groups that may be substituted.

The "aryl group that may be substituted" is exemplified by C_{6-14} aryl such as phenyl, naphthyl, anthryl, phenanthryl and acenaphthylenyl, with preference given to phenyl, 1-naphthyl and 2-naphthyl. Said aryl may have 1 to 2 optionally chosen substituents at any possible positions, these substituents including hydroxy, alkoxy groups that may be substituted (e.g., C_{1-3} alkoxys such as methoxy, ethoxy and propoxy), halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and alkyl groups that may be substituted (e.g., C_{1-3} alkyls such as methyl, ethyl and propyl). These alkoxy groups and alkyl groups may each have 1 to 2 optionally chosen substituents at any possible positions, these substituents including phosphono groups that may be substituted (e.g., dimethoxyphosphoryl, diethoxyphosphoryl).

The "cycloalkyl group that may be substituted" is exemplified by C_{3-7} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The kinds and number of substituents for the cycloalkyl group that may be substituted are the same as those of the substituents for the above-described aryl group that may be substituted.

The "cycloalkenyl group that may be substituted" is exemplified by C_{3-6} cycloalkenyl groups such as cyclopropenyl, cyclobutenyl, cyclopentenyl and cyclohexenyl. The kinds and number of substituents for the cycloalkenyl group that may be substituted are the same as those of the substituents for the above-described aryl group that may be substituted.

The "heterocyclic group that may be substituted" is exemplified by aromatic heterocyclic groups having at least 1 hetero atom selected from atoms of oxygen, sulfur and nitrogen as a ring-constituting atom (ring atom), and saturated or unsaturated non-aromatic heterocyclic groups (aliphatic heterocyclic groups), with preference given to aromatic heterocyclic groups. The aromatic heterocyclic group is exemplified by 5- to 7-membered aromatic heterocyclic groups containing 1 atom of sulfur, nitrogen or oxygen, 5- to 6-membered aromatic heterocyclic groups containing 2 to 4 atoms of nitrogen and 5- or 6-membered aromatic heterocyclic groups containing 1 to 2 atoms of nitrogen and 1 atom of sulfur or oxygen. These aromatic heterocyclic groups may be condensed with a 6-membered ring containing 2 or fewer atoms of nitrogen, a benzene ring or a 5-membered ring containing 1 atom of sulfur. Such aromatic heterocyclic groups include aromatic monocyclic heterocyclic groups (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl) and aromatic condensed heterocyclic groups (e.g., benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl), with preference given to quinolyl, isoquinolyl, furyl, thienyl, indolyl, isoindolyl, pyrazinyl, pyridyl, pyrimidinyl etc. The non-aromatic heterocyclic group is exemplified by 5- to 7-membered non-aromatic heterocyclic groups containing 1 atom of sulfur, nitrogen or oxygen, and 4- to 7-membered non-aromatic heterocyclic groups containing 1 atom of nitrogen and 3 or fewer atoms selected from nitrogen, oxygen and sulfur. Such non-aromatic heterocyclic groups include oxylanyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperizyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl and piperazinyl. The substituent for said heterocyclic group that may be substituted is exemplified by alkyl groups having 1 to 3 carbon atoms (e.g., methyl, ethyl, propyl).

Such carboxyls that may be esterified include -COOH, (lower C_{1-6} alkoxy)carbonyls (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.-butoxycarbonyl, sec.-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, neopentyloxycarbonyl, tert.-pentyloxycarbonyl) and (C_{6-10} aryloxy)carbonyls (e.g., phenoxycarbonyl, 1-naphthoxycarbonyl), (C_{7-13} aralkyloxy)carbonyls (e.g., benzyloxycarbonyl), (e.g., with preference given to the carboxyl group, methoxycarbonyl and ethoxycarbonyl.

The substituent for said carbamoyl group that may be substituted is exemplified by lower (C_{1-6}) alkyls that may be substituted (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl), C_{3-6} cycloalkyl groups that may be substituted (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), C_{6-10} aryl groups that may be substituted (e.g., phenyl, 1-naphthyl, 2-naphthyl) and C_{7-13} aralkyl groups that may be substituted (e.g., benzyl, phenethyl); 1 or 2 of these substituents, whether identical or not, may be present. The substituent for said lower (C_{1-6}) alkyl that may be substituted and C_{3-6} cycloalkyl group that may be substituted is exemplified by carboxyl groups that may be esterified, aromatic heterocyclic groups (e.g., furyl, thienyl, indolyl, isoindolyl, pyrazinyl, pyridyl, pyrimidinyl, imidazolyl), amino groups, hydroxyl groups and phenyl groups. The substituent for said aryl group that may be substituted and aralkyl group that may be substituted is exemplified by halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and carboxyl groups that may be esterified. Also, 2 substituents on the nitrogen atom may cooperate with the nitrogen atom to form a cyclic amino group, such cyclic amino groups including 1-azetidinyl, 1-pyrrolidinyl, piperidino, morpholino and 1-piperazinyl.

The substituent for said amino group that may be substituted is exemplified by lower (C_{1-6}) alkyls that may be substituted for (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl), C_{3-6} cycloalkyl groups that may be substituted (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), C_{6-10} aryl groups that may be substituted (e.g., phenyl, 1-naphthyl, 2-naphthyl) and C_{7-13} aralkyl groups that may be substituted (e.g., benzyl, phenethyl); 1 or 2 of these substituents, whether identical or not, may be present. The substituent for said lower (C_{1-6}) alkyl that may be substituted and C_{3-6} cycloalkyl group that may be substituted is exemplified by carboxyl groups that may be esterified, aromatic heterocyclic groups (e.g., furyl, thienyl, indolyl, isoindolyl, pyrazinyl, pyridyl, pyrimidyl, imidazolyl), amino groups, hydroxyl groups and phenyl groups. The substituent for said aryl group that may be substituted and aralkyl group that may be substituted is exemplified by halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and carboxyl groups that may be esterified. Also, 2 substituents on the nitrogen atom may cooperate with the nitrogen atom to form a cyclic amino group, such cyclic amino groups including 1-azetidinyl, 1-pyrrolidinyl, piperidino, morpholino and 1-piperazinyl.

The substituent for said hydroxyl group that may be substituted is exemplified by lower (C_{1-6}) alkyls that may be substituted (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl), C_{3-6} cycloalkyl groups that may be substituted (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), C_{6-10} aryl groups that may be substituted (e.g., phenyl, 1-naphthyl, 2-naphthyl) and C_{7-13} aralkyl groups that may be substituted (e.g., benzyl, phenethyl).

The substituent for said thiol group that may be substituted is exemplified by lower (C_{1-6}) alkyls that may be substituted (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl), C_{3-6} cycloalkyl groups that may be substituted (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), C_{6-10} aryl groups that may be substituted for (e.g., phenyl, 1-naphthyl, 2-naphthyl) and C_{7-13} aralkyl groups that may be substituted (e.g., benzyl, phenethyl).

The substituent for said phosphono group that may be substituted is exemplified by lower (C_{1-6}) alkyls (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl), lower (C_{1-6}) alkoxys (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec.-butoxy, tert.-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, isohexyloxy). Said phosphono groups include phosphoryl, dimethoxyphosphoryl, diethoxyphosphoryl, dipropoxyphosphoryl, diisopropoxyphosphoryl, ethylenedioxyphosphoryl, trimethylenedioxyphosphoryl and tetramethylenedioxyphosphoryl.

When the "hydrocarbon group that may be substituted," shown by R^5 or R^6, is an alicyclic hydrocarbon group or an aryl group, the substituent may be an aliphatic hydrocarbon group that may be substituted. Said aliphatic hydrocarbon group is exemplified by the same saturated or unsaturated (preferably saturated) aliphatic hydrocarbon groups as those exemplifying the "hydrocarbon group that may be substituted," shown by R^5 or R^6 above, with preference given to alkyl groups (e.g., C_{1-3} alkyls such as methyl, ethyl and propyl). The aliphatic hydrocarbon group may have 1 or 2 optionally chosen substituents at any possible positions, these substituents including phosphono groups that may be substituted (e.g., phosphoryl, dimethoxyphosphoryl, diethoxyphosphoryl).

The "heterocyclic group that may be substituted," shown by R^5 or R^6, is exemplified by aromatic heterocyclic groups having at least 1 hetero atom selected from atoms of oxygen, sulfur and nitrogen as a ring-constituting atom (ring atom), and saturated or unsaturated non-aromatic heterocyclic groups (aliphatic heterocyclic groups), with preference given to aromatic heterocyclic groups.

Such aromatic heterocyclic groups are exemplified by 5- to 7-membered heterocyclic groups containing 1 atom of sulfur, nitrogen or oxygen, 5- to 6-membered heterocyclic groups containing 2 to 4 atoms of nitrogen and 5- or 6-membered aromatic heterocyclic groups containing 1 or 2 atoms of nitrogen and 1 atom of sulfur or oxygen. These aromatic heterocyclic groups may have condensed with a 6-membered ring containing 2 or fewer atoms of nitrogen, a benzene ring or a 5-membered ring containing 1 atom of sulfur. Such aromatic heterocyclic groups include aromatic monocyclic heterocyclic groups (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4-, 5- or 6-pyrimidinyl, 2-pyrazinyl, triazinyl) and aromatic condensed heterocyclic groups (e.g., benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenathridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl), with preference given to quinolyl, isoquinolyl, furyl, thienyl, indolyl, isoindolyl, pyrazinyl, pyridyl, pyrimidinyl etc.

Such non-aromatic heterocyclic groups are exemplified by 5- to 7-membered non-aromatic heterocyclic groups containing 1 atom of sulfur, nitrogen or oxygen, and 4 - to 7-membered non-aromatic heterocyclic groups containing 1 atom of nitrogen and 3 or fewer atoms selected from nitrogen, oxygen and sulfur (e.g., oxylanyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperizyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, homopiperidyl, pyrrolinyl, imidazolidinyl). These non-aromatic heterocyclic groups may be condensed with a benzene ring, a 6-membered ring containing 2 or fewer atoms of nitrogen, or a 5-membered ring containing 1 atom of sulfur. Specifically, such condensed non-aromatic heterocyclic groups include chromanyl, isochromanyl, indolinyl, isoindolinyl, thiochromanyl and isothiochromanyl.

The "heterocyclic group that may be substituted," shown by R^5 or R^6, may have 1 to 3 optionally chosen substituents at any possible positions. Such substituents include aryl groups that may be substituted, cycloalkyl or cycloalkenyl groups that may be substituted, heterocyclic groups that may be substituted, carboxyl groups that may be esterified, carbamoyl groups that may be substituted, amino groups that may be substituted, hydroxyl groups that may be substituted, thiol groups that may be substituted, halogens (e.g., fluorine, chlorine, bromine, iodine), phosphono groups that may be substituted, and aliphatic hydrocarbon groups that may be substituted.

Said aryl groups that may be substituted, cycloalkyl or cycloalkenyl groups that may be substituted, heterocyclic groups that may be substituted for, carboxyl groups that may be esterified, carbamoyl groups that may be substituted, amino groups that may be substituted for, hydroxyl groups that may be substituted, thiol groups that may be substituted, halogens (e.g., fluorine, chlorine, bromine, iodine), phosphono groups that may be substituted, and aliphatic hydrocarbon groups that may be substituted are exemplified by the same substituents as those for the "hydrocarbon group that may be substituted," shown by R^5 and R^6 above.

R^5 and R^6, in cooperation with the adjoining nitrogen atom, may bind together to form a heterocyclic ring that may contain 1 more hetero atom (e.g., oxygen, nitrogen, sulfur), such heterocyclic groups including 1-azetidinyl, 1-pyrrolidinyl, piperidino, morpholino, 1-piperazinyl and 1-homopiperazinyl. These heterocyclic groups may each have 1 or 2 substituents at any possible positions, these substituents including alkyls (e.g., C_{1-3} alkyls), carboxyl groups and hydroxyl groups.

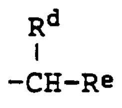
The "hydrocarbon group that may be substituted," shown by R^5 or R^6 above, is exemplified by alkyl groups, preferably C_{1-10} alkyls, with greater preference given to straight or branched lower alkyls having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, tert.-pentyl, hexyl, isohexyl, 4-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl) etc. Preferable substituents for the "hydrocarbon group that may be substituted" are aryls that may be substituted (preferably phenyl etc.), heterocyclic groups that may be substituted and carboxyl groups that may be esterified.

More preferably, the "hydrocarbon group that may be substituted," shown by R^5 and R^6, is an alkyl group substituted with an aryl or heterocyclic group. Said alkyl substituted with an aryl is exemplified by groups resulting from binding of a monocyclic or condensed polycyclic aromatic hydrocarbon group having 6 to 14 carbon atoms (e.g., phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl) and a lower alkyl having 1 to 6 carbon atoms (preferably C_{1-4} alkyl) (e.g., benzyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, 1-phenylpropyl, α-

naphthylmethyl, α-naphthylethyl, β-naphthylmethyl, β-naphthylethyl). Said alkyl substituted with a heterocyclic group is exemplified by groups resulting from binding of an aromatic heterocyclic group and a lower alkyl having 1 to 6 carbon atoms (preferably C_{1-4} alkyl group). Such aromatic heterocyclic groups include 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazolyl, benz[b]furanyl, isobenzofuranyl, benz[b]thienyl, 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl and 1H-imidazo[4,5-b]pyrazin-2-yl, with preference given to 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and 4-imidazolyl etc.

With respect to the combination of R^5 and R^6, it is preferable that one be a hydrogen atom, and the other be sec.-butyl, benzyl, isobutyl or isopropyl, with preference given to benzyl.

