Studies on Neurokinin Antagonists. 3. Design and Structure-Activity Relationships of New Branched Tripeptides N^{α}-(Substituted L-aspartyl, L-ornithyl, or L-lysyl)-*N*-methyl-*N*-(phenylmethyl)-L-phenylalaninamides as Substance P Antagonists†

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As an extension of our study on discovering a novel substance P (SP) antagonist, we designed new branched tripeptides containing L-aspartic acid (2 and 5), L-ornithine (3 and 6), and L-lysine (4 and 7) by reconstructing the structure of the previously reported tripeptide SP antagonist [Ac-Thr-D-Trp(CHO)-Phe-NMeBzl (1), FR113680]. The strategy for this design was based on the postulate that the dipeptide half D-Trp(CHO)-Phe-NMeBzl in 1 is essential for receptor recognition. Molecular modeling studies implied that these newly designed tripeptides could mimic the spatial orientations of the essential dipeptide structure. As expected, all of these compounds potently inhibited ^{3}H-SP (1 nM) binding to guinea pig lung membranes in the 10^{-8} M range. The 1*H*-indol-3-ylcarbonyl derivatives (5-7) were slightly more potent than the corresponding 1*H*-indol-2-ylcarbonyl derivatives (2-4), as predicted by the molecular modeling studies. The structure-activity relationships studies on the selected 1*H*-indol-3-ylcarbonyl derivatives indicated that the threonine moiety at the side chain can be modified into a variety of structures without any significant loss of the activity. Furthermore in the L-lysine series, even dipeptide compounds having nothing or a simple acyl group at the ϵ-amino group, such as N^{α}-[N^{α}-(1*H*-indol-3-ylcarbonyl)-L-lysyl]-*N*-methyl-*N*-(phenylmethyl)-L-phenylalaninamide (**18b**), exhibited potent activity. These dipeptides belong to a new structural class of SP antagonist.

Introduction

Substance P (SP), a member of the neurokinin family,[1] exerts its function by binding to the NK_1 receptor.[2] Of the implied physiological roles of SP, we have been particularly interested in its involvement in asthma which is now considered to be caused, at least in part, through the "neurogenic inflammation" mechanism.[3] Although new potent peptide type[4,5] and nonpeptide type[6-9] of SP antagonists have recently been disclosed, we have independently been working on discovering a novel SP antagonist. Indeed, in the preceding papers[10,11] we reported the design and structure-activity relationships (SAR) of a novel tripeptide SP antagonist, N^{α}-[N^{α}-(N^{α}-acetyl-L-threonyl)-N^{1}-formyl-D-tryptophyl]-*N*-methyl-*N*-(phenylmethyl)-L-phenylalaninamide [Ac-Thr-D-Trp(CHO)-Phe-NMeBzl (1), FR113680]. This newly discovered SP antagonist acted specifically on the NK_1 receptor[12,13] and also exhibited potent *in vitro* and *in vivo* activities.[14] In this paper, we report our continuing studies in this area and the discovery of a new structural type of SP antagonist by utilizing 1 as a lead compound.

Design of New Branched Tripeptides

As previously reported,[10,11] the SAR studies on 1 revealed that the D-Trp(CHO)-Phe-NMeBzl structure including the stereochemistry is essential for receptor recognition and also that the N^{α}-acetylthreonine part is necessary but variable.[15] It seemed likely, therefore, that a different type of compound might still exert activity, if it could mimic the desired spatial positions of the essential components in 1 (presumably the indole nucleus and the two benzene rings). We thus designed some new branched tripeptides through the chemical modification of 1 (Scheme I). The strategy for this design was based on the following considerations. We initially decided to keep the Phe-NMeBzl substructure unaltered and to modify the other parts. In order to introduce the remaining essential component, an indole nucleus, we attached an additional α-amino acid to the α-amino part in the Phe-NMeBzl structure. Furthermore, substitution of an indolylcarbonyl group at the α-amino part in a newly introduced α-amino acid would be one of the possible approaches providing the proper spatial position for the indole nucleus. In this regard, the configuration of the α-amino acid would be L, when compared to the D-configuration of the tryptophan in 1. We thus chose L-aspartic acid, L-ornithine, and L-lysine for this purpose, due to the possibility that an additional appendage can be introduced into their side chains. Subsequently we decided on concrete structures of the indolylcarbonyl substituent and the L-threonine component. We attempted to synthesize both 1*H*-indol-2-ylcarbonyl and 1*H*-indol-3-ylcarbonyl derivatives, although the molecular modeling study described later implies that the 3-ylcarbonyl derivative is preferable. The formyl group at the indole nitrogen, which was shown to impart a significant increase of activity,[10] was omitted because of the difficulty of its synthesis. As an appendage which corresponds to the N^{α}-acetylthreonine moiety in 1,

† A part of this paper was presented at the International Symposium on Substance P and Related Peptides—Pain, Inflammation, Visceral and CNS Functions (November 3-6, Shizuoka in Japan, 1992). Abbreviations follow IUPAC-IUB Joint Commission on Biochemical Nonemclature for amino acids and peptides: *Eur. J. Biochem.* 1980, *138*, 9-37. Additional abbreviations used herein are as follows: WSCD, 1-ethyl-3-[3-(*N*,*N*-dimethylamino)propyl]carbodiimide; HOBT, 1-hydroxybenzotriazole; DMF, dimethylformamide; IPE, diisopropyl ether; THF, tetrahydrofuran.

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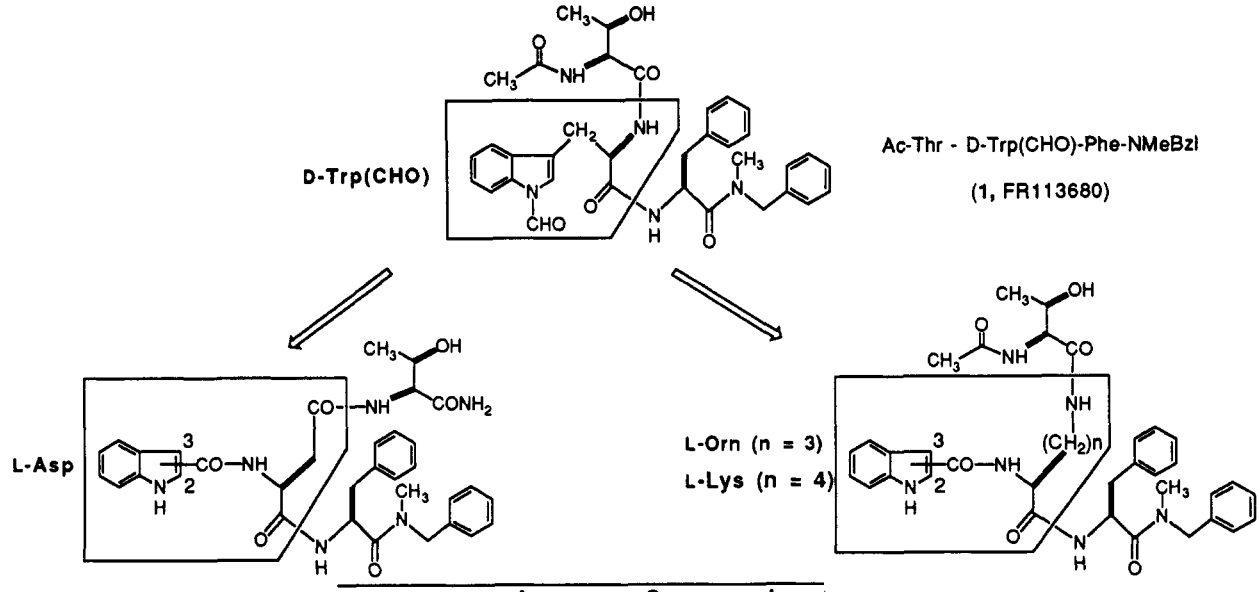
Scheme I. Design of New Branched Tripeptides



	L-Asp	L-Orn	L-Lys
2-position	2	3	4
3-position	5	6	7

we introduced an L-threoninamide into the side chain of L-aspartic acid, and a N^{α}-acetylthreonine into the side chains of L-ornithine and L-lysine. The branched tripeptides **2–7** which were designed in this way can be classified as a novel type of peptide SP antagonists. It would be expected that the indole nucleus and the two benzene rings in these molecules mimic the desired spatial orientations and thereby contribute to exerting SP antagonist activity.

Molecular Modeling Study

To better understand the above design concept we conducted a computer-assisted molecular modeling study on the newly designed tripeptides **2–7** and their parent compound **1**. The purpose was to obtain more precise information as to how closely these compounds resemble each other in terms of spatial orientations of the essential components for receptor recognition. We therefore adopted an in-house program, FIT, which is designed to inspect the similarity of spatial orientations of two or more molecules by superimposing some selected points in them.[16]

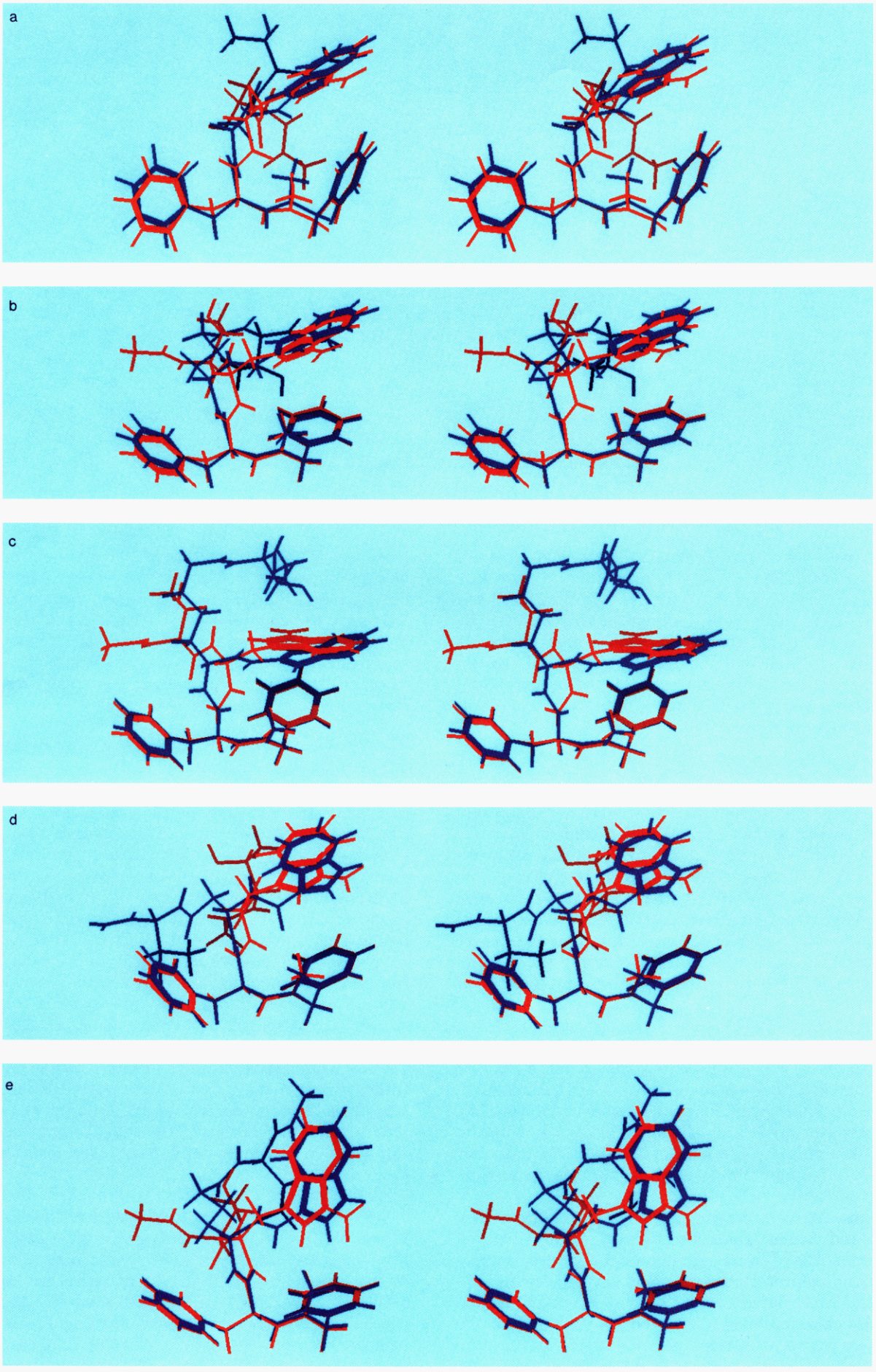
As the starting conformation of **1** for the superimposition procedure,[17] we arbitrarily selected one of the low-energy conformations, which were obtained through molecular mechanics (MM) calculations using MAXIMIN2,[18] because we had no information on its bioactive conformation. As the starter for **2–7**, on the other hand, we chose the energy-minimized conformation in which the molecular geometry of the superimposed parts is as close as possible to that of **1**.[19]

The results of superimposition (Figure 1) indicated that all sets of **1** and each branched tripeptide seem to match well around the essential components for receptor recognition, namely the indole part and two benzene rings in the Phe-NMeBzl structure. The extent of superimposition could be more precisely estimated by rms value of the distances between all corresponding atoms and also by calculated energy penalty for conformation change through the superimposition procedure. It was indicated from these data (Table I) that all the branched tripeptides could be superimposable on **1** within the allowed energy level. Furthermore, the 1*H*-indol-3-ylcarbonyl derivatives (**5–7**) seemed to be more preferable than the corresponding 1*H*-indol-2-ylcarbonyl derivatives (**2–4**). These results would not necessarily predict the desired activity of newly designed branched tripeptides but at least gave us the motivation to synthesize them.

Chemistry

The branched tripeptides **2** and **5** containing an L-aspartic acid were synthesized along the routes as depicted in Scheme II. The starting dipeptide, Boc-Asp(OBzl)-Phe-NMeBzl (**8**), was prepared from *N*-methyl-*N*-(phenylmethyl)-L-phenylalaninamide hydrochloride[11] by the mixed anhydride method. After removing the Boc group by treatment with hydrochloric acid in dioxane, the resulting amine hydrochloride was acylated with 1*H*-indole-2-carboxylic acid by the WSCD–HOBT method[20] to give **9**. Compound **10** was also produced in good yield from the corresponding amine hydrochloride using 1*H*-indole-3-carbonyl chloride[21] after silylation with bis(trimethylsilyl)acetamide. The benzyl esters in **9** and **10** were cleaved by catalytic hydrogenation and subsequently the obtained carboxylic acids **11** and **12** were condensed with a threoninamide by the WSCD–HOBT method to afford desired compounds **2** and **5**. In order to examine the influence of modification at the β-carboxylic acid in compound **5**, four more derivatives **13a–d** were similarly prepared.

