Studies on Neurokinin Antagonists. 4. Synthesis and Structure–Activity Relationships of Novel Dipeptide Substance P Antagonists: 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 and Its Related Compounds†

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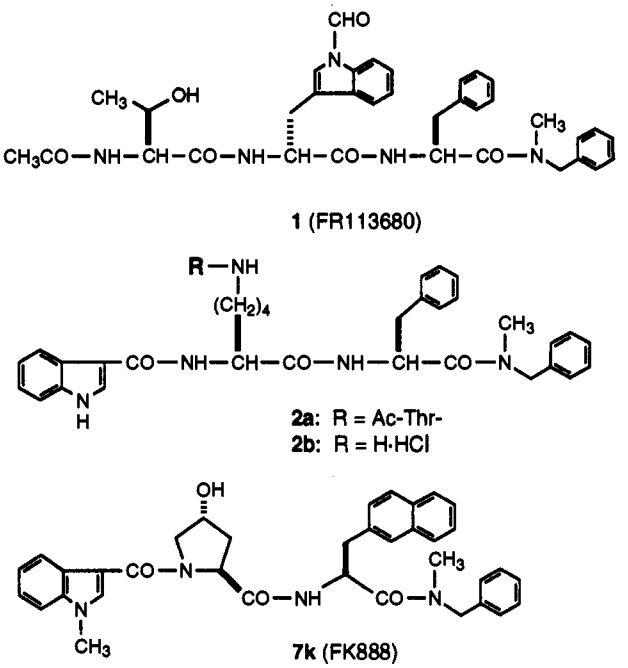
As an extension of our studies on discovering a novel substance P (SP) antagonist, we modified the previously reported dipeptide, N^2-[N^2-(1*H*-indol-3-ylcarbonyl)-L-lysyl]-*N*-methyl-*N*-(phenylmethyl)-L-phenylalaninamide (**2b**). The lysine part in **2b** was first optimized to a (2*S*,4*R*)-hydroxyproline derivative (**3h**), which is 2-fold more potent than **2b** in [^{3}H]SP binding assay using guinea pig lung membranes. Next we modified the 1*H*-indol-3-ylcarbonyl part in **3h**. Introduction of a methyl group at the indole nitrogen enhanced the oral activity, while retaining the binding activity. Finally, we modified the phenylalanine part to culminate in the most potent compound **7k** (FK888), which is a potent SP antagonist with NK_1 selectivity as well as oral activity.

Recently, intense interest has been focused on discovering antagonists for the neurokinins, i.e., substance P (SP), neurokinin A, and neurokinin B.[1] These peptides are known to exert their biological activity by specific binding to three distinct receptors, NK_1, NK_2, and NK_3.[2] Since the physiological significance of the neurokinins has been both centrally and peripherally implied, potential clinical applications of their antagonists would be expected.

Historically, the exploratory study on neurokinin antagonists was initiated by Folkers' group who reported the synthesis of SP analogs in the late 1970s.[3] Their approach has so far produced peptide type antagonists, e.g., (D-Arg^2,D-Trp^{7,9},Leu^{11})-SP (Spantide)[4] and further modified analog Spantide II.[5] Other structural classes of peptide antagonists have been also reported, such as cyclic peptides[6] and SP analogs in which the peptide bond was modified.[7] Apart from these synthetic approaches, a chemical file screening or random screening method has been applied to the search for neurokinin antagonists. This method has led to the discovery of non-peptide antagonists CP-96,345,[8] RP-67,580,[9] SR-48,968,[10] and so on.[11]

Independent of these discoveries, we have searched for a low-molecular-weight SP antagonist, which can be applied as a remedy for respiratory diseases such as asthma or bronchitis, because an involvement of SP in these diseases was suggested.[12] In the preceding papers,[13,14] we reported the discovery of a potent tripeptide SP antagonist, Ac-Thr-D-Trp(CHO)-Phe-NMeBzl (**1**, FR113680). Subsequently, we designed a novel branched tripeptide, compound **2a**, by reconstructing the structure of **1**, and we also demonstrated that even a dipeptide **2b** worked as an antagonist.[15] The discovery of **2b** successfully reduced the molecular size by one amino acid unit. However, **2b** was found to exhibit about half potency in the binding assay in comparison with **1** and also to be inactive when administered orally. We thus continued our search for a more potent compound with better pharmacological features. This paper deals with the chemical modification of **2b**, thereby leading to a highly potent 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 (**7k**, FK888).[16,17]

Chart 1



Strategy for Chemical Modification of 2b. As shown

† Abbreviations follow IUPAC–IUB Joint Commission on Biochemical Nomenclature 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; NMeBzl,*N*-methyl-*N*-(phenylmethyl)amide; (2*S*,4*R*)Hyp, *trans*-4-hydroxy-L-proline; (2*S*,4*S*)Hyp, *cis*-4-hydroxy-L-proline; Phe(2-F), 2-fluoro-L-phenylalanine; Phe(3-F), 3-fluoro-L-phenylalanine; Phe(4-F), 4-fluoro-L-phenylalanine; Phe(3-CF_3), 3-(trifluoromethyl)-L-phenylalanine; Phe(4-CF_3), 4-(trifluoromethyl)-L-phenylalanine; Phe(4-OMe), 4-methoxy-L-phenylalanine; Phe(4-NO_2), 4-nitro-L-phenylalanine; Phe(4-NH_2), 4-amino-L-phenylalanine; Phe(4-NHMs), 4-(mesylamino)-L-phenylalanine; Nal, 3-(2-naphthyl)-L-alanine; Nal(6-Me), 3-[2-(6-methylnaphthyl)]-L-alanine; Nal(6-Cl), 3-[2-(6-chloronaphthyl)]-L-alanine; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; IPE, diisopropyl ether; THF, tretrahydrofuran; HPLC, high-performance liquid chromatography.

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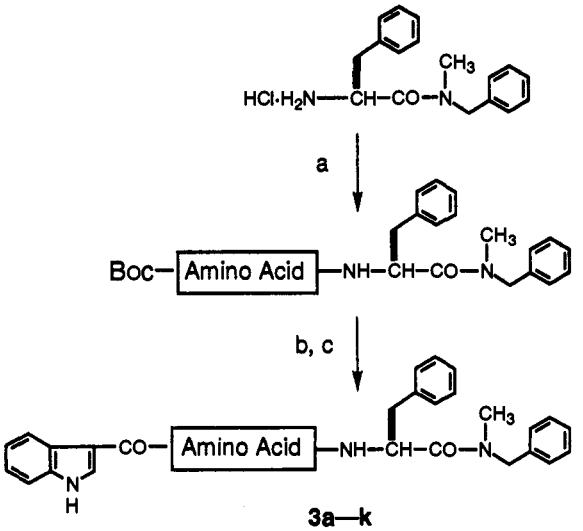
Scheme 1.[a] Synthesis of Dipeptides **3a–k**



[a] (a) Boc-protected amino acid, WSCD–HOBT; (b) HCl, dioxane–CH_2Cl_2; (c) 1*H*-indol-3-ylcarbonyl chloride, bis(trimethylsilyl)-acetamide, CH_2Cl_2. Synthesis of compound 3c is described in ref 15.

in our preceding paper,[15] the L-lysine part in **2a** was able to accept various modifications on its ϵ-amino group without a significant loss of the binding affinity, but the amino acid was strictly required to be L configurated. Hence we supposed that the role of the L-lysine part in **2a** or **2b** was to give a favored spatial orientation of the three aromatic rings, i.e., indole nucleus and two benzenes in the phenylalaninamide part. If we could find an appropriate surrogate which functions in this role instead of the L-lysine, we would have an antagonist with a new structure. According to this postulate, we first planned to modify this part in **2b** into various natural or unnatural L-amino acids. After finding an appropriate surrogate, we could continue to optimize the other parts, the 1*H*-indol-3-ylcarbonyl and the phenylalanine parts. However, throughout the studies the *N*-methyl-*N*-(phenylmethyl)-amide structure at the carboxy terminal was kept fixed, because earlier this particular structure was shown to be ideal for both binding potency and stability to enzymatic metabolism.[14a]

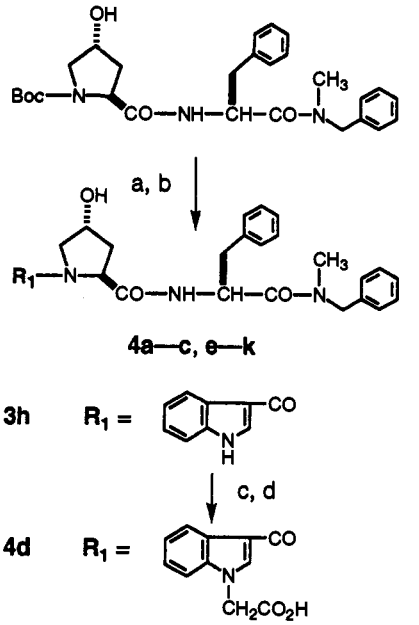
Chemistry

The dipeptide derivatives **3a–k**, which have an 1*H*-indol-3-ylcarbonyl group at the amino terminal, were prepared from H-Phe-NMeBzl·HCl[14a] through the following three-step sequence (Scheme 1): coupling with a Boc-protected amino acid by the WSCD–HOBT method,[18] deprotection of the Boc group with hydrochloric acid in dioxane, and acylation with 1*H*-indol-3-ylcarbonyl chloride in the presence of bis(trimelthylsilyl)acetamide.

The (2*S*,4*R*)Hyp-Phe derivatives **4a–k**, except **4d**, were prepared from Boc-(2*S*,4*R*)Hyp-Phe-NMeBzl by deprotection of the Boc group and subsequent acylation with the corresponding acid using the WSCD–HOBT method (**4a–c,e,g**) or with the corresponding acid chloride (**4f,h–k**) (Scheme 2). Compound **4d** was prepared from **3h** by alkylation with *tert*-butyl bromoacetate using phase-transfer catalyst, followed by cleavage of the *tert*-butyl ester with trifluoroacetic acid.

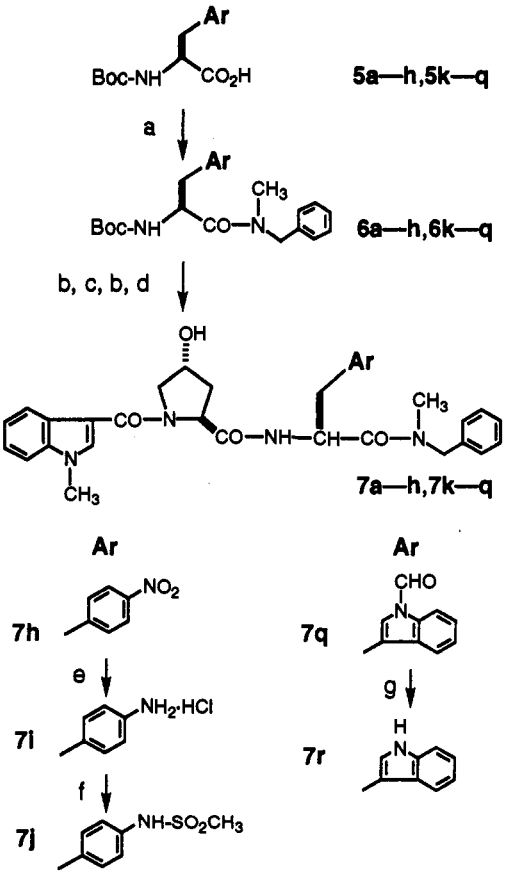
Compounds **7a–h** and **7k–q** were synthesized by a method similar to that utilized for **4a** from N^2-Boc-*N*-methyl-*N*-(phenylmethyl)-3-substituted-L-alaninamides **6**, which were prepared from the corresponding Boc-protected L-amino acids **5** (Scheme 3). Catalytic hydrogenation of **7h** gave **7i**, which was converted into **7j** by acylation with methanesulfonyl chloride. Removal of the formyl group[19] in **7q** afforded **7r**.