When one of R^5 and R^6 is a hydrogen atom, the other is exemplified by a group represented by formula (Ia-aa):



$$-\underset{}{\overset{R^d}{\overset{|}{C}}}H-R^e \qquad \text{(Ia-aa)}$$

wherein R^d represents a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted; R^e represents a carboxyl group that may be esterified or a carbamoyl group that may be substituted.

With respect to formula (Ia-aa), the "hydrocarbon group that may be substituted," shown by R^d, is exemplified by the same hydrocarbon groups as those for the "hydrocarbon group that may be substituted," shown by R^1, R^2 or R^3 above.

The "hydrocarbon group that may be substituted," shown by R^d, may have 1 to 3 optionally chosen substituents at any possible positions, these substituents being exemplified by the same substituents as those for the "hydrocarbon group that may be substituted," shown by R^1, R^2 or R^3 above.

With respect to formula (Ia-aa), the "heterocyclic group that may be substituted," shown by R^d, is exemplified by the same heterocyclic groups exemplifying the "heterocyclic group that may be substituted," shown by R^1, R^2 or R^3 above.

The "heterocyclic group that may be substituted," shown by R^d, may have 1 to 3 optionally chosen substituents at any possible positions, these substituents being exemplified by the same substituents as those for the "heterocyclic group that may be substituted," shown by R^1, R^2 or R^3 above.

The "hydrocarbon group that may be substituted for," shown by R^d, is exemplified by alkyl groups, preferably C_{1-10} alkyl, with greater preference given to linear or branched lower alkyls having 1 to 6 carbon atoms (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, tert.-pentyl, hexyl, isohexyl, 4-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl). Preferable substituents for the "hydrocarbon group that may be substituted" are aryls that may be substituted (preferably phenyl etc.), heterocyclic rings that may be substituted, and carboxyl groups that may be esterified.

With respect to formula (Ia-aa), the "carboxyl group that may be esterified" shown by R^e, is exemplified by carboxy, (lower C_{1-6} alkoxy)carbonyls (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.-butoxycarbonyl, sec.-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, neopentyloxycarbonyl, tert.-pentyloxycarbonyl) and (C_{6-10} aryloxy)carbonyls (e.g., phenoxycarbonyl, 1-naphthoxycarbonyl), (C_{7-13} aralkyloxy)carbonyls (e.g.,benzyloxycarbonyl), with preference given to the carboxyl group, methoxycarbonyl and ethoxycarbonyl.

With respect to formula (Ia-aa), the substituent for the "carbamoyl group that may be substituted," shown by R^e, is exemplified by lower (C_{1-6}) alkyls that may be substituted (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl, tert.-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl), C_{3-6} cycloalkyl groups that may be substituted (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), C_{6-10} aryl groups that may be substituted (e.g., phenyl, 1-naphthyl, 2-naphthyl) and C_{7-13} aralkyl groups that may be substituted (e.g., benzyl, phenethyl); 1 or 2 of these substituents, whether identical or not, may be present. The substituent for said lower (C_{1-6}) alkyl that may be substituted and C_{3-6} cycloalkyl group that may be substituted is exemplified by carboxyl groups that may be esterified, aromatic heterocyclic groups (e.g., furyl, thienyl, indolyl, isoindolyl, pyrazinyl, pyridyl, pyrimidinyl, imidazolyl), amino groups, hydroxyl groups and phenyl groups. The substituent for said aryl group that may be substituted and aralkyl group that may be substituted is exemplified by halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and carboxyl groups that may be esterified. Also, 2 substituents on the nitrogen atom may cooperate with the nitrogen atom to form a cyclic amino group, such cyclic amino groups including 1-azetidinyl, 1-pyrrolidinyl, piperidino, morpholino and 1-piperazinyl.

With respect to the combination of m and n in general formula (I), it is preferable that i) m be 1 and n be 1, ii) m be 1 and n be 0, or iii) m be 0 and n be 0.

In the present invention, the salt of the compound of general formula (Ia), (I), (I') or (I") is preferably a physiologically acceptable salt, exemplified by salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids and salts with basic or acidic amino acids. Preferable salts with inorganic bases include alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as calcium salt and magnesium salt; and aluminum salt. Preferable salts with organic bases include ammonium salts and salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine and N,N'-dibenzylethylenediamine. Preferable salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid. Preferable salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid. Preferable salts with basic amino acids include salts with arginine, lysine and ornithine. Preferable salts with acidic amino acids include salts with aspartic acid and glutamic acid.

Production methods for the compound (I), (Ia), (I') or (I") of the present invention are hereinafter described in detail.

When the starting compound used in each of the reactions for synthesizing the below-described desired compounds, the starting compound has an amino group, carboxyl group or hydroxyl group as a substituent, these substituents may have a protective group in common use in peptide chemistry etc.; the desired compound can be obtained by removing, as appropriate, the protective group after completion of the reaction.

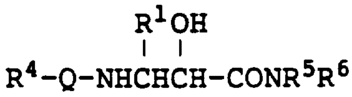
Amino-protecting groups include, for example, formyl, C_{1-6} alkylcarbonyl groups (e.g., acetyl, ethylcarbonyl), phenylcarbonyl group, C_{1-6} alkyl-oxycarbonyl groups (e.g., methoxycarbonyl, ethoxycarbonyl), phenyloxycarbonyl group, C_{7-10} aralkyl-carbonyl group (e.g., benzylcarbonyl), trityl group, phthaloyl group and N,N-dimethylaminomethylene group, which are optionally substituted. Examples of the substituents which these groups optionally have, include halogen atoms (e.g., fluorine, chlorine, bromine, iodine), C_{1-6} alkyl-carbonyl groups (e.g., methylcarbonyl, ethylcarbonyl, butylcarbonyl) and nitro groups, the number of substituents being 1 to 3.

Examples of the carboxyl-protecting groups include C_{1-6} alkyl groups (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, tert.-butyl), phenyl, trityl and silyl, which are optionally substituted. Examples of the substituents which these groups optionally have, include halogen atoms (e.g., fluorine, chlorine, bromine, iodine), formyl, C_{1-6} alkyl-carbonyl groups (e.g., acetyl, ethylcarbonyl, butylcarbonyl) and nitro groups, the number of substituents being 1 to 3.

Examples of the hydroxyl-protecting groups include C_{1-6} alkyl groups (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, tert.-butyl), phenyl, C_{7-10} aralkyl groups (e.g., benzyl), formyl, C_{1-6} alkyl-carbonyl groups (e.g., acetyl, ethylcarbonyl), phenyloxycarbonyl, benzoyl, C_{7-10} aralkyl-carbonyl groups (e.g., benzylcarbonyl), pyranyl, furanyl and silyl, which are optionally substituted. Examples of substituents which these groups optionally have, include halogen atoms (e.g., fluorine, chlorine, bromine, iodine), C_{1-6} alkyl groups (e.g., methyl, ethyl, n-propyl), phenyl, C_{7-10} aralkyl groups (e.g., benzyl) and nitro groups, the number of substituents being 1 to 4.

Protecting groups can be removed by commonly known methods or modifications thereof, including treatments with acids, bases, reducing agents, ultraviolet rays, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate etc.

Compound (Ia) can be produced by subjecting to an oxidation reaction described in detail below a compound represented by general formula (IIa):

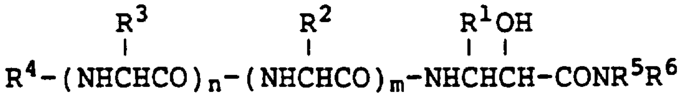


$$R^4\text{-Q-NH}\overset{R^1}{\text{C}}\text{H}\overset{\text{OH}}{\text{C}}\text{H-CONR}^5R^6$$

(IIa)

wherein Q represents a direct bond or 1 or 2 amino acid residues that may be substituted; R^1 represents a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted; R^4 represents a carboxyl group that may be esterified or an acyl group; R^5 and R^6, whether identical or not, independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted; R^5 and R^6 may bind together to form a ring.

Compound (I) can be produced by subjecting to an oxidation reaction described in detail below a compound represented by general formula (II):

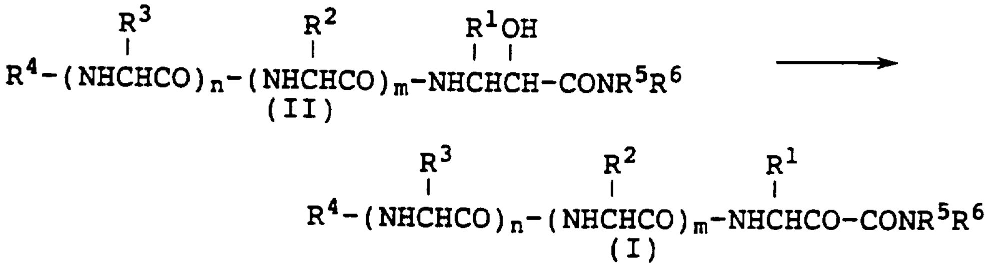


$$R^4\text{-(NH}\overset{R^3}{\text{C}}\text{HCO)}_n\text{-(NH}\overset{R^2}{\text{C}}\text{HCO)}_m\text{-NH}\overset{R^1}{\text{C}}\text{H}\overset{\text{OH}}{\text{C}}\text{H-CONR}^5R^6$$

(II)

wherein R^1, R^2 and R^3, whether identical or not, independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted for; R^4 represents a carboxyl group that may be esterified or an acyl group; R^5 and R^6, whether identical or not, independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group which may be substituted for; R^5 and R^6 may bind together to form a ring; m and n, whether identical or not, independently represent 0 or 1. Compound (I') and (I") can be produced by the same manner as mentioned above in production of compounds (I) and (Ia).

Method A



$$R^4\text{-}(NH\overset{R^3}{C}HCO)_n\text{-}(NH\overset{R^2}{C}HCO)_m\text{-}NH\overset{R^1}{C}H\overset{OH}{C}H\text{-}CONR^5R^6 \quad (II) \longrightarrow$$

$$R^4\text{-}(NH\overset{R^3}{C}HCO)_n\text{-}(NH\overset{R^2}{C}HCO)_m\text{-}NH\overset{R^1}{C}HCO\text{-}CONR^5R^6 \quad (I)$$

In the above formulas, the symbols have the same definitions as those shown above.

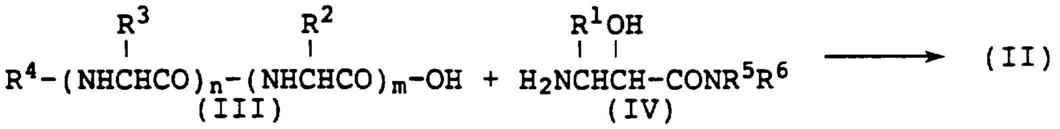
This oxidation is carried out by a known oxidizing reaction. Such reactions include chromic acid oxidations such as Jones' oxidation, using chromium oxide-sulfuric acid-pyridine, Collins oxidation, using chromium oxide-pyridine complex, oxidation with pyridinium chlorochromate (PCC) and oxidation with pyridinium dichromate (PDC); oxidation with activated DMSO, described in detail for method B below; and oxidation with oxoammonium salt.

In the case of an optically active configuration, this oxidation is advantageously carried out by activated dimethyl sulfoxide (DMSO) oxidation. Activated DMSO oxidation is carried out in a solvent in the presence of both DMSO and an electrophilic reagent. This solvent is exemplified by ethers such as ethyl ether, isopropyl ether, tetrahydrofuran and dioxane, aromatic hydrocarbons such as benzene, toluene and xylene, halogenated hydrocarbons such as chloroform and dichloromethane, N,N-dimethylformamide (DMF), pyridine and dimethyl sulfoxide, chosen as appropriate according to the kind of electrophilic reagent. Methods of activated DMSO oxidation include the dicyclohexylcarbodiimide (DCC) method, the acetic anhydride method, the phosphorus pentoxide method, the chlorine method, the sulfur trioxide-pyridine method, the ketenimine-enamine method and the mercury (II) acetate method, named according to the electrophilic reagent used. This oxidation is advantageously carried out by a modification of the dicyclohexylcarbodiimide (DCC) method, in which oxidation is achieved using the pyridine salt of trifluoroacetic acid as a catalyst and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl) as a DMSO activator reagent. This reaction can also be carried out with dimethyl sulfoxide as a solvent. The amount of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl) used is 1 to 10 mol, preferably 2 to 5 mol per mol of compound (II). The amount of the pyridine salt of trifluoroacetic acid used is 0.1 to 2 mol per mol of compound (II). Reaction temperature is -70 to 80°C, preferably -20 to 40°C, reaction time being 0.5 to 10 hours.

Ketoamide derivatives (Ia) and (I) thus obtained may be isolated and purified by known means of separation and purification such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, redissolution and chromatography.

Compound (II) for the present invention can, for example, be produced as follows:

Method B



$$R^4\text{-}(NH\overset{R^3}{\overset{|}{C}}HCO)_n\text{-}(NH\overset{R^2}{\overset{|}{C}}HCO)_m\text{-}OH + H_2N\overset{R^1}{\overset{|}{C}}H\overset{OH}{\overset{|}{C}}H\text{-}CONR^5R^6 \longrightarrow (II)$$

(III) (IV)

In the above formulas, the symbols have the same definitions as those shown above.

