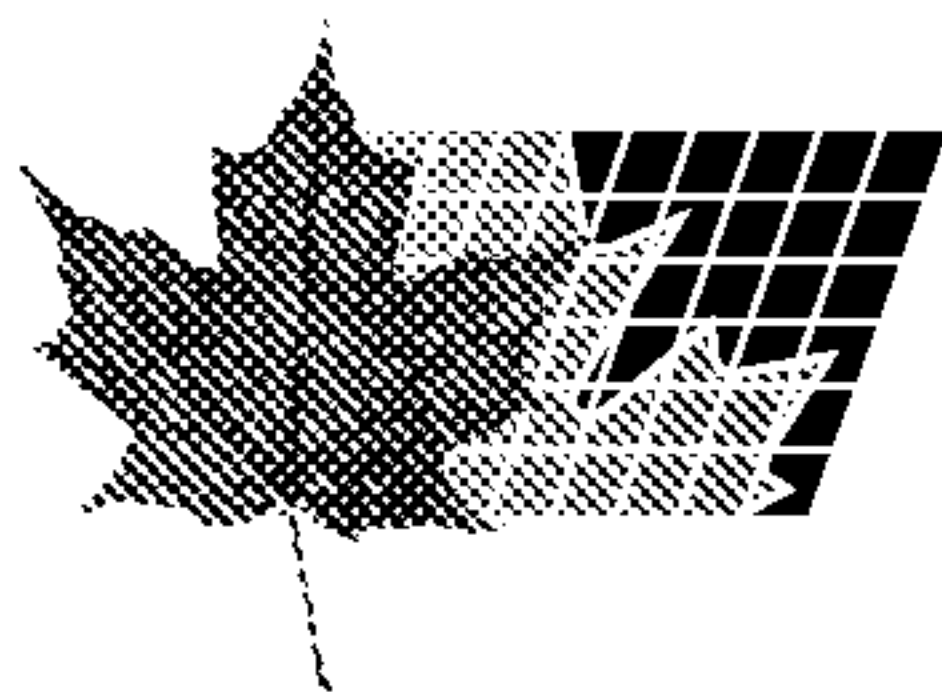




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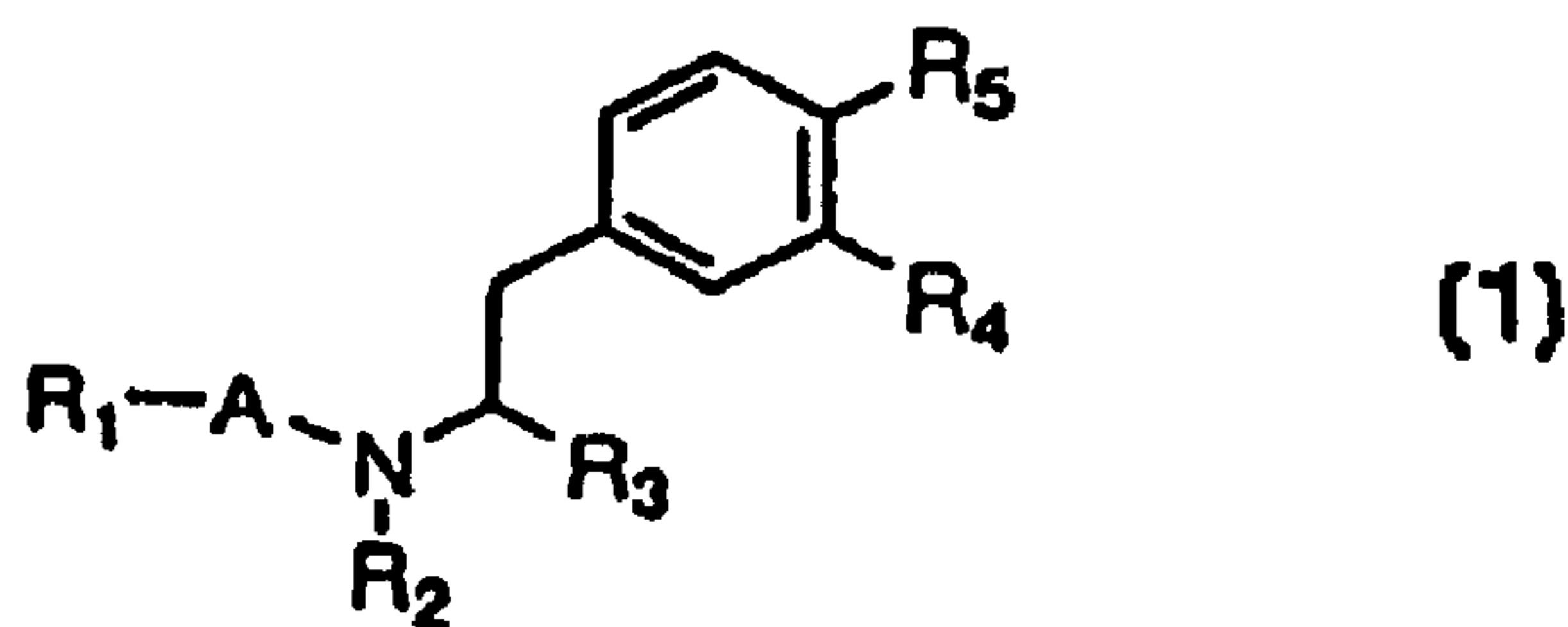
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(54) **DERIVES DE PHENYLETHYLAMINE**

(54) **PHENETHYLAMINE DERIVATIVES**



(57) La présente invention concerne des composés représentés par la formule générale, en l'occurrence des dérivés de phényléthylamine présentant entre autres une activité antagoniste au récepteur de la motiline. Dans cette formule générale (I), A est notamment radical d'acide aminé; R₁ est notamment R₆-CO-; R₂ est notamment hydrogène; R₃ est notamment -CO-R₇; R₄ est notamment alkyle; R₅ est notamment hydroxy; R₆ est notamment alkyle; et R₇ est notamment une amine.

(57) Compounds represented by general formula (1) which are phenethylamine derivatives exhibiting a motilin receptor antagonism etc. and being useful as drugs, wherein A represents an amino acid residue, etc.; R₁ represents R₆-CO-, etc.; R₂ represents hydrogen, etc.; R₃ represents -CO-R₇, etc.; R₄ represents alkyl, etc.; R₅ represents hydroxy, etc.; R₆ represents alkyl, etc.; and R₇ represents amino, etc.



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(21) 国際出願番号 PCT/JP98/03627 (22) 国際出願日 1998年8月14日(14.08.98) (30) 優先権データ 特願平9/255879 1997年8月15日(15.08.97) JP 特願平10/186802 1998年5月28日(28.05.98) JP (71) 出願人 (米国を除くすべての指定国について) 中外製薬株式会社 (CHUGAI SEIYAKU KABUSHIKI KAISHA)[JP/JP] 〒115-8543 東京都北区浮間5丁目5番1号 Tokyo, (JP) (72) 発明者 ; および (75) 発明者 / 出願人 (米国についてのみ) 小竹健一郎(KOTAKE, Ken-ichiro)[JP/JP] 小園敏郎(KOZONO, Toshiro)[JP/JP] 佐藤 勉(SATO, Tsutomu)[JP/JP] 高梨契典(TAKANASHII, Hisanori)[JP/JP] 〒412-8513 静岡県御殿場市駒門1丁目135番地 中外製薬株式会社内 Shizuoka, (JP)		(74) 代理人 弁理士 社本一夫, 外(SHAMOTO, Ichio et al.) 〒100-0004 東京都千代田区大手町二丁目2番1号 新大手町ビル206区 ユアサハラ法律特許事務所 Tokyo, (JP) (81) 指定国 AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO特許 (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), ユーロパ特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), 欧州特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). 添付公開書類 国際調査報告書
(54) Title: PHENETHYLAMINE DERIVATIVES (54) 発明の名称 フェネチルアミン誘導体 (57) Abstract Compounds represented by general formula (1) which are phenethylamine derivatives exhibiting a motilin receptor antagonism etc. and being useful as drugs, wherein A represents an amino acid residue, etc.; R ₁ represents R ₆ -CO-, etc.; R ₂ represents hydrogen, etc.; R ₃ represents -CO-R ₇ , etc.; R ₄ represents alkyl, etc.; R ₅ represents hydroxy, etc.; R ₆ represents alkyl, etc.; and R ₇ represents amino, etc. (1)		

SPECIFICATION

PHENETHYLAMINE DERIVATIVES

TECHNICAL FIELD

This invention relates to phenethylamine derivatives
5 that typically function as a motilin receptor antagonist and
which are useful as medicines.

BACKGROUND ART

Motilin, which is one of the gastrointestinal hormones,
is a straight-chained peptide consisting of 22 amino acids
10 and is well known to be responsible for regulating the
motility of the gastrointestinal tract in animals
including human. It has been reported that exogenously
administered motilin causes contractions in humans and dogs
that are similar to interdigestive migrating contractions,
15 thus promoting gastric emptying (Itoh et al., Scand. J.
Gastroenterol., 11, 93-110 (1976); Peeters et al.,
Gastroenterology 102, 97-101 (1992)). Hence, erythromycin
derivatives which are an agonist of motilin are under
development as an gastrointestinal tract motor activity
20 enhancer (Sato et al., J. Pharmacol. Exp. Therap., 271,
574-579 (1994); Larrey et al., J. Med. Chem., 38, 1793-1798
(1995); Drug of the Future, 19, 910-912 (1994)).

Peptide and polypeptide derivatives have been reported
as antagonists of motilin receptors (Depoortere et al., Eur.
25 J. Pharmacol., 286, 241-247 (1995); Poitras et al., Biochem.
Biophys. Res. Commun., 205, 449-454 (1994); Takanashi et al.,
J. Pharmacol. Exp. Ther., 273, 624-628 (1995)). These
derivatives are used as a pharmacological tool in the study

of the action of motilin on the motility of the gastrointestinal tract and in the research and development of medicines in the field of the art contemplated by the invention.

5 Motilin receptors had been known to exist principally in the duodenum but recently it has been shown that they also exist in the large intestine, or the lower part of the gastrointestinal tract (William et al., Am. J. Physiol., 262, G50-G55 (1992)), and this indicates the possibility that
10 motilin is involved not only in the motility of the upper part of the gastrointestinal tract but also in the motility of its lower part.

Reports have also been made of the cases of hypermotilinemia in patients with irritable bowel syndrome
15 who were manifesting diarrhea and in patients with irritable bowel syndrome who were under stress (Preston et al., Gut, 26, 1059-1064 (1985); Fukudo et al., Tohoku J. Exp. Med., 151, 373-385 (1987)) and this suggests the possibility that increased blood motilin levels are involved in the disease.
20 Other diseases that have been reported to involve hypermotilinemia include crohn's disease, ulcerative colitis, pancreatitis, diabetes mellitus, obesity, malabsorption syndrome, bacterial diarrhea, atrophic gastritis and postgastroenterectomy syndrome. The antagonists of motilin
25 receptors have the potential to ameliorate irritable bowel syndrome and other diseased states accompanied by increased blood motilin levels.

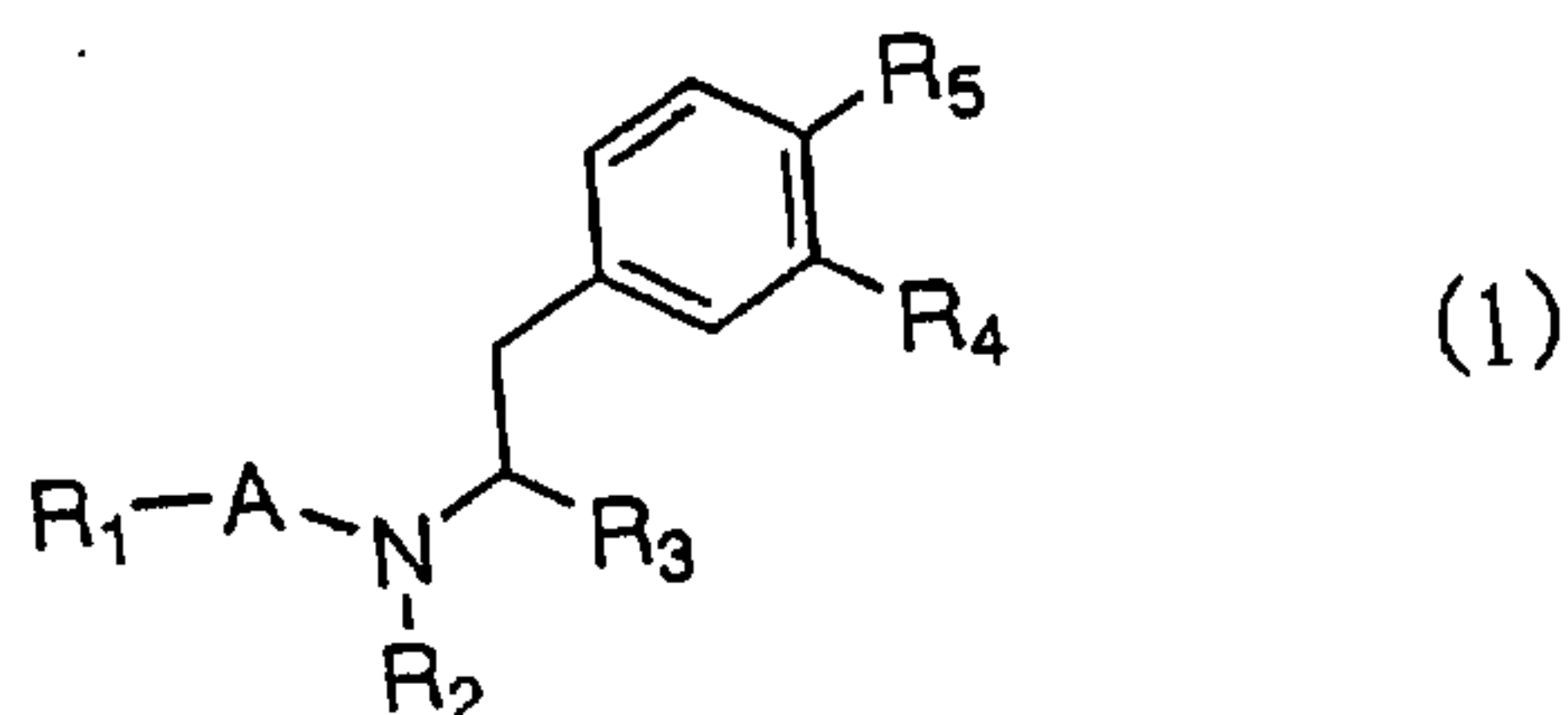
DISCLOSURE OF INVENTION

An object of the invention is to provide phenethylamine derivatives that function as an antagonist of motilin receptors and which are useful as medicines.

The present inventors conducted repeated intensive studies in an attempt to develop compounds having an outstanding motilin receptor antagonistic action. As a result, they found that phenethylamine derivatives represented by the general formula (1) were an excellent antagonist of motilin receptors. The present invention has been accomplished on the basis of this finding.

Thus, the present invention provides compounds represented by the general formula (1), hydrates thereof or pharmaceutically acceptable salts thereof:

15



(wherein A is an amino acid residue or an α -substituted amino acid residue, provided that A binds with $-NR_2-$ to form an amide;

R_1 is an optionally substituted straight-chained or branched alkyl group having 2 - 7 carbon atoms, an optionally substituted straight-chained or branched alkenyl group having 3 - 8 carbon atoms, or an optionally substituted straight-chained or branched alkynyl group having 3 - 8 carbon atoms;

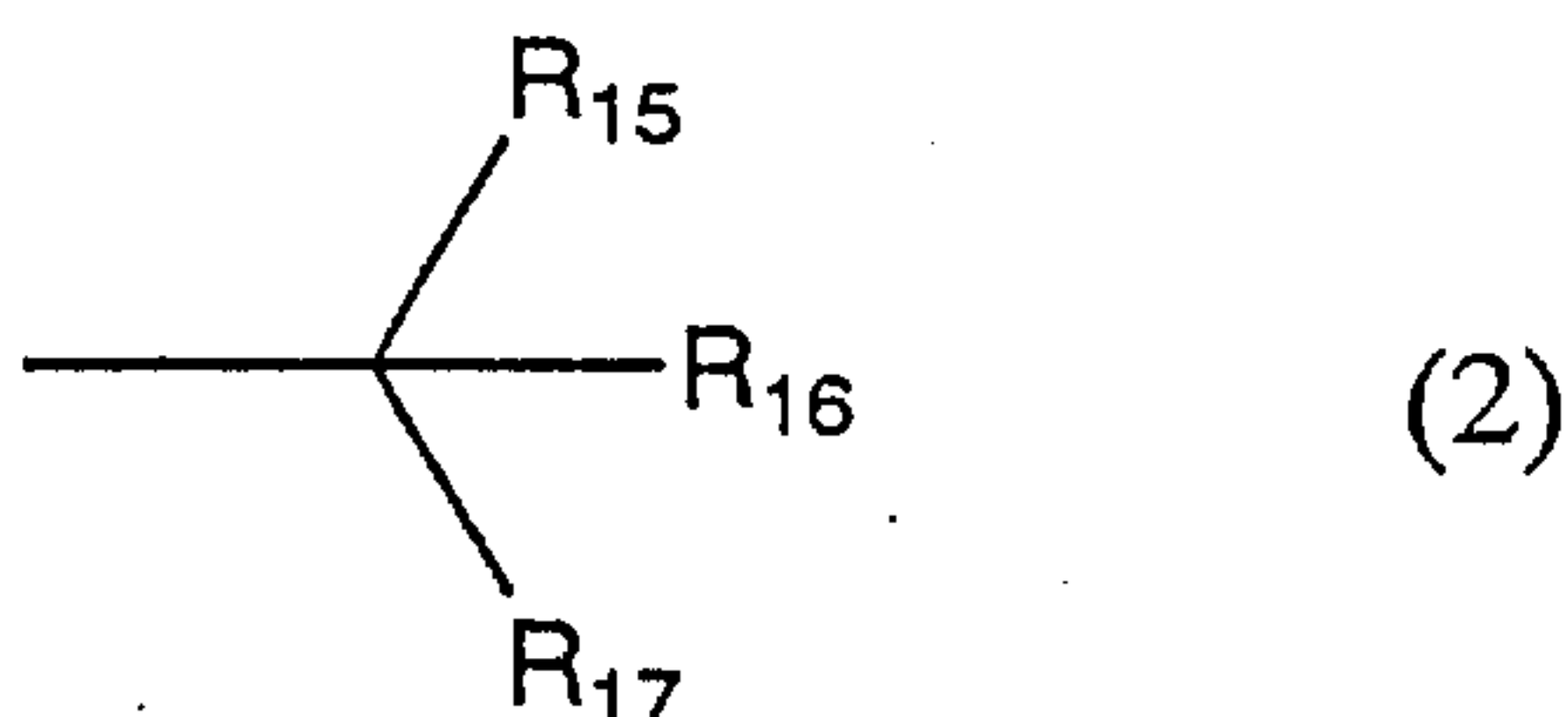
R_2 is a hydrogen atom or an optionally substituted

straight-chained or branched alkyl group having 1 - 3 carbon atoms;

R_3 is $-CO-R_7$, an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, an optionally substituted straight-chained or branched alkenyl group having 2 - 5 carbon atoms or an optionally substituted straight-chained or branched alkynyl group having 2 - 5 carbon atoms;

R_4 is a hydrogen atom, a straight-chained or branched alkyl group having 1 - 6 carbon atoms, a straight-chained or branched alkenyl group having 2 - 6 carbon atoms, a straight-chained or branched alkynyl group having 2 - 6 carbon atoms, or the general formula (2):

15



R_5 is a hydrogen atom or $-OR_8$;

R_6 is an optionally substituted straight-chained or branched alkyl group having 1 - 6 carbon atoms, an optionally substituted straight-chained or branched alkenyl group having 2 - 7 carbon atoms, an optionally substituted alkynyl group having 2 - 7 carbon atoms, a cycloalkyl group having 3 - 7 carbon atoms that may be fused to a benzene ring or a heterocyclic ring, an optionally substituted aromatic ring having 6 - 12 carbon atoms, an optionally substituted saturated or unsaturated heterocyclic ring

having 3 - 12 carbon atoms, $-N(R_9)R_{10}$ or $-OR_{11}$;

R_7 is a hydrogen atom, an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, a cycloalkyl group having 3 - 7 carbon atoms,
5 $-N(R_{12})R_{13}$ or $-OR_{14}$;

R_8 is a hydrogen atom or a straight-chained alkyl group having 1 - 4 carbon atoms;

R_9 and R_{10} , which may be the same or different, each represent a hydrogen atom, an optionally substituted
10 straight-chained or branched alkyl group having 1 - 5 carbon atoms, an optionally substituted straight-chained or branched alkenyl group having 2 - 6 carbon atoms, an optionally substituted straight-chained or branched alkynyl group having 2 - 6 carbon atoms, a cycloalkyl group having 3
15 - 6 carbon atoms that may be fused to a benzene ring or a heterocyclic ring, or an optionally substituted aromatic ring having 6 - 12 carbon atoms;

R_{11} is an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, an
20 optionally substituted straight-chained branched alkenyl group having 2 - 6 carbon atoms, an optionally substituted straight-chained or branched alkynyl group having 2 - 6 carbon atoms, a cycloalkyl group having 3 - 6 carbon atoms that may be fused to a benzene ring or a heterocyclic ring,
25 or an optionally substituted aromatic ring having 6 - 12 carbon atoms;

R_{12} and R_{13} , which may be the same or different, each represent a hydrogen atom, a straight-chained or branched

alkyl group having 1 - 4 carbon atoms or a cycloalkyl group having 3 - 7 carbon atoms;

R_{14} is a hydrogen atom, a straight-chained or branched alkyl group having 1 - 6 carbon atoms, or a cycloalkyl group having 3 - 7 carbon atoms;

R_{15} is a hydrogen atom or a methyl group;

R_{16} and R_{17} , when taken together, represent a cycloalkyl or cycloalkenyl group having 3 - 7 carbon atoms).

The present invention also provides a medicine containing a compound of the general formula (1) as an active ingredient. Further, the invention provides a motilin receptor antagonist containing said compound. The invention also provides a gastrointestinal motility suppressor containing said compound as an active ingredient. Further, the invention provides a therapeutic of hypermotilinemia containing said compound as an active ingredient.

In the definition of the compounds represented by the general formula (1), the amino acid residue as A may be of any types commonly known in the art, as exemplified by α -, β - and γ -amino acid residues. Specific examples include glycine (Gly), alanine (Ala), valine (Val), leucine (Leu), isoleucine (Ile), phenylalanine (Phe), tyrosine (Tyr), tryptophan (trp), histidine (His), asparagine (Asn), glutamine (Gln), aspartic acid (Asp), glutamic acid (Glu), lysine (Lys), serine (Ser), threonine (Thr), methionine (Met), proline (Pro), β -alanine (β -Ala), hydroxyproline (Hyp), citrulline (Cit), ornithine (Orn), phenylglycine

(Phg), norvaline (Nva), aminoisobutyric acid (Aib), homophenylalanine (Hph), 2-thienylalanine (Thi), γ aminobutyric acid (γ -Abu), cyclohexylglycine (Chg), cyclohexylalanine (Cha), tert-leucine (Tle), aminoadipic acid (Aad), diaminobutyric acid (Dab), homoserine (Hse), aminobutyric acid (Abu), 2-aminobenzoic acid (2-Abz), thioproline (Thz), 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic), 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (Tiq), 1-aminocyclopropanecarboxylic acid (Apc), 1-aminocyclobutanecarboxylic acid, 1-aminocyclopentanecarboxylic acid and 1-aminocyclohexanecarboxylic acid (Ahc); preferred are valine (Val), leucine (Leu), isoleucine (Ile), phenylalanine (Phe), tyrosine (Tyr), tryptophan (Trp), phenylglycine (Phg), hydroxyproline (Hyp), homophenylalanine (Hph), cyclohexylglycine (Chg), cyclohexylalanine (Cha), tert-leucine (Tle) and 2-thienylalanine; more preferred are valine (Val), leucine (Leu), isoleucine (Ile), phenylalanine (Phe), phenylglycine (Phg) and cyclohexylalanine (Cha). These amino acid residues and $N\alpha$ -amino acid residues may be any of L-, D- and DL-forms, with the L-form being preferred.

The $N\alpha$ -substituted amino acid residue as A is such that a hydrogen atom in the amino group in the α -position of any one of the above-mentioned α -amino acid residues is substituted. Examples of the substituent on the $N\alpha$ -substituted amino acid residue include a straight-chained or branched alkyl group having 1 - 3 carbon atoms that may be substituted by a benzene ring and the like, and a methyl group is preferred.

Examples of the α -amino acid residue in the $N\alpha$ -substituted amino acid residue as A include the amino acids mentioned above; preferred are Val, Leu, Ile, Phe, Tyr, Trp, Phg, Chg, Cha, Tle and Thi; more preferred are Val, Leu, Ile,
 5 Phe, Phg and Cha.

Examples of the $N\alpha$ -substituted amino acid residue as A include N-methylvaline (N-Me-Val), N-methyllleucine (N-Me-Leu), N-methylisoleucine (N-Me-Ile), N-methylphenylalanine (N-Me-Phe), N-methyltyrosine (N-Me-Tyr), N-methyltryptophan
 10 (N-Me-Trp), N-methylphenylglycine (N-Me-Phg), N-methylcyclohexylglycine (N-Me-Chg), N-methylcyclohexylalanine (N-Me-Cha), N-methyl-tert-leucine (N-Me-Tle), and N-methyl-2-thienylalanine (N-Me-Thi); preferred are N-Me-Val, N-Me-Leu, N-Me-Ile, N-Me-Phe, N-Me-Phg and N-Me-Cha; more preferred as
 15 N-Me-Val and N-Me-Phg.

The definition of R_1 includes R_6 -CO-, in which R_6 may be an optionally substituted straight-chained or branched alkyl group having 1 - 6 carbon atoms, preferably a straight-chained or branched alkyl group having 1 - 5 carbon
 20 atoms, more preferably a straight-chained or branched alkyl group having 2 - 3 carbon atoms, with an ethyl group being particularly preferred.

In the definition of R_6 -CO- as R_1 , R_6 may be an optionally substituted straight-chained or branched alkenyl group having 2 - 7 carbon atoms, preferably a straight-
 25 chained or branched alkenyl group having 4 - 6 carbon atoms.

In the definition of R_6 -CO- as R_1 , R_6 may be an optionally substituted straight-chained or branched alkynyl

group having 2 - 7 carbon atoms, preferably a straight-chained or branched alkynyl group having 4 - 6 carbon atoms.

In the definition of R_6 -CO- as R_1 , R_6 may be an optionally substituted straight-chained or branched alkyl group having 1 - 6 carbon atoms, an optionally substituted straight-chained or branched alkenyl group having 2 - 7 carbon atoms or an optionally substituted straight-chained or branched alkynyl group having 2 - 7 carbon atoms, and exemplary substituents include an amino group, a methylamino group, an ethylamino group, a dimethylamino group, a trimethylammonium group, a hydroxyl group, a carboxyl group, an aminocarbonyl group, an aminocarbonylamino group, a pyridylthio group, a methylthio group, a phenyl group, a 3-indolyl group, a 4-hydroxyphenyl group, a 2-thienyl group, a 2-furyl group, a 3-imidazolyl group and a cyclohexyl group; preferred are an amino group, a methylamino group, a phenyl group, a 3-indolyl group, a 4-hydroxyphenyl group, a 2-thienyl group, a 2-furyl group and a cyclohexyl group; more preferred are an amino group and a phenyl group. The above-mentioned alkyl, alkenyl and alkynyl groups may have one or more of the above-mentioned substituents, which may be the same or different.

In the definition of R_6 -CO- as R_1 , R_6 may be an optionally substituted straight-chained or branched alkyl group having 1 - 6 carbon atoms, preferably a straight-chained or branched alkyl group of 2 - 3 carbon atoms having one or more of the above-mentioned substituents, which may be the same or different; notably, a 1-amino-2-phenylethyl

group, a 1-methylamino-2-phenylethyl group, a 1-amino-2-(3-indolyl)ethyl group, a 1-amino-2-(4-hydroxy)phenylethyl group, a 1-amino-2-(2-thienyl)ethyl group, a 1-amino-2-(2-furyl)ethyl group, a 1-amino-2-cyclohexylethyl group and a
5 2-phenylpropyl group are preferred, and a 1-amino-2-phenylethyl group is particularly preferred.

In the definition of R_6 -CO- as R_1 , R_6 may be an optionally substituted straight-chained or branched alkenyl group having 2 - 7 carbon atoms, preferably a straight-
10 chained or branched alkenyl group of 4 - 6 carbon atoms having one or more of the above-mentioned substituents.

In the definition of R_6 -CO- as R_1 , R_6 may be an optionally substituted straight-chained or branched alkynyl group having 2 - 7 carbon atoms, preferably a straight-
15 chained or branched alkynyl group of 4 - 6 carbon atoms having one or more of the above-mentioned substituents.

In the definition of R_6 -CO- as R_1 , R_6 may be a cycloalkyl group having 3 - 7 carbon atoms that may be fused to a benzene ring or a heterocyclic ring, and examples of
20 the heterocyclic ring include aliphatic or aromatic 5- or 6-membered rings containing one or two hetero atoms selected from among O, N and S; specific examples include pyridine, pyrazine, furan, thiophene, pyrrole and imidazole.

In the definition of R_6 -CO- as R_1 , R_6 may be a
25 cycloalkyl group having 3 - 7 carbon atoms that may be fused to a benzene ring or a heterocyclic ring, preferably a cycloalkyl group having 3 - 7 carbon atoms that is fused to a benzene ring, with a 1-benzocyclobutyl group being

particularly preferred.

In the definition of R_6 -CO- as R_1 , R_6 may be an optionally substituted aromatic ring having 6 - 12 carbon atoms, as exemplified by a benzene ring and a naphthalene
5 ring.

In the definition of R_6 -CO- as R_1 , R_6 may be an optionally substituted aromatic ring having 6 - 12 carbon atoms and exemplary substituents include a hydroxyl group, a methoxy group, a phenoxy group, a benzyloxy group, a tert-
10 butyloxy group, an amino group, a methylamino group, a dimethylamino group, an ethylamino group, a carboxyl group, and a methoxycarbonyl group. The aromatic ring may have one or more of the above-mentioned substituents, which may be the same or different.

15 In the definition of R_6 -CO- as R_1 , R_6 may be an optionally substituted saturated or unsaturated heterocyclic ring having 3 - 12 carbon atoms, as exemplified by aliphatic or aromatic 5- to 10-membered monocyclic or fused rings containing one or more hetero atoms selected from among O, N
20 and S; specific examples include pyrrolidine, piperidine, piperazine, tetrahydroisoquinoline, pyridine, pyrazine, furan, thiophene, pyrrole, imidazole, quinoline, indole, benzimidazole and benzofuran.

In the definition of R_6 -CO- as R_1 , R_6 may be an
25 optionally substituted saturated or unsaturated heterocyclic ring having 3 - 12 carbon atoms and exemplary substituents include a hydroxyl group, a methoxy group, a phenoxy group, a benzyloxy group, a tert-butyloxy group, an amino group, a

methylamino group, a dimethylamino group, an ethylamino group, a carboxyl group and a methoxycarbonyl group. The heterocyclic ring may have one or more of the above-mentioned substituents, which may be the same or different.

5 In the definition of R_6 -CO- as R_1 , R_6 may be an optionally substituted saturated or unsaturated heterocyclic ring having 3 - 12 carbon atoms, as exemplified by the above-mentioned heterocyclic rings that may have one or more of the above-mentioned substituents, which may be the same
10 or different.

 In the definition of R_6 -CO- as R_1 , R_6 may be $-N(R_9)R_{10}$, in which R_9 and R_{10} may each represent an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, preferably a straight-chained or
15 branched alkyl group having 1 - 4 carbon atoms, more preferably a straight-chained alkyl group having 1 - 2 carbon atoms, with a methyl group being particularly preferred.

 In the definition of R_6 -CO- as R_1 , R_6 may be $-N(R_9)R_{10}$,
20 in which R_9 and R_{10} may each represent an optionally substituted straight-chained or branched alkenyl group having 2 - 6 carbon atoms, preferably a straight-chained or branched alkenyl group having 3 - 6 carbon atoms.

 In the definition of R_6 -CO- as R_1 , R_6 may be $-N(R_9)R_{10}$,
25 in which R_9 and R_{10} may each represent an optionally substituted straight-chained or branched alkynyl group having 2 - 6 carbon atoms, preferably a straight-chained or branched alkynyl group having 3 - 6 carbon atoms.

In the definition of R_6 -CO- as R_1 , R_6 may be $-N(R_9)R_{10}$, in which R_9 and R_{10} each represent an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, an optionally substituted straight-chained or branched alkenyl group having 2 - 6 carbon atoms or an optionally substituted straight-chained or branched alkynyl group having 2 - 6 carbon atoms. Exemplary substituents include an amino group, a hydroxyl group, a carboxyl group, an aminocarbonyl group, an aminocarbonylamino group, a pyridylthio group, a methylthio group, a phenyl group, a 3-indolyl group, a 4-hydroxyphenyl group, a thienyl group, a 2-furyl group, a 3-imidazolyl group, and a cyclohexyl group; preferred are an amino group, a phenyl group, a 3-indolyl group, a 4-hydroxyphenyl group, a 2-thienyl group, a 2-furyl group and a cyclohexyl group; more preferred is a phenyl group. These alkyl, alkenyl and alkynyl groups may have one or more of the above-mentioned substituents, which may be the same or different.

In the definition of R_6 -CO- as R_1 , R_6 may be $-N(R_9)R_{10}$, in which R_9 and R_{10} may each represent an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, preferably a methyl group having one or more of the above-mentioned substituents, more preferably a benzyl group, a 3-indolylmethyl group, a p-hydroxybenzyl group, a 2-thienylmethyl group, a 2-furylmethyl group or a cyclohexylmethyl group, with a benzyl group being particularly preferred.

In the definition of R_6 -CO- as R_1 , R_6 may be $-N(R_9)R_{10}$,

in which R_9 and R_{10} may each represent an optionally substituted straight-chained or branched alkenyl group having 2 - 6 carbon atoms, preferably a straight-chained or branched alkenyl group having 3 - 6 carbon atoms.

5 In the definition of R_6 -CO- as R_1 , R_6 may be $-N(R_9)R_{10}$, in which R_9 and R_{10} may each represent an optionally substituted straight-chained or branched alkynyl group having 2 - 6 carbon atoms, preferably a straight-chained or branched alkynyl group having 3 - 6 carbon atoms.

10 In the definition of R_6 -CO- as R_1 , R_6 may be $-N(R_9)R_{10}$, in which R_9 and R_{10} may each represent a cycloalkyl group having 3 - 6 carbon atoms that may be fused to a benzene ring or a heterocyclic ring, and the heterocyclic ring may be exemplified by aliphatic or aromatic 5- or 6-membered
15 ring containing one or two hetero atoms selected from among O, N and S; specific examples of such heterocyclic ring include pyridine, pyrazine, furan, thiophene, pyrrole and imidazole.

 In the definition of R_6 -CO- as R_1 , R_6 may be $-N(R_9)R_{10}$,
20 in which R_9 and R_{10} may each represent a cycloalkyl group having 3 - 6 carbon atoms that may be fused to a benzene ring or a heterocyclic ring, and such cycloalkyl group is a cyclopropyl group, a cyclobutyl group, a cyclopentyl group or a cyclohexyl group.

25 In the definition of R_6 -CO- as R_1 , R_6 may be $-N(R_9)R_{10}$, in which R_9 and R_{10} may each represent a cycloalkyl group having 3 - 6 carbon atoms that may be fused to a benzene ring or a heterocyclic ring, as exemplified by a cycloalkyl

group having 3 - 6 carbon atoms that may be fused to a benzene ring or one or more of the heterocyclic rings mentioned above.

In the definition of R_6 -CO- as R_1 , R_6 may be $-N(R_9)R_{10}$,
 5 in which R_9 and R_{10} may each represent an optionally substituted aromatic ring having 6 - 12 carbon atoms, as exemplified by a benzene ring and a naphthalene ring.

In the definition of R_6 -CO- as R_1 , R_6 may be $-N(R_9)R_{10}$,
 in which R_9 and R_{10} may each represent an optionally
 10 substituted aromatic ring having 6 - 12 carbon atoms, and exemplary substituents include a hydroxyl group, a methoxy group, a phenoxy group, a benzyloxy group, a tert-butyloxy group, an amino group, a methylamino group, a dimethylamino group, an ethylamino group, a carboxyl group and a
 15 methoxycarbonyl group. The aromatic ring may have one or more of these substituents, which may be the same or different.

While R_9 and R_{10} in $-N(R_9)R_{10}$ in R_6 in R_6 -CO- as R_1 has the definitions set forth above, $-N(R_9)R_{10}$ is preferably a
 20 benzylamino group or a benzylmethylamino group.

In the definition of R_6 -CO- as R_1 , R_6 may be $-OR_{11}$, in which R_{11} may be an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, preferably a straight-chained or branched alkyl group having
 25 1 - 4 carbon atoms, more preferably a straight-chained alkyl group having 1 - 2 carbon atoms, with a methyl group being particularly preferred.

In the definition of R_6 -CO- as R_1 , R_6 may be $-OR_{11}$, in

which R_{11} may be an optionally substituted straight-chained or branched alkenyl group having 2 - 6 carbon atoms, preferably a straight-chained or branched alkenyl group having 3 - 6 carbon atoms.

5 In the definition of R_6 -CO- as R_1 , R_6 may be $-OR_{11}$, in which R_{11} may be an optionally substituted straight-chained or branched alkynyl group having 2 - 6 carbon atoms, preferably a straight-chained or branched alkynyl group having 3 - 6 carbon atoms.

10 In the definition of R_6 -CO- as R_1 , R_6 may be $-OR_{11}$, in which R_{11} is an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, an optionally substituted straight-chained or branched alkenyl group having 2 - 6 carbon atoms or an optionally substituted
15 straight-chained or branched alkynyl group having 2 - 6 carbon atoms. Exemplary substituents include an amino group, a hydroxyl group, a carboxyl group, an aminocarbonyl group, an aminocarbonylamino group, a pyridylthio group, a methylthio group, a phenyl group, a 3-indolyl group, a 4-
20 hydroxyphenyl group, a 2-thienyl group, a 2-furyl group, a 3-imidazolyl group and a cyclohexyl group; preferred are an amino group, a phenyl group, a 3-indolyl group, a 4-hydroxyphenyl group, a 2-thienyl group, a 2-furyl group and a cyclohexyl group; more preferred is a phenyl group. The
25 above-mentioned alkyl, alkenyl and alkynyl groups may have one or more of the above-mentioned substituents, which may be the same or different.

In the definition of R_6 -CO- as R_1 , R_6 may be $-OR_{11}$,

in which R_{11} may be an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, preferably a methyl group having one or more of the above-mentioned substituents, more preferably a benzyl group, a 3-indolylmethyl group, a p-hydroxybenzyl group, a 2-thienylmethyl group, a 2-furylmethyl group, and a cyclohexylmethyl group, with a benzyl group being particularly preferred.

In the definition of R_6 -CO- as R_1 , R_6 may be $-OR_{11}$, in which R_{11} may be an optionally substituted straight-chained or branched alkenyl group having 2 - 6 carbon atoms, preferably a straight-chained or branched alkenyl group having 3 - 6 carbon atoms.

In the definition of R_6 -CO- as R_1 , R_6 may be $-OR_{11}$, in which R_{11} may be an optionally substituted straight-chained or branched alkynyl group having 2 - 6 carbon atoms, preferably a straight-chained or branched alkynyl group having 3 - 6 carbon atoms.

In the definition of R_6 -CO- as R_1 , R_6 may be $-OR_{11}$, in which R_{11} may be a cycloalkyl group having 3 - 6 carbon atoms that may be fused to a benzene ring or a heterocyclic ring, and the heterocyclic ring may be exemplified by an aliphatic or aromatic 5- or 6-membered ring containing one or two hetero atoms selected from among O, N and S. Specific examples of such heterocyclic ring include pyridine, pyrazine, furan, thiophene, pyrrole and imidazole.

In the definition of R_6 -CO- as R_1 , R_6 may be $-OR_{11}$, in which R_{11} may be a cycloalkyl group having 3 - 6 carbon

atoms that may be fused to a benzene ring or a heterocyclic ring, and the cycloalkyl group is a cyclopropyl group, a cyclobutyl group or a cyclopentyl group.

In the definition of R_6 -CO- as R_1 , R_6 may be $-OR_{11}$, in
5 which R_{11} may be a cycloalkyl group having 3 - 6 carbon atoms that may be fused to a benzene ring or a heterocyclic ring, as exemplified by a cycloalkyl group having 3 - 6 carbon atoms that may be fused to a benzene ring or one or more of the above-mentioned heterocyclic rings.

10 In the definition of R_6 -CO- as R_1 , R_6 may be $-OR_{11}$, in which R_{11} may be an optionally substituted aromatic ring having 6 - 12 carbon atoms, as exemplified by a benzene ring and a naphthalene ring.

In the definition of R_6 -CO- as R_1 , R_6 may be $-OR_{11}$, in
15 which R_{11} may be an optionally substituted aromatic ring having 6 - 12 carbon atoms, and exemplary substituents include a hydroxyl group, a methoxy group, a phenoxy group, a benzyloxy group, a tert-butyloxy group, an amino group, a methylamino group, a dimethylamino group, an ethylamino
20 group, a carboxyl group, and a methoxycarbonyl group. The aromatic ring may have one or more of the above-mentioned substituents, which may be the same or different.

In the definition of R_6 -CO- as R_1 , R_6 may be $-OR_{11}$, in
which R_{11} may be an optionally substituted aromatic ring
25 having 6 - 12 carbon atoms, as exemplified by a benzene ring and a naphthalene ring that optionally have one or more of the above-mentioned substituents, which may be the same or different.

While R_{11} in $-OR_{11}$ in R_6 in R_6-CO- as R_1 has the definitions set forth above, $-OR_8$ is preferably a benzyloxy group.

While R_6 in R_6-CO- as R_1 has the definitions set forth above, preferred examples of R_6 include a 1-amino-2-phenylethyl group, a 1-methylamino-2-phenylethyl group, a 1-amino-2-(3-indolyl)ethyl group, a 1-amino-2-(4-hydroxy)phenylethyl group, a 1-amino-2-(2-thienyl)ethyl group, a 1-amino-2-(2-furyl)ethyl group, a 1-amino-2-cyclohexylethyl group, a 2-phenylpropyl group, a 1-benzocyclobutyl group, a benzylamino group and a benzyloxy group, with a 1-amino-2-phenylethyl group being particularly preferred.