As shown in Scheme III, the branched tripeptides containing an L-ornithine (**3** and **6**) and an L-lysine (**4** and **7**) were produced from the starting dipeptides **14a,b**, which were prepared similarly to **8**. These dipeptides were converted into 1*H*-indol-2-ylcarbonyl derivatives **15a,b** and 1*H*-indol-3-ylcarbonyl derivatives **16a,b** by the same procedures as described in the aspartic acid series. The benzyloxycarbonyl (Z) groups of **15a,b** and **16a,b** were cleaved by catalytic hydrogenation in the presence of hydrochloric acid, and then the obtained amine hydro-


a
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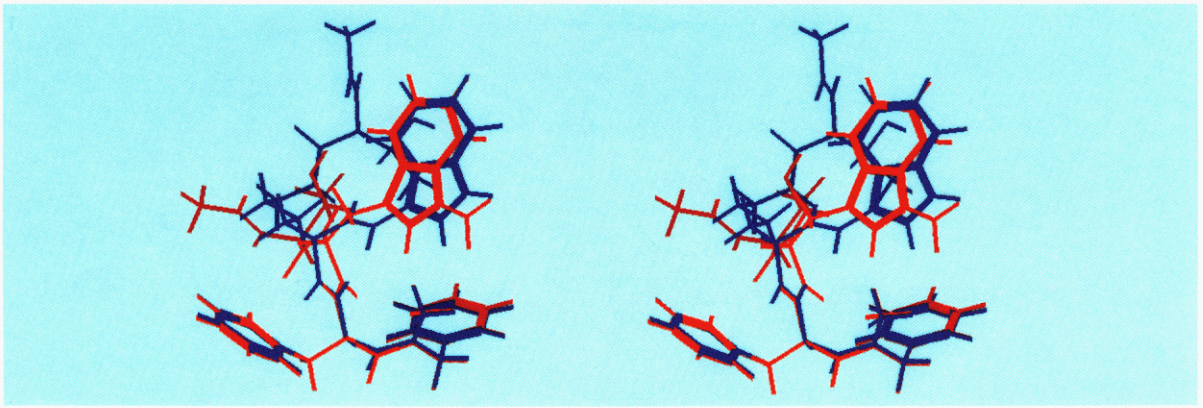
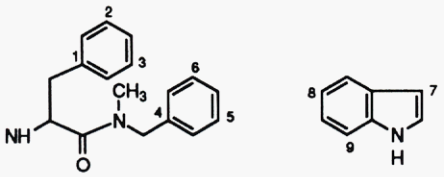


Figure 1. Stereoview of the three-dimentional structures of newly designed tripeptides **2–7** (in blue) and compound **1** (in red), after superimposing procedures using an in-house program FIT: a–c, 1*H*-indol-2-ylcarbonyl derivatives **2–4**; d–f: 1*H*-indol-3-ylcarbonyl derivatives **5–7**.

Table I. Similarity of Spatial Orientations of the Essential Components for Receptor Recognition in New Branched Tripeptides **2–7** and Their Parent Compound **1**



atom number	distance between two atoms (Å)[a]					
	2	**3**	**4**	**5**	**6**	**7**
1	0.03	0.01	0.02	0.02	0.02	0.02
2	0.80	0.71	0.15	0.25	0.09	0.03
3	0.77	0.71	0.21	0.13	0.08	0.10
4	0.32	0.14	0.06	0.08	0.07	0.07
5	0.19	0.13	0.10	0.08	0.10	0.07
6	0.08	0.12	0.06	0.05	0.07	0.14
7	1.05	1.53	2.04	1.34	1.19	1.23
8	0.70	1.02	1.32	0.71	0.24	0.20
9	0.00	0.01	0.05	0.21	0.56	0.61
rms (Å)[b]	0.57	0.70	0.82	0.52	0.45	0.47
energy penalty[c] (kcal/mol)	6.2	13.2	12.4	6.4	4.6	8.1
energy penalty for compound 1[d]	7.0	6.8	10.5	4.3	4.2	4.2

[a] The distance between corresponding two atoms after superimposing compounds **2–7** with the parent compound **1**. The atoms were selected as noted in ref 17 and are numbered as shown above. [b] Root mean square value of the distances. [c] The energy difference of compounds **2–7** between the two structures, before and after superimposition with compound **1**. [d] The energy difference of compound **1** between the two structures, before and after superimposition with compounds **2–7**.

chlorides **17a,b** and **18a,b** were converted into desired compounds **3**, **4**, **6**, and **7** through the following three-step sequence: condensation with Boc-threonine by the WSCD–HOBT method, deprotection of the Boc group by treatment with hydrochloric acid, and acetylation with acetic anhydride. To elucidate the role of the ε-side chain in compound **7**, the following nine L-lysine derivatives, **22a–d**, **23**, and **24a–d**, were synthesized. The branched tripeptides **22a–d** were produced from **18b** and the corresponding protected amino acids by methods similar to that of **7**. Acylated L-lysine derivatives **23** and **24a–d** were also obtained from **18b** by condensation with *N*,*N*-diethyl-β-alanine using the WSCD–HOBT method and by treatment with an appropriate acylating agent, respectively. D-Lysine analog **19** was obtained from the D-lysine isomer of **14b**, according to the method used in the synthesis of **7** (scheme not shown).

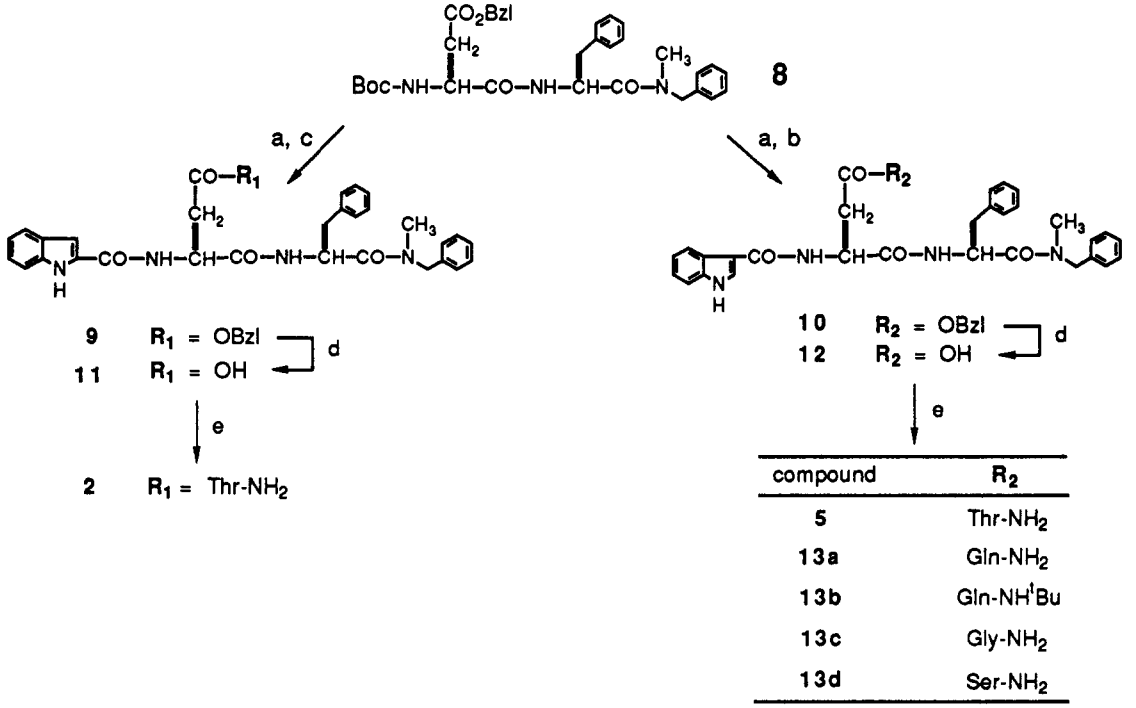
Several branched tripeptides having no indole moiety at the α-amino termini were synthesized for SAR studies (Scheme IV). Removal of the β-benzyl ester of **8** by catalytic hydrogenation and subsequent condensation with threoninamide yielded Boc derivative **25a**, which was converted into unsubstituted compound **25b** by deprotection of the Boc group. Boc derivative **26a** was prepared from **14b** through a four-step sequence: cleavage of the Z group by catalytic hydrogenation, coupling of Z-threonine, catalytic hydrogenation, and acetylation with acetic anhydride. Cleavage of the Boc group of **26a** produced unsubstituted compound **26b**, which was derivatized with acetic anhydride and benzoyl chloride to afford **26c** and **26d**, respectively.

Structure–Activity Relationships

To evaluate the activity of new branched tripeptides **2–7** and their derivatives, we employed a receptor binding assay using guinea pig lung membranes and tritium-labeled SP. As shown in Table II, all of compounds **2–7** exhibited significant activity, albeit with a several times reduced potency, when compared to the parent compound **1**, which has an IC_{50} value of $(5.8 \pm 0.78) \times 10^{-9}$ M, as reported in the preceding paper.[11] However, the IC_{50} values of these compounds still remain in the 10^{-8} M range, although the L-ornithine derivative **3**, having an 1*H*-indol-2-ylcarbonyl group, is an exception (10^{-7} M range). The L-lysine derivative **7**, having a 1*H*-indol-3-ylcarbonyl group, was found to be the most potent, exhibiting a potency of about half of that of the parent tripeptide **1**. The other 1*H*-indol-3-ylcarbonyl derivatives (L-aspartic acid **5** and L-ornithine **6**) and L-lysine derivative **4**, having a 1*H*-indol-2-ylcarbonyl group, were slightly less potent than **7**. It was obviously indicated that the 1*H*-indol-3-ylcarbonyl derivatives were significantly more potent than the corresponding 1*H*-indol-2-ylcarbonyl derivatives, as shown in each set of **2** vs **5** and **3** vs **6**, although the difference was quite small in the case of L-lysine derivatives **4** and **7**. These results seem to be, at least qualitatively, consistent with the speculation based on the above mentioned molecular modeling study.

We subsequently implemented chemical modification of the selected L-aspartic acid and L-lysine derivatives (**5** and **7**) having a 1*H*-indol-3-ylcarbonyl group. In this study we focused on the appendage parts, namely the threon-

Scheme II.[a] Synthesis of Di- and Tripeptide Derivatives Containing L-Aspartic Acid



compound	R_2
5	Thr-NH_2
13a	Gln-NH_2
13b	Gln-NH^tBu
13c	Gly-NH_2
13d	Ser-NH_2

[a] (a) HCl, dioxane–CH_2Cl_2; (b) 1*H*-indole-3-carbonyl chloride, bis(trimethylsilyl)acetamide, CH_2Cl_2; (c) 1*H*-indole-2-carboxylic acid, WSCD–HOBT, DMF; (d) H_2, Pd/C, EtOH; (e) amino acid amides, WSCD–HOBT, DMF.

inamide in **5** and the N^{α}-acetylthreonine in **7**, and on the indolylcarbonyl moiety as well. In the aspartic acid series (Table III), the threoninamide part was modified into other amino acid structures (**13a–d**). These four compounds were comparable in activity to compound **5**, with IC_{50} values of 10^{-8} M range, suggesting that the threoninamide part is quite variable in this series of compounds. On the other hand, the following two compounds, **25a**, which carries a Boc in place of the 1*H*-indol-3-ylcarbonyl group, and **25b**, which has an unsubstituted amino group, were shown to be completely inactive. In the lysine series (Table IV), the N^{α}-acetylthreonine part was similarly substituted into various amino acids. The activities of Boc-threonine (**20**), acetylglycine (**22b**), acetylserine (**22c**), and acetyl-β-alanine (**22d**) were comparable to that of **7**. However, unprotected threonine (**21**) and acetylglutamine (**22a**) exhibited a 2-fold increase in activity. Furthermore, compound **23**, having an *N*,*N*-diethyl-β-alanine structure, was also found to be potent. These results demonstrate that the N^{α}-acetylthreonine part at ε-amino group in **7** is again quite variable. On the contrary, compounds **26a–d**, which have a Boc, hydrogen, acetyl, and benzoyl instead of the 1*H*-indol-3-ylcarbonyl group, were completely inactive, as similarly seen in the aspartic acid series. In addition, it is quite noteworthy that compound **19**, the D-lysine isomer of **7**, was completely inactive.

