Structure–Activity Relationships (SAR) of [D-Arg^2]Dermorphin(1—4) Analogues, N^{α}-Amidino-Tyr-D-Arg-Phe-X[1)]

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Received January 7, 2002; accepted March 8, 2002

In investigating the development of compounds with potent analgesic effects after oral administration, 74 C-terminal analogues (N^{α}-amidino-Tyr-D-Arg-Phe-X), based on the structure of N^{α}-amidino-Tyr-D-Arg-Phe-MeβAla-OH (ADAMB), were synthesized. Their analgesic activity was evaluated using the mouse-tail pressure test after both subcutaneous and oral administration, and the structure–activity relationships (SAR) were examined in detail. The results clearly indicated that compounds containing β-amino acid without a side chain at the X position are preferable for expression of potent analgesic activity, and that the free carboxyl group is superior in its analgesic activity to that of the esterified or amidated carboxy group at the C-terminal. In addition, *N*-methylation of the amide bond at the 4th position contributed to improved analgesic activity. These results indicated that the strong and long-lasting analgesic effect of ADAMB is expressed by the synergistic effects of N^{α}-amidination, the *N*-methylation of the amide bond at the 4th position and the carbon chain length (β-Ala) of the residue at the 4th position, and that this is the most suitable structure.

Key words D-Arg^2-dermorphin analogue; opioid peptide; SAR; analgesic activity; oral administration; ADAMB

Dermorphin (H-Tyr-D-Ala-Phe-Gly-Tyr-Pro-Ser-NH_2)[2)] isolated from the skin of a South American frog (*Phyllomedusa sauvagei*) exhibits a high affinity and selectivity with μ-opioid receptor leading to potent opioid activity. The minimum active amino acid sequence of Dermorphin is derived from the N-terminal tetrapeptide (H-Tyr-D-Ala-Phe-Gly-),[3)] and a number of tetrapeptide analogues have been synthesized and their SAR (structure activity relationship), including opioid activity, receptor selectivity and affinity, were investigated.[4,5)] Marked elevation of activity obtained by the replacement of D-Ala with D-Arg at the 2nd position[6)] led to the synthesis of a number of [D-Arg^2]dermorphin derivatives, with their SAR being studied in great detail.[7—10)] For example, H-Tyr-D-Arg-Phe-Sar-OH (DAS-DER)[11)] investigated by Sasaki *et al.* is a compound prepared by *N*-methylation of the 4th position of H-Tyr-D-Arg-Phe-Gly-OH, the N-terminal tetrapeptide of [D-Arg^2]dermorphin, and is reported to have a higher affinity, selectivity and analgesic activity than its parent compound. H-Tyr-D-Arg-Phe-βAla-OH (TAPA)[12,13)] found by Chaki *et al.* is prepared by replacement of the 4th Gly with β-Ala and also exhibits a very strong antinociceptive action. In the mouse-tail pressure test, in comparison to morphine, the compound exhibited a comparative effect after oral (*p.o.*) administration, 388-fold activity after intracerebroventricular administration, 1440-fold activity after intrathecal administration and 15-fold antinociceptive activities after subcutaneous (s.c.) administration, respectively, with these activity being sustained over a long period of time. Furthermore, Marastoni *et al.* investigated dermorphin derivatives in detail and reported that those with an introduced amidino group at the N-terminal show improved analgesic activity and reduced receptor selectivity in comparison to N-terminal free derivatives.[14)] Thus, the possibility of dermorphin derivatives as analgesic agents was recognized, and we designed a novel dermorphin tetrapeptide N^{α}-amidino-Tyr-D-Arg-Phe-MeβAla-OH (ADAMB) based on the structures of several dermorphin tetrapeptide analogues. Antinociceptive activity of ADAMB was assessed using the tail pressure test in mice after s.c. and *p.o.* administration. ADAMB showed a strong oral antinociceptive activity, with an ED_{50} of 5.8 mg/kg *versus* 22.2 mg/kg for morphine, as well as a 38-fold stronger activity after s.c. administration. ADAMB also showed long-lasting antinociceptive activity, with 50% of the maximum effect persisting in the tail-pressure test at 10 h after *p.o.* administration (10 mg/kg). In contrast, orally administered morphine (80 mg/kg) showed a rapid decrease of activity in the same test and its antinociceptive effect disappeared within 4 h.[15)]

In the present study, 74 C-terminal analogues (N^{α}-amidino-Tyr-D-Arg-Phe-X), based on the structure of ADAMB, were synthesized to further investigate the potent analgesic effects after *p.o.* administration. Their analgesic activities were evaluated using the mouse-tail pressure test after both s.c. and *p.o.* administration, and the SAR examined in detail.