In its definition, R_1 may be an optionally substituted straight-chained or branched alkyl group having 2 - 7 carbon atoms, preferably a straight-chained or branched alkyl group having 3 - 4 carbon atoms, with a propyl group being particularly preferred.

In its definition, R_1 may be an optionally substituted straight-chained or branched alkenyl group having 3 - 8 carbon atoms, preferably a straight-chained or branched alkenyl group having 4 - 8 carbon atoms, more preferably a straight-chained or branched alkenyl group having 5 - 7 carbon atoms.

In its definition, R_1 may be an optionally substituted straight-chained or branched alkynyl group having 3 - 8 carbon atoms, preferably a straight-chained or branched alkynyl group having 3 - 7 carbon atoms, more preferably a

straight-chained or branched alkynyl group having 5 - 7 carbon atoms.

In its definition, R_1 may be an optionally substituted straight-chained or branched alkyl group having 2 - 7 carbon atoms, an optionally substituted straight-chained or branched alkenyl group having 3 - 8 carbon atoms, or an optionally substituted straight-chained or branched alkynyl group having 3 - 8 carbon atoms. Exemplary substituents include an amino group, a methylamino group, an ethylamino group, a dimethylamino group, a hydroxyl group, a carboxyl group, an aminocarbonyl group, an aminocarbonylamino group, a pyridylthio group, a methylthio group, a phenyl group, a 3-indolyl group, a 4-hydroxyphenyl group, a 2-thienyl group, a 2-furyl group, a 3-imidazolyl group, and a cyclohexyl group; preferred are an amino group, a phenyl group, a 3-indolyl group, a 4-hydroxyphenyl group, a 2-thienyl group, a 2-furyl group, and a cyclohexyl group; more preferred are an amino group and a phenyl group. The above-described alkyl, alkenyl and alkynyl groups may have one or more of the above-mentioned substituents, which may be the same or branched.

The optionally substituted straight-chained or branched alkyl group as R_1 which has 2 - 7 carbon atoms is preferably a straight-chained or branched alkyl group of 3 - 4 carbon atoms that has one or more of the above-mentioned substituents, which may be the same or different. Preferred examples include a 2-amino-3-phenylpropyl group, a 2-amino-3-(3-indolyl)propyl group, a 2-amino-3-(4-

hydroxy)phenylpropyl group, a 2-amino-3-(2-thienyl)propyl group, a 2-amino-3-(2-furyl)propyl group, a 2-amino-3-cyclohexylpropyl group, and a 3-phenylbutyl group, with a 2-amino-3-phenylpropyl group being particularly preferred.

5 The optionally substituted straight-chained or branched alkenyl group as R_1 which has 3 - 8 carbon atoms is preferably a straight-chained or branched alkenyl group of 4 - 8 carbon atoms that has one or more of the above-mentioned substituents.

10 The optionally substituted straight-chained or branched alkynyl groups as R_1 which has 2 - 7 carbon atoms is preferably a straight-chained or branched alkynyl group of 3 - 7 carbon atoms that has one or more of the above-mentioned substituents.

15 While R_1 has the definitions set forth above, it is preferably a phenylalaninoyl group, an N-Me phenylalaninoyl group, a β -(3-indolyl)alaninoyl group, a tyrosinoyl group, a β -(2-thienyl)alaninoyl group, a β -(2-furyl)alaninoyl group, a β -cyclohexylalaninoyl group, a 3-phenylbutyryl group, a 1-
20 benzocyclobutylcarbonyl group, a benzylaminocarbonyl group or a benzyloxycarbonyl group, with a phenylalaninoyl group being particularly preferred.

 In its definition, R_2 may be an optionally substituted straight-chained or branched alkyl group having 1 - 3 carbon
25 atoms, as exemplified by a methyl group, an ethyl group, a propyl group and an isopropyl group; preferred are a methyl group and an ethyl group, and a methyl group is more preferred.

Exemplary substituents for the optionally substituted straight-chained or branched alkyl group as R_2 which has 1 - 3 carbon atoms include a phenyl group, a hydroxyl group, an amino group and a carboxyl group. The alkyl group may optionally have one or more of these substituents, which may be the same or different.

The optionally substituted straight-chained or branched alkyl group as R_2 which has 1 - 3 carbon atoms is preferably a methyl group.

10 While R_2 has the definitions set forth above, it is preferably a hydrogen atom or a methyl group.

In its definition, R_3 may be $-CO-R_7$, in which R_7 may be an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, preferably a straight-
15 chained or branched alkyl group having 1 - 3 carbon atoms.

In its definition, R_3 may be $-CO-R_7$, in which R_7 may be an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, and exemplary substituents include a halogen, an amino group, a hydroxyl group and an
20 alkoxy group, with halogen being preferred.

In its definition, R_3 may be $-CO-R_7$, in which R_7 may be an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, preferably a straight-
chained or branched alkyl group having one or more of the
25 above-mentioned substituents which are the same as each other, more preferably a fluoromethyl group or a chloromethyl group.

In its definition, R_3 may be $-CO-R_7$, in which R_7 may be

a cycloalkyl group having 3 - 7 carbon atoms, preferably a cycloalkyl group having 3 - 5 carbon atoms.

In its definition, R_3 may be $-\text{CO}-R_7$, in which R_7 may be $\text{N}(\text{R}_{12})\text{R}_{13}$, wherein R_{12} and R_{13} may be a straight-chained or
 5 branched alkyl group having 1 - 4 carbon atoms, preferably a straight-chained alkyl group having 1 - 2 carbon atoms, more preferably a methyl group.

In its definition, R_3 may be $-\text{CO}-R_7$, in which R_7 may be $\text{N}(\text{R}_{12})\text{R}_{13}$, wherein R_{12} and R_{13} may be a cycloalkyl group having
 10 3 - 7 carbon atoms, preferably a cycloalkyl group having 3 - 5 carbon atoms.

In its definition, R_3 may be $-\text{CO}-R_7$, in which R_7 may be $\text{N}(\text{R}_{12})\text{R}_{13}$, wherein R_{12} and R_{13} , which may be the same or different, are preferably a hydrogen atom or a methyl group.

15 While R_{12} and R_{13} in $-\text{N}(\text{R}_{12})\text{R}_{13}$ in R_7 in $-\text{CO}-R_7$ as R_3 have the definitions set forth above, $-\text{N}(\text{R}_9)\text{R}_{10}$ is preferably an amino group or a methylamino group.

In its definition, R_3 may be $-\text{CO}-R_7$, in which R_7 may be $-\text{OR}_{14}$, wherein R_{14} may be a straight-chained or branched
 20 alkyl group having 1 - 6 carbon atoms, preferably a straight-chained alkyl group having 1 - 2 carbon atoms, more preferably a methyl group.

In its definition, R_3 may be $-\text{CO}-R_7$, in which R_7 may be $-\text{OR}_{14}$, wherein R_{14} may be a cycloalkyl group having 3 - 7
 25 carbon atoms, which is a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group or a cycloheptyl group, with a cyclopropyl group being preferred.

While R_{14} in $-\text{OR}_{14}$ in R_7 in $-\text{CO}-R_7$ as R_3 has the

definitions set forth above, $-OR_{14}$ is preferably a hydroxyl group or a methoxy group.

While $-CO-R_7$ as R_3 has the definitions set forth above, it is preferably an amido group or an N-methylamido group.

5 In its definition, R_3 may be an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, preferably a straight-chained or branched alkyl group having 1 - 3 carbon atoms, with a methyl group being particularly preferred.

10 In its definition, R_3 may be an optionally substituted straight-chained or branched alkenyl group having 2 - 5 carbon atoms, preferably a straight-chained or branched alkenyl group having 2 - 3 carbon atoms.

15 In its definition, R_3 may be an optionally substituted straight-chained or branched alkynyl group having 2 - 5 carbon atoms, preferably a straight-chained alkynyl group having 2 - 3 carbon atoms.

20 In its definition, R_3 may be an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, an optionally substituted straight-chained or branched alkenyl group having 2 - 5 carbon atoms or an optionally substituted straight-chained or branched alkynyl group having 2 - 5 carbon atoms. Exemplary substituents include an amino group, an alkylamino group, a hydroxyl group, an alkoxy group, a carboxyl group, a halogen, etc.,
25 with an amino group being particularly preferred. The above-described alkyl, alkenyl and alkynyl groups may optionally have one or more of the above-mentioned

substituents, which may be the same or different.

The optionally substituted straight-chained or branched alkyl group as R_3 which has 1 - 5 carbon atoms is preferably a methyl group and an aminomethyl group.

5 While R_3 has the definitions set forth above, it is preferably an amido group, an N-methylamido group, a methyl group or an aminomethyl group, with an amido group and a methyl group being particularly preferred.

10 In its definition, R_4 may be a straight-chained or branched alkyl group having 1 - 6 carbon atoms, preferably a straight-chained or branched alkyl group having 2 - 5 carbon atoms, more preferably a branched alkyl group having 3 - 5 carbon atoms, with a tert-butyl group being particularly preferred.

15 In its definition, R_4 may be a straight-chained or branched alkenyl group having 2 - 6 carbon atoms, preferably a straight-chained or branched alkenyl group having 3 - 5 carbon atoms, more preferably a branched alkenyl group having 3 - 5 carbon atoms.

20 In its definition, R_4 may be a straight-chained or branched alkynyl group having 2 - 6 carbon atoms, preferably a straight-chained or branched alkynyl group having 3 - 5 carbon atoms, more preferably a branched alkynyl group having 3 - 5 carbon atoms.

25 In its definition, R_4 may have the general formula (2), in which R_{15} is preferably a methyl group.

In the general formula (2) as R_4 , R_{16} and R_{17} when taken together may form a cycloalkyl group having 3 - 7 carbon

atoms, which is preferably a cycloalkyl group having 3 - 5 carbon atoms.

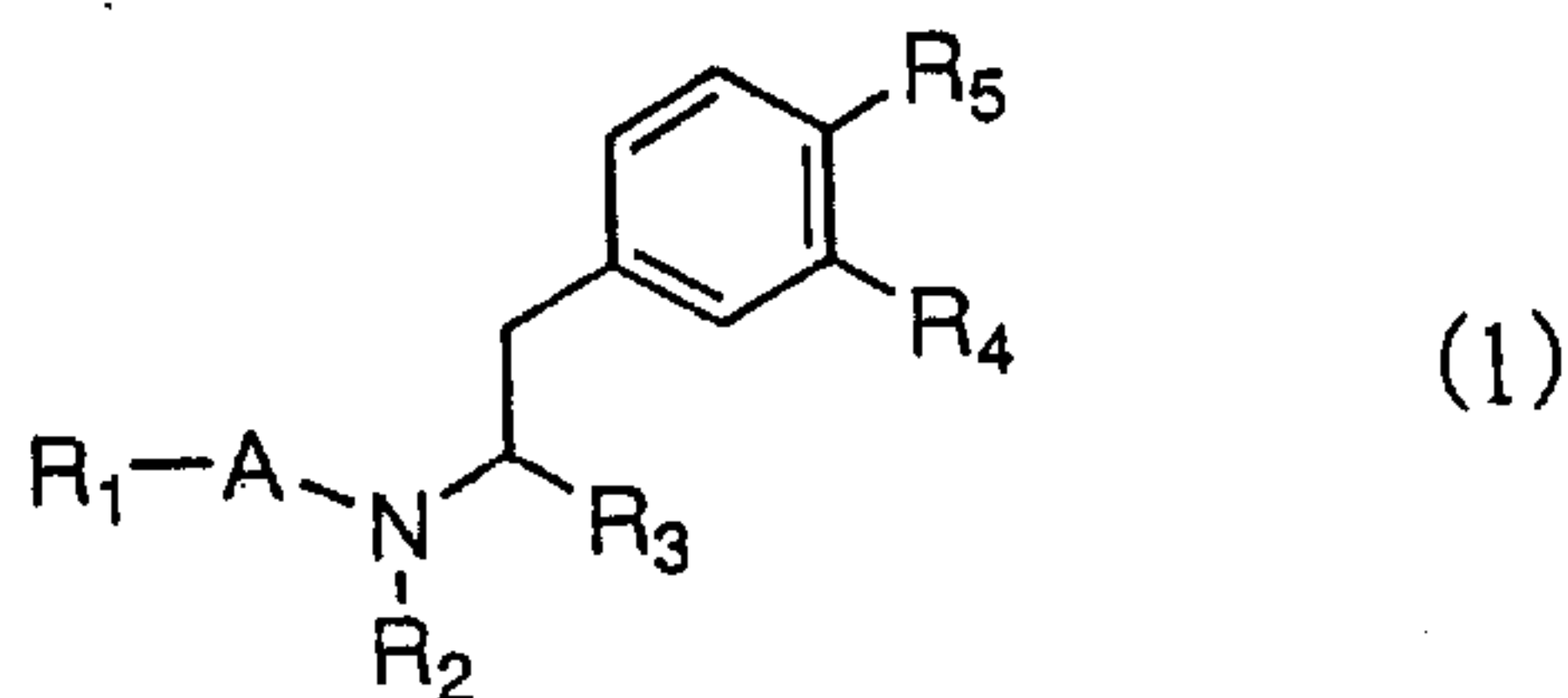
In the general formula (2) as R_4 , R_{16} and R_{17} when taken together may alternatively form a cycloalkenyl group having 3 - 7 carbon atoms, which is preferably a cycloalkenyl group having 4 - 6 carbon atoms.

The preferred examples of R_4 are an isopropyl group, a tert-butyl group, a 1,1-dimethylpropyl group, and a 1,1-dimethyl-2-propenyl group, with a tert-butyl group being particularly preferred.

In its definition, R_5 may represent $-OR_{12}$, in which R_{12} may be a straight-chained alkyl group having 1 - 4 carbon atoms, preferably a methyl group and an ethyl group, more preferably a methyl group.

The preferred examples of R_5 are a hydroxyl group and a methoxy group, with a hydroxyl group being particularly preferred.

The preferred examples of the compound represented by the general formula (1):



25 (where R_1 , R_2 , R_3 , R_4 and R_5 have the same meanings as defined above) are: Phe-Hyp-Tyr(3-tBu)-NH₂, Phe-Thz-Tyr(3-tBu)-NH₂, Phe-Pro-Tyr(3-tBu)-NH₂, Phe-Phg-Tyr(3-tBu)-NH₂, Phe-Phg-Phe(3-tBu-4-methoxy)-NH₂, Phe-N-Me-Phg-Tyr(3-tBu)-NH₂, Phe-

N-Me-D-Phg-Tyr(3-tBu)-NH₂, Phe-Phe-Tyr(3-tBu)-NH₂, Phe-Cha-Tyr(3-tBu)-NH₂, Phe-Chg-Tyr(3-tBu)-NH₂, Phe-Tle-Tyr(3-tBu)-NH₂, Phe-Val-Tyr(3-tBu)-NH₂, Phe-Leu-Tyr(3-tBu)-NH₂, Phe-Tyr-Tyr(3-tBu)-NH₂, Phe-Hph-Tyr(3-tBu)-NH₂, Phe-Thi-Tyr(3-tBu)-NH₂, Phe-Ile-Tyr(3-tBu)-NH₂, Phe-Thr-Tyr(3-tBu)-NH₂, Phe-Trp-Tyr(3-tBu)-NH₂, Tyr-Phg-Tyr(3-tBu)-NH₂, Phg-Phg-Tyr(3-tBu)-NH₂, Trp-Phg-Tyr(3-tBu)-NH₂, Cha-Phg-Tyr(3-tBu)-NH₂, Hph-Phg-Tyr(3-tBu)-NH₂, N-(α -methylhydrocinnamyl)-Phg-Tyr(3-tBu)-NH₂, Phe-N-Me-Val-Tyr(3-tBu)-NH₂, N-(α -methylhydrocinnamyl)-N-Me-D-Phg-Tyr(3-tBu)-NH₂, Phe-Val-N-Me-Tyr(3-tBu)-NH₂, Phe-Phg-Tyr(3-tBu)-NHMe, Phg-Phg-Tyr(3-tBu)-OH, N-(3-phenylbutyryl)-Phg-Tyr(3-tBu)-NH₂, N-(benzylaminocarbonyl)-N-Me-D-Phe-Tyr(3-tBu)-NH₂, N-(benzyloxycarbonyl)-Phg-Tyr(3-tBu)-NH₂, N-(benzyloxycarbonyl)-N-Me-Val-Tyr(3-tBu)-NH₂, N-(S)-3-phenylbutyryl-Phg-Tyr(3-tBu)-NH₂, N-((R)-3-phenylbutyryl)-Phg-Tyr(3-tBu)-NH₂, L- α -(3-methyl-2-butenyl)glycinoyl-N-Me-Val-Tyr(3-tBu)-NH₂, α -(4-pentynyl)glycinoyl-N-Me-Val-Tyr(3-tBu)-NH₂, N-(2-amino-3-phenylpropyl)-Phg-Tyr(3-tBu)-NH₂, N-(2-amino-3-phenylpropyl)-Val-Tyr(3-tBu)-NH₂, N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methyl-2-(N-methyl-N-phenylalaninoylamino)butanamide, and Phe-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂, N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methyl-2-[N-methyl-N-(N-Me-phenylalaninoyl)amino]butanamide, and the more preferred examples are: Phe-Phg-Tyr(3-tBu)-NH₂, Phe-N-Me-D-Phg-Tyr(3-tBu)-NH₂, Phe-Phe-Tyr(3-tBu)-NH₂, Phe-Cha-Tyr(3-tBu)-NH₂, Phe-Val-Tyr(3-tBu)-NH₂, Phe-Leu-Tyr(3-tBu)-NH₂, Phe-Tyr-Tyr(3-tBu)-NH₂, Phe-Hph-Tyr(3-tBu)-NH₂, Phe-Ile-Tyr(3-tBu)-NH₂, Trp-Phg-

Tyr(3-tBu)-NH₂, Cha-Phg-Tyr(3-tBu)-NH₂, Phe-N-Me-Val-Tyr(3-tBu)-NH₂, Phe-Val-N-Me-Tyr(3-tBu)-NH₂, Phe-Phg-Tyr(3-tBu)-NHMe, N-(benzylaminocarbonyl)-N-Me-D-Phe-Tyr(3-tBu)-NH₂, N-(S)-3-phenylbutyryl-Phg-Tyr(3-tBu)-NH₂, N-(2-amino-3-phenylpropyl)-Phg-Tyr(3-tBu)-NH₂, N-(2-amino-3-phenylpropyl)-Val-Tyr(3-tBu)-NH₂, N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methyl-2-(N-methyl-N-phenylalaninoylamino)butanamide, Phe-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂, and N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methyl-2-[N-methyl-N-(N-Me-phenylalaninoyl)-amino]butanamide.

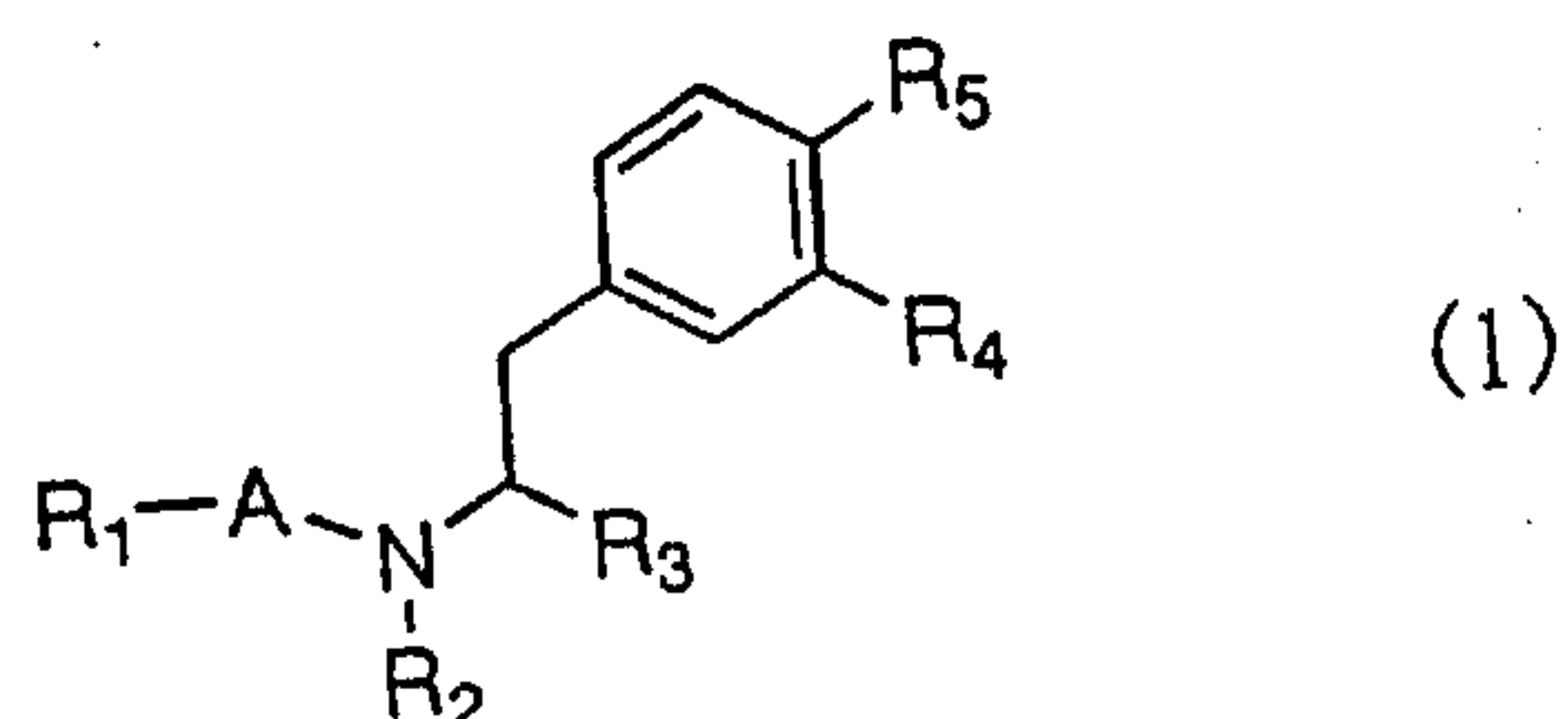
Salt-forming acids include inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as acetic acid, oxalic acid, maleic acid, fumaric acid, citric acid, tartaric acid, methanesulfonic acid and trifluoroacetic acid.

The compounds of the present invention can occur as optical isomers and the respective optical isomers and mixtures thereof are all included within the scope of the invention.

The compounds of the invention can also be obtained as hydrates.

BEST MODE FOR CARRYING OUT THE INVENTION

The compounds represented by the general formula (1)



5

(where A, R₁, R₂, R₃, R₄ and R₅ respectively have the same meanings as defined above) are amino acid derivatives containing dipeptides or tripeptides and can be produced by either the solid-phase process or the liquid-phase process.

10 In the production by the solid-phase process, an automatic organic synthesizer is typically used but it may be replaced by the manual procedure.

Almost all amino acids that compose the compounds of the invention are commercially available and readily

15 purchasable. Those which are not commercially available can be produced by well-known established methods such as the Strecker synthesis, the Bucherer method, the acetamide malonate ester method, and the method of alkylating : glycine ester of which amino group is protected.

20 To produce p-hydroxy-m-substituted phenylalanine esters, tyrosine esters [Tyr-OR₁₄ (where R₁₄ has the same meaning as defined above)] which are either commercially available or obtainable by esterifying tyrosine are subjected to conventional procedures of organic synthesis,

25 for example, the Friedel-Crafts reaction in the presence of proton acids or Lewis acids so that the substituent R₄ (which is a special case of the foregoing definition where R₄ is an alkyl group, an alkenyl group or an alkynyl group;

this restriction applies to the present paragraph) is introduced in m-position. Note that the substituent R_4 need not be introduced at this stage but may be introduced at any stage of the production.

5 If the α -amino group in the p-hydroxy-m-substituted phenylalanine ester is O-alkylated after protection with, for example, a benzyloxycarbonyl, one can obtain a product in which R_8 in $-OR_8$ is an alkyl group. If R_5 in the product is a hydrogen atom or an alkoxy group, it is subsequently
10 N α -alkylated to give a product where R_2 is an alkyl group. The hydroxyl group as R_5 is N-alkylated after protection with, for example, a benzyl group or any other group that can be readily removed at a later stage, and then deprotected to give a product where R_2 is an alkyl group and
15 R_5 is a hydroxyl group.

Depending on R_3 , a desired structure can be obtained by performing various conversions using ester groups of substituted phenylalanine esters in which the amino acid group and others are appropriately protected.

20 Take, for example, the case where R_3 is an amide; the α -amino group protected substituted phenylalanine ester is directly reacted with the amine $HN(R_{12})R_{13}$ or condensed with the amine $HN(R_{12})R_{13}$ after being converted to a carboxylic acid in the useful manner, whereby the ester is converted to
25 an α -amino group protected substituted phenylalanine amide.

If R_3 is a substituted alkyl group, the α -amino group protected substituted phenylalanine ester is reduced to an aldehyde or an alcohol which, in turn, are converted to a

halogen-substituted alkyl group, a hydroxyalkyl group, an aminoalkyl group, a methyl group, and so forth.

Almost all types of N α -substituted amino acids are commercially available and readily purchasable; those which
5 are not commercially available can be produced by well-known established methods such as the one of reacting α -bromo-carboxylic acid units with a primary amine (J. Med. Chem., 37, 2678 (1994)) and the one of treating an amino group protected amino acid or an ester thereof with a base and an
10 alkylating agent to effect its N-alkylation.

The N α -amino group, as well as β -Ala and γ -Abu amino groups in amino acids can efficiently be protected with a fluorenyl methyloxycarbonyl (Fmoc) group, a tert-butoxycarbonyl (Boc) group, a benzyloxycarbonyl (Z) group
15 and the like. A group that is preferably used to protect amino groups in solid-phase synthesis is an Fmoc group. Functional groups in side chains can be protected in various ways with various groups; the carboxyl group in the Asp, Glu or Aad residue is protected as a tert-butyl ester (OtBu);
20 the hydroxyl group in the Ser, Thr or Tyr residue is protected with a tert-butyl (tBu) group; the hydroxyl group in the Hse residue is protected with a triphenylmethyl (Trt) group; the imidazolyl group in the His residue, the side-chain amino group in the Dab, Orn or Lys residue or the
25 indole group in the tryptophan residue is protected with a Boc group. Note that amino acid residues can be protected with other protective groups.

Various methods may be used to activate the carboxyl

group and they include: the use of benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP); the use of O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU); the use of
 5 diisopropyl carbodiimide (DIC); N-ethyl-N'-3-dimethylaminopropyl carbodiimide (WSCl); the use of dicyclohexyl carbodiimide (DCC); the use of diphenylphosphorylazide (DPPA); the combination of one of these reagents with 1-hydroxybenzotriazole (HOBT) or N-
 10 hydroxysuccinimide (HONSu); the mixed acid anhydride method using isobutyl chloroformate etc.; the use of an amino acid in which the α -carboxyl group is in the form of a pentafluorophenyl ester (OPfp), an amino acid in which the α -carboxyl group is in the form of a p-nitrophenyl ester
 15 (ONP), or an amino acid in which the α -carboxyl group is in the form of an N-hydroxysuccinimide ester (OSu); the combination of one of these amino acids with HOBT. If necessary, a base such as triethylamine (TEA), diisopropylethylamine (DIEA), N-methylmorpholine (NMM) or 4-
 20 dimethylaminopyridine (DMAP) may be added to accelerate the reaction.

A compound in which R_1 is $N(R_9)R_{10}-CO-$ (where R_9 and R_{10} have the same meanings as defined above) can be produced via various processes including the mixing, under stirring, of
 25 an amino acid (A) with a reagent such as N,N'-carbonyldiimidazole, phosgene, triphosgene or p-nitrophenyl chlorocarbonate, followed by addition of $HN(R_9)R_{10}$, as well as the reacting of dipeptide units with $R_9(R_{10})N=C=O$ or

$R_9(R_{10})NC(=O)Cl$.

A compound in which R_1 is $R_{11}O-CO-$ can be produced via various processes including the coupling of a substituted phenylalanine amide with $N-(CO_2R_{11})$ -amino acid and the
5 reacting of the amino group in an amino acid (A) moiety with $ClCO_2R_{11}$.

To produce a compound in which R_1 is an alkyl group, an alkenyl group or an alkynyl group, a corresponding alkyl halide or aldehyde having the substituent protected as
10 required is used to alkylate the amino group in an amino acid (A) moiety in the usual manner, optionally followed by deprotection.

The compounds of the invention can also be produced by applying the specific methods of production to be described
15 in the examples that follow.

The subject application claims priority on the basis of Japanese Patent Application Nos. 255879/1997 and 186802/1998 and all disclosures in their specifications shall be incorporated herein by reference.

20 Examples

On the pages that follow, the production of the compounds of the invention is described more specifically by reference to examples, to which the invention is by no means limited. In the following examples, unless otherwise noted,
25 the amino acid residues and $N\alpha$ -amino acid residues are in the L-form.

In order to demonstrate the utility of the compounds of the invention, representative examples of them were

subjected to pharmacological tests on the motilin receptor antagonistic action and the results are described under Tests. The chemical structural formulae or chemical names of the compounds produced in the examples are set forth in
5 Tables A-1 to A-7 and Tables B-1 to B-11.

Table A-1

Example No.	Structural formula or chemical name
1	Phe-Hyp-Tyr(3-tBu)-NH ₂
2	Phe-Tic-Tyr(3-tBu)-NH ₂
3	Phe-Thz-Tyr(3-tBu)-NH ₂
4	Phe-2-Abz-Tyr(3-tBu)-NH ₂
5	Phe-Phg-Tyr(3-tBu)-NH ₂
6	Phe-D-Hyp-Tyr(3-tBu)-NH ₂
7	Phe-Pro-Tyr(3-tBu)-NH ₂
8	Phe-D-Pro-Tyr(3-tBu)-NH ₂
9	Phe-Phg-Phe(3-tBu-4-methoxy)-NH ₂
10	Phe-Phe-Tyr(3-tBu)-NH ₂
11	Phe-Val-Tyr(3-tBu)-NH ₂
12	Phe-Phg-Tyr-NH ₂
13	Phe-Ala-Tyr(3-tBu)-NH ₂
14	Phe-Leu-Tyr(3-tBu)-NH ₂
15	Val-Phg-Tyr(3-tBu)-NH ₂
16	Leu-Phg-Tyr(3-tBu)-NH ₂
17	Phe-Gly-Tyr(3-tBu)-NH ₂

Table A-2

Example No.	Structural formula or chemical name
18A	Phe-N-Me-Phg-Tyr(3-tBu)-NH ₂
18B	Phe-N-Me-D-Phg-Tyr(3-tBu)-NH ₂
19	N-benzyl-N-(4-pyridylthioacetyl)-Phg-Tyr(3-tBu)-NH ₂
20	Phe-Phg-tYR(3-tBu)-OH
21	Phe-Tyr-Tyr(3-tBu)-NH ₂
22	Phe-Hph-Tyr(3-tBu)-NH ₂
23	Phe-Thi-Tyr(3-tBu)-NH ₂
24	Phe-β-Ala-Tyr(3-tBu)-NH ₂
25	Phe-γ-Abu-Tyr(3-tBu)-NH ₂
26	Phe-Aib-Tyr(3-tBu)-NH ₂
27	Phe-Ile-Tyr(3-tBu)-NH ₂
28	Phe-Chg-Tyr(3-tBu)-NH ₂
29	Phe-Cha-Tyr(3-tBu)-NH ₂
30	Phe-Tle-Tyr(3-tBu)-NH ₂
31	Phe-Asp-Tyr(3-tBu)-NH ₂
32	Phe-Glu-Tyr(3-tBu)-NH ₂
33	Phe-Aad-Tyr(3-tBu)-NH ₂

Table A-3

Example No.	Structural formula or chemical name
34	Phe-Asn-Tyr(3-tBu)-NH ₂
35	Phe-Gln-Tyr(3-tBu)-NH ₂
36	Phe-Cit-Tyr(3-tBu)-NH ₂
37	Phe-Dab-Tyr(3-tBu)-NH ₂
38	Phe-Orn-Tyr(3-tBu)-NH ₂
39	Phe-Lys-Tyr(3-tBu)-NH ₂
40	Phe-Ser-Tyr(3-tBu)-NH ₂
41	Phe-Hse-Tyr(3-tBu)-NH ₂
42	Phe-Thr-Tyr(3-tBu)-NH ₂
43	Phe-Abu-Tyr(3-tBu)-NH ₂
44	Phe-Nva-Tyr(3-tBu)-NH ₂
45	Phe-Met-Tyr(3-tBu)-NH ₂
46	Phe-His-Tyr(3-tBu)-NH ₂
47	Phe-Trp-Tyr(3-tBu)-NH ₂
48	Phe-Tiq-Tyr(3-tBu)-NH ₂
49	N-(4-pyridylthioacetyl)-Phg-Tyr(3-tBu)-NH ₂
50	N-(1-benzocyclobutanecarbonyl)-Phg-Tyr(3-tBu)-NH ₂

Table A-4

Example No.	Structural formula or chemical name
51	N-(2-indolecarbonyl)-Phg-Tyr(3-tBu)-NH ₂
52	Tyr-Phg-Tyr(3-tBu)-NH ₂
53	Phg-Phg-Tyr(3-tBu)-NH ₂
54	Thi-Phg-Tyr(3-tBu)-NH ₂
55	Trp-Phg-Tyr(3-tBu)-NH ₂
56	His-Phg-Tyr(3-tBu)-NH ₂
57	N-((±)-3-phenylbutyryl)-Phg-Tyr(3-tBu)-NH ₂
58	N-(2-biphenylcarbonyl)-Phg-Tyr(3-tBu)-NH ₂
59	β-Ala-Phg-Tyr(3-tBu)-NH ₂
60	Aib-Phg-Tyr(3-tBu)-NH ₂
61	Ile-Phg-Tyr(3-tBu)-NH ₂
62	Chg-Phg-Tyr(3-tBu)-NH ₂
63	Cha-Phg-Tyr(3-tBu)-NH ₂
64	Tle-Phg-Tyr(3-tBu)-NH ₂
65	Asp-Phg-Tyr(3-tBu)-NH ₂
66	Aad-Phg-Tyr(3-tBu)-NH ₂
67	Asn-Phg-Tyr(3-tBu)-NH ₂

Table A-5

Example No.	Structural formula or chemical name
68	Gln-Phg-Tyr(3-tBu)-NH ₂
69	Cit-Phg-Tyr(3-tBu)-NH ₂
70	Dab-Phg-Tyr(3-tBu)-NH ₂
71	Lys-Phg-Tyr(3-tBu)-NH ₂
72	Ser-Phg-Tyr(3-tBu)-NH ₂
73	Hse-Phg-Tyr(3-tBu)-NH ₂
74	Thr-Phg-Tyr(3-tBu)-NH ₂
75	Abu-Phg-Tyr(3-tBu)-NH ₂
76	Nva-Phg-Tyr(3-tBu)-NH ₂
77	Met-Phg-Tyr(3-tBu)-NH ₂
78	Pro-Phg-Tyr(3-tBu)-NH ₂
79	Hyp-Phg-Tyr(3-tBu)-NH ₂
80	Tic-Phg-Tyr(3-tBu)-NH ₂
81	Tiq-Phg-Tyr(3-tBu)-NH ₂
82	2-Abz-Phg-Tyr(3-tBu)-NH ₂
83	Hph-Phg-Tyr(3-tBu)-NH ₂
84	N-(α -methylhydrocinnamoyl)-Phg-Tyr(3-tBu)-NH ₂

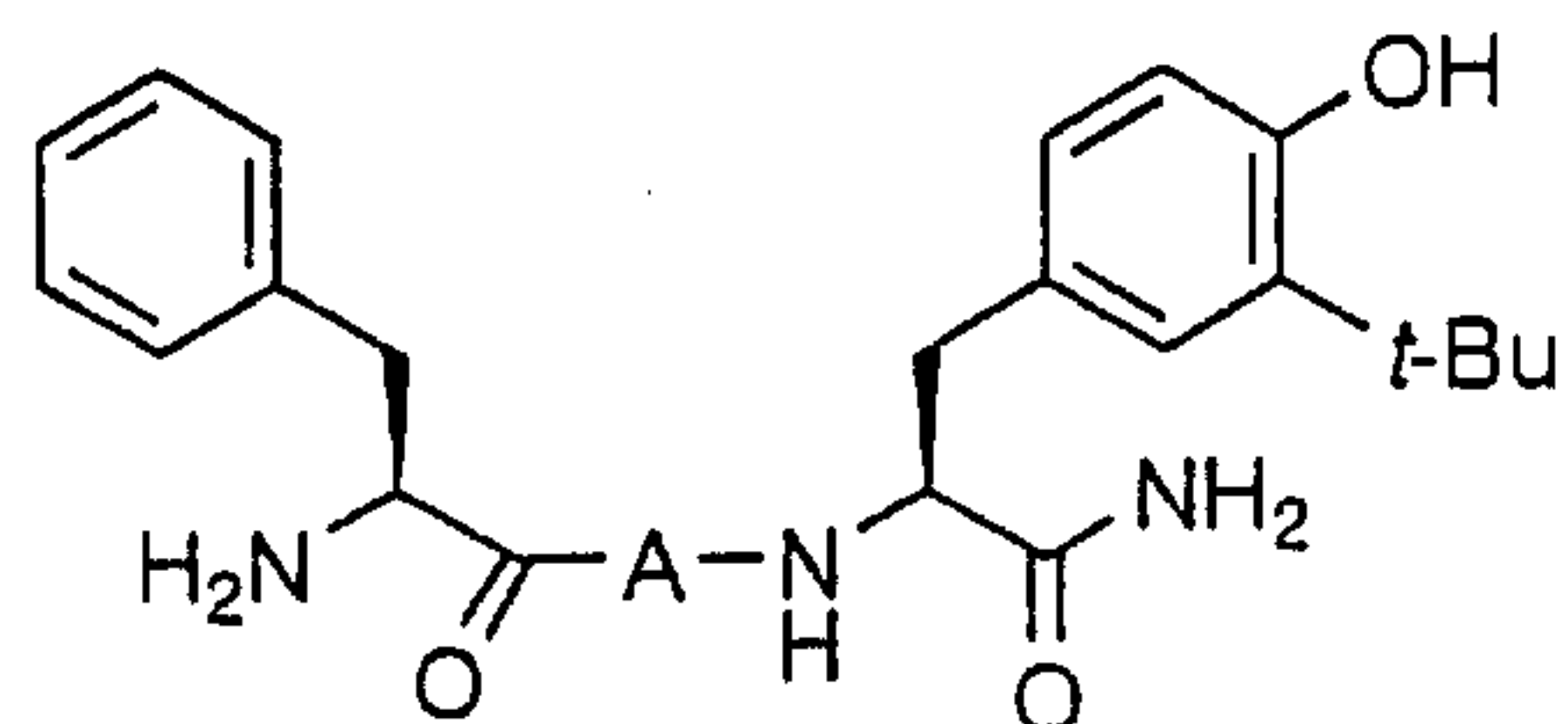
Table A-6

Example No.	Structural formula or chemical name
85	N-(α -methylcinnamoyl)-Phg-Tyr(3-tBu)-NH ₂
86	N-(3-quinolinecarbonyl)-Phg-Tyr(3-tBu)-NH ₂
87	N-(3-furanacryloyl)-Phg-Tyr(3-tBu)-NH ₂
88	Phe-D-Phg-Tyr(3-tBu)-NH ₂
89	Phe-N-Me-Val-Tyr(3-tBu)-NH ₂
90	N-(α -methylhydrocinnamoyl)-N-Me-D-Phg-Tyr(3-tBu)-NH ₂
91	Phe-Val-N-Me-Tyr(3-tBu)-NH ₂
92	Phe-Phg-Tyr(3-tBu)-NHMe
93	Phe-Apc-Tyr(3-tBu)-NHMe
94	Phe-Ahc-Tyr(3-tBu)-NHMe
95	N-acetyl-transHyp(O-benzyl)-Tyr(3-tBu)-NHMe
96	Phe-Cha-Phe(3-tBu)-NH ₂
97	N-(benzylaminocarbonyl)-N-Me-D-Phg-Tyr(3-tBu)-NH ₂
98	N-(benzyloxycarbonyl)-Phg-Tyr(3-tBu)-NHMe
99	N-(benzyloxycarbonyl)-N-Me-Val-Tyr(3-tBu)-NH ₂
100	N-((R)-3-phenylbutyryl)-Phg-Tyr(3-tBu)-NH ₂
101	N-((S)-3-phenylbutyryl)-Phg-Tyr(3-tBu)-NH ₂
102	N-((R)-3-phenylbutyryl)-D-Phg-Tyr(3-tBu)-NH ₂