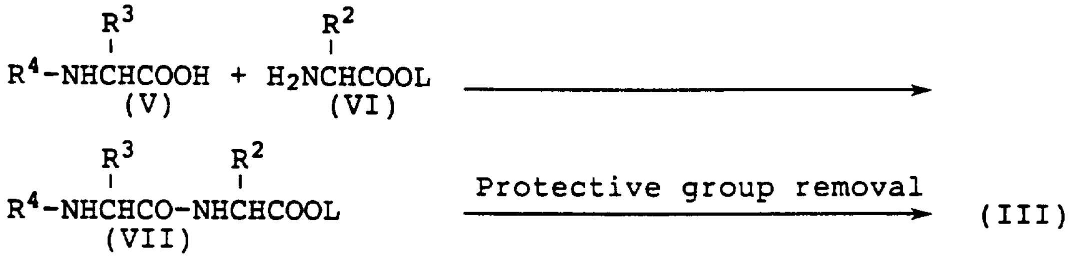
In this method, compound (III), its derivative reactive at the carboxyl group thereof, or a salt thereof is reacted with compound (IV), its derivative reactive at the amino group thereof, or a salt thereof to yield compound (II). Preferable derivatives of compound (IV) reactive at the amino group thereof include Schiff's base type imino or enamine form tautomeric isomers resulting from reaction of compound (IV) and a carbonyl compound such as aldehyde or ketone; silyl derivatives resulting from reaction of compound (IV) and a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide or bis(trimethylsilyl)urea; and derivatives resulting from reaction of compound (IV) and phosphorus trichloride or phosgene. Preferable salts of compound (IV) and its reactive derivatives are exemplified by the same acid adduct salts as specified for compound (I) above.

Preferable derivatives of compound (III) reactive at the carboxyl group thereof include acid halides, acid anhydrides, activated amides and activated esters. Other preferable reactive derivatives include acid chlorides; acid azides; mixed acid anhydrides such as those with a substituted phosphoric acid such as dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid or halogenated phosphoric acid, or with dialkylphosphorous acid, sulfurous acid, thiosulfuric acid or sulfuric acid, or with a sulfonic acid such as methanesulfonic acid, or with an aliphatic carboxylic acid, such as acetic acid, propionic acid, butyric acid, isobutyropivalic acid, pentanoic acid, isopentanoic acid or trichloroacetic acid, or with an aromatic carboxylic acid such as benzoic acid; symmetric acid anhydrides; activated amides with imidazole, 4-substitutional imidazole, dimethylpyrazole, triazole or tetrazole; activated esters such as cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl ester, vinyl ester, propargyl ester, p-nitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthio ester, p-nitrophenyl ester, p-cresylthio ester, carboxymethylthio ester, pyranyl ester, pyridyl ester, piperidyl ester and 8-quinolylthio ester; and esters with N-hydroxy compounds such as N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide and 1-hydroxy-1H-benzotriazole. These reactive derivatives can be optionally chosen according to the kind of compound (III) used. Preferable salts of reactive derivatives of compound (III) include salts with bases, exemplified by alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as calcium salt and magnesium salt, ammonium salt, and organic base salts such as trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt and N,N-dibenzylethylenediamine salt. This reaction is normally carried out in an ordinary solvent such as water, an alcohol such as methanol or ethanol, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide or pyridine, but can be carried out in any other organic solvent, as long as it does not interfere with the reaction. These ordinary solvents may be used in mixture with water.

When compound (III) is used in the form of free acid or salt thereof, this reaction is preferably carried out in the presence of an ordinary condensing agent such as N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, N,N'-carbonylbis(2-methylimidazole), pentamethyleneketene-N-cyclohexylimine, diphenylketene-N-cyclohexylimine, ethoxyacetylene, 1-alkoxy-1-chloroethylene, trialkyl phosphite, ethyl polyphosphate, isopropyl polyphosphate, phosphorus oxychloride, diphenylphosphorylazide, thionyl chloride, oxalyl chloride, a lower alkyl haloformate such as ethyl chloroformate or isopropyl chloroformate, triphenylphosphine, 2-ethyl-7-hydroxybenzisoxazolium salt, 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt, N-hydroxybenzotriazole, 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole, or what is called Wilsmeier reagent as prepared by reaction of N,N'-dimethylformamide and thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, or the like. This reaction may also be carried out in the presence of an inorganic or organic base such as alkali metal hydrogen carbonate tri(lower)alkylamine, pyridine, N-(lower)-alkylmorpholine or N,N-di(lower)alkylbenzylamine. Although reaction temperature is not subject to limitation, this reaction is normally carried out under cooling to heating conditions.

Starting material compound (III) for method B is produced by methods C through J as follows:

Method C



$$\underset{(V)}{R^4\text{-NH}\overset{R^3}{\text{C}}\text{HCOOH}} + \underset{(VI)}{\text{H}_2\text{N}\overset{R^2}{\text{C}}\text{HCOOL}} \longrightarrow$$

$$\underset{(VII)}{R^4\text{-NH}\overset{R^3}{\text{C}}\text{HCO-NH}\overset{R^2}{\text{C}}\text{HCOOL}} \xrightarrow{\text{Protective group removal}} \text{(III)}$$

In the above formulas, L represents a carboxy-protecting group; the other symbols have the same definitions as those given above.

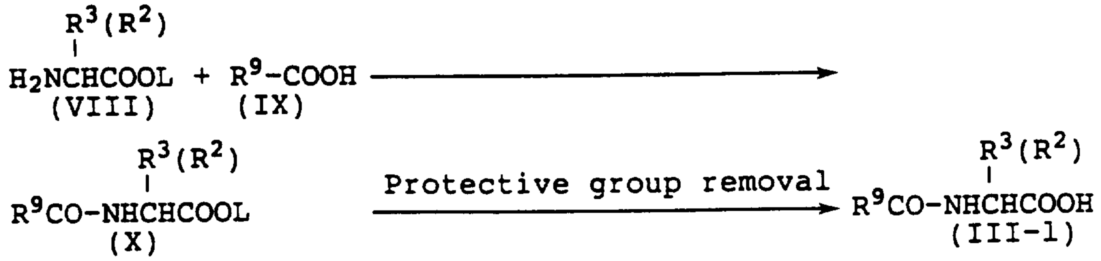
The carboxy-protecting group for L is exemplified by protecting groups in common use in the field of peptide synthesis, such as ester derivatives.

In this method, compound (V), its derivative reactive at the carboxyl group thereof, or a salt thereof is reacted with compound (VI), its derivative reactive at the amino group thereof, or a salt thereof to yield compound (VII), which is then subjected to a deprotecting reaction to remove the carboxy-protecting group to yield compound (III). The reaction of compound (V), its derivative reactive at the carboxyl group thereof, or a salt thereof and compound (VI), its derivative reactive at the amino group thereof, or a salt thereof is carried out in the same manner as method B.

The deprotecting reaction of compound (VII) to remove its carboxy-protecting group can be achieved by any common method of carboxy-protecting group removing reaction, such as deprotection by hydrolysis, reduction or Lewis acid. When the carboxy-protecting group is an ester, it can be removed by hydrolysis or Lewis acid, preferably in the presence of a base or acid. Preferable bases include inorganic bases such as alkali metal hydroxides (e.g., sodium hydroxide, potassium hydroxide), alkaline earth metal hydroxides (e.g., magnesium hydroxide, calcium hydroxide), alkali metal carbonates (e.g., sodium carbonate, potassium carbonate), alkaline earth metal carbonates (e.g., magnesium carbonate, calcium carbonate), alkali metal bicarbonates (e.g., sodium bicarbonate, potassium bicarbonate), alkali metal acetates (e.g., sodium acetate, potassium acetate), alkaline earth metal phosphates (e.g., magnesium phosphate, calcium phosphate), alkali metal hydrogen phosphates (e.g., disodium hydrogen phosphate, dipotassium hydrogen phosphate), and organic bases such as trialkylamines (e.g., trimethylamine, triethylamine), picoline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]non-5-ene and 1,8-diazabicyclo[5.4.0]-7-undecene. Hydrolysis using a base is often carried out in water or a hydrophilic organic solvent or mixture thereof. Preferable acids include organic acids (e.g., formic acid, acetic acid) and inorganic acids (e.g., hydrochloric acid, hydrobromic acid, sulfuric acid). This hydrolysis is normally carried out in an organic solvent, water or a mixture thereof. Reaction temperature, not subject to limitation, is chosen as appropriate, according to the kind of carboxy-protecting group and method of deprotection. Deprotection using a Lewis acid is achieved by reacting compound (VII) or a salt thereof with a Lewis acid such as a boron trihalide (e.g., boron trichloride, boron trifluoride), a titanium tetrahalide (e.g., titanium tetrachloride, titanium tetrabromide), an aluminum halide (e.g., aluminum chloride, aluminum bromide) or a trihaloacetic acid (e.g., trichloroacetic acid, trifluoroacetic acid). This deprotecting reaction is preferably carried out in the presence of a cation capturing agent (e.g., anisole, phenol) and normally carried out in a solvent which does not interfere with the reaction, such as a nitroalkane (e.g., nitromethane, nitroethane), an alkylene halide (e.g., methylene chloride, ethylene chloride), diethyl ether or carbon disulfide. These solvents may be used in mixture.

Deprotection by reduction is preferably applied to removing the protecting groups such as esters of haloalkyls (e.g., 2-iodoethyl, 2,2,2-trichloroethyl) and esters of aralkyls (e.g., benzyl). Methods of reduction for this deprotecting reaction include reduction with a combination of a metal (e.g., zinc, zinc amalgam) or a chromium compound salt (e.g., primary chromium chloride, primary chromium acetate) and an organic or inorganic acid (e.g., acetic acid, propionic acid, hydrochloric acid), and ordinary catalytic reduction in the presence of an ordinary metal catalyst (e.g., palladium-carbon, Raney nickel). Although reaction temperature is not subject to limitation, this reaction is normally carried out under cooling, room temperature or heating conditions.

Method D

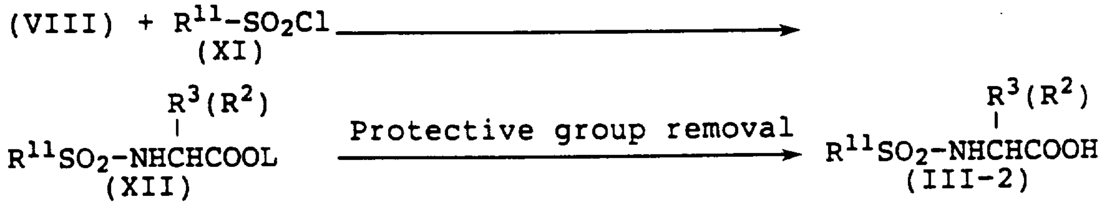


$$\underset{(VIII)}{H_2N\overset{\overset{R^3(R^2)}{|}}{C}HCOOL} + \underset{(IX)}{R^9\text{-}COOH} \longrightarrow \underset{(X)}{R^9CO\text{-}NH\overset{\overset{R^3(R^2)}{|}}{C}HCOOL} \xrightarrow{\text{Protective group removal}} \underset{(III\text{-}1)}{R^9CO\text{-}NH\overset{\overset{R^3(R^2)}{|}}{C}HCOOH}$$

In the above formulas, the symbols have the same definitions as those shown above.

In this method, compound (IX), its derivative reactive at the carboxyl group thereof, or a salt thereof is reacted with compound (VIII), its derivative reactive at the amino group thereof, or a salt thereof to yield compound (X), which is then subjected to a deprotecting reaction to remove its carboxy-protecting group to yield compound (III-1). This method is carried out in the same manner as method C.

Method E

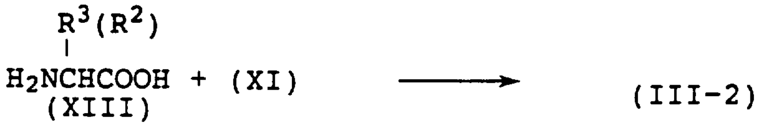


$$(VIII) + \underset{(XI)}{R^{11}\text{-}SO_2Cl} \longrightarrow \underset{(XII)}{R^{11}SO_2\text{-}NH\overset{\overset{R^3(R^2)}{|}}{C}HCOOL} \xrightarrow{\text{Protective group removal}} \underset{(III\text{-}2)}{R^{11}SO_2\text{-}NH\overset{\overset{R^3(R^2)}{|}}{C}HCOOH}$$

In the above formulas, the symbols have the same definitions as those shown above.

In this method, compound (XI) or a salt thereof is reacted with compound (VIII) or a salt thereof to yield compound (XII), which is then subjected to a deprotecting reaction to remove its carboxy-protecting group to yield compound (III-2). The reaction of compounds (VIII) and (XI) is carried out in an appropriate solvent. This solvent is exemplified by aromatic hydrocarbons such as benzene, toluene and xylene, ethers such as dioxane, tetrahydrofuran and dimethoxyethane, alcohols such as methanol, ethanol and propanol, ethyl acetate, acetonitrile, pyridine, N,N-dimethylformamide, dimethyl sulfoxide, chloroform, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, acetone, 2-butanone and mixtures thereof. The reaction of compounds (VIII) and (XI) is carried out in the presence of an appropriate base, exemplified by alkali metal salts such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate and sodium hydrogen carbonate, amines such as pyridine, triethylamine and N,N-dimethylaniline, sodium hydride and potassium hydride. The amount of these bases used is preferably about 1 to 5 mol per mol of compound (VIII). The reaction is normally carried out at -20 to 150°C, preferably about -10 to 100°C. Compound (XII) thus obtained is subjected to a deprotecting reaction to yield compound (III-2). This deprotection is carried out in the same manner as the deprotecting reaction in method C.

Method F



$$\underset{\text{(XIII)}}{\mathrm{H_2N\overset{R^3(R^2)}{\overset{|}{C}H}COOH}} + \text{(XI)} \longrightarrow \text{(III-2)}$$

In the above formulas, the symbols have the same definitions as those shown above.

In this method, compound (XIII) or a salt thereof is reacted with compound (XI) or a salt thereof to yield compound (III-2). This sulfonylation is normally carried out under what is called Schotten Baumann's conditions, in which amino acid derivative (XIII), prepared as a sodium salt in an aqueous solution, is reacted with compound (XI) and then acidified.