Scheme 2.[a] Synthesis of (2*S*,4*R*)Hyp-Phe Derivatives **4a–k**



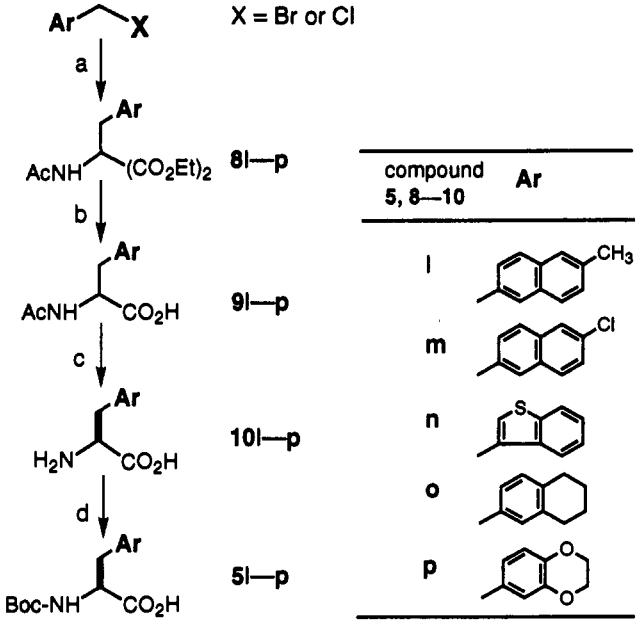
[a] (a) HCl, dioxane–CH_2Cl_2; (b) acid component, WSCD–HOBT, or acid chloride, Et_3N, CH_2Cl_2; (c) *tert*-butyl bromoacetate, cetyltrimethylammonium chloride, NaOH, CH_2Cl_2; (d) trifluoroacetic acid, anisole, CH_2Cl_2.

Scheme 3.[a] Synthesis of Compounds **7a–r**



[a] (a) *N*-Methyl-*N*-(phenylmethyl)amine, WSCD·HCl–HOBT, CH_2Cl_2; (b) HCl, EtOAc; (c) Boc-(2*S*,4*R*)Hyp-OH, WSCD–HOBT, CH_2Cl_2; (d) 1-methyl-1*H*-indole-3-carboxylic acid, WSCD–HOBT, CH_2Cl_2; (e) H_2, Pd/C, HCl, EtOH; (f) MsCl, Et_3N, CH_2Cl_2; (g) 0.1 N NaOH, MeOH.

Scheme 4.[a] Synthesis of Unnatural Amino Acids



[a] (a) NaOEt, diethyl 2-acetamidomalonate, EtOH; (b) KOH, H_2O; (c) Acylase Amano 15000, pH 7.5; (d) $(Boc)_2O$, Et_3N, acetone–H_2O.

The unnatural L-amino acids **10l–p** were synthesized by the conventional acetamidomalonate method with some modifications[20] and then converted to the Boc derivatives **5l–p** (Scheme 4). Optical resolution of the acetylated racemates **9l–p** were performed by treatment with the commercially available acylase.[21] The optical purities of these amino acids were confirmed by HPLC analyses of the corresponding Boc derivatives **5l–p** using a chiral column.[22]

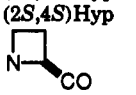
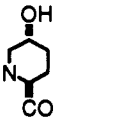
Structure–Activity Relationships

To evaluate the *in vitro* activity of the compounds synthesized in this paper, we employed a receptor binding assay using guinea pig lung membranes and tritium-labeled SP.[13] We also assessed the *in vivo* activity to inhibit airway edema induced by SP in guinea pigs after oral administration of the tested compounds.[17]

Modification of the L-Lysine Part in 2b (Table 1). The L-lysine part in **2b** was changed to various natural or unnatural amino acids. Of the six compounds **3a–f**, L-proline (**3f**) was most potent in the binding assay, with the IC_{50} value of 5.4 nM. L-Serine (**3b**) and L-asparagine (**3d**) retained the activity, but the two compounds with an achiral amino acid, glycine (**3a**) and 2-aminoisobutyric acid (**3e**), were less potent. In contrast, L-aspartic acid (**3c**) and D-proline (**3g**) were completely inactive. To investigate the effect of modifications on the L-proline part in **3f**, four more compounds **3h–k** were tested. The introduction of a hydroxy group (**3h** and **3i**) resulted in retention of the binding activity, regardless of the configuration of the hydroxy group. Reduction of the ring size, (2*S*)-azetidine-2-carboxylic acid derivative **3j**, did not change the activity. However, the homologous hydroxyproline **3k** was only weakly active.

The new dipeptides containing an L-proline or an L-hydroxyproline (**3f**, **3h**, **3i**) were found to be several times more potent than the parent compound **2b**. We chose, however, **3h** as a new lead compound for further chemical modification, based on the following reasons. One reason is that the starting amino acid (2*S*,4*R*)-hydroxyproline is commercially available in large quantities, whereas (2*S*,4*S*)-hydroxyproline is expensive or must be synthesized from (2*S*,4*R*)-hydroxyproline through several steps.[23] Another reason is that a hydroxy group can contribute to increasing water solubility.

Table 1. Modification of the L-Lysine Part in **2b**

compd	amino acid	inhibn of [^{3}H]SP (IC_{50}, nM)[a]
2b	Lys·HCl	14 (n = 2)
3a	Gly	33 (n = 2)
3b	Ser	11 (n = 2)
3c	Asp	*b*
3d	Asn	9 (n = 2)
3e	Aib[c]	23 (n = 2)
3f	Pro	5.4 (n = 2)
3g	D-Pro	*b*
3h	(2*S*,4*R*)Hyp	7.4 (n = 2)
3i	(2*S*,4*S*)Hyp	4.6
3j		8.0
3k		289

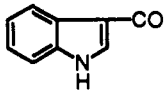
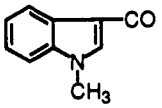
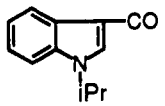
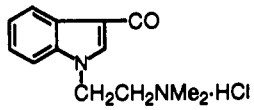
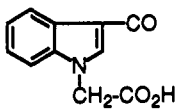
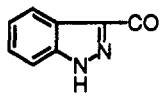
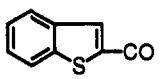
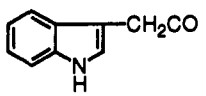
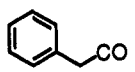
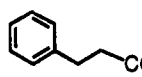
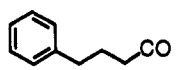
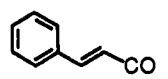
[a] The IC_{50} values were determined by a single experiment unless otherwise noted. Every assay was performed in duplicate. Eight experimental sets were performed for the compounds listed in this table. In every assay, compound 1 was used as a positive control and the IC_{50} value of 1 fell in the range of 6.1 ± 0.8 nM (mean ± SE).[b] No significant inhibition was observed at the concentration of 100 ng/mL. [c] 2-Aminoisobutyric acid.

Modification of the Amino Terminal Part in 3h (Table 2). Of the alkylated compounds at the indole nitrogen, methyl (**4a**) and 2-(*N*,*N*-dimethylamino)ethyl (**4c**) retained potency in the receptor binding assay, whereas isopropyl (**4b**) and carboxymethyl (**4d**) were less potent than **3h**. Replacement of the indole to a 1*H*-indazole (**4e**) resulted in retention of the activity, but 2-benzo[*b*]thienylcarbonyl (**4f**) exhibited less potency. Elongation of the side chain by one methylene unit (**4g**) brought a great loss of the activity. Besides the above compounds, three phenyalkanoyl compounds (**4h–j**) were tested and 3-phenylpropionyl (**4i**) showed maximum activity with an IC_{50} value in the 10^{-8} M range. The modification of the ethylene tether in **4i** to a (*E*)-double bond, i.e., cinnamoyl (**4k**), led to an increase of the activity.

Some of the compounds which showed potent binding affinity were tested for *in vivo* activity after oral administration. Compounds **4a** and **4b** were more potent than the parent compound **3h**. In addition, **4f** and **4k** also exhibited comparable potency. In contrast to these four compounds, **4c** was almost inactive in this test despite having the most potent binding affinity (IC_{50} = 3.5 nM). 1*H*-Indazol-3-ylcarbonyl derivative **4e** was also inactive. On the basis of the above results, we selected **4a** as a lead compound and implemented further modification on the phenylalanine part.

Modification of the Phenylalanine Part in 4a (Table 3). Introduction of a fluorine atom into the 2-, 3-, and 4-positions (**7a–c**) and a trifluoromethyl group into the 3- and 4-positions (**7d**, **7e**) did not change the binding affinity. Other 4-substituted compounds with various functional groups (**7f–i**) were all potently active, with IC_{50} values in the nanomolar range. Compound **7j** having a large mesylamino group was much less potent than the other 4-substituted derivatives. Among the compounds with a bicyclic aromatic L-amino acid, naphthylalanine (**7k**), 3-(2,3-dihydro-1,4-benzodioxin-6-yl)-L-alanine (**7p**), formyltryptophan (**7q**), and tryptophan (**7r**) were highly potent.

Table 2. Modification of the Amino Terminal Part in 3h

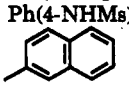
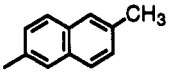
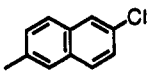
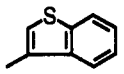
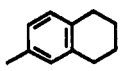
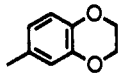
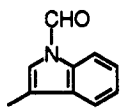
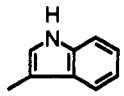
compd	R_1	inhibn of [^{3}H]SP binding (IC_{50}, nM)[a]	suppression of airway edema induced by SP[b] (10 mg/kg, po, inhibn %)
3h		7.4	8 (at 100 mg/kg)
4a		6.4	51
4b		15.9	48
4c		3.5	2
4d		49.7	ND[c]
4e		5.0	0
4f		19.9	37
4g		*d*	ND
4h		139	ND
4i		14.0	4
4j		32	ND
4k		9.0	47

[a] The IC_{50} values were determined by a single experiment unless otherwise noted. Every assay was performed in duplicate. Seven experimental sets were performed for the compounds listed in this table. In every assay, compound 1 was used as a positive control and the IC_{50} value of 1 fell in the range of 5.5 ± 0.3 nM (mean ± SE).[b] Two animals were used in each experiment. The drugs were administered as a DMSO solution. [c] Not determined. [d] 55% inhibition at 100 ng/mL.

However, (6-methylnaphthyl)- and (6-chloronaphthyl)-alanines (**7l**, **7m**) and other bicyclic amino acids (**7n**, **7o**) were all approximately 10 times less potent than **7k**.