Table A-7

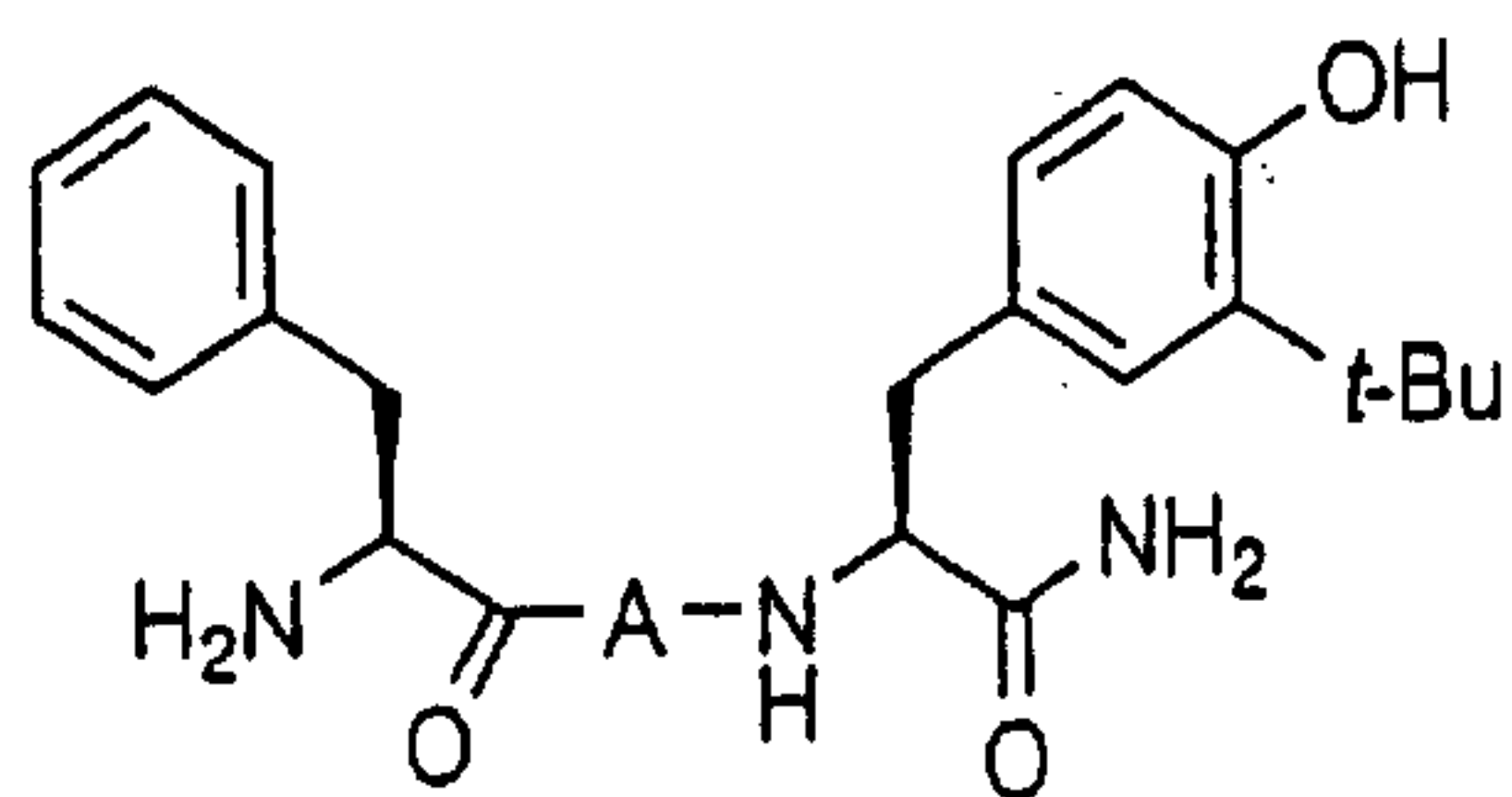
Example No.	Structural formula or chemical name
103	N-((S)-3-phenylbutyryl)-D-Phg-Tyr(3-tBu)-NH ₂
104	L-α-(3-methyl-2-butenyl)glycinoyl-N-Me-Val-Tyr-(3-tBu)-NH ₂
105	α-(4-pentynyl)glycinoyl-N-Me-Val-Tyr(3-tBu)-NH ₂
106	α-(2-butyryl)glycinoyl-N-Me-Val-Tyr(3-tBu)-NH ₂
107	N-((S)-3-phenylbutyryl)-N-Me-Val-Tyr(3-tBu)-NH ₂
108	N-((R)-3-phenylbutyryl)-N-Me-val-Tyr(3-tBu)-NH ₂
109	N-(β-aminohydrocinnamoyl)-N-Me-Val-Tyr(3-tBu)-NH ₂
110	N-(2-amino-3-phenylpropyl)-Phg-Tyr(3-tBu)-NH ₂
111	N-(2-amino-3-phenylpropyl)-N-Me-Phg-Tyr(3-tBu)-NH ₂
112	N-(phenylpyruvinoyl)-N-Me-Val-Tyr(3-tBu)-NH ₂
113	N-phenyl-Gly-N-Me-Val-Tyr(3-tBu)-NH ₂
114	N-Me-N-phenyl-Gly-N-Me-Val-Tyr(3-tBu)-NH ₂
115	N-(3-phenylbutyl)-Val-Tyr(3-tBu)-NH ₂
116	N-(2-amino-3-phenylpropyl)-Val-Tyr(3-tBu)-NH ₂
117	2-[(2-amino-3-phenylpropyl)amino]-N-[2-amino-1-[(3-tert-butyl-4-hydroxyphenyl)methyl]ethyl]-3-methylbutanamide
118	N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methyl-2-(N-methyl-N-phenylalaninoylamino)butanamide
119	Phe-N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂
120	N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methyl-2-(N-methyl-N-Me-phenylalaninoylamino)butanamide
121	N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-N-Me-3-methyl-2-(N-methyl-N-phenylalaninoylamino)butanamide

Table B-1



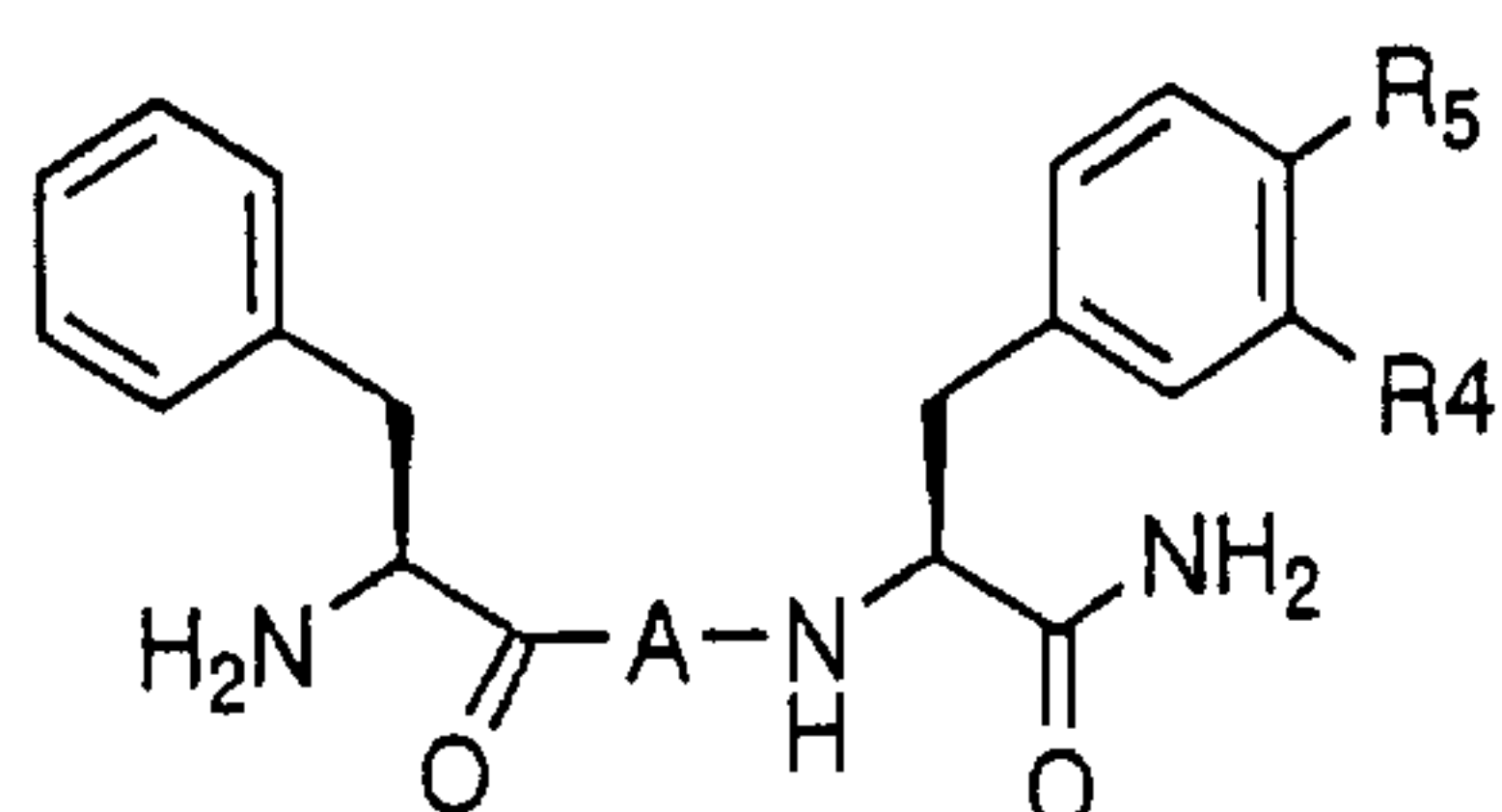
Ex. No.	A	Ex. No.	A	Ex. No.	A
1		8		18B	
2		10		21	
3		11		22	
4		13		23	
5		14		24	
6		17		25	
7		18A		26	

Table B-2



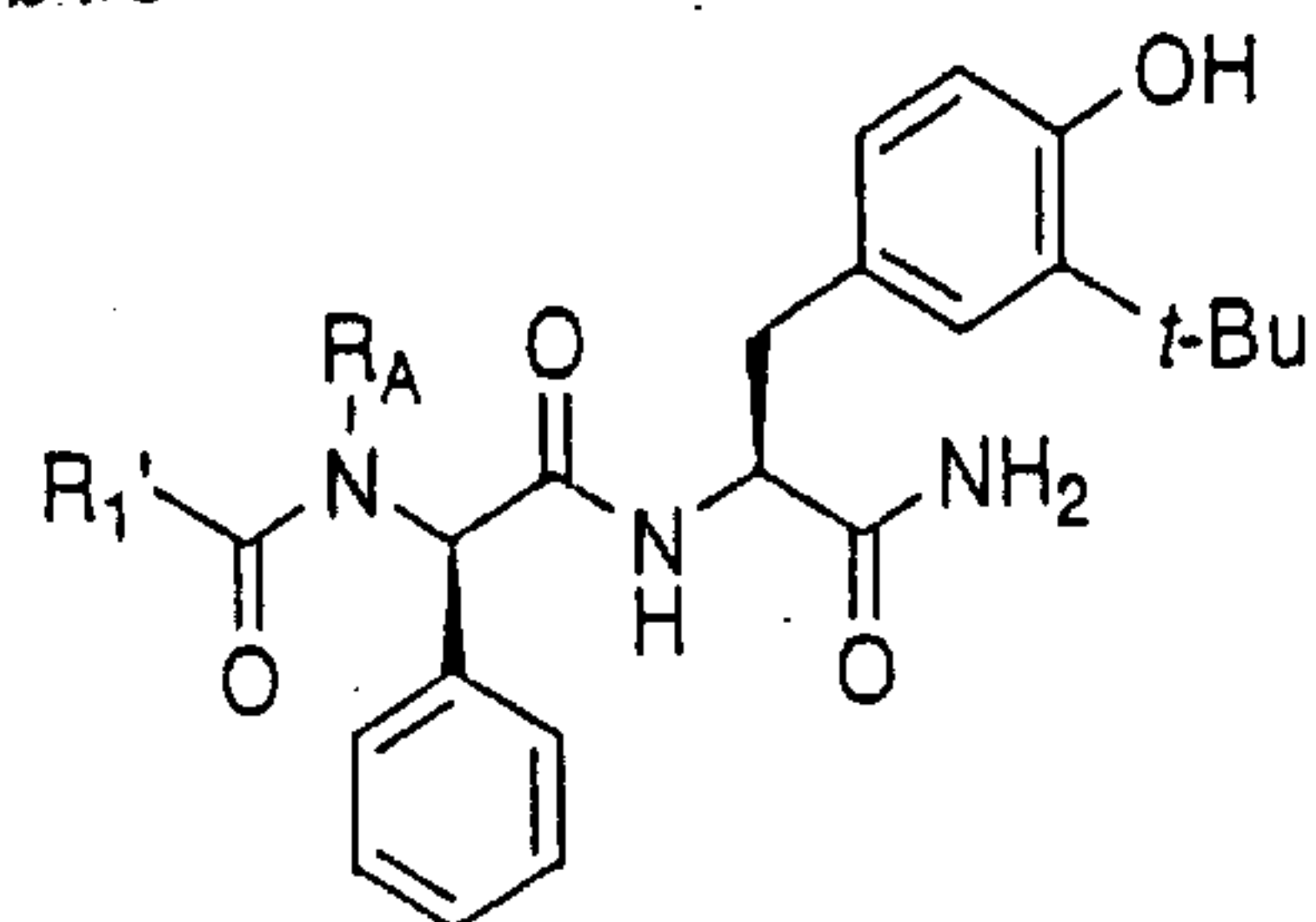
Ex. No.	A	Ex. No.	A	Ex. No.	A
27		34		41	
28		35		42	
29		36		43	
30		37		44	
31		38		45	
32		39		46	
33		40		47	

Table B-3



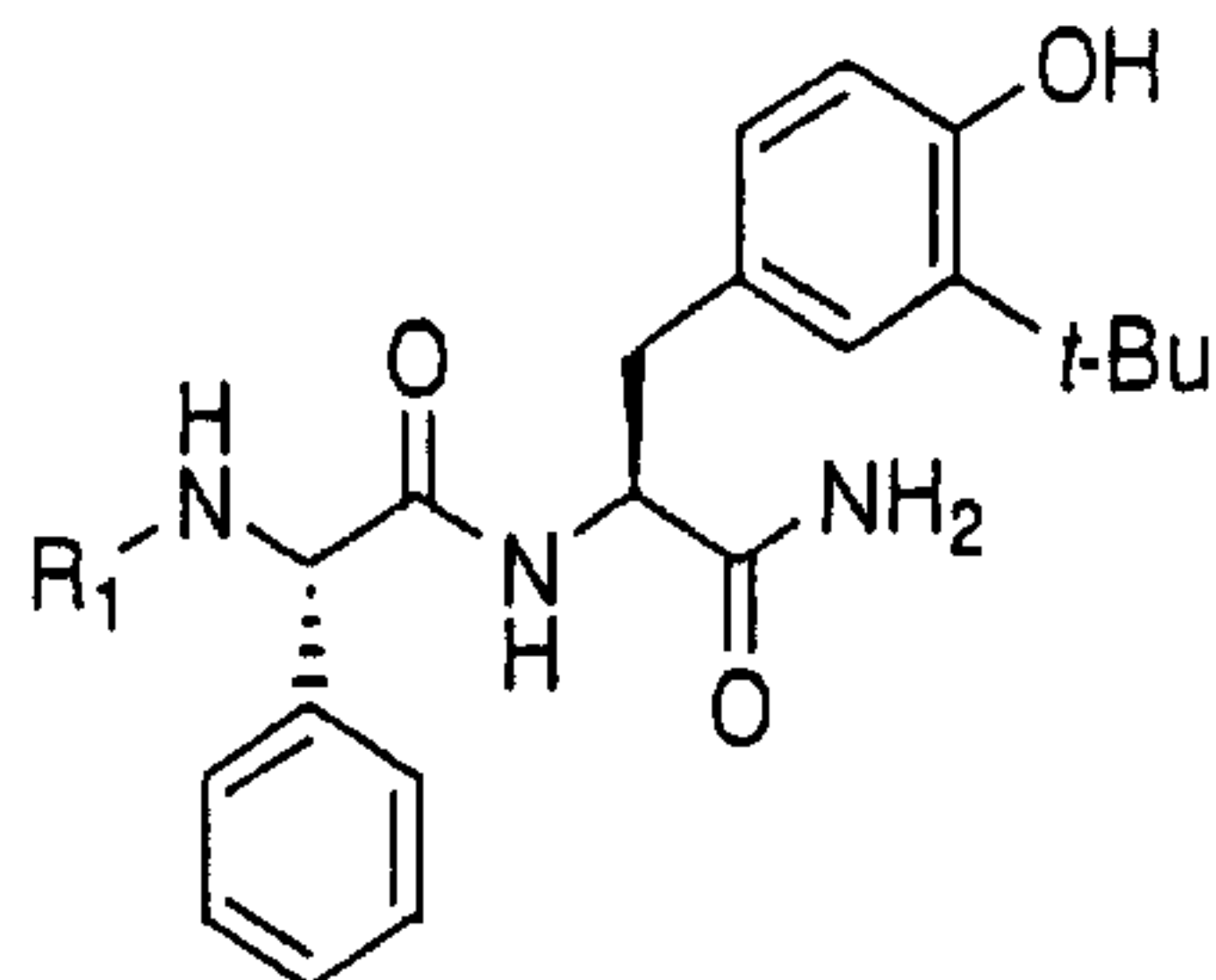
Ex. No.	A	R ₅	R ₄
9		OCH ₃	<i>t</i> -Bu
12		OH	H
48		OH	<i>t</i> -Bu
88		OH	<i>t</i> -Bu
89		OH	<i>t</i> -Bu
96		H	<i>t</i> -Bu

Table B-4



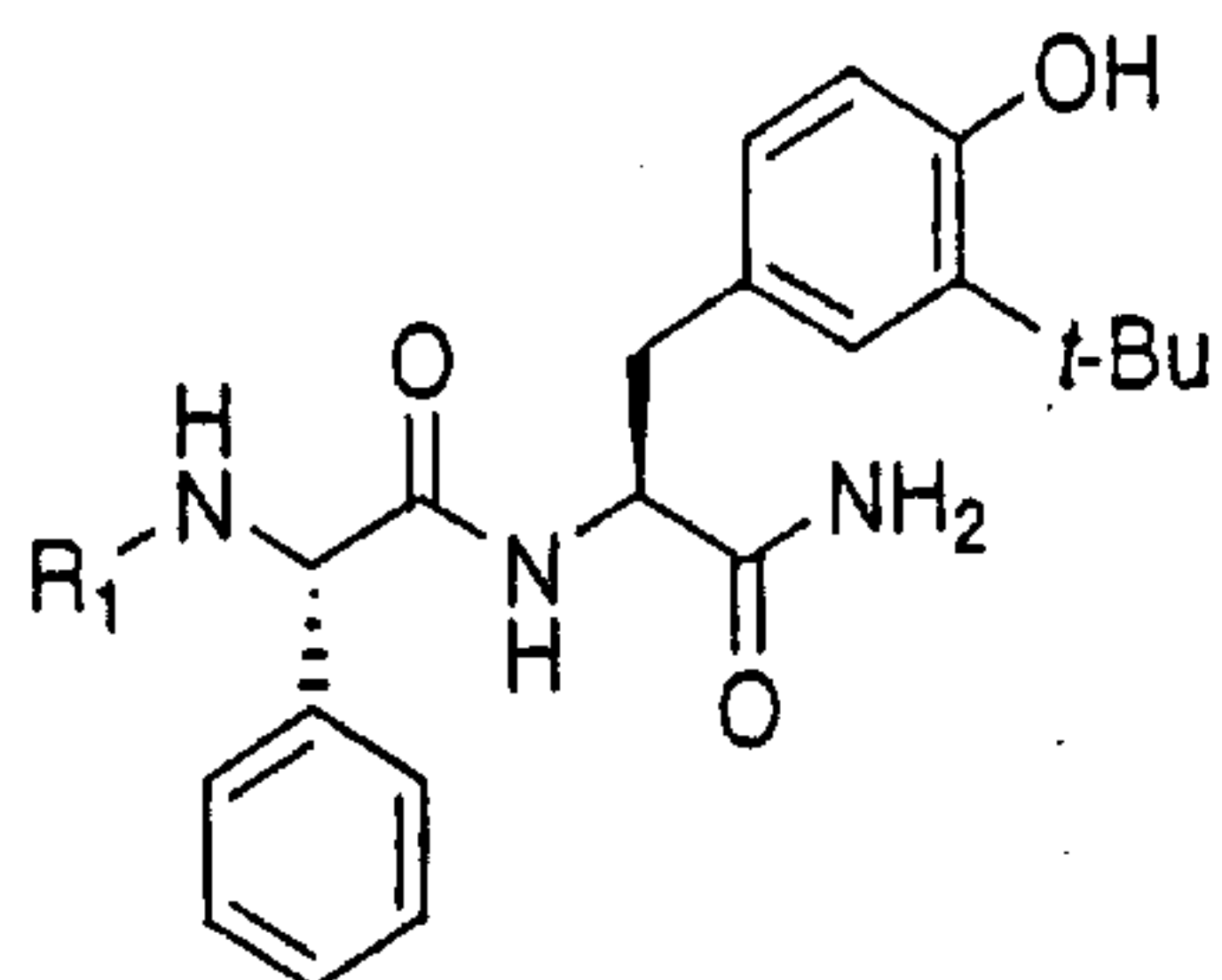
Ex. No.	R ₁ '	R _A
90		CH ₃
97		CH ₃
102		H
103		H

Table B-5



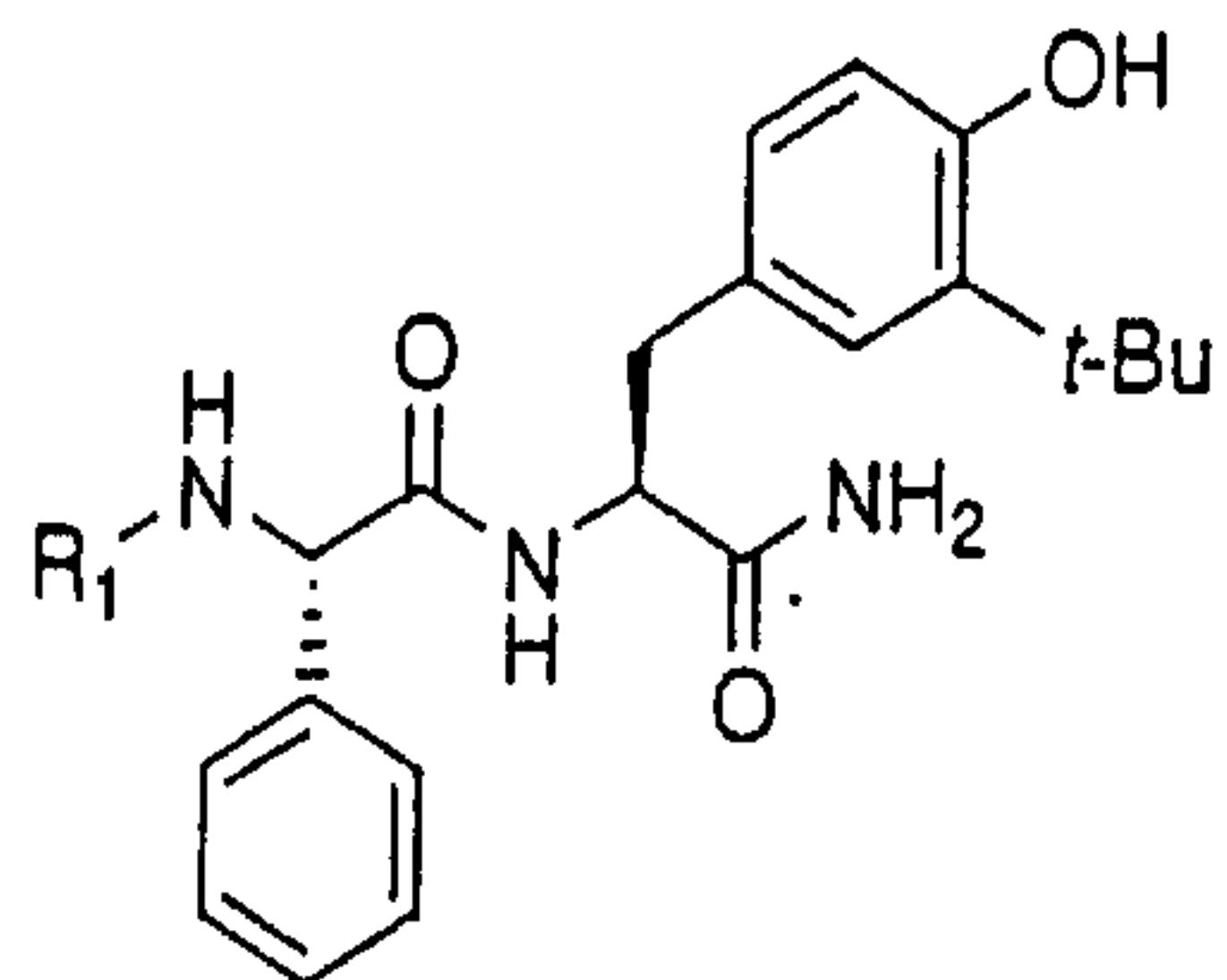
Ex. No.	R ₁	Ex. No.	R ₁	Ex. No.	R ₁
15		54		61	
16		55		62	
49		56		63	
50		57		64	
51		58		65	
52		59		66	
53		60		67	

Table B-6



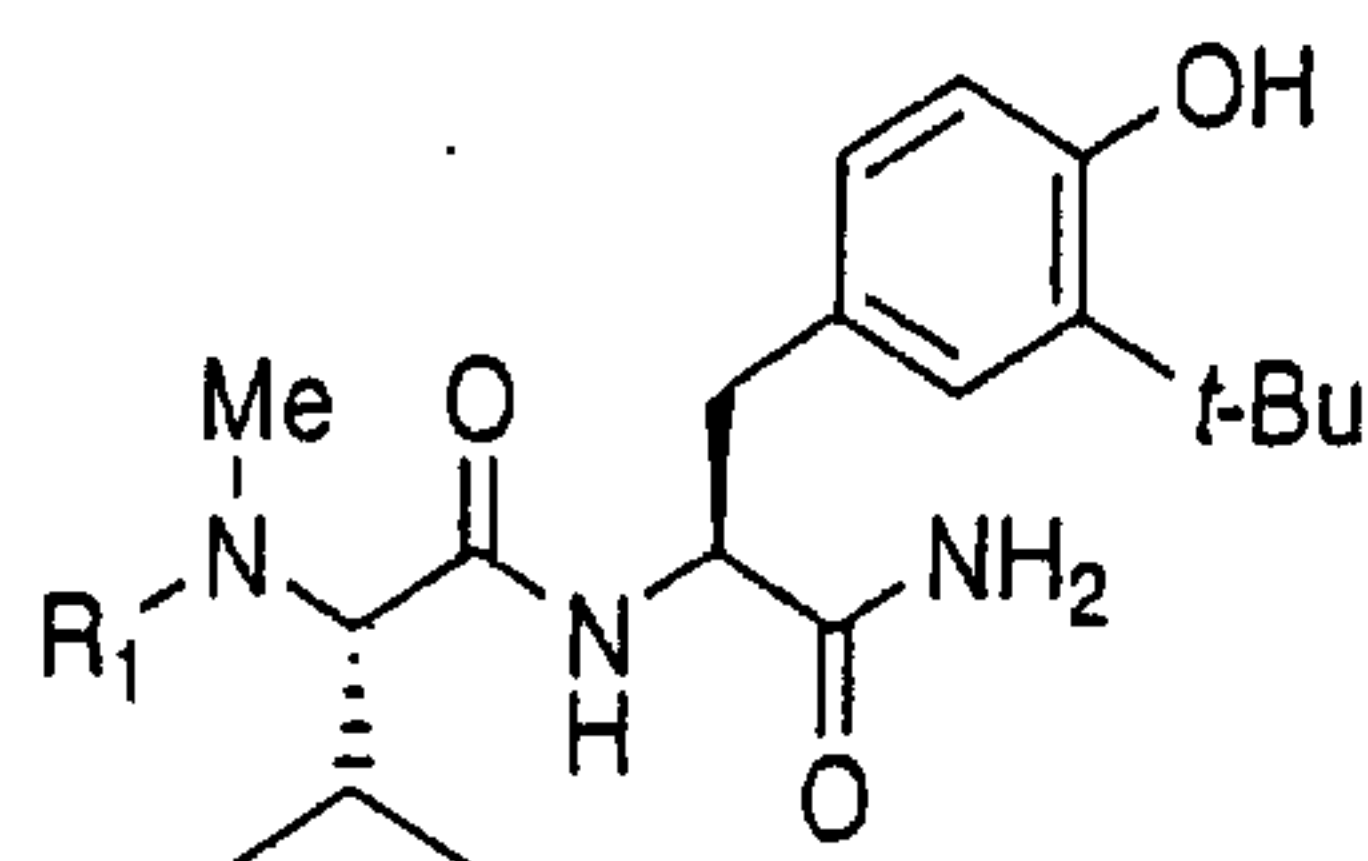
Ex. No.	R ₁	Ex. No.	R ₁	Ex. No.	R ₁
68		75		82	
69		76		83	
70		77		84	
71		78		85	
72		79		86	
73		80		87	
74		81			

Table B-7



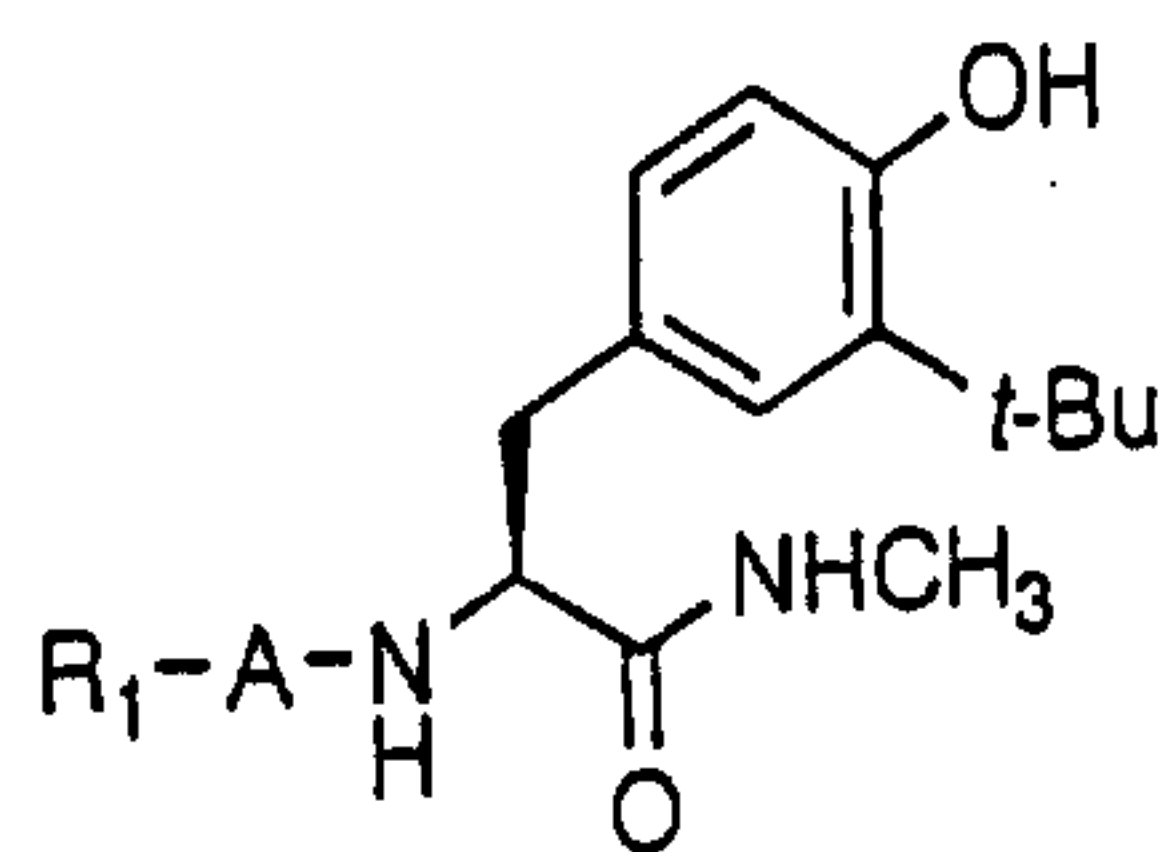
Ex. No.	R ₁
100	
101	
110	

Table B-8



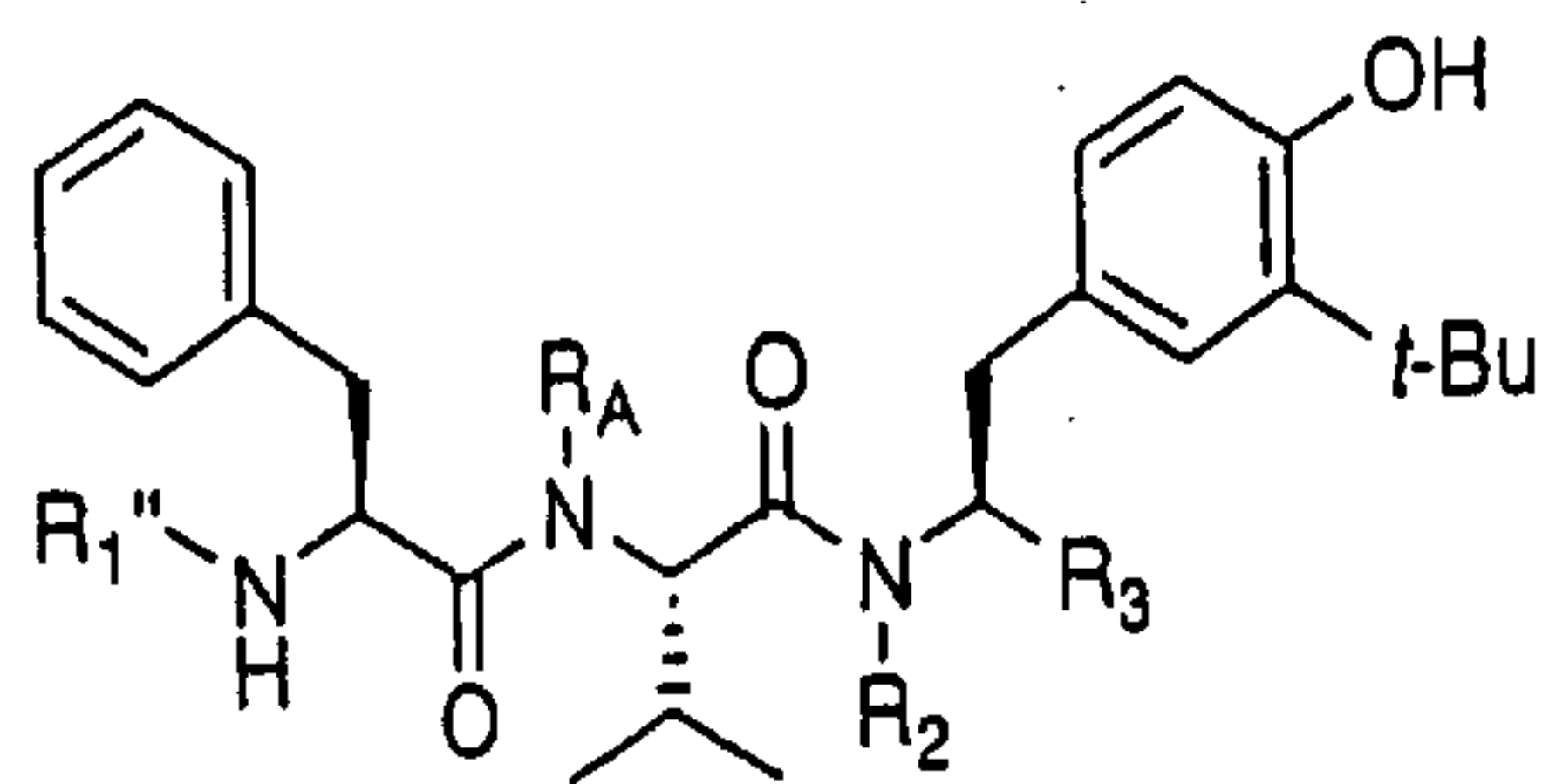
Ex. No.	R ₁	Ex. No.	R ₁
99		109	
104		112	
105		113	
106		114	
107			
108			