Chemistry All analogues were synthesized by the solution method using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCI·HCl) with 1-hydroxy-benzotriazole (HOBt) as a coupling reagent. As shown in Chart 1, the invariable tripeptide segment [N^{α}-(*N*,*N*′-bis-Cbz)-amidino-Tyr(Bn)-D-Arg(Cbz_2)-Phe-OH (**I**)] was first prepared by stepwise-elongation. This tripeptide (**I**) was subsequently condensed with the appropriate amino acid derivative X(PG), where PG represents a protecting group if necessary. Each of the resulting products was dissolved in acetic acid and subjected to catalytic hydrogenation in the presence of Pd-C. The catalyst was removed and the reaction mixture was concentrated under reduced pressure. Final purification was accomplished by a reverse phase flash column chromatography eluted with aqueous CH_3CN containing 0.1 N–acetic acid and subsequently lyophilized to give the desired peptides in the form of powder (>95% purity by HPLC analysis). The final structure of the product was confirmed by ^{1}H-NMR and FAB mass spectra.

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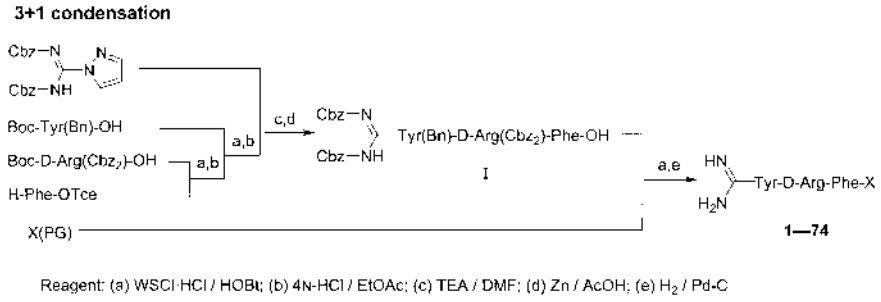


Chart 1. Synthesis of C-Terminal Analogues of [D-Arg^2]Dermorphin Tetrapeptide

Antinociceptive Assays The compounds synthesized here were tested for their *in vivo* antinociceptive potency using the tail pressure test in mice after s.c. and *p.o.* administration. The percent of maximum possible effect (% of MPE) value was measured at fixed doses, 1 mg/kg s.c. and 10 mg/kg *p.o.*, primarily to evaluate the activity of synthesized compounds. Then, analogues with high potency were evaluated for their ED_{50} values by the method of Litchfield and Wilcoxon[35] to compare their antinociceptive activities. These values were calculated from the values obtained at the time of peak effect after either peptide or morphine administration.

Results and Discussion

A number of investigations of opioid peptides were carried out and several essential structural requirements for the improvement of μ-selectivity and analgesic activity summarized.[16,17] Among them, amidation of the C-terminal carboxyl group, its reduction to alcohol residues and *N*-methylation of the 4th amide bond were found to be effective for 4th amino acid residue in the dermorphin tetrapeptide and structurally related peptides. Based on the strong antinociceptive action observed in ADAMB after *p.o.* administration, C-terminal analogues (N^{α}-amidino-Tyr-D-Arg-Phe-X) were synthesized to further investigate the SAR on the oral antinociception that would lead to the elucidation of the structural requirements for oral activity as well as the development of more potent analogues.

Table 1 enumerates the analgesic activity of dermorphin derivatives **1**—**74** synthesized in the present study: N^{α}-amidino-Tyr-D-Arg-Phe-X, morphine, dermorphin and [D-Arg^2]dermorphin(1—4)-NH_2.