The *in vivo* activity of these compounds, when administered orally, did not necessarily correspond with their binding activity. Among the substituted phenylalanine derivatives (**7a–j**), 4-trifluoromethyl (**7e**) exhibited the most potent activity in the *in vivo* test (83% inhibition at 10 mg/kg). In contrast, 4-hydroxy (**7f**), 4-amino (**7i**), and 4-mesylamino (**7j**) almost completely lacked oral activity. The other substituted phenylalanine derivatives were less potent than the unsubstituted phenylalanine derivative **4a**. Of the bicyclic aromatic L-amino acid derivatives, naphthylalanine (**7k**) exhibited the greatest oral activity (86% inhibition at 10 mg/kg). The other compounds with

Table 3. Modification of the Phenylalanine Part in 4a

compd	Ar	inhibn of [^{3}H]SP binding (IC_{50}, nM)[a]	suppression of airway edema induced by SP[b] (po, inhibn %) 100 mg/kg	10 mg/kg
4a	Ph	6.4	75	51
7a	Ph (2-F)	14.0	35	ND[c]
7b	Ph (3-F)	9.2	85	46
7c	Ph (4-F)	4.3	96	30
7d	Ph (3-CF_3)	3.5	66	ND
7e	Ph (4-CF_3)	4.9	94	83
7f	Ph (4-OH)	1.8	11	ND
7g	Ph (4-OMe)	7.6	91	29
7h	Ph (4-NO_2)	7.0	39	19
7i	Ph (4-NH_2·HCl)	5.4	0	ND
7j	Ph(4-NHMs)	25.3	0	ND
7k		1.7[d]	94	86
7l		23.0	28	ND
7m		27.3	ND	ND
7n		10.3	99	34
7o		11.6	87	69
7p		1.1	1	ND
7q		3.5	21	ND
7r		1.7	7	ND

[a] The IC_{50} values were determined by a single experiment unless otherwise noted. Every assay was performed in duplicate. Eleven experimental sets were performed for the compounds listed in this table. In every assay, compound 1 was used as a positive control and the IC_{50} value of 1 fell in the range of 5.9 ± 1.0 nM (mean ± SE).[b] Two animals were used in each experiment. The drugs were administered as a DMSO solution. [c] Not determined. [d] This binding assay was performed at 4 °C throughout the studies in this paper. In an earlier paper (ref 17a), the IC_{50} of compound **7k** was reported as 6.9 nM where the experiment was performed at 25 °C.

bicyclic L-amino acids were only moderately or weakly active. In addition, 3-(2,3-dihydro-1,4-benzodioxin-6-yl)-L-alanine (**7p**), and two L-tryptophan derivatives (**7q** and **7r**) were almost inactive in this test despite potent *in vitro* binding activity.

The oral activity of the two potent compounds, **7e** and **7k**, was further evaluated in the same test except that drugs were administered as 0.5% methylcellulose suspension. Compound **7k** again exhibited potent inhibitory effect, and the ED_{50} value was 4.2 mg/kg (n = 5). In contrast, compound **7e** was less potent than **7k** (43% inhibition at 10 mg/kg). From these results, compound **7k** was shown to be orally the most potent in our series of compounds.

Discussion

In the course of our studies on searching for low molecular weight SP antagonists from a known octapeptide

antagonist, we reported the tripeptide **1**[14] and the branched tripeptide **2a** which led to the discovery of the dipeptide antagonist **2b**.[15] However, we found that **2b** was unsatisfactory in both *in vitro* activity and oral absorption. We thus continued our studies to find a better compound in terms of chemical and pharmacological features by using **2b** as a new lead compound. There were several possibilities for structural optimization, but we focused on modifications to the amino terminal structure as well as the side chains of the dipeptide part in **2b**, while keeping the carboxy terminal structure unchanged.

First we searched for a surrogate for L-lysine, because the role of this part was implied to help the essential aromatic components, the indole and two benzene rings, to align into the desired spatial orientations.[15] As shown in Table 1, a variety of basic and neutral L-amino acids is acceptable, but acidic L-aspartic (**3c**) and D-proline (**3g**) are absolutely refused. Achiral amino acids such as glycine (**3a**) and 2-aminoisobutyric acid (**3c**) were also shown to be unfavorable. These results suggest that this part plays the role in providing the desired spatial orientations to the essential aromatic components rather than in providing an additional interaction with the receptor. The best surrogate for L-lysine is L-proline or 4-hydroxy-L-proline in terms of the potent binding activity. However, we selected compound **3h** having a (2*S*,4*R*)-hydroxyproline for further chemical modification because of the reasons described previously.

Subsequently we modified the 1*H*-indol-3-ylcarbonyl part in **3h** (Table 2). Alkylation on the indole nitrogen can be accepted to retain potent binding activity, although a carboxy is unfavored also in this case. In addition, other aromatic structures could substitute for the indole. However, the side chain length of this part seems to be critical as shown in compounds **4g** and **4h–j**, suggesting that the relative distance between this part and the other moieties in the molecule is strictly required for efficient binding to the receptor. Regarding oral absorption, alkylation of the indol nitrogen, particularly with a methyl group, seems to contribute to increasing the activity. We thus concluded that the best fit for the amino terminal part in **3h** is the (1-methyl-1*H*-indol-3-yl)carbonyl structure (**4a**) in terms of the binding potency and oral absorption.

Finally we optimized the phenylalanine moiety in **4a**. As shown in the previous paper,[13] an aromatic functionality such as a L-phenylalanine is essential in this part. We therefore limited the modifications of this part to substituted L-phenylalanines or bicyclic aromatic L-amino acids. Electronic and lipophilic features of the substituent tend not to influence the binding activity, and some of bicyclic aromatic L-amino acids including an L-2-naphthylalanine (**7k**) had potent binding activity. Regarding oral absorption, increasing lipophilicity such as introduction of a trifluoromethyl (**7e**) or an L-2-naphthylalanine (**7k**) tends to enhance the activity. These facts imply that this class of compounds is absorbed through the lipid bilayer on the digestive tracts by a simple diffusion mechanism.

Of the compounds with the potent *in vivo* and oral activities, we selected **7k** for further developments. As reported previously,[16,17] this compound has been pharmacologically defined as an NK_1 selective antagonist and is now being developed in clinical stage as an antiasthma agent.

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 spectrometer AC-200T (Brucker); chemical shifts were recorded in parts per million (ppm) downfield from tetramethylsilane. Mass spectra (atomospheric pressure chemical ionization, APCI) were recorded on M1000H mass spectrometer (Hitachi, Japan). 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 (20:1); D, $CHCl_3$–MeOH–AcOH (8:1:1); E, *n*-BuOAc–*n*-BuOH–AcOH–H_2O (80:15:40:24). Silica gel column chromatography was performed on Kieselgel 60 (230–400 mesh) (E. Merck, A.G., Darmstadt, Germany). Extraction solvents were dried over magnesium sulfate. Solvents used for reactions were dried over 3A molecular sieves. The acylase for optical resolution of amino acids was from Amano Pharmaceutical Co., Ltd. (Nagoya, Japan). The following Boc-protected amino acids were commercially available: Boc-Gly-OH, Boc-Asn-OH, Boc-Pro-OH, Boc-D-Pro-OH, Boc-Tyr-OH (Kokusan Chemicals Co., Ltd., Tokyo, Japan), Boc-Ser-OH, Boc-(2*S*,4*R*)Hyp-OH (Eibeiss Co. Ltd., Yokohama, Japan), and Boc-Aib-OH, Boc-Phe(4-NO_2)-OH, Boc-Phe(4-OMe)-OH (Sigma Chemical Co., St. Louis, MO). The following Boc-protected L-amino acids were prepared from commercially available L-amino acids according to the usual procedure with di-*tert*-butyl dicarbonate:[24] Boc-Phe(2-F)-OH,[25] Boc-Phe(3-F)-OH,[25] Boc-Phe(4-F)-OH,[25] Boc-Phe(3-CF_3)-OH [mp 140–141 °C, $[\alpha]^{25}_D$ = +4.40° (*c* = 2.0, MeOH)], Boc-Phe-(4-CF_3)-OH,[25] Boc-(2*S*,4*S*)Hyp-OH,[26] (2*S*)-*N*[1]-Boc-azetidine-2-carboxylic acid [mp 97–98 °C, $[\alpha]^{25}_D$ = −120.5° (*c* = 1.0, meOH)], and (2*S*,5*R*)-*N*[1]-Boc-5-hydroxypiperidine-2-carboxylic acid [mp 191–193 °C, $[\alpha]^{25}_D$ = −39.09° (*c* = 0.52, MeOH)]. The starting amino acids Phe(2-F), Phe(3-F), Phe(4-F), Phe(3-CF_3), and Phe-(4-CF_3) were purchased from Asahi Glass Co., ltd. (Tokyo, Japan), and (2*S*,4*S*)Hyp, (2*S*)-azetidine-2-carboxylic acid, (2*S*,5*R*)-5-hydroxypiperidine-2-carboxylic acid were from Sigma Chemical Co. (St. Louis, MO). Boc-Nal-OH (**5k**) was synthesized according to the method in the literature.[27] The reagents WSCD and HOBT were purchased from Eibeiss Co., Ltd. (Yokohama, Japan). Other materials were all commercially available.

Biological Experiments. Receptor Binding Assay. Binding assays were performed by incubating the guinea pig lung membranes in a buffer solution (50 mM Tris-HCl pH 7.5, 5 mM $MnCl_2$, 0.02% BSA, 2 μg/mL chymostatin, 4 μg/mL leupeptin, 40 μg/mL bacitracin) containing [^{3}H]SP (1 nM) at 4 °C for 0.5 h with or without test compounds. At the end of the incubation period, the reaction mixture was filtered through a GF/B glass filter, and the radioactivity was counted in a scintillation counter. Specific binding was defined as binding which was displacable by 5 μM unlabeled SP. The IC_{50} value of the tested compounds was estimated from the displacement curve of the specific binding. The assays were performed in duplicate.

Substance P Induced Airway Edema in Guinea Pigs. Male Hartley strain guinea pigs were given intravenously a solution containing substrate P (1.3 μg/kg) together with Evans Blue dye (20 mg/kg) and heparin (200 IU/kg). Animals were stunned 10 min later, and the trachea and main bronchi were removed. The tissue dye content was colorimetrically quantified after extraction by the light absorbance at 620 nm. The test drug or control vehicle was administered 30 min prior to the challenge of substance P.