Table B-9



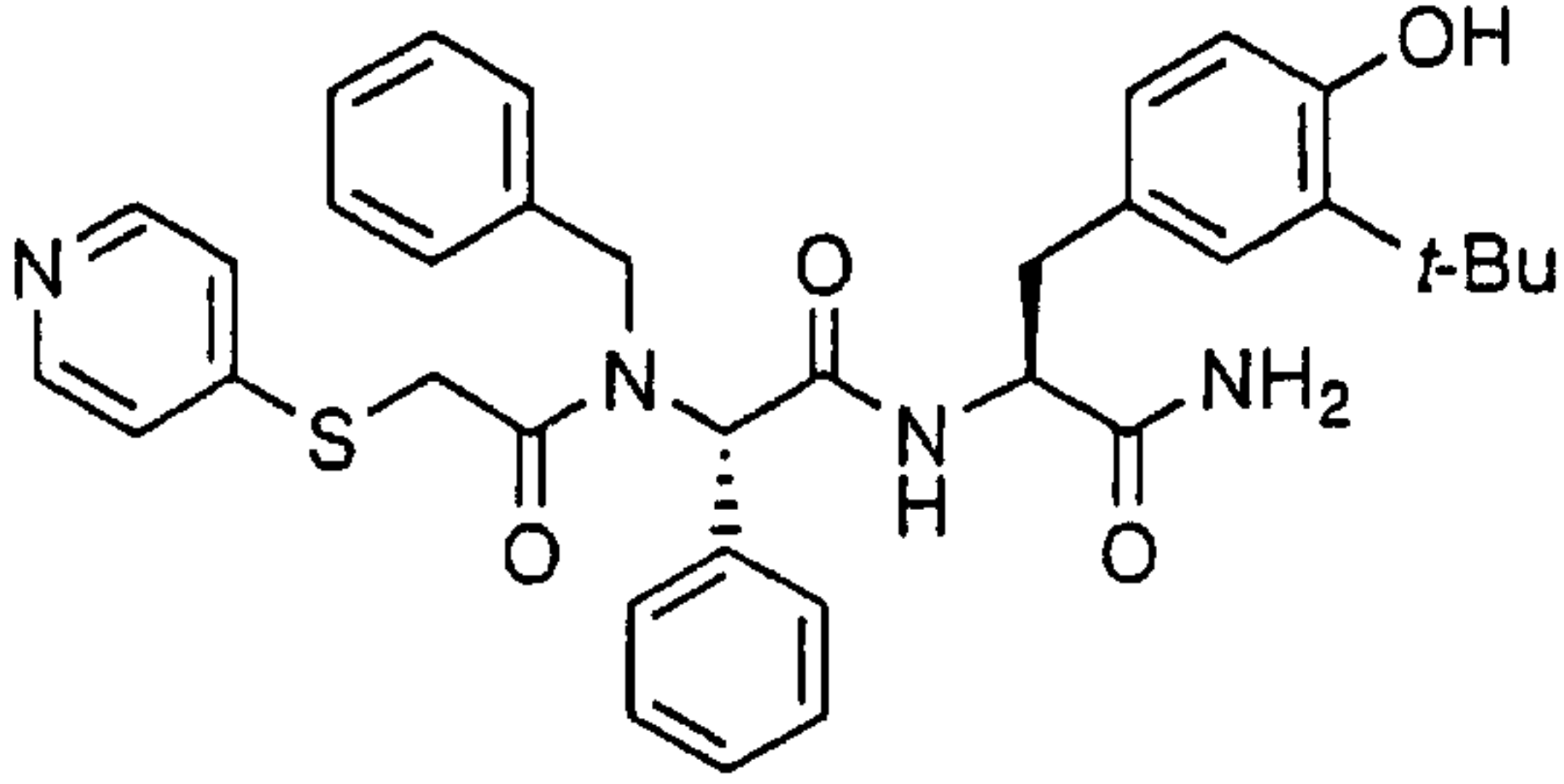
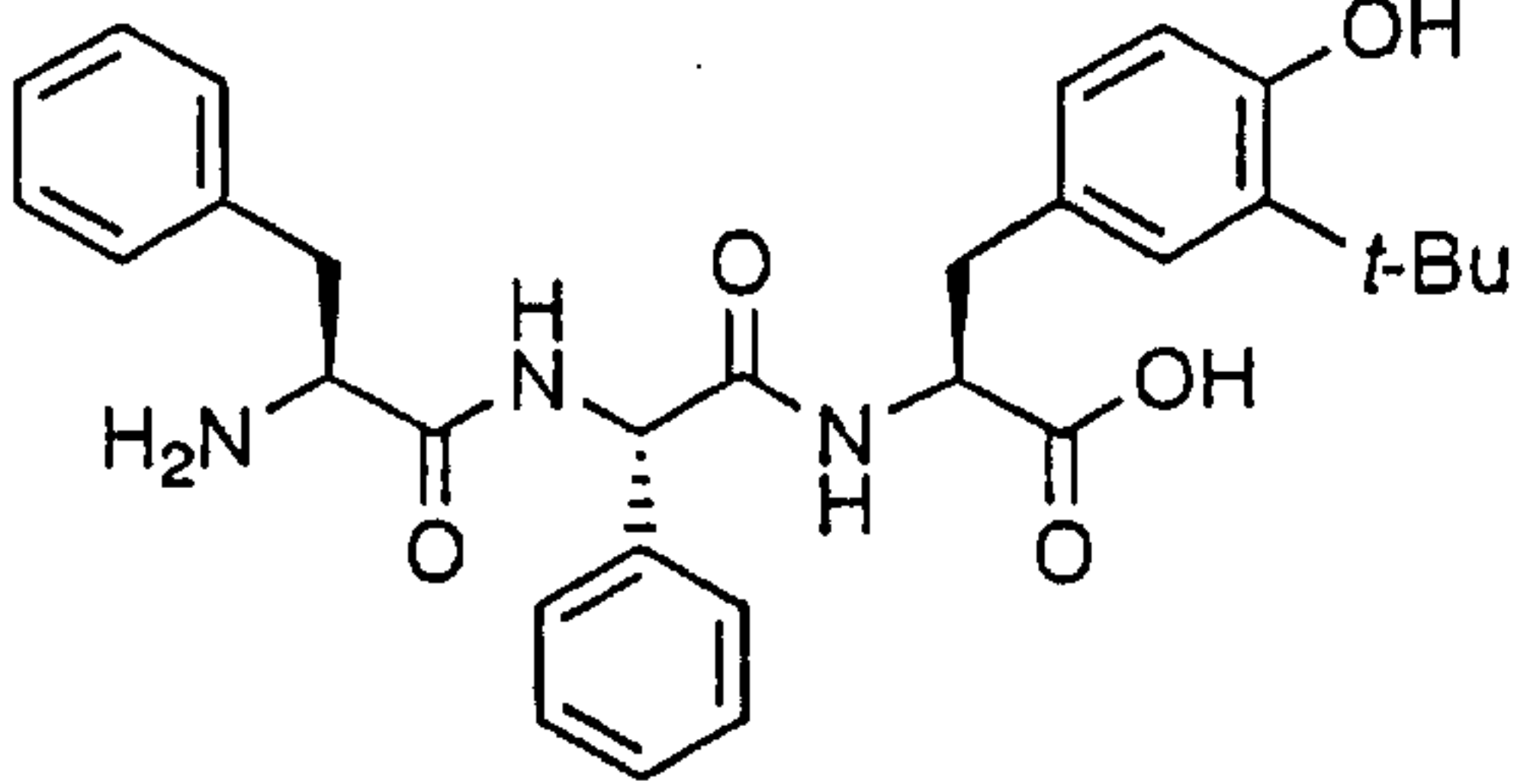
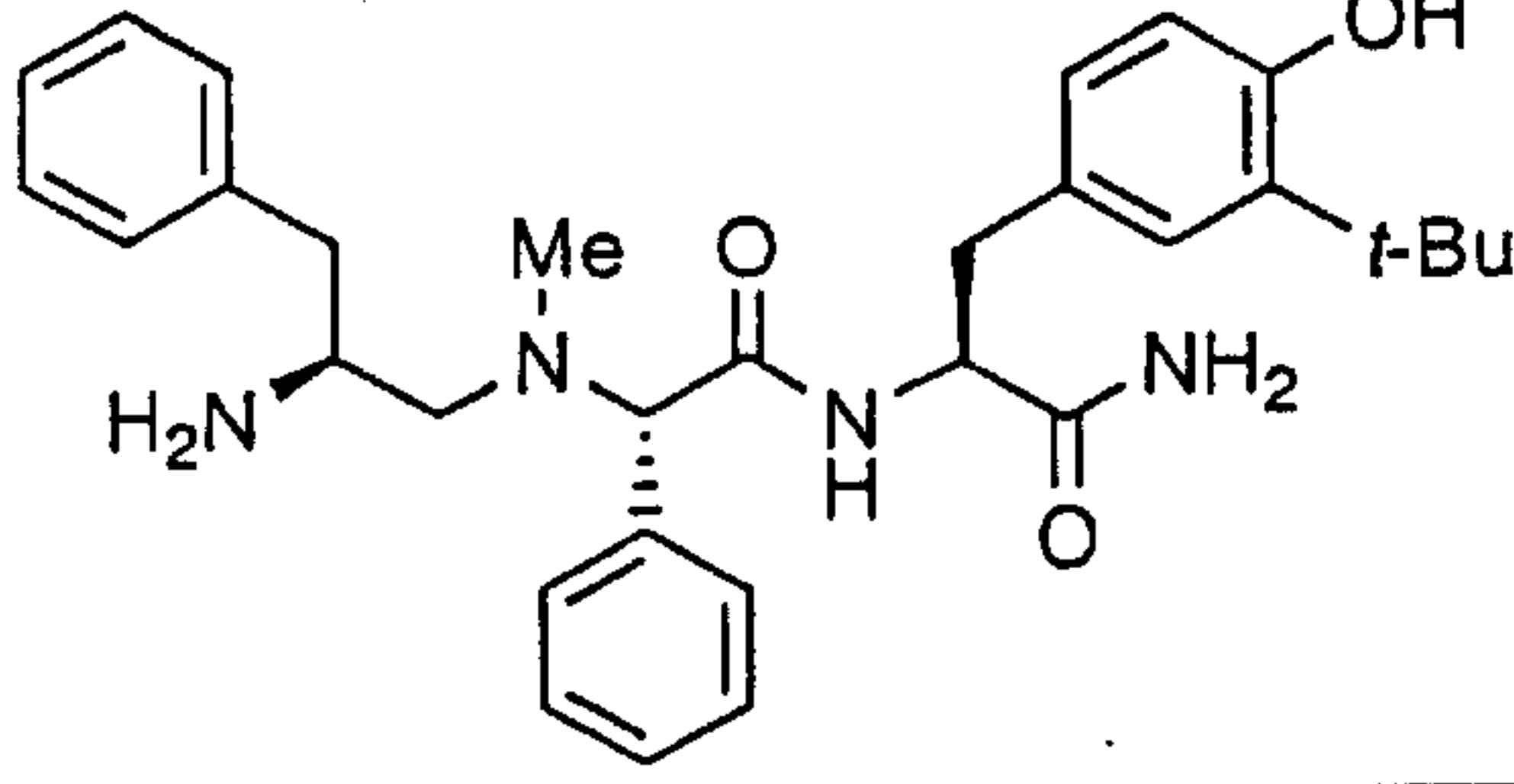
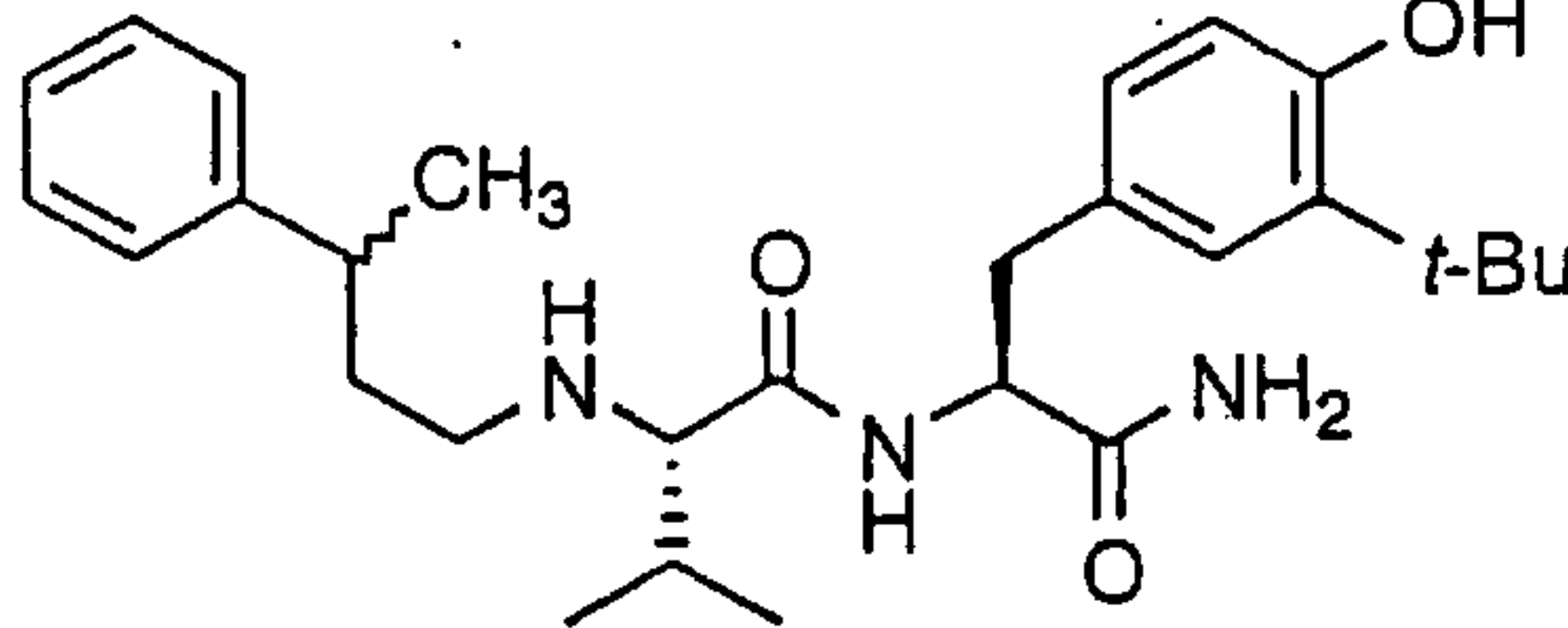
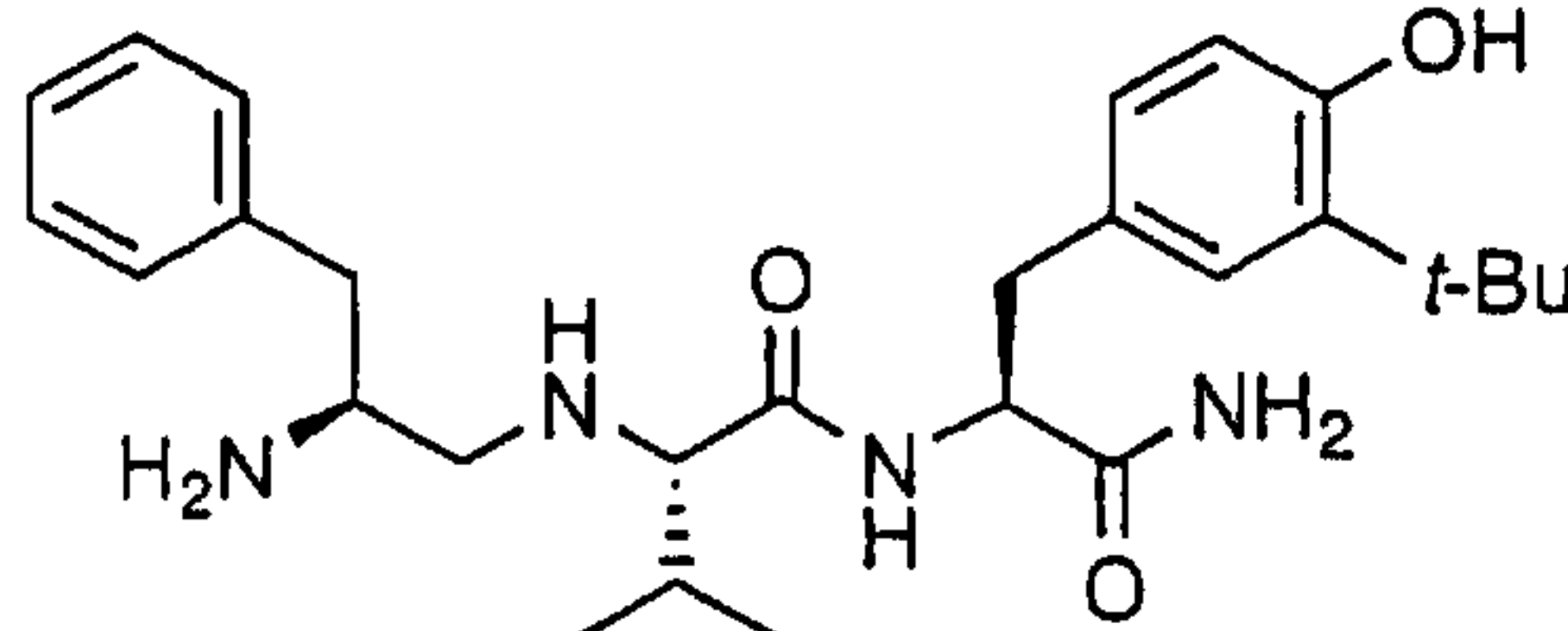
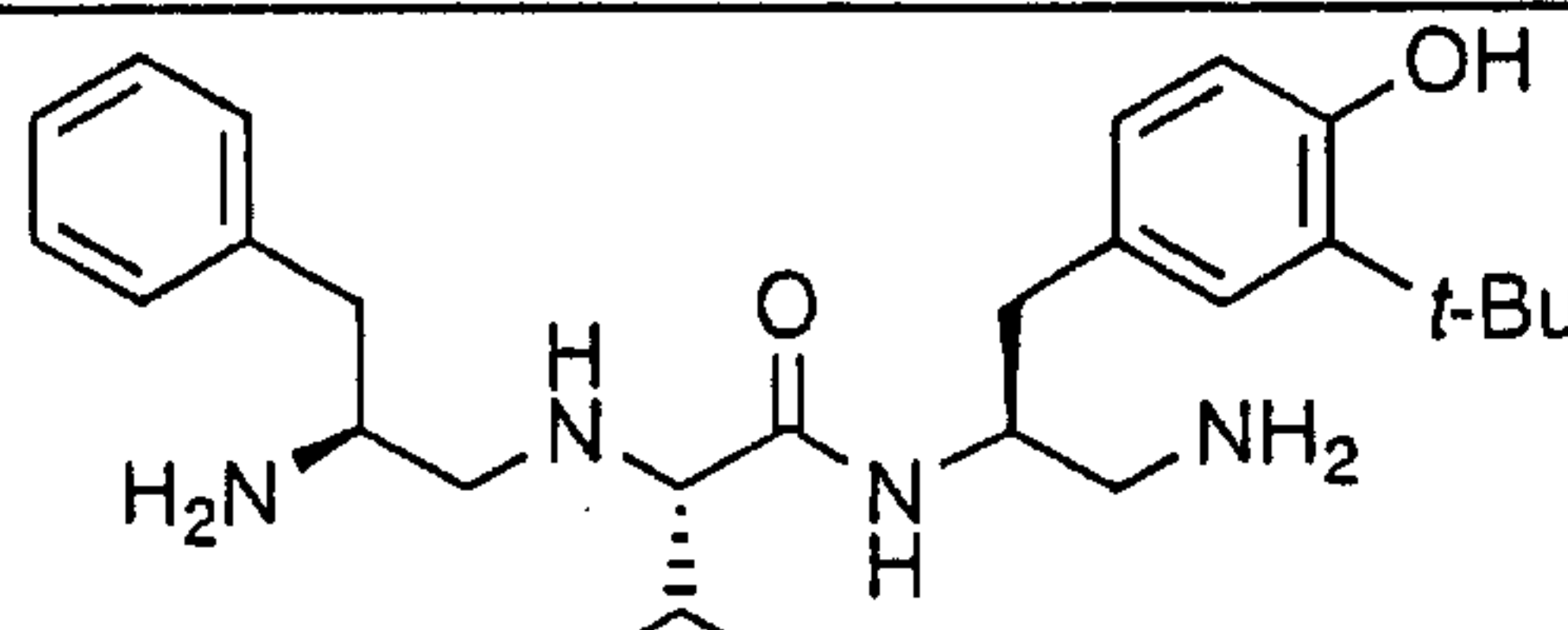
Ex. No.	R ₁ -A-
92	
93	
94	
95	
98	

Table B-10



Ex. No.	R ₁ ''	R _A	R ₂	R ₃
91	H	H	CH ₃	-CONH ₂
118	H	CH ₃	H	CH ₃
119	H	CH ₃	CH ₃	-CONH ₂
120	CH ₃	CH ₃	H	CH ₃
121	H	CH ₃	CH ₃	CH ₃

Table B-11

Ex. No.	Structural Formula
19	
20	
111	
115	
116	
117	

In the following examples, HPLC retention times (RT in minutes) were measured by either one of the following methods a - e.

Method a: HPLC was performed with HITACHI L-6300 using
5 Waters μ BONDASPHERE 5 μ C18 300 Å (300 angstroms, 3.9 x 150 mm) as a column. The eluting solution A was 0.1% trifluoroacetic acid (TFA) in distilled water and the eluting
solution B was 0.1% TFA in acetonitrile (MeCN). The linear
gradient was created by 0 - 70% of solution B for 35 minutes
10 at a flow rate of 1 ml/min. The detection wavelength was 280 nm (UV).

Method b: Same as method a, except that the linear gradient was created by 0 - 60% of solution B for 30 minutes at a flow rate of 1 ml/min.

15 Method c: Same as method a, except that the linear gradient was created by 20 - 60% of solution B for 40 minutes at a flow rate of 1 ml/min.

Method d: Same as method a, except that Waters μ BONDASPHERE
5 μ C18 100 Å (100 angstroms, 3.9 x 150 mm) was used as a
20 column.

Method e: Same as method a, except that HPLC was performed with SHIMADZU LC-10AD.

If necessary, the crude product was purified by HPLC which was performed with Waters 600E or Gilson 306 using
25 YMC-Pack ODS (120 angstroms, 250 x 20 mm I.D.) as a column. The eluting solution A was 0.1% TFA in distilled water and the eluting solution B was 0.1% TFA in MeCN. The linear gradient was created at a flow rate of 10 ml/min, and the

detection wavelength was 280 nm (UV).

Mass spectra (MA) were taken by EI-MS using SHIMADZU GCMS-QP1000 or GCMS-QP5050A or by FAB-MS using JASCO 70-250SEQ.

5 NMR was measured by the following method f or g.

Method f: Burucher DX-500 (500 MHz) was used as a measuring instrument.

Method g: JEOL JNM-EX-270 (270 MHz) was used as a measuring instrument.

10 Various commercial resins can conveniently be used as a solid phase and they include Rink Amide Resin of NovaBiochem, Fmoc-2,4-dimethoxy-4'-(carboxymethyloxy)-benzhydrylamine linked to Aminomethyl Resin of Bachem, and Wang Resin of Watanabe Kagaku K.K., which were used as
15 appropriate in the following examples.

Coupling in solid-phase synthesis can conveniently be performed by the following first to fifth methods, which were used as appropriate in the following examples.

Method 1: Using 1.5 - 2 equivalents of an acid component
20 (e.g. amino acid, N α -substituted amino acid or carboxylic acid), 3 equivalents of BOP and 3 equivalents of HOBT (relative to resin), 3 ml of N,N-dimethylformamide (DMF) for 0.1 mmol of resin, and 6 equivalents of NMM, shaking was done for 1.5 - 2 hours.

25 Method 2: Using 1.5 - 2 equivalents of an acid component and 3 equivalents of HATU (relative to resin), 3 ml of DMF for 0.1 mmol of resin, and 6 equivalents of NMM, shaking was done for 1.5 - 2 hours.

Method 3: Using 1.5 - 2 equivalents of an acid component and 3 equivalents of HOBT (relative to resin), 3 ml of DMF for 0.1 mmol of resin, and 3.2 equivalents of DIC, shaking was done for 2 hours.

- 5 Method 4: Using 5 equivalents of an acid component and 0.1 equivalent of DMAP (relative to resin), 3 ml of DMF for 0.1 mmol of resin, and 5 equivalents of DIC, shaking was done for 4 hours.

Method 5: Using 2 equivalents of an active ester (e.g. Pfp ester) of an acid component and 3 equivalents of HOBT (relative to resin), and 3 ml of DMF for 0.1 mmol of resin, shaking was done for 2 hours.

For constructing α -substituted amino acid residues, the sixth method described below is convenient and was used in the following examples as appropriate.

Method 6: Using 10 equivalents of a substituted or unsubstituted bromoacetic acid, 3 ml of DMF for 0.1 mmol of resin, and 13 equivalents of DIC, shaking was done for 30 minutes; after filtering, reacylation was done under the same conditions and repeated washing was effected with DMF; 60 equivalents of an amine dissolved in dimethyl sulfoxide (DMSO) was added to the mixture, which was shaken for 2 hours.

The following is a specific procedure of solid-phase synthesis. The reaction vessel is charged with a solid-phase resin, such as Rink Amide Resin, which is swollen by addition of a suitable solvent such as DMF; subsequently, 20% piperidine/DMF is added and repeated washing is effected

with DMF. To the washed mixture, an acid component is coupled by method 1. Using either one of the first to sixth coupling methods, the procedure is repeated as many times as the acid components to be coupled. The order of steps of deprotecting and cleaving the resin product is not fixed and they may be interchanged or performed simultaneously. The step of cleavage is completed by shaking in an aqueous solution of 95% TFA at room temperature for 30 - 45 minutes. After the end of the cleavage step, the resin is filtered off and the filtrate is concentrated and dried under reduced pressure to give a phenylalanine derivative in crude form.

The following is a specific method that may be employed to deprotect amino acids in solid-phase synthesis. If the resin is used in an amount of 0.025 - 0.1 mmol, an Fmoc group can be removed by a process consisting of the steps of adding 5 ml of 20% piperidine/DMF for 0.1 mmol of the resin, shaking for 5 minutes, filtering, then adding another 5 ml of 20% piperidine/DMF, shaking for 20 - 30 minutes, filtering and repeated washing with DMF. If the resin is used in an amount of 0.2 mmol, an Fmoc group can be removed by a process consisting of the steps of adding 7 ml of 20% piperidine/DMF, for 5 minutes, filtering, then adding another 7 ml of 20% piperidine/DMF, filtering and repeated washing with DMF. Boc, tBu and Trt groups can be removed in the cleavage step, with deprotection and cleavage being effected simultaneously.

Example 1

Phe-Hyp-Tyr(3-tBu)-NH₂

(1) Synthesis of Tyr(3-tBu)-OMe

To a solution of 25.0 g (0.108 mol) of Tyr-OMe·HCl in 500 ml of tert-butyl acetate, 18 ml (0.204 mol) of 70% HCl was added and the mixture was stirred at room temperature for 4 days. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in 400 ml of ethyl acetate; thereafter, the solution was poured into 800 ml of a saturated aqueous solution of NaHCO₃ and the mixture was stirred. The organic layer was taken out and washed first with a saturated aqueous solution of NaHCO₃, then with saturated brine, dried with anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. To the resulting residue, 500 ml of ether was added and the mixture was stirred overnight at room temperature. The precipitating crystals were recovered by filtration to give Tyr(3-tBu)-OMe in 10.9 g (40%).

NMR(method g, DMSO-d₆): δ 1.39(9H, s), 1.85(3H, brs), 2.81(1H, dd, J=14.0, 7.6Hz), 3.02(1H, dd, J=14.0, 5.1Hz), 3.70(1H, dd, J=7.6, 5.1Hz), 3.73(3H, s), 6.57(1H, d, J=8.2Hz), 6.86(1H, dd, J=8.2, 1.8Hz), 7.04(1H, d, J=1.8Hz)

(2) Synthesis of Fmoc-Tyr(3-tBu)-OH

To a solution of 2.0 g (8.0 mmol) of Tyr(3-tBu)-OMe in 40 ml of methanol, 8.8 ml (8.8 mmol) of 1 N aqueous sodium hydroxide was added dropwise under cooling with ice and the mixture was stirred for 2 hours, followed by stirring at room temperature for additional 4 hours. The reaction mixture was concentrated under reduced pressure and 1 N HCl was added under cooling with ice for pH adjustment to 9; to

the reaction being maintained at pH 8 - 9, a solution of 3.0 g (8.8 mmol) of Fmoc-OSu in 1,4-dioxane (40 ml) and a saturated aqueous solution of sodium hydrogencarbonate were alternately added dropwise and the mixture was stirred at room temperature for 1 day. After being rendered acidic with hydrochloric acid, the reaction mixture was extracted with ethyl acetate and the ethyl acetate layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crude product was subjected to silica gel column chromatography (eluting solvents were ethyl acetate:n-hexane = 1:1 and acetic acid supplemented ethyl acetate:n-hexane = 1:1); to remove the acetic acid used in eluting, the fractions were washed with water, dried with anhydrous magnesium sulfate and concentrated under reduced pressure to give Fmoc-Tyr(3-tBu)-OH in 2.3 g (yield: 61%).

NMR(method g, CDCl₃): δ 1.38(9H,s), 3.09(2H,m), 4.19(1H,m), 4.39(2H,d,J=7Hz), 4.64(1H,m), 5.19(1H,d,J=8Hz), 6.58(1H,d,J=8Hz), 6.84(1H,d,J=8Hz), 7.05(1H,br s), 7.26-7.77(8H,m)

(3) Synthesis of Phe-Hyp-Tyr(3-tBu)-NH₂

A reaction vessel was charged with 22 mg (0.1 mmol) of Rink Amide Resin (0.45 mmol/g); after being swelled with DMF, the resin was treated with piperidine to remove Fmoc. Subsequently, Fmoc-Tyr(3-tBu)-OH was coupled by method 1. After filtering and washing with DMF, the resin was treated with piperidine to remove Fmoc. Subsequently, Fmoc-Hyp-OH was coupled by method 2. After filtering and washing with

DMF, the resin was treated again with piperidine to remove Fmoc. Subsequently, Boc-Phe-OH was coupled by method 2. After the end of the reaction, filtering, washing with DMF and washing with methylene chloride (DCM) were performed and
 5 cleavage was effected with 3 ml of a 95% aqueous solution of TFA. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in 2 ml of DMF, followed by HPLC purification. The active fractions were collected, concentrated and freeze-dried to yield a TFA salt
 10 of the titled compound in 23.2 mg.

HPLC (method b): RT17.15

FAB-MS: 497(M+H⁺)

NMR(method f, DMSO-d₆): δ 1.32(9H, s), 1.75(1H, ddd, J=13, 8, 5Hz),
 2.00(1H, dd, J=13, 8Hz), 2.76(1H, dd, J=14, 8Hz),
 15 2.86(1H, dd, J=14, 6Hz), 2.92(1H, dd, J=14, 7Hz),
 3.09(1H, dd, J=14, 6Hz), 3.18(1H, dd, J=10, 4Hz),
 3.54(1H, d, J=10Hz), 4.25(1H, brs), 4.29-4.38(2H, m),
 4.46(1H, dd, J=8, 8Hz), 5.13(1H, d, J=3Hz), 6.65(1H, d, J=8Hz),
 6.88(1H, dd, J=8, 2Hz), 7.01(1H, d, J=2Hz), 7.02(1H, s), 7.23-
 20 7.43(6H, m), 7.89(1H, d, J=8Hz), 8.09(3H, brs), 9.09(1H, s)

Example 2

Phe-Tic-Tyr(3-tBu)-NH₂

Substituting Fmoc-Tic-OH for the Fmoc-Hyp-OH used in Example 1(3), the procedure of Example 1 was repeated to
 25 yield a TFA salt of the titled compound in 34.4 mg.

HPLC (method b): RT21.56

FAB-MS: 543(M+H⁺)

NMR(method g, DMSO-d₆): δ 1.30(9H, s), 2.58-3.24(6H, m),

4.27-4.85(5H,m), 6.56-7.41(14H,m), 7.81-8.36(4H,m),
9.09-9.11(1H,m)

Example 3

Phe-Thz-Tyr(3-tBu)-NH₂

- 5 Substituting Fmoc-Thz-OH for the Fmoc-Hyp-OH used in Example 1(3), the procedure of Example 1 was repeated to yield a TFA salt of the titled compound in 20.2 mg.

HPLC (method b):RT19.31

FAB-MS:499 (M+H⁺)

- 10 NMR(method g,DMSO-d₆): δ 1.32(9H,s), 2.70-3.15(6H,m),
4.16(1H,d,J=9Hz), 4.39(1H,m), 4.62(1H,m), 4.82(1H,t,J=7Hz),
5.02(1H,d,J=9Hz), 6.64(1H,d,J=8Hz), 6.82-7.41(9H,m),
8.00-8.13(4H,m), 9.10(1H,s)

Example 4

- 15 Phe-2-Abz-Tyr(3-tBu)-NH₂

Substituting Fmoc-2-ABz-OH for the Fmoc-Hyp-OH used in Example 1(3), the procedure of Example 1 was repeated to yield a TFA salt of the titled compound in 6.9 mg.

HPLC (method b):RT20.99

- 20 FAB-MS:503(M+H⁺)

NMR(method g,DMSO-d₆): δ 1.29(9H,s), 2.81-3.10(4H,m),
4.28(1H,m), 4.52(1H,m), 6.64(1H,d,J=8Hz), 6.94(1H,d,J=8Hz),
7.14-7.68(11H,m), 8.14(1H,d,J=8Hz), 8.31(2H,brs),
8.67(1H,d,J=8Hz), 9.10(1H,s), 11.27(1H,s)

- 25 Example 5

Phe-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Phg-OH for the Fmoc-Hyp-OH used in Example 1(3), the procedure of Example 1 was repeated

(except that Fmoc-Phg-OH and Boc-Phe-OH were coupled by method 1) to yield a TFA salt of the titled compound in 17.7 mg.

HPLC (method b): RT19.52

5 FAB-MS: 517(M+H⁺)

NMR(method f, DMSO-d₆): δ 1.32(9H, s), 2.74(1H, dd, J=14, 8Hz),
2.89(1H, dd, J=14, 5Hz), 2.92(1H, dd, J=14, 8Hz),
3.07(1H, dd, J=14, 5Hz), 4.17(1H, brs), 4.39(1H, ddd, J=8, 8, 5Hz),
5.60(1H, d, J=8Hz), 6.65(1H, d, J=8Hz), 6.87(1H, dd, J=8, 1Hz),
10 6.98(1H, s), 7.06(1H, d, J=1Hz), 7.10-7.50(11H, m), 8.09(3H, brs),
8.48(1H, d, J=8Hz), 9.06(1H, d, J=8Hz), 9.09(1H, s)

Example 6

Phe-D-Hyp-Tyr(3-tBu)-NH₂

(1) Synthesis of Fmoc-D-Hyp-OH

15 262 mg (2.0 mmol) of D-Hyp-OH was dissolved in 5 ml of a saturated aqueous solution of sodium hydrogencarbonate under stirring and a mixture of 742 mg (2.2 mmol) of Fmoc-OSu and 10 ml of 1,4-dioxane was added dropwise under cooling with ice; thereafter, and the mixture was stirred at
20 room temperature for 3 days. In the meantime, a saturated aqueous solution of sodium hydrogencarbonate was added as appropriate to keep the pH of the reaction mixture at 8 - 9. After being rendered acidic with hydrochloric acid under cooling with ice, the reaction mixture was subjected to
25 extraction with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crude product was purified by silica gel

column chromatography (eluting solvents were chloroform and acetic acid supplemented chloroform:methanol = 10:1); to remove the acetic acid used in eluting, the fractions were once concentrated under reduced pressure and dissolved again
5 in ethyl acetate; thereafter, the solution was washed with water, dried with anhydrous magnesium sulfate and concentrated under reduced pressure to give a colorless powder in 660 mg (93%).

NMR(method g,DMSO-d₆): δ 1.89-2.29(2H,m), 3.26-3.56(3H,m),
10 4.10-4.47(4H,m), 5.15(1H,br s), 7.28-7.94(8H,m),
12.64(1H,brs)

(2) Synthesis of Phe-D-Hyp-Tyr(3-tBu)-NH₂

A reaction vessel was charged with 213 mg (0.1 mmol) of Rink Amide Resin (0.47 mmol/g); after being swelled with
15 DMF, the resin was treated with pyridine to remove Fmoc. Subsequently, Fmoc-Tyr(3-tBu)-OH was coupled by method 1. After filtering and washing with DMF, the resin was treated with piperidine to remove Fmoc. Subsequently, Fmoc-D-Hyp-OH was coupled by method 2. After filtering and washing with
20 DMF, the resin was treated with piperidine to remove Fmoc. Subsequently, Fmoc-Phe-OH was coupled by method 2. After filtering and washing with DMF, the resin was treated again with piperidine to remove Fmoc. After the end of the reaction, filtering, washing with DMF and washing with DCM
25 were performed and cleavage was effected with 3 ml of a 95% aqueous solution of TFA. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in 2 ml of DMF, followed by HPLC purification.

The active fractions were collected, concentrated and freeze-dried to yield a TFA salt of the titled compound in 21.5 mg. HPLC (method d):RT16.68

FAB-MS:497(M+H⁺)

- 5 NMR(method g, DMSO-d₆): δ 1.32(9H,s), 1.45-1.76(2H,m),
2.62-3.09(4H,m), 3.59-4.78(6H,m), 5.14(1H,br s),
6.64(1H,d,J=8Hz), 6.82(1H,d,J=6Hz), 7.00(1H,s), 7.13(2H,s),
7.23-7.36(5H,m), 8.16(3H,brs), 8.41(1H,d,J=9Hz), 9.08(1H, s)

Example 7

- 10 Phe-Pro-Tyr(3-tBu)-NH₂

Substituting Fmoc-Pro-OH·AcOEt for the Fmoc-d-Hyp-OH used in Example 6(2), the procedure of Example 6(2) was repeated to yield a TFA salt of the titled compound in 27.0 mg.

- 15 HPLC (method b):RT18.87

FAB-MS:481(M+H⁺)

- NMR(method g, DMSO-d₆): δ 1.32(9H,s), 1.38-2.10(4H,m),
2.75(1H,dd,J=14,9Hz), 2.84-3.85(5H,m), 4.25-4.49(3H,m),
6.64(1H,d,J=8Hz), 6.82-7.35(9H,m), 7.70-8.30(4H,m),
20 9.09(1H,s)

Example 8

Phe-D-Pro-Tyr(3-tBu)-NH₂

- Substituting Fmoc-D-Pro-OH·AcOEt for the Fmoc-D-Hyp-OH used in Example 6(2), the procedure of Example 6(2) was
25 repeated to yield a TFA salt of the titled compound in 33.6 mg.

HPLC (method b):RT19.87

FAB-MS:481(M+H⁺)

NMR(method g, DMSO-d₆): δ 1.31(9H,s), 1.41-2.04(4H,m),
 2.55-3.51(6H,m), 4.15-4.70(3H,m), 6.61-6.67(1H,m),
 6.80-6.83(1H,m), 6.98-7.01(1H,m), 7.12-7.34(7H,m),
 8.02-8.39(4H,m), 9.08(1H,s)

5 Example 9

Phe-Phg-Phe(3-tBu-4-methoxy)-NH₂

(1) Synthesis of Z-Tyr(3-t-Bu)-OMe

To a solution of Tyr(3-tBu)-OMe (1.1 g) in H₂O (10 ml),
 0.7 g (6.57 mmol) of NaHCO₃ and 0.92 ml (6.57 mmol) of Z-Cl
 10 were added under cooling with ice and the mixture was
 stirred at room temperature for 1 hour. The reaction
 mixture was diluted with ethyl acetate and washed with water
 and saturated brine. The organic layer was dried with
 anhydrous sodium sulfate and concentrated under reduced
 15 pressure. The resulting residue was subjected to silica gel
 column chromatography (eluting solvent; ethyl acetate:n-
 hexane = 1:2) to give Z-Tyr(3-t-Bu)-OMe in 1.44 g (85%).
 NMR(method g, CDCl₃): δ 1.36(9H,s), 3.04(2H,brd,J=5.6Hz),
 3.72(3H,s), 4.57-4.68(1H,m), 4.97(1H,brs), 5.10(2H,s),
 20 5.20(1H,brd,J=7.9Hz), 6.55(1H,d,J=7.9Hz),
 6.78(1H,dd,J=2.0,7.9Hz), 6.95(1H,d,J=2.0Hz), 7.26-7.41(5H,m)

(2) Synthesis of Z-Phe(3-tBu-4-methoxy)-OMe

To a solution of Z-Tyr(3-tBu)-OMe (0.4 g) in acetone
 (3 ml), 0.22 g (1.56 mmol) of K₂CO₃ and 0.65 ml (10.4 mmol)
 25 of methyl iodide were added at room temperature and the
 mixture was heated under reflux for 5 hours. The reaction
 mixture was concentrated under reduced pressure and the
 resulting residue was subjected to silica gel column

chromatography (eluting solvent; ethyl acetate:n-hexane = 1:2) to give Z-Phe(3-tBu-4-methoxy)-OMe in 0.10 g (24%).

NMR(method g, CDCl₃): δ 1.33(9H,s), 3.05(2H,brd,J=5.6Hz),

3.72(3H,s), 3.81(3H,s), 4.57-4.68(1H,m), 5.10(2H,s),

5 5.19(1H,brd,J=7.9Hz), 6.76(1H,d,J=8.2Hz),

6.90(1H,dd,J=2.0,8.2Hz), 6.96(1H,d,J=2.0Hz), 7.26-7.40(5H,m)

(3) Synthesis of Phe(3-tBu-4-methoxy)-OMe

To a solution of Z-Phe(3-tBu-4-methoxy)-OMe (0.17 g) in methanol (2 ml), 10% palladium carbon (0.02 g) was added
10 at room temperature and the mixture was stirred in a hydrogen atmosphere for 20 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent was ethyl acetate) to
15 give Phe(3-tBu-4-methoxy)-OMe in 88 mg (77%).

EI-MS:265(M⁺)

NMR(method g, CDCl₃): δ 1.35(9H,s), 2.81(1H,dd,J=13.6,7.8Hz),

3.02(1H,dd,J=13.6,5.0Hz), 3.67-3.71(1H,m), 3.73(3H,s),

3.81(3H,s), 6.80(1H,d,J=8.2Hz), 7.00(1H,dd,J=2.0,8.2Hz),

20 7.05(1H,d,J=2.0Hz)

(4) Synthesis of Fmoc-Phe(3-tBu-4-methoxy)-OH

To a solution of 87 mg (0.33 mmol) of Phe(3-tBu-4-methoxy)-OMe in 2 ml of methanol, 0.4 ml (0.4 mmol) of 1 N aqueous sodium hydroxide was added dropwise under cooling
25 with ice and the mixture was stirred for 1 hour, followed by stirring for additional 3 hours at room temperature. The reaction mixture was concentrated under reduced pressure and adjusted to pH 9 by addition of 1 N hydrochloric acid and a

saturated aqueous solution of sodium hydrogencarbonate. To the thus adjusted reaction mixture, a solution of 122 mg (0.36 mmol) of Fmoc-OSu in 2 ml of 1,4-dioxane was added dropwise and the mixture was stirred for 3 hours at room temperature. The reaction mixture was rendered acidic with hydrochloric acid and extracted with ethyl acetate; the ethyl acetate layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crude product was purified by preparative thin-layer chromatography (developing solvents were CHCl_3 and CHCl_3 :methanol = 4:1) to give Fmoc-Phe(3-tBu-4-methoxy)-OH in 125 mg (80%).

NMR(method g, CDCl_3): δ 1.33(9H,s), 2.99-3.21(2H,m), 3.76(3H,s), 4.12(1H,m), 4.32(2H,m), 4.57(1H,br s), 5.25(1H,d,J=6Hz), 6.74(1H,d,J=8Hz), 6.95(1H,d,J=8Hz), 7.06(1H,br s), 7.22-7.74(8H,m)

(5) Synthesis of Phe-Phg-Phe(3-tBu-4-methoxy)- NH_2

Substituting Fmoc-Phe(3-tBu-4-methoxy)-OH for the Fmoc-Tyr(3-tBu)-OH used in Example 5 and using 213 mg (0.1 mmol) of Rink Amide Resin (0.47 mmol/g) as a resin, the procedure of Example 5 was repeated to yield a TFA salt of the titled compound in 18.8 mg.

HPLC (method e): RT22.70

FAB-MS: 531($\text{M}+\text{H}^+$)

NMR(method f, $\text{DMSO}-d_6$): δ 1.30(9H,s), 2.78(1H,dd,J=14,9Hz), 2.90(1H,dd,J=14,8Hz), 2.94(1H,dd,J=14,5Hz), 3.04(1H,dd,J=14,5Hz), 3.69(3H,s), 4.17(1H,brs), 4.43(1H,ddd,J=14,9,8Hz), 5.60(1H,d,J=8Hz), 6.82(1H,d,J=8Hz),

7.01(1H,s), 7.06(1H,dd,J=8,1Hz), 7.15(1H,d,J=1Hz),
7.17-7.48(11H,m), 8.08(3H,brs), 8.54(1H,d,J=8Hz),
9.06(1H,d,J=8Hz)

Example 10

5 Phe-Phe-Tyr(3-tBu)-NH₂

Substituting Fmoc-Phe-OH for the Fmoc-Phg-OH used in
Example 5 and using 213 mg (0.1 mmol) of Rink Amide Resin
(0.47 mmol/g) as a resin, the procedure of Example 5 was
repeated to yield a TFA salt of the titled compound in

10 20.5 g.

HPLC (method e):RT19.41

FAB-MS:531(M+H⁺)

NMR(method f,DMSO-d₆): δ 1.31(9H,s), 2.74(1H,dd,J=14,8Hz),
2.82(1H,dd,J=14,9Hz), 2.87(1H,dd,J=14,9Hz),
15 2.89(1H,dd,J=14,5Hz), 3.03(1H,dd,J=14,4Hz),
3.10(1H,dd,J=14,4Hz), 4.00(1H,brs), 4.40(1H,ddd,J=8,8,5Hz),
4.61(1H,ddd,J=9,8,4Hz), 6.65(1H,d,J=8Hz),
6.87(1H,dd,J=8,2Hz), 7.00-7.10(2H,m), 7.15-7.28(10H,m),
7.30(1H,s), 7.98(3H,brs), 8.23(1H,d,J=8Hz), 8.66(1H,d,J=8Hz),
20 9.07(1H,s)

Example 11

Phe-Val-Tyr(3-tBu)-NH₂

Substituting Fmoc-Val-OH for the Fmoc-Phg-OH used
in Example 5 and using 213 mg (0.1 mmol) of Rink Amide
25 Resin (0.47 mmol/g) as a resin, the procedure of Example 5
was repeated to yield a TFA salt of the titled compound in
28.4 mg.

HPLC (method e):RT18.68

FAB-MS: 483(M+H⁺)

NMR(method f, DMSO-d₆): δ 0.83(3H,d,J=7Hz), 0.84(3H,d,J=7Hz),
 1.31(9H,s), 1.96(1H,dqq,J=7,6,6Hz), 2.71(1H,dd,J=14,9Hz),
 2.86(1H,dd,J=14,6Hz), 2.88(1H,dd,J=14,8Hz),
 5 3.03(1H,dd,J=14,5Hz), 4.13(1H,brs), 4.25(1H,dd,J=9,6Hz),
 4.40(1H,ddd,J=9,8,6Hz), 6.65(1H,d,J=8Hz),
 6.88(1H,dd,J=8,2Hz), 6.99(1H,s), 7.05(1H,d,J=2Hz), 7.13-
 7.25(5H,m), 7.35(1H,s), 8.05(1H,d,J=8Hz), 8.07(3H,brs),
 8.43(1H,d,J=9Hz), 9.08(1H,s)

10 Example 12

Phe-Phg-Tyr-NH₂

Substituting Fmoc-Tyr(tBu)-OH for the Fmoc-Tyr(3-tBu)-
 OH used in Example 5 and using 213 mg (0.1 mmol) of Rink
 Amide Resin (0.47 mmol) as a resin, the procedure of Example
 15 5 was repeated to yield a TFA salt of the titled compound in
 21.7 mg.

HPLC (method e): RT13.40

FAB-MS: 461(M+H⁺)

NMR(method f, DMSO-d₆): δ 2.73(1H,dd,J=14,8Hz),
 20 2.89(1H,dd,J=14,5Hz), 2.93(1H,dd,J=14,8Hz),
 3.07(1H,dd,J=14,5Hz), 4.17(1H,dd,J=8,5Hz),
 4.39(1H,ddd,J=8,8,5Hz), 5.59(1H,d,J=8Hz), 6.63(2H,d),
 6.99(1H,s), 7.03(2H,d), 7.20-7.50(11H,m), 8.05(3H,brs),
 8.45(1H,d,J=8Hz), 9.06(1H,d,J=8Hz), 9.16(1H,s)

25 Example 13

Phe-Ala-Tyr(3-tBu)-NH₂

Substituting Fmoc-Ala-OH·H₂O for the Fmoc-D-Hyp-OH
 used in Example 6(2), the procedure of Example 6(2) was

repeated (except that Fmoc-Ala-OH·H₂O and Fmoc-Phe-OH were coupled by method 1) to yield a TFA salt of the titled compound in 27.8 mg.