(1) Tripeptide Analogues As mentioned above, amidation of the C-terminal carboxyl group or reduction to alcohol moiety has been known to be effective in improving μ-selectivity and analgesic activity among the structural requirements. Thus, tripeptide derivatives with various introduced amines and amino alcohols were synthesized based on the structure of ADAMB. Furthermore, SAR studies on [D-Arg^2]dermorphin with substituted D-Arg at the 2nd position have shown that the N-terminal tripeptide (H-Tyr-D-Arg-Phe-NH_2) is a minimally active structure[18] and introduction of the methyl group to the C-terminal amide, including *N*-methylamide or *N*,*N*-dimethylamide, provided a marked improvement in activity.[19] Further improvement of analgesic activity was anticipated with the introduction of the amidino group at the N-terminal.[14,15] Thus, 16 tripeptide derivatives with an introduced amidino group were synthesized and their analgesic activity compared. No significant analgesic activity (after s.c. or *p.o.* administration) was found in the synthesized tripeptide analogues **1**—**16**. However, the *N*-methylated compound **7** exhibited some improved analgesic activity in comparison to compound **6** without *N*-methylation, indicating the positive effect of *N*-methylation at the 4th position.

(2) Substitution with Another Amino Acid SAR studies of the N-terminal free tetrapeptide analogue, H-Tyr-D-Arg-Phe-X, have reported on the importance of a proper carbon chain length (C2—3) at position 4, existence of electron-withdrawing atoms (oxygen) which work as hydrogen bonding acceptors, and an amide bond between Phe-X in biological activity.[20] From these observations, compounds with high affinity, selectivity and analgesic activity such as TAPA were found.[12,13] These compounds exhibited weak analgesic activity after *p.o.* administration.[12] Therefore, compounds with the amidino group, N^{α}-amidino-Tyr-D-Arg-Phe-X derivatives, at the N-terminal amino group, were further substituted with various substituents at the C-terminal amino acid residues, anticipating high analgesic activity. These analgesic activities were evaluated after both s.c. and *p.o.* administration. Among the derivatives **17**—**35** at the X-position, marked analgesic activity was observed in derivatives **21**, **22** and **25** after s.c. administration which were substituted with Sar-OH, Sar-OMe and Ala-OH, respectively, but with no marked activity after *p.o.* administration. However, *N*-methylation at the 4th position was effective to the analgesic activity increase in comparison to compounds **17** and **21**, compounds **18** and **22**.

In the other substituted derivatives **36**—**50** with neutral amino acids, compounds **43**, **45**, **47**, **49** and **50** containing cyclic or substituted β-amino acids exhibited superior analgesic activity to that of morphine after both s.c. and *p.o.* administration. A γ-amino acid substituted compound **36** with an elongated chain length showed a significant decline in activity. The above results indicate that β-amino acid moiety at the X-position in N^{α}-amidino-Tyr-D-Arg-Phe-X is desirable for high analgesic activity.

Marked analgesic activity was observed in aminosulfonic acid derivatives **55**, **56** with no side chain among the analogues having either basic amino acid (**51**, **52**) or acidic amino acid (**53**—**56**).

(3) Modification of C-Terminal Carboxyl Group The C-terminal substituted products of ADAMB, including C-terminal oxyesters **57**—**61** and amide derivatives **62**—**68**, were synthesized to explore better analgesic compounds after *p.o.* administration. The ester derivatives were anticipated to show improved intestinal absorption due to increased lipophilicity and improved analgesic activity after *p.o.* ad-

Table 1. Analgesic Activity of C-Terminal Analogues of Dermorphin Tetrapeptide: N^{α}-Amidino-Tyr-D-Arg-Phe-X