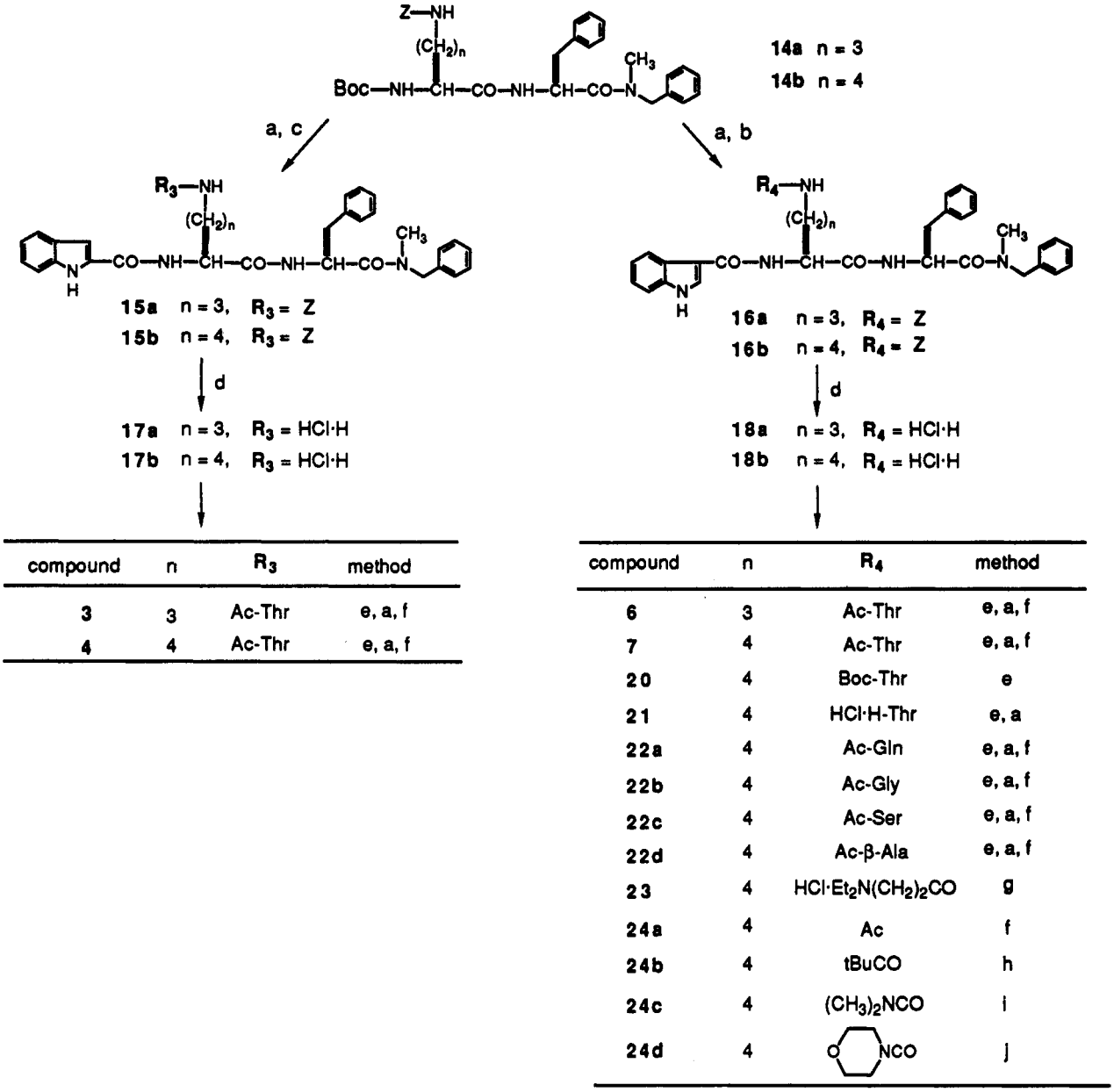
On the basis of the results of the above SAR studies, we subsequently examined the activity of dipeptide compounds, which have no amino acid structure at the ε-amine of lysine in compound **7**. The results are also shown in Table IV. The activities of Z-protected (**15b**), trimethylacetyl (**24b**), and morpholin-4-ylcarbonyl (**24d**) derivatives were reduced, when compared to that of **7**. However, acetyl (**24a**) and dimethylcarbamoyl (**24c**) derivatives retained their potency. It is quite important that compound **18b**, in which the ε-amine is unprotected, was shown to be still potently active. In spite of its simplified structure comprising only two amino acids, this compound was almost equally potent to the tripeptide **7**.

Discussion

In an attempt to discover a new structural class of SP antagonist, we designed some branched tripeptides **2–7** based on the previously reported tripeptide **1**. In this design process, we paid particular attention to the spatial orientations of the essential components in **1**, which were deduced as the indole nucleus and the two benzene rings from the previous structure–activity analysis of **1** and its related compounds. The molecular modeling study on these designed tripeptides using an in-house program FIT demonstrated that all the tripeptides could be superimposed upon **1** around the essential components and also that the 1*H*-indol-3-ylcarbonyl derivatives (**5–7**) would be preferable compared to the corresponding 1*H*-indol-2-ylcarbonyl derivatives (**2–4**). As expected, these newly designed tripeptides were found to exhibit significant activity in the receptor binding assay, although the 3-yl derivatives are superior in potency to the corresponding 2-yl derivatives. By contrast, compound **19**, the D-lysine analog of **7**, was completely inactive and the compounds lacking the indole moiety, namely compounds **25a,b** and **26a–d**, were also inactive. It can be concluded from these results that the desired spatial orientations of the essential components are obviously realized in the newly designed tripeptides, particularly in the potent 1*H*-indol-3-ylcarbonyl derivatives.

Recently, Lowe has proposed a three-point binding model for interaction of CP-96,345, a novel nonpeptide SP antagonist, with the NK_1 receptor.[6b] Those three points are claimed to be (1) the ion-pair site interaction with the bridgehead nitrogen, (2) the accessory binding site interaction with the benzhydryl group, and (3) the specificity site interaction with the (2-methoxybenzyl)-amino side chain. However, our series of compounds lack

Scheme III.[a] Synthesis of Di- and Tripeptide Derivatives Containing L-Ornithine and L-Lysine



compound	n	R_3	method
3	3	Ac-Thr	e, a, f
4	4	Ac-Thr	e, a, f

compound	n	R_4	method
6	3	Ac-Thr	e, a, f
7	4	Ac-Thr	e, a, f
20	4	Boc-Thr	e
21	4	HCl·H-Thr	e, a
22a	4	Ac-Gln	e, a, f
22b	4	Ac-Gly	e, a, f
22c	4	Ac-Ser	e, a, f
22d	4	Ac-β-Ala	e, a, f
23	4	HCl·$Et_2N(CH_2)_2CO$	g
24a	4	Ac	f
24b	4	tBuCO	h
24c	4	$(CH_3)_2NCO$	i
24d	4		j

[a] (a) HCl, dioxane–CH_2Cl_2; (b) 1*H*-indole-3-carbonyl chloride, bis(trimethylsilyl)acetamide, CH_2Cl_2; (c) 1*H*-indole-2-carboxylic acid, WSCD–HOBT, DMF; (d) H_2, Pd/C, HCl, EtOH–THF; (e) Boc-amino acid, WSCD–HOBT, CH_2Cl_2–DMF; (f) acetic anhydride, Et_3N, CH_2Cl_2; (g) HCl·$Et_2N(CH_2)_2CO_2H$, WSCD–HOBT, DMF; (h) trimethylacetyl chloride, Et_3N, CH_2Cl_2; (i) dimethylcarbamoyl chloride, Et_3N, CH_2Cl_2; (j) morpholin-4-ylcarbonyl chloride, Et_3N, CH_2Cl_2.

these essential elements required for CP-96,345 and its analogs. For instance, our series of compounds do not need a basic nitrogen to make an ion-pair with an acidic residue in the receptor. For this reason, it seems that our series of compounds do not fit the proposed model. We are now carrying out studies to elucidate the binding mode of our compounds at the NK_1 receptor.

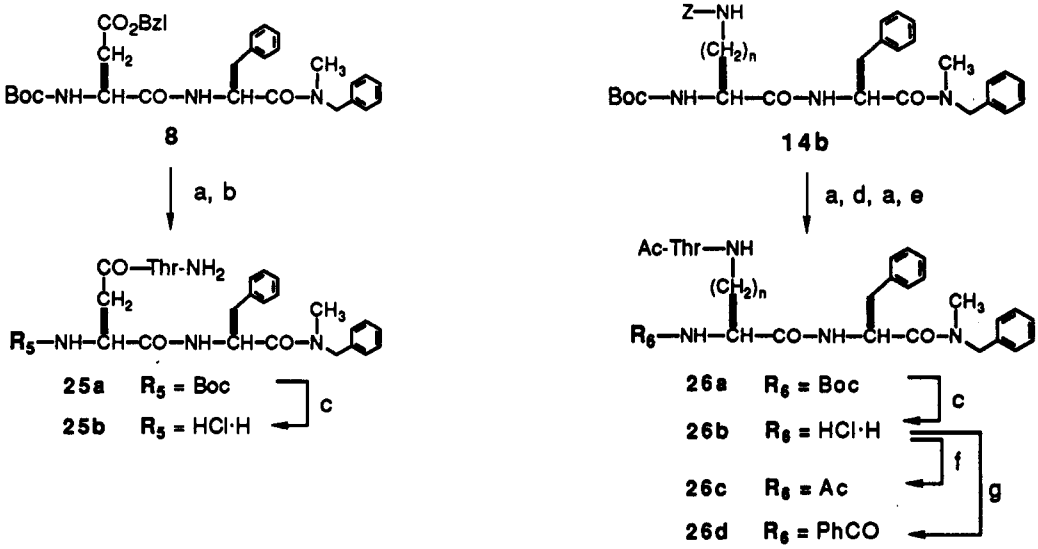
The SAR studies on the selected L-aspartic acid derivative **5** and L-lysine derivative **7** indicated that the appendages, respectively the threoninamide and N^{α}-acetylthreonine parts, are quite variable and can be modified into other various amino acids without significant loss of activity. Furthermore, it is quite noteworthy that even the dipeptide compounds (**18b** and **24a–d**), having nothing or a simple acyl group at the ε-amino side chain in **7**, exhibited comparable activity to the parent tripeptide **1**. These findings suggest that the amino acid residue adjacent to the Phe-NMeBzl structure can accept a wide variety of modifications irrespective of the nature of the substituent.

The discovery of these effective dipeptide structures, a new structural class of SP antagonists, successfully led to a reduction of the molecular size of the parent tripeptide **1** by one amino acid unit. More directly, these dipeptide compounds were utilized as new lead compounds for successive chemical modification, leading to the discovery of a potent and NK_1-selective SP antagonist, N^2-[(4*R*)-4-hydroxy-1-[(1-methyl-1*H*-indol-3-yl)carbonyl]-L-prolyl]-*N*-methyl-*N*-(phenylmethyl)-3-(2-naphthyl)-L-alaninamide (FK888).[22,23] The design concept and SAR studies on this compound will be discussed in the following paper.[24]

Experimental Section

Instruments and Materials. Melting points were measured on Mel-Temp (Mitamura Riken Kogyo, Japan) and are uncorrected. Proton NMR spectra were recorded on a 200-MHz

Scheme IV.[a] Synthesis of Derivatives with No Indole Moiety



[a] (a) H_2, Pd/C; (b) HCl·H-Thr-NH_2, WSCD–HOBT, DMF; (c) HCl, dioxane–CH_2Cl_2; (d) Z-Thr-OH, WSCD·HCl–HOBT, CH_2Cl_2; (e) acetic anhydride, CH_2Cl_2; (f) acetic anhydride, Et_3N, CH_2Cl_2; (g) benzoyl chloride, Et_3N, CH_2Cl_2.

Table II. Binding Activity of New Branched Tripeptides 2–7

compound	component amino acid	indole substitution	inhibition of ^{3}H-SP binding (IC_{50}, M)[a]
2	L-Asp		5.4×10^{-8} ($n = 2$)
3	L-Orn	2-position	12.5×10^{-8}
4	L-Lys		1.9×10^{-8} ($n = 2$)
5[b]	L-Asp		2.3×10^{-8} ($n = 2$)
6	L-Orn	3-position	2.1×10^{-8} ($n = 2$)
7[b]	L-Lys		1.3×10^{-8} ($n = 2$)

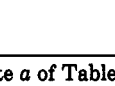
[a] The IC_{50} values were determined by a single experiment unless otherwise noted. The concentration of ^{3}H-SP was 1 nM. Each assay was performed in duplicate. [b] These compounds were selected as new leads for further SAR studies.

Table III. Modification of Threoninamide and Indole Parts in Compound 5

compound	R_2	R_5	inhibition of ^{3}H-SP binding, relative activity (compound 5 as 100)[a,b]
5	Thr-NH_2		100
13a	Gln-NH_2		56
13b	Gln-NH^{t}Bu		96
13c	Gly-NH_2		128
13d	Ser-NH_2		100
25a		Boc	c
25b		HCl·H	c

[a] See footnote *a* of Table II. [b] The IC_{50} value of the compound 5 was 2.3×10^{-8} M as shown in Table II. [c] No inhibition was observed at the concentration of 100 ng/mL.

Table IV. Modification of N^{α}-Acetylthreonine and Indole Parts in Compound 7

compound	R_4	R_6	inhibition of ^{3}H-SP binding, relative activity (compound 7 as 100)[a,b]
	Tripeptide Derivatives		
7	Ac-Thr		100 ($n = 2$)
19	(D-Lys isomer of 7)		c
20	Boc-Thr		98
21	HCl·H-Thr		218
22a	Ac-Gln		193
22b	Ac-Gly		98
22c	Ac-Ser		136
22d	Ac-β-Ala		82
23	HCl·$Et_2N(CH_2)_2CO$		189
26a		Boc	c
26b		HCl·H	c
26c		Ac	c
26d		PhCO	c
	Dipeptide Derivatives		
15b	Z		22
18b	HCl·H		91 ($n = 2$)
24a	Ac		87 ($n = 2$)
24b	^{t}BuCO		44 ($n = 2$)
24c	$(CH_3)_2NCO$		144 ($n = 2$)
24d			53

[a] See footnote *a* of Table II. [b] The IC_{50} value of the compound 7 was 1.3×10^{-8} M as shown in Table II. [c] See footnote *c* of Table III.

spectrometer AC-200T (Brucker), unless otherwise noted, or on a 90-MHz spectrometer EM-390 (Varian); chemical shifts were recorded in parts per million (ppm) downfield from tetramethylsilane. Mass spectra (FAB) were recorded on a Finnigan MAT TSQ-70. IR spectra were taken with an IR-408 spectrometer (Shimadzu, Kyoto, Japan). Optical rotations were recorded on a DIP-360 (Nihon Bunkoh, Co. Ltd., Japan) polarimeter. Elemental analyses were performed on a Perkin-Elmer 2400 CHN analyzer. Analytical results were within ±0.4% of the theoretical values unless otherwise noted. Thin-layer chromatography was performed on precoated silica gel plate Kieselgel $60F_{254}$ (E. Merck, A.G., Darmstadt, Germany). Solvent systems were as follows: A, $CHCl_3$–MeOH–EtOAc (4:1:1); B, $CHCl_3$–MeOH (10:1); C, $CHCl_3$–MeOH–AcOH (8:1:1), D, *n*-BuOAc–*n*-BuOH–AcOH–H_2O (80:15:40:24); E, toluene–EtOAc (4:1). Silica gel column chromatography was performed on Kieselgel-60 (230–400 mesh) (E. Merck, A. G., Darmstadt, Germany) or silica gel 60 K230 (230–400 mesh) (Katayama Chemicals Co. Ltd., Japan). Extraction solvents were dried over magnesium sulfate. Solvents used for reactions were dried over 3A molecular sieves. The following amino acid derivatives were commercially available: Boc-Gln-OH and Boc-Asp(OBzl)-OH (Peptide Institute, Minoh, Japan); Boc-Orn(Z)-OH, Boc-Lys(Z)-OH, Boc-β-Ala-OH, Boc-Gly-OH, Boc-D-Lys(Z)-OH, Z-Thr-OH, HCl·H-Thr-NH_2, HCl·H-Ser-NH_2, HCl·H-Gly-NH_2, and HCl·H-Gln-NH_2, (Kokusan Chemicals Co. Ltd., Tokyo, Japan); Boc-Thr-OH and Boc-Ser-OH, (Eibeiss Co. Ltd., Yokohama, Japan); *N,N*-diethyl-β-alanine·HCl, (Tokyo Kasei Kogyo Co. Ltd., Tokyo, Japan). The reagents WSCD and HOBT were purchased from Eibeiss Co. Ltd. (Yokohama, Japan). 1*H*-Indole-2-carboxylic acid and 1*H*-indole-3-carboxylic acid were from Tokyo Kasei Kogyo Co. Ltd. (Tokyo, Japan). Other reagents were commercially available. These materials were used without further purification.