Synthesis of the Unnatural L-Amino Acids. Diethyl 2-Substituted-2-acetamidomalonates (8l–p). These unknown compounds were synthesized according to the method described in the literature.[20] **8l**: 58.3% yield; mp 126–127 °C. **8m**: 54.0% yield; mp 138–140 °C. **8n**: 62.0% yield; mp 104–105 °C. **8o**: 63.0% yield; mp 107–109 °C. **8p**: 62.0% yield; mp 97–99 °C. The starting materials for **8l–p** were as follows: 2-(bromomethyl)-6-methylnaphthalene,[28] 2-(chloromethyl)-6-chloronaphthalene,[29]

3-(chloromethyl)-benzo[*b*]thiophene,[30] 6-(bromomethyl)-1,2,3,4-tetrahydronaphthalene,[31] and 6-(chloromethyl)-2,3-dihydro-1,4-benzodioxin.[32]

N^2-Acetyl-3-substituted-DL-alanines (9l–p). These compounds were obtained by alkaline hydrolysis of 8l–p according to the method described in the literature.[25] **9l**: 85.7% yield; mp 183–185 °C. Anal. ($C_{16}H_{17}NO_4 \cdot 0.75H_2O$) C, H, N. **9m**: 95.4% yield; mp 164–165 °C. Anal. ($C_{15}H_{14}ClNO_3 \cdot 0.75H_2O$) C, H, N. **9n**: 92.9% yield; mp 148–150 °C. Anal. ($C_{13}H_{13}NO_3S$) C, H, N. [Preparation of **9n** from 3-(3-benzo[*b*]thienyl)-DL-alanine was reported:[21] mp 154–156 °C]; **9o**: 61.5% yield; mp 147–149 °C. Anal. ($C_{15}H_{19}NO_3$) C, H, N. **9p**: 86.8% yield; mp 157–159 °C. Anal. ($C_{13}H_{15}NO_5$) C, H, N.

H-Nal(6-Me)-OH (10l). Ac-DL-Nal(6-Me)-OH (9l, 6.6 g, 24.3 mmol) was dissolved in 1 N sodium hydroxide (25 mL). To the resulting solution (pH 7.5) were added $CoCl_2 \cdot 6H_2O$ (33 mg) and powder of acylase (Acylase Amano 15000, 0.33 g). The mixture was stirred at 37 °C overnight. During the first 4 h of this reaction period, the pH was maintained 7.5 by addition of 1 N sodium hydroxide. The resulting precipitates were collected by filtration, washed with water, and dried to give 10l (2.84 g, 50.9%): mp 220 °C dec; $[\alpha]^{25}_D = -31.4°$ (c = 0.57, AcOH). The other unnatural L-amino acids **10m–p** were similarly prepared. **10m**: 47.8% yield, mp 227 °C dec; $[\alpha]^{25}_D = -24.6°$ (c = 1.0, AcOH). **10n**: 39.3% yield, mp 248 °C dec; $[\alpha]^{25}_D = +0.58°$ (c = 1.0, 1 N NaOH). **10o**: 44.2% yield, mp 210 °C dec; $[\alpha]^{25}_D = -5.02°$ (c = 0.54, 1 N NaOH). **10p** was used for the next step without isolation.[33]

N^2-Boc-3-substituted-L-alanines (5l–p). These compounds were prepared from 10l–p with di-*tert*-butyl dicarbonate as described in the literature.[24] **5l**: 87.5% yield; mp 122 °C dec (IPE–*n*-Hex); $[\alpha]^{25}_D = +29.2°$ (c = 1.0, MeOH). Anal. ($C_{19}H_{23}NO_4$) C, H, N. **5m**: 95.0% yield; mp 146–148 °C (IPE–*n*-Hex); $[\alpha]^{25}_D = +27.0°$ (c = 0.55, MeOH). Anal. ($C_{18}H_{20}ClNO_4$) C, H, N. **5n**: quantitative yield; $[\alpha]^{25}_D = -18.1°$ (c = 1.0, MeOH). **5o**: 88.8% yield; $[\alpha]^{25}_D = +18.0°$ (c = 0.53, MeOH). **5p**: quantitative yield; $[\alpha]^{25}_D = +10.4°$ (c = 1.0, MeOH). **5n–p** were obtained as oils and were used for the next reaction without further purification.

Optical Purity of the Boc-Protected Unnatural Amino Acids. The optical purity of the synthetic Boc-protected amino acids 5l–p were confirmed by HPLC by using a chiral column Chiral AGP (ChromTech) (4-mm i.d., 10 cm) at room temperature. The eluent was a mixed solvent of 0.02 M phosphate buffer (pH 6.0) and EtOH (10:1). The flow rate was 0.9 mL/min. The content of the D-isomer was quantified by using Boc-D-amino acid as a standard. Boc-D-amino acids were prepared from N^2-acetyl-D-amino acids (the byproducts of the optical resolution step) by acid hydrolysis [concentrated HCl–AcOH (1:1), reflux, 6 h] and subsequent treatment with di-*tert*-butyl dicarbonate. In the case of 5l, the retention time of the L-isomer was 6.0 min and that of the D-isomer was 7.7 min with baseline separation. For all cases of 5l–p, the content of the D-isomer was below 0.5%.

Synthesis of N^2-Boc-*N*-methyl-*N*-(phenylmethyl)-2-substituted-L-alaninamides. Boc-Nal-NMeBzl (6k). A solution of Boc-Nal-OH (5k) (15.9 g, 50.5 mmol), *N*-methyl-*N*-(phenylmethyl)amine (6.12 g, 50.5 mmol), and HOBT (6.83 g, 50.5 mmol) in CH_2Cl_2 (160 mL) was ice-cooled. To this solution was added WSCD·HCl (10.7 g, 55.6 mmol). The resulting solution was stirred at this temperature for 2 h and overnight at room temperature and then concentrated, diluted with 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. The residue was crystallized from EtOAc–IPE to give **6k** (18.0 g, 85%): mp 100–101 °C; $[\alpha]^{25}_D = -4.5°$ (c = 1.0, MeOH). Anal. ($C_{26}H_{30}N_2O_3$) C, H, N.

The following compounds, **6a–h,l–q** were prepared similarly to **6k** from the corresponding Boc-protected amino acid. **Boc-Phe(2-F)-NMeBzl (6a)**: 96.2% yield; mp 74–75 °C (IPE–*n*-Hex); $[\alpha]^{25}_D = -0.96°$ (c = 1.0, MeOH). Anal. ($C_{22}H_{27}FN_2O_3$) C, H, N. **Boc-Phe(3-F)-NMeBzl (6b)**: 71.0% yield; mp 102–104 °C (EtOAc–IPE); $[\alpha]^{25}_D = -0.46°$ (c = 1.0, MeOH). Anal. ($C_{22}H_{27}FN_2O_3$) C, H, N. **Boc-Phe(4-F)-NMeBzl (6c)**: 85.2% yield; mp 89–90 °C (IPE–*n*-Hex); $[\alpha]^{25}_D = +2.2°$ (c = 1.0, MeOH). Anal. ($C_{22}H_{27}FN_2O_3$) C, H, N. **Boc-Phe(3-CF_3)-NMeBzl (6d)**: 89.1% yield; mp 105.5–106.5 °C (IPE–*n*-Hex); $[\alpha]^{25}_D = -2.9°$ (c = 1.0, MeOH). Anal. ($C_{23}H_{27}F_3N_2O_3$) C, H, N. **Boc-Phe(4-CF_3)-NMeBzl (6e)**: 78.2% yield; mp 86–88 °C (EtOAc–*n*-Hex); $[\alpha]^{25}_D = -6.7°$ (c = 1.0, MeOH). Anal. ($C_{23}H_{27}F_3N_2O_3$) C, H, N. **Boc-Tyr-NMeBzl (6f)**: 90.1% yield; mp 111–113 °C (EtOAc–IPE); $[\alpha]^{25}_D = +10.72°$ (c = 1.0, MeOH). Anal. ($C_{22}H_{28}N_2O_4$) C, H, N. **Boc-Phe(4-OMe)-NMeBzl (6g)**: 85.5% yield; mp 72–73 °C (IPE–*n*-Hex); $[\alpha]^{25}_D = +9.0°$ (c = 0.5, MeOH). Anal. ($C_{23}H_{30}N_2O_4$) C, H, N. **Boc-Phe(4-NO_2)-NMeBzl (6h)**: 89.2% yield; mp 110–111 °C (EtOAc–IPE); $[\alpha]^{25}_D = -17.6°$ (c = 1.0, MeOH). Anal. ($C_{22}H_{27}N_3O_5$) C, H, N. **Boc-Nal(6-Me)-NMeBzl (6l)**: 91.2% yield; mp 114–115 °C (EtOAc–IPE); $[\alpha]^{25}_D = -4.7°$ (c = 1.0, MeOH). Anal. ($C_{22}H_{27}N_2O_3$) H, N; C: calcd, 74.97; found, 75.57. **Boc-Nal(6-Cl)-NMeBzl (6m)**: 64.4% yield; mp 99–103 °C (EtOAc–IPE); $[\alpha]^{25}_D = -7.9°$ (c = 0.86, MeOH). Anal. ($C_{26}H_{29}ClN_2O_3$) C, H, N. **N^2-Boc-*N*-methyl-*N*-(phenylmethyl)-3-(3-benzo[*b*]thienyl)-L-alaninamide (6n)**: 88.3% yield; mp 87–89 °C (IPE); $[\alpha]^{25}_D = +11.6°$ (c = 0.89, MeOH). Anal. ($C_{24}H_{28}N_2O_3S$) C, H, N. The compounds **6o–q** were obtained as oils and used for the next step without further purification.

Synthesis of Dipeptides Acylated with 1*H*-Indol-3-ylcarbonyl Group. (1*H*-Indol-3-ylcarbonyl)-(2*S*,4*R*)Hyp-Phe-NMeBzl (3h). A solution of Boc-(2*S*,4*R*)Hyp-OH (1.80 g, 7.78 mmol), H-Phe-NMeBzl·HCl[14a] (2.37 g, 7.78 mmol), and HOBT (1.05 g, 7.78 mmol) in CH_2Cl_2 (50 mL) was ice-cooled. To this solution was added WSCD (1.21 g, 7.8 mmol). The resulting solution was stirred at this temperature for 1 h and at room temperature overnight. The reaction mixture was concentrated, 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. Evaporation of the solvent gave Boc-(2*S*,4*R*)Hyp-Phe-NMeBzl as an amorphous solid (3.8 g, quantitative yield). This product (3.8 g, 7.89 mmol) was dissolved in CH_2Cl_2 (35 mL). The solution was ice-cooled, and 4 N hydrochloric acid (30 mL) in dioxane was added. The solution was stirred at this temperature for 10 min and at room temperature for 1 h. The reaction mixture was concentrated, and the residue obtained was triturated with IPE. The precipitates, which were identified as H-(2*S*,4*R*)Hyp-Phe-NMeBzl·HCl, were collected by filtration. This hydrochloride (3.67 g) was dissolved in CH_2Cl_2 (30 mL), and the solution was ice-cooled. To the solution were added bis(trimethylsilyl)acetamide (5.65 g, 27.8 mmol) and 1*H*-indol-3-ylcarbonyl chloride (1.70 g, 9.47 mmol). 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 **3h** as an amorphous solid (3.3 g, 93.6%): $[\alpha]^{25}_D = -130.6°$ (c = 2, $CHCl_3$); IR (Nujol) 3250, 1630, 1590 (sh), 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.7–2.1 (2 H, m), 2.65–3.1 (5 H, m), 3.65 (d, J = 10 Hz) and 3.9 (m) (1H), 4.2–4.6 (3 H, m), 4.7 (1 H, m), 4.9–5.1 (2 H, m), 6.9–7.3 (12 H, m), 7.45 (1 H, d, J = 7 Hz), 7.85 (1 H, br s), 8.03 (1 H, d, J = 7 Hz), 8.4 (1 H, m), 11.64 (1 H, s); R_f = 0.41 (system A). Anal. ($C_{31}H_{32}N_4O_4 \cdot 0.5H_2O$) C, H, N.