HPLC (method e): RT17.82

5 FAB-MS: 455(M+H⁺)

NMR(method f, DMSO-d₆): δ 1.22(3H,d,J=6Hz), 1.31(9H,s),
2.71(1H,dd,J=14,9Hz), 2.86(1H,dd,J=14,9Hz),
2.87(1H,dd,J=14,5Hz), 3.06(1H,dd,J=14,5Hz), 4.04(1H,brs),
4.30-4.40(2H,m), 6.65(1H,d,J=8Hz), 6.86(1H,dd,J=8,2Hz),
10 7.03(1H,d,J=2Hz), 7.04(1H,s), 7.17-7.27(5H,m), 7.39(1H,s),
8.01(1H,d,J=8Hz), 8.06(3H,brs), 8.58(1H,d,J=8Hz), 9.08(1H,s)

Example 14

Phe-Leu-Tyr(3-tBu)-NH₂

Substituting Fmoc-Leu-OH for the Fmoc-Ala-OH·H₂O used
15 in Example 13, the procedure of Example 13 was repeated to
yield a TFA salt of the titled compound in 31.6 mg.

HPLC (method e): RT20.02

FAB-MS: 497(M+H⁺)

NMR(method f, DMSO-d₆): δ 0.86(3H,d,J=6Hz), 0.89(3H,d,J=6Hz),
20 1.31(9H,s), 1.43(2H,dd,J=7,7Hz), 1.61(1H,tqq,J=7,6,6Hz),
2.73(1H,dd,J=14,8Hz), 2.81-2.93(2H,m), 3.09(1H,dd,J=14,5Hz),
4.04(1H,brs), 4.31-4.42(2H,m), 6.64(1H,d,J=8Hz),
6.85(1H,dd,J=8,2Hz), 7.02(1H,d,J=2Hz), 7.03(1H,s), 7.18-
7.26(5H,m), 7.37(1H,s), 8.00(1H,d,J=8Hz), 8.05(3H,brs),
25 8.56(1H,d,J=8Hz), 9.08(1H,s)

Example 15

Val-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Val-OH for the Fmoc-Phe-OH used in

Example 6(2) and also substituting Fmoc-Phg-OH for Fmoc-D-Hyp, the procedure of Example 6(2) was repeated (except that Fmoc-Val-OH and Fmoc-Phg-OH were coupled by method 1) to yield a TFA salt of the titled compound in 18.2 mg.

5 HPLC (method e):RT17.64

FAB-MS:469(M+H⁺)

NMR(method g,DMSO-d₆): δ 0.90(3H,d,J=7Hz), 0.91(3H,d,J=7Hz),
1.31(9H,s), 2.02(1H,m), 2.72(1H,dd,J=14,9Hz),
2.87(1H,dd,J=14,5Hz), 3.77(1H,m), 4.42(1H,m),
10 5.61(1H,d,J=8Hz), 6.60(1H,d,J=8Hz), 6.80(1H,dd,J=8,2Hz),
6.99-7.01(2H,m), 7.25-7.45(6H,m), 8.03(3H,br s),
8.46(1H,d,J=8Hz), 8.94(1H,d,J=8Hz), 9.07(1H,s)

Example 16

Leu-Phg-Tyr(3-tBu)-NH₂

15 Substituting Fmoc-Leu-OH for the Fmoc-Phe-OH used in Example 6(2) and also substituting Fmoc-Phg-OH for Fmoc-D-Hyp, the procedure of Example 6(2) was repeated (except that Fmoc-Leu-OH and Fmoc-Phg-OH were coupled by method 1) to yield a TFA salt of the titled compound in 19.3 mg.

20 HPLC (method e):RT18.74

FAB-MS:483(M+H⁺)

NMR(method g,DMSO-d₆): δ 0.87(3H,d,J=7Hz), 0.89(3H,d,J=7Hz),
1.32(9H,s), 1.50-1.65(3H,m), 2.73(1H,dd,J=14,8Hz),
2.87(1H,dd,J=14,5Hz), 3.93(1H,m), 4.41(1H,m),
25 5.59(1H,d,J=8Hz), 6.62(1H,d,J=8Hz), 6.81(1H,dd,J=8,1Hz),
6.99-7.01(2H,m), 7.28-7.44(6H,m), 8.06(3H,br s),
8.43(1H,d,J=8Hz), 9.08(1H,s), 9.09(1H,d,J=8Hz)

Example 17

Phe-Gly-Tyr(3-tBu)-NH₂

Substituting Fmoc-Gly-OPfp for the Fmoc-Phg-OH used in Example 5 and using 213 mg (0.1 mmol) of Rink Amide Resin (0.47 mmol/g) as a resin, the procedure of Example 5 was repeated (except that Fmoc-Gly-OPfp was coupled by method 5) to yield a TFA salt of the titled compound in 20.8 mg.

HPLC (method d): RT17.23

FAB-MS: 441(M+H⁺)

NMR(method f, DMSO-d₆): δ 1.32(9H, s), 2.64(1H, dd, J=14, 9Hz),
 2.88(1H, dd, J=14, 5Hz), 2.91(1H, dd, J=14, 8Hz),
 3.07(1H, dd, J=14, 5Hz), 3.65(1H, dd, J=17, 6Hz),
 3.90(1H, dd, J=17, 6Hz), 4.07(1H, brs), 4.36(1H, ddd, J=9, 8, 5Hz),
 6.64(1H, d, J=8Hz), 6.85(1H, dd, J=8, 1Hz), 7.01(1H, d, J=1Hz),
 7.06(1H, s), 7.20-7.35(5H, m), 7.45(1H, s), 8.10(3H, brs),
 8.19(1H, d, J=8Hz), 8.62(1H, dd, J=6, 6Hz), 9.09(1H, s)

Example 18

18A: Phe-N-Me-Phg-Tyr(3-tBu)-NH₂

18B: Phe-N-Me-D-Phg-Tyr(3-tBu)-NH₂

A reaction vessel was charged with 213 mg (0.1 mmol) of Rink Amide Resin (0.47 mmol/g); after being swelled with DMF, the resin was treated with piperidine to remove Fmoc. Subsequently, Fmoc-Tyr(3-tBu)-OH was coupled by method 1. After filtering and washing with DMF, the resin was treated with piperidine to remove Fmoc. Subsequently, using α-bromophenylacetic acid and 40% aqueous methylamine, coupling was done by method 6 to construct Nα-substituted amino acid residues. After filtering and washing with DMF, Boc-Phe-OH was coupled by method 2. After the end of the reaction,

filtering and washing with DMF and DCM were effected,
 followed by cleavage with 3 ml of 95% aqueous TFA. The
 reaction mixture was concentrated under reduced pressure and
 the residue was dissolved in 2 ml of DMF, followed by HPLC
 5 purification. The active fractions were collected,
 concentrated and freeze-dried to yield TFA salts of the
 titled compounds in respective amounts of 21.9 mg (18A) and
 12.9 mg (18B).

18A HPLC (method c):RT16.64

10 FAB-MS:531(M+H⁺)

NMR(method g, DMSO-d₆): δ 1.27(9H,s), 2.45(3H,s),
 2.62-3.11(4H,m), 4.60(2H,m), 6.07(1H,s), 6.41(2H,d,J=7Hz),
 6.56(1H,d,J=8Hz), 6.71(1H,d,J=8Hz), 7.05-7.32(11H,m),
 8.29(3H,br s), 8.39(1H,d,J=9Hz), 9.13(1H,s)

15 18B HPLC (method c):RT14.20

FAB-MS:531(M+H⁺)

NMR(method f, DMSO-d₆): δ 1.28(9H,s), 2.47(3H,s),
 2.70(1H,dd,J=14,9Hz), 2.87(1H,dd,J=14,5Hz), 2.96(2H,d,J=7Hz),
 4.42(1H,ddd,J=5,9,8Hz), 4.49(1H,brs), 6.27(1H,s),
 20 6.62(1H,d,J=8Hz), 6.92(1H,dd,J=8,2Hz), 7.00(1H,s), 7.05-
 7.36(11H,m), 7.45(1H,s), 8.14(3H,brs), 8.32(1H,d,J=8Hz),
 9.04(1H,s)

Example 19

N-benzyl-N-(4-pyridylthioacetyl)-Phg-Tyr(3-tBu)-NH₂

25 A reaction vessel was charged with 213 mg (0.1 mmol)
 of Rink Amide Resin (0.47 mmol/g); after being swelled with
 DMF, the resin was treated with piperidine to remove Fmoc.
 Subsequently, Fmoc-Tyr(3-tBu)-OH was coupled by method 1.

After filtering and washing with DMF, the resin was treated with piperidine to remove Fmoc. Subsequently, using α -bromophenylacetic acid and benzylamine, coupling was done by method 6 to construct N α -substituted amino acid residues.

- 5 After filtering and washing with DMF, a mixture of 1.5 ml of DMF, 1.5 ml of NMM and 34 mg (0.2 mmol) of 4-pyridyl-thioacetic acid, and 114 mg (0.3 mmol) of HATU were added, followed by shaking for 2 hours to effect coupling. After the end of the reaction, filtering, and washing with DMF,
- 10 DCM and methanol were effected and the resin was dried. Cleavage was performed with 3 ml of 95% aqueous TFA. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in 2 ml of DMF, followed by HPLC purification. The active fractions were collected,
- 15 concentrated and freeze-dried to yield a TFA salt of the titled compound in 19.8 mg as a mixture of diastereomers.
- HPLC (method b): RT 22.90, 23.39

FAB-MS: 611 (M+H⁺)

Example 20

- 20 Phe-Phg-Tyr(3-tBu)-OH

Using 274 mg (0.2 mmol) of Wang Resin (0.73 mmol/g) as a resin, the procedure of Example 5 was repeated (except that Fmoc-Tyr(3-tBu)-OH was coupled by method 4) to yield a TFA salt of the titled compound in 31.2 mg.

- 25 HPLC (method b): RT 20.62

FAB-MS: 518 (M+H⁺)

NMR (method f, DMSO-d₆): δ 1.31 (9H, s), 2.82 (1H, dd, J=14, 8Hz), 2.89 (1H, dd, J=14, 8Hz), 2.94 (1H, dd, J=14, 5Hz),

3.04(1H,dd,J=14,5Hz), 4.10(1H,brs), 4.35(1H,ddd,J=8,8,5Hz),
5.61(1H,d,J=8Hz), 6.66(1H,d,J=8Hz), 6.84(1H,dd,J=8,1Hz),
7.04(1H,d,J=1Hz), 7.15-7.45(10H,m), ca7.9(ambiguous,br),
8.68(1H,d,J=8Hz), 9.02(1H,d,J=8Hz), 9.14(1H,s)

5 Example 21

Phe-Tyr-Tyr(3-tBu)-NH₂

Substituting Fmoc-Tyr(tBu)-OH for the Fmoc-Phg-OH used
in Example 5 and using 107 mg (0.05 mmol) of Rink Amide
Resin (0.47 mmol/g) as a resin, the procedure of Example 5
10 was repeated (except that after cleavage, the reaction
mixture was concentrated under reduced pressure and the
residue was dissolved in 3 ml of methanol, followed by
another concentrating under reduced pressure) to yield a TFA
salt of the titled compound in 15.8 mg.

15 HPLC (method e):RT18.78

FAB-MS:547(M+H⁺)

Example 22

Phe-Hph-Tyr(3-tBu)-NH₂

Substituting Fmoc-Hph-OH for the Fmoc-Tyr(tBu)-OH used
20 in Example 21, the procedure of Example 21 was repeated to
yield a TFA salt of the titled compound in 19.4 mg.

HPLC (method e):RT21.53

FAB-MS:545(M+H⁺)

Example 23

25 Phe-Thi-Tyr(3-tBu)-NH₂

Substituting Fmoc-Thi-OH for the Fmoc-Tyr(tBu)-OH used
in Example 21, the procedure of Example 21 was repeated to
yield a TFA salt of the titled compound in 21.5 mg.

HPLC (method e):RT19.65

FAB-MS:537(M+H⁺)

Example 24

Phe-β-Ala-Tyr(3-tBu)-NH₂

- 5 Substituting Fmoc-β-Ala-OH for the Fmoc-Tyr(tBu)-OH used in Example 21, the procedure of Example 21 was repeated to yield a TFA salt of the titled compound in 29.4 mg.

HPLC (method e):RT17.51

FAB-MS:455(M+H⁺)

10 Example 25

Phe-γ-Abu-Tyr(3-tBu)-NH₂

 Substituting Fmoc-γ-Abu-OH for the Fmoc-Tyr(tBu)-OH used in Example 21, the procedure of Example 21 was repeated to yield a TFA salt of the titled compound in 34.4 mg.

15 HPLC (method e):RT17.59

FAB-MS:469(M+H⁺)

Example 26

Phe-Aib-Tyr(3-tBu)-NH₂

- Substituting Fmoc-Aib-OH for the Fmoc-Tyr(tBu)-OH used
20 in Example 21, the procedure of Example 21 was repeated to yield a TFA salt of the titled compound in 27.2 mg.

HPLC (method e):RT19.82

FAB-MS:469(M+H⁺)

Example 27

25 Phe-Ile-Tyr(3-tBu)-NH₂

 Substituting Fmoc-Ile-OPfp for the Fmoc-Tyr(tBu)-OH used in Example 21, the procedure of Example 21 was repeated (except that Fmoc-Ile-OPfp was coupled by method 5) to yield

a TFA salt of the titled compound in 18.9 mg.

HPLC (method e):RT19.35

FAB-MS:497(M+H⁺)

Example 28

5 Phe-Chg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Chg-OH for the Fmoc-Tyr(tBu)-OH used in Example 21, the procedure of Example 21 was repeated. The crude product was dissolved in DMSO and purified by HPLC; the active fractions were collected, concentrated and
10 freeze-dried to yield a TFA salt of the titled compound in 10.1 mg.

HPLC (method e):RT20.54

FAB-MS:523(M+H⁺)

NMR(method g, DMSO-d₆): δ 0.82-1.20(5H,m), 1.31(9H,s), 1.46-1.
15 73(6H,m), 2.70(1H,dd,J=14,9Hz), 2.82-2.90(2H,m), 3.02(1H,dd,
J=14,5Hz), 4.10(1H,br s), 4.24(1H,t,J=8Hz), 4.42(1H,dd,J=13,
5Hz), 6.64(1H,d,J=8Hz), 6.86(1H,dd,J=8,1Hz), 7.00(1H,s), 7.0
4(1H,d,J=1Hz), 7.18(5H,s), 7.34(1H,s), 8.01-8.04(4H,m), 8.42
(1H,d,J=9Hz), 9.07(1H,s)

20 Example 29

Phe-Cha-Tyr(3-tBu)-NH₂

Substituting Fmoc-Cha-OH for the Fmoc-Chg-OH used in Example 28, the procedure of Example 28 was repeated to yield a TFA salt of the titled compound in 10.0 mg.

25 HPLC (method e):RT22.35

FAB-MS:537(M+H⁺)

NMR(method g, DMSO-d₆): δ 0.81-1.25(5H,m), 1.31(9H,s),
1.40-1.77(8H,m), 2.68-2.89(3H,m), 3.09(1H,dd,J=14,4Hz),

4.02(1H,br s), 4.33-4.38(2H,m), 6.63(1H,d,J=8Hz),
6.85(1H,dd,J=8,1Hz), 7.01-7.04(2H,m), 7.23(5H,s), 7.35(1H,s),
7.98(1H,d,J=8Hz), 8.03(3H,br s), 8.55(1H,d,J=8Hz),
9.07(1H,s)

5 Example 30

Phe-Tle-Tyr(3-tBu)-NH₂

Substituting Fmoc-Tle-OH for the Fmoc-Tyr(tBu)-OH used
in Example 21, the procedure of Example 21 was repeated to
yield a TFA salt of the titled compound in 23.8 mg.

10 HPLC (method e):RT18.87

FAB-MS:497(M+H⁺)

Example 31

Phe-Asp-Tyr(3-tBu)-NH₂

Substituting Fmoc-Asp(OtBu)-OH for the Fmoc-Tyr(tBu)-
15 OH used in Example 21 and using MeCN instead of methanol to
dissolve the residue, the procedure of Example 21 was
repeated to yield a TFA salt of the titled compound in
30.2 mg.

HPLC (method e):RT17.13

20 FAB-MS:499(M+H⁺)

Example 32

Phe-Glu-Tyr(3-tBu)-NH₂

Substituting Fmoc-Glu(OtBu)-OH for the Fmoc-Tyr(tBu)-
OH used in Example 21 and using MeCN instead of methanol as
25 a solvent to dissolve the residue, the procedure of Example
21 was repeated to yield a TFA salt of the titled compound
in 28.2 mg.

HPLC (method e):RT17.37

FAB-MS:513(M+H⁺)

Example 33

Phe-Aad-Tyr(3-tBu)-NH₂

Substituting Fmoc-Aad(OtBu)-OH for the Fmoc-Tyr(tBu)-OH used in Example 21 and using MeCN instead of methanol as a solvent to dissolve the residue, the procedure of Example 21 was repeated to yield a TFA salt of the titled compound in 31.8 mg.

HPLC (method e):RT17.54

10 FAB-MS:527(M+H⁺)

Example 34

Phe-Asn-Tyr(3-tBu)-NH₂

Substituting Fmoc-Asn-OH for the Fmoc-Tyr(tBu)-OH used in Example 21, the procedure of Example 21 was repeated to yield a TFA salt of the titled compound in 21.5 mg.

HPLC (method e):RT17.04

FAB-MS:498(M+H⁺)

Example 35

Phe-Gln-Tyr(3-tBu)-NH₂

20 Substituting Fmoc-Gln-OPfp for the Fmoc-Tyr(tBu)-OH used in Example 21), the procedure of Example 21 was repeated (except that Fmoc-Gln-OPfp was coupled by method 5) to yield a TFA salt of the titled compound in 27.2 mg.

HPLC (method e):RT16.90

25 FAB-MS:512(M+H⁺)

Example 36

Phe-Cit-Tyr(3-tBu)-NH₂

Substituting Fmoc-Cit-OH for the Fmoc-Tyr(tBu)-OH used

in Example 21, the procedure of Example 21 was repeated to yield a TFA salt of the titled compound in 25.6 mg.

HPLC (method e):RT16.68

FAB-MS:541(M+H⁺)

5 Example 37

Phe-Dab-Tyr(3-tBu)-NH₂

Substituting Fmoc-Dab(Boc)-OH for the Fmoc-Tyr(tBu)-OH used in Example 21, the procedure of Example 21 was repeated to yield a TFA salt of the titled compound in 29.1 mg.

10 HPLC (method e):RT16.07

FAB-MS:484(M+H⁺)

Example 38

Phe-Orn-Tyr(3-tBu)-NH₂

Substituting Fmoc-Orn(Boc)-OH for the Fmoc-Tyr(tBu)-OH used in Example 21), the procedure of Example 21 was repeated to yield a TFA salt of the titled compound in 33.7 mg.

HPLC (method e):RT16.04

FAB-MS:498(M+H⁺)

20 Example 39

Phe-Lys-Tyr(3-tBu)-NH₂

Substituting Fmoc-Lys(Boc)-OH for the Fmoc-Tyr(tBu)-OH used in Example 21), the procedure of Example 21 was repeated to yield a TFA salt of the titled compound in 29.2 mg.

HPLC (method e):RT16.49

FAB-MS:512(M+H⁺)

Example 40

Phe-Ser-Tyr(3-tBu)-NH₂

Substituting Fmoc-Ser(tBu)-OH for the Fmoc-Tyr(tBu)-OH used in Example 21, the procedure of Example 21 was repeated to yield a TFA salt of the titled compound in 25.5 mg.

5 HPLC (method e):RT17.31

FAB-MS:471(M+H⁺)

Example 41

Phe-Hse-Tyr(3-tBu)-NH₂

Substituting Fmoc-Hse(Trt)-OH for the Fmoc-Tyr(tBu)-OH used in Example 21, the procedure of Example 21 was repeated. After concentrating the cleavage cocktail, re-precipitation was effected with diethyl ether to yield a TFA salt of the titled compound in 7.8 mg.

HPLC (method e):RT17.64

15 FAB-MS:485(M+H⁺)

Example 42

Phe-Thr-Tyr(3-tBu)-NH₂

Substituting Fmoc-Thr(tBu)-OH for the Fmoc-Tyr(tBu)-OH used in Example 21, the procedure of Example 21 was repeated to yield a TFA salt of the titled compound in 24.1 mg.

HPLC (method e):RT17.40

FAB-MS:485(M+H⁺)

Example 43

Phe-Abu-Tyr(3-tBu)-NH₂

Substituting Fmoc-Abu-OH for the Fmoc-Tyr(tBu)-OH used in Example 21, the procedure of Example 21 was repeated to yield a TFA salt of the titled compound in 19.6 mg.

HPLC (method e):RT18.55

FAB-MS:469(M+H⁺)

Example 44

Phe-Nva-Tyr(3-tBu)-NH₂

Substituting Fmoc-Nva-OH for the Fmoc-Tyr(tBu)-OH used
5 in Example 21, the procedure of Example 21 was repeated to
yield a TFA salt of the titled compound in 19.8 mg.

HPLC (method e):RT18.82

FAB-MS:483(M+H⁺)

Example 45

10 Phe-Met-Tyr(3-tBu)-NH₂

Substituting Fmoc-Met-OH for the Fmoc-Tyr(tBu)-OH used
in Example 21, the procedure of Example 21 was repeated to
yield a TFA salt of the titled compound in 24.3 mg.

HPLC (method e):RT18.79

15 FAB-MS:515(M+H⁺)

Example 46

Phe-His-Tyr(3-tBu)-NH₂

Substituting Fmoc-His(Boc)-OH for the Fmoc-Tyr(tBu)-OH
used in Example 21, the procedure of Example 21 was repeated
20 to yield a TFA salt of the titled compound in 26.7 mg.

HPLC (method e):RT16.78

FAB-MS:521(M+H⁺)

Example 47

Phe-Trp-Tyr(3-tBu)-NH₂

25 Substituting Fmoc-Trp(Boc)-OH for the Fmoc-Tyr(tBu)-OH
used in Example 21, the procedure of Example 21 was repeated
to yield a TFA salt of the titled compound in 14.5 mg.

HPLC (method e):RT20.76

FAB-MS: 570(M+H⁺)

Example 48

Phe-Tiq-Tyr(3-tBu)-NH₂

Substituting Fmoc-Tiq-OH for the Fmoc-Tyr(tBu)-OH used
5 in Example 21, the procedure of Example 21 was repeated to
yield a TFA salt of the titled compound in 23.7 mg.

HPLC (method e): RT 21.87

FAB-MS: 543(M+H⁺)

Example 49

10 N-(4-pyridylthioacetyl)-Phg-Tyr(3-tBu)-NH₂

A reaction vessel was charged with 91 mg (0.05 mmol)
of Fmoc-2,4-dimethoxy-4'-(carboxymethyloxy)-benzhydrylamine
linked to Aminomethyl Resin (0.55 mmol/g); after being
swelled with DMF, the resin was treated with piperidine to
15 remove Fmoc. Subsequently, Fmoc-Tyr(3-tBu)-OH was coupled
by method 1. After filtering and washing with DMF, the
resin was treated with piperidine to remove Fmoc.
Subsequently, Fmoc-Phg-OH was coupled by method 3. After
filtering and washing with DMF, the resin was treated again
20 with piperidine to remove Fmoc. Subsequently, a mixture of
1.5 ml of DMF, 0.5 ml of NMM and 17 mg (0.1 mmol) of 4-
pyridylthioacetic acid, as well as 23 mg (0.15 mmol) of HOBT
and 25 ml (0.16 mmol) of DIC were added, followed by shaking
for 2 hours to effect coupling. After the end of the
25 reaction, filtering and washing with DMF, DCM and methanol
were performed and the resin was subsequently dried.
Cleavage was also performed with 2 ml of 95% aqueous TFA.
The reaction mixture was concentrated under reduced pressure

and the residue was dissolved in 3 ml of methanol, followed by reconcentrating under reduced pressure to yield a TFA salt of the titled compound in 27.8 mg.

HPLC (method a):RT17.55

5 FAB-MS:521(M+H⁺)

Example 50

N-(1-benzocyclobutanecarbonyl)-Phg-Tyr(3-tBu)-NH₂

Substituting 1-benzocyclobutanecarboxylic acid for the 4-pyridylthioacetic acid used in Example 49, the procedure of Example 49 was repeated (except that 1-benzocyclobutanecarboxylic acid was coupled by method 3) to yield the titled compound in 23.8 mg as a mixture of diastereomers.

HPLC (method a):RT23.43, 23.68

FAB-MS:500(M+H⁺)

15 Example 51

N-(2-indolecarbonyl)-Phg-Tyr(3-tBu)-NH₂

Substituting 2-indolecarboxylic acid for the 1-benzocyclobutanecarboxylic acid used in Example 50, the procedure of Example 50 was repeated to yield the titled compound in 8.0 mg.

HPLC (method a):RT24.64

FAB-MS:513(M+H⁺)

Example 52

Tyr-Phg-Tyr(3-tBu)-NH₂

25 A reaction vessel was charged with 91 mg (0.05 mmol) of Fmoc-2,4-dimethoxy-4'-(carboxymethyloxy)-benzhydrylamine linked to Aminomethyl Resin (0.55 mmol/g); after being swelled with DMF, the resin was treated with piperidine to

remove Fmoc. Subsequently, Fmoc-Tyr(3-tBu)-OH was coupled by method 1. After filtering and washing with DMF, the resin was treated with piperidine to remove Fmoc.

Subsequently, Fmoc-Phg-OH was coupled by method 3. After
5 filtering and washing with DMF, the resin was treated with piperidine to remove Fmoc. Subsequently, Fmoc-Tyr(tBu)-OH was coupled by method 3. After filtering and washing with DMF, the resin was treated again with piperidine to remove Fmoc. After the end of the reaction, washing was effected
10 with DCM and methanol and the resin was subsequently dried. Cleavage was performed with 2 ml of 95% aqueous TFA. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in 3 ml of methanol, followed by reconcentrating under reduced pressure to yield a TFA salt
15 of the titled compound in 26.2 mg.

HPLC (method a):RT17.43

FAB-MS:533(M+H⁺)

Example 53

Phg-Phg-Tyr(3-tBu)-NH₂

20 Substituting Fmoc-Phg-OH for the Fmoc-Tyr(tBu)-OH used in Example 52, the procedure of Example 52 was repeated to yield a TFA salt of the titled compound in 23.2 mg.

HPLC (method a):RT18.42

FAB-MS:503(M+H⁺)

25 Example 54

Thi-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Thi-OH for the Fmoc-Tyr(tBu)-OH used in Example 52, the procedure of Example 52 was repeated to

yield a TFA salt of the titled compound in 27.4 mg.

HPLC (method a):RT18.43

FAB-MS:523(M+H⁺)

Example 55

5 Trp-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Trp(Boc)-OH for the Fmoc-Tyr(tBu)-OH used in Example 52, the procedure of Example 52 was repeated to yield a TFA salt of the titled compound in 20.9 mg.

HPLC (method a):RT19.84

10 FAB-MS:556(M+H⁺)

Example 56

His-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-His(Boc)-OH for the Fmoc-Tyr(tBu)-OH used in Example 52, the procedure of Example 52 was repeated to yield a TFA salt of the titled compound in 14.4 mg.

HPLC (method a):RT15.12

FAB-MS:507(M+H⁺)

Example 57

N-((±)-3-phenylbutyryl)-Phg-Tyr(3-tBu)-NH₂

20 Substituting (±)-3-phenylbutyric acid for the 1-benzocyclobutanecarboxylic acid used in Example 50 and using 107 mg (0.05 mmol) of Rink Amide Resin (0.47 mmol/g) as a resin, the procedure of Example 50 was repeated (except that Fmoc-Phg-OH was coupled by method 1 and 3-phenylbutyric acid
25 by method 2) to yield the titled compound in 18.1 mg.

HPLC (method a):RT25.19

FAB-MS:516(M+H⁺)

Example 58

N-(2-biphenylcarbonyl)-Phg-Tyr(3-tBu)-NH₂

Substituting 2-biphenylcarboxylic acid for the 3-phenylbutyric acid used in Example 57, the procedure of Example 57 was repeated to yield the titled compound in
5 15.1 mg.

HPLC (method a):RT26.23

FAB-MS:550(M+H⁺)

Example 59

β-Ala-Phg-Tyr(3-tBu)-NH₂

10 A reaction vessel was charged with 45 mg (0.025 mmol) of Fmoc-2,4-dimethoxy-4'-(carboxymethyloxy)-benzhydrylamine linked to Aminomethyl Resin (0.55 mmol/g); after being swelled with DMF, the resin was treated with piperidine to remove Fmoc. Subsequently, Fmoc-Tyr(3-tBu)-OH was coupled
15 by method 1. After filtering and washing with DMF, the resin was treated with piperidine to remove Fmoc. Subsequently, Fmoc-Phg-OH was coupled by method 3. After washing with DMF, DCM and methanol, the resin was dried.

The dried resin was transferred into a reaction vessel
20 of model ACT-496 MOS (product of Advanced ChemTech). After being swelled with DMF, the resin was treated with piperidine to remove Fmoc. Subsequently, 0.5 ml of a mixture of Fmoc-β-Ala-OH, HOBt and DMF (Fmoc-β-Ala-OH in 0.050 mmol and HOBt in 0.075 mmol), as well as 0.25 ml of
25 DIC/DMF (DIC in 0.080 mmol) were added, followed by shaking for 2 hours. After filtering and washing with DMF, the resin was treated again with piperidine to remove Fmoc. After the end of the reaction, washing was effected with DCM

and cleavage was performed with 1 ml of 95% aqueous TFA.

After recovering the reaction mixture by filtration, another 1 ml of 95% aqueous TFA was added, followed by shaking for 30 minutes. The filtrates were combined and concentrated under reduced pressure, and the residue was dissolved in 3 ml of methanol, which was concentrated again to yield a TFA salt of the titled compound in 13.4 mg.

HPLC (method e):RT16.72

FAB-MS:441(M+H⁺)

10 Example 60

Aib-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Aib-OH for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 15.3 mg.

15 HPLC (method e):RT17.12

FAB-MS:455(M+H⁺)

Example 61

Ile-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Ile-OH for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 15.4 mg.

HPLC (method e):RT18.25

FAB-MS:483(M+H⁺)

Example 62

25 Chg-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Chg-OH for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 12.2 mg.

HPLC (method e):RT19.61

FAB-MS:509(M+H⁺)

Example 63

Cha-Phg-Tyr(3-tBu)-NH₂

- 5 Substituting Fmoc-Cha-OH for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 16.7 mg.

HPLC (method e):RT21.34

FAB-MS:523(M+H⁺)

10 Example 64

Tle-Phg-Tyr(3-tBu)-NH₂

 Substituting Fmoc-Tle-OH for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 14.9 mg.

15 HPLC (method e):RT18.02

FAB-MS:483(M+H⁺)

Example 65

Asp-Phg-Tyr(3-tBu)-NH₂

- Substituting Fmoc-Asp(OtBu)-OPfp for the Fmoc-β-Ala-OH
20 used in Example 59, the procedure of Example 59 was repeated (except that 0.25 ml of DIC/DMF was not added in coupling of Fmoc-Asp(OtBu)-OPfp) to yield a TFA salt of the titled compound in 18.1 mg.

HPLC (method e):RT16.42

25 FAB-MS:485(M+H⁺)

Example 66

Aad-Phg-Tyr(3-tBu)-NH₂

 Substituting Fmoc-Aad(OtBu)-OH for the Fmoc-β-Ala-OH

used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 16.8 mg.

HPLC (method e):RT16.79

FAB-MS:513(M+H⁺)

5 Example 67

Asn-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Asn-OH for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated to yield 17.2 mg of the titled compound.

10 HPLC (method e):RT16.17

FAB-MS:484(M+H⁺)

Example 68

Gln-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Gln-OPfp for the Fmoc-Asp(OtBu)-OPfp used in Example 65, the procedure of Example 65 was repeated to yield a TFA salt of the titled compound in 15.9 mg.

HPLC (method e):RT16.39

FAB-MS:498(M+H⁺)

Example 69

20 Cit-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Cit-OH for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated to yield to yield a TFA salt of the titled compound in 15.3 mg.

HPLC (method e):RT16.36

25 FAB-MS:527(M+H⁺)

Example 70

Dab-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Dab(Boc)-OH for the Fmoc-β-Ala-OH

used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 15.3 mg.

HPLC (method e):RT15.28

FAB-MS:470(M+H⁺)

5 Example 71

Lys-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Lys(Boc)-OH for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 16.8 mg.

10 HPLC (method e):RT15.21

FAB-MS:498(M+H⁺)

Example 72

Ser-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Ser(tBu)-OH for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 15.4 mg.

HPLC (method e):RT16.30

FAB-MS:457(M+H⁺)

Example 73

20 Hse-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Hse(Trt)-OH for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 24.9 mg.

HPLC (method e):RT16.50

25 FAB-MS:471(M+H⁺)

Example 74

Thr-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Thr(tBu)-OH for the Fmoc-β-Ala-OH

used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 15.5 mg.

HPLC (method e):RT16.41

FAB-MS:471(M+H⁺)

5 Example 75

Abu-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Abu-OH for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 13.6 mg.

10 HPLC (method e):RT16.90

FAB-MS:455(M+H⁺)

Example 76

Nva-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Nva-OH for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 13.9 mg.

HPLC (method e):RT17.79

FAB-MS:469(M+H⁺)

Example 77

20 Met-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Met-OH for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 11.6 mg.

HPLC (method e):RT18.09

25 FAB-MS:501(M+H⁺)

Example 78

Pro-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Pro-OH·AcOEt for the Fmoc-β-Ala-OH

used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 14.8 mg.

HPLC (method e):RT17.02

FAB-MS:467(M+H⁺)

5 Example 79

Hyp-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Hyp-OH for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 11.2 mg.

10 HPLC (method e):RT16.54

FAB-MS:483(M+H⁺)

Example 80

Tic-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Tic-OH for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 16.1 mg.

HPLC (method e):RT19.56

FAB-MS:529(M+H⁺)

Example 81

20 Tiq-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Tiq-OH for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 14.7 mg.

HPLC (method e):RT19.33

25 FAB-MS:529(M+H⁺)

Example 82

2-Abz-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-2-Abz-OH for the Fmoc-β-Ala-OH used

in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 15.2 mg.

HPLC (method e):RT21.38

FAB-MS:489(M+H⁺)

5 Example 83

Hph-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-Hph-OH for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated to yield a TFA salt of the titled compound in 16.0 mg.

10 HPLC (method e):RT20.72

FAB-MS:531(M+H⁺)

Example 84

N-(α-methylhydrocinnamoyl)-Phg-Tyr(3-tBu)-NH₂

Substituting α-methylhydrocinnamic acid for the Fmoc-β-Ala-OH used in Example 59, the procedure of Example 59 was repeated (except that prior to cleavage, no treatment for removing Fmoc was performed since this was unnecessary) to yield 15.2 mg of the titled compound.

HPLC (method e):RT25.22

20 FAB-MS:516(M+H⁺)

Example 85

N-(α-methylcinnamoyl)-Phg-Tyr(3-tBu)-NH₂

Substituting α-methylcinnamic acid for the α-methylhydrocinnamic acid used in Example 84, the procedure of Example 84 was repeated to yield 16.4 mg of the titled compound.

HPLC (method e):RT26.18

FAB-MS:514(M+H⁺)

Example 86

N-(3-quinolinecarbonyl)-Phg-Tyr(3-tBu)-NH₂

Substituting 3-quinolinecarboxylic acid for the α -methyl-hydrocinnamic acid used in Example 84, the procedure of Example 84 was repeated to yield 16.9 mg of the titled compound.

HPLC (method e): RT20.73

FAB-MS: 525(M+H⁺)

Example 87

10 N-(3-furanacryloyl)-Phg-Tyr(3-tBu)-NH₂

Substituting 3-furanacrylic acid for the α -methylhydro-cinnamic acid used in Example 84, the procedure of Example 84 was repeated to yield 8.2 mg of the titled compound.

15 HPLC (method e): RT23.08

FAB-MS: 490(M+H⁺)

Example 88

Phe-D-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-D-Phg-OH for the Fmoc-Phg-OH used in Example 5 and using 182 mg (0.1 mmol) of Fmoc-2,4-dimethoxy-4'-(carboxymethyloxy)-benzhydrylamine linked to Aminomethyl Resin (0.55 mmol/g), the procedure of Example 5 was repeated (except that Fmoc-D-Phg-OH and Boc-Phe-OH were coupled by method 3) to yield a TFA salt of the titled compound in 15.4 mg.

HPLC (method a): RT20.96

FAB-MS: 517(M+H⁺)

NMR(method g, DMSO-d₆): δ 1.27(9H, s), 2.57-3.06(4H, m),

4.28-4.35(2H,m), 5.63(1H,d,J=8Hz), 6.53(1H,d,J=8Hz),
 6.70(1H,d,J=8Hz), 6.79(2H,d,J=7Hz), 7.00-7.29(11H,m),
 7.51(1H,s), 8.20(3H,brs), 8.71(1H,d,J=8Hz), 9.07(1H,s),
 9.13(1H,d,J=8Hz)

5 Example 89

Phe-N-Me-Val-Tyr(3-tBu)-NH₂

(1) Synthesis of Z-Tyr(3-tBu)-NH₂

To a solution of 15.3 mg (39.8 mmol) of Z-Tyr(3-tBu)-
 OMe in 100 ml of 1,4-dioxane, 100 ml of 2 N aqueous sodium
 10 hydroxide was added and the mixture was stirred at room
 temperature for 2 hours and a half. The reaction mixture
 was rendered acidic by addition of 2 N hydrochloric acid,
 extracted with ethyl acetate, washed first with water, then
 with saturated brine. The organic layer was dried with
 15 anhydrous sodium sulfate and the solvent was distilled off
 under reduced pressure; the resulting residue was dissolved
 in 100 ml of DMF, followed by addition of NMM and ethyl
 chloroformate in respective amounts of 4.77 mg (43.4 mmol)
 and 4.15 ml (43.4 mmol) at -15°C. The reaction mixture was
 20 stirred with bubbling of ammonia gas for one hour and a half,
 and then left to stand at room temperature, diluted with
 ethyl acetate, washed first with water, then with saturated
 brine. The organic layer was dried with anhydrous sodium
 sulfate and concentrated under reduced pressure; the
 25 resulting residue was subjected to silica gel column
 chromatography (eluting solvent; methylene chloride:methanol
 = 100:1) to give Z-Tyr(3-tBu)-NH₂ in 10.9 g (74%).

(2) Synthesis of Tyr(3-tBu)-NH₂

To a solution of 9.89 g (26.7 mmol) of Z-Tyr(3-tBu)-NH₂ in 350 ml of methanol, 3.5 g of 10% palladium carbon was added and the mixture was stirred in a hydrogen atmosphere at room temperature for 10 hours. After filtering, the filtrate was concentrated under reduced pressure and the resulting residue was subjected to silica gel column chromatography (eluting solvent; methylene chloride:methanol = 20:1) to yield Tyr(3-tBu)-NH₂ in 5.11 g (81%).

NMR(method g, CDCl₃): δ 1.40(9H,s), 2.64(1H,dd,J=9.6,13.9Hz), 3.18(1H,dd,J=4.0,13.9Hz), 3.49(1H,s), 3.58(1H,dd,J=4.0,9.6Hz), 5.45(1H,brs), 6.65(1H,d,J=7.9Hz), 6.92(1H,dd,J=2/0,12.0Hz), 7.10(1H,d,J=2.0Hz), 6.94(1H,d,6.6Hz), 7.2-7.4(8H,m), 7.7-7.9(2H,m), 8.46(1H,d,7.6Hz), 9.06(1H,d)

15 (3) Synthesis of Z-N-Me-Val-Tyr(3-tBu)-NH₂

To a solution of 400 mg (1.52 mmol) of Z-N-Me-Val-OH, 300 mg (1.27 mmol) of Tyr(3-tBu)-NH₂ and 230 mg (1.52 mmol) of HOBT in 7 ml of DMF, 0.24 ml (1.52 mmol) of DIC was added dropwise under cooling with ice and the mixture was stirred at room temperature for 15 hours and a half. The reaction mixture was diluted with ethyl acetate and washed with saturated brine. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of methylene chloride, methanol and aqueous ammonia at a ratio of 100:3:1) to give 810 mg of Z-N-Me-Val-Tyr(3-tBu)-NH₂.

(4) Synthesis of Boc-Phe-N-Me-Val-Tyr(3-tBu)-NH₂

A mixture of 810 mg of Z-N-Me-Val-Tyr(3-tBu)-NH₂ and 300 mg of 10% palladium carbon in 50 ml of methanol was stirred under a hydrogen stream for 13 hours and a half. The reaction mixture was filtered and the filtrate was
5 distilled off under reduced pressure. To a solution in DMF (12 ml) of 470 mg (1.35 mmol) of the resulting N-Me-Val-Tyr(3-tBu)-NH₂, 390 mg (1.48 mmol) of Boc-Phe-OH and 230 mg (1.48 mmol) of HOBT, 0.23 ml (1.48 mmol) of DIC was added dropwise under cooling with ice and the mixture was stirred
10 at room temperature for 13 hours and a half. The reaction mixture was diluted with ethyl acetate and washed with saturated brine. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column
15 chromatography (eluting solvent consisting of methylene chloride, methanol and aqueous ammonia at a ratio of 100:3:1) to give Boc-Phe-N-Me-Val-Tyr(3-tBu)-NH₂ in 380 mg (47%).