Receptor Binding Assay Using Guinea Pig Lung Membranes. This experiment was implemented according to the method described in the preceding papers.[10,11]

Molecular Modeling Studies. The energy-optimized structures of compounds 1 and 2–7 were constructed by SYBYL

(version 5.5) software package (TRIPOS Associates Inc., St. Louis, MO 63144) according to the method described in the text. All the calculations were performed on a VAX6310 computer. MOLGRAPH (Daikin Kogyo, Ltd., Japan) was used as a graphic tool.

Synthesis of Starting N^{in}-Boc-dipeptides. Boc-Asp(OBzl)-Phe-NMeBzl (8). A solution of Boc-Asp(OBzl)-OH (3.23 g, 10 mmol) and *N*-methylmorpholine (1.01 g, 10 mmol) in CH_2Cl_2 (30 mL) was cooled to −20 °C. To this solution was added isobutyl chloroformate (1.37 g, 10 mmol) in CH_2Cl_2 (5 mL) dropwise during 7 min. The resulting mixture was stirred at −20 °C for 20 min. Then the solution was cooled to −35 °C and a solution of HCl·H-Phe-NMeBzl[11] (3.05 g, 10 mmol) and *N*-methylmorpholine (1.12 mL, 10 mmol) in CH_2Cl_2 (20 mL) was added. The mixture was stirred for 2 h, while the temperature was gradually raised to 0 °C. The reaction mixture was washed successively with water, sodium hydrogen carbonate solution, 0.5 N hydrochloric acid, and brine. After evaporation, the residue obtained was crystallized from IPE–ether, filtered, and dried to give 8 (3.97 g, 69.2%): mp 56–57 °C; $[\alpha]^{25}_D$ = +3.87° (*c* = 1.16, $CHCl_3$); IR (Nujol) 3300, 1736, 1690, 1660, 1640 (sh), 1515 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.48 (9 H, s), 2.58 (2 H, s), 2.8–3.17 (5 H, m), 4.2 (1 H, m), 4.4–4.7 (2 H, m), 5.17 (2 H, s), 5.2 (1 H, m), 5.58 (1 H, d, *J* = 8 Hz), 7.1 (1 H, m), 7.2–7.5 (15 H, m); R_f = 0.69 (system E). Anal. ($C_{33}H_{39}N_3O_6$) C, H, N.

The following protected dipeptides, **14a,b** and **27**, were prepared similarly to **8**.

Boc-Orn(Z)-Phe-NMeBzl (14a) was prepared from HCl·H-Phe-NMeBzl and Boc-Orn(Z)-OH: 93.1% yield; mp 74–74.5 °C (EtOAc–IPE); $[\alpha]^{25}_D$ = −1.61° (*c* = 1.24, $CHCl_3$); IR (Nujol) 3360, 3300, 1690, 1655, 1635, 1520 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.2–1.6 (4 H, m), 1.38 (9 H, s), 2.72 and 2.79 (3 H, 2 s), 2.8–3.1 (4 H, m), 3.9 (1 H, m), 4.6–4.7 (2 H, m), 5.0 (1 H, m), 5.02 (2 H, s), 6.84 (1 H, d, *J* = 8 Hz), 7.0–7.4 (16 H, m), 8.16 (1 H, m); R_f = 0.60 (system B). Anal. ($C_{35}H_{44}N_4O_6$) C, H, N.

Boc-Lys(Z)-Phe-NMeBzl (14b) was prepared from HCl·H-Phe-NMeBzl and Boc-Lys(Z)-OH: 87.4% yield; mp 112–113 °C (IPE); $[\alpha]^{25}_D$ = −6.21° (*c* = 1.0, $CHCl_3$); IR (Nujol) 3370, 3310, 1700, 1690 (sh), 1660, 1645, 1630, 1538 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.1–1.55 (6 H, m), 1.37 (9 H, s), 2.72 and 2.80 (3 H, 2 s), 2.8–3.05 (4 H, m), 3.86 (1 H, m), 4.44 and 4.49 (2 H, 2 s), 5.0 (2 H, s), 5.0 (1 H, m), 6.8 (1 H, m), 7.0–7.4 (16 H, m), 8.16 (1 H, d, *J* = 8 Hz); R_f = 0.63 (system B). Anal. ($C_{36}H_{46}N_4O_6$) C, H, N.

Boc-D-Lys(Z)-Phe-NMeBzl (27) was prepared from HCl·H-Phe-NMeBzl and Boc-D-Lys(Z)-OH: 93.1% yield; mp 64–65 °C (EtOAc–IPE); $[\alpha]^{25}_D$ = +17.20° (*c* = 1.0, $CHCl_3$); IR (Nujol) 3330, 1690, 1656, 1640, 1520 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.0–1.4 (6 H, m), 1.36 (9 H, s), 2.78 and 2.88 (3 H, 2 s), 2.8–3.05 (4 H, m), 3.93 (1 H, m), 4.4–4.7 (2 H, m), 5.0 (1 H, m), 5.0 (2 H, s), 6.64 and 6.71 (1 H, 2 d, *J* = 8 Hz), 7.0–7.4 (16 H, m), 8.28 and 8.38 (1 H, 2 d, *J* = 8 Hz); R_f = 0.63 (system B). Anal. ($C_{36}H_{46}N_4O_6$) C, H, N.

Synthesis of N^{in}-(1*H*-Indol-2-ylcarbonyl)-dipeptides. (1*H*-Indol-2-ylcarbonyl)-Asp(OBzl)-Phe-NMeBzl (9). To a solution of **8** (1.09 g, 1.90 mmol) in CH_2Cl_2 (20 mL) was added 4 N hydrochloric acid (20 mL) in dioxane under ice cooling. The reaction mixture was stirred at this temperature for 1 h and at room temperature for an additional 1 h. The mixture was concentrated and the residue was triturated with IPE, filtered, and dried under vacuum to give HCl·H-Asp(OBzl)-Phe-NMeBzl (1.03 g). This dipeptide hydrochloride, 1*H*-indole-2-carboxylic acid (306 mg, 1.9 mmol), and HOBT (257 mg, 1.9 mmol) were dissolved in DMF (15 mL). The mixture was ice-cooled and WSCD (295 mg, 1.9 mmol) was added thereto. The mixture was stirred at this temperature for 1 h and at room temperature for an additional 3 h. The mixture was concentrated under vacuum, diluted with water, and extracted with EtOAc. The organic layer was washed successively with water, sodium hydrogen carbonate solution, 0.5 N hydrochloric acid, and brine. After evaporation, the crude material obtained was purified on a column of silica gel (20 g) eluting with $CHCl_3$–MeOH (100:1 to 100:2.5, gradient elution) to give **9** as an amorphous solid (980 mg, yield 83.8%): $[\alpha]^{25}_D$ = −16.60° (*c* = 1.03, $CHCl_3$); IR (Nujol) 3250, 1735, 1645 (sh), 1630, 1545 cm^{-1}; ^{1}H NMR (90 MHz, DMSO-d_6) δ 2.65–3.1 (4 H, m), 2.79 (3 H, s), 4.40 (2 H, s), 4.8–5.1 (2 H, m), 5.05 (2 H, s), 6.9–7.3 (13 H, m), 7.25 (5 H, s), 7.45 (1 H, d, *J* = 8 Hz), 7.60 (1 H, d, *J* = 8 Hz), 8.3 (1 H, d, *J* = 8 Hz), 8.65 (1 H, d, *J* = 8 Hz), 11.60 (1 H, s); R_f = 0.81 (system B). Anal. ($C_{37}H_{38}N_4O_5$) C, H, N.

The following compounds, **15a,b**, were prepared similarly to **9**.

(1*H*-Indol-2-ylcarbonyl)-Orn(Z)-Phe-NMeBzl (15a) was prepared from **14a**: 59.0% yield (amorphous solid); $[\alpha]^{25}_D$ = −3.25° (*c* = 1.03, DMF); IR (Nujol) 3290, 1700, 1625, 1542 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.4–1.8 (4 H, m), 2.72 and 2.80 (2 H, 2 s), 2.8–3.1 (4 H, m), 4.44 and 4.49 (2 H, 2 s), 4.5 (1 H, m), 5.0 (2 H, s), 5.0 (1 H, m), 7.0–7.3 (19 H, m), 7.44 (1 H, d, *J* = 8 Hz), 7.63 (1 H, d, *J* = 8 Hz), 8.3–8.5 (2 H, m), 11.60 (1 H, s); R_f = 0.67 (system B). Anal. ($C_{39}H_{41}N_5O_5 \cdot H_2O$) C, H, N.

(1*H*-Indol-2-ylcarbonyl)-Lys(Z)-Phe-NMeBzl (15b) was prepared from **14b**: 60.1% yield (amorphous solid); $[\alpha]^{25}_D$ = −1.01° (*c* = 0.50, DMF); IR (Nujol) 3200, 1670, 1610, 1540 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.2–1.8 (6 H, m), 2.72 and 2.88 (2 H, 2 s), 2.9–3.1 (4 H, m), 4.4–4.6 (3 H, m), 4.99 (2 H, s), 5.0 (1 H, m), 7.0–7.3 (13 H, m), 7.32 (5 H, s), 7.44 (1 H, d, *J* = 8 Hz), 7.62 (1 H, d, *J* = 8 Hz), 8.36 (1 H, d, *J* = 8 Hz), 8.45 (1 H, d, *J* = 8 Hz), 11.59 (1 H, s); R_f = 0.65 (system B). Anal. ($C_{40}H_{43}N_5O_5$) C, H, N.

(1*H*-Indol-2-ylcarbonyl)-Asp-Phe-NMeBzl (11). The benzyl ester **9** (4.5 g, 7.3 mmol) was dissolved in a mixed solvent of EtOH (100 mL) and THF (30 mL). The solution was hydrogenated over 5% Pd (0.9 g) on charcoal under atmospheric pressure for 4 h. The mixture was filtered and evaporated to give **11** as an amorphous solid (3.23 g, 83.7%); $[\alpha]^{25}_D$ = −27.87° (*c* = 0.50, DMF); IR (Nujol) 3250, 1710, 1630, 1540 cm^{-1}; ^{1}H NMR (90 MHz, DMSO-d_6) δ 2.4–3.0 (4 H, m), 2.72 and 2.79 (3 H, 2 s), 4.43 (2 H, m), 4.7–5.2 (2 H, m), 6.9–7.3 (13 H, m), 7.55 (1 H, d, *J* = 8 Hz), 7.63 (1 H, d, *J* = 8 Hz), 8.2 (1 H, d, *J* = 8 Hz), 8.6 (1 H, d, *J* = 8 Hz), 11.71 (1 H, br s); R_f = 0.10 (system B), MS (FAB) *m/z* 527.1 $(M + H)^+$.

(1*H*-Indol-2-ylcarbonyl)-Orn-Phe-NMeBzl·HCl (17a). Compound **15a** (1.0 g, 1.52 mmol) was dissolved in a mixed solvent of EtOH (40 mL) and THF (20 mL), and 4 N hydrochloric acid (0.45 mL, 1.8 mmol) was added. The solution was hydrogenated with 5% Pd (0.3 g) on charcoal under atmospheric pressure for 2 h. After filtration of the mixture, the solvent was evaporated to dryness under reduced pressure. The residue was triturated with ether, filtered, and dried to give **17a** as an amorphous solid (0.74 g, 86.7%); $[\alpha]^{25}_D$ = +2.07° (*c* = 0.48, DMF); IR (Nujol) 3400, 3250, 2720, 2650, 1625, 1540 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.6–1.9 (4 H, m), 2.73 and 2.80 (3 H, 2 s), 2.7–3.1 (4 H, m), 4.4–4.7 (3 H, m), 4.98 (1 H, m), 7.0–7.4 (13 H, m), 7.45 (1 H, d, *J* = 8 Hz), 7.63 (1 H, d, *J* = 8 Hz), 8.01 (3 H, br s), 8.55 (1 H, d, *J* = 8 Hz), 8.60 (1 H, d, *J* = 8 Hz), 11.70 (1 H, s); R_f = 0.27 (system C); MS (FAB) *m/z* 526.3 $(M + H)^+$. Anal. ($C_{31}H_{36}Cl_1N_5O_3 \cdot 2H_2O$) C, H, N.

(1*H*-Indol-2-ylcarbonyl)-Lys-Phe-NMeBzl·HCl (17b) was prepared from **15b** similarly to **17a**: 84.5% yield (amorphous solid); $[\alpha]^{25}_D$ = +5.53° (*c* = 0.53, DMF); IR (Nujol) 3250, 2700–2650, 1625, 1540 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.2–1.8 (6 H, m), 2.72 and 2.81 (3 H, 2 s), 2.7–3.1 (4 H, m), 4.4–4.6 (3 H, m), 5.0 (1 H, m), 7.0–7.3 (13 H, m), 7.45 (1 H, d, *J* = 8 Hz), 7.63 (1 H, d, *J* = 8 Hz), 7.93 (3 H, br s), 8.51 (2 H, 2 d, *J* = 8 Hz), 11.67 (1 H, s); R_f = 0.55 (system D); MS (FAB) *m/z* 540.3 $(M + H)^+$. Anal. ($C_{32}H_{38}Cl_1N_5O_3 \cdot 1.5H_2O$) C, H, N.

Synthesis of N^{in}-(1*H*-Indol-3-ylcarbonyl)-Dipeptides. 1*H*-Indole-3-carbonyl Chloride. To a suspension of 1*H*-indole-3-carboxylic acid (15.8 g, 98 mmol) in CH_2Cl_2 (300 mL) was added oxalyl chloride (12.8 mL, 0.147 mol). The mixture was stirred under reflux for 3 h. After concentration of the mixture, *n*-hexane (200 mL) was added to the residue. The crystalline materials were collected by filtration and immediately dried under vacuum to give the subject product (16.9 g, 96.0%); mp 133–135 °C. This compound was stored under dry nitrogen until use.