Compounds **3a,b,d–g,i–k** were prepared similarly to **3h** from the common starting material H-Phe-NMeBzl·HCl, using the corresponding Boc-protected amino acids and 1*H*-indol-3-ylcarbonyl chloride.

(1*H*-Indol-3-ylcarbonyl)-Gly-Phe-NMeBzl (3a): 92.1% yield (amorphous solid); $[\alpha]^{25}_D = -8.8°$ (c = 1.0, $CHCl_3$); IR (Nujol) 3250, 1630, 1540 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.76 and 2.83 (3 H, 2 s), 2.8–3.1 (4 H, m), 3.7–4.0 (2 H, m), 4.3–4.8 (2 H, m), 5.0 (1 H, m), 7.0–7.3 (12 H, m), 7.4–7.5 (1 H, m), 8.0–8.2 (3 H, m), 8.3–8.5 (1 H, m), 11.57 (1 H, s); R_f = 0.58 (system A). Anal. ($C_{28}H_{28}N_4O_3 \cdot 0.5H_2O$) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Ser-Phe-NMeBzl (3b): 75.2% yield (amorphous solid); $[\alpha]^{25}_D = -4.3°$ (c = 1.0, DMF); IR (Nujol) 3270, 1625, 1535 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.72 and 2.81 (3 H, 2 s), 2.8–3.1 (2 H, m), 3.6–3.7 (2 H, m), 4.3–4.7 (3 H, m), 4.92 (1 H, t, J = 6 Hz), 5.03 (1 H, m), 7.0–7.3 (12 H, m), 7.5 (1 H, m), 7.8 (1 H, m), 8.1–8.2 (2 H, m), 8.3–8.4 (1 H, m), 11.62 (1 H, s); R_f = 0.48 (system A). Anal. ($C_{29}H_{30}N_4O_4$) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Asn-Phe-NMeBzl (3d): 32.2% yield; mp 199–200 °C (EtOAc–IPE); $[\alpha]^{25}_D$ = −21.4° (*c* = 1.0, DMF); IR (Nujol) 3290, 1665, 1630, 1535 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.45–2.70 (2 H, m), 2.73 and 2.81 (3 H, 2 s), 2.8–3.1 (2 H, m), 4.3–4.6 (2 H, m), 4.75–5.05 (2 H, m), 6.93 (1 H, s), 7.0–7.4 (13 H, m), 7.4–7.5 (1 H, m), 8.0–8.4 (4 H, m), 11.63 (1 H, s); R_f = 0.47 (system B). Anal. ($C_{30}H_{31}N_5O_4$·0.5H_2O) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Aib-Phe-NMeBzl (3e): 59.5% yield (amorphous solid); $[\alpha]^{25}_D$ = +12.4° (*c* = 0.88, DMF); IR (Nujol) 3270, 1630, 1535, 1495 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.41 and 1.45 (6 H, 2 s), 2.70 and 2.87 (3 H, 2 s), 2.8–3.1 (2 H, m), 4.3–4.7 (2 H, m), 4.9–5.1 (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), 11.60 (1 H, s); R_f = 0.47 (system B). Anal. ($C_{30}H_{32}N_4O_3$·0.5H_2O) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-Pro-Phe-NMeBzl (3f): 49.4% yield (amorphous solid); $[\alpha]^{25}_D$ = −93.1° (*c* = 0.62, $CHCl_3$); IR (Nujol) 3250, 1640, 1590, 1520 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75–1.85 (2 H, m), 1.96–2.05 (2 H, m), 2.43 and 2.80 (3 H, 2 s), 2.94–3.13 (2 H, m), 3.45–3.5 (2 H, m), 4.12 (1 H, d, *J* = 10 Hz), 4.50 (1 H, d, *J* = 10 Hz), 4.67–4.8 (1 H, m), 5.1 (1 H, m), 6.98–7.30 (14 H, m), 7.52 (1 H, m), 8.13 (1 H, m), 10.21 (1 H, s); R_f = 0.60 (system A). Anal. ($C_{31}H_{32}N_4O_3$·0.5H_2O) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-D-Pro-Phe-NMeBzl (3g): 70.7% yield (amorphous solid) $[\alpha]^{25}_D$ = +59.4° (*c* = 0.52, MeOH); IR (Nujol) 3250, 1650, 1630, 1590, 1530 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.4–2.1 (4 H, m), 2.75–3.1 (5 H, m), 3.71 (2 H, m), 4.3–4.7 (3 H, m), 4.85–5.15 (1 H, m), 7.0–7.3 (12 H, m), 7.43 (1 H, d, *J* = 7.5 Hz), 7.80 (1 H, br s), 8.06 (1 H, d, *J* = 7.4 Hz), 8.4–8.6 (1 H, m), 11.6 (1 H, s); R_f = 0.40 (system A). Anal. ($C_{31}H_{32}N_4O_3$) C, H, N.

(1*H*-Indol-3-ylcarbonyl)-(2*S*,4*S*)Hyp-Phe-NMeBzl (3i): 48.3% yield; mp 234–236 °C (EtOH–H_2O); $[\alpha]^{25}_D$ = −72.2° (*c* = 0.49, MeOH); IR (Nujol) 3440, 3250, 1665, 1630, 1595 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.65–1.85 (1 H, m), 2.20–2.45 (1 H, m), 2.67 and 2.72 (3 H, 2 s), 2.7–3.1 (2 H, m), 3.7 (1 H, m), 3.85–4.0 (1 H, m), 4.15–4.3 (1 H, m), 4.40 (2 H, s), 4.55–4.7 (1 H, m), 4.80–5.05 (1 H, m), 5.28 (1 H, br s), 6.9–7.0 (2 H, m), 7.0–7.3 (10 H, m), 7.44 (1 H, d, *J* = 7.5 Hz), 7.86 (1 H, s), 8.02 (1 H, d, *J* = 8 Hz), 8.45 (1 H, d, *J* = 8 Hz), 11.66 (1 H, s); R_f = 0.45 (system B). Anal. ($C_{31}H_{32}N_4O_4$·0.5H_2O) C, H, N.

***N*^{2}-[[(2*S*)-1-(1*H*-Indol-3-ylcarbonyl)azetidin-2-yl]carbonyl]-*N*-methyl-*N*-(phenylmethyl)-L-phenylalaninamide (3j)**: 19.8% yield (amorphous solid); $[\alpha]^{25}_D$ = −170.0° (*c* = 0.50, MeOH); IR (Nujol) 3180, 1640, 1630, 1590, 1570 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.9–2.1 (1 H, m), 2.3–2.5 (1 H, m), 2.74 and 2.84 (3 H, 2 s), 2.8–3.1 (2 H, m), 4.1–4.6 (4 H, m), 4.8–5.1 (2 H, m), 7.0–7.4 (12 H, m), 7.4–7.5 (1 H, m), 7.78 (1 H, s), 8.15 (1 H, d, *J* = 8 Hz), 8.5–8.7 (1 H, m), 11.74 (1 H, s); R_f = 0.63 (system A). Anal. ($C_{30}H_{30}N_4O_3$) C, H, N.

***N*^{2}-[[(2*S*,5*R*)-5-Hydroxy-1-(1*H*-indol-3-ylcarbonyl)piperidin-2-yl]carbonyl]-*N*-methyl-*N*-(phenylmethyl)-L-phenylalaninamide (3k)**: 68.9% yield (amorphous solid); $[\alpha]^{25}_D$ = −101.6° (*c* = 0.50, MeOH); IR (Nujol) 3250, 1645, 1520 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.3–1.6 (2 H, m), 1.7–2.1 (2 H, m), 2.79 and 2.89 (3 H, 2 s), 2.9–3.3 (3 H, m), 3.6–3.7 (1 H, m), 3.9–4.1 (1 H, m), 4.35–4.65 (2 H, m), 4.72 (1 H, d, *J* = 3 Hz), 4.9–5.1 (2 H, m), 7.0–7.4 (12 H, m), 7.44 (1 H, d, *J* = 7 Hz) 7.7–7.9 (2 H, m), 8.1–8.2 (1 H, m), 11.53 (1 H, s); R_f = 0.46 (system B). Anal. ($C_{32}H_{34}N_4O_4$·0.75H_2O) C, H, N.

Synthesis of Dipeptides Acylated with the (1-Methyl-1*H*-indol-3-yl)carbonyl Group. [(1-Methyl-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Nal-NMeBzl (7k). The starting material **6k** (21.3 g, 50.9 mmol) was dissolved in EtOAc (53 mL), and the solution was ice-cooled. To this solution was added 4 N hydrochloric acid (140 mL) in EtOAc. The mixture was stirred at this temperature for 10 min and at room temperature for 80 min and was concentrated under reduced pressure. The crystalline residue obtained was collected by filtration, washed with EtOAc, and dried to give H-Nal-NMeBzl·HCl (17.0 g, 94.3% yield): mp 156–158 °C; $[\alpha]^{25}_D$ = +24.0° (*c* = 1.0, MeOH). This hydrochloride (17.0 g, 47.9 mmol), Boc-(2*S*,4*R*)Hyp-OH (11.1 g, 47.9 mmol), and HOBT (6.47 g, 47.9 mmol) were suspended in CH_2Cl_2. The mixture was ice-cooled, and WSCD (7.42 g, 47.9 mmol) was added. The mixture was stirred at this temperature for 0.5 h and for 2 h at room temperature, concentrated, diluted with 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 Boc-(2*S*,4*R*)Hyp-Nal-NMeBzl as a amorphous solid (27.8 g, quantitative yield). This crude product (27.8 g) was dissolved in CH_2Cl_2 (280 mL), and the solution was ice-cooled. To this solution was added 4 N hydrochloric acid (210 mL) in EtOAc. This mixture was stirred at this temperature for 5 min and at room temperature for 45 min and was concentrated under reduced pressure. The residue was triturated with IPE, filtered, and dried to give H-(2*S*,4*R*)Hyp-Nal-NMeBzl·HCl (22.5 g, quantitative yield). This hydrochloride (48 mmol), 1-methyl-1*H*-indole-3-carboxylic acid[34] (8.57 g, 48.9 mmol), and HOBT (6.50 g, 48.1 mmol) were mixed in CH_2Cl_2 (440 mL) and the solution was ice-cooled. To this solution was added WSCD (7.60 g, 49 mmol). The mixture was stirred at this temperature for 1 h and at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was diluted with 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. The crude material was crystallized from EtOAc to give **7k** (26.0 g, 91.9%): mp 115 °C; $[\alpha]^{25}_D$ = −142.5° (*c* = 1.0, MeOH); IR (Nujol) 3430, 3300, 1656, 1600, 1574, 1535 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.7–2.2 (2 H, m), 2.71 and 2.80 (3 H, 2 s), 3.0–3.25 (2 H, m), 3.6–3.7 (1 H, m), 3.85 (3 H, s), 3.8–4.0 (1 H, m), 4.2–4.55 (3 H, m), 4.65–4.8 (1 H, m), 5.0–5.2 (2 H, m), 6.9–7.3 (7 H, m), 7.4–7.55 (4 H, m), 7.7–7.9 (5 H, m), 8.08 (1 H, d, *J* = 7 Hz), 8.5–8.6 (1 H, m); R_f = 0.55 (system A); MS (APCI) *m/z* 589 (M + 1)$^+$. Anal. ($C_{36}H_{36}N_4O_4$) C, H, N.