(5) Synthesis of Phe-N-Me-Val-Tyr(3-tBu)-NH₂

20 A solution of 380 mg (0.638 mmol) of Boc-Phe-N-Me-Val-Tyr(3-tBu)-NH₂ in 15 ml of TFA was stirred at room temperature for one hour and a half. The reaction solution was concentrated under reduced pressure and the resulting residue was diluted with ethyl acetate and washed first with
25 saturated aqueous NaHCO₃, then with saturated brine. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure; thereafter, the resulting residue was subjected to silica gel column

chromato-graphy (eluting solvent consisting of methylene chloride, methanol and aqueous ammonia at a ratio of 100:10:1) to give Phe-N-Me-Val-Tyr(3-tBu)-NH₂ in 240 mg (76%)

5 FAB-MS:497(M+H⁺)

NMR(method g, CDCl₃):δ 0.74(2H,d,J=6.6Hz),
 0.79(1H,d,J=6.6Hz), 0.89(1H,d,J=6.6Hz), 0.92(2H,d,J=6.6Hz),
 1.36(3H,s), 1.38(6H,s), 2.27-2.35(1H,m), 2.71(2H,s),
 2.81(1H,s), 2.77-3.19(4H,m), 3.56-3.61(2/3H,m), 3.80-
 10 3.90(1/3H,m), 3.95(2/3H,d,J=10.9Hz), 4.46(1/3H,d,J=11.2Hz),
 4.55-4.65(1/3H,m), 4.70-4.85(2/3H,m), 6.60-7.40(8H,m)

Example 90

N-(α-methylhydrocinnamoyl)-N-Me-D-Phg-Tyr(3-tBu)-NH₂

(1) Synthesis of Z-N-Me-Phg-Tyr(3-tBu)-NH₂

15 To a solution of 3.28 g (11.0 mmol) of Z-N-Me-Phg-OH,
 2.16 g (9.17 mmol) of Tyr(3-tBu)-NH₂ and 1.40 g (9.17 mmol)
 of HOBT in 60 ml of DMF, 1.42 ml (9.17 mmol) of DIC was
 added dropwise under cooling with ice and the mixture was
 stirred for 4 hours under cooling with ice. The reaction
 20 mixture was diluted with ethyl acetate and washed with
 saturated brine. The organic layer was dried with anhydrous
 sodium sulfate and concentrated under reduced pressure; the
 resulting residue was subjected to silica gel column
 chromatography (eluting solvent consisting of methylene
 25 chloride, methanol and aqueous ammonia at a ratio of
 100:5:1) to give Z-N-Me-Phg-Tyr(3-tBu)-NH₂ in 4.03 g (85%).

(2) Synthesis of N-Me-D-Phg-Tyr(3-tBu)-NH₂

A mixture of Z-N-Me-Phg-Tyr(3-tBu)-NH₂ (4.03 g) and

10% palladium carbon (2.0 g) in methanol (200 ml) was stirred in a hydrogen atmosphere for 4 hours. The reaction mixture was filtered and the filtrate was distilled off under reduced pressure; the resulting residue was subjected
5 to silica gel column chromatography (eluting solvent consisting of methylene chloride, methanol and aqueous ammonia at a ratio of 100:5:1) to give N-Me-Phg-Tyr(3-tBu)-NH₂ in 1.48 g (50%) and of N-Me-D-Phg-Tyr(3-tBu)-NH₂ in 920 mg (31%).

10 (3) Synthesis of N-(α -methylhydrocinnamoyl)-N-Me-D-Phg-Tyr(3-tBu)-NH₂

To a solution of α -methylhydrocinnamic acid (141 mg) in 10 ml of thionyl chloride, DMF (0.01 ml) was added and the mixture was stirred at 80°C for 1.5 hours. The reaction
15 mixture was distilled off under reduced pressure and the resulting residue was dissolved in methylene chloride; the solution was added to a solution of 300 mg (0.78 mmol) of N-Me-D-Phg-Tyr(3-tBu)-NH₂ and 260 mg (3.13 mmol) of NaHCO₃ in 6 ml of H₂O and the mixture was stirred at room temperature
20 for 45 minutes. The reaction mixture was diluted with ethyl acetate and washed first with water, then with saturated brine. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column
25 chromatography (eluting solvent; ethyl acetate:n-hexane = 4:1) to yield N-(α -methylhydrocinnamoyl)-N-Me-D-Phg-Tyr(3-tBu)-NH₂ in 210 mg (51%).

EI-MS: 529(M⁺)

NMR(method g, CDCl₃): δ 1.18(3/2H,d,J=6.3Hz),
 1.25(3/2H,d,J=6.9Hz), 1.35(9H,s), 2.64-3.14(6H,m),
 2.73(3/2H,s), 2.81(3/2H,s), 4.67(1H,dd,J=7.4,14.0Hz),
 5.09(1/2H,s), 5.38(1H,brd,J=8.9Hz), 5.47(1/2H,s),
 5 5.75(1/2H,s), 5.77(1/2H,s), 5.86(1/2H,s),
 6.06(1/2H,brd,J=7.9Hz), 6.48-6.72(2H,m), 6.86-7.00(2H,m),
 7.14-7.34(9H,m)

Example 91

Phe-Val-N-Me-Tyr(3-tBu)-NH₂

10 (1) Synthesis of Z-Phe(3-tBu-4-benzyloxy)-OMe

To a solution of 1.05 g (2.73 mmol) of Z-Tyr(3-tBu)-OMe in 10 ml of DMF, 120 mg (3.00 mmol) of sodium hydride (60% in oil) and 0.357 ml (3.00 mmol) of benzyl bromide were added under cooling with ice and the mixture was stirred for
 15 4 hours. After neutralization with saturated aqueous ammonium chloride, the reaction mixture was extracted with ethyl acetate and washed first with water, then with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure;
 20 the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 1:5) to give Z-Phe(3-tBu-4-benzyloxy)-OMe in 688 mg (53%).

(2) Synthesis of Z-N-Me-Phe(3-tBu-4-benzyloxy)-OMe

To a solution of 680 mg (1.43 mmol) of Z-Phe(3-tBu-4-benzyloxy)-OMe in 8 ml of DMF, 74.4 mg (1.86 mmol) of sodium
 25 hydride (60% in oil) and 0.134 ml (2.15 mmol) of methyl iodide were added under cooling with ice and the mixture was stirred for 1 hour. After neutralization with saturated

aqueous ammonium chloride, the reaction mixture was extracted with ethyl acetate and washed first with water, then with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 1:4) to give Z-N-Me-Phe(3-tBu-4-benzyloxy)-OMe in 659 mg (94%).

(3) Synthesis of N-Me-Tyr(3-tBu)-NH₂

10 To a solution of 655 mg (1.34 mmol) of Z-N-Me-Phe(3-tBu-4-benzyloxy)-OMe in 8 ml of 1,4-dioxane, 2 ml of 2 N aqueous sodium hydroxide was added under cooling with ice and the mixture was stirred at room temperature for 1 hour. The reaction mixture was rendered acidic by addition of 2 N
15 hydrochloric acid, extracted with chloroform and washed first with water, then with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure; the resulting residue was dissolved in 5 ml of DMF and 0.183 ml
20 (1.66 mmol) of NMM and 0.159 ml (1.66 mmol) of ethyl chloroformate were added to the solution at -15°C, followed by stirring for 20 minutes. The reaction mixture was stirred with bubbling of ammonia gas for additional 30 minutes, left to stand at room temperature, diluted with
25 ethyl acetate and washed first with water, then with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure; the resulting residue was dissolved in 7

ml of methanol and after addition of 20% palladium hydroxide on carbon (100 mg), the mixture was stirred in a hydrogen atmosphere at room temperature for 4 hours. After filtering, the filtrate was concentrated under reduced pressure to give
5 N-Me-Tyr(3-tBu)-NH₂ in 314 mg (94%).

(4) Synthesis of Boc-Val-N-Me-Tyr(3-tBu)-NH₂

To a solution of 120 mg (0.480 mmol) of N-Me-Tyr(3-tBu)-NH₂, 156 mg (0.718 mmol) of Boc-Val-OH and 110 mg (0.718 mmol) of HOBt in 2 ml of DMF, 0.111 ml (0.718 mmol)
10 of DIC was added under cooling with ice and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and washed first with saturated aqueous NaHCO₃, then with water, and finally with saturated brine. The organic layer was dried with anhydrous
15 magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 2:1) to give Boc-Val-N-Me-Tyr(3-tBu)-NH₂ in 147 mg (68%).

(5) Synthesis of Z-Phe-Val-N-Me-Tyr(3-tBu)-NH₂

20 To a solution of 146 mg (0.325 mmol) of Boc-Val-N-Me-Tyr(3-tBu)-NH₂ in 2 ml of methylene chloride, 1 ml of TFA was added and the mixture was stirred at room temperature for 30 minutes. The solvent was distilled off under reduced pressure. To a solution of the resulting TFA salt of Val-N-Me-Tyr(3-tBu)-NH₂ in 2 ml of DMF, 0.1 ml of TEA, 219 mg
25 (0.348 mmol) of Z-Phe-ONp and 93.5 mg (0.765 mmol) of DMAP were added and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl

acetate and washed first with saturated aqueous NaHCO_3 , then with water and finally with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure; the resulting residue
 5 was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 1:1) to give Z-Phe-Val-N-Me-Tyr(3-tBu)- NH_2 in 189 mg (92%).

(6) Synthesis of Phe-Val-N-Me-Tyr(3-tBu)- NH_2

To a solution of 183 mg (0.290 mmol) of Z-Phe-Val-N-Me-Tyr(3-tBu)- NH_2 in 3 ml of methanol, 100 mg of 10%
 10 palladium carbon was added and the mixture was stirred in a hydrogen atmosphere at room temperature for 5 hours. After filtering, the filtrate was concentrated under reduced pressure and the resulting residue was subjected to silica
 15 gel column chromatography (eluting solvent; ethyl acetate:methanol = 10:1) to yield Phe-Val-N-Me-Tyr(3-tBu)- NH_2 in 108 mg (75%).

NMR(method g, CDCl_3): δ 0.69(3H,dd,J=6.9,17.8Hz),
 0.89(3H,dd,J=6.9,14.5Hz), 1.36(9/2H,s), 1.39(9/2H,s),
 20 2.67(1H,dd,J=9.6,13.5Hz), 2.78-2.94(1H,m), 2.97(3/2H,s),
 3.09(3/2H,s), 3.12-3.40(2H,m), 3.59(1H,ddd,J=3.6,9.3,10.2Hz),
 4.34-4.42(1/2H,m), 4.68(1/2H,dd,J=6.6,11.1Hz),
 4.79(1/2H,dd,J=7.9,8.9Hz), 5.18-5.26(1/2H,m), 5.35(1/2H,brs),
 5.49(1/2H,brs), 6.60(1H,dd,J=7.9,12.2Hz),
 25 6.86(1H,ddd,J=1.6,6.3,6.3Hz), 7.06(1H,s), 7.16-7.34(5H,m),
 7.76(1/2H,brs), 7.85(1/2H,d,J=8.9Hz), 7.95(1/2H,d,J=7.9Hz)

Example 92

Phe-Phg-Tyr(3-tBu)-NHMe

(1) Synthesis of Tyr(3-tBu)-NHMe

To a solution of 10.6 g (42.0 mmol) of Tyr(3-tBu)-OMe in 80 ml of methanol, 80 ml of a solution of 40% methylamine in methanol and 0.41 g of sodium cyanide were added and the mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in methylene chloride, followed by washing first with water, then with saturated brine. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 20:1:0.1) to give Tyr(3-tBu)-NHMe in 7.3 g (70%).

(2) Synthesis of Phe-Phg-Tyr(3-tBu)-NHMe

To a solution of 150 mg (0.597 mmol) of Boc-Phg-OH, 136 mg (0.542 mmol) of Tyr(3-tBu)-NHMe, 110 mg (0.813 mmol) of HOBt and 99 mg (0.813 mmol) of DMAP in 3 ml of DMF, 156 mg (0.813 mmol) of WSCI·HCl was added under cooling with ice and the mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with ethyl acetate and washed first with saturated aqueous NaHCO₃, then with water, and finally with saturated brine. After drying the organic layer with anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure and the resulting residue was dissolved in 3 ml of methylene chloride, followed by addition of 2 ml of TFA. After being stirred at room temperature for 15 minutes, the reaction mixture was

distilled off under reduced pressure and the resulting residue was dissolved in methylene chloride, followed by washing with saturated aqueous NaHCO_3 , then with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure to give a TFA salt of Phg-Tyr(3-tBu)-NHMe. To a solution of 0.44 g of this TFA salt, 158 mg (0.597 mmol) of Boc-Phe-OH, 110 mg (0.813 mmol) of HOBt and 165 mg (1.36 mmol) of DMAP in 5 ml of DMF, 156 mg (0.813 mmol) of WSCI·HCl was added under cooling with ice and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate and washed first with saturated aqueous NaHCO_3 , then with water and finally with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure; the resulting residue was dissolved in 4 ml of methylene chloride and after adding 4 ml of TFA, the mixture was stirred at room temperature for 40 minutes. The reaction mixture was distilled off under reduced pressure and the resulting residue was dissolved in methylene chloride, followed by washing first with saturated aqueous NaHCO_3 , then with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 20:1:0.1) to yield Phe-Phg-Tyr(3-tBu)-NHMe in 158 mg (55% in four steps).

FAB-MS: 531 (M+H⁺)

NMR(method g, DMSO-d₆): δ 1.30(9H,s), 1.78(1H,brs),
 2.6-3.0(4H,m), 3.17(3H,d,J=4.6Hz), 3.45-3.50(1H,m),
 4.05-4.15(1H,m), 4.3-4.4(1H,m), 5.48(1H,s),
 5 6.64(1H,d,J=8.3Hz), 6.81(1H,dd,J=2.0,8.3Hz),
 6.97(1H,d,J=2.0Hz), 7.17-7.28(10H,m), 7.71(1H,m),
 8.45(1H,brs), 8.48(1H,d,J=8.2Hz), 9.11(1H,s)

Example 93

Phe-Apc-Tyr(3-tBu)-NHMe

10 (1) Synthesis of Z-Apc-Tyr(3-tBu)-NHMe

To a solution of 206 mg (0.877 mmol) of Z-Apc-OH, 219
 mg (0.876 mmol) of Tyr(3-tBu)-NHMe, 178 mg (1.32 mmol) of
 HOBT and 214 mg (1.75 mmol) of DMAP in 3 ml of DMF, 252 mg
 (1.31 mmol) of WSCI·HCl was added and the mixture was
 15 stirred at room temperature for 2 hours. The reaction
 mixture was diluted with ethyl acetate and washed first with
 saturated aqueous NaHCO₃, then with water and finally with
 saturated brine. The organic layer was dried with anhydrous
 magnesium sulfate and concentrated under reduced pressure;
 20 the resulting residue was subjected to silica gel column
 chromatography (eluting solvent; ethyl acetate:n-hexane =
 1:1) to give 205 mg (50%) of Z-Apc-Tyr(3-tBu)-NHMe.

(2) Synthesis of Boc-Phe-Apc-Tyr(3-tBu)-NHMe

To a solution of 201 mg (0.430 mmol) of Z-Apc-Tyr(3-
 25 tBu)-NHMe in 3 ml of methanol, 100 mg of 10% palladium
 carbon was added and the mixture was stirred in a hydrogen
 atmosphere at room temperature for 2 hours. After filtering,
 the filtrate was distilled off under reduced pressure and

the resulting residue was dissolved in 3 ml of DMF; to the solution under cooling with ice, 228 mg (0.859 mmol) of Boc-Phe-OH, 380 mg (0.859 mmol) of BOP and 0.472 ml (4.30 mmol) of NMM were added and the mixture was stirred at room
5 temperature for 3 days. The reaction mixture was diluted with ethyl acetate and washed first with saturated aqueous NaHCO₃, then with water and finally with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure; the resulting
10 residue was subjected to silica gel column chromatography (eluting solvent; hexane:ethyl acetate = 1:1) to give Boc-Phe-Apc-Tyr(3-tBu)-NHMe in 108 mg (43%).

(3) Synthesis of Phe-Apc-Tyr(3-tBu)-NHMe

To a solution of 103 mg (0.178 mmol) of Boc-Phe-Apc-Tyr(3-tBu)-NHMe in 2 ml of methylene chloride, 1 ml of TFA
15 was added. After being stirred at room temperature for 1 hour, the reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in methylene chloride, followed by washing first with saturated
20 aqueous NaHCO₃, then with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous
25 ammonia at a ratio of 10:1:0.1) to yield Phe-Apc-Tyr(3-tBu)-NHMe in 68.4 mg (80%).

NMR(method g, CDCl₃): δ 1.10-1.40(4H,m), 1.36(9H,s),
2.83(3H,d,J=4.6Hz), 2.80-3.15(2H,m), 3.30-3.70(3H,m),

4.91(1H,dd,J=7.6,9.7Hz), 5.56(1H,brs), 6.56(1H,d,J=7.9Hz),
 6.73(1H,brs), 6.89(1H,dd,J=2.0,7.9Hz), 7.02(1H,d,J=2.0Hz),
 7.10-7.40(6H,m)

Example 94

5 Phe-Ahc-Tyr(3-tBu)-NHMe

(1) Synthesis of Z-Ahc-Tyr(3-tBu)-NHMe

To a solution of 400 mg (1.44 mmol) of Z-Ahc-OH, 360 mg (1.44 mmol) of Tyr(3-tBu)-NHMe, 389 mg (2.88 mmol) of HOBT and 351 mg (2.88 mmol) of DMAP in 5 ml of DMF, 552 mg
 10 (2.88 mmol) of WSCI·HCl was added under cooling with ice and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate and washed first with saturated aqueous NaHCO₃, then with water and finally with saturated brine. The organic layer was
 15 dried with magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 1:2) to give Z-Ahc-Tyr(3-tBu)-NHMe in 203 mg (28%).

(2) Synthesis of Z-Phe-Ahc-Tyr(3-tBu)-NHMe

20 To 192 mg (0.377 mmol) of Z-Ahc-Tyr(3-tBu)-NHMe in a mixture of methanol (2 ml) and 1,4-dioxane (1 ml), 100 mg of 10% palladium carbon was added and the mixture was stirred overnight in a hydrogen atmosphere at room temperature. After filtering, the filtrate was concentrated under reduced
 25 pressure and the resulting residue was dissolved in 2 ml of DMF; to the solution under cooling with ice, 190 mg (0.452 mmol) of Z-Phe-ONp and 69.1 mg (0.566 mmol) of DMAP were added and the mixture was stirred overnight at room

temperature. The reaction mixture was diluted with ethyl acetate and washed first with saturated aqueous NaHCO_3 , then with water and finally with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 2:1) to give Z-Phe-Ahc-Tyr(3-tBu)-NHMe in 217 mg (88%).

(3) Synthesis of Phe-Ahc-Tyr(3-tBu)-NHMe

To a solution of 192 mg (0.320 mmol) of Z-Phe-Ahc-Tyr(3-tBu)-NHMe in 2 ml of methanol, 100 mg of 10% palladium carbon was added and the mixture was stirred overnight in a hydrogen atmosphere at room temperature. After filtering, the filtrate was concentrated under reduced pressure and the resulting residue was subjected to silica gel column chromatography (eluting solvent; chloroform:methanol = 10:1) to yield Phe-Ahc-Tyr(3-tBu)-NHMe in 136 mg (81%).

EI-MS: 523($M^+ + 1$)

NMR(method g, CDCl_3): δ 1.00-1.90(10H,m), 1.37(9H,s), 2.64-2.80(1H,m), 2.75(3H,d,J=4.6Hz), 2.90-3.15(2H,m), 3.22-3.40(2H,m), 4.52-4.62(1H,m), 6.19(1H,d,J=8.3Hz), 6.77(1H,d,J=7.9Hz), 6.83(1H,d,J=7.9Hz), 6.98(1H,s), 7.12-7.38(7H,m), 7.96(1H,s)

Example 95

N-acetyl-transHyp(O-benzyl)-Tyr(3-tBu)-NHMe

(1) Synthesis of Boc-transHyp(O-benzyl)-Tyr(3-tBu)-OMe

To a solution of 300 mg (0.933 mmol) of Boc-transHyp(O-benzyl)-OH, 281 mg (1.12 mmol) of Tyr(3-tBu)-OMe,

189 mg (1.40 mmol) of HOBt and 171 mg (1.40 mmol) of DMAP in 7 ml of DMF, 268 mg (1.40 mmol) of WSCI·HCl was added under cooling with ice and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate and washed first with saturated aqueous NaHCO₃, then with water and finally with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 1:1) to give Boc-transHyp(O-benzyl)-Tyr(3-tBu)-OMe in 505 mg (97%).

(2) Synthesis of transHyp(O-benzyl)-Tyr(3-tBu)-NHMe

To a solution of 500 mg (0.901 mmol) of Boc-transHyp(O-benzyl)-Tyr(3-tBu)-OMe in 5 ml of methanol, 5 ml of a solution of 40% methylamine in methanol and 10 mg of sodium cyanide were added and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in methylene chloride, followed by washing first with water, then with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure; the resulting residue was dissolved in 5 ml of methylene chloride and 3 ml of TFA was added. After being stirred at room temperature for 15 minutes, the reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in methylene chloride, followed by washing first with saturated aqueous NaHCO₃, then with

saturated brine. The organic layer was dried with anhydrous magnesium and the solvent was distilled off under reduced pressure to transHyp(O-benzyl)-Tyr(3-tBu)-NHMe in give 380 mg (93%).

5 (3) Synthesis of N-acetyl-transHyp(O-benzyl)-Tyr(3-tBu)-NHMe

To a solution of 104 mg (0.229 mmol) of transHyp(O-benzyl)-Tyr(3-tBu)-NHMe in 1 ml of methylene chloride, 1 ml of pyridine and 0.024 ml (0.344 mmol) of acetyl chloride were added under cooling with ice and the mixture was
 10 stirred for 40 minutes. The reaction mixture was diluted with methylene chloride and washed with saturated aqueous NaHCO₃; then, the organic layer was dried with anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The resulting residue was subjected to
 15 silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 20:1:0.1) to yield N-acetyl-transHyp(O-benzyl)-Tyr(3-tBu)-NHMe in 94 mg (83%).

FAB-MS: 496 (M+H⁺)

20 NMR(method g, CDCl₃): δ 1.36(9H,s), 1.93(3H,s),
 2.23(2H,dd,J=7.2,6.9Hz), 2.74(3H,d,J=5.0Hz),
 2.98(1H,dd,J=6.9,14Hz), 3.10(1H,dd,J=6.5,14Hz),
 3.50(2H,m), 4.18(1H,m), 4.4-4.6(4H,m), 5.88(1H,s),
 6.28(1H,m), 6.60(1H,d,J=7.9Hz), 6.62(1H,s),
 25 6.81(1H,dd,J=2.0,5.2Hz), 6.99(1H,d,J=2.0Hz),
 7.26-7.38(5H,m)

Example 96

Phe-Cha-Phe(3-tBu)-NH₂

(1) Synthesis of N-[bis(methylthio)methylene]-3-t-butylphenyl-alanine

To a solution of 1.78 g (15.8 mmol) of potassium t-butoxide in 30 ml of THF, a solution of 3.28 g (15.8 mmol) of N-[bis(methylthio)-methylene]glycine ethyl ester (Angew. Chem. Internat. Edit., 14, 426 (1975)) and 2.39 g (10.5 mmol) of 3-t-butylbenzyl bromide (Eur. J. Med. Chem., 23, 477 (1988)) in 10 ml of THF was added at -78°C and the mixture was stirred at room temperature for 1 hour. Under cooling with ice, 10 ml of water was added, then 5 ml of 2 N aqueous sodium hydroxide was added and the mixture was stirred at room temperature for another 1 hour. Under cooling with ice, 2 N hydrochloric acid was added to the reaction mixture to render it acidic; the reaction mixture was extracted with chloroform and washed first with water, then with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate) to give N-[bis(methylthio)methylene]-3-t-butylphenylalanine in 577 mg (16%).

(2) Synthesis of Phe(3-tBu)-NH₂

To a solution of 492 mg (1.51 mmol) of N-[bis-(methylthio)methylene]-3-t-butylphenylalanine in 5 ml of DMF, 0.183 ml (1.66 mmol) of NMM and 0.159 ml (1.66 mmol) of ethyl chloroformate were added at -15°C and the mixture was stirred for 30 minutes. The reaction mixture was stirred with bubbling of ammonia gas for another 30 minutes, left to

stand at room temperature, diluted with ethyl acetate and washed first with water, then with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure; the
5 resulting residue was dissolved in 3 ml of 1,4-dioxane and, after adding 1 ml of 2 N hydrochloric acid, the solution was stirred at room temperature for 3 days. Under cooling with ice, the solution was neutralized with saturated aqueous NaHCO_3 , extracted with chloroform, and washed first with
10 water, then with saturated brine. The organic layer was dried with magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; chloroform:methanol = 10:1) to give $\text{Phe}(3\text{-tBu})\text{-NH}_2$ in 210 mg (63%).

15 EI-MS: 221 ($\text{M}^+ + 1$)

NMR (g method, CDCl_3): δ 1.32 (9H, s), 2.69 (1H, dd, $J=9.6, 13.5\text{Hz}$), 3.29 (1H, dd, $J=4.0, 13.5\text{Hz}$), 3.62 (1H, dd, $J=4.0, 9.6\text{Hz}$), 5.38 (1H, brs), 7.00-7.38 (4H, m)

(3) Synthesis of Boc-Cha-Phe(3-tBu)-NH₂

20 To a solution of 205 mg (0.932 mmol) of $\text{Phe}(3\text{-tBu})\text{-NH}_2$, 351 mg (1.21 mmol) of Boc-Cha-OH, 164 mg (1.21 mmol) of HOBT and 148 mg (1.21 mmol) of DMAP in 4 ml of DMF, 232 mg (1.21 mmol) of WSCI·HCl was added under cooling with ice and the mixture was stirred at room temperature for 1 hour. The
25 reaction mixture was diluted with ethyl acetate and washed first with saturated aqueous NaHCO_3 , then with water and finally with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated under

reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 2:1) to give Boc-Cha-Phe(3-tBu)-NH₂ in 326 mg (74%).

5 (4) Synthesis of Z-Phe-Cha-Phe(3-tBu)-NH₂

To a solution of 322 mg (0.681 mmol) of Boc-Cha-Phe(3-tBu)-NH₂ in 2 ml of methylene chloride, 1 ml of TFA was added and the mixture was stirred at room temperature for 2 hours. The solvent was distilled off under reduced pressure
10 to give a TFA salt of Cha-Phe(3-tBu)-NH₂; to a solution of the TFA salt in 2 ml of DMF, 0.1 ml of TEA, 343 mg (0.817 mmol) of Z-Phe-ONp and 125 mg (1.02 mmol) of DMAP were added and the mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with ethyl acetate and
15 washed first with saturated aqueous NaHCO₃, then with water and finally with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent;
20 chloroform:methanol = 10:1) to give Z-Phe-Cha-Phe(3-tBu)-NH₂ in 192 mg (43%).

(5) Synthesis of Phe-Cha-Phe(3-tBu)-NH₂

To a solution of 188 mg (0.287 mmol) of Z-Phe-Cha-Phe(3-tBu)-NH₂ in 3 ml of methanol, 100 mg of 10% palladium
25 carbon was added and the mixture was stirred overnight in a hydrogen atmosphere at room temperature. After filtering, the filtrate was concentrated under reduced pressure and the resulting residue was subjected to silica gel column

chromatography (eluting solvent, chloroform:methanol = 10:1) to yield Phe-Cha-Phe(3-tBu)-NH₂ in 69.0 mg (46%).

EI-MS: 520(M⁺)

NMR(method g, CDCl₃): δ 0.80-1.75(13H,m) 1.29(9H,s),
 5 2.70(1H,dd,J=8.6,13.5Hz), 3.00-3.28(3H,m),
 3.40(1H,dd,J=4.0,8.6Hz), 4.18-4.32(1H,m),
 4.66(1H,dd,J=6.9,6.9Hz), 5.32(1H,brs), 6.20(1H,brs),
 6.50(1H,d,J=7.9Hz), 7.01(1H,d,J=6.3Hz), 7.12-7.38(7H,m),
 7.58(1H,d,J=6.9Hz)

10 Example 97

N-(benzylaminocarbonyl)-N-Me-D-Phg-Tyr(3-tBu)-NH₂

To a solution of benzylamine (27 mg) in methylene chloride (2 ml), 74 mg (0.25 mmol) of triphosgene and 0.04 ml of DIEA were added under cooling with ice and the
 15 mixture was stirred at room temperature for 45 minutes. The reaction mixture was distilled off under reduced pressure and the resulting residue was dissolved in methylene chloride and added to a solution of 100 mg (0.26 mmol) of N-Me-D-Phg-Tyr(3-tBu)-NH₂ and 84 mg (0.99 mmol) of
 20 NaHCO₃ in 2 ml of H₂O, and the mixture was stirred at room temperature for 5 hours. The reaction mixture was diluted with methylene chloride and washed first with water, then with saturated brine. The organic layer was dried with anhydrous sodium sulfate and the solvent was distilled off
 25 under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 100:10:1) to yield N-(benzylamino-carbonyl)-N-Me-D-

Phg-Tyr(3-tBu)-NH₂ in 70 mg (54%).

EI-MS: 498(M⁺-18)

NMR(method g, CDCl₃): δ 1.34(9H,s), 2.72(3H,s),
 2.93(1H,dd,J=7.6,14.3Hz), 3.05(1H,dd,J=5.8,14.3Hz),
 5 4.40(2H,brd,J=5.3Hz), 4.68(1H,dd,J=7.6,13.9Hz), 4.99-
 5.12(1H,m), 5.70-5.38(1H,m), 5.40(1H,brs), 6.14-6.32(2H,m),
 6.55(1H,d,J=7.9Hz), 6.66(1H,dd,J=1.8,8.1Hz), 6.97(1H,
 d,J=10.2Hz), 7.07-7.16(1H,m), 7.25-7.36(10H,m)

Example 98

10 N-(benzyloxycarbonyl)-Phg-Tyr(3-tBu)-NHMe

(1) Synthesis of Z-Phg-Tyr(3-tBu)-OMe

To a solution of Z-Phg-OSu (640 mg) in DMF (10 ml),
 463 mg (1.84 mmol) of Tyr(3-tBu)-OMe and 408 mg (3.34 mmol)
 of DMAP were added and the mixture was stirred at room
 15 temperature for 1 hour. The reaction mixture was diluted
 with ethyl acetate and washed first with saturated aqueous
 NaHCO₃, then with water and finally with saturated brine.
 The organic layer was dried with anhydrous magnesium sulfate
 and concentrated under reduced pressure; the resulting
 20 residue was subjected to silica gel column chromatography
 (eluting solvent; ethyl acetate:n-hexane = 1:1) to give Z-
 Phg-Tyr(3-tBu)-OMe in 905 mg (quantitative).

(2) Synthesis of N-(benzyloxycarbonyl)-Phg-Tyr(3-tBu)-NHMe

To a solution of 900 mg (1.73 mmol) of Z-Phg-Tyr(3-
 25 tBu)-OMe in 10 ml of methanol, 10 ml of a solution of 40%
 methylamine in methanol and 10 mg of sodium cyanide were
 added and the mixture was stirred overnight at room
 temperature. The reaction mixture was concentrated under

reduced pressure and the resulting residue was dissolved in methylene chloride, followed by washing first with water, then with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 2:1) to yield N-(benzyloxycarbonyl)-Phg-Tyr(3-tBu)-NHMe in 737 mg (82%).

FAB-MS: 518 (M+H⁺)

10 NMR(method g, DMSO-d₆): δ 1.30(9H,s), 2.57(3H,d,J=4.3Hz), 2.5-2.9(2H,m) 3.30(1H,d,J=5.3Hz), 4.0-4.1(1H,m), 4.2-4.4(1H,m), 5.03(2H,s), 5.28(1H,d,J=8.5Hz), 6.5-6.8(2H,m), 6.94(1H,d,6.6Hz), 7.2-7.4(8H,m), 7.7-7.9(2H,m), 8.46(1H,d,7.6Hz), 9.06(1H,d)

15 Example 99

N-(benzyloxycarbonyl)-N-Me-Val-Tyr(3-tBu)-NH₂

To a solution of 1.70 g (7.20 mmol) of Tyr(3-tBu)-NH₂, 2.10 g (7.92 mmol) of Z-N-Me-Val-OH, 1.07 g (7.92 mmol) of HOBt and 970 mg (7.94 mmol) of DMAP in 20 ml of DMF, 1.52 g (7.93 mmol) of WSCI·HCl was added under cooling with ice and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate and washed first with saturated aqueous NaHCO₃, then with water and finally with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 2:1) to yield N-(benzyloxycarbonyl)-N-Me-

Val-Tyr(3-tBu)-NH₂ in 3.30 g (95%).

FAB-MS: 484 (M+H⁺)

NMR(method g, CDCl₃): δ 0.83(3H,d,J=6.6Hz),
 0.88(3H,d,J=6.6Hz), 1.36(9H,s), 2.15-2.30(1H,m), 2.75(3H,s),
 5 2.80-3.05(2H,m), 4.02(1H,d,J=10.9Hz), 4.52-4.64(1H,m),
 5.13(2H,s), 5.39(1H,brs), 5.88(1H,brs), 6.40-6.84(3H,m),
 7.08(1H,s), 7.28-7.42(5H,m)

Example 100

N-((R)-3-phenylbutyryl)-Phg-Tyr(3-tBu)-NH₂

10 A reaction vessel was charged with 182 mg (0.1 mmol)
 of Fmoc-2,4-dimethoxy-4-(carboxymethyloxy)-benzhydrylamine
 linked to Aminomethyl Resin (0.55 mmol/g); after being
 swelled with DMF, the resin was treated with piperidine to
 remove Fmoc. Subsequently, Fmoc-Tyr(3-tBu)-OH was coupled
 15 by method 1. After filtering and washing with DMF, the
 resin was treated with piperidine to remove Fmoc.
 Subsequently, Fmoc-Phg-OH was coupled by method 3. After
 filtering and washing with DMF, the resin was treated again
 with piperidine to remove Fmoc. Subsequently, (R)-3-
 20 phenylbutyric acid was coupled by method 3. After the end
 of the reaction, filtering and washing with DMF and DCM were
 effected, followed by drying of the resin. Cleavage was
 effected with 3 ml of 95% aqueous TFA. The reaction
 solution was concentrated under reduced pressure and the
 25 residue was dissolved in 1 ml of DMF, followed by HPLC
 purification. The active fractions were collected,
 concentrated and freeze-dried to yield 15.6 mg of the titled
 compound.

HPLC (method a):RT22.96

FAB-MS:516(M+H⁺)

NMR(method f,DMSO-d₆): δ 1.16(3H,d,J=7Hz), 1.32(9H,s),
2.41(1H,dd,J=14,8Hz), 2.56(1H,dd,J=14,8Hz),
5 2.74(1H,dd,J=14,9Hz), 2.89(1H,dd,J=14,5Hz),
3.15(1H,ddq,J=8,8,7Hz), 4.38(1H,ddd,J=9,8,5Hz),
5.42(1H,d,J=8Hz), 6.63(1H,d,J=8Hz), 6.81(1H,dd,J=8,2Hz),
7.01(2H,brs), 7.05-7.30(11H,m), 8.30(1H,d,J=8Hz),
8.31(1H,d,J=8Hz), 9.08(1H,s)

10 Example 101

N-((S)-3-phenylbutyryl)-Phg-Tyr(3-tBu)-NH₂

Substituting (S)-3-phenylbutyric acid for the (R)-3-phenylbutyric acid used in Example 100, the procedure of Example 100 was repeated to yield 13.3 mg of the titled
15 compound.

HPLC (method a):RT23.00

FAB-MS:516(M+H⁺)

NMR(method f,DMSO-d₆): δ 1.11(3H,d,J=8Hz), 1.30(9H,s),
2.40(1H,dd,J=14,6Hz), 2.52(1H,dd,J=14,10Hz),
20 2.69(1H,dd,J=14,9Hz), 2.89(1H,dd,J=14,5Hz),
3.13(1H,ddq,J=10,6,8Hz), 4.36(1H,ddd,J=9,8,5Hz),
5.47(1H,d,J=8Hz), 6.62(1H,d,J=8Hz), 6.79(1H,dd,J=8,2Hz),
6.99(1H,d,J=2Hz), 7.00(1H,s), 7.10-7.30(11H,m),
8.20(1H,d,J=8Hz), 8.43(1H,d,J=8Hz), 9.08(1H,s)

25 Example 102

N-((R)-3-phenylbutyryl)-D-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-D-Phg-OH for the Fmoc-Phg-OH used in Example 100, the procedure of Example 100 was repeated to

yield 7.2 mg of the titled compound.

HPLC (method a):RT23.07

FAB-MS:516(M+H⁺)

NMR(method g, DMSO-d₆): δ 1.13(3H,d,J=7Hz), 1.27(9H,s),
 5 2.38-2.64(3H,m), 2.88(1H,dd,J=14,4Hz), 3.15(1H,m),
 4.26(1H,m), 5.50(1H,d,J=8Hz), 6.53(1H,d,J=8Hz),
 6.69(1H,dd,J=8,1Hz), 6.98(1H,brs), 7.10-7.42(12H,m),
 8.48(1H,d,J=8Hz), 8.54(1H,d,J=8Hz), 9.06(1H,s)

Example 103

10 N-((S)-3-phenylbutyryl)-D-Phg-Tyr(3-tBu)-NH₂

Substituting Fmoc-D-Phg-OH for the Fmoc-Phg-OH used in Example 101, the procedure of Example 101 was repeated to yield 16.1 mg of the titled compound.

HPLC (method a):RT22.98

15 FAB-MS:516(M+H⁺)

NMR(method g, DMSO-d₆): δ 1.17(3H,d,J=7Hz), 1.27(9H,s),
 2.39-2.65(3H,m), 2.91(1H,dd,J=14,3Hz), 3.16(1H,m),
 4.28(1H,m), 5.42(1H,d,J=8Hz), 6.55(1H,d,J=8Hz),
 6.73(1H,dd,J=8,1Hz), 6.80-7.44(13H,m), 8.37(1H,d,J=8Hz),
 20 8.58(1H,d,J=8Hz), 9.07(1H,s)

Example 104

L- α -(3-methyl-2-butenyl)glycinoyl-N-Me-Val-Tyr(3-tBu)-NH₂

To a solution in 6 ml of DMF of 228 mg (0.653 mmol) of the N-Me-Val-Tyr(3-tBu)-NH₂ prepared in Example 89, 340 mg
 25 (1.40 mmol) of Boc-L- α -(3-methyl-2-butenyl)glycine (Bioorg. Med. Chem. Lett., 2, 387 (1992)) and 189 mg (1.40 mmol) of HOBt, 0.22 ml (1.40 mmol) of DIC was added under cooling with ice. After being stirred at room temperature for a day,

the reaction mixture was diluted with ethyl acetate and washed first with saturated aqueous NaHCO_3 , then with water and finally with saturated brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated
 5 under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 50:1:0.1) to give Boc-L- α -(3-methyl-2-butenyl)-glycinoyl-N-Me-Val-Tyr(3-tBu)- NH_2 in 0.17 g (45%).

10 Subsequently, 1 ml of TFA was added to a solution of Boc-L- α -(3-methyl-2-butenyl)glycinoyl-N-Me-Val-Tyr(3-tBu)- NH_2 (0.17 g) in methylene chloride (2 ml) and the mixture was stirred at room temperature for 10 minutes. The reaction mixture was concentrated under reduced pressure and
 15 the resulting residue was diluted with methylene chloride. The solution was washed with saturated aqueous NaHCO_3 . The resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 20:1:0.1) to
 20 yield L- α -(3-methyl-2-butenyl)glycinoyl-N-Me-Val-Tyr(3-tBu)- NH_2 in 131 mg (93%).

FAB-MS: 475($\text{M}+\text{H}^+$)

NMR(method g, CDCl_3): δ 0.79(2H,d,J=6.6Hz),
 0.82(1H,d,J=6.6Hz), 0.89(1H,d,J=6.3Hz), 0.95(2H,d,J=6.3Hz),
 25 1.36(6H,s), 1.38(3H,s), 1.62(3H,s), 1.69(3H,s),
 2.2-2.4(3H,m), 2.67(2H,s), 2.9-3.1(2H,m), 2.97(1H,s),
 3.40(6.5/10H,m), 3.65(3.5/10H,m), 4.00(6.5/10H,d,J=10.9Hz),
 4.39(3.5/10H,d,J=10.9Hz), 4.50-4.80(1H,m), 4.95-5.10(1H,m),

5.57(1H,brs), 5.91(3/10H,brs), 6.07(7/10H,brs), 6.60-
6.72(23/10H,m), 6.87-6.96(1H,m), 7.03(7/10H,s),
7.09(3/10H,s), 9.19(7/10H,d,J=7.6Hz)

Example 105

5 α -(4-pentynyl)glycinoyl-N-Me-Val-Tyr(3-tBu)-NH₂

(1) Synthesis of Boc-DL- α -(4-pentynyl)glycine

To a solution of 0.45 g (4.00 mmol) of potassium t-butoxide in 6 ml of THF, 690 mg (3.33 mmol) of N-[bis(methyl-thio)methylene]glycine ethyl ester in 2 ml of
10 THF was added at -78°C in a nitrogen atmosphere. After stirring for 15 minutes, a solution of 777 mg (4.00 mmol) of 5-iodo-1-pentyne (J. Chem. Soc. Perkin Trans. I, 2909 (1990)) in 2 ml of THF was added and the mixture was stirred at room temperature for 1.5 hours. To the reaction mixture,
15 saturated aqueous NaHCO₃ was added and extraction was effected with ethyl acetate. The organic layer was washed with saturated brine, dried with anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The resulting residue was dissolved in a mixture of dioxane
20 (2 ml) and water (4 ml) and, after adding 4 ml of a solution of 10% hydrochloric acid in methanol, the reaction mixture was stirred overnight at room temperature. Thereafter, 2 N aqueous NaOH was added to the reaction mixture to make it alkaline and it was extracted with methylene chloride; then,
25 dioxane (5 ml) and di-tert-butyl dicarbonate (1.5 g) were added to the aqueous layer. After being stirred overnight, the aqueous layer was rendered acidic by addition of 2 N hydrochloric acid, extracted with methylene chloride and

dried with anhydrous magnesium sulfate; thereafter, the solvent was distilled off under reduced pressure to give 0.46 g of Boc-DL- α -(4-pentynyl)glycine in crude form.