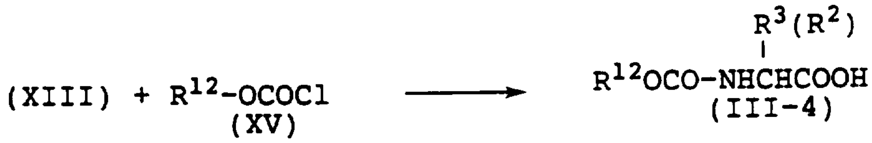
Method G

$$(XIII) + \underset{(XIV)}{R^9\text{-COCl}} \longrightarrow \underset{(III\text{-}1)}{R^9\text{CO-NH}\overset{R^3(R^2)}{\overset{|}{\text{C}}}\text{HCOOH}}$$

In the above formulas, the symbols have the same definitions as those shown above.

In this method, compound (XIII) or a salt thereof is reacted with compound (XIV) or a salt thereof to yield compound (III-1). This acylation is carried out in the same manner as method F.

Method H

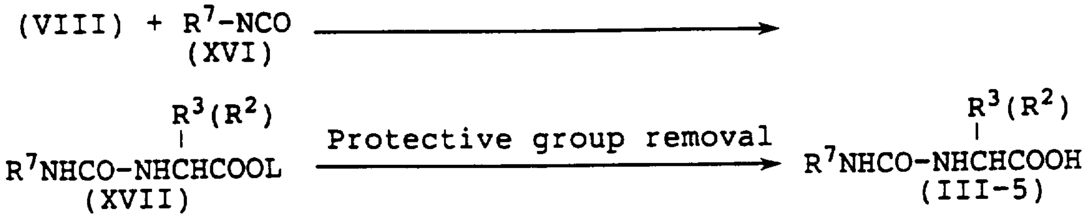


$$(XIII) + \underset{(XV)}{R^{12}\text{-OCOCl}} \longrightarrow \underset{(III\text{-}4)}{R^{12}\text{OCO-NH}\overset{R^3(R^2)}{\overset{|}{\text{C}}}\text{HCOOH}}$$

In the above formulas, the symbols have the same definitions as those shown above.

In this method, compound (XIII) or a salt thereof is reacted with compound (XV) or a salt thereof to yield compound (III-4). This method is carried out in the same manner as method G.

Method I



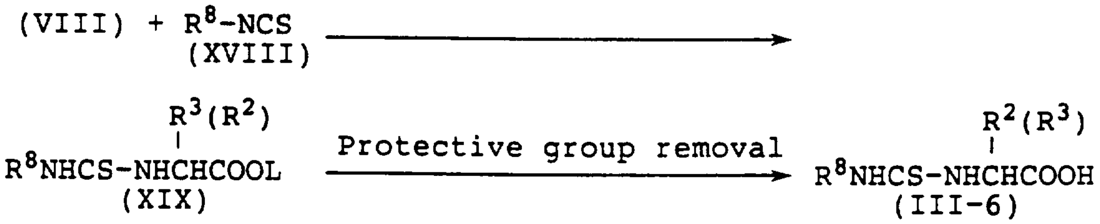
$$(VIII) + \underset{(XVI)}{R^7\text{-NCO}} \longrightarrow$$

$$\underset{(XVII)}{R^7\text{NHCO-NH}\overset{R^3(R^2)}{\overset{|}{\text{C}}}\text{HCOOL}} \xrightarrow{\text{Protective group removal}} \underset{(III\text{-}5)}{R^7\text{NHCO-NH}\overset{R^3(R^2)}{\overset{|}{\text{C}}}\text{HCOOH}}$$

In the above formulas, the symbols have the same definitions as those shown above.

In this method, compound (VIII) or a salt thereof is reacted with compound (XVI) to yield compound (XVII), which is then subjected to a deprotecting reaction to remove its carboxy-protecting group to yield compound (III-5). The reaction of compound (VIII) or a salt thereof and compound (XVI) is carried out in an appropriate solvent. This solvent is exemplified by aromatic hydrocarbons such as benzene, toluene and xylene, ethers such as dioxane, tetrahydrofuran and dimethoxyethane, ethyl acetate, acetonitrile, pyridine, N,N-dimethylformamide, dimethyl sulfoxide, chloroform, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, acetone, 2-butanone and mixtures thereof. The amount of compound (XVI) used is preferably about 1 to 5 mol per mol of compound (VIII). The reaction is normally carried out at -20 to 150°C, preferably about -10 to 100°C. Compound (XVII) thus obtained is subjected to a deprotecting reaction to yield compound (III-5). This deprotection is carried out in the same manner as the deprotection in method C.

Method J



$$(\mathrm{VIII}) + \underset{(\mathrm{XVIII})}{R^8\text{-NCS}} \longrightarrow$$

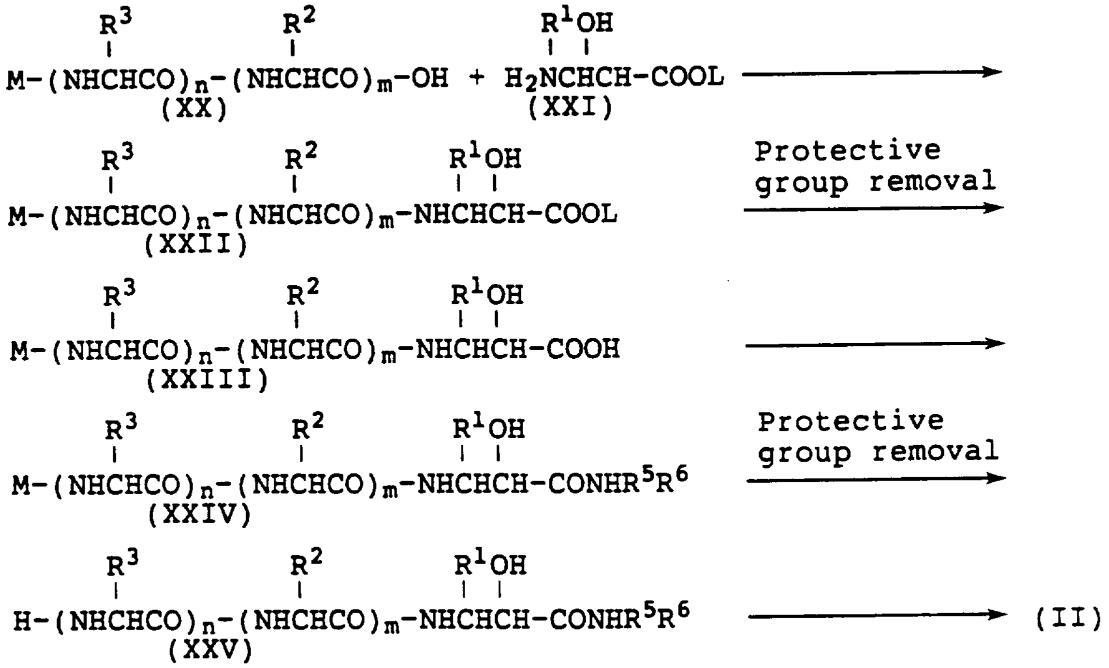
$$\underset{(\mathrm{XIX})}{R^8\mathrm{NHCS\text{-}NH}\overset{R^3(R^2)}{\overset{|}{\mathrm{C}}}\mathrm{HCOOL}} \xrightarrow{\text{Protective group removal}} \underset{(\mathrm{III\text{-}6})}{R^8\mathrm{NHCS\text{-}NH}\overset{R^2(R^3)}{\overset{|}{\mathrm{C}}}\mathrm{HCOOH}}$$

In the above formulas, the symbols have the same definitions as those shown above.

In this method, compound (VIII) or a salt thereof is reacted with compound (XVIII) to yield compound (XIX), which is then subjected to a deprotecting reaction to remove its carboxy-protecting group to yield compound (III-6). This reaction is carried out in the same manner as method I.

Starting material compound (II) for method A can also be produced as follows:

Method K



$$\mathrm{M\text{-}(NH\overset{R^3}{\overset{|}{C}}HCO)_n\text{-}(NH\overset{R^2}{\overset{|}{C}}HCO)_m\text{-}OH} \;+\; \mathrm{H_2N\overset{R^1}{\overset{|}{C}}H\overset{OH}{\overset{|}{C}}H\text{-}COOL} \longrightarrow$$

(XX) (XXI)

$$\mathrm{M\text{-}(NH\overset{R^3}{\overset{|}{C}}HCO)_n\text{-}(NH\overset{R^2}{\overset{|}{C}}HCO)_m\text{-}NH\overset{R^1}{\overset{|}{C}}H\overset{OH}{\overset{|}{C}}H\text{-}COOL} \xrightarrow{\text{Protective group removal}}$$

(XXII)

$$\mathrm{M\text{-}(NH\overset{R^3}{\overset{|}{C}}HCO)_n\text{-}(NH\overset{R^2}{\overset{|}{C}}HCO)_m\text{-}NH\overset{R^1}{\overset{|}{C}}H\overset{OH}{\overset{|}{C}}H\text{-}COOH} \longrightarrow$$

(XXIII)

$$\mathrm{M\text{-}(NH\overset{R^3}{\overset{|}{C}}HCO)_n\text{-}(NH\overset{R^2}{\overset{|}{C}}HCO)_m\text{-}NH\overset{R^1}{\overset{|}{C}}H\overset{OH}{\overset{|}{C}}H\text{-}CONHR^5R^6} \xrightarrow{\text{Protective group removal}}$$

(XXIV)

$$\mathrm{H\text{-}(NH\overset{R^3}{\overset{|}{C}}HCO)_n\text{-}(NH\overset{R^2}{\overset{|}{C}}HCO)_m\text{-}NH\overset{R^1}{\overset{|}{C}}H\overset{OH}{\overset{|}{C}}H\text{-}CONHR^5R^6} \longrightarrow \text{(II)}$$

(XXV)

In the above formulas, M represents an amino-protecting group; the other symbols have the same definitions as those shown above.

The amino-protecting group for M is exemplified by protecting groups in common use in the field of peptide synthesis, such as oxycarbonyl derivatives, with preference given to benzyloxycarbonyl.

In this method, compound (XX), its derivative reactive at the carboxyl group thereof, or a salt thereof is reacted with compound (XXI), its derivative reactive at the amino group thereof, or a salt thereof to yield compound (XXII), which is then subjected to a deprotecting reaction to remove its carboxyl-protecting group to yield compound (XXIII). The reaction of compound (XX), its derivative reactive at the carboxyl group thereof, or a salt thereof and compound (XXI), its derivative reactive at the amino group thereof, or a salt thereof is carried out in the same manner as method B. The carboxyl-protecting group-removing reaction of compound (XXII) can be carried out by the method described for method C above. Compound (XXIII), its derivative reactive at the carboxyl group thereof, or a salt thereof is reacted with an amine derivative or a salt thereof to yield compound (XXIV), which is then subjected to a deprotecting reaction to remove its amino-protecting group to yield compound (XXV). The reaction of compound (XXIII), its derivative reactive at the carboxyl group thereof, or a salt thereof and an amine derivative or a salt thereof is carried out in the same manner as method B. In the amino-protecting group-removing reaction of compound (XXIV), the amino-protecting group can be removed by any commonly used method of reaction to remove the amino-protecting group. For example, the benzyloxycarbonyl group is removed by catalytic reduction in the presence of a commonly used metal catalyst (e.g., palladium-carbon, Raney nickel). Reaction temperature is not subject to limitation; the reaction is normally carried out under cooling, room temperature or heating conditions. Compound (XXV) is then acylated in the same manner as the reaction of compounds (VIII) and (IX) in method D or the reaction of compounds (XIII) and (XIV) in method G, sulfonylated in the same manner as the reaction of compounds (VIII) and (XI) in method E, oxycarbonylated in the same manner as the reaction of compounds (VIII) and (XV) in method H, carbamoylated in the same manner as the reaction of compounds (VIII) and (XVI) in method I, and then thiocarbamoylated in the same manner as the reaction of compounds (VIII) and (XVIII) in method J, to yield compound (II).

In the present invention, the compound of general formula (I), (Ia), (I') or (I") can be administered orally or non-orally, as formulated at an effective dose with a physiologically acceptable carrier, in the form of solid preparations such as tablets, capsules, granules and powders, or liquid preparations such as syrups and injectable preparations.

Pharmaceutically acceptable carriers are various organic or inorganic carrier substances in common use as pharmaceutical materials, including excipients, lubricants, binders and disintegrating agents for solid preparations, and solvents, dissolution aids, suspending agents, isotonizing agents, buffers and soothing agents for liquid preparations. Other pharmaceutical additives such as preservatives, antioxidants, coloring agents and sweetening agents may be used as necessary.

Preferable excipients include lactose, sucrose, D-mannitol, starch, crystalline cellulose and light silicic anhydride.

Preferable lubricants include magnesium stearate, calcium stearate, talc and colloidal silica.

Preferable binders include crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and polyvinylpyrrolidone.

Preferable disintegrating agents include starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, cross carmelose sodium and carboxymethyl starch sodium.

Preferable solvents include water for injection, alcohol, propylene glycol, macrogol, sesame oil and corn oil.

Preferable dissolution aids include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, tris-aminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate.

Preferable suspending agents include surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and monostearic glycerol; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose.

Preferable isotonizing agents include sodium chloride, glycerol and D-mannitol.

Preferable buffers include buffer solutions of phosphates, acetates, carbonates and citrates.

Preferable soothing agents include benzyl alcohol.

Preferable preservatives include p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Preferable antioxidants include sulfites and ascorbic acid.