(1*H*-Indol-3-ylcarbonyl)-Asp(OBzl)-Phe-NMeBzl (10). The dipeptide hydrochloride HCl·H-Asp(OBzl)-Phe-NMeBzl (3.02 g), obtained from **8** (3.20 g, 5.58 mmol) as described in the synthesis of **9**, was dissolved in CH_2Cl_2 (30 mL) and bis(trimethylsilyl)acetamide (2.27 g, 11.2 mmol) was added. The solution was ice-cooled and freshly prepared 1*H*-indole-3-carbonyl chloride (1.0 g, 5.58 mmol) was added. The reaction mixture was stirred at this temperature for 2 h and concentrated under vacuum. The residue was dissolved in THF (50 mL) and treated with 1 N hydrochloric acid (10 mL) at room temperature for 1 h. The mixture was diluted with water and extracted with EtOAc.

The organic layer was washed successively with water, sodium hydrogen carbonate solution, 0.5 N hydrochloric acid, and brine. After evaporation, the crude material obtained was purified on a column of silica gel (50 g) eluting with $CHCl_3$–MeOH (100:1 to 100:2.5, gradient elution) to give **10** as an amorphous solid (3.3 g, 93.6%); $[\alpha]^{25}_D$ = +7.87° (*c* = 0.94, $CHCl_3$); IR (Nujol) 3270, 1740, 1635, 1620, 1550, 1540 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.6–3.3 (4 H, m), 2.64 and 2.81 (3 H, 2 s), 4.27 (1 H, d, *J* = 15 Hz), 4.67 (1 H, d, *J* = 15 Hz), 5.0–5.3 (2 H, m), 5.13 (2 H, s), 7.03 (5 H, s), 7.0–7.7 (15 H, m), 7.8–8.1 (2 H, m), 9.67 (1 H, s); R_f = 0.70 (system A). Anal. ($C_{37}H_{36}N_4O_5$) H, N; C: calcd, 72.06; found, 71.49.

The following compounds, **16a,b** and **28**, were prepared similarly to **10**.

(1*H*-Indol-3-ylcarbonyl)-Orn(Z)-Phe-NMeBzl (16a) was prepared from **14a**: 88.2% yield (amorphous solid); $[\alpha]^{25}_D$ = −20.10° (*c* = 1.0, DMF); IR (Nujol) 3430, 3270, 1715, 1620, 1550 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.4–1.8 (4 H, m), 2.72 and 2.80 (3 H, 2 s), 2.8–3.1 (4 H, m), 4.43 and 4.50 (2 H, 2 s), 4.5 (1 H, m), 4.95 (1 H, m), 5.01 (2 H, s), 7.0–7.35 (18 H, m), 7.4 (1 H, m), 7.8 (1 H, d, *J* = 8 Hz), 8.1–8.2 (2 H, m), 8.40 (1 H, d, *J* = 8 Hz), 11.61 (1 H, s); R_f = 0.62 (system A). Anal. ($C_{39}H_{41}N_5O_5$) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Lys(Z)-Phe-NMeBzl (16b) was prepared from **14b**: 47.9% yield (amorphous solid); $[\alpha]^{25}_D$ = −19.47° (*c* = 1.0, DMF); IR (Nujol) 3400, 3250, 1700, 1608, 1520 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.2–2.0 (4 H, m), 2.57 and 2.72 (3 H, 2 s), 2.8–3.25 (4 H, m), 4.0–4.7 (2 H, m), 4.75–5.4 (2 H, m), 4.96 (2 H, s), 7.20 (2 H, s), 6.85–7.4 (15 H, m), 7.6–8.2 (3 H, m), 9.65 (1 H, s); R_f = 0.54 (system A). Anal. ($C_{40}H_{43}N_5O_5 \cdot H_2O$) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-D-Lys(Z)-Phe-NMeBzl (28) was prepared from **27**: 81.2% yield (amorphous solid); $[\alpha]^{25}_D$ = +15.43° (*c* = 1.0, DMF); IR (Nujol) 3200, 1710, 1660, 1640, 1610, 1540 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.1–1.6 (6 H, m), 2.79 and 2.88 (3 H, 2 s), 2.8–3.0 (4 H, m), 4.35–4.8 (3 H, m), 4.99 (2 H, s), 5.0 (1 H, m), 7.05–7.45 (19 H, m), 7.68 and 7.74 (1 H, 2 d, *J* = 8 Hz), 8.1–8.2 (2 H, m), 8.44 and 8.55 (1 H, 2 d, *J* = 8 Hz), 11.6 (1 H, s); R_f = 0.54 (system A). Anal. ($C_{40}H_{43}N_5O_5$) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Asp-Phe-NMeBzl (12) was prepared from **10** similarly to **11**: 87.3% yield; $[\alpha]^{25}_D$ = −56.47° (*c* = 1.0, DMF); IR (Nujol) 3430, 3200, 1720, 1672, 1635, 1605, 1580, 1536 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6) δ 2.6–3.0 (4 H, m), 2.89 (3 H, s), 4.3–4.6 (2 H, m), 4.7–5.1 (2 H, m), 6.9–7.5 (13 H, m), 7.8–8.2 (4 H, m), 11.5 (1 H, s), 12.1 (1 H, br s); R_f = 0.10 (system A), MS (FAB) *m/z* 527.6 $(M + H)^+$. Anal. ($C_{30}H_{30}N_4O_5$) H, N; C: calcd, 68.43; found, 67.97.

The following compounds, **18a,b** and **29**, were prepared similarly to **17a**.

(1*H*-Indol-3-ylcarbonyl)-Orn-Phe-NMeBzl·HCl (18a) was prepared from **16a**: 87.0% yield (amorphous solid); $[\alpha]^{25}_D$ = −2.69° (*c* = 0.97, DMF); IR (Nujol) 3200, 1625, 1535 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.5–1.8 (4 H, m), 2.72 and 2.80 (3 H, 2 s), 2.7–3.1 (4 H, m), 4.37 (1 H, d, *J* = 15 Hz), 4.49 (1 H, d, *J* = 15 Hz), 4.55 (1 H, m), 4.97 (1 H, m), 7.0–7.3 (13 H, m), 7.44 (1 H, m), 7.96 (3 H, br s), 8.1–8.3 (2 H, m), 8.46 (1 H, m), 11.7 (1 H, s); R_f = 0.39 (system D); MS (FAB) *m/z* 526.4 $(M + H)^+$. Anal. ($C_{31}H_{36}Cl_1N_5O_3 \cdot 2.0H_2O$) H, N; C: calcd, 62.25; found, 61.81.

(1*H*-Indol-3-ylcarbonyl)-Lys-Phe-NMeBzl·HCl (18b) was prepared from **16b**: 87.1% yield (amorphous solid); $[\alpha]^{25}_D$ = −14.40° (*c* = 1.09, DMF); IR (Nujol) 3400–3100, 2750–2600, 1630, 1535 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.2–1.8 (6 H, m), 2.72 and 2.80 (3 H, 2 s), 2.6–2.8 (2 H, m), 2.90 (1 H, dd, *J* = 7, 14 Hz), 3.03 (1 H, dd, *J* = 7, 14 Hz), 4.4–4.6 (3 H, m), 5.0 (1 H, m), 7.0–7.35 (13 H, m), 7.44 (1 H, m), 7.95 (3 H, br s), 8.1–8.15 (2 H, m), 8.4 (1 H, d, *J* = 8 Hz), 11.7 (1 H, d, *J* = 2 Hz); R_f = 0.41 (system D); MS (FAB) *m/z* 540.4 $(M + H)^+$. Anal. ($C_{32}H_{38}Cl_1N_5O_3 \cdot 1.5H_2O$) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-D-Lys-Phe-NMeBzl·HCl (29) was prepared from **28**: 93.7% yield (amorphous solid); $[\alpha]^{25}_D$ = +11.94° (*c* = 0.49, DMF); IR (Nujol) 3250, 2650, 1625, 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.2–1.65 (6 H, m), 2.6–2.8 (2 H, m), 2.79 and 2.92 (3 H, 2 s), 2.8–3.1 (2 H, m), 4.4–4.8 (3 H, m), 5.0 (1 H, m), 7.0–7.3 (13 H, m), 7.4 (1 H, m), 7.95 (3 H, br s), 8.15 (1 H, d, *J* = 8 Hz), 8.21 (1 H, d, *J* = 8 Hz), 8.50 and 8.60 (1 H, 2 d, *J* = 8 Hz), 11.7 (1 H, br s); R_f = 0.38 (system D). Anal. ($C_{32}H_{38}Cl_1N_5O_3 \cdot 1.5H_2O$) C, H, N.

Synthesis of N^{in}-(Indolylcarbonyl)-tripeptides Containing L-Aspartic Acid. (1*H*-Indol-2-ylcarbonyl)-Asp(Thr-NH_2)-Phe-NMeBzl (2). The dipeptide carboxylic acid **11** (480 mg, 0.91 mmol), threoninamide hydrochloride (140 mg, 0.91 mmol), and HOBT (123 mg, 0.91 mmol) were dissolved in DMF (12 mL). The mixture was ice-cooled and WSCD (155 mg, 1.0 mmol) was added thereto. The mixture was stirred at this temperature for 1 h and at room temperature for an additional 3 h. The mixture was concentrated under vacuum, and then water and EtOAc were added to the residue. The resulting precipitates were collected by filtration to give **2** (562 mg, 98.5%): mp 238–240 °C (EtOAc) dec; $[\alpha]^{25}_D$ = +0.05° (*c* = 0.97, DMF); IR (Nujol) 3380, 3300, 3280 (sh), 1665, 1640, 1620, 1545 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6) δ 0.98 (3 H, d, *J* = 6 Hz), 2.6–3.1 (4 H, m), 2.72 and 2.78 (3 H, 2 s), 3.9–4.2 (3 H, m), 4.3–4.6 (2 H, m), 4.7–5.1 (3 H, m), 6.9–7.4 (14 H, m), 7.46 (1 H, d, *J* = 8 Hz), 7.65 (1 H, d, *J* = 8 Hz), 7.75 (1 H, d, *J* = 8 Hz), 8.3 (1 H, d, *J* = 8 Hz), 8.6 (1 H, d, *J* = 7 Hz), 11.58 (1 H, s); R_f = 0.43 (system A). Anal. ($C_{34}H_{38}N_6O_6 \cdot 0.5H_2O$) H, N; C: calcd, 64.24; found, 63.42.

The following peptides, **5** and **13a–d**, were prepared similarly to **2**.

(1*H*-Indol-3-ylcarbonyl)-Asp(Thr-NH_2)-Phe-NMeBzl (5) was prepared from **12** and threoninamide hydrochloride: 44.8% yield; mp 135–140 °C (EtOH–H_2O); $[\alpha]^{25}_D$ = −17.17° (*c* = 1.0, DMF); IR (Nujol) 3250, 1670, 1630, 1605 (sh), 1535 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6) δ 0.97 (3 H, d, *J* = 6 Hz), 2.5–3.0 (4 H, m), 2.71 and 2.77 (3 H, 2 s), 3.8–4.2 (2 H, m), 4.3–4.5 (2 H, m), 4.6–5.1 (3 H, m), 6.9–7.5 (15 H, m), 7.6–8.3 (5 H, m); R_f = 0.18 (system C). Anal. ($C_{34}H_{38}N_6O_6 \cdot H_2O$) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Asp(Gln-NH_2)-Phe-NMeBzl (13a) was prepared from **12** and glutaminamide hydrochloride: 68.1% yield; mp 232–234 °C (EtOAc) dec; $[\alpha]^{25}_D$ = −20.35° (*c* = 0.56, DMF); IR (Nujol) 3440, 3320, 3220 (sh), 1680, 1625, 1605, 1530, 1500 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.6–1.8 (1 H, m), 1.8–2.0 (1 H, m), 2.08 (2 H, t, *J* = 7 Hz), 2.5–2.7 (2 H, m), 2.74 and 2.80 (3 H, 2 s), 4.16 (1 H, m), 4.32 (1 H, d, *J* = 15 Hz), 4.56 (1 H, d, *J* = 15 Hz), 4.8–5.0 (2 H, m), 6.71 (1 H, s), 7.0–7.5 (16 H, m), 8.1–8.32 (5 H, m), 11.67 (1 H, s); R_f = 0.13 (system C); MS (FAB) *m/z* 654.2 $(M + H)^+$. Anal. ($C_{35}H_{39}N_7O_6 \cdot H_2O$) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Asp(Gln-NH^{t}Bu)-Phe-NMeBzl (13b). To a solution of Boc-Gln-OH (4.93 g, 20 mmol) and HOBT (2.7 g, 20 mmol) in DMF (100 mL) was added WSCD·HCl (3.82 g, 20 mmol) at −15 °C. The mixture was stirred at this temperature for 15 min, and *tert*-butylamine (1.46 g, 20 mmol) dissolved in DMF (5 mL) was added. The mixture was stirred at this temperature for 1 h and at room temperature for 2 h. The reaction mixture was concentrated under vacuum and the residue was diluted with water and extracted with EtOAc. The organic layer was washed successively with water, sodium hydrogen carbonate solution, 0.5 N hydrochloric acid, and brine. After evaporation, the residue obtained was crystallized from EtOAc to give Boc-Gln-NH^{t}Bu (3.58 g, 59.4%): mp 169–170 °C; $[\alpha]^{25}_D$ = −12.52° (*c* = 1.0, MeOH). This compound (0.63 g, 2.09 mmol) was treated with 4 N hydrochloric acid (10 mL) in dioxane under ice cooling. The mixture was stirred at this temperature for 1 h and at room temperature for an additional 1 h. The mixture was concentrated and the residue was triturated with IPE, filtered, and dried under vacuum to give the hydrochloride HCl·H-Gln-NH^{t}Bu as a hygroscopic solid. This hydrochloride and the acid **12** (1.10 g, 2.09 mmol) were coupled similarly to the synthesis of **5** to give **13b** as an amorphous solid (1.12 g, 75.5%): $[\alpha]^{25}_D$ = −28.02° (*c* = 0.97, DMF); IR (Nujol) 3250, 1660 (sh), 1640, 1630, 1540 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6) δ 1.5–2.2 (4 H, m), 1.24 (9 H, s), 2.5–3.0 (4 H, m), 2.71 and 2.78 (3 H, 2 s), 4.0–4.6 (3 H, m), 4.6–5.0 (2 H, m), 6.61 (1 H, s), 6.9–7.5 (15 H, m), 7.8–8.2 (5 H, m), 11.60 (1 H, s); R_f = 0.35 (system A). Anal. ($C_{39}H_{47}N_7O_6 \cdot 1.5H_2O$) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Asp(Gly-NH_2)-Phe-NMeBzl (13c) was prepared from **12** and glycinamide hydrochloride: 96% yield; mp 165–167 °C (EtOAc); $[\alpha]^{25}_D$ = −18.22° (*c* = 1.07, DMF); IR (Nujol) 3390, 3330, 3240, 3100, 1662, 1640, 1605, 1510 cm^{-1}; ^1H NMR (90 MHz, DMSO-d_6) δ 2.5–2.95 (4 H, m), 2.73 and 2.78 (3 H, 2 s), 3.63 (2 H, d, *J* = 5 Hz), 4.2–4.6 (2 H, m), 4.75–5.1 (2 H, m), 6.95–7.6 (15 H, m), 7.9–8.3 (5 H, m); R_f = 0.43 (system C). Anal. ($C_{32}H_{34}N_6O_5 \cdot 1.5H_2O$) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Asp(Ser-NH_2)-Phe-NMeBzl (13d) was prepared from **12** and serinamide hydrochloride: 85% yield (amorphous solid); $[\alpha]^{25}_D = -24.17°$ ($c = 1.06$, DMF); IR (Nujol) 3250, 1640 (sh), 1625, 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.5–2.8 (2 H, m), 2.74 and 2.80 (3 H, 2 s), 2.8–3.06 (2 H, m), 3.5–3.66 (2 H, m), 4.20 (1 H, m), 4.3–4.6 (2 H, m), 4.8–5.0 (3 H, m), 7.0–7.5 (15 H, m), 8.0–8.4 (5 H, m), 11.65 (1 H, s); $R_f = 0.44$ (system C); MS (FAB) m/z 613.3 $(M + H)^+$. Anal. ($C_{33}H_{36}N_6O_6 \cdot 1.5H_2O$) C, H, N.