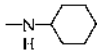
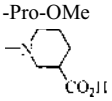
No.	X	MPE %[a]		ED_{50} (mg/kg)[a,b]	
		s.c. 1 mg/kg	*p.o.* 10 mg/kg	s.c.	*p.o.*
	Morphine	4.9	12.9	3.3	22.2
	Dermorphin	31.05	10.21	3.95	
	(D-Arg^2)-Dermorphin(1—4)-NH_2	11.28	3.15		
(1) Tripeptide analogues					
1	N^{α}-Amidino-Tyr-D-Arg-Phe-OH	0.34	0.52		
2	-NHMe	6.36	5.96		
3	-NHEt	4.57	1.71		
4	-NH(*n*-Pr)	3.67	6.61		
5	-NH(*n*-Hex)	0.00	0.00		
6	-Gly-ol	13.30	8.93		
7	-Sar-ol	46.50	12.68		
8	$-NH(CH_2)_2OMe$	14.74	8.35		
9	-Ala-ol	7.58	6.35		
10	-D-Ala-ol	12.48	5.84		
11	$-NH(CH_2)_3OH$	7.73	4.93		
12	$-NH(CH_2)_4OH$	16.00	10.80		
13	$-NH(CH_2)_2C_6H_5$	4.83	3.62		
14		5.95	0.00		
15		6.13	22.03		
16		21.59	10.19		
(2) Substitution by another amino acid					
1) Gly substitution					
17	-Gly-OH	58.49	3.59		
18	-Gly-OMe	61.97	6.88		
19	$-Gly-NH_2$	15.06	0.00		
20	-Gly-NHMe	18.72	10.92		
21	-Sar-OH	89.71	26.13	0.38	17.8
22	-Sar-OMe	93.68	31.18		
23	-(Et)Gly-OH	46.53	25.75	1.2	>40.0
24	-(*n*-Pr)Gly-OH	38.52	5.93		
2) Ala substitution					
25	-Ala-OH	100.00	0.00	0.18	>40.0
26	-Ala-OMe	82.36	5.27	0.40	
27	$-Ala-NH_2$	39.91	5.28		
28	-Ala-NHMe	8.03	9.51		
29	-MeAla-OH	4.54	2.20		
30	-D-Ala-OH	30.44	7.49		
31	-D-Ala-OMe	8.14	3.08		
32	$-D-Ala-NH_2$	10.08	5.86		
33	-D-Ala-NHMe	9.40	1.18		
34	-D-MeAla-OH	22.72	6.39		
35	-D-MeAla-OMe	43.06	3.55		
3) Substitution by neutral amino acid					
36	-GABA-OH	28.43	11.91		
37		11.45	7.14		
38	-Leu-OH	8.25	3.83		
39	-Nva-OH	7.11	0.37		
40	-Phe-OH	19.47	14.46		
41	-Pro-OH	3.50	10.96		
42	-Pro-OMe	4.93	6.85		
43		92.04	28.82	0.25	
44	-(*R*,*S*)*β*Pro-OH	77.14	43.75	0.60	40.0
45		85.57	31.08	0.53	

Table 1. (Continued)

No.	X	MPE %[a]		ED_{50} (mg/kg)[a,b]	
		s.c. 1 mg/kg	*p.o.* 10 mg/kg	s.c.	*p.o.*
46	-αAib-OH	19.14	8.17		
47	-(*R*,*S*)βAib-OH	83.14	11.86	0.54	>40.0
48	-(*R*)αAbu-OH	10.32	0.11		
49	-(*S*)αAbu-OH	73.25	12.53	0.46	>40.0
50	-(*R*,*S*)βAbu-OH	77.95	34.98	0.69	27.3
4) Substitution by basic amino acid					
51	-Arg-NH_2	3.37	5.99		
52	-D-Arg-NH_2	0.32	1.95		
5) Substitution by acidic amino acid					
53	-Asp-OH	7.30	8.52		
54	-Asu-OH	0.00	4.60		
55	-$NH(CH_2)_2SO_3H$	75.59	28.11	0.54	
56	-$NHCH_2SO_3H$	67.10	17.43		
(3) Modification of C-terminal carboxyl group					
ADAMB	-MeβAla-OH	100.00	82.23	0.089	5.8
57	-MeβAla-OMe	100.00	59.75	0.12	8.9
58	-MeβAla-OEt	100.00	53.54	0.16	9.0
59	-MeβAla-O(*n*-Pr)	100.00	54.98	0.11	9.9
60	-MeβAla-O(*n*-Hex)	100.00	55.48	0.11	9.5
61	-MeβAla-OPOM	100.00	41.59	0.16	14.2
62	-MeβAla-NH_2	99.00	44.29	0.31	24.6
63	-MeβAla-NHMe	44.69	10.00		
64	-MeβAla-NHEt	9.24	16.25		
65	-MeβAla-$N(Me)_2$	17.54	5.34		
66	-MeβAla-$N(Et)_2$	5.62	13.98		
67	-MeβAla-NH(*n*-Hex)	2.74	0.00		
68	-MeβAla-NH(*n*-Pr)	8.99	5.27		
(4) Substitution of *N*-methyl group					
69	-βAla-OH	93.05	18.30	0.32	18.4
70	-βAla-OMe	96.96	12.85		
71	-EtβAla-OH			0.15	16.0
72	-EtβAla-OMe	59.72	6.86		
73	-(*n*-Pr)βAla-OH	100.00	16.29	0.25	
74	-BnβAla-OH	8.23	0.00		

a) Data are given as the mean value for groups of 10 mice. *b*) ED_{50} values were calculated from the values obtained at the time of peak effect after administration.