The compound represented by general formula (I), (Ia), (I') or (I") or a salt thereof can be orally or non-orally used by inhalation, rectal injection or local administration. It can be used as a pharmaceutical composition or preparation (e.g., powders, granules, tablets, pills, capsules, injectable preparations, syrups, emulsions, elixirs, suspensions, solutions), which may contain one or more inventive compounds with pharmaceutically acceptable carriers (e.g., adjutants, excipients, shaping agents and/or diluents).

Pharmaceutical compositions can be prepared as pharmaceutical preparations by ordinary methods. In the present specification, "non-oral" includes subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection and drip infusion. Injectable preparations, e.g., aqueous or oily suspensions for aseptic injection, can be prepared by methods known in relevant fields, using an appropriate dispersing agent or wetting agent and a suspending agent. The aseptic injectable preparation thus obtained may be an aseptically injectable solution or suspension in a diluent or solvent which permits non-toxic non-oral administration, such as an aqueous solution. Acceptable vehicles or solvents include water, Ringer's solution and isotonic saline. It is also possible to use aseptic non-volatile oils in common use as solvents or suspending media. For this purpose any non-volatile oil or fatty acid can be used, including natural, synthetic or semi-synthetic fatty oils or acids, and natural, synthetic or semi-synthetic mono- or di- or triglycerides.

Suppositories for rectal administration may be produced as a mixture of the drug and an appropriate non-irritative shaping agent, such as cacao butter or polyethylene glycol, which is solid at normal temperatures and liquid at intestinal temperatures and melts and releases the drug in the rectum.

Solid dosage forms for oral administration include the above-mentioned forms such as powders, granules, tablets, pills and capsules. In these dosage forms, the active ingredient compound may be mixed with at least one additive such as sucrose, lactose, cellulose sugar, mannitol, maltitol, dextran, starch, agar, alginate, chitin, chitosan, pectin, gum tragacanth, gum arabic, gelatin, collagen, casein, albumin, synthetic or semi-synthetic polymer or glyceride. Such dosage forms may contain additional additives as usual, including inert diluents, lubricants such as magnesium stearate, preservatives such as paraben and sorbic acid, antioxidants such as ascorbic acid, α-tocopherol and cysteine, disintegrating agents, binders, thickening agents, buffers, sweeteners, flavoring agents and perfumes. Tablets and pills may be produced with enteric coating. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, syrups, elixirs, suspensions and solutions, which may contain inert diluents, such as water, in common use in relevant fields.

The dose for a particular patient is determined according to age, body weight, general health status, sex, dietary status, administration time, method of administration, excretion rate, drug combination, severity of the illness being treated and other factors.

Since the compound represented by general formula (I), (Ia), (I') or (I") or a salt thereof possesses potent cathepsin L inhibitory activity, it excellently suppresses bone resorption, and can be safely used at low toxicity. The compounds (Ia), (I), (I') or (I") of the present invention can therefore be advantageously used to prevent or treat osteoporosis in mammals (e.g., mice, rats, rabbits, dogs, cats, bovines, swines, humans).

When the compound (Ia), (I), (I') or (I") of the present invention or a salt thereof is used as a prophylactic/therapeutic agent for osteoporosis, its daily dose for an adult (50 kg), varying depending on the patient condition, body weight, type of compound, route of administration and other factors, is normally about 1 to 500 mg, preferably about 10 to 500 mg for oral administration, and about 1 to 300 mg, preferably about 5 to 100 mg for non-oral administration.

Best Mode for Carrying out the Invention

The actions of compounds (Ia), (I), (I') or (I") are hereinafter described by means of the following experimental examples.

Experimental Example 1

Determination of human cathepsin L inhibitory activity

Purified recombinant human cathepsin L was diluted with a diluent [0.1% Brij 35 (produced by Sigma Corporation)] to a concentration of 1 μg/ml. To 1 μl of this enzyme dilution, 46 μl of the diluent, 2 μl of 0.1 M DTT and 25 μl of an activator/buffer (340 mM sodium acetate, 60 mM acetic acid, 4 mM disodium EDTA, pH 5.5) were added. To this mixture, a 1 μl sample, previously diluted to 10^{-2} M with dimethyl sulfoxide (DMSO), and 25 μl of 20 μM Z-Phe-Arg-NHMec (enzyme substrate solution) were added, followed by incubation at 30°C for 10 minutes, after which 100 μl of a reaction stopper (100 mM sodium monochloroacetate, 30 mM sodium acetate, pH 4.3) was added. This reaction was carried out on a 96-well fluoroplate (produced by Labo Systems).

After the reaction was stopped, the fluorescence intensity of free aminomethylcoumarin was determined at a wavelength of 450 nm (excitation wavelength = 365 nm), using a fluorometer FCA (produced by Baxter). For control, 1 μl of sample-free DMSO was added instead; the fluorometric value obtained from this control reaction was taken as 100% activity. When the residual activity was not higher than 10%, the sample solution was further diluted and then assayed for residual activity in the same procedure as above to obtain the IC_{50} value. The results are shown in Table 1.

Table 1

Compound (Example No.)	Cathepsin L Inhibitory Activity [IC_{50} Value (M)]
1	1.1×10^{-8}
7	1.1×10^{-8}
9	7.9×10^{-8}
13	3.4×10^{-8}
14	8.1×10^{-8}
15	1.8×10^{-9}
16	2.3×10^{-9}
19	0.4×10^{-9}
21	0.36×10^{-9}
23	3.6×10^{-9}
26	1.7×10^{-8}

Experimental Example 2

Bone resorption-suppressing action

Bone resorption was measured by the method of Raisz [Journal of Clinical Investigation, 44, 103-116 (1965)]. Specifically, one Sprague-Dawley rat at 18 days of gestation was given 50 μCi of ^{45}Ca (calcium isotope, in $CaCl_2$ solution) by subcutaneous injection. On the following day, the animal was laparotomized and fetal rats aseptically removed. Both forearm bones (radius and ulna) were cut from the body of each fetus under an anatomical microscope, and connective tissue and cartilage were removed to the maximum possible extent, to prepare bone culture samples. Each bone fragment was pre-cultured at 37°C for 24 hours in 0.6 ml of a medium (Fitton-Jackson modification, GIBCO Laboratories, the United States) prepared by adding bovine serum albumin (final concentration 2 mg/ml), after which it was transferred to the same medium as above but containing each compound (final concentration 10 μM) and cultured for two more days. ^{45}Ca radioactivity in the medium and ^{45}Ca radioactivity in the bone were then measured; the percent ratio of ^{45}Ca released from the bone to the medium was calculated using the following equation:

$$\text{Percent ratio of } {}^{45}\text{Ca released from bone to medium} = \frac{({}^{45}\text{Ca count in the medium})}{({}^{45}\text{Ca count in the medium}) + ({}^{45}\text{Ca count in the bone})} \times 100$$

For control, bone fractions from fetuses of the same litter were cultured for two days in the absence of the test compound. The mean ± standard deviation for the values from 5 bone fragments in each group were calculated, and their percent ratios to the control were calculated. The results are shown in Table 2.

Table 2

Compound (Example No.)	Bone Resorption-suppressing Action [^{45}Ca Release Rate (Percent to Control)]
2	77
3	82
12	67
14	77
19	61
25	60
26	60

The present invention is hereinafter described in more detail by means of, but is not limited to, the following reference examples and working examples. Optical rotation was determined at 20 to 25°C. The room temperature ranged from about 15°C to about 25°C.

In the following reference examples and working examples, the component amino acids used are of the L-configuration, unless otherwise stated. When shown by abbreviations, their notation is in accordance with the IUPAC (International Union of Pure and Applied Chemistry)-IUB (International Union of Biochemistry) Biochemical Nomenclature, e.g., Gly for glycine, Leu for leucine and Ile for isoleucine.

Example 1

N-Benzyloxycarbonyl-L-isoleucyl-(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid benzylamide (5.0 g) was dissolved in a mixed solvent of dimethyl sulfoxide (DMSO) (20 ml) and toluene (60 ml). To this solution, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl) (5.4 g) and pyridinium trifluoroacetate (1.6 g) were added at room temperature. After 1 hour of stirring, the reaction mixture was poured over ice water and extracted with ethyl acetate. The organic layer was washed by sequential additions of an aqueous citric acid solution, water, aqueous $NaHCO_3$ and saline and dried ($MgSO_4$). After the solvent was distilled off under reduced pressure, the resulting light yellow solid was washed with ethyl acetate-hexane to yield a white solid of N-benzyloxycarbonyl-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide (4.15 g, 83%).

Melting point: 201-202°C

$[\alpha]_D$ = -33.5° (c 0.35, MeOH) (20°C)

Elemental analysis (for $C_{31}H_{35}N_3O_5$)

Calculated: C, 70.30; H, 6.66; N, 7.93

Found : C, 70.12; H, 6.48; N, 8.12

Example 2

The same procedure as in Example 1 was followed to yield N-[(3S)-3-dibenzylacetylamino-2-oxo-4-phenylbutyryl]-L-leucine methyl ester.

Melting point: 120-121°C

$[\alpha]_D$ = -7.5° (c 0.48, MeOH) (20°C)

Example 3

The same procedure as in Example 1 was followed to yield N-[(3S)-3-dibenzylacetylamino-2-oxo-4-phenylbutyryl]-L-leucine benzylamide.

Melting point: 172-174°C

$[\alpha]_{Hg}$ = +37.5° (c 0.31, DMSO) (20°C)

Example 4

The same procedure as in Example 1 was followed to yield (3S)-3-dibenzylacetylamino-2-oxo-4-phenylbutyric acid benzylamide.

Melting point: 157-158°C

$[\alpha]_D$ = -24.6° (c 0.50, MeOH)

Example 5

The same procedure as in Example 1 was followed to yield N-[(3S)-3-dibenzylacetylamino-2-oxo-4-phenylbutyryl]-β-methyl-L-aspartic acid benzylamide.

Melting point: 178-179°C

$[\alpha]_{Hg}$ = +54.4° (c 0.60, DMSO) (20°C)

Example 6

N-[(3S)-3-dibenzylacetylamino-2-oxo-4-phenylbutyryl]-β-methyl-L-aspartic acid benzylamide (0.30 g) was dissolved in a mixed solvent of tetrahydrofuran (THF) (6 ml) and methanol (4 ml). To this solution, an aqueous solution of potassium hydroxide (65 mg) was added under ice cooling conditions. After stirring under ice cooling conditions for 5 hours, the reaction mixture was acidified with 1 N hydrochloric acid and extracted with ethyl acetate. After the organic layer was dried ($MgSO_4$), the solvent was distilled off under reduced pressure. The resulting light yellow oily substance crystallized from ethyl acetate-hexane to yield a white crystal of N-[(3S)-3-dibenzylacetylamino-2-oxo-4-phenylbutyryl]-L-aspartic acid benzylamide (0.18 g, 61%).

Melting point: 178-179°C

$[\alpha]_{Hg}$ = +54.4° (c 0.60, DMSO) (20°C)

Example 7

The same procedure as in Example 1 was followed to yield a colorless crystal of N-(1-naphthalenesulfonyl)-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide.

Melting point: 183-185°C

$[\alpha]_D$ = +28.5° (c 0.35, DMSO) (20°C)

Example 8

The same procedure as in Example 1 was followed to yield a white solid of N-benzyloxycarbonyl-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid 2-pyridylmethylamide.

Melting point: 164-165°C

$[\alpha]_{Hg}$ = +31.5° (c 0.60, DMSO) (20°C)

Example 9

The same procedure as in Example 1 was followed to yield a white solid of N-benzyloxycarbonyl-L-isoleucyl-

(3S)-3-amino-2-oxo-4-phenylbutyric acid 4-pyridylmethylamide.

Melting point: 204-205°C

[α]$_D$ = -1.4° (c 0.74, DMSO) (20°C)

Example 10

The same procedure as in Example 1 was followed to yield a light yellow solid of N-benzyloxycarbonyl-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid p-diethylphosphonomethylphenylamide.

Melting point: 139-140°C

[α]$_D$ = -6.4° (c 0.88, DMSO) (20°C)

Example 11

The same procedure as in Example 1 was followed to yield a white solid of N-benzyloxycarbonyl-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid isobutylamide.

Melting point: 215-216°C

[α]$_D$ = +9.9° (c 1.00, DMSO) (20°C)

Example 12

The same procedure as in Example 1 was followed to yield a white solid of N-benzyloxycarbonyl-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid 3-(2-oxopyrrolidin-1-yl)propylamide.

Melting point: 268-269°C

[α]$_D$ = +2.5° (c 0.93, DMSO) (20°C)

Example 13

The same procedure as in Example 1 was followed to yield a white crystal of N-(quinoline-2-carbonyl)-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide.

Melting point: 181-182°C

[α]$_D$ = +34.5° (c 0.79, DMSO) (20°C)

Example 14

The same procedure as in Example 1 was followed to yield a white solid of N-(p-diethylphosphonomethyl-cinnamoyl)-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide.

Melting point: 207-209°C

$[\alpha]_D$ = +22.7° (c 0.893, DMSO) (20°C)

Example 15

The same procedure as in Example 1 was followed to yield a colorless crystal of N-(1-naphthalenesulfonyl)-L-phenylalanyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide.

Melting point: 189-191°C

$[\alpha]_D$ = +11.9° (c 0.87, DMSO) (20°C)

Example 16

The same procedure as in Example 1 was followed to yield a colorless crystal of N-(1-naphthalenesulfonyl)-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid 4-pyridylmethylamide.