Synthesis of N^{α}-(Indolylcarbonyl)-tripeptides Containing L-Ornithine and L- and D-Lysines. (1*H*-Indol-3-ylcarbonyl)-Lys(Boc-Thr)-Phe-NMeBzl (20). The dipeptide amine hydrochloride **18b** (600 mg, 1.04 mmol), Boc-Thr-OH (228 mg, 1.04 mmol), and HOBT (140 mg, 1.04 mmol) were dissolved in a mixed solvent of CH_2Cl_2 (15 mL) and DMF (15 mL). The mixture was ice-cooled and WSCD (171 mg, 1.1 mmol) was added thereto. The mixture was stirred at this temperature for 1 h and at room temperature for an additional 2 h. The mixture was concentrated under vacuum and the residue was diluted in water and extracted with EtOAc. The organic layer was washed successively with diluted sodium hydrogen carbonate solution, 0.5 N hydrochloric acid, and brine. After evaporation, the crude material obtained was purified on a column of silica gel (50 g) eluting with $CHCl_3$–MeOH (20:1) to give **20** as an amorphous solid (0.73 g, 81.2%): $[\alpha]^{25}_D = -21.37°$ ($c = 0.52$, DMF); IR (Nujol) 3400, 3250, 1710, 1690 (sh), 1655 (sh), 1620, 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.01 (3 H, d, $J = 6$ Hz), 1.2–1.4 (4 H, m), 1.5–1.7 (2 H, m), 1.37 (9 H, s), 2.72 and 2.80 (3 H, 2 s), 2.8–3.2 (4 H, m), 3.75–3.9 (2 H, m), 4.4–4.5 (3 H, m), 4.72 (1 H, d, $J = 5.8$ Hz), 5.0 (1 H, m), 6.25 (1 H, d, $J = 8.5$ Hz), 7.0–7.3 (12 H, m), 7.43 (1 H, m), 7.7–7.8 (2 H, m), 8.1–8.2 (2 H, m), 8.36 (1 H, d, $J = 8$ Hz), 11.61 (1 H, d, $J = 2$ Hz); $R_f = 0.20$ (system B), MS (FAB) m/z 741.4 $(M + H)^+$. Anal. ($C_{41}H_{52}N_6O_7$) C, H, N.

The following compounds, **30–37**, were prepared similarly to **20**.

(1*H*-Indol-2-ylcarbonyl)-Orn(Boc-Thr)-Phe-NMeBzl (30) was prepared from **17a**: 97.5% yield (amorphous solid); $[\alpha]^{25}_D = -4.55°$ ($c = 0.48$, DMF); IR ($CHCl_3$) 3290, 1705 (sh), 1660, 1625, 1540 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.02 (3 H, d, $J = 6$ Hz), 1.36 (9 H, s), 1.3–1.8 (4 H, m), 2.73 and 2.80 (3 H, 2 s), 2.8–3.15 (4 H, m), 3.8–4.0 (2 H, m), 4.4–4.6 (3 H, m), 4.74 (1 H, d, $J = 6$ Hz), 5.0 (1 H, m), 6.26 (1 H, d, $J = 8$ Hz), 7.0–7.3 (13 H, m), 7.44 (1 H, d, $J = 8$ Hz), 7.63 (1 H, d, $J = 8$ Hz), 7.80 (1 H, m), 8.32–8.45 (2 H, m), 11.6 (1 H, s); $R_f = 0.62$ (system A), MS (FAB) m/z 727.3 $(M + H)^+$.

(1*H*-Indol-2-ylcarbonyl)-Lys(Boc-Thr)-Phe-NMeBzl (31) was prepared from **17b**: 92.1% yield (amorphous solid); $[\alpha]^{25}_D = -1.50°$ ($c = 0.51$, DMF); IR ($CHCl_3$) 3430 (sh), 3280, 1705 (sh), 1655 (sh), 1625, 1535 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.01 (3 H, d, $J = 6$ Hz), 1.37 (9 H, s), 1.2–1.5 (4 H, m), 1.5–1.8 (2 H, m), 2.73 and 2.80 (3 H, 2 s), 2.8–3.2 (4 H, m), 3.75–3.9 (2 H, m), 4.35–4.50 (3 H, m), 4.72 (1 H, d, $J = 6$ Hz), 5.0 (1 H, m), 6.24 (1 H, d, $J = 8$ Hz), 7.0–7.3 (13 H, m), 7.44 (1 H, d, $J = 8$ Hz), 7.63 (1 H, d, $J = 8$ Hz), 7.77 (1 H, t, $J = 5$ Hz), 8.35 (1 H, d, $J = 8$ Hz), 8.43 (1 H, d, $J = 8$ Hz), 11.59 (1 H, s); $R_f = 0.50$ (system B). Anal. ($C_{41}H_{52}N_6O_7 \cdot 1.2H_2O$) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Orn(Boc-Thr)-Phe-NMeBzl (32) was prepared from **18a**: 61.8% yield (amorphous solid); $[\alpha]^{25}_D = -19.6°$ ($c = 0.53$, DMF); IR (Nujol) 3250, 1705 (sh), 1655, 1625, 1530 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.32 (3 H, d, $J = 6$ Hz), 1.41 (9 H, s), 1.4–2.0 (4 H, m), 2.67 and 2.81 (3 H, 2 s), 2.10 (1 H, s), 2.85–3.15 (4 H, m), 3.7–4.1 (1 H, m), 4.1–4.75 (5 H, m), 4.85–5.25 (3 H, m), 5.78 (1 H, d, $J = 8$ Hz), 6.9–7.4 (12 H, m), 7.7–8.2 (3 H, m), 9.65 (1 H, br s); $R_f = 0.52$ (system A), MS (FAB) m/z 727.3 $(M + H)^+$.

(1*H*-Indol-3-ylcarbonyl)-Lys(Boc-Gln)-Phe-NMeBzl (33) was prepared from **18b**: 88.8% yield; mp 130–131 °C; $[\alpha]^{25}_D = -20.78°$ ($c = 0.51$, DMF); IR (Nujol) 3350, 3290, 1690, 1650, 1625, 1520 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.2–1.5 (4 H, m), 1.36 (9 H, s), 1.55–1.9 (4 H, m), 2.03 (2 H, t, $J = 8$ Hz), 2.72 and 2.81 (3 H, 2 s), 2.8–3.1 (4 H, m), 3.84 (1 H, m), 4.4–4.5 (3 H, m), 5.0 (1 H, m), 6.76 (2 H, s), 7.0–7.3 (13 H, m), 7.35 (1 H, d, $J = 7$ Hz), 7.8 (2 H, m), 8.1–8.2 (2 H, m), 8.37 (1 H, d, $J = 8$ Hz), 11.60 (1 H, s); $R_f = 0.36$ (system A). Anal. ($C_{42}H_{53}N_7O_7 \cdot H_2O$) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Lys(Boc-Gly)-Phe-NMeBzl (34) was prepared from **18b**: 85.9% yield (amorphous solid); $[\alpha]^{25}_D = -20.10°$ ($c = 1.0$, DMF); IR (Nujol) 3290, 1630, 1535 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.1–1.5 (4 H, m), 1.37 (9 H, s), 1.5–1.8 (2 H, m), 2.72 and 2.81 (3 H, 2 s), 2.8–3.1 (4 H, m), 3.49 (2 H, d, $J = 6$ Hz), 4.3–4.6 (3 H, m), 4.9–5.1 (1 H, m), 6.87 (1 H, t, $J = 6$ Hz), 6.9–7.4 (12 H, m), 7.44 (1 H, d, $J = 7$ Hz), 7.7–7.9 (2 H, m), 8.1–8.2 (2 H, m), 8.36 (1 H, d, $J = 8$ Hz), 11.60 (1 H, s); $R_f = 0.20$ (system B). Anal. $C_{39}H_{48}N_6O_6 \cdot H_2O$ (C, H, N).

(1*H*-Indol-3-ylcarbonyl)-Lys(Boc-Ser)-Phe-NMeBzl (35) was prepared from **18b**: 81.5% yield (amorphous solid); $[\alpha]^{25}_D = -22.40°$ ($c = 0.45$, DMF); IR ($CHCl_3$) 3440 (sh), 3300, 1705 (sh), 1655 (sh), 1625, 1540 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.2–1.5 (4 H, m), 1.37 (9 H, s), 1.6–1.7 (2 H, m), 2.72 and 2.81 (3 H, 2 s), 2.85–3.1 (4 H, m), 3.52 (2 H, m), 3.9 (1 H, m), 4.4–4.5 (3 H, m), 4.78 (1 H, t, $J = 6$ Hz), 4.9–5.0 (1 H, m), 6.53 (1 H, d, $J = 8$ Hz), 7.0–7.3 (11 H, m), 7.4 (1 H, m), 7.8 (2 H, m), 8.1–8.2 (2 H, m), 8.35 (1 H, d, $J = 8$ Hz), 11.59 (1 H, s); $R_f = 0.54$ (system A). MS (FAB) m/z 727.3 $(M + H)^+$.

(1*H*-Indol-3-ylcarbonyl)-Lys(Boc-β-Ala)-Phe-NMeBzl (36) was prepared from **18b**: 76.7% yield (amorphous solid); $[\alpha]^{25}_D = -19.30°$ ($c = 1.04$, DMF); IR (Nujol) 3280, 1630, 1535 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.2–1.5 (4 H, m), 1.36 (9 H, s), 1.5–1.8 (2 H, m), 2.20 (2 H, t, $J = 7$ Hz), 2.72 and 2.81 (3 H, 2 s), 2.8–3.2 (6 H, m), 4.3–4.6 (3 H, m), 4.9–5.1 (1 H, m), 6.7–6.8 (1 H, m), 7.0–7.4 (12 H, m), 7.4–7.5 (1 H, m), 7.7–7.9 (2 H, m), 8.1–8.2 (2 H, m), 8.37 (1 H, d, $J = 8$ Hz), 11.60 (1 H, s); $R_f = 0.57$ (system C). Anal. ($C_{40}H_{50}N_6O_6 \cdot H_2O$) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-D-Lys(Boc-Thr)-Phe-NMeBzl (37) was prepared from **29**: 88.2% yield (amorphous solid); $[\alpha]^{25}_D = +13.66°$ ($c = 0.53$, DMF); IR (Nujol) 3400, 3250, 1705 (sh), 1660 (sh), 1630, 1540 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.00 (3 H, d, $J = 6.2$ Hz), 1.1–1.6 (6 H, m), 1.37 (9 H, s), 2.79 and 2.91 (3 H, 2 s), 2.8–3.1 (4 H, m), 3.8–3.9 (2 H, m), 4.39 (1 H, d, $J = 15$ Hz), 4.50 (1 H, d, $J = 15$ Hz), 4.5 (1 H, m), 4.73 (1 H, d, $J = 6$ Hz), 5.0 (1 H, m), 6.25 (1 H, d, $J = 8$ Hz), 7.0–7.3 (12 H, m), 7.4 (1 H, m), 7.7–7.8 (2 H, m), 8.1–8.2 (2 H, m), 8.43 and 8.53 (1 H, 2 d, $J = 8$ Hz), 11.59 (1 H, s); $R_f = 0.40$ (system B); MS (FAB) m/z 741.4 $(M + H)^+$.

(1*H*-Indol-3-ylcarbonyl)-Lys(Ac-Thr)-Phe-NMeBzl (7). Compound **20** (0.82 g, 1.11 mmol) was dissolved in CH_2Cl_2 (5 mL). To this solution was added 4 N hydrochloric acid (5 mL) in dioxane under ice cooling. The mixture was stirred at this temperature for 15 min and at room temperature for 0.5 h. The mixture was concentrated and the residue was triturated with IPE, and filtered to give **(1*H*-indol-3-ylcarbonyl)-Lys(H-Thr)-Phe-NMeBzl·HCl (21**, 660 mg, 87.8%); $[\alpha]^{25}_D = -6.91°$ ($c = 0.53$, DMF); IR (Nujol) 3250, 1670, 1640 (sh), 1620, 1530 cm^{-1}; ^1H NMR (DMSO-d_6 + D_2O) δ 1.01 (3 H, d, $J = 5.6$ Hz), 1.2–1.5 (4 H, m), 1.5–1.8 (2 H, m), 2.73 and 2.81 (3 H, 2 s), 2.8–3.2 (4 H, m), 3.5 (1 H, d, $J = 6.8$ Hz), 3.85 (1 H, dq, $J = 5.6, 6.8$ Hz), 4.4–4.5 (3 H, m), 5.0 (1 H, m), 7.0–7.3 (12 H, m), 7.47 (1 H, m), 8.1–8.2 (2 H, m); $R_f = 0.43$ (system D); MS (FAB) m/z 641.4 $(M + H)^+$. This hydrochloride (660 mg, 0.97 mmol) was dissolved in DMF (15 mL). The solution was cooled to −15 °C, and triethylamine (197 mg, 1.95 mmol) and acetic anhydride (99 mg, 0.97 mmol) were added. After stirring at this temperature for 0.5 h, the mixture was concentrated under vacuum and the residue was diluted with water and extracted with EtOAc. The organic layer was washed successively with diluted sodium hydrogen carbonate solution, 0.5 N hydrochloric acid, and brine. The precipitates which appeared in the extract were collected to give **7** (0.36 g, 47.5%): mp 198–201 °C (EtOAc); $[\alpha]^{25}_D = -21.00°$ ($c = 1.0$, DMF); IR (Nujol) 3250, 1660 (sh), 1635, 1620, 1550 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.0 (3 H, d, $J = 6$ Hz), 1.2–1.5 (4 H, m), 1.5–1.8 (2 H, m), 1.89 (3 H, s), 2.72 and 2.80 (3 H, 2 s), 2.8–3.1 (4 H, m), 3.91 (1 H, m), 4.11 (1 H, dd, $J = 4.3, 8.3$ Hz), 4.4–4.5 (3 H, m), 4.76 (1 H, d, $J = 5.2$ Hz), 5.0 (1 H, m), 6.9–7.3 (12 H, m), 7.44 (1 H, m), 7.68 (1 H, d, $J = 8$ Hz), 7.7–7.8 (2 H, m), 8.1–8.2 (2 H, m), 8.36 (1 H, d, $J = 8$ Hz), 11.59 (1 H, d, $J = 2.5$ Hz); $R_f = 0.27$ (system C). Anal. ($C_{38}H_{46}N_6O_6 \cdot 0.5EtOAc$) H, N; C: calcd, 66.10; found, 65.57.