NMR(method g, CDCl_3): δ 1.45(9H,s), 1.60-1.70(2H,m),

5 1.80(1H,m), 1.97(1H,t, $J=2.6\text{Hz}$), 1.98(1H,m),
2.25(2H,dt, $J=2.6, 6.9\text{Hz}$), 4.35(1H,brs), 5.02(1H,brs)

(2) Synthesis of Boc- α -(4-pentynyl)glycinoyl-N-Me-Val-Tyr(3-tbu)- NH_2

To a solution in DMF (5 ml) of 034 g (1.41 mmol) of
10 the crude Boc-DL- α -(4-pentynyl)glycine, 200 mg (0.572 mmol)
of N-Me-Val-Tyr(3-tBu)- NH_2 prepared in accordance with
Example 89 and 150 mg (1.14 mmol) of HOBT, 0.18 ml (1.14
mmol) of DIC was added under cooling with ice. After being
stirred at room temperature for 19 hours, the reaction
15 mixture was diluted with ethyl acetate and washed with
saturated aqueous NaHCO_3 , water and saturated brine. The
organic layer was dried with anhydrous magnesium sulfate and
concentrated under reduced pressure; the resulting residue
was subjected to silica gel column chromatography (eluting
20 solvent consisting of chloroform, methanol and aqueous
ammonia at a ratio of 50:1:0.1) to give Boc- α -(4-
pentynyl)glycinoyl-N-Me-Val-Tyr(3-tBu)- NH_2 both as a
compound of low polarity in an amount of 202 mg (61%) and as
a compound of high polarity in an amount of 65 mg (20%).
25 (3) Synthesis of α -(4-pentynyl)glycinoyl-N-Me-Val-Tyr(3-
tBu)- NH_2

Each of the above-mentioned compounds of low polarity
(195 mg) and high polarity (60 mg) was dissolved in 2 ml of

methylene chloride and, after adding 1 ml of TFA, the
 mixtures were stirred at room temperature for 15 minutes.
 The solvent was distilled off under reduced pressure and the
 resulting residue was diluted with methylene chloride. The
 5 organic layer was washed with saturated aqueous NaHCO_3 . The
 resulting residue was subjected to silica gel column
 chromatography (eluting solvent consisting of chloroform,
 methanol and aqueous ammonia at a ratio of 20:1:0.1) to
 yield α -(4-pentynyl)-glycinoyl-N-Me-Val-Tyr(3-tBu)- NH_2 from
 10 the compound of low polarity in an amount of 101 mg (63%)
 and from the compound of high polarity in an amount of 17 mg
 (34%).

Compound of low polarity

FAB-MS: 473($\text{M}+\text{H}^+$)

15 NMR(method g, CDCl_3): δ 0.75(3H,d,J=6.6Hz),
 0.91(3H,d,J=6.3Hz), 1.37(9H,s), 1.4-1.8(4H,m),
 1.93(1H,t,J=2.5Hz), 2.17-2.27(3H,m), 2.69(3H,s),
 2.82(1H,dd,J=10.1,14.2Hz), 3.18(1H,dd,J=5.6,14.2Hz),
 3.53(1H,m), 4.52(1H,d,J=10.9Hz), 4.63(1H,m),
 20 5.90(1H,brs), 6.31(1H,brs), 6.64(1H,d,J=7.3Hz),
 6.65(1H,d,J=7.9Hz), 6.78(1H,d,J=7.9Hz), 7.06(1H,s)

Compound of high polarity

FAB-MS: 473($\text{M}+\text{H}^+$)

NMR(method g, CDCl_3): δ 0.78-0.97(6H,m), 1.37(6H,s),
 25 1.39(3H,s), 1.4-1.8(4H,m), 1.96(1H,m), 2.17-2.22(2H,m),
 2.33(1H,m), 2.66(2H,s), 2.87-3.11(2H,m), 2.97(1H,s),
 3.43-3.69(14/10H,m), 3.98(7/10H,d,J=10.9Hz), 4.42(3/10H,
 d,J=10.9Hz), 4.48-4.76(1H,m), 5.43(1H,brs), 5.81(3/10H,brs),

6.08(7/10H,brs), 6.62-6.77(2H,m), 6.81(3/10H,d,J=7.9Hz),
 6.90(7/10H,d,J=7.9Hz), 7.03(7/10H,s), 7.10(3/10H,s),
 9.03(6/10H,d,J=7.3Hz)

Example 106

5 α -(2-butyryl)glycinoyl-N-Me-Val-Tyr(3-tBu)-NH₂

(1) Synthesis of Boc-DL- α -(2-butyryl)glycine ethyl ester

To a solution of 0.40 g (3.55 mmol) of potassium
 t-butoxide in 6 ml of THF, 610 mg (2.96 mmol) of N-
 [bis(methyl-thio)methylene]glycine ethyl ester in 2 ml of
 10 THF was added at -78°C. After stirring for 20 minutes, a
 solution of 640 mg (3.55 mmol) of 1-iodo-2-butyne (Chem.
 Lett., 621 (1981)) in 2 ml of THF was added and the
 resulting mixture was stirred at room temperature for 30
 minutes. Saturated aqueous NaHCO₃ was added to the reaction
 15 mixture, which was extracted with ethyl acetate. The
 organic layer was washed with saturated brine, dried with
 anhydrous magnesium sulfate and the solvent was distilled
 off under reduced pressure. The resulting residue was
 dissolved in a mixture of dioxane (2 ml) and water (4 ml)
 20 and, after adding 10% hydrochloric acid in methanol (4 ml),
 the mixture was stirred overnight at room temperature.
 Thereafter, the reaction mixture was neutralized with 2 N
 aqueous NaOH, rendered alkaline with saturated aqueous
 NaHCO₃, extracted with methylene chloride, dried with
 25 anhydrous sodium carbonate and the solvent was distilled off
 under reduced pressure.

To a solution of the resulting residue in 5 ml of
 methylene chloride, di-tert-butyl bicarbonate (0.65 g) was

added and the mixture was stirred for 1 hour. The reaction mixture was washed with water, dried with anhydrous magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 1:6) to give Boc-DL- α -(2-butynyl)glycine ethyl ester in 575 mg (76%).

NMR(method g, CDCl_3): δ 1.29(3H,t,J=7.3Hz), 1.46(9H,s), 1.77(3H,t,J=2.6Hz), 2.56-2.77(2H,m), 4.18-4.27(2H,m), 4.38(1H,m), 5.30(1 H,brs)

(2) Synthesis of Boc- α -(2-butynyl)glycinoyl-N-Me-Val-Tyr(3-tBu)- NH_2

To a solution of 570 mg (2.23 mmol) of Boc-DL- α -(2-butynyl)glycine ethyl ester in a solvent system of methanol (6 ml) and water (2 ml), 140 mg (3.35 mmol) of lithium hydroxide monohydrate was added and the mixture was stirred at room temperature for 2 hours. The mixture was rendered acidic with 2 N hydrochloric acid under cooling with ice, extracted with methylene chloride, dried with anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure to give Boc-DL- α -(2-butynyl)glycine in 0.50 g (quantitative).

To a solution in DMF (4 ml) of 123 mg (0.541 mmol) of the Boc-DL- α -(2-butynyl)glycine, 378 mg (1.08 mmol) of N-Me-Val-Tyr(3-tBu)- NH_2 prepared in accordance with Example 89 and 146 mg (1.08 mmol) of HOBT, 0.13 ml (0.811 mmol) of DIC was added under cooling with ice. After being stirred overnight at room temperature, the reaction mixture was

diluted with ethyl acetate and washed with saturated aqueous NaHCO₃, water and saturated brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 50:1:0.1) to give Boc- α -(2-butynyl)glycinoyl-N-Me-Val-Tyr(3-tBu)-NH₂ both as a compound of low polarity in an amount of 138 mg and as a compound of high polarity in an amount of 59 mg.

(3) Synthesis of α -(2-butynyl)glycinoyl-N-Me-Val-Tyr(3-tBu)-NH₂

Each of the above-mentioned compounds of low polarity (138 mg) and high polarity (59 mg) was dissolved in 2 ml of methylene chloride and, after adding 1 ml of TFA, the mixtures were stirred at room temperature for 15 minutes. The solvent was distilled off under reduced pressure and the resulting residue was diluted with methylene chloride, followed by washing with saturated aqueous NaHCO₃. The resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 20:1:0.1) to yield α -(2-butynyl)glycinoyl-N-Me-Val-Tyr(3-tBu)-NH₂ from the compound of low polarity in an amount of 80 mg and from the compound of high polarity in an amount of 47 mg.

Compound of low polarity

FAB-MS: 459(M+H⁺)

NMR(method g, CDCl₃): δ 0.75(3H, d, J=6.6Hz),

0.90(3H,d,J=6.6Hz), 1.38(9H,s), 1.77(3H,s),
 2.1-2.5(6H,m), 2.74(3H,s), 2.81(1H,dd,J=9.9,14.2Hz),
 3.18(1H,dd,J=5.6,14.2Hz), 3.66(1H,dd,J=5.0,7.6Hz),
 4.47(1H,d,J=11.2Hz), 4.57(1H, m), 5.66(1H,brs), 6.26(1H,brs),
 5 6.47(1H,d,J=7.3Hz), 6.64(1H,d,J=7.9Hz), 6.78(1H,d,J=7.9Hz),
 7.05(1H,s)

Compound of high polarity

FAB-MS: 459(M+H⁺)

NMR(method g, CDCl₃): δ 0.78-0.96(6H,m), 1.38(6H,s),
 10 1.39(3H,s), 1.78(3H,s), 2.30-2.45(4H,m), 2.68(2H,s),
 2.92-3.13(2H,m), 2.97(1H,s), 3.48(1H,dd,J=4.3,9.2Hz),
 3.98(7/10H,d,J=11.2Hz), 4.42(3/10H, d,J=11.2Hz), 4.53-
 4.78(1H,m), 5.52(1H,brs), 6.14(1H,brs), 6.62-6.70(2H,m),
 6.81(3/10H,d,J=7.9Hz), 6.90(7/10H,d,J=7.9Hz), 7.04(7/10H,s),
 15 7.10(3/10H,s), 9.10(1H,d,J=7.3Hz)

Example 107

N-((S)-3-phenylbutyryl)-N-Me-Val-Tyr(3-tBu)-NH₂

To a solution in DMF (3 ml) of 0.11 ml (0.736 mmol) of
 (S)-3-phenyl-n-butyric acid, 234 mg (0.670 mmol) of N-Me-
 20 Val-Tyr(3-tBu)-NH₂ prepared in accordance with Example 89,
 and 99 mg (0.736 mmol) of HOBT, 0.11 ml (0.736 mmol) of DIC
 was added under cooling with ice. After being stirred at
 room temperature for 25 hours, the reaction mixture was
 diluted with ethyl acetate and washed with saturated NaHCO₃,
 25 water and saturated brine. The organic layer was dried with
 anhydrous magnesium sulfate and concentrated under reduced
 pressure; the resulting residue was subjected to silica gel
 column chromatography (eluting solvent consisting of

chloroform, methanol and aqueous ammonia at a ratio of 50:1:0.1) to yield N-((S)-3-phenylbutyryl)-N-Me-Val-Tyr(3-tBu)-NH₂ in 259 mg (78%).

EI-MS: 496(M⁺)

5 NMR(method g, CDCl₃): δ 0.76(3H,d,J=6.6Hz),
 0.89(3H,d,J=6.3Hz), 1.27(3H,d,J=6.9Hz), 1.34(9H,s),
 2.17-2.31(1H,m), 2.38-2.57(2H,m), 2.72(3H,s),
 2.81(1H,dd,J=8.2,14.2Hz), 2.96(1H,dd,J=6.3,14.2Hz),
 3.34(1H,m), 4.46(1H,d,J=11.2Hz), 4.56(1H,m), 5.50(1H,s),
 10 5.59(1H,brs), 6.00(1H,brs), 6.45(1H,d,J=7.9Hz),
 6.66(1H,d,J=7.6Hz), 6.78(1H,dd,J=1.7,7.9Hz),
 7.05(1H,d,J=1.7Hz), 7.20-7.36(5H,m)

Example 108

N-((R)-3-phenylbutyryl)-N-Me-Val-Tyr(3-tBu)-NH₂

15 To a solution in DMF (3 ml) of 0.085 ml (0.558 mmol)
 of (R)-3-phenyl-n-butyric acid, 150 mg (0.429 mmol) of N-Me-
 Val-Tyr(3-tBu)-NH₂ prepared in accordance with Example 89,
 and 75 mg (0.558 mmol) of HOBT, 0.087 ml (0.558 mmol) of DIC
 was added under cooling with ice. After being stirred at
 20 room temperature for 25 hours, the reaction mixture was
 diluted with ethyl acetate and washed with saturated NaHCO₃,
 water and saturated brine. The organic layer was dried with
 anhydrous magnesium sulfate and concentrated under reduced
 pressure; the resulting residue was subjected to silica gel
 25 column chromatography (eluting solvent consisting of
 chloroform, methanol and aqueous ammonia at a ratio of
 50:1:0.1) to yield N-((R)-3-phenylbutyryl)-N-Me-Val-Tyr(3-
 tBu)-NH₂ in 186 mg (87%).

EI-MS: 497($M^+ + 1$)

NMR(method g, $CDCl_3$): δ 0.51(3H,d,J=6.6Hz),
 0.82(3H,d,J=6.6Hz), 1.31(3H,d,J=7.3Hz), 1.38(9H,s),
 2.04-2.23(1H,m), 2.38(1H,dd,J=7.3,14.8Hz),
 5 2.65(1H,dd,J=7.6,14.8Hz), 2.73(3H,s),
 2.90(1H,dd,J=7.9,14.2Hz), 3.00(1H,dd,J=6.3,14.2Hz),
 3.30(1H,m), 4.36(1H,d,J=10.9Hz), 4.60(1H, m),
 5.67(1H,brs), 5.99(1H,brs), 6.15(1H,brs),
 6.63(1H,d,J=8.3Hz), 6.76(1H,d,J=7.9Hz),
 10 6.82(1H,d,J=7.9Hz), 7.07(1H,s), 7.17-7.29(5H,m)

Example 109

N-(β -aminohydrocinnamoyl)-N-Me-Val-Tyr(3-tBu)-NH₂

To a mixture of 0.67 g (4.05 mmol) of β -aminohydrocinnamic acid, 0.45 g (4.26 mmol) of sodium carbonate, 2.5
 15 ml of 2 N aqueous NaOH, 8 ml of water and 8 ml of dioxane, 0.93 g (4.26 mmol) of di-tert-butyl dicarbonate was added and the resulting mixture was stirred at room temperature for 3 hours. Under cooling with ice, the reaction mixture was rendered acidic with conc. hydrochloric acid, extracted
 20 with methylene chloride, dried with anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure to give 1.14 g of N-Boc- β -aminohydrocinnamic acid.

To a solution in DMF (5 ml) of 0.27 g (1.03 mmol) of N-Boc- β -aminohydrocinnamic acid, 0.24 g (0.687 mmol) of N-
 25 Me-Val-Tyr(3-tBu)-NH₂ prepared in accordance with Example 89 and 0.23 g (1.72 mmol) of HOBT, 0.27 ml (1.72 mmol) of DIC was added under cooling with ice. After being stirred at room temperature for a day, the reaction mixture was diluted

with ethyl acetate and washed with saturated aqueous NaHCO_3 , water and saturated brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel
5 column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 60:1:0.1) to give N-(N-boc- β -aminohydro-cinnamoyl)-N-Me-Val-Tyr(3-tBu)- NH_2 in 291 mg (71%).

A portion (285 mg) of the N-(N-Boc- β -aminohydro-
10 cinnamoyl)-N-Me-Val-Tyr(3-tBu)- NH_2 was dissolved in 2 ml of methylene chloride and, after adding 1 ml of TFA, the mixture was stirred at room temperature for 15 minutes. The solvent was distilled off under reduced pressure and the resulting residue was diluted with methylene chloride and
15 washed with saturated aqueous NaHCO_3 . The resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 20:1:0.1) to yield N-(β -aminohydro-cinnamoyl)-N-Me-Val-Tyr(3-tBu)- NH_2 in 197 mg (83%).

20 FAB-MS: 497($\text{M}+\text{H}^+$)

Example 110

N-(2-amino-3-phenylpropyl)-Phg-Tyr(3-tBu)- NH_2

To a solution of 120 mg (0.325 mmol) of Phg-Tyr(3-tBu)- NH_2 and 112 mg (0.396 mmol) of Z-phenylalaninal (J. Org.
25 Chem., 57, 28 (1992)) in 3 ml of MeCN, 0.1 ml of acetic acid and 41.5 mg (0.661 mmol) of sodium cyanoborohydride were added under cooling with ice and the resulting mixture was stirred for 2 hours. After adding water, the reaction

mixture was extracted with ethyl acetate and washed with water and saturated brine. The organic layer was dried with magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; chloroform:methanol = 20:1) to give N-(2-benzoxycarbonylamino-3-phenylpropyl)-Phg-Tyr(3-tBu)-NH₂ in 187 mg (89%).

To a solution of 40.0 mg (0.0664 mmol) of N-(2-benzoxycarbonylamino-3-phenylpropyl)-Phg-Tyr(3-tBu)-NH₂ in methanol (1 ml), 10% palladium carbon (15.0 mg) was added and the mixture was stirred overnight in a hydrogen atmosphere at room temperature. After filtering, the filtrate was concentrated under reduced pressure and the resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 10:1:0.1) to yield N-(2-amino-3-phenylpropyl)-Phg-Tyr(3-tBu)-NH₂ in 29.0 mg (92%).

EI-MS: 503(M⁺+1)

NMR(method g, CDCl₃): δ 1.36(9H,s), 2.20-3.05(7H,m), 3.47(1H,s) 4.08(1H,d, J=4.6Hz), 4.54-4.72(1H,m), 5.56(1H,brs), 6.56(1H,d,J=7.9Hz), 6.81(1H,d,J=7.9Hz), 7.02-7.30(11H,m), 8.01(1H,d,J=8.4Hz)

Example 111

N-(2-amino-3-phenylpropyl)-N-Me-Phg-Tyr(3-tBu)-NH₂

To a solution of 60.0 mg (0.0943 mmol) of N-(2-benzoxycarbonylamino-3-phenylpropyl)-Phg-Tyr(3-tBu)-NH₂ in MeCN (1 ml), 0.081 ml (0.94 mmol) of 35% aqueous

formaldehyde, 0.1 ml of acetic acid and 18.7 mg (0.283 mmol) of sodium cyanoborohydride were added under cooling with ice and the resulting mixture was stirred for 2 hours. The reaction mixture was diluted with water, extracted with
 5 chloroform and washed with saturated brine. The organic layer was dried with magnesium sulfate and the solvent was distilled off under reduced pressure. The resulting residue was dissolved in methanol (1 ml) and, after adding palladium carbon (15.0 mg), the solution was stirred at room
 10 temperature for 3 days in a hydrogen atmosphere. After filtering, the filtrate was concentrated under reduced pressure and the resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of
 15 10:1:0.1) to yield N-(2-amino-3-phenyl-propyl)-N-Me-Phg-Tyr(3-tBu)-NH₂ in 29.7 mg (61%).

FAB-MS: 517(M+H⁺)

NMR(method g, CDCl₃): δ 1.38(9H,s), 2.07(2H,s),
 2.16-3.20(7H,m), 3.47(3H,s), 4.13(1H,s), 4.60-4.80(1H,m),
 20 5.46-5.60(1H,m), 6.52-7.32(13H,m), 8.15(1H,d,J=7.9Hz)

Example 112

N-(phenylpyruvinoyl)-N-Me-Val-Tyr(3-tBu)-NH₂

To a solution of 179 mg (1.09 mmol) of phenylpyruvic acid in methylene chloride (2 ml), 0.079 ml (1.1 mmol) of
 25 thionyl chloride was added and the resulting mixture was stirred at 60°C for 1 hour. The reaction mixture was distilled off under reduced pressure and the resulting residue was dissolved in methylene chloride (2 ml); to the

solution, 190 mg (0.544 mmol) of N-Me-Val-Tyr(3-tBu)-NH₂ and 0.152 ml (1.09 mmol) of triethylamine were added under cooling with ice. After stirring at room temperature for 2 hours, water was added to the reaction mixture, which was
 5 then extracted with chloroform and washed with saturated brine. The organic layer was dried with magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of methylene chloride, methanol
 10 and aqueous ammonia at a ratio of 20:1:0.1) to yield N-(phenylpyruvinoyl)-N-Me-Val-Tyr(3-tBu)-NH₂ in 50.7 mg (19%).
 NMR(method g, CDCl₃): δ 0.97(3H,d,J=6.6Hz), 0.99(3H,d,J=6.6Hz), 1.37(9H,s), 2.30-2.52(1H,m), 2.85(3H,s), 2.92-3.16(2H,m), 4.53(1H,d,J=10.9Hz),
 15 4.63(1H,dd,J=7.3,7.3Hz), 5.46(2H,brs), 5.84(1H,brs), 6.59(1H,d,J=7.9Hz), 6.95(1H,d,J=6.9Hz), 7.12(1H,s), 7.44(2H,t,J=7.6Hz), 7.60-7.70(1H,m), 7.95(2H, d,J=7.6Hz)

Example 113

N-phenyl-Gly-N-Me-Val-Tyr(3-tBu)-NH₂

20 To a solution of 108 mg (0.430 mmol) of Boc-N-phenyl-Gly in THF (1 ml), 0.048 ml (0.44 mmol) of N-methylmorpholine, 0.056 ml (0.43 mmol) of isobutyl chloroformate, a solution of 100 mg (0.287 mmol) of N-Me-Val-Tyr(3-tBu)-NH₂ in DMF (1 ml), and 0.060 ml (0.43 mmol)
 25 of triethylamine were added at -15°C and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate and washed successively with saturated NaHCO₃, water and saturated

brine. The organic layer was dried with magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 1:1) to give Boc-N-phenyl-Gly-N-Me-Val-Tyr(3-tBu)-NH₂ in 139 mg (83%).

To a solution of 130 mg (0.223 mmol) of Boc-N-phenyl-Gly-N-Me-Val-Tyr(3-tBu)-NH₂ in methylene chloride (1 ml), TFA (1 ml) was added and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in methylene chloride, followed by successive washing with saturated aqueous NaHCO₃ and saturated brine. The organic layer was dried with magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 10:1:0.1) to yield N-phenyl-Gly-N-Me-Val-Tyr(3-tBu)-NH₂ in 69.7 mg (65%).
FAB-MS: 483(M+H⁺)

NMR(method g, CDCl₃): δ 0.78(3H,d,J=6.6Hz), 0.94(3H,d,J=6.3Hz), 1.35(9H,s), 2.16-2.36(1H,m), 2.66(3H,s), 2.78(1H,dd,J=10.2,14.2Hz), 3.13(1H,dd,J=5.5,14.2Hz), 3.42(1H,d,J=16.5Hz), 3.74(1H,d,J=16.5Hz), 4.48-4.64(2H,m), 4.86(1H,brs), 5.39(1H,brs), 6.07(1H,brs), 6.27(1H,d,J=8.3Hz), 6.34(1H,d,J=7.2Hz), 6.67(2H,d,J=8.3Hz), 6.74-6.84(1H,m), 7.05(1H,s), 7.24-7.30(1H,m)

Example 114

N-Me-N-phenyl-Gly-N-Me-Val-Tyr(3-tBu)-NH₂

To a solution of 184 mg (0.646 mmol) of Z-N-phenyl-Gly in THF (2 ml), 0.071 mg (0.65 mmol) of NMM, 0.084 ml (0.65 mmol) of isobutyl chloroformate, a solution of 150 mg (0.430 mmol) of N-Me-Val-Tyr(3-tBu)-NH₂ in DMF (2 ml) and 0.090 ml (0.65 mmol) of triethylamine were added under cooling with ice and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with ethyl acetate and washed successively with saturated aqueous NaHCO₃, water and saturated brine. The organic layer was dried with magnesium sulfate and the solvent was distilled off under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 2:1) to give Z-N-(phenyl)-Gly-N-Me-Val-Tyr(3-tBu)-NH₂ in 186 mg (70%).

To a solution of 180 mg (0.292 mmol) of Z-N-phenyl-Gly-N-Me-Val-Tyr(3-tBu)-NH₂ in methanol (2 ml), 10% palladium carbon (100 mg) was added and the mixture was stirred overnight in a hydrogen atmosphere at room temperature. To the reaction mixture, 0.50 ml (5.83 mmol) of 35% formaldehyde was added and the mixture was stirred for additional 3 hours in a hydrogen atmosphere at room temperature. After filtering, water was added to the filtrate and the mixture was extracted with chloroform and washed with saturated brine. The organic layer was dried with magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 2:1) to yield N-Me-N-phenyl-Gly-N-Me-Val-Tyr(3-

tBu)-NH₂ in 32.0 mg (22%).

FAB-MS: 497(M+H⁺)

NMR(method g, CDCl₃): δ 0.78(3H,d,J=6.9Hz),
 0.88(3H,d,J=6.3Hz), 1.37(9H,s), 2.18-2.36(1H,m),
 5 2.63(1H,d,J=4.6Hz), 2.84(3H,s), 2.88-2.96(1H,m), 2.99(3H,s),
 3.92(1H,d,J=16.5Hz), 4.06(1H,d,J=16.5Hz), 4.12(1H,d,J=7.3Hz),
 4.62(1H,dd,J=6.6,7.9Hz), 5.35(2H,brs), 5.92(1H,brs),
 6.56(1H,d,J=7.9Hz), 6.64(2H,d,J=7.9Hz), 6.74(1H,t,J=7.9Hz),
 6.82(1H,d,7.9Hz), 7.08(1H,s), 7.21(2H,t,J=7.9Hz),
 10 7.35(1H,d,J=4.0Hz)

Example 115

N-(3-phenylbutyl)-Val-Tyr(3-tBu)-NH₂

To a solution of 330 mg (0.985 mmol) of Val-Tyr(3-tBu)-NH₂ and 146 mg (0.986 mmol) of phenylbutylaldehyde in
 15 MeCN (2 ml), 0.1 ml of acetic acid and 124 mg (1.97 mmol) of sodium cyanoborohydride were added under cooling with ice and the resulting mixture was stirred at room temperature for 3 hours. Water was added to the reaction mixture, which was extracted with ethyl acetate and washed with saturated
 20 brine. The organic layer was dried with magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; chloroform:methanol = 10:1) to yield N-(3-phenylbutyl)-Val-Tyr(3-tBu)-NH₂ in 236 mg (51%).

25 FAB-MS: 468(M+H⁺)

NMR(method g, CDCl₃): δ 0.57(4/3H,d,J=6.9Hz),
 0.62(5/3H,d,J=6.9Hz), 0.75(4/3H,d,J=6.6Hz),
 0.62(5/3H,d,J=6.6Hz), 1.23(3H,d,J=6.9Hz), 1.38(9H,s),

1.56-1.76(2H,m), 1.86-2.02(1H,m), 2.20-2.32(1H,m),
 2.36(4/9H,d,J=6.9Hz), 2.39(5/9H,d,J=6.9Hz), 2.64-2.74(1H,m),
 2.76(1H,d,J=4.3Hz), 2.94-3.08(2H,m), 4.50-4.64(1H,m),
 5.10-5.28(1H,m), 5.88(5/9H,brs), 6.00(4/9H,brs),
 5 6.59(1H,d,J=7.9Hz), 6.93(1H,d,J=7.9Hz), 7.06(1H,s),
 7.10-7.36(5H,m), 7.64-7.76(1H,m)

Example 116

N-(2-amino-3-phenylpropyl)-Val-Tyr(3-tBu)-NH₂

To a solution of 106 mg (0.316 mmol) of Val-Tyr(3-
 10 tBu)-NH₂ and 90.0 mg (0.318 mmol) of Z-phenylalaninal in THF
 (2 ml), 300 mg of magnesium sulfate and 40.0 mg (0.637 mmol)
 of sodium cyanoborohydride were added under cooling with ice
 and the resulting mixture was stirred at room temperature
 for 2 hours. After filtering, water was added to the
 15 filtrate, which was extracted with chloroform and washed
 with saturated brine. The organic layer was dried with
 magnesium sulfate and concentrated under reduced pressure;
 the resulting residue was subjected to silica gel column
 chromatography (eluting solvent; chloroform:methanol = 20:1)
 20 to give N-[2-benzoxycarbonylamino)-3-phenylpropyl]-Val-
 Tyr(3-tBu)-NH₂ in 95.7 mg (50%).

To a solution of 94.1 mg (0.156 mmol) of N-[2-
 (benzoxycarbonylamino)-3-phenylpropyl]-Val-Tyr(3-tBu)-NH₂ in
 methanol (2 ml), palladium carbon (50.0 mg) was added and
 25 the mixture was stirred overnight in a hydrogen atmosphere
 at room temperature. After filtering, the filtrate was
 concentrated under reduced pressure and the resulting
 residue was subjected to silica gel column chromatography

(eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 10:1:0.1) to yield N-(2-amino-3-phenylpropyl)-Val-Tyr(3-tBu)-NH₂ in 47.0 mg (64%).

FAB-MS: 469 (M+H⁺)

5 NMR(method g, CDCl₃): δ 0.75(3H,d,J=6.9Hz),
 0.87(3H,d,J=6.9Hz), 1.38(9H,s), 1.90-2.08(1H,m), 2.38-
 2.54(3H,m), 2.66-2.78(1H,m), 2.81(1H,d,J=4.6Hz), 2.92-
 3.08(2H,m), 4.60-4.72(1H,m), 5.20-5.36(1H,m), 6.55(1H,brs),
 6.61(1H,d,J=7.9Hz), 6.92(1H,d,J=7.9Hz), 7.07(1H,s),
 10 7.13(2H,d,J=6.9Hz), 7.16-7.36(3H,m), 7.74(1H,d,J=8.2Hz)

Example 117

2-[(2-amino-3-phenylpropyl)amino]-N-[2-amino-1-[(3-tert-butyl-4-hydroxyphenyl)methyl]ethyl]-3-methyl butanamide

(1) Synthesis of N-[2-(benzoxycarbonylamino)-1-[(3-tert-butyl-4-hydroxyphenyl)methyl]ethyl]-2-(tert-butoxycarbonylamino)-3-methyl butanamide

To a solution of 2.00 g (7.97 mmol) of Tyr(3-tBu)-OMe in a mixture of 1,4-dioxane (15 ml) and water (15 ml), 929 mg (8.76 mmol) of sodium carbonate and 1.91 g (8.75 mmol) of di-tert-butyl dicarbonate were added under cooling with ice and the resulting mixture was stirred for 2 hours. Under cooling with ice, saturated aqueous NH₄Cl was added and the mixture was extracted with chloroform and washed with saturated brine. The organic layer was dried with magnesium sulfate and the solvent was distilled off under reduced pressure; the resulting residue was dissolved in a mixture of ethanol (20 ml) and THF (20 ml); under cooling with ice, 520 mg (23.9 mmol) of lithium borohydride was added to the

solution and the mixture was stirred for 4 hours. To the reaction mixture, 2 N aqueous HCl was added, followed by extraction with chloroform and washing with water and saturated brine. The organic layer was dried with magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 1:1) to give [1-[(3-tert-butyl-4-hydroxyphenyl)methyl]-2-hydroxyethyl]carbamic acid tert-butyl ester in 2.26 g (88%).

To a solution of 2.26 g (7.00 mmol) of the [1-[(3-tert-butyl-4-hydroxyphenyl)methyl]-2-hydroxyethyl]carbamic acid tert-butyl ester in THF (25 ml), 3.67 g (14.0 mmol) of triphenylphosphine, 2.06 g (14.0 mmol) of phthalimide and 2.76 ml (14.0 mmol) of diisopropyl azodicarboxylate were added under cooling with ice and the resulting mixture was stirred for 1 hour. After adding water, the reaction mixture was extracted with ethyl acetate and washed with saturated brine. The organic layer was dried with magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 1:2) to give a mixture containing [1-[(3-tert-butyl-4-hydroxyphenyl)methyl]-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)ethyl]carbamic acid tert-butyl ester.

To a solution in methanol (15 ml) of the mixture containing [1-[(3-tert-butyl-4-hydroxyphenyl)methyl]-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)ethyl]carbamic acid tert-butyl ester, hydrazine monohydrate (2 ml) was added and the

resulting mixture was stirred at room temperature for 4 hours. After filtering, the filtrate was concentrated under reduced pressure and the resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 10:1:0.1) to give [2-amino-1-[(3-tert-butyl-4-hydroxyphenyl)methyl]ethyl]carbamic acid tert-butyl ester in 1.55 g (69%).

To a solution of 1.53 g (4.75 mmol) of [2-amino-1-[(3-tert-butyl-4-hydroxyphenyl)methyl]ethyl]carbamic acid tert-butyl ester in methylene chloride (20 ml), 0.725 ml (5.23 mmol) of triethylamine and 0.746 ml (5.23 mmol) of benzyl chloroformate were added and the resulting mixture was stirred for 15 minutes. Under cooling with ice, saturated aqueous NaHCO₃ was added and the mixture was extracted with methylene chloride and washed with saturated brine. The organic layer was dried with magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 1:1) to give [2-(benzoxycarbonylamino)-1-[(3-tert-butyl-4-hydroxyphenyl)-methyl]ethyl]carbamic acid tert-butyl ester in 1.78 g (82%).

NMR(method g, CDCl₃): δ 1.39(9H,s), 1.40(9H,s), 2.60-2.80(2H,m), 3.08-3.38(2H,m), 3.80-3.94(1H,m), 4.58-4.72(1H,m), 5.10(2H,s), 5.28(1H,brs), 6.59(1H,d,J=7.9Hz), 6.85(1H,d,J=7.9Hz), 7.02(1H,s), 7.34(5H,brs)

To a solution of 402 mg (0.882 mmol) of [2-(benzoxycarbonylamino)-1-[(3-tert-butyl-4-hydroxyphenyl)-methyl]-

ethyl]carbamic acid tert-butyl ester in methylene chloride (2 ml), TFA (2 ml) was added and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was distilled off under reduced pressure and the resulting
5 residue was dissolved in DMF (3 ml); to the solution, 287 mg (1.32 mmol) of Boc-Val, 179 mg (1.32 mmol) of HOBt, 162 mg (1.33 mmol) of DMAP and 254 mg (1.32 mmol) of WSCI·HCl were added and the resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted
10 with ethyl acetate and washed successively with saturated aqueous NaHCO₃, water and saturated brine. The organic layer was dried with magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl
15 acetate:n-hexane = 1:1) to give N-[2-(benzoxycarbonylamino)-1-[(3-tert-butyl-4-hydroxyphenyl)-methyl]ethyl]-2-(tert-butoxycarbonylamino)-3-methyl butanamide in 363 mg (74%).
(2) Synthesis of 2-[(2-amino-3-phenylpropyl)amino]-N-[2-amino-1-[(3-tert-butyl-4-hydroxyphenyl)methyl]ethyl]-3-
20 methyl butanamide

To a solution of 436 mg (0.786 mmol) of N-[2-(benzoxycarbonylamino)-1-[(3-tert-butyl-4-hydroxyphenyl)methyl]ethyl]-2-(tert-butoxycarbonylamino)-3-methyl butanamide in methylene chloride (2 ml), TFA (2 ml)
25 was added and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure and to the residue, saturated aqueous NaHCO₃ was added under cooling with ice and the mixture was

extracted with chloroform and washed with saturated brine. The organic layer was dried with magnesium sulfate and the solvent was distilled off under reduced pressure; the resulting residue was dissolved in MeCN (3 ml) and under
5 cooling with ice, 245 mg (0.866 mmol) of Z-phenylalaninal, 0.1 ml of acetic acid and 98.8 mg (1.57 mmol) of sodium cyanoborohydride were added to the solution, which was then stirred for 3 hours. After adding water, the solution was extracted with chloroform and washed with saturated brine.
10 The organic layer was dried with magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 1:1) to give N-[2-benzoxycarbonylamino-1-[(3-tert-butyl-4-hydroxyphenyl)-methyl]ethyl]-2-[[2-(benzoxycarbonylamino)-3-phenylpropyl]-amino]-3-methyl butanamide in 282 mg (50%).

To a solution of 132 mg (0.183 mmol) of N-[2-benzoxycarbonylamino-1-[(3-tert-butyl-4-hydroxyphenyl)-methyl]ethyl]-2-[[2-(benzoxycarbonylamino)-3-phenylpropyl]-amino]-3-methyl butanamide in methanol (2 ml), 10% palladium
20 carbon (80 mg) was added and the mixture was stirred in a hydrogen atmosphere at room temperature for 2 days. After filtering, the filtrate was concentrated under reduced pressure and the resulting residue was subjected to silica
25 gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 10:1:0.1) to yield 2-[(2-amino-3-phenyl-propyl)amino]-N-[2-amino-1-[(3-tert-butyl-4-hydroxyphenyl)-methyl]ethyl]-3-

methyl butanamide in 24.2 mg (29%).

FAB-MS: 455 (M+H⁺)

NMR (method g, CDCl₃): δ 0.70 (3H, dd, J=2.0, 6.6 Hz),
 0.84 (3H, d, J=6.9 Hz), 1.37 (9H, s), 1.98-2.04 (1H, m), 2.24-
 5 2.86 (9H, m), 2.94-3.12 (1H, m), 4.10-4.26 (1H, m),
 6.62 (1H, d, J=7.9 Hz), 6.87 (1H, d, J=7.9 Hz), 7.00 (1H, s), 7.12-
 7.34 (5H, m)

Example 118

N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methyl-
 10 2-(N-methyl-N-phenylalaninoylamino)butanamide

(1) Synthesis of Z-N,O-dibenzyl-Tyr(3-tBu)-OMe

To a solution of 3.0 g (7.78 mmol) of Z-Tyr(3-tBu)-OMe
 in DMF (20 ml), 0.68 g (17.1 mmol) of sodium hydride was
 added under cooling with ice and the mixture was stirred for
 15 15 minutes; thereafter, 2.3 ml (19.5 mmol) of benzyl bromide
 was added. After stirring for additional 3 hours, saturated
 aqueous NaHCO₃ was added to the reaction mixture, which was
 extracted with ethyl acetate and washed with water and
 saturated brine. The organic layer was dried with anhydrous
 20 magnesium sulfate and concentrated under reduced pressure;
 the resulting residue was subjected to silica gel column
 chromatography (eluting solvent; ethyl acetate:n-hexane =
 1:5) to give Z-N,O-dibenzyl-Tyr(3-tBu)-OMe in 4.14 g (94%).

(2) Synthesis of N-benzyl-2-(4-benzyloxy-3-tert-
 25 butylphenyl)-1-methyl-N-(benzyloxycarbonyl)ethylamine

To a solution of 4.14 g (7.32 mmol) of Z-N,O-dibenzyl-
 Tyr(3-tBu)-OMe in a mixture of ethanol (36 ml) and THF (6
 ml), 11.0 ml (22.0 mmol) of a solution of 2 M lithium

borohydride in THF was added under cooling with ice and the resulting mixture was stirred overnight at room temperature. After adding water, the reaction mixture was extracted with ethyl acetate, washed with saturated brine, dried with
5 anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The resulting residue was dissolved in methylene chloride (50 ml) and under cooling with ice, 2.0 ml (14.4 ml) of triethylamine and 0.72 ml (9.36 mmol) of methanesulfonyl chloride were added in
10 succession and the resulting mixture was stirred for 30 minutes. The reaction mixture was washed with saturated aqueous NaHCO₃ and the organic layer was dried with anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure; there-after, the resulting
15 residue was dissolved in THF (10 ml) and 28.0 ml (28.0 mmol) of a solution of 1 M lithium triethylborohydride in THF was added. After stirring the mixture for 3 hours, water was added under cooling with ice and extraction was effected with methylene chloride. The organic layer was dried with
20 anhydrous magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate:n-hexane = 1:5) to give N-benzyl-2-(4-benzyloxy-3-tert-butylphenyl)-1-methyl-N-(benzyloxycarbonyl)ethylamine in
25 2.35 g (61%).

(3) Synthesis of 2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethylamine

A suspension of 2.35 g (4.50 mmol) of N-benzyl-2-(4-

benzyloxy-3-tert-butylphenyl)-1-methyl-N-

(benzyloxycarbonyl)-ethylamine and 0.50 g of a 20% palladium
hydride on carbon catalyst in methanol (30 ml) was stirred
overnight in a hydrogen atmosphere. After filtering off the
5 catalyst, the solvent was distilled off under reduced
pressure to give 2-(3-tert-butyl-4-hydroxyphenyl)-1-
methylethyl-amine in 0.90 g (96%).

NMR(method g, CDCl₃): δ 1.16(3H,d,J=6.6Hz), 1.39(9H,s),
2.45(1H,dd,J=4.9, 13.3Hz), 2.69(1H,dd,J=4.9,13.3Hz),
10 3.15(1H,m), 3.5(2H,brs), 6.58(1H,d,J=7.9Hz),
6.83(1H,dd,J=1.6,7.9Hz), 7.03(1H,d,J=1.6Hz)

(4) Synthesis of N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-
methylethyl]-3-methyl-2-(methylamino)butanamide

To a solution of 0.31 g (1.50 mmol) of 2-(3-tert-
15 butyl-4-hydroxyphenyl)-1-methylethylamine, 0.40 g (1.50
mmol) of Z-N-Me-Val-OH and 0.30 g (2.25 mmol) of HOBT in DMF
(5 ml), 0.35 ml (2.25 mmol) of DIC was added under cooling
with ice. After being stirred at room temperature for 2
hours, the reaction mixture was diluted with ethyl acetate
20 and washed successively with saturated aqueous NaHCO₃, water
and saturated brine. The organic layer was dried with
anhydrous magnesium sulfate and concentrated under reduced
pressure; the resulting residue was subjected to silica gel
column chromatography (eluting solvent; chloroform:methanol
25 = 125:1) to give 2-[N-(benzyloxycarbonyl)-N-methylamino]-N-
[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-
methylbutanamide in 0.55 g (81%).

A suspension of 0.54 g (1.19 mmol) of 2-[N-(benzyloxy-

carbonyl)-N-methylamino]-N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methylbutanamide and 0.10 g of a 20% palladium hydroxide on carbon catalyst in methanol (8 ml) was stirred in a hydrogen atmosphere for 2 hours.

5 After filtering off the catalyst, the solvent was distilled off under reduced pressure to give N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methyl-2-(methyl-amino)butanamide in 0.36 g (95%).

(5) N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methyl-2-(N-methyl-N-phenylalaninoylamino)butanamide

To a solution of 0.36 g (1.12 mmol) of N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methyl-2-(methyl-amino)butanamide, 0.75 g (2.81 mmol) of Boc-Phe-OH and 0.38 g (2.81 mmol) of HOBT in DMF (5 ml), 0.44 ml (2.81 mmol) of
15 DIC was added under cooling with ice. After being stirred at room temperature for 2.5 days, the reaction mixture was diluted with ethyl acetate and washed successively with saturated aqueous NaHCO₃, water and saturated brine. The organic layer was dried with anhydrous magnesium sulfate and
20 concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; chloroform:methanol = 80:1) to give N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-2-[N-(N-Boc-phenylalaninoyl)-N-methylamino]-3-methylbutanamide in 333 mg (52%).

25 The N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-2-[N-(N-Boc-phenylalaninoyl)-N-methylamino]-3-methylbutanamide (333 mg) was dissolved in methylene chloride (4 ml) and, after adding TFA (2 ml), the solution

was stirred at room temperature for 10 minutes. The solvent was distilled off under reduced pressure and the resulting residue was diluted with methylene chloride and washed with saturated aqueous NaHCO_3 . The resulting residue was

5 subjected to silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 75:1:0.1) to yield N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methyl-2-(N-methyl-N-phenylalaninoylamino)butanamide in 164 mg (60%).