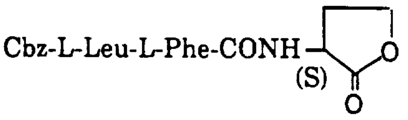
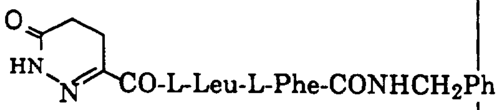
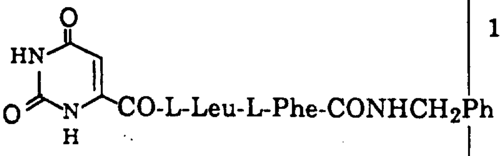
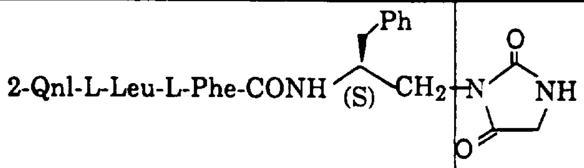
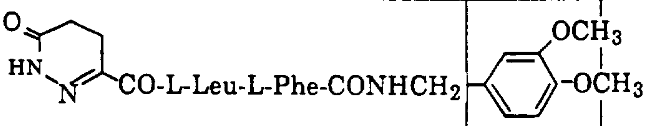
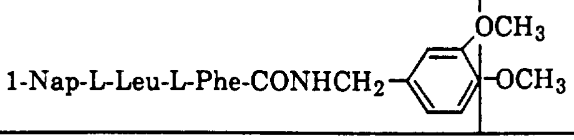
Melting point: 162-163°C

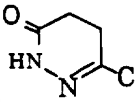
$[\alpha]_D$ = +16.9° (c 0.38, DMSO) (20°C)

Examples 17-27

By substantially the same procedure as in Example 1, compounds shown in Table 3 were produced.

Table 3

No. of Example		m.p. (°C)	Recrystalization solvent	Optical Rotation $[\alpha]_D$
17	$(C_3H_7)_2CHCO$-L-Val-L-Phe-$CONHCH_2Ph$	239-241	DMF-H_2O	+10.6°(c= 0.81,DMSO)
18		169-171	-	-10.3°(c= 0.79,DMSO)
19		178-179 1)	-	3) +48.7°(c= 0.74,DMSO)
20	1-Nap-L-Leu-L-Phe-$CONHCH_2Ph$	172-173	-	+5.7°(c= 0.85,DMSO)
21		199-200	-	+11.1°(c= 0.38,DMSO)
22		212-213 2)	-	+37.0°(c= 0.84,DMSO)
23		179-180 2)	-	-6.5°(c= 0.78,DMSO)
24		161-162	-	-153.7°(c= 0.68,CH_3OH)

No. of Example		m.p. (°C)	Recrystalization solvent	Optical Rotation $[\alpha]_D$
25	Cbz-L-Leu-L-Leu-L-Phe-CONHCH$_2$Ph	200-201	-	+6.9°(c=0.53,DMSO)
26	2-Qnl-L-Leu-L-Leu-L-Phe-CONHCH$_2$Ph	207-208	-	+49.6°(c=0.75,DMSO)
27	 CO-L-Ile-L-Phe-CONHCH$_2$Ph	165-166 2)	-	-53.2°(c=0.67,DMSO)

1) 1/4hydrate, 2) 1/2hydrate, 3) $[\alpha]_{Hg}$ value
Val=valine, Phe=phenylalanine, Leu=leucine, Ile=isoleucine, Ph=phenyl, Cbz=benzyloxycarbonyl, 1-Nap=1-naphthalenesulfonyl, 2-Qnl=quinoline-2-carbonyl, DMF=N,N-dimethylformamide, DMSO=dimethyl sulfoxide

Reference Example 1

N-benzyloxycarbonyl-L-isoleucyl-(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid benzylamide (4.7 g) and 5% Pd-C (2.5 g) were added to a mixed solvent of tetrahydrofuran (THF) (20 ml) and methanol (20 ml), followed by stirring at room temperature for 1 hour in a hydrogen atmosphere. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in N,N-dimethylformamide (DMF) (30 ml). To this solution, α-naphthalenesulfonyl chloride (2.1 g) and N,N-dimethylaminopyridine (1.2 g) were added under ice cooling conditions. After 15 hours of stirring under ice cooling conditions, the reaction mixture was poured over ice-water and extracted with ethyl acetate. The organic layer was washed by sequential additions of an aqueous citric acid solution, water, an aqueous NaHCO$_3$ solution and saline and dried (MgSO$_4$). After the solvent was distilled off under reduced pressure, the resulting residue was washed with ethyl acetate to yield a colorless crystal of N-(1-naphthalenesulfonyl)-L-isoleucyl-(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid benzylamide (4.75 g).

Melting point: 178-179°C

$[\alpha]_D$ = +5.7° (c 0.52, DMSO) (20°C)

Elemental analysis (for $C_{33}H_{37}N_3O_5S$)

Calculated: C, 67.44; H, 6.35; N, 7.15

Found : C, 67.22; H, 6.45; N, 7.15

Reference Example 2

The same procedure as in Reference Example 1 was followed to yield a colorless crystal of N-(1-naphthalenesulfonyl)-L-phenylalanyl-(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid benzylamide.

Melting point: 210-211°C

$[\alpha]_D$ = -40.1° (c 0.76, DMSO) (20°C)

Reference Example 3

The same procedure as in Reference Example 1 was followed to yield a colorless crystal of N-(1-naphthalenesulfonyl)-L-isoleucyl-(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid 4-pyridylmethylamide.

Melting point: 210-211°C

$[\alpha]_D$ = -3.2° (c 0.21, DMSO) (20°C)

Reference Example 4

N-Benzyloxycarbonyl-L-isoleucyl-(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid benzylamide (4.5 g) and 5% Pd-C (2.2 g) were added to a mixed solvent of tetrahydrofuran (THF) (30 ml) and methanol (30 ml), followed by stirring at room temperature for 2 hours in a hydrogen atmosphere. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure. The resulting residue and quinoline-2-carboxylic acid (1.54 g) were dissolved in N,N-dimethylformamide (DMF) (40 ml). To this solution, 1-hydroxybenzotriazole (HOBt) (1.43 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl) (1.79 g) were added under ice cooling conditions. After stirring at room temperature for 16 hours, the reaction mixture was poured over ice-water and extracted with ethyl acetate. The organic layer was washed by sequential additions of an aqueous citric acid solution, water, an aqueous $NaHCO_3$ solution and saline and dried ($MgSO_4$). After the solvent was distilled off under reduced pressure, the resulting residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (4:1) to yield a colorless crystal of N-(quinoline-2-carbonyl)-L-isoleucyl-(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid benzylamide (4.2 g).

Melting point: 157-158°C

$[\alpha]_D$ = +2.6° (c 0.87, MeOH) (20°C)

Elemental analysis (for $C_{33}H_{36}N_4O_4$)

Calculated: C, 71.72; H, 6.57; N, 10.14

Found : C, 71.68; H, 6.58; N, 10.05

Reference Example 5

The same procedure as in Reference Example 4 was followed to yield a light yellow crystal of N-(4-diethylphosphonomethylcinnamoyl)-L-isoleucyl-(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid benzylamide.

Melting point: 153-154°C

$[\alpha]_D$ = -14.8° (c 0.76, MeOH) (20°C)

Reference Example 6

To a solution of N-benzyloxycarbonyl-(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid (3.0 g) and L-isoleucine methyl ester hydrochloride (1.74 g) in N,N-dimethylformamide (DMF), triethylamine (1.4 ml), 1-hydroxybenzotriazole (HOBt) (1.54 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl) (1.92 g) were added under ice cooling conditions. After stirring at room temperature for 16 hours, the reaction mixture was poured over ice-water and extracted with ethyl acetate. The organic layer was washed by sequential additions of an aqueous citric acid solution, water, an aqueous $NaHCO_3$ solution and saline and dried ($MgSO_4$).

After the solvent was distilled off under reduced pressure, the resulting residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (2:1) to yield a colorless crystal of N-[(2R,3S)-2-benzyloxycarbonylamino-3-hydroxy-4-phenylbutyryl]-L-isoleucine methyl ester (2.3 g).

Melting point: 120-121°C

$[\alpha]_D$ = -58.5° (c 0.78, MeOH) (20°C)

Elemental analysis (for $C_{25}H_{32}N_2O_6$)

Calculated: C, 65.77; H, 7.06; N, 6.14

Found : C, 65.78; H, 6.95; N, 6.08

Reference Example 7

The same procedure as in Reference Example 4 was followed to yield a colorless crystal of N-[(2R,3S)-2-dibenzylacetylamino-3-hydroxy-4-phenylbutyryl]-L-isoleucine methyl ester.

Melting point: 130-131°C

$[\alpha]_D$ = -47.8° (c 0.63, MeOH) (20°C)

Reference Example 8

The same procedure as in Reference Example 4 was followed to yield a colorless needle of (2R,3S)-2-dibenzylacetylamino-3-hydroxy-4-phenylbutyric acid methyl ester.

Melting point: 107-108°C

$[\alpha]_D$ = -84.8° (c 0.53, MeOH) (20°C)

Reference Example 9

To a solution of (2R,3S)-2-dibenzylacetylamino-3-hydroxy-4-phenylbutyric acid methyl ester (4.3 g) in a mixed solvent of tetrahydrofuran (THF) (20 ml) and methanol (10 ml), an aqueous solution of potassium hydroxide (1.2 g) was added dropwise under ice cooling conditions. After stirring under ice cooling conditions for 6 hours, the reaction mixture was acidified with 1 N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with saline and dried ($MgSO_4$). After the solvent was distilled off under reduced pressure, the resulting white solid was recrystallized from ethyl acetate-hexane to yield a colorless crystal of (2R,3S)-2-dibenzylacetylamino-3-hydroxy-4-phenylbutyric acid (3.0 g).

Melting point: 128-130°C

$[\alpha]_D$ = -60.3° (c 0.38, $CHCl_3$) (20°C)

Elemental analysis (for $C_{26}H_{27}NO_4\cdot 1/4H_2O$)

Calculated: C, 74.00; H, 6.57; N, 3.32

Found : C, 74.09; H, 6.50; N, 3.17

Reference Example 10

The same procedure as in Reference Example 6 was followed to yield a colorless crystal of (2R,3S)-2-dibenzylacetylamino-3-hydroxy-4-phenylbutyric acid benzylamide.

Melting point: 148-149°C

$[\alpha]_D$ = -15.7° (c 0.99, MeOH) (20°C)

Reference Example 11

The same procedure as in Reference Example 9 was followed to yield a colorless crystal of N-[(2R,3S)-2-dibenzylacetylamino-3-hydroxy-4-phenylbutyryl]-L-isoleucine.

Melting point: 93-94°C

$[\alpha]_D$ = -35.9° (c 0.65, DMSO) (20°C)

Reference Example 12

The same procedure as in Reference Example 6 was followed to yield a colorless crystal of N-[(2R,3S)-2-dibenzylacetylamino-3-hydroxy-4-phenylbutyryl]-L-isoleucine benzylamide.

Melting point: 156-158°C

$[\alpha]_D$ = -49.5° (c 0.61, MeOH) (20°C)

Reference Example 13

The same procedure as in Reference Example 4 was followed to yield a colorless crystal of N-benzyloxycarbonyl-L-isoleucyl-(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid methyl ester.

Melting point: 128-130°C

$[\alpha]_D$ = -77.1° (c 0.36, DMSO) (20°C)

Reference Example 14

The same procedure as in Reference Example 9 was followed to yield a white solid of N-benzyloxycarbonyl-L-isoleucyl-(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid.

Melting point: 180-181°C

$[\alpha]_D$ = -64.3° (c 0.43, DMSO) (20°C)

Reference Example 15

The same procedure as in Reference Example 6 was followed to yield a white solid of N-benzyloxycarbonyl-L-isoleucyl-(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid benzylamide.

Melting point: 178-179°C

$[\alpha]_D$ = -21.8° (c 0.52, MeOH) (20°C)

Reference Example 16

The same procedure as in Reference Example 6 was followed to yield a white solid of N-benzyloxycarbonyl-L-isoleucyl-(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid 2-pyridylmethylamide.

Melting point: 156-157°C

$[\alpha]_D$ = -22.2° (c 0.47, DMSO) (20°C)

Reference Example 17

The same procedure as in Reference Example 6 was followed to yield a white solid of N-benzyloxycarbonyl-L-isoleucyl-(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid 4-pyridylmethylamide.

Melting point: 223-225°C

$[\alpha]_D$ = -21.5° (c 0.60, DMSO) (20°C)

Reference Example 18

The same procedure as in Reference Example 6 was followed to yield a white solid of N-benzyloxycarbonyl-L-isoleucyl-(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid 4-diethylphosphonomethylphenylamide.

Melting point: 145-146°C

$[\alpha]_D$ = -31.1° (c 0.89, DMSO) (20°C)

Reference Example 19

The same procedure as in Reference Example 6 was followed to yield a white solid of N-benzyloxycarbonyl-L-isoleucyl-(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid isobutylamide.

Melting point: 185-186°C

$[\alpha]_D = -40.7°$ (c 0.57, DMSO) (20°C)

Reference Example 20

The same procedure as in Reference Example 6 was followed to yield a white solid of N-benzyloxycarbonyl-L-isoleucyl-(2R,3S)-3-amino-2-hydroxy-4-phenylbutyric acid 3-(2-oxopyrrolidin-1-yl)propylamide.