The following compounds, **3**, **4**, **6**, **19**, and **22a–d**, were prepared similarly to **7** from the corresponding Boc-protected intermediates.

(1*H*-Indol-2-ylcarbonyl)-Orn(Ac-Thr)-Phe-NMeBzl (3) was prepared from **30**: 38.9% yield; mp 113–115 °C (EtOAc); $[\alpha]^{25}_D = -4.23°$ ($c = 0.97$, DMF); IR (Nujol) 3270, 1658 (sh), 1640

(sh), 1625, 1550 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.01 (3 H, d, J = 6 Hz), 1.4–1.8 (6 H, m), 1.90 (3 H, s), 2.73 and 2.80 (3 H, 2 s), 2.8–3.1 (4 H, m), 3.95 (1 H, m), 4.12 (1 H, dd, J = 4.2, 8.6 Hz), 4.4–4.7 (3 H, m), 4.79 (1 H, d, J = 5.2 Hz), 5.0 (1 H, m), 6.9–7.3 (13 H, m), 7.44 (1 H, d, J = 8 Hz), 7.63 (1 H, d, J = 8 Hz), 7.80 (1 H, t, J = 4 Hz), 8.4–8.45 (2 H, m), 11.6 (1 H, s); R_f = 0.56 (system A). Anal. ($C_{37}H_{44}N_6O_6$·0.5H_2O) C, H, N.

(1*H*-Indol-2-ylcarbonyl)-Lys(Ac-Thr)-Phe-NMeBzl (4) was prepared from **31**: 69.1% yield (amorphous solid); $[\alpha]^{25}_D$ = −0.29° (c = 1.0, DMF); IR (Nujol) 3300, 1640, 1625, 1542 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.00 (3 H, d, J = 6 Hz), 1.2–1.5 (4 H, m), 1.6–1.75 (2 H, m), 1.89 (3 H, s), 2.73 and 2.80 (3 H, 2 s), 2.8–3.1 (4 H, m), 3.93 (1 H, m), 4.11 (1 H, dd, J = 4.1, 8.4 Hz), 4.4–4.5 (3 H, m), 4.76 (1 H, d, J = 5 Hz), 5.0 (1 H, m), 7.0–7.3 (13 H, m), 7.44 (1 H, m), 7.63 (1 H, d, J = 8 Hz), 7.68 (1 H, d, J = 8 Hz), 7.76 (1 H, d, J = 8 Hz), 8.36 (1 H, d, J = 8 Hz), 8.44 (1 H, d, J = 8 Hz), 11.59 (1 H, s); R_f = 0.51 (system A); MS (FAB) m/z 683.2 (M + H)$^+$. Anal. ($C_{38}H_{46}N_6O_6$·0.5H_2O) C, H; N: calcd, 12.15; found, 11.70.

(1*H*-Indol-3-ylcarbonyl)-Orn(Ac-Thr)-Phe-NMeBzl (6) was prepared from **32**: 57.8% yield; mp 133–137 °C (EtOAc); $[\alpha]^{25}_D$ = −22.30° (c = 1.0, DMF); IR (Nujol) 3260, 1620 (sh), 1545 cm^{-1}; ^{1}H NMR (90 MHz, DMSO-d_6) δ 1.0 (3 H, d, J = 6 Hz), 1.3–1.8 (6 H, m), 1.89 (3 H, s), 2.70 and 2.77 (3 H, 2 s), 2.8–3.2 (4 H, m), 3.8–4.25 (3 H, m), 4.3–4.6 (2 H, m), 4.71 (1 H, d, J = 6 Hz), 4.8–5.1 (1 H, m), 6.9–7.8 (15 H, m), 8.0–8.4 (4 H, m), 11.6 (1 H, br s); R_f = 0.28 (system A). Anal. ($C_{37}H_{44}N_6O_6$) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-D-Lys(Ac-Thr)-Phe-NMeBzl (19) was prepared from **37**: 70.7% yield (amorphous solid); $[\alpha]^{25}_D$ = +15.04° (c = 1.0, DMF); IR (Nujol) 3250, 1655 (sh), 1630, 1530 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.00 (3 H, d, J = 6.2 Hz), 1.1–1.6 (6 H, m), 1.89 (3 H, s), 2.78 and 2.91 (3 H, 2 s), 2.8–3.1 (4 H, m), 3.93 (1 H, m), 4.11 (1 H, dd, J = 4.1, 8.4 Hz), 4.35–4.8 (4 H, m), 5.0 (1 H, m), 7.0–7.3 (12 H, m), 7.43 (1 H, m), 7.6–7.8 (3 H, m), 8.1–8.2 (2 H, m), 8.42 and 8.54 (1 H, 2 d, J = 8 Hz), 11.57 (1 H, s); R_f = 0.50 (system A); MS (FAB) m/z 683.3 (M + H)$^+$. Anal. ($C_{38}H_{46}N_6O_6$·H_2O) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Lys(Ac-Gln)-Phe-NMeBzl (22a) was prepared from **33**: 78.1% yield; mp 190–192 °C (EtOAc); $[\alpha]^{25}_D$ = −20.82° (c = 0.50, DMF); IR (Nujol) 3440, 3300, 1652, 1624, 1530 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.2–1.5 (4 H, m), 1.5–1.9 (4 H, m), 2.05 (2 H, m), 2.72 and 2.81 (3 H, 2 s), 2.8–3.1 (4 H, m), 4.2 (1 H, m), 4.4–4.6 (3 H, m), 5.0 (1 H, m), 6.75 (1 H, s), 7.0–7.3 (13 H, m), 7.43 (1 H, d, J = 7 Hz), 7.65–8.0 (3 H, m), 8.1–8.2 (2 H, m), 8.37 (1 H, d, J = 8 Hz), 11.6 (1 H, s); R_f = 0.20 (system C); MS (FAB) m/z 710.4 (M + H)$^+$. Anal. ($C_{39}H_{47}N_7O_6$·H_2O) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Lys(Ac-Gly)-Phe-NMeBzl (22b) was prepared from **34**: 71.0% yield (amorphous solid); $[\alpha]^{25}_D$ = −20.78° (c = 0.51, DMF); IR (Nujol) 3220, 1640 (sh), 1600, 1520 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.2–1.5 (4 H, m), 1.5–1.8 (2 H, m), 1.84 (3 H, s), 2.72 and 2.81 (3 H, 2 s), 2.8–3.1 (4 H, m), 3.62 (2 H, d, J = 5.5 Hz), 4.4–4.6 (3 H, m), 5.0 (1 H, m), 7.0–7.3 (12 H, m), 7.44 (1 H, m), 7.8 (2 H, m), 8.0–8.2 (2 H, m), 8.37 (1 H, d, J = 8 Hz), 11.6 (1 H, s); R_f = 0.13 (system B). Anal. ($C_{36}H_{42}N_6O_5$·H_2O) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Lys(Ac-Ser)-Phe-NMeBzl (22c) was prepared from **35**: 78.5% yield (amorphous solid); $[\alpha]^{25}_D$ = −21.98° (c = 0.53, DMF); IR (Nujol) 3260, 1655 (sh), 1620, 1530 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.2–1.5 (4 H, m), 1.6–1.75 (2 H, m), 1.86 (3 H, s), 2.72 and 2.80 (3 H, 2 s), 2.8–3.1 (4 H, m), 3.52 (2 H, m), 4.22 (1 H, m), 4.4–4.6 (3 H, m), 4.82 (1 H, t, J = 5.6 Hz), 5.0 (1 H, m), 7.0–7.3 (13 H, m), 7.43 (1 H, m), 7.7–7.9 (3 H, m), 8.1–8.2 (2 H, m), 8.36 (1 H, d, J = 8 Hz), 11.59 (1 H, d, J = 2.5 Hz); R_f = 0.34 (system A); MS (FAB) m/z 669.3 (M + H)$^+$. Anal. ($C_{37}H_{44}N_6O_6$·2.0H_2O) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Lys(Ac-β-Ala)-Phe-NMeBzl (22d) was prepared from **36**: 64.8% yield; mp 165–168 °C (EtOAc); $[\alpha]^{25}_D$ = −20.44° (c = 0.54, DMF); IR (Nujol) 3220, 1650 (sh), 1610, 1510 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.2–1.5 (4 H, m), 1.5–1.7 (2 H, m), 1.76 (3 H, s), 2.20 (2 H, t, J = 7 Hz), 2.72 and 2.81 (3 H, 2 s), 2.9–3.1 (4 H, m), 3.20 (2 H, dt, J = 6, 7 Hz), 4.4–4.6 (3 H, m), 5.0 (1 H, m), 7.0–7.3 (12 H, m), 7.4 (1 H, m), 7.7–7.9 (3 H, m), 8.1–8.2 (2 H, m), 8.37 (1 H, d, J = 8 Hz), 11.59 (1 H, s); R_f = 0.13 (system B). Anal. ($C_{37}H_{44}N_6O_5$·0.5H_2O) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Lys(*N*,*N*-diethyl-β-alanyl)-Phe-NMeBzl·HCl (23). A mixture of **18b** (1.0 g, 1.74 mmol), *N*,*N*-diethyl-β-alanine hydrochloride (350 mg, 1.93 mmol), and HOBT (238 mg, 1.75 mmol) in DMF (25 mL) was ice-cooled and WSCD (271 mg, 1.75 mmol) was added thereto. The mixture was stirred at this temperature for 1 h and at room temperature for 5 h. During this reaction period, *N*-methylmorpholine (300 mg, 3 mmol) and WSCD·HCl (33 mg, 0.17 mmol) were added to the mixture. The solution was concentrated and the residue was diluted with water. The resulting solution was acidified to pH 2 and extracted with EtOAc twice. The aqueous layer was neutralized to pH 8 with sodium hydrogen carbonate solution and extracted with EtOAc. The organic layer was concentrated to a 15-mL volume. This solution was treated with 4 N hydrochloric acid (0.35 mL) in dioxane under ice cooling. To the mixture were added Et_2O and water. The aqueous layer that separated was lyophilized to give **23** as an amorphous solid (803 mg, 65.8%): IR (Nujol) 3200, 1630, 1535 cm^{-1}; ^{1}H NMR (90 MHz, DMSO-d_6) δ 1.17 (6 H, t, J = 7 Hz), 1.2–1.9 (6 H, m), 2.5–2.7 (2 H, m), 2.73 and 2.80 (3 H, 2 s), 2.9–3.4 (10 H, m), 4.4–4.6 (3 H, m), 4.8–5.1 (1 H, m), 7.0–7.3 (14 H, m), 7.4 (1 H, m), 8.1–8.4 (3 H, m), 10.3 (1 H, br s), 11.7 (1 H, s); R_f = 0.22 (system D); MS (FAB) m/z 667.5 (M + H)$^+$.

Synthesis of Acylated Dipeptides at ε-Amino Group of L-Lysine. (1*H*-Indol-3-ylcarbonyl)-Lys(Ac)-Phe-NMeBzl (24a). To an ice-cooled solution of **18b** (97.3 mg, 0.169 mmol) and triethylamine (35 mg, 0.35 mmol) in CH_2Cl_2 (5 mL) was added acetic anhydride (17 mg, 0.17 mmol). The mixture was stirred for 10 min at this temperature and diluted with EtOAc. The mixture was washed successively with water, sodium hydrogen carbonate solution, 0.5 N hydrochloric acid, and brine. After concentration, the crude product was purified on a silica gel (6 g) column chromatography eluting with $CHCl_3$–MeOH (100:1 to 95:5, gradient elution) to give **24a** as an amorphous solid (65 mg, 66.1%): $[\alpha]^{25}_D$ = −25.17° (c = 0.44, DMF); IR (Nujol) 3200, 1650 (sh), 1595, 1510 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.2–1.5 (4 H, m), 1.5–1.7 (2 H, m), 1.77 (3 H, s), 2.72 and 2.81 (3 H, 2 s), 2.8–3.1 (4 H, m), 4.4–4.6 (3 H, m), 5.0 (1 H, m), 7.0–7.3 (12 H, m), 7.4 (1 H, m), 7.75–7.8 (2 H, m), 8.1–8.2 (2 H, m), 8.37 (1 H, d, J = 8 Hz), 11.61 (1 H, s); R_f = 0.35 (system B); MS (FAB) m/z 581.7 (M + H)$^+$. Anal. ($C_{34}H_{39}N_5O_4$·H_2O) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Lys(trimethylacetyl)-Phe-NMeBzl (24b) was prepared from **18b** similarly to **24a**, except using trimethylacetyl chloride: 85.9% yield (amorphous solid); $[\alpha]^{25}_D$ = −23.40° (c = 0.52, DMF); IR (Nujol) 3250, 1655 (sh), 1640, 1612, 1540 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.05 (9 H, s), 1.2–1.5 (4 H, m), 1.5–1.7 (2 H, m), 2.72 and 2.80 (3 H, 2 s), 2.8–3.1 (4 H, m), 4.4–4.5 (3 H, m), 5.0 (1 H, m), 7.0–7.3 (12 H, m), 7.4–7.45 (2 H, m), 7.75 (1 H, m), 8.1–8.2 (2 H, m), 8.36 (1 H, d, J = 8 Hz), 11.60 (1 H, s); R_f = 0.46 (system B); MS (FAB) m/z 624.3 (M + H)$^+$. Anal. ($C_{37}H_{45}N_5O_4$·0.5H_2O) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Lys(dimethylcarbamoyl)-Phe-NMeBzl (24c) was prepared from **18b** similarly to **24a**, except using dimethylcarbamoyl chloride and a prolonged reaction period (48 h): 80.9% yield (amorphous solid); $[\alpha]^{25}_D$ = −27.10° (c = 0.52, DMF); IR (Nujol) 3220, 1660 (sh), 1640 (sh), 1615, 1530 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.2–1.5 (4 H, m), 1.5–1.8 (2 H, m), 2.73 and 2.80 (3 H, 2 s), 2.74 (6 H, s), 2.9–3.1 (4 H, m), 4.4–4.5 (3 H, m), 5.0 (1 H, m), 6.21 (1 H, t, J = 5 Hz), 7.0–7.3 (12 H, m), 7.45 (1 H, m), 7.75–7.8 (1 H, m), 8.1–8.2 (2 H, m), 8.37 (1 H, d, J = 8 Hz), 11.61 (1 H, s); R_f = 0.44 (system B); MS (FAB) m/z 611.3 (M + H)$^+$. Anal. ($C_{35}H_{42}N_6O_4$·H_2O) H, N; C: calcd, 68.86; found, 66.81.