10 EI-MS: 468($\text{M}^+ + 1$)

NMR(method g, CDCl_3): δ 0.72(3/2H,d,J=6.6Hz), 0.81(3/2H,d,J=6.6Hz), 0.93(3/2H,d,J=6.6Hz), 0.94(3/2H,d,J=6.3Hz), 1.07(3/2H,d,J=6.6Hz), 1.08(3/2H,d,J=6.6Hz), 1.37(4H,s), 1.40(5H,s), 2.23-

15 2.42(1H,m), 2.43-2.90(3H,m), 2.75(5/3H,s), 2.84(4/3H,s), 3.19(1/2H,dd,J=4.3,13.8Hz), 3.62(1/2H,m), 3.82-3.88(1H,m), 4.23(1H,m), 4.47(2/5H,d,J=10.9Hz), 6.00(3/5H,d,J=8.2Hz), 6.61(2/5H,d,J=7.9Hz), 6.66(3/5H,dd,J=2.0,7.9Hz), 6.77(3/5H,d,J=7.9Hz), 6.83(2/5H,dd,J=2.0,7.9Hz),

20 6.99(3/5H,d,J=2.0Hz), 7.05(2/5H,d,J=2.0Hz), 7.1-7.4(7H,m), 8.22(3/5H,d,J=8.3Hz)

Example 119

Phe-N-Me-Val-N-Me-Tyr(3-tBu)- NH_2

(1) Synthesis of Z-N-Me-Val-N-Me-Tyr(3-tBu)-OMe

25 To a solution of 3.25 g of Z-N-Me-Val-OH, 2.2 g of N-Me-Tyr(3-tBu)-OMe and 1.88 g of HOBT in DMF (30 ml), DIC (1.9 ml) was added under cooling with ice and the mixture was stirred at room temperature for 23 hours. Water was

added to the reaction mixture and extraction was effected with ether. The extract was washed with saturated brine and the organic layer was dried with sodium sulfate. After distilling off the solvent under reduced pressure, the
5 resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 100:10:1) to give Z-N-Me-Val-N-Me-Tyr(3-tBu)-OMe in 1.96 g (47%).

(2) Synthesis of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

10 To a solution of 1.96 g of Z-N-Me-Val-N-Me-Tyr(3-tBu)-OMe in 1,4-dioxane (40 ml), 2 N NaOH (5 ml) was added at room temperature and the mixture was stirred for 2 hours. The reaction mixture was adjusted to pH 3 with dilute hydrochloric acid and extracted with ethyl acetate. The
15 extract was washed with saturated brine and the organic layer was dried with sodium sulfate. The solvent was distilled off under reduced pressure to give Z-N-Me-Val-N-Me-Tyr(3-tBu)-OH. To a solution of this Z-N-Me-Val-N-Me-Tyr(3-tBu)-OH in THF (20 ml), ethyl chloroformate (0.40 ml)
20 and NMM (0.46 ml) were added under cooling with ice and the mixture was stirred for 15 minutes. Subsequently, ammonia gas was bubbled into the reaction mixture for 5 minutes. The solvent was distilled off under reduced pressure and the precipitating salt was filtered off and washed with ethyl
25 acetate. The solvent was distilled off under reduced pressure and the resulting residue was subjected to silica gel column chromatography (eluting solvent; n-hexane:ethyl acetate = 2:3) to give Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ in

1.17 g (61%).

(3) Synthesis of N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

A mixture of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (1.17 g) and 20% palladium hydroxide on carbon (0.24 g) in methanol
5 (20 ml) was stirred at room temperature in a hydrogen atmosphere for 1 hour. The reaction mixture was filtered and washed with methanol. The solvent was distilled off under reduced pressure and the resulting residue was subjected to silica gel column chromatography (eluting
10 solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 100:10:1) to give N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ in 609 mg (71%).

(4) Synthesis of Z-Phe-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

To a solution of Z-Phe-OH (742 mg) in THF (3 ml),
15 isobutyl chloroformate (0.32 ml) and NMM (0.27 ml) were added under cooling with ice and the mixture was stirred for 15 minutes. Subsequently, a solution of N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (600 mg) in THF (3 ml) was added and the mixture was stirred at room temperature for 10 hours. Water
20 was added to the reaction mixture and extraction was effected with ethyl acetate. The extract was washed with saturated brine, dried with sodium sulfate, and concentrated under reduced pressure. The resulting residue was subjected to silica gel column chromatography (eluting solvent; n-
25 hexane:acetone = 3:2) to give Z-Phe-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ in 611 mg (58%).

(5) Synthesis of Phe-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

A mixture of Z-Phe-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

(610 mg) and 10% palladium carbon (100 mg) in methanol (15 ml) was stirred at room temperature in a hydrogen atmosphere for 17 hours. The reaction mixture was filtered and washed with methanol. The solvent was distilled off under reduced pressure and the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl acetate) to yield Phe-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ in 431 mg (89%).

EI-MS: 511(M⁺+1)

NMR(method g, CDCl₃): δ 0.50(9/10H,d,J=6.3Hz),

0.75(9/10H,d,J=6.6Hz), 0.79(21/10H,d,J=6.9Hz),
0.93(21/10H,d,J=6.6Hz), 1.34(63/10H,s), 1.39(27/10H,s),
2.15-2.99(46/10H,m), 2.46(21/10H,s), 2.78(21/10H,s),
3.02(9/10H,s), 3.03(9/10H,s), 3.15(7/10H,dd,J=14.9,5.9Hz),
3.33(3/10H,dd,J=13.9,6.9Hz), 3.72(7/10H,dd,J=8.9,5.0Hz),
3.91(3/10H,dd,J=8.1,5.1Hz), 4.92(3/10H,d,J=10.9Hz), 5.02-
5.09(14/10H,m), 5.29(7/10H,brs), 5.49(7/10H,dd,J=10.7,5.8Hz),
5.98(7/10H,brs), 6.32(7/10H,d,J=7.9Hz), 6.60-6.67(6/10H,m),
6.72(7/10H,dd,J=7.9,2.0Hz), 6.97(3/10H,dd,J=7.9,2.0Hz),
7.10-7.39(67/10H,m)

Example 120

N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methyl-2-[N-methyl-N-(N-Me-phenylalaninoyl)amino]butanamide

To a solution of 115 mg (0.359 mmol) of N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methyl-2-

(methylamino)butanamide and 170 mg (0.610 mmol) of Boc-N-Me-Phe-OH in methylene chloride (1.5 ml), 318 mg (0.718 mmol) of BOP and 0.10 ml (0.718 mmol) of TEA were added in succession under cooling with ice. After being stirred at

room temperature for 2 days, the reaction mixture was diluted with methylene chloride and washed with water. The organic layer was dried with anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; chloroform:methanol = 150:1) to give N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-2-[N-(N-Boc-N-Me-phenylalaninoyl)-N-methylamino]-3-methylbutanamide in 149 mg (71%).

A portion (145 mg) of the N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-2-[N-(N-Boc-N-Me-phenylalaninoyl)-N-methylamino]-3-methylbutanamide was dissolved in methylene chloride (2 ml) and, after adding TFA (1 ml), the solution was stirred at room temperature for 15 minutes. The solvent was distilled off under reduced pressure and the resulting residue was diluted with methylene chloride and washed with saturated aqueous NaHCO₃. The resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 80:1:0.1) to yield N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methyl-2-[N-methyl-N-(N-Me-phenylalaninoyl)amino]butanamide in 86 mg (72%).

EI-MS: 481(M⁺)

NMR(method g, CDCl₃): δ 0.52(1H,d,J=6.6Hz), 0.78(2H,d,J=6.6Hz), 0.93(3H,d,J=6.3Hz), 1.08(1H,d,J=6.6Hz), 1.13(2H,d,J=6.6Hz), 1.36(5H,s), 1.39(4H,s), 2.1-2.3(1H,m), 2.25(2H,s), 2.32(1H,s), 2.5-2.9(3H,m), 2.59(2H,s), 2.62(1H,s), 3.08(1/2H,d,J=6.6Hz), 3.58(1/2H,t,J=6.3Hz),

3.65-3.73(1/2H,m), 4.07-4.25(3/5H,m), 4.46(2/5H, d,J=11.2Hz),
5.62(1/2H,brs), 6.06(1/2H,d,J=8.3Hz), 6.59-6.64(1H,m), 6.75-
6.94(1H,m), 7.01-7.12(1H,m), 7.2-7.4(6H,m),
8.18(1/2H,d,J=8.3Hz)

5 Example 121

N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-N-Me-3-methyl-2-(N-methyl-N-phenylalaninoylamino)butanamide

(1) Synthesis of 2-(4-benzyloxy-3-tert-butylphenyl)-N-(benzyloxycarbonyl)-N-Me-1-methylethylamine

10 To a solution in ethanol (18 ml) and THF (3 ml) of
1.60 g (3.27 mmol) of Z-N-Me-Phe(3-tBu-4-benzyloxy)-OMe
prepared in accordance with Example 91, 4.9 ml (9.80 mmol)
of a solution of 2 M lithium borohydride in THF was added
under cooling with ice and the mixture was stirred overnight
15 at room temperature. After addition of water, the reaction
mixture was extracted with ethyl acetate and the extract was
washed with saturated brine, dried with anhydrous magnesium
sulfate, and the solvent was distilled off under reduced
pressure. The resulting residue was dissolved in methylene
20 chloride (15 ml); after adding 0.88 ml (6.32 mmol) of
triethylamine and 0.27 ml (3.47 mmol) of methanesulfonyl
chloride successively under cooling with ice, the solution
was stirred for 30 minutes. The reaction mixture was washed
with saturated aqueous NaHCO₃ and the organic layer was
25 dried with anhydrous magnesium sulfate and concentrated
under reduced pressure. The resulting residue was then
subjected to silica gel column chromatography (eluting
solvent; ethyl acetate:n-hexane = 1:2) to give mesylate in

0.88 g (50% in two steps). To a solution of the mesylate (0.88 g, 1.62 mmol) in THF (5 ml), 5.8 ml (5.8 mmol) of a solution of 1 M lithium triethylborohydride in THF was added. After stirring for 1.5 hours, water was added to the
5 reaction mixture under cooling with ice and it was then extracted with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; ethyl
10 acetate:n-hexane = 1:5) to give 2-(4-benzyloxy-3-tert-butyl-phenyl)-N-(benzyloxycarbonyl)-N-Me-1-methylethylamine in 0.50 g (68%).

(2) Synthesis of 2-(3-tert-butyl-4-hydroxyphenyl)-N-Me-1-methylethylamine

15 A suspension of 0.49 g (1.09 mmol) of 2-(4-benzyloxy-3-tert-butyl-phenyl)-N-(benzyloxycarbonyl)-N-Me-1-methylethylamine and 0.10 g of a 20% palladium hydroxide on carbon catalyst in methanol (5 ml) was stirred in a hydrogen atmosphere for 2.5 hours. After filtering off the catalyst,
20 the solvent was distilled off under reduced pressure to give 2-(3-tert-butyl-4-hydroxyphenyl)-N-Me-1-methylethylamine in 0.23 g (96%).

NMR(method g, CDCl₃): δ 1.12(3H,d,J=6.3Hz), 1.38(9H,s), 2.42(s, 3H), 2.64(2H,d,J=6.6Hz), 2.75-2.90(1H,m), 6.55(1H,d,J=7.9Hz),
25 6.84(1H,dd,J=1.6,7.9Hz), 7.04(1H,d,J=1.6Hz)

(3) Synthesis of N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-N-Me-3-methyl-2-methylaminobutanamide

To a solution of 0.22 g (0.994 mmol) of 2-(3-tert-

butyl-4-hydroxyphenyl)-N-Me-1-methylethylamine, 0.55 mg
(2.09 mmol) of Z-N-Me-Val-OH and 0.30 g (1.99 mmol) of HOBT
in DMF (3 ml), 0.31 ml (1.99 mmol) of DIC was added under
cooling with ice. After being stirred at room temperature
5 for 38 hours, the reaction mixture was diluted with ethyl
acetate and washed with saturated aqueous NaHCO₃, water and
saturated brine. The organic layer was dried with anhydrous
magnesium sulfate and concentrated under reduced pressure.
The resulting residue was subjected to silica gel column
10 chromatography (eluting solvent; ethyl acetate:n-hexane =
1:4) to give 2-[N-(benzyloxycarbonyl)-N-methylamino]-N-[2-
(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-N-Me-3-
methylbutanamide in 155 mg (33%).

A solution of 150 mg (0.320 mmol) of 2-[N-(benzyloxy-
15 carbonyl)-N-methylamino]-N-[2-(3-tert-butyl-4-
hydroxyphenyl)-1-methylethyl]-N-Me-3-methylbutanamide and
0.02 g of a 20% palladium hydroxide on carbon catalyst in
methanol (2 ml) was stirred in a hydrogen atmosphere for 3
hours. After filtering off the catalyst, the solvent was
20 distilled off under reduced pressure to give N-[2-(3-tert-
butyl-4-hydroxyphenyl)-1-methylethyl]-N-Me-3-methyl-2-
(methylamino)butanamide in 97 mg (92%).

(4) Synthesis of N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-
methylethyl]-N-Me-3-methyl-2-(N-methyl-N-phenylalaninoyl-
25 amino)butanamide

To a solution of 93 mg (0.278 mmol) of N-[2-(3-tert-
butyl-4-hydroxyphenyl)-1-methylethyl]-N-Me-3-methyl-2-
(methylamino)butanamide and 125 mg (0.473 mmol) of Boc-Phe-

OH in methylene chloride (1.5 ml), 246 mg (0.556 mmol) of BOP and 0.077 ml (0.556 mmol) of TEA were successively added under cooling with ice. After being stirred at room temperature for 2.5 days, the reaction mixture was diluted with methylene chloride and washed with water. The organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure; the resulting residue was subjected to silica gel column chromatography (eluting solvent; chloroform:methanol = 150:1) to give N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-2-[N-(N-Boc-phenylalaninoyl)-N-methylamino]-N-Me-3-methylbutanamide in 108 mg (67%).

The thus obtained N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-2-[N-(N-Boc-phenylalaninoyl)-N-methylamino]-N-Me-3-methylbutanamide (108 mg) was dissolved in methylene chloride (2 ml) and, after adding TFA (1 ml), the solution was stirred at room temperature for 15 minutes. The solvent was distilled off under reduced pressure and the resulting residue was diluted with methylene chloride and washed with saturated aqueous NaHCO₃. The resulting residue was subjected to silica gel column chromatography (eluting solvent consisting of chloroform, methanol and aqueous ammonia at a ratio of 60:1:0.1) to yield N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-N-Me-3-methyl-2-(N-methyl-N-phenylalaninoylamino)butanamide in 71 mg (80%).

EI-MS: 481(M⁺)

NMR(method g, CDCl₃): δ 0.41(3H,d,J=6.6Hz), 0.74(3H,d,J=6.6Hz), 1.08(3H,d,J=6.6Hz), 1.36(9H,s),

2.07-2.24(1H,m), 2.55-2.76(2H,m), 2.81(3H,s),
 2.86-3.00(2H,m), 2.90(3H,s), 3.94(1H,t,J=6.6Hz),
 4.94(1H,d,J=10.9Hz), 5.02-5.11(1H,m), 6.61(1H,d,J=8.3Hz),
 6.89(1H,dd,J=2.0,7.9Hz), 7.00(1H,d,J=1.7Hz), 7.10-7.35(6H,m)

5 Test 1

Motilin receptor binding test

A motilin receptor binding test was conducted in the following manner [Bormans et al., Regul. Peptides, 15, 143 (1986)]. The duodenum was extracted from a slaughtered
 10 rabbit, had the mucous membrane separated and homogenized in 50 mM Tris-HCl buffer to prepare a receptor sample. The sample was incubated together with ¹²⁵I motilin 25 pM and thereafter the radioactivity bound to the receptor was measured. Specific binding was defined as the difference
 15 between the radioactivity in the case of no adding and that in the case of adding a great excess amount of motilin (10⁻⁷ M). The activity of the drug was expressed by IC₅₀ (in nM), as the concentration sufficient to reduce the specific binding by 50%. The results are shown in Table C-1.

20 Test 2

Action on the contraction of a specimen of longitudinal muscle in the duodenum extracted from a rabbit

The action on the motilin-induced contraction of a specimen of longitudinal muscle in the duodenum extracted
 25 from a rabbit was investigated by the following method. A duodenum specimen extracted from a slaughtered rabbit (3 x 10 mm) was suspended in an organ bath (10 ml) such that the longitudinal muscle would run vertically; the bath was

filled with a Krebs solution kept at 28°C. A mixed gas (95% O₂ and 5% CO₂) was continuously bubbled into the Krebs solution and the contraction of the duodenum specimen was recorded isotonically (with a 1-g load) via an isotonic transducer (TD-111T of Nihon Koden, K.K.) The degree of contraction was expressed in relative values, with the contraction by acetylcholine at a dose of 10⁻⁴ M being taken as 100%. The activity of the drug was calculated as pA₂ value indicating its effect on the dose-dependent muscle contraction by the motilin put into the organ bath. The results are shown in Table C-1.

Table C-1

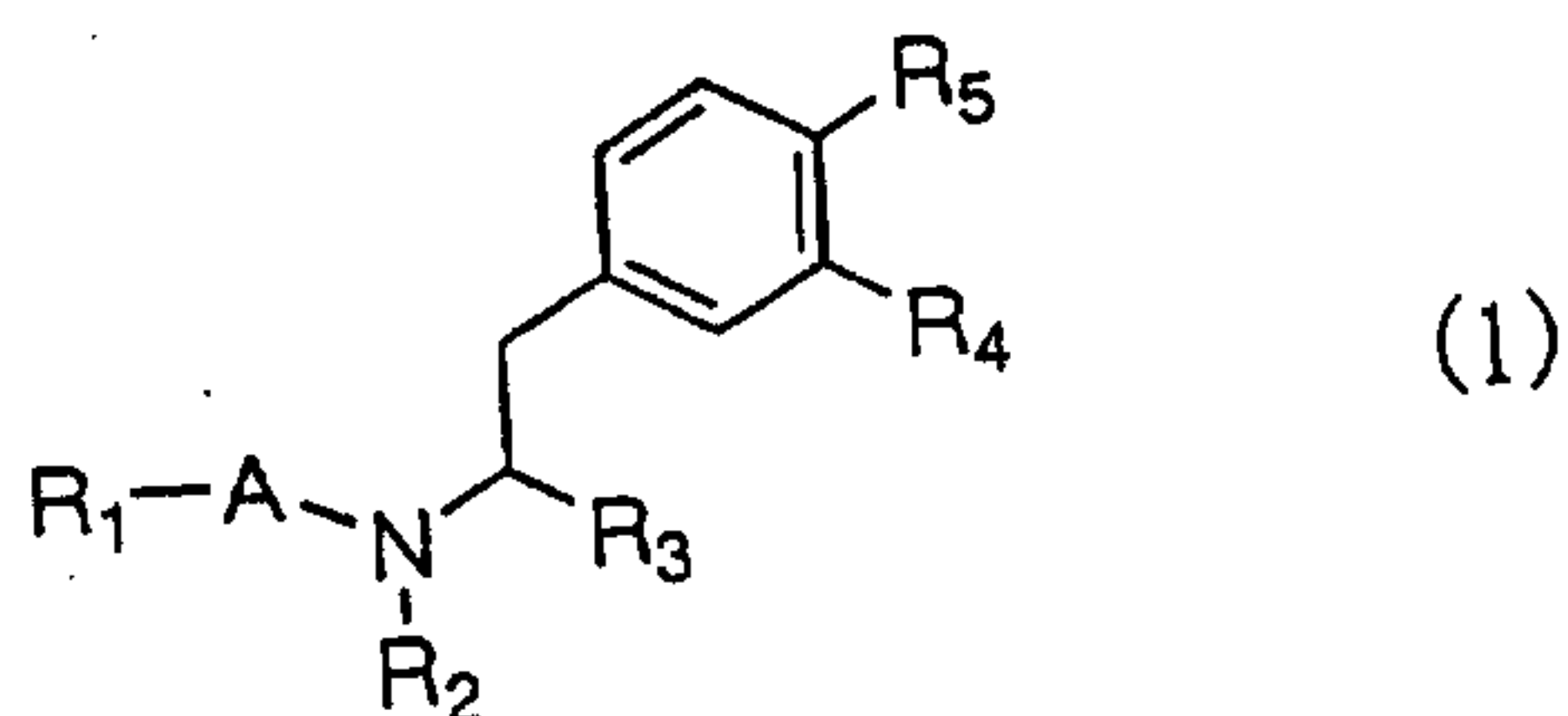
Example No.	Motilin receptor binding test, IC ₅₀ (nM)	Contraction suppressing test, pA ₂
5	12	7.81
18B	3.7	8.58
118	1.9	8.43
119	4.3	8.59

15 Industrial Applicability

The compounds of the invention typically function as a motilin receptor antagonist and are useful as medicines including therapeutics of irritable bowel syndrome.

CLAIMS

1. A compound represented by the general formula (1), a hydrate thereof or a pharmaceutically acceptable salt thereof:



(wherein A is an amino acid residue or an N α -substituted amino acid residue, provided that A binds with -NR₂- to form an amide;

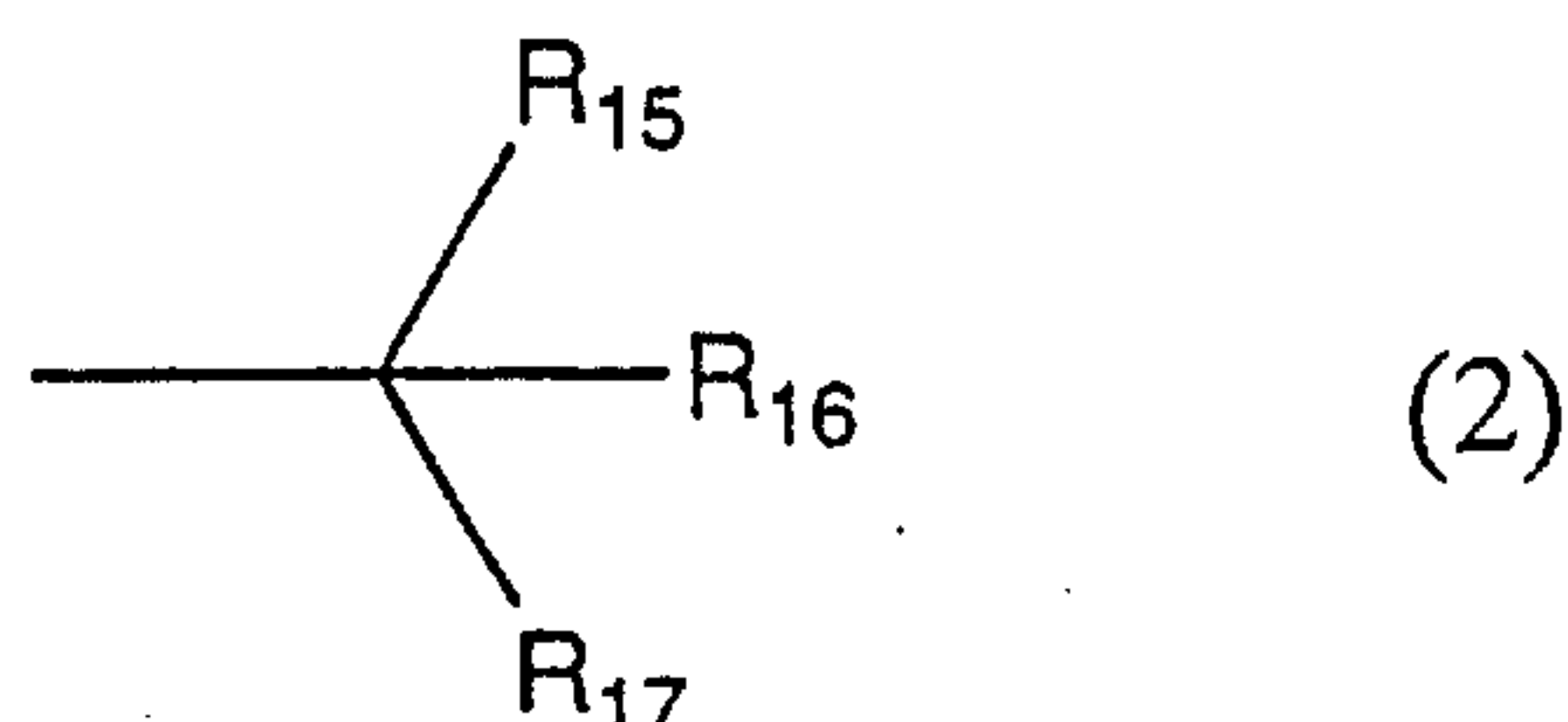
R₁ is an optionally substituted straight-chained or branched alkyl group having 2 - 7 carbon atoms, an optionally substituted straight-chained or branched alkenyl group having 3 - 8 carbon atoms, or an optionally substituted straight-chained or branched alkynyl group having 3 - 8 carbon atoms;

R₂ is a hydrogen atom or an optionally substituted straight-chained or branched alkyl group having 1 - 3 carbon atoms;

R₃ is -CO-R₇, an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, an optionally substituted straight-chained or branched alkenyl group having 2 - 5 carbon atoms or an optionally substituted straight-chained or branched alkynyl group having 2 - 5 carbon atoms;

R₄ is a hydrogen atom, a straight-chained or branched

alkyl group having 1 - 6 carbon atoms, a straight-chained or branched alkenyl group having 2 - 6 carbon atoms, a straight-chained or branched alkynyl group having 2 - 6 carbon atoms, or the general formula (2):



R_5 is a hydrogen atom or $-OR_8$;

R_6 is an optionally substituted straight-chained or branched alkyl group having 1 - 6 carbon atoms, an optionally substituted straight-chained or branched alkenyl group having 2 - 7 carbon atoms, an optionally substituted alkynyl group having 2 - 7 carbon atoms, a cycloalkyl group having 3 - 7 carbon atoms that may be fused to a benzene ring or a heterocyclic ring, an optionally substituted aromatic ring having 6 - 12 carbon atoms, an optionally substituted saturated or unsaturated heterocyclic ring having 3 - 12 carbon atoms, $-N(R_9)R_{10}$ or $-OR_{11}$;

R_7 is a hydrogen atom, an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, a cycloalkyl group having 3 - 7 carbon atoms, $-N(R_{12})R_{13}$ or $-OR_{14}$;

R_8 is a hydrogen atom or a straight-chained alkyl group having 1 - 4 carbon atoms;

R_9 and R_{10} , which may be the same or different, each represent a hydrogen atom, an optionally substituted

straight-chained or branched alkyl group having 1 - 5 carbon atoms, an optionally substituted straight-chained or branched alkenyl group having 2 - 6 carbon atoms, an optionally substituted straight-chained or branched alkynyl group having 2 - 6 carbon atoms, a cycloalkyl group having 3 - 6 carbon atoms that may be fused to a benzene ring or a heterocyclic ring, or an optionally substituted aromatic ring having 6 - 12 carbon atoms;

R_{11} is an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, an optionally substituted straight-chained branched alkenyl group having 2 - 6 carbon atoms, an optionally substituted straight-chained or branched alkynyl group having 2 - 6 carbon atoms, a cycloalkyl group having 3 - 6 carbon atoms that may be fused to a benzene ring or a heterocyclic ring, or an optionally substituted aromatic ring having 6 - 12 carbon atoms;

R_{12} and R_{13} , which may be the same or different, each represent a hydrogen atom, a straight-chained or branched alkyl group having 1 - 4 carbon atoms or a cycloalkyl group having 3 - 7 carbon atoms;

R_{14} is a hydrogen atom, a straight-chained or branched alkyl group having 1 - 6 carbon atoms, or a cycloalkyl group having 3 - 7 carbon atoms;

R_{15} is a hydrogen atom or a methyl group;

R_{16} and R_{17} , when taken together, represent a cycloalkyl or cycloalkenyl group having 3 - 7 carbon atoms).

2. The compound according to claim 1, a hydrate thereof

or a pharmaceutically acceptable salt thereof, wherein A in the general formula (1) is valine (Val), leucine (Leu), isoleucine (Ile), phenylalanine (Phe), tyrosine (Tyr), tryptophan (Trp), phenylglycine (Phg), hydroxyproline (Hyp), homophenylalanine (Hph), cyclohexylglycine (Chg), cyclohexylalanine (Cha), tert-leucine (Tle), 2-thienylalanine (Thi), N-methylvaline (N-Me-Val), N-methylleucine (N-Me-Leu), N-methylisoleucine (N-Me-Ile), N-methylphenylalanine (N-Me-Phe), N-methylphenylglycine (N-Me-Phg), N-methylcyclohexylalanine (N-Me-Cha) or N-methyl-tert-leucine (N-Me-Tle).

3. The compound according to any one of claims 1 and 2, a hydrate thereof or a pharmaceutically acceptable salt thereof, wherein R_1 in the general formula (1) is a phenylalaninoyl group, a N-Me-phenylalaninoyl group, a β -(3-indolyl)alaninoyl group, a tyrosinoyl group, a β -(2-thienyl)alaninoyl group, a β -(2-furyl)alaninoyl group, a β -cyclohexylalaninoyl group, a 3-phenylbutyryl group, a 1-benzocyclobutylcarbonyl group, a benzylaminocarbonyl group or a benzyloxycarbonyl group.

4. The compound according to any one of claims 1 - 3, a hydrate thereof or a pharmaceutically acceptable salt thereof, wherein R_2 in the general formula (1) is a hydrogen atom or a methyl group.

5. The compound according to any one of claims 1 - 4, a hydrate thereof or a pharmaceutically acceptable salt thereof,

wherein R_3 in the general formula (1) is an amido group, an

N-methylamido group, a methyl group or an aminomethyl group.

6. The compound according to any one of claims 1 - 5, a hydrate thereof or a pharmaceutically acceptable salt thereof,

wherein R_4 in the general formula (1) is an isopropyl group, a tert-butyl group (tBu), a 1,1-dimethylpropyl group or a 1,1-dimethyl-2-propenyl group.

7. The compound according to any one of claims 1 - 6, a hydrate thereof or a pharmaceutically acceptable salt thereof, wherein R_5 in the general formula (1) is a hydroxyl group or a methoxy group.

8. The compound according to claim 1, a hydrate thereof or a pharmaceutically acceptable salt thereof, wherein A in the general formula (1) is valine (Val), leucine (Leu), isoleucine (Ile), phenylalanine (Phe), tyrosine (Tyr), tryptophan (Trp), phenylglycine (Phg), hydroxyproline (Hyp), homophenylalanine (Hph), cyclohexylglycine (Chg), cyclohexylalanine (Cha), tert-leucine (Tle), 2-thienylalanine (Thi), N-methylvaline (N-Me-Val), N-methylleucine (N-Me-Leu), N-methylisoleucine (N-Me-Ile), N-methylphenylalanine (N-Me-Phe), N-methylphenylglycine (N-Me-Phg), N-methylcyclohexylalanine (N-Me-Cha) or N-methyl-tert-leucine (N-Me-Tle); R_1 is a phenylalaninoyl group, a N-Me-phenylalaninoyl group, a β -(3-indolyl)alaninoyl group, a tyrosinoyl group, a β -(2-thienyl)alaninoyl group, a β -(2-furyl)alaninoyl group, a β -cyclohexylalaninoyl group, a 3-phenylbutyryl group, a 1-benzocyclobutylcarbonyl group, a benzylaminocarbonyl group or a benzyloxycarbonyl group; R_2

is a hydrogen atom or a methyl group; R_3 is an amido group, an N-methylamido group, a methyl group or an aminomethyl group; R_4 is an isopropyl group, a tert-butyl group (tBu), a 1,1-dimethylpropyl group or a 1,1-dimethyl-2-propenyl group; and R_5 is a hydroxyl group or a methoxy group.

9. The compound according to claim 1, a hydrate thereof or a pharmaceutically acceptable salt thereof which are selected from the group of compounds consisting of Phe-Phg-Tyr(3-tBu)-NH₂, Phe-N-Me-D-Phg-Tyr(3-tBu)-NH₂, Phe-Phe-Tyr(3-tBu)-NH₂, Phe-Cha-Tyr(3-tBu)-NH₂, Phe-Val-Tyr(3-tBu)-NH₂, Phe-Leu-Tyr(3-tBu)-NH₂, Phe-Tyr-Tyr(3-tBu)-NH₂, Phe-Hph-Tyr(3-tBu)-NH₂, Phe-Ile-Tyr(3-tBu)-NH₂, Trp-Phg-Tyr(3-tBu)-NH₂, Cha-Phg-Tyr(3-tBu)-NH₂, Phe-Val-N-Me-Tyr(3-tBu)-NH₂, Phe-Phg-Tyr(3-tBu)-NHMe, N-(benzylaminocarbonyl)-N-Me-D-Phe-Tyr(3-tBu)-NH₂, N-(S)-3-phenylbutyryl-Phg-Tyr(3-tBu)-NH₂, N-(2-amino-3-phenylpropyl)-Phg-Tyr(3-tBu)-NH₂, N-(2-amino-3-phenylpropyl)-Val-Tyr(3-tBu)-NH₂, N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methyl-2-(N-methyl-N-phenylalaninoylamino)butanamide, Phe-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂, and N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl]-3-methyl-2-[N-methyl-N-(N-Me-phenylalaninoyl)amino]butanamide.

10. A medicine containing the compound according to any one of claims 1 - 9 as an active ingredient.

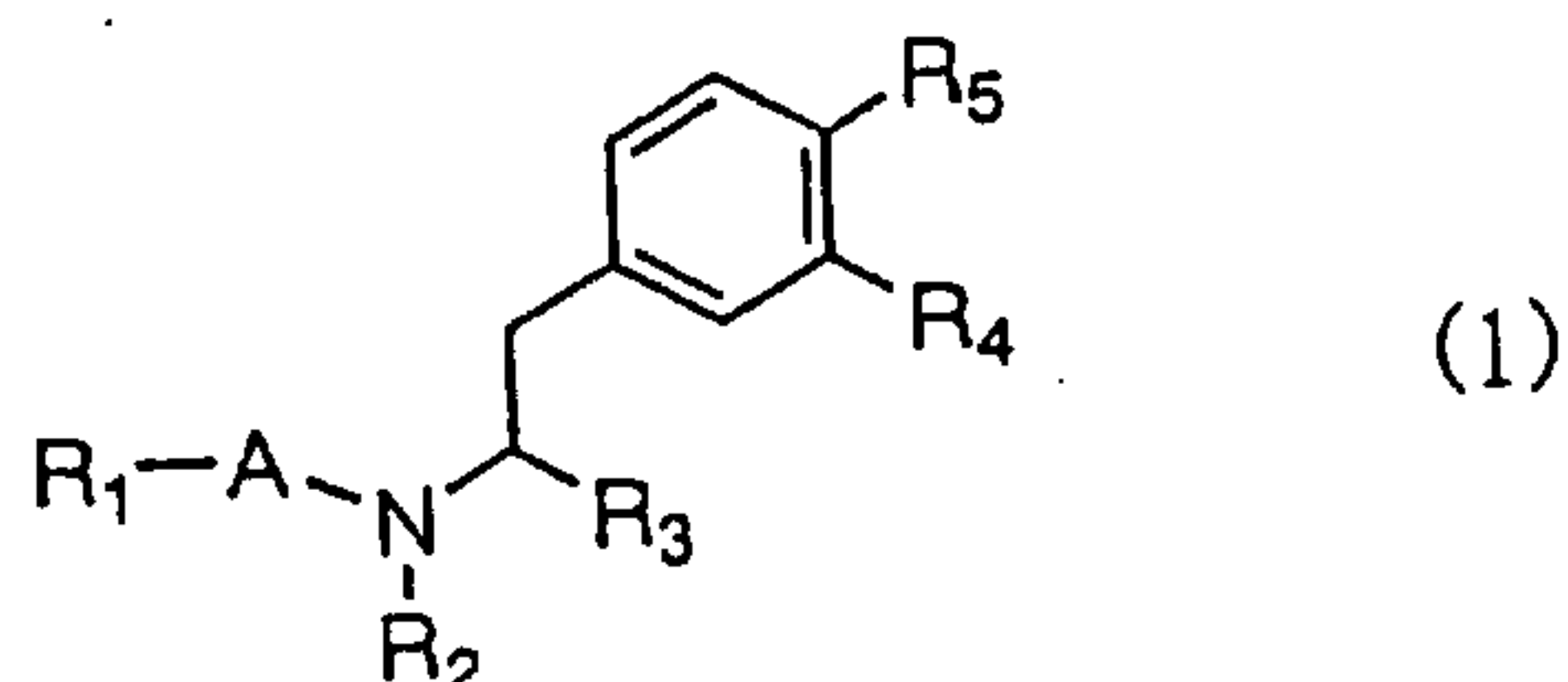
11. A motilin receptor antagonist containing the compound according to any one of claims 1 - 9.

12. A gastrointestinal motility suppressor containing the compound according to any one of claims 1 - 9 as an active

ingredient.

13. A therapeutic of hypermotilinemia containing the compound according to any one of claims 1 - 9 as an active ingredient.

14. A compound represented by the general formula (1), a hydrate thereof or a pharmaceutically acceptable salt thereof:



(wherein A is an amino acid residue or an N α -substituted amino acid residue other than an N-substituted glycine, provided that A binds with -NR₂- to form an amide;

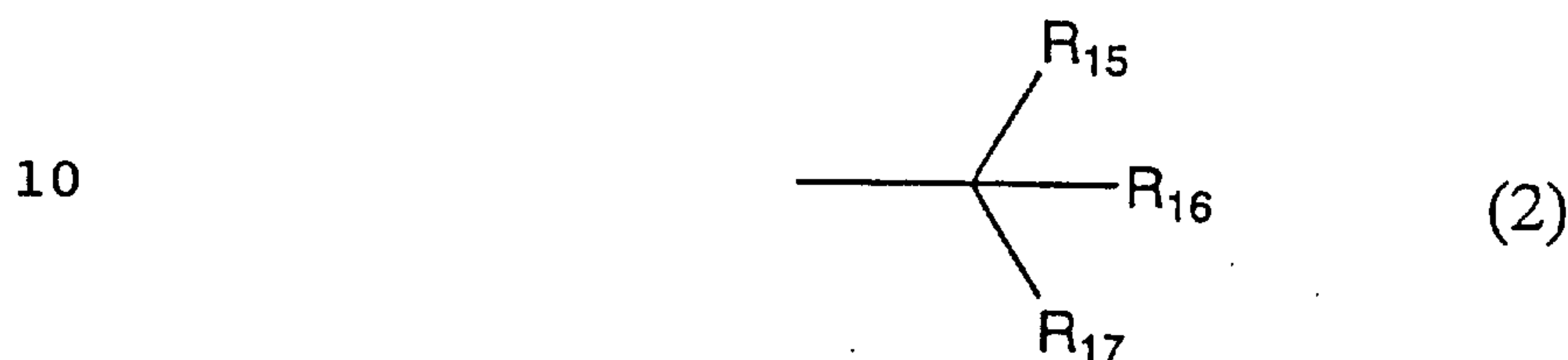
R₁ is an optionally substituted straight-chained or branched alkyl group having 2 - 7 carbon atoms, an optionally substituted straight-chained or branched alkenyl group having 3 - 8 carbon atoms, or an optionally substituted straight-chained or branched alkynyl group having 3 - 8 carbon atoms;

R₂ is a hydrogen atom or an optionally substituted straight-chained or branched alkyl group having 1 - 3 carbon atoms;

R₃ is -CO-R₇, an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, an optionally substituted straight-chained or branched alkenyl group having 2 - 5 carbon atoms or an optionally

substituted straight-chained or branched alkynyl group having 2 - 5 carbon atoms;

R_4 is a straight-chained or branched alkyl group having 1 - 6 carbon atoms, a straight-chained or branched alkenyl group having 2 - 6 carbon atoms, a straight-chained or branched alkynyl group having 2 - 6 carbon atoms, or the general formula (2):



R_5 is a hydrogen atom or $-OR_8$;

R_6 is an optionally substituted straight-chained or branched alkyl group having 1 - 6 carbon atoms, an optionally substituted straight-chained or branched alkenyl group having 2 - 7 carbon atoms, an optionally substituted alkynyl group having 2 - 7 carbon atoms, a cycloalkyl group having 3 - 7 carbon atoms that may be fused to a benzene ring or a heterocyclic ring, an optionally substituted aromatic ring having 6 - 12 carbon atoms, an optionally substituted saturated or unsaturated heterocyclic ring having 3 - 12 carbon atoms, $-N(R_9)R_{10}$ or $-OR_{11}$;

R_7 is a hydrogen atom, an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, a cycloalkyl group having 3 - 7 carbon atoms, $-N(R_{12})R_{13}$ or $-OR_{14}$;

R_8 is a hydrogen atom or a straight-chained alkyl

group having 1 - 4 carbon atoms;

R_9 and R_{10} , which may be the same or different, each represent a hydrogen atom, an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, an optionally substituted straight-chained or branched alkenyl group having 2 - 6 carbon atoms, an optionally substituted straight-chained or branched alkynyl group having 2 - 6 carbon atoms, a cycloalkyl group having 3 - 6 carbon atoms that may be fused to a benzene ring or a heterocyclic ring, or an optionally substituted aromatic ring having 6 - 12 carbon atoms;

R_{11} is an optionally substituted straight-chained or branched alkyl group having 1 - 5 carbon atoms, an optionally substituted straight-chained branched alkenyl group having 2 - 6 carbon atoms, an optionally substituted straight-chained or branched alkynyl group having 2 - 6 carbon atoms, a cycloalkyl group having 3 - 6 carbon atoms that may be fused to a benzene ring or a heterocyclic ring, or an optionally substituted aromatic ring having 6 - 12 carbon atoms;

R_{12} and R_{13} , which may be the same or different, each represent a hydrogen atom, a straight-chained or branched alkyl group having 1 - 4 carbon atoms or a cycloalkyl group having 3 - 7 carbon atoms;

R_{14} is a hydrogen atom, a straight-chained or branched alkyl group having 1 - 6 carbon atoms, or a cycloalkyl group having 3 - 7 carbon atoms;

R_{15} is a hydrogen atom or a methyl group;

R_{16} and R_{17} , when taken together, represent a cycloalkyl or cycloalkenyl group having 3 - 7 carbon atoms).