Compounds **4a** and **7a–h,l–q** were prepared similarly to **7k** from the corresponding *N*^{2}-Boc-*N*-methyl-*N*-(phenylmethyl)-2-substituted-L-alaninamides.

[(1-Methyl-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Phe-NMeBzl (4a) was prepared from Boc-Phe-NMeBzl:[14a] 74.6% yield; mp 122–124 °C (EtOH); $[\alpha]^{25}_D$ = −113.1° (*c* = 0.57, MeOH); IR (Nujol) 3400, 3250, 1656, 1630, 1600, 1570 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.7–2.1 (2 H, m), 2.69 and 2.77 (3 H, 2 s), 2.9–3.1 (2 H, m), 3.6–3.7 (1 H, m), 3.85 (1 H, m), 3.9 (3 H, s), 4.2–4.6 (3 H, m), 4.7 (1 H, m), 4.9–5.1 (2 H, m), 7.0–7.3 (12 H, m), 7.49 (1 H, d, *J* = 8 Hz), 7.9 (1 H, br s), 8.1 (1 H, d, *J* = 8 Hz), 8.4 (1 H, m); R_f = 0.43 (system A); MS (APCI) *m/z* 539 (M + 1)$^+$. Anal. ($C_{32}H_{34}N_4O_4$) C, H, N.

[(1-Methyl-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Phe(2-F)-NMeBzl (7a) was prepared from **6a**: 79.4% yield; mp 113–114 °C (EtOAc–IPE); $[\alpha]^{25}_D$ = −107.6° (*c* = 0.52, MeOH); IR (Nujol) 3420, 3290, 3100, 1655, 1640, 1600, 1570, 1535 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.7–1.9 (1 H, m), 1.9–2.1 (1 H, m), 2.67 and 2.83 (3 H, 2 s), 2.8–3.2 (2 H, m), 3.6 (1 H, m), 3.7–4.0 (4 H, m), 4.2–5.0 (1 H, m), 5.0 (2 H, m), 6.9–7.4 (11 H, m), 7.50 (1 H, d, *J* = 8 Hz), 7.9 (1 H, s), 8.05 (1 H, d, *J* = 8 Hz), 8.4 (1 H, m); R_f = 0.20 (system C); MS (APCI) *m/z* 557 (M + 1)$^+$. Anal. ($C_{32}H_{33}FN_4O_4$) H, N; C: calcd, 69.05; found, 68.49.

[(1-Methyl-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Phe(3-F)-NMeBzl (7b) was prepared from **6b**: 80.2% yield; mp 193–194 °C (EtOAc–IPE); $[\alpha]^{25}_D$ = −127.1° (*c* = 1.0, MeOH); IR (Nujol) 3350, 3270, 1685, 1650, 1590, 1545 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.7–1.9 (1 H, m), 1.9–2.1 (1 H, m), 2.71 and 2.84 (3 H, 2 s), 2.8–3.1 (2 H, m), 3.65 (1 H, m), 3.85 (3 H, s), 3.9 (1 H, m), 4.29 (1 H, br s), 4.43 (2 H, s), 4.7 (1 H, m), 4.9–5.1 (2 H, m), 7.0–7.3 (11 H, m), 7.49 (1 H, d, *J* = 8 Hz), 7.89 (1 H, br s), 8.06 (1 H, d, *J* = 8 Hz), 8.4 (1 H, m); R_f = 0.60 (system A); MS (APCI) *m/z* 557 (M + 1)$^+$. Anal. ($C_{32}H_{33}FN_4O_4$) C, H, N.

[(1-Methyl-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Phe(4-F)-NMeBzl (7c) was prepared from **6c**: 71.7% yield; mp 109–111 °C (EtOAc–IPE); $[\alpha]^{25}_D$ = −117.4° (*c* = 0.5, MeOH); IR (Nujol) 3430, 3270, 1655, 1635, 1605, 1570, 1535 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.7–2.1 (2 H, m), 2.70 and 2.81 (3 H, 2 s), 2.8–3.1 (2 H, m), 3.65 (1 H, m), 3.86 (3 H, s), 3.9 (1 H, m), 4.2–4.6 (3 H, m), 4.7 (1 H, m), 4.9 (1 H, m), 5.0 (1 H, m), 6.9–7.4 (11 H, m), 7.49 (1 H, d, *J* = 8 Hz), 8.0 (1 H, br s), 8.06 (1 H, d, *J* = 8 Hz), 8.4 (1 H, m); R_f = 0.61 (system A); MS (APCI) *m/z* 557 (M + 1)$^+$. Anal. ($C_{32}H_{33}FN_4O_4$·0.5H_2O) C, H, N.

[(1-Methyl-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Phe(3-CF_3)-NMeBzl (7d) was prepared from **6d**: 75.7% yield; mp 171–172 °C (EtOAc–IPE); $[\alpha]^{25}_D$ = −116.7° (*c* = 0.51, MeOH); IR (Nujol) 3360, 1685, 1655, 1580, 1565, 1530 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.6–1.8 (1 H, m), 1.8–2.1 (1 H, m), 2.71 and 2.85 (3 H, 2 s), 2.8–3.3 (2 H, m), 3.6 (1 H, m), 3.7–4.0 (1 H, m), 3.86 (3 H, s), 4.2–4.7 (4 H, m), 4.8–5.1 (1 H, m), 5.0 (1 H, m), 6.9–7.3 (7

H, m), 7.3–7.7 (5 H, m), 7.9 (1 H, s), 8.05 (1 H, d, J = 8 Hz), 8.3–8.6 (1 H, m); R_f = 0.54 (system C); MS (APCI) m/z 607 $(M + 1)^+$. Anal. ($C_{33}H_{33}F_3N_4O_4$) C, H, N.

[(1-Methyl-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Phe(4-CF_3)-NMeBzl (7e) was prepared from **6e**: 6.28% yield; mp 183–184 °C (EtOAc–IPE); $[\alpha]^{25}_D$ = −116.1° (c = 1.0, MeOH); IR (Nujol) 3270, 1680, 1655, 1580, 1570, 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.6–1.9 (1 H, m), 1.9–2.1 (1 H, m), 2.72 and 2.85 (3 H, 2 s), 2.9–3.2 (2 H, m), 3.66 (1 H, d, J = 5 Hz), 3.85 (3 H, s), 3.8–4.0 (1 H, m), 4.2–4.5 (3 H, m), 4.6 (1 H, m), 5.0 (2 H, m), 7.0–7.6 (12 H, m), 7.99 (1 H, s), 8.07 (1 H, d, J = 8 Hz), 8.5 (1 H, m); R_f = 0.50 (system A); MS (APCI) m/z 607 $(M + 1)^+$. Anal. ($C_{33}H_{33}F_3N_4O_4$) C, H, N.

[(1-Methyl-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Tyr-NMeBzl (7f) was prepared from **6f**: 65.7% yield (amorphous solid); $[\alpha]^{25}_D$ = −119.1° (c = 0.52, MeOH); IR (Nujol) 3270, 1630, 1530, 1515 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.8–2.2 (2 H, m), 2.67 and 2.75 (3 H, 2 s), 2.8–3.0 (2 H, m), 3.6–3.7 (1 H, m), 3.8–3.9 (1 H, m), 3.85 (3 H, s), 4.3–4.5 (3 H, m), 4.7–4.8 (1 H, m), 4.9 (1 H, m), 5.0 (1 H, m), 6.53–6.65 (2 H, m), 6.9–7.3 (9 H, m), 7.5 (1 H, d, J = 8 Hz), 7.9 (1 H, s), 8.06 (1 H, d, J = 8 Hz), 8.41 (1 H, m), 9.23 (1 H, s); R_f = 0.30 (system A); MS (APCI) m/z 555 $(M + 1)^+$. Anal. ($C_{32}H_{34}N_4O_5 \cdot 1.2H_2O$) C, H, N.

[(1-Methyl-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Phe(4-OMe)-NMeBzl (7g) was prepared from **6g**: 63.4% yield; mp 172–173 °C (IPE); $[\alpha]^{25}_D$ = −121.2° (c = 1.0, MeOH); IR (Nujol) 3430, 3280, 1655, 1630, 1510 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.7–1.9 (1 H, m), 1.9–2.1 (1 H, m), 2.69 and 2.76 (3 H, 2 s), 2.8–3.0 (2 H, m), 3.6–3.8 (1 H, m), 3.69 (3 H, s), 3.85 (3 H, s), 3.9 (1 H, m), 4.3–4.5 (3 H, m), 4.7 (1 H, m), 4.9 (1 H, m), 5.0 (1 H, m), 6.7–7.4 (10 H, m), 7.49 (2 H, d, J = 8 Hz), 7.89 (1 H, s), 8.06 (1 H, d, J = 8 Hz), 8.40 (1 H, m); R_f = 0.54 (system A); MS (APCI) m/z 569 $(M + 1)^+$. Anal. ($C_{33}H_{36}N_4O_5$) C, H, N.

[(1-Methyl-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Phe(4-NO_2)-NMeBzl (7h) was prepared from **6h**: 67.8% yield; mp 183–184 °C (IPE); $[\alpha]^{25}_D$ = −118.2° (c = 1.0, MeOH); IR (Nujol) 3280, 1690, 1650, 1585, 1545, 1520, 1450 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.7–1.9 (1 H, m), 1.9–2.1 (1 H, m), 2.74 and 2.88 (3 H, 2 s), 2.9–3.2 (2 H, m), 3.6 (1 H, m), 3.85 (3 H, s), 3.9 (1 H, s), 4.2–4.7 (4 H, m), 5.0 (2 H, m), 7.0–7.6 (10 H, m), 7.8–8.1 (4 H, m), 8.5 (1 H, m); R_f = 0.48 (system A); MS (APCI) m/z 584 $(M + 1)^+$. Anal. ($C_{32}H_{33}N_5O_6$), C, H, N.

[(1-Methyl-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Nal(6-Me)-NMeBzl (7l) was prepared from **6l**: 47.7% yield; mp 126 °C (EtOAc); $[\alpha]^{25}_D$ = −133.5° (c = 0.54, MeOH); IR (Nujol) 3420, 3270, 1660, 1630, 1535 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.7–2.1 (2 H, m), 1.7–2.1 (2 H, m), 2.45 (3 H, s), 2.70 and 2.78 (3 H, 2 s), 3.0–3.2 (2 H, m), 3.7 (1 H, m), 3.85 (3 H, s), 3.9 (1 H, s), 4.2–4.5 (3 H, m), 4.7 (1 H, m), 5.0–5.2 (2 H, m), 6.9–7.7 (14 H, m), 7.87 (1 H, s), 8.05 (1 H, d, J = 8 Hz), 8.5 (1 H, m); R_f = 0.50 (system A); MS (APCI) m/z 603 $(M + 1)^+$. Anal. ($C_{37}H_{38}N_4O_4$) C, H, N.