Melting point: 153-154°C

$[\alpha]_D = -35.2°$ (c 0.59, MeOH) (20°C)

Reference Example 21

L-Phenylalaninol (15.1 g) and triethylamine (14.7 ml) were added to a mixed solvent of dichloromethane (50 ml) and tetrahydrofuran (THF) (50 ml). To this suspension, ethyl chloroformate (9.5 ml) was added dropwsie under ice cooling conditions. After stirring at room temperature for 1 hour, the reaction mixture was concentrated. The residue was diluted with ethyl acetate and washed with water and saline, and dried ($MgSO_4$). After the solvent was distilled off under reduced pressure, the resulting residue was dissolved in a mixed solvent of dimethyl sulfoxide (DMSO) (100 ml) and dichloromethane (50 ml). To this solution, triethylamine (35 ml) was added and cooled with ice. After a solution of sulfur trioxide-pyridine complex (40 g) in dimethyl sulfoxide (DMSO) (160 ml) was added dropwise, the reaction mixture was stirred at the same temperature for 2 hours. The reaction mixture was poured over ice-water and extracted with ethyl acetate. The organic layer was washed by sequential additions of an aqueous citric acid solution, water and an aqueous $NaHCO_3$ solution, and dried ($MgSO_4$). After the solvent was distilled off under reduced pressure, the resulting yellow oily substance was added to a mixture of dichloromethane (300 ml) and water (300 ml). Sodium cyanide (5.3 g), acetic anhydride (10.3 ml) and benzyltributylammonium chloride (7.5 g) were then added, followed by vigorous stirring at room temperature for 5 hours. The organic layer was separated, washed with brine and dried ($MgSO_4$). After the solvent was distilled off under reduced pressure, the resulting yellow oily substance was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (1:2) to yield a light yellow oily substance of a diastereomeric mixture (R:S = 5:2) of (2S)-1-cyano-2-ethoxycarbonylamino-3-phenylpropyl acetate (19.9 g).

1H-NMR (δ ppm in $CDCl_3$): 1.21 & 1.26 (3H, each t, J=7.0 Hz), 2.13 & 2.17 (3H, each s), 2.8-3.2 (2H, m), 4.0-4.2 (2H, m), 4.2-4.5 (1H, m), 4.7-5.0 (1H, m), 5.38 & 5.40 (1H, each d, J=5.8 Hz), 7.1-7.4 (5H, m)

Reference Example 22

(2S)-1-cyano-2-ethoxycarbonylamino-3-phenylpropyl acetate (30 g) was added to 6 N hydrochloric acid (140 ml), followed by refluxing for 3 days. After the reaction mixture was concentrated, the residue was added to a 2% hydrochloric acid solution in methanol (200 ml), followed by refluxing for 2 days. After the solvent was distilled off under reduced pressure, the resulting residue was dissolved in water. After being washed with ethyl acetate, this aqueous solution was turned basic with $NaHCO_3$. The water layer was twice extracted with chloroform; the resulting organic layers were combined and dried ($MgSO_4$). After the solvent was distilled off under reduced pressure, the resulting brown solid was recrystallized from ethyl acetate-hexane to yield a colorless needle of (3S,2R)-3-amino-2-hydroxy-4-phenylbutyric acid methyl ester (9.0 g).

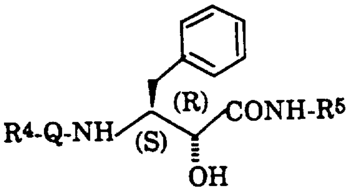
Melting point: 108-109°C

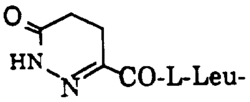
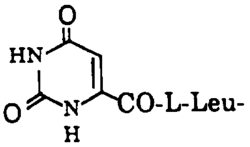
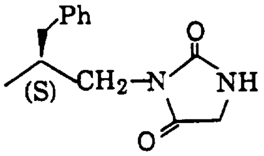
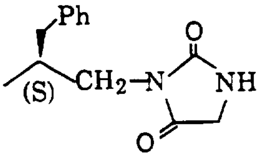
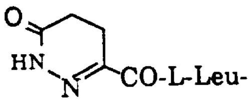
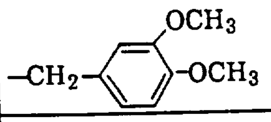
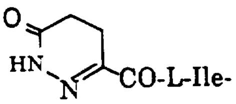
$[\alpha]_D = -34.2°$ (c 0.60, MeOH) (20°C)

Reference Examples 23-31

By substantially the same procedure as in Reference Example 4, compounds shown in Table 4 were produced.

Table 4



No. of R. Ex.	R^4-Q-	R^5	m.p. (°C)	Optical Rotation $[\alpha]_D$
23	$(C_3H_7)_2$CH-L-Val-	-CH_2Ph	203-204 1)	-30.3°(c=0.81,DMSO)
24		-CH_2Ph	198-199	-27.1°(c=0.69,DMSO)
25		-CH_2Ph	178-179 2)	-13.1°(c=0.78,DMSO)
26	Cbz-L-Leu-		228-230 1)	-32.5°(c=0.57,DMSO)
27	2-Qnl-L-Leu-		164-165 1)	+3.1°(c=0.78,DMSO)
28			206-207 1)	-51.9°(c=0.51,CH_3OH)
29	Cbz-L-Leu-L-Leu-	-CH_2Ph	215-217 2)	-32.2°(c=0.83,DMSO)
30	2-Qnl-L-Leu-L-Leu-	-CH_2Ph	127-128	+14.8°(c=0.58,CH_3OH)
31		-CH_2Ph	209-210	-15.2°(c=0.45,DMSO)

1) 1/2hydrate, 2) 1/4hydrate

Val=valine, Leu=leucine, Ile=isoleucine, DMSO=dimethylsulfoxide, Ph=phenyl, Cbz=benzyloxycarbonyl, 2-Qnl=quinoline-2-carbonyl

Reference Example 32

To a solution of (3S,2R)-3-amino-2-hydroxy-4-phenylbutyric acid methyl ester (3.3 g) and N-benzyloxycarbonyl-L-valine (4.2 g) in N,N-dimethylformamide (DMF) (40 ml), 1-hydroxybenzotriazole (HOBt) (2.7 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD•HCl) (3.4 g) were added under ice cooling conditions. After stirring at room temperature for 18 hours, the reaction mixture was poured over ice-water and extracted with ethyl acetate. The ethyl acetate layer was washed by sequential additions of water, an aqueous citric acid solution, water, an aqueous $NaHCO_3$ solution and saline and dried ($MgSO_4$). After the solvent was distilled off under reduced pressure, the resulting solid was filtered and washed with ethyl acetate-hexane to yield (2R,3S)-3-[N-[N-benzyloxycarbonyl-L-valyl]amino]-2-hydroxy-4-phenylbutyric acid methyl ester.

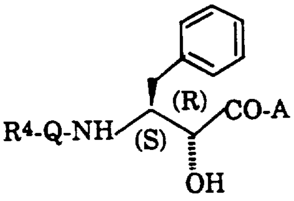
Melting point: 131-132°C

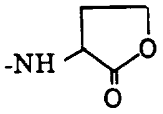
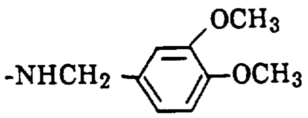
$[\alpha]_D = -98.3°$ (c=0.33, CH_3OH).

Reference Examples 33-37

By substantially the same procedure as in Reference Example 32, compounds shown in Table 5 were produced.

Table 5



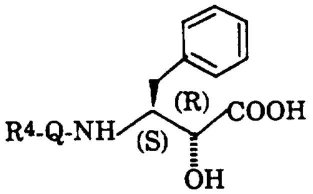
No. of R. Ex.	R^4-Q-	A	m.p. (°c)	Optical Rotation $[\alpha]_D$
33	Cbz-L-Val-	$-NHCH_2Ph$	171 - 172	-21.0°(c=0.87,CH_3OH)
34	Cbz-L-Leu-	$-OCH_3$	107 - 108	-101.5°(c=0.94,CH_3OH)
35	Cbz-L-Leu-		201 - 202	-52.8°(c=0.77,DMSO)
36	Cbz-L-Leu-	$-NHCH_2Ph$	173 - 174	-27.7°(c=0.78,DMSO)
37	Cbz-L-Leu-		142 - 143	-27.1°(c=0.80,CH_3OH)

Val=valine, Leu=leucine, Ph=phenyl, Cbz=benzyloxycarbonyl, DMSO=dimethyl sulfoxide

Reference Examples 38 and 39

By substantially the same procedure as in Reference Example 9, compounds shown in Table 6 were produced.

Table 6



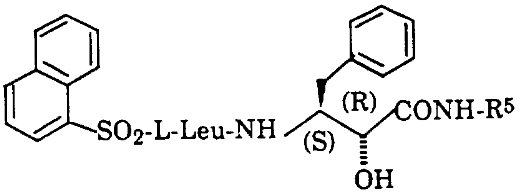
No. of R. Ex.	R^4-Q-	m.p. (°C)	Optical Rotation $[\alpha]_D$
38	Cbz-L-Val-	188-189	-63.7°(c=0.87,CH_3OH)
39	Cbz-L-Leu-	141-142	-89.6°(c=0.85,CH_3OH)

Val=valine, Leu=leucine, Cbz=benzyloxycarbonyl, DMSO=dimethyl sulfoxide

Reference Examples 40 and 41

By substantially the same procedure as in Reference Example 1, compounds shown in Table 7 were produced.

Table 7



No. of R. Ex.	R^5	m.p. (°C)	Optical Rotation $[\alpha]_D$
40	benzyl	181-182	-49.0°(c=0.74, dimethyl sulfoxide)
41	3,4-dimethoxybenzyl	102-103[1)]	-135.1°(c=0.62,methanol)

1) 1/2hydrate

Reference Example 42

To a solution of N-benzyloxycarbonyl-L-phenylalaninol (2.0 g), triphenylphosphine (Ph_3P) (1.9 g), hydantoin (0.71 g) and tetrahydrofuran (THF) (50 ml), diethyl azodicarboxylate (DEAD) (1.24 g) was added dropwise under

ice cooling conditions. After stirring at room temperature for 16 hours, the reaction mixture was poured over ethyl acetate and washed by sequential additions of water, an aqueous $NaHCO_3$ solution and brine, and dried ($MgSO_4$). After the solvent was distilled off under reduced pressure, the resulting residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (3:1, v/v) to yield 1-[(2S)-2-(N-benzyloxycarbonylamino)-3-phenylpropyl]hydantoin (1.15 g, 44%).
Melting point: 159-160°C
$[\alpha]_D$ = +15° (c=0.79, CH_3OH).

Preparation Examples

A cathepsin L inhibitor comprising inventive compound (I) or (Ia) or a salt thereof as an active ingredient can, for example, be produced with the following formulations:

1. Capsules

(1)	N-(p-diethylphosphonomethylcinnamoyl)-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide	10 mg
(2)	Lactose	90 mg
(3)	Microcrystalline cellulose	70 mg
(4)	Magnesium stearate	10 mg
	Total	180 mg per capsule

Components (1), (2) and (3) and a half portion of component (4) are mixed and granulated. To these granules, the remaining portion of component (4) is added, and the whole mixture is packed in a gelatin capsule.

2. Tablets

(1)	N-benzyloxycarbonyl-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide	10 mg
(2)	Lactose	35 mg
(3)	Corn starch	150 mg
(4)	Microcrystalline cellulose	30 mg
(5)	Magnesium stearate	5 mg

Total 230 mg per tablet

Components (1), (2) and (3), a two-third portion of component (4) and a half portion of component (5) are mixed and granulated. To these granules, the remaining portions of components (4) and (5) are added, and the whole mixture is tableted by compressive tableting.

3. Injectable preparation

(1) N-(quinoline-2-carbonyl)-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide	10 mg
(2) Inositol	100 mg
(3) Benzyl alcohol	20 mg
Total	130 mg per ampule

Components (1), (2) and (3) are dissolved in distilled water for injection to a final quantity of 2 ml, and the solution is packed in an ampule. The entire procedure is performed aseptically.

4. Capsules

(1) N-(1-naphthalenesulfonyl)-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid 4-pyridylmethylamide	10 mg
(2) Lactose	90 mg
(3) Microcrystalline cellulose	70 mg
(4) Magnesium stearate	10 mg
Total	180 mg per capsule

Components (1), (2) and (3) and a half portion of component (4) are mixed and granulated. To these granules, the remaining portion of component (4) is added, and the whole mixture is packed in a gelatin capsule.

5. Tablets

(1) N-(1-naphthalenesulfonyl)-L-phenylalanyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide	10 mg
(2) Lactose	35 mg

(3) Corn starch		150 mg
(4) Microcrystalline cellulose		30 mg
(5) Magnesium stearate		5 mg
	Total	230 mg per tablet

Components (1), (2) and (3), a two-third portion of component 4 and a half portion of component (5) are mixed and granulated. To these granules, the remaining portions of components (4) and (5) are added, and the whole mixture is tableted by compressive tableting.

6. Injectable preparation

(1) N-benzyloxycarbonyl-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid isobutylamide		10 mg
(2) Inositol		100 mg
(3) Benzyl alcohol		20 mg
	Total	130 mg per ampule

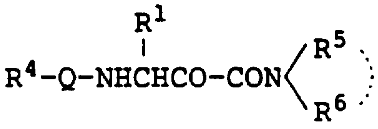
Components (1), (2) and (3) are dissolved in distilled water for injection to a final quantity of 2 ml, and the solution is packed in an ampule. The entire procedure is performed aseptically.

Industrial Applicability

Since the compound represented by general formula (I), (Ia), (I') or (I") or a salt thereof possesses potent cathepsin L inhibitory activity, it excellently suppresses bone resorption, and it can therefore be advantageously used to prevent or treat osteoporosis in mammals.