(1*H*-Indol-3-ylcarbonyl)-Lys(morpholin-4-ylcarbonyl)-Phe-NMeBzl (24d). A solution of **18b** (0.70 g, 1.2 mmol), morpholine-4-carbonyl chloride (0.18 g, 1.2 mmol), and *N*-methylmorpholine (242 mg, 2.4 mmol) was stirred at room temperature overnight. The mixture was concentrated under vacuum and the residue was diluted in water and extracted with EtOAc. The organic layer was washed successively with diluted sodium hydrogen carbonate solution, 0.5 N hydrochloric acid, and brine. After evaporation, the crude material obtained was purified on a column of silica gel (25 g) eluting with $CHCl_3$–MeOH (20:1) to give **24d** as an amorphous solid (287 mg, 36.7%): $[\alpha]^{25}_D$ = −24.87° (c = 0.80, DMF); IR (Nujol) 3270, 1630, 1540 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.2–1.8 (6 H, m), 2.72 and 2.80 (3 H, 2 s), 2.8–3.1

(4 H, m), 3.1–3.3 (4 H, m), 3.4–3.6 (4 H, m), 4.3–4.6 (3 H, m), 4.9–5.1 (1 H, m), 6.40–6.55 (1 H, m), 7.0–7.4 (12 H, m), 7.4–7.5 (1 H, m), 7.77 (1 H, d, J = 8 Hz), 8.1–8.2 (4 H, m), 8.37 (1 H, d, J = 8 Hz), 11.60 (1 H, s); R_f = 0.47 (system B). Anal. ($C_{37}H_{44}N_6O_5 \cdot H_2O$) C, H, N.

Synthesis of Other Branched Tripeptides. Boc-Asp(Thr-NH_2)-Phe-NMeBzl (25a). Compound 8 was hydrogenated as described in the synthesis of 12 to give Boc-Asp-Phe-NMeBzl: 91.7% yield; mp 157–158 °C (EtOAc–IPE) dec; $[\alpha]^{25}_D$ = –31.33° (c = 1.0, DMF); IR (Nujol) 3310, 2600, 1704, 1650, 1610, 1520 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.38 (9 H, s), 2.41 (1 H, dd, J = 10, 18 Hz), 2.55 (1 H, dd, J = 6, 18 Hz), 2.72 and 2.78 (3 H, 2 s), 2.85 (1 H, dd, J = 6.9, 13 Hz), 2.99 (1 H, dd, J = 7.4, 13 Hz), 4.2 (1 H, m), 4.39 (1 H, d, J = 15 Hz), 4.48 (1 H, d, J = 15 Hz), 4.9 (1 H, m), 7.0–7.4 (11 H, m), 8.1 (1 H, m), 12.29 (1 H, br s); R_f = 0.35 (system A). This compound was condensed with threoninamide hydrochloride as described in the synthesis of 2 to give **25a**: 60.1% yield; mp 117–119 °C (MeOH–H_2O); $[\alpha]^{25}_D$ = –6.04° (c = 1.0, DMF); IR (Nujol) 3420, 3350, 1690, 1655, 1630, 1520 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.03 (3 H, d, J = 6 Hz), 1.36 (9 H, s), 2.4–2.5 (2 H, m), 2.72 and 2.77 (3 H, 2 s), 2.8–3.1 (2 H, m), 4.0–4.1 (2 H, m), 4.3 (1 H, m), 4.5–4.6 (2 H, m), 4.8–5.0 (2 H, m), 7.0–7.3 (13 H, m), 7.62 (1 H, d, J = 8 Hz), 8.16 (1 H, m); R_f = 0.46 (system C). Anal. ($C_{30}H_{41}N_5O_7 \cdot H_2O$) C, H, N.

H-Asp(Thr-NH_2)-Phe-NMeBzl·HCl (25b). Compound **25a** (242 mg, 0.415 mmol) was treated with 4 N hydrochloric acid (10 mL) in dioxane for 20 min under ice cooling. The mixture was concentrated under reduced pressure and the residue was triturated with ether, filtered, and dried to give **25b** as an amorphous solid (197 mg, 91.4%): $[\alpha]^{25}_D$ = +15.96° (c = 1.0, DMF); IR (Nujol) 3250, 1680, 1640, 1540 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.05 (3 H, d, J = 6.2 Hz), 2.6–3.1 (4 H, m), 2.74 and 2.81 (3 H, 2 s), 4.0–4.2 (3 H, m), 4.33 (1 H, d, J = 15 Hz), 4.60 (1 H, d, J = 15 Hz), 4.9 (1 H, m), 7.0–7.4 (12 H, m), 8.22 (3 H, br s), 8.26 (1 H, m), 8.98 (1 H, d, J = 8 Hz); R_f = 0.26 (system D); MS (FAB) m/z 484.3 (M + H)$^+$. Anal. ($C_{25}H_{34}Cl_1N_5O_5 \cdot 1.5H_2O$) C, H, N.

Boc-Lys(Z-Thr)-Phe-NMeBzl (38). The dipeptide **14b** (3.11 g, 4.93 mmol) was dissolved in a mixed solvent of EtOH (60 mL) and THF (30 mL). This solution was hydrogenated over 5% Pd on charcoal (0.7 g) under atmospheric pressure for 2 h. After filtration and concentration of the filtrate, the obtained residue was dissolved in CH_2Cl_2 (50 mL) with Z-Thr-OH (1.27 g, 5 mmol) and HOBT (0.675 g, 5 mmol). Then WSCD·HCl (0.955 g, 5 mmol) was added thereto under ice cooling. The solution was stirred at this temperature for 1 h and at room temperature for 2 h and then concentrated, diluted in water, and extracted with EtOAc. The organic layer was washed successively with sodium hydrogen carbonate solution, water, 0.5 N hydrochloric acid, and brine and evaporated under reduced pressure to give **38** (3.6 g, quantitative yield): $[\alpha]^{25}_D$ = –3.40° (c = 1.0, $CHCl_3$); IR ($CHCl_3$) 3320, 1725, 1710, 1650 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.04 (3 H, d, J = 6 Hz), 1.1–1.5 (6 H, m), 1.38 (9 H, s), 2.73 and 2.80 (3 H, 2 s), 2.8–3.1 (4 H, m), 3.8–3.9 (3 H, m), 4.4–4.5 (2 H, m), 4.75 (1 H, d, J = 5.6 Hz), 4.99 (1 H, d, J = 13.8 Hz), 5.0 (1 H, m), 5.08 (1 H, d, J = 13.8 Hz), 6.8–6.9 (2 H, m), 7.0–7.4 (15 H, m), 7.81 (1 H, t, J = 7 Hz), 8.14 (1 H, d, J = 8.2 Hz); R_f = 0.66 (system A); MS (FAB) m/z 732.6 (M + H)$^+$.

Boc-Lys(Ac-Thr)-Phe-NMeBzl (26a). Compound **38** (3.36 g, 4.59 mmol) was dissolved in EtOH (60 mL) and the solution was hydrogenated over 0.75 g of 5% palladium on charcoal under atmospheric pressure for 2 h. After filtration and concentration, the residue (2.59 g) was dissolved in CH_2Cl_2 (40 mL) and acetic anhydride (449 mg) was added with ice cooling. The mixture was washed successively with sodium hydrogen carbonate solution and brine, and concentrated. The crude material was purified by a silica gel chromatography (80 g) eluting with $CHCl_3$–MeOH (2%) to give **26a** (2.04 g, 73.6%): mp 101–102 °C (EtOAc–IPE); $[\alpha]^{25}_D$ = –17.13° (c = 1.0, $CHCl_3$); IR (Nujol) 3300, 1685 (sh), 1655, 1640, 1520 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.01 (3 H, d, J = 6 Hz), 1.1–1.5 (6 H, m), 1.38 (9 H, s), 1.90 (3 H, s), 2.73 and 2.80 (3 H, 2 s), 2.8–3.1 (4 H, m), 3.8–4.0 (2 H, m), 4.11 (1 H, dd, J = 4.3, 8.6 Hz), 4.44 and 4.49 (2 H, 2 s), 4.77 (1 H, d, J = 5.1 Hz), 5.0 (1 H, m), 6.83 (1 H, m), 7.0–7.35 (10 H, m), 7.66–7.8 (2 H, m), 8.14 (1 H, d, J = 8 Hz); R_f = 0.42 (system B). Anal. ($C_{34}H_{49}N_5O_7 \cdot 0.5H_2O$) C, H, N.

H-Lys(Ac-Thr)-Phe-NMeBzl·HCl (26b) was prepared from **26a** similarly to **25b**: 96.5% yield (amorphous solid); $[\alpha]^{25}_D$ = +30.40° (c = 1.0, DMF); IR (Nujol) 3250, 2650, 1660 (sh), 1640, 1545 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.01 (3 H, d, J = 6 Hz), 1.2–1.5 (4 H, m), 1.7–1.8 (2 H, m), 1.91 (3 H, s), 2.75 and 2.81 (3 H, 2 s), 2.9–3.1 (4 H, m), 3.7 (1 H, m), 3.97 (1 H, m), 4.10 (1 H, dd, J = 4.2, 8.4 Hz), 4.39 (1 H, d, J = 14.9 Hz), 4.51 (1 H, d, J = 14.9 Hz), 4.98 (1 H, m), 7.0–7.3 (10 H, m), 7.8–7.9 (2 H, m), 8.27 (3 H, br s), 9.06 (1 H, d, J = 8 Hz); R_f = 0.31 (system D); MS (FAB) m/z 540.4 (M + H)$^+$. Anal. ($C_{29}H_{42}Cl_1N_5O_5 \cdot 1.5H_2O$) C, H; N: calcd, 11.61; found, 10.69.

Ac-Lys(Ac-Thr)-Phe-NMeBzl (26c). To an ice-cooled solution of compound **26b** (510 mg, 0.885 mmol) in CH_2Cl_2 (15 mL) were added triethylamine (179 mg, 1.77 mmol) and acetic anhydride (90 mg, 0.885 mmol). The solution was stirred for 10 min at this temperature, washed successively with sodium hydrogen carbonate solution and brine, and concentrated. The crude product was purified on a column of silica gel (12 g) eluting with $CHCl_3$–MeOH (30:1 to 15:1, gradient elution) to give **26c** as an amorphous solid (0.45 g, 87.3%): mp 156–159 °C (EtOAc); $[\alpha]^{25}_D$ = –6.95° (c = 1.0, $CHCl_3$); IR (Nujol) 3300, 1655 (sh), 1640, 1630, 1540 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.01 (3 H, d, J = 6.3 Hz), 1.0–1.6 (6 H, m), 1.83 (3 H, s), 1.90 (3 H, s), 2.72 and 2.79 (3 H, 2 s), 2.8–3.1 (4 H, m), 3.94 (1 H, m), 4.11 (1 H, dd, J = 4.2, 8.6 Hz), 4.23 (1 H, m), 4.37 (1 H, d, J = 15 Hz), 4.50 (1 H, d, J = 15 Hz), 4.77 (1 H, d, J = 5.2 Hz), 4.93 (1 H, m), 7.0–7.3 (10 H, m), 7.6–7.7 (2 H, m), 7.89 (1 H, d, J = 8 Hz), 8.33 (1 H, d, J = 8.2 Hz); R_f = 0.48 (system A). Anal. ($C_{31}H_{43}N_5O_6 \cdot 0.5H_2O$) C, H, N.

Benzoyl-Lys(Ac-Thr)-Phe-NMeBzl (26d) was prepared similarly to **26c**, except using benzoyl chloride: 61.6% yield; mp 129–131 °C (EtOAc); $[\alpha]^{25}_D$ = –8.91° (c = 1.0, $CHCl_3$); IR (Nujol) 3300, 1655 (sh), 1640, 1630, 1525 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.00 (3 H, d, J = 6.3 Hz), 1.2–1.5 (4 H, m), 1.5–1.7 (2 H, m), 1.89 (3 H, s), 2.72 and 2.80 (3 H, 2 s), 2.8–3.1 (4 H, m), 3.92 (1 H, m), 4.10 (1 H, dd, J = 4.3, 8.6 Hz), 4.38 (1 H, d, J = 15 Hz), 4.49 (1 H, d, J = 15 Hz), 4.75 (1 H, d, J = 5.2 Hz), 5.0 (1 H, m), 7.0–7.3 (11 H, m), 7.4–7.9 (7 H, m), 8.3–8.4 (2 H, m); R_f = 0.54 (system A). Anal. ($C_{36}H_{45}N_5O_6 \cdot H_2O$) C, H, N.

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(16) In the program FIT, the variable torsion angles are optimized to minimize the error function *E*, which is defined in eq 1:

$$E = \sum w_i d_i + A \qquad (1)$$

where d_i is the distance between *i*th corresponding atomic pair which is selected for superimposing the molecules and w_i is weight factor on *i*th atomic pair. *A* in eq 1 is the conformational energy term adopted to avoid unfavorable conformations. The value of *A* is defined as the Lennard–Jones type nonbonded potential-function which is used in the SYBYL default force field (see ref 18):

$$A = \sum [k_{ab} \times (1.0/L^{12} - 2.0/L^{6})]$$

where k_{ab} is the geometric mean of the *k* constants associated between atom a and atom b, and *L* is the distance between the two atoms divided by the sum of their radii.

(17) The following nine carbon atoms were selected for the superimposition procedure: the 1-, 3-, and 5-positions of the both benzene rings in the Phe-NMeBzl structure and the 3-, 5-, and 7-positions in the indole nucleus.

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