[(1-Methyl-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Nal(6-Cl)-NMeBzl (7m) was prepared from **6m**: 68.9% yield (amorphous solid); $[\alpha]^{25}_D$ = −140.5° (c = 0.54, MeOH); IR (Nujol) 3430, 3320, 1650, 1635, 1600, 1535 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.7–2.1 (2 H, m), 2.72 and 2.82 (3 H, 2 s), 3.0–3.2 (2 H, m), 3.65 (1 H, m), 3.85 (3 H, s), 3.9 (1 H, m), 4.2–4.5 (3 H, m), 4.7 (1 H, m), 5.0 (1 H, m), 5.1 (1 H, m), 6.9–8.1 (16 H, m), 8.5 (1 H, m); R_f = 0.61 (system A); MS (APCI) m/z 623 $(M + 1)^+$. Anal. ($C_{36}H_{35}ClN_4O_4$) H, N; C: calcd, 69.39; found, 68.98.

N^2-[(4*R*)-4-Hydroxy-1-[(1-methyl-1*H*-indol-3-yl)carbonyl]-L-prolyl]-*N*-methyl-*N*-(phenylmethyl)-3-(3-benzo[*b*]thienyl)-L-alaninamide (7n) was prepared from **6n**: 53.1% yield (amorphous solid); $[\alpha]^{25}_D$ = −110.1° (c = 0.62, MeOH); IR (Nujol) 3250, 1660, 1630, 1535 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.7–2.1 (2 H, m), 2.71 (3 H, s), 3.1–3.4 (2 H, m), 3.65 (1 H, m), 3.86 (3 H, s), 3.9 (1 H, m), 4.3–4.6 (3 H, m), 4.7 (1 H, m), 5.0 (1 H, m), 5.2 (1 H, m), 7.0–7.5 (11 H, m), 7.8–8.1 (4 H, m), 8.6 (1 H, m); R_f = 0.55 (system A); MS (APCI) m/z 595 $(M + 1)^+$. Anal. ($C_{34}H_{34}N_4O_4S$) C, H, N.

N^2-[(4*R*)-4-Hydroxy-1-[(1-methyl-1*H*-indol-3-yl)carbonyl]-L-prolyl]-*N*-methyl-*N*-(phenylmethyl)-3-(1,2,3,4-tetrahydronaphthalen-6-yl)-L-alaninamide (7o) was prepared from **6o**: 48.8% yield; mp 118–128 °C (EtOAc); $[\alpha]^{25}_D$ = −111.4° (c = 0.54, MeOH); IR (Nujol) 3450, 3300, 3100, 1660, 1630, 1605 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.69 (4 H, s), 1.7–2.1 (2 H, m), 2.6 (4 H, s), 2.71 and 2.80 (3 H, 2 s), 2.9 (2 H, m), 3.69 (1 H, m), 3.85 (3 H, s), 3.9 (1 H, m), 4.3–4.5 (3 H, m), 4.7 (1 H, m), 4.95 (1 H, m), 5.01 (1 H, m), 6.8–7.5 (13 H, m), 7.9 (1 H, m), 8.04 (1 H, d, J = 8 Hz), 8.4 (1 H, m); R_f = 0.55 (system A); MS (APCI) m/z 593 $(M + 1)^+$. Anal. ($C_{36}H_{40}N_4O_4$) C, H, N.

N^2-[(4*R*)-4-Hydroxy-1-[(1-methyl-1*H*-indol-3-yl)carbonyl]-L-prolyl]-*N*-methyl-*N*-(phenylmethyl)-3-(2,3-dihydro-1,4-benzodioxin-6-yl)-L-alaninamide (7p) was prepared from **6p**: 62.1% yield (amorphous solid); $[\alpha]^{25}_D$ = −113.9° (c = 0.54, MeOH); IR (Nujol) 3300, 1660, 1630, 1590, 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.8–2.2 (2 H, m), 2.70 and 2.81 (3 H, 2 s), 2.6–3.0 (2 H, m), 3.65 (1 H, m), 3.85 (3 H, s), 3.9 (1 H, m), 4.19 (4 H, s), 4.2–4.9 (5 H, m), 5.0 (1 H, m), 6.5–6.8 (3 H, m), 7.0–7.3 (7 H, m), 7.49 (1 H, d, J = 8 Hz), 7.9 (1 H, m), 8.05 (1 H, d, J = 8 Hz), 8.3 (1 H, m); R_f = 0.50 (system A); MS (APCI) m/z 597 $(M + 1)^+$. Anal. ($C_{34}H_{36}N_4O_6 \cdot 1H_2O$) C, H, N.

[(1-Methyl-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Trp(CHO)-NMeBzl (7q) was prepared from **6q**: 96.3% yield (amorphous solid); $[\alpha]^{25}_D$ = −114.2° (c = 1.0, MeOH); IR (Nujol) 3300, 1710, 1635, 1605, 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.7–2.2 (2 H, m), 2.64 and 2.66 (3 H, 2 s), 3.0–3.3 (2 H, m), 3.6–4.0 (5 H, m), 4.3–4.8 (4 H, m), 5.0–5.2 (2 H, m), 7.0–8.3 (15 H, m), 8.7 (1 H, m), 9.2 and 9.6 (1 H, 2 br s); R_f = 0.47 (system A); MS (APCI) m/z 606 $(M + 1)^+$. Anal. ($C_{35}H_{35}N_5O_5 \cdot 0.8H_2O$) C, H; N: calcd, 11.29; found, 10.80.

[(1-Methyl-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Trp-NMeBzl (7r). The compound **7q** (670 mg, 1.11 mmol) was dissolved in MeOH (30 mL). To this solution was added 0.1 N sodium hydroxide (11.1 mL), and the mixture was stirred at room temperature for 20 min. The mixture was concentrated under reduced pressure, diluted with water, and extracted with EtOAc twice. The combined organic layer was washed with brine, and concentrated. The residue was triturated with IPE, filtered, and dried to give **7r** as an amorphous solid (573 mg, 89.4% yield): $[\alpha]^{25}_D$ = −99.6° (c = 1.0, MeOH); IR (Nujol) 3300, 1630, 1600 (sh), 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.7–2.2 (2 H, m), 2.64 and 2.66 (3 H, 2 s), 2.9–3.3 (2 H, m), 3.6–4.0 (5 H, m), 4.2–4.4 (3 H, m), 4.7–4.8 (1 H, m), 5.0–5.2 (2 H, m), 6.8–7.6 (13 H, m), 7.89 (1 H, br s), 8.06 (1 H, d, J = 7 Hz), 8.43 (1 H, br s), 10.83 and 10.87 (1 H, 2 s); R_f = 0.50 (system A); MS (APCI) m/z 578 $(M + 1)^+$. Anal. ($C_{34}H_{35}N_5O_4 \cdot 0.5H_2O$) C, H, N.

[(1-Methyl-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Phe(4-NH_2)-NMeBzl·HCl (7i). A solution of the compound **7h** (0.60 g, 1.03 mmol) in MeOH (40 mL) was hydrogenated over 10% Pd on charcoal (0.06 g) under atomospheric pressure. The mixture was filtered and concentrated. The residue was dissolved in THF (6 mL) and treated with 4 N hydrochloric acid (0.28 mL) in dioxane under ice cooling. The mixture was concentrated, and the residue was triturated with ether, filtered, and dried to give **7i** as an amorphous solid (0.58 g, 91.0% yield): mp 173 °C dec; $[\alpha]^{25}_D$ = −104.1° (c = 0.51, MeOH); IR (Nujol) 3300, 1630, 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.7–2.1 (2 H, m), 2.71 and 2.85 (3 H, 2 s), 2.9–3.2 (2 H, m), 3.6–3.7 (1 H, m), 3.85 (3 H, s), 3.9 (1 H, m), 4.2–4.6 (4 H, m), 4.7 (1 H, m), 5.0 (1 H, m), 7.0–7.6 (12 H, m), 7.9 (1 H, s), 8.06 (1 H, d, J = 7 Hz), 8.45 (1 H, m), 10.3 (3 H, br s); R_f = 0.46 (system A); MS (APCI) m/z 554 $(M + 1)^+$. Anal. ($C_{32}H_{36}ClN_5O_4 \cdot 2.5H_2O$) C, H, N.

[(1-Methyl-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Phe(4-NHMS)-NMeBzl (7j). To an ice-cooled mixture of compound **7i** (0.20 g, 0.34 mmol) and pyridine (107 mg, 1.36 mmol) in CH_2Cl_2 (10 mL) was added methanesulfonyl chloride (47 mg, 0.41 mmol). The mixture was stirred at this temperature for 0.5 h and at room temperature for 3 h. The mixture was concentrated under reduced pressure, diluted with 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. The crude product was purified on a silica gel column (10 g) eluting with $CHCl_3$–MeOH (50:1 to 30:1, gradient elution) to give **7j** as an amorphous solid (158 mg, 73.6% yield): $[\alpha]^{25}_D$ = −110.1° (c = 0.54, MeOH); IR (Nujol) 3350, 3150, 1630, 1600 (sh), 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.7–2.1 (2 H, m), 2.70 and 2.80 (3 H, 2 s), 2.89 (3 H, s), 2.8–3.1 (2 H, m), 3.65 (1 H, m), 3.86 (3 H, s), 3.9 (1 H, m), 4.2–4.6 (3 H, m), 4.7 (1 H, m), 4.8–5.0 (2 H, m), 7.0–7.3 (11 H, m), 7.49 (1 H, d, J = 8 Hz), 7.89 (1 H, s), 8.05 (1 H, d, J = 8 Hz), 8.40 (1 H, m), 9.64 (1 H, s); R_f = 0.50 (system A); MS (APCI) m/z 632 $(M + 1)^+$. Anal. ($C_{33}H_{37}N_5O_6S \cdot 1.2H_2O$) C, H, N.

Synthesis of Dipeptides Acylated with Other Groups.

Compounds **4b,c,e,g** were prepared in a manner similar to the acylation to provide compound **7k**, except that the starting amine was H-(2*S*,4*R*)Hyp-Phe-NMeBzl·HCl and the corresponding acid component was used.

[(1-Isopropyl-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Phe-NMeBzl (4b). A mixture of 1*H*-indole-3-carboxylic acid methyl ester[35] (4.87 g, 27.8 mmol), isopropyl bromide (6.84 g, 55.6 mmol), and potassium carbonate (7.68 g, 55.6 mmol) in DMF (50 mL) was stirred at 70 °C for 2 h. The mixture was concentrated under reduced pressure, diluted with water, and extracted with ether. The organic layer was concentrated, and the crude material was purified by silica gel column chromatography (65 g), eluting with a mixed solvent of CH_2Cl_2 and EtOAc (9:1) to give 1-isopropyl-1*H*-indole-3-carboxylic acid methyl ester as an oil (3.27 g, 54.0% yield). This product was dissolved in MeOH (50 mL), and 1 N NaOH (30 mL) was added. The solution was heated under reflux for 6 h. The mixture was concentrated under reduced pressure, diluted with water (20 mL), and acidified with 1 N hydrochloric acid under ice cooling. The precipitates were collected by filtration, washed with water, and dried to give 1-isopropyl-1*H*-indole-3-carboxylic acid (2.78 g, 91.1% yield from the methyl ester): mp 133–134 °C. This compound was coupled with H-(2*S*,4*R*)Hyp-Phe-NMeBzl·HCl to give **4b**: 60.7% yield; mp 92–96 °C (EtOAc–EtOH); $[\alpha]^{25}_D = -113.5°$ ($c = 0.52$, MeOH); IR (Nujol) 3430, 3300, 1660, 1630, 1605, 1545 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.5 (6 H, br s), 1.7–2.1 (2 H, m), 2.69 and 2.77 (3 H, 2 s), 2.8–3.2 (2 H, m), 3.6–4.1 (2 H, m), 4.2–4.5 (3 H, m), 4.6–5.0 (4 H, m), 6.9–7.3 (12 H, m), 7.58 (1 H, d, $J = 8$ Hz), 7.89 (1 H, br s), 8.04 (1 H, d, $J = 8$ Hz), 8.45 (1 H, m); $R_f = 0.48$ (system A); MS (APCI) m/z 567 $(M + 1)^+$.