CLAIMS

1. A cathepsin L inhibitor comprising a compound of the formula (Ia):

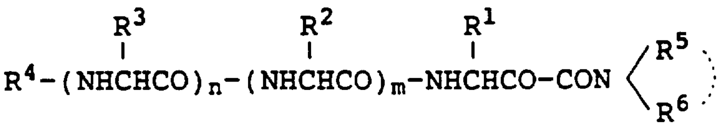


$$R^4\text{-Q-NH}\overset{\displaystyle R^1}{\overset{|}{\text{C}}}\text{HCO-CON}\left\langle\begin{matrix}R^5\\ R^6\end{matrix}\right.$$

(Ia)

wherein Q represents a direct bond or 1 or 2 amino acid residues that may be substituted; R^1 represents a hydrogen atom or a hydrocarbon or heterocyclic group that may be substituted; R^4 represents an acyl group or a carboxyl group that may be esterified and R^5 and R^6 independently represent a hydrogen atom or a hydrocarbon or heterocyclic group that may be substituted or R^5 and R^6 may bind together to form a ring; or a salt thereof.

2. A cathepsin L inhibitor of claim 1, wherein the compound is one of the formula (I):



$$R^4\text{-}(\text{NH}\overset{\displaystyle R^3}{\overset{|}{\text{C}}}\text{HCO})_n\text{-}(\text{NH}\overset{\displaystyle R^2}{\overset{|}{\text{C}}}\text{HCO})_m\text{-NH}\overset{\displaystyle R^1}{\overset{|}{\text{C}}}\text{HCO-CON}\left\langle\begin{matrix}R^5\\ R^6\end{matrix}\right.$$

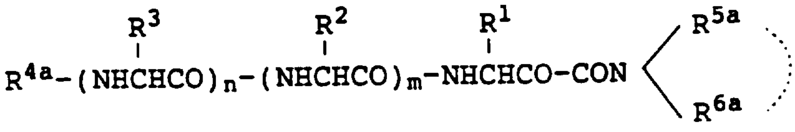
(I)

wherein R^1, R^2 and R^3 independently represent a hydrogen atom or a hydrocarbon or heterocyclic group that may be substituted; R^4 represents an acyl group or a carboxyl group that may be esterified and R^5 and R^6 independently represent a hydrogen atom or a hydrocarbon or heterocyclic group that may be substituted or R^5 and R^6 may bind together to form a ring; m and n independently represent 0 or 1; or a salt thereof.

3. A method for inhibiting a cathepsin L activity of a mammal which comprises administering to said mammal a pharmaceutically effective amount of a compound of the formula (Ia) in claim 1.

4. Use of a compound of the formula (Ia) in claim 1 for the manufacture of a medicament to be used as a cathepsin L inhibitor.

5. A compound of the formula (I')



$$R^{4a}\text{-}(\mathrm{NH}\overset{R^3}{\mathrm{C}}\mathrm{HCO})_n\text{-}(\mathrm{NH}\overset{R^2}{\mathrm{C}}\mathrm{HCO})_m\text{-}\mathrm{NH}\overset{R^1}{\mathrm{C}}\mathrm{HCO\text{-}CON}\begin{matrix}R^{5a}\\ R^{6a}\end{matrix} \qquad (I')$$

wherein R^1, R^2 and R^3 independently represent a hydrogen atom or a hydrocarbon or heterocyclic group that may be substituted; R^{4a} is a group represented by the formula $-COR^a$ or $-SO_2R^b$ wherein R^a and R^b are independently an optionally substituted aryl or aromatic heterocyclic group; R^{5a} and R^{6a} independently represent a straight-chain or branched C_{1-6} alkyl group which may be substituted with an optionally substituted aryl or aromatic heterocyclic group or an optionally esterified carboxyl group and m and n independently represent 0 or 1; provided that where R^a is an optionally substituted aromatic heterocyclic group, R^{5a} and R^{6a} independently represent a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl or aromatic heterocyclic group or an optionally esterified carboxyl group; or a salt thereof.

6. A compound of claim 5, wherein R^1, R^2 and R^3 independently represent a hydrogen atom or (A) a hydrocarbon group selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkinyl, C_{3-12} cycloalkyl, C_{5-12} cycloalkenyl, C_{5-12} cycloalkadienyl, C_{3-7} cycloalkyl-C_{1-8} alkyl, C_{5-7} cycloalkenyl-C_{1-8} alkyl and C_{6-14} aryl or (B) a heterocyclic group selected from the group consisting of a 5- to 7-membered aromatic heterocyclic group containing 1 atom of sulfur, nitrogen and oxgen, 5- or 6-membered aromatic heterocyclic group containing 2 to 4 atoms of nitrogen or 5- or 6-membered aromatic heterocyclic group

containing 1 or 2 atoms of nitrogen and 1 atom of sulfur and oxgen which may be condensed with a 6-membered ring containing 2 or fewer atoms of nitrogen, a benzene ring or a 5-memebred ring containing 1 atom of sulfur and a 5- to 7-membered non-aromatic heterocyclic group containing 1 atom of sulfur, nitrogen and oxgen or 4- to 7-membered non-aromatic heterocyclic group containing 1 atom of nitrogen and 3 or fewer atoms selected from nitrogen, oxgen and sulfur which may be condensed with a benzene ring, a 6-membered ring containing 2 or fewer atoms of nitrogen, or a 5-membered ring containing 1 atom of sulfur which hydrocarbon or heterocyclic group may have 1 to 3 substituents selected from the group consisting of (i) a C_{6-14} aryl group which may be substituted with hydroxy, C_{1-3} alkoxy, halogen or C_{1-3} alkyl, (ii) a C_{3-7} cycloalkyl or C_{3-6} cycloalkenyl group which may be substituted with hydroxy, C_{1-3} alkoxy, halogen or C_{1-3} alkyl, (ii) a C_{3-7} cycloalkyl or C_{3-6} cycloalkenyl group which may be substituted with hydroxy, C_{1-3} alkoxy, halogen or C_{1-3} alkyl, (iii) a heterocyclic group selected from the group consisting of a 5- to 7-membered aromatic heterocyclic group containing 1 atom of sulfur, nitrogen or oxgen, 5- or 6-membered aromatic heterocyclic group containing 2 to 4 atoms of nitrogen or 5- or 6-membered aromatic heterocyclic group containing 1 or 2 atoms of nitrogen and 1 atom of sulfur or oxgen which may condense with a 6-membered ring containing 2 or fewer atoms of nitrogen, a benzene ring or a 5-memebred ring containing 1 atom of sulfur and a 5- to 7-membered non-aromatic heterocyclic group containing 1 atom of sulfur, nitrogen or oxgen or 4- to 7-membered non-aromatic heterocyclic group containing 1 atom of nitrogen and 3 or fewer atoms selected from nitrogen, oxgen and sulfur which may condense with a benzene ring, a 6-membered ring containing 2 or fewer atoms of nitrogen, or a 5-membered ring containing 1 atom of sulfur which heterocyclic group may be substituted with C_{1-3} alkyl, (iv) carboxyl, (C_{1-6} alkoxy) carbonyl, (C_{6-10} aryloxy)carbonyl or (C_{7-13} ararkyloxy)carbonyl, (v) a carbamoyl group which may be substituted with C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl or C_{7-13} ararkyl, (vi) an amino group which may be substituted with C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl or C_{7-13} ararkyl, (vii) a hydroxyl gorup which may be substituted with C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl or C_{7-13} ararkyl, (viii) a thiol group which may be substituted with C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl or C_{7-13} ararkyl, (ix) halogen and (x) a phosphono group which may be substituted with C_{1-6} alkyl or C_{1-6} alkoxy;

R^a and R^b are independently (A) a C_{6-10} aryl group or (B) a 5- to 7-membered aromatic heterocyclic group containing 1 atom of sulfur, nitrogen or oxgen, 5- or 6-membered aromatic heterocyclic group containing 2 to 4 atoms of nitrogen or 5- or 6-membered aromatic heterocyclic group containing 1 or 2 atoms of nitrogen and 1 atom of sulfur or oxgen which may be condensed with a 6-membered ring containing 2 or fewer atoms of nitrogen, a benzene ring or a 5-memebred ring containing 1 atom of sulfur in which the aryl or heterocyclic group may be substituted with C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or halogen;

R^{5a} and R^{6a} independently represent a straight-chain or branched C_{1-6} alkyl group which may be substituted with (A) a C_{6-10} aryl group, (B) a 5- to 7-membered aromatic heterocyclic group containing 1 atom of sulfur, nitrogen or oxgen, 5- or 6-membered aromatic heterocyclic group containing 2 to 4 atoms of nitrogen or 5- or 6-membered aromatic heterocyclic group containing 1 or 2 atoms of nitrogen and 1 atom of sulfur or oxgen which may be condensed with a 6-membered ring containing 2 or fewer atoms of nitrogen, a benzene ring or a 5-memebred ring containing 1 atom of sulfur in which the aryl or heterocyclic group may be substituted with C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or halogen, or (C) carboxy, (C_{1-6}

alkoxy)carbonyl, (C_{6-10} aryloxy)carbonyl or (C_{7-13} ararkyloxy)carbonyl.

7. A compound of claim 5, wherein the aryl group for R^a and R^b is naphthyl.

8. A compound of claim 5, wherein the aromatic heterocyclic group for R^a and R^b is quinolyl.

9. A compound of claim 5, wherein one of R^{5a} and R^{6a} is a hydrogen atom and the other is benzyl.

10. A compound of claim 5, wherein R' is a straight-chain or branched C_{1-6} alkyl group which is substituted with a phenyl gorup.

11. A compound of claim 5, wherein R^2 and R^3 are independently a straight-chain or branched C_{1-6} alkyl gorup.

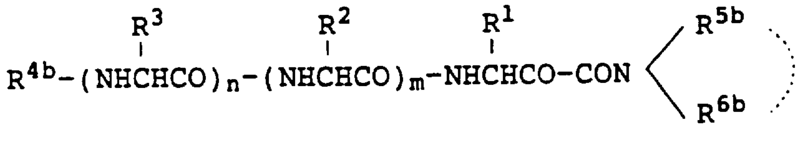
12. A compound of N-(quinoline-2-carbonyl)-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutanoic benzylamide, or a salt thereof.

13. A compound of N-[N-(6-oxo-1,4,5,6-tetrahydropyridazine-3-carbonyl)-L-leucyl]-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide, or a salt thereof.

14. A compound of N-benzyloxycarbonyl-L-leucyl-L-leucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide, or a salt thereof.

15. A compound of N-(quinoline-2-carbonyl)-L-leucyl-L-leucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide, or a salt thereof.

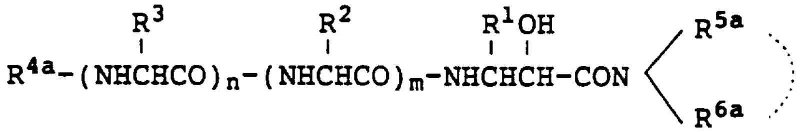
16. A compound of the formula (I")



$$R^{4b}\text{-}(\mathrm{NH}\overset{R^3}{\mathrm{C}}\mathrm{HCO})_n\text{-}(\mathrm{NH}\overset{R^2}{\mathrm{C}}\mathrm{HCO})_m\text{-}\mathrm{NH}\overset{R^1}{\mathrm{C}}\mathrm{HCO}\text{-}\mathrm{CON}\left\langle\begin{matrix}R^{5b}\\R^{6b}\end{matrix}\right. \qquad (I")$$

wherein R^1, R^2 and R^3, whether identical or not, independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted; R^{4b} is represented by the formula $-COR^c$ wherein R^c is a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl or aromatic heterocyclic group; R^{5b} and R^{6b} independently represent a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl group or an esterified carboxyl group; and m and n independently represent 0 or 1; or a salt thereof.

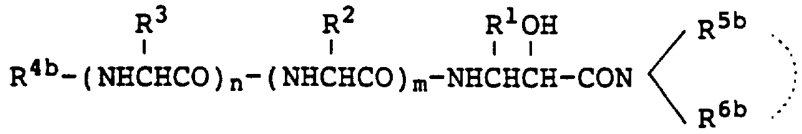
17. A method of producing a compound of claim 5 which comprises subjecting a compound of the formula (II')



$$R^{4a}-(NH\overset{R^3}{C}HCO)_n-(NH\overset{R^2}{C}HCO)_m-NH\overset{R^1}{C}H\overset{OH}{C}H-CON\left\langle \begin{matrix} R^{5a} \\ R^{6a} \end{matrix} \right. \qquad (II')$$

wherein R^1, R^2 and R^3 independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted; R^{4a} is a group represented by the formula $-COR^a$ or $-SO_2R^b$ wherein R^a and R^b are independently an optionally substituted aryl or aromatic heterocyclic group and R^{5a} and R^{6a} independently represent a straight-chain or branched C_{1-6} alkyl group which may be substituted with an optionally substituted aryl or aromatic heterocyclic group or an optionally esterified carboxyl group; provided that where R^a is an optionally substituted aromatic heterocyclic group and R^{5a} and R^{6a} independently represent a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl or aromatic heterocyclic group or an optionally esterified carboxyl group; or a salt thereof, to an oxidation reaction.

18. A method of producing a compound of claim 16 which comprises subjecting a compound of the formula (II")



$$R^{4b}-(NH\overset{R^3}{C}HCO)_n-(NH\overset{R^2}{C}HCO)_m-NH\overset{R^1}{C}H\overset{OH}{C}H-CON\left\langle \begin{matrix} R^{5b} \\ R^{6b} \end{matrix} \right. \qquad (II'')$$

wherein R^1, R^2 and R^3 independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted; R^{4b} is a group represented by the formula -COR^c wherein R^c is a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl or aromatic heterocyclic group and R^{5b} and R^{6b} independently represent a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl group or an esterified carboxyl group; or a salt thereof, to an oxidation reaction.

19. A composition which comprises a compound of claim 5.

20. A composition which comprises a compound of claim 16.