[[1-[2-(*N*,*N*-Dimethylamino)ethyl]-1*H*-indol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Phe-NMeBzl·HCl (4c). The amine H-(2*S*,4*R*)Hyp-Phe-NMeBzl·HCl was acylated with 1-[2-(*N*,*N*-dimethylamino)ethyl]-1*H*-indole-3-carboxylic acid.[36] The free amine obtained was treated with 4 N hydrochloric acid in dioxane (2 equiv) in THF, concentrated, triturated with IPE, filtered, and dried to give **4c**: 34.9% yield (amorphous solid); $[\alpha]^{25}_D = -93.2°$ ($c = 0.58$, MeOH); IR (Nujol) 3250, 2650, 1630, 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.75–2.1 (2 H, m), 2.7–3.1 (11 H, m), 3.5 (2 H, m), 3.6–4.0 (2 H, m), 4.3–4.5 (3 H, m), 4.6–5.0 (5 H, m), 7.0–7.3 (12 H, m), 7.73 (1 H, d, $J = 8$ Hz), 8.0–8.2 (2 H, m), 8.47 (1 H, m), 11.28 (1 H, br s); $R_f = 0.25$ (system D); MS (APCI) m/z 596 $(M + 1)^+$.

[(1*H*-Indazol-3-yl)carbonyl]-(2*S*,4*R*)Hyp-Phe-NMeBzl (4e) was prepared by acylation with 1*H*-indazole-3-carboxylic acid:[37] 80.1% yield (amorphous solid); $[\alpha]^{25}_D = -156.9°$ ($c = 0.53$, MeOH); IR (Nujol) 3400, 3220, 1670, 1630, 1615, 1570 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.8–2.3 (2 H, m), 2.59, 2.72 and 2.79 (3 H, 3 s), 2.9–3.1 (2 H, m), 3.7 (1 H, m), 4.1 (1 H, m), 4.2–4.6 (3 H, m), 4.7–4.8 (1 H, m), 5.0 (2 H, m), 5.35 (1 H, m), 6.8–7.3 (11 H, m), 7.4 (1 H, m), 7.6 (1 H, m), 8.17 (1 H, d, $J = 8$ Hz), 8.55 (1 H, m); $R_f = 0.50$ (system A); MS (APCI) m/z 526 $(M + 1)^+$. Anal. ($C_{30}H_{38}N_6O_4$) C, H. N.

[(1*H*-Indol-3-yl)acetyl]-(2*S*,4*R*)Hyp-Phe-NMeBzl (4g) was prepared by acylation with 1*H*-indole-3-acetic acid: 73.8% yield (amorphous solid); $[\alpha]^{25}_D = -63.5°$ ($c = 1.0$, MeOH); IR (Nujol) 3430, 3300, 1645, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.8–2.0 (1 H, m), 2.0–2.2 (1 H, m), 2.7–3.2 (5 H, m), 3.3–3.5 (2 H, m), 3.7 (2 H, s), 4.1–4.3 (1 H, m), 4.3–4.6 (3 H, m), 4.9–5.1 (2 H, m), 6.9–7.6 (15 H, m), 8.35 and 8.82 (1 H, 2 d, $J = 8$ Hz), 10.85 and 10.89 (1 H, 2 s); $R_f = 0.56$ (system A); MS (APCI) m/z 539 $(M + 1)^+$. Anal. ($C_{32}H_{34}N_4O_4 \cdot 0.8H_2O$) C, H, N.

[[1-(Carboxymethyl)-1*H*-indol-3-yl]carbonyl]-(2*S*,4*R*)-Hyp-Phe-NMeBzl (4d). The mixture of the compound **3h** (5.0 g, 9.53 mmol), cetyltrimethylammonium chloride (313 mg), and powdered sodium hydroxide (1.52 g, 38 mmol) in CH_2Cl_2 (100 mL) was ice-cooled. To the mixture was added *tert*-butyl bromoacetate (1.88 g, 9.63 mmol). The mixture was stirred at this temperature for 1 h. The mixture was neutralized with 1 N hydrochloric acid (25 mL), concentrated under reduced pressure, and diluted with water. The pH was adjusted to 3 with 1 N hydrochloric acid, and the mixture was extracted with EtOAc twice. The combined extracts were washed with water and brine. After concentration, the crude product was purified by silica gel column chromatography (120 g), eluting with $CHCl_3$–MeOH (1.5% to 2.5, gradient elution) to give [[1-[(*tert*-butyloxycarbonyl)methyl]-1*H*-indol-3-yl]carbonyl]-(2*S*,4*R*)Hyp-Phe-NMeBzl as an amorphous solid (4.12 g, 67.8%). This product (6.45 mmol) and anisole (4 mL) were dissolved in CH_2Cl_2 (30 mL) and treated with trifluoroacetic acid (10 mL) under ice cooling for 1 h. The mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with cold sodium hydrogen carbonate solution twice. The aqueous layer was acidified with 3 N hydrochloric acid and was extracted with EtOAc three times. The combined extract was washed with brine and concentrated. The residue was triturated with EtOAc–IPE, filtered, and dried to give **4d** as amorphous solid (3.51 g, 93.5%): $[\alpha]^{25}_D = -97.2°$ ($c = 0.53$, MeOH); IR (Nujol) 3300, 1730, 1620, 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.75–2.1 (2 H, m), 2.70 and 2.78 (3 H, 2 s), 2.8–3.2 (2 H, m), 3.6–4.0 (2 H, m), 4.31 (1 H, br s), 4.42 (2 H, s), 4.8–5.1 (2 H, m), 5.0 (1 H, m), 5.12 (2 H, m), 7.0–7.3 (12 H, m), 7.45 (1 H, d, $J = 8$ Hz), 7.93 (1 H, s), 8.07 (1 H, d, $J = 7$ Hz), 8.44 (1 H, m); $R_f = 0.31$ (system A); MS (APCI) m/z 583 $(M + 1)^+$. Anal. ($C_{33}H_{34}N_4O_6 \cdot 1.5H_2O$) H, N; C: calcd, 65.01; found, 64.52.

(2-Benzo[*b*]thienylcarbonyl)-(2*S*,4*R*)Hyp-Phe-NMeBzl (4f). To an ice-cooled solution of H-(2*S*,4*R*)Hyp-Phe-NMeBzl·HCl (0.90 g, 2.15 mmol) in CH_2Cl_2 (18 mL) were added *N*-methylmorpholine (434 mg, 4.3 mmol) and 2-benzo[*b*]-thienylcarbonyl chloride (433 mg, 2.2 mmol). The reaction mixture was stirred at this temperature for 1 h. The mixture was washed successively with sodium hydrogen carbonate solution and brine and concentrated. The crude product was purified by silica gel chromatography (30 g), eluting with CH_2Cl_2–MeOH (30:1), and crystallized with a mixed solvent of EtOH–IPE–*n*-Hex to give **4f** (0.84 g, 77.8%): mp 154–155 °C; $[\alpha]^{25}_D = -81.3°$ ($c = 0.55$, MeOH); IR (Nujol) 3400, 3300, 1660, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.7–2.4 (2 H, m), 2.60, 2.72, and 2.78 (2 H, 3 s), 2.8–3.2 (2 H, m), 3.6–4.2 (2 H, m), 4.2–4.8 (4 H, m), 5.0 (1 H, m), 5.15 (1 H, m), 6.8–7.3 (10 H, m), 7.3–7.6 (2 H, m), 7.9–8.1 (3 H m,), 8.55 (1 H, d, $J = 8$ Hz); $R_f = 0.31$ (system C); MS (APCI) m/z 542 $(M + 1)^+$. Anal. ($C_{31}H_{31}N_3O_4S$) C, H, N.

Compounds **4h–k** were prepared in a similar manner to the preparation of **4f**, except using the corresponding acid chloride.

(Phenylacetyl)-(2*S*,4*R*)Hyp-Phe-NMeBzl (4h): 78.4% yield (amorphous solid); IR (Nujol) 3290, 1630, 1490 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.7–2.2 (2 H, m), 2.7–3.4 (7 H, m), 3.64 (2 H, s), 4.1–4.6 (4 H, m), 4.8–5.1 (2 H, m), 7.0–7.4 (15 H, m), 8.35 and 8.8 (1 H, 2 d, $J = 8$ Hz); $R_f = 0.50$ (system D); MS (APCI) m/z 500 $(M + 1)^+$.

(3-Phenylpropionyl)-(2*S*,4*R*)Hyp-Phe-NMeBzl (4i): 81.8% yield (amorphous solid); IR (film) 3300, 1630, 1495 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.7–2.6 (4 H, m), 2.6–3.1 (7 H, m), 3.25–3.7 (2 H, m), 4.1–4.6 (4 H, m), 4.8–5.1 (2 H, m), 7.0–7.3 (15 H m), 8.4 and 8.8 (1 H, m); $R_f = 0.58$ (system D); MS (APCI) m/z 514 $(M + 1)^+$.

(4-Phenylbutyryl)-(2*S*,4*R*)Hyp-Phe-NMeBzl (4j): 84.3% yield (amorphous solid); IR (film) 3300, 1630, 1495 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.6–2.5 (7 H, m), 2.5–3.1 (6 H, m), 3.2–3.6 (2 H, m), 4.1–4.6 (4 H, m), 4.9–5.1 (2 H, m), 7.0–7.4 (15 H m), 8.3 and 8.7 (1 H, 2 d, $J = 8$ Hz); $R_f = 0.57$ (system D); MS (APCI) m/z 528 $(M + 1)^+$.

***trans*-Cinnamoyl-(2*S*,4*R*)Hyp-Phe-NMeBzl (4k)**: 61.6% yield (amorphous solid); $[\alpha]^{25}_D = -92.5°$ ($c = 0.54$, MeOH); IR (film) 3250, 1640, 1595, 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.7–2.2 (2 H, m), 2.73 and 2.79 (3 H, 2 s), 2.89 (1 H, dd, $J = 6$, 13.5 Hz), 3.04 (1 H, dd, $J = 5$, 13.5 Hz), 3.5–3.9 (2 H, m), 4.2–4.8 (4 H, m), 4.9–5.2 (2 H, m), 6.7–7.8 (17 H, m), 8.4 and 8.9 (1 H, 2d, $J = 8$ Hz); $R_f = 0.58$ (system A); MS (APCI) m/z 512 $(M + 1)^+$. Anal. ($C_{31}H_{33}N_3O_4$) C, H, N.

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