ministration. Methyl to *n*-hexyl esters of ADAMB were synthesized, however, none of the anticipated superior analgesic activity after *p.o.* administration compared to that of the free carboxyl group, ADAMB, was found, although high activity after s.c. administration was observed. The length of the alkyl chain did not affected the activity. Derivative **61**, having prodrug moiety of pivaloyloxymethyl ester (POM) also showed no improved analgesic activity after *p.o.* administration. A slower onset of the antinociceptive activity would be expected for these C-terminal ester derivatives due to a time lag in the metabolization to ADAMB. However, the times of peak effect after administration were almost the same as that of ADAMB (data not shown). Furthermore, extension of the analgesic effect expected of ester derivative was not observed. It was thus thought that the C-terminal ester derivative itself displayed analgesic activity, and that the ester moiety decreased analgesic activity compared with that of ADAMB.

In amide derivatives **62**—**68** where improved analgesic activity and stability to enzymic degradation was anticipated, potent analgesic activity was observed in the non-substituted amide compound **62**. However, overall, alkylamide derivatives exhibited very slight activity. Unlike the ester derivatives, C-terminal amide derivatives could be resistant to enzymic degradation, therefore, more potent and long-lasting analgesic activities can be expected. However, the amide derivative **62** of ADAMB decreased analgesic activity. Moreover, the longer the alkyl chain length became and the greater the number of the *N*-substituents, the more analgesic activity decreased. Amidation of the C-terminal carboxyl group would therefore interrupt the peptide-receptor interaction.

(4) Substitution of *N*-Methyl Group The structural requirement of *N*-methylation of the amide bond at the 4th position for the improved μ-selectivity and analgesic activity mentioned above led to the introduction of various *N*-alkyl groups based on the structure of ADAMB and the anticipated improvement in analgesic activity. Thus, *N*-ethyl (**71**), which elongates the *N*-alkyl chain, and *N*-*n*-propyl (**73**) and *N*-benzyl (**74**) derivatives were synthesized. However, no improved analgesic activity compared to the *N*-methylation was observed, with activity particularly decreasing after *p.o.* administration.

Introduction of the *N*-alkyl group to the amide group at the 4th position provided the highest activity in the methyl group. The structural requirement for the improved analgesic activity of opioid peptides suggested improved resistance to enzymic degradation for *N*-methylation of the amide group at the 4th position.[21] However, [D-Arg^2]dermorphin(1—4) de-

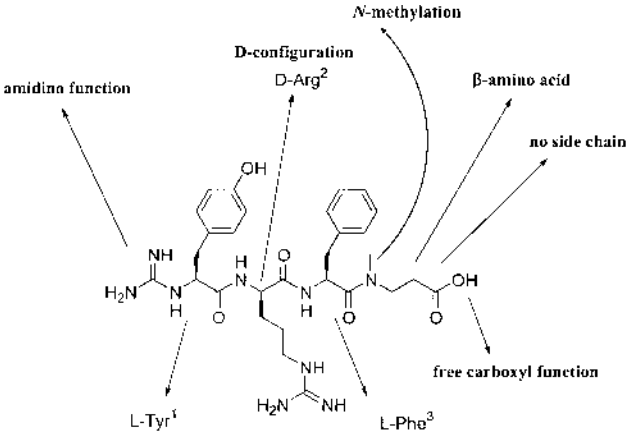


Fig. 1. Summary of Structural Requirements for Antinociceptive Activity

rivatives have already been reported to exhibit very high resistance to enzymic degradation,[8,14,22] and TAPA with introduced βAla to the 4th position was reported as being highly stable.[23] Thus, the *N*-methyl group in the 4th amide may contribute not only to stability against enzymic degradation but also to improved activity together with some other factors such as interaction with a receptor. *N*-Methylamide binding is more likely to take *cis*-configuration than that of conventional amide bonds.[24,25] The NMR spectra of some analogues prepared in the present study, including *N*-methylated Sar and MeβAla at the 4th position, showed a splitting of signals. This indicates two conformations of *cis*- and *trans*-forms in the solution. The *N*-methyl proton signal of MeβAla of ADAMB split at an area ratio of 2 : 3. Results of NMR studies suggested the presence of *cis*-isomers, indicating the contribution of deviation to *cis*-amide bonds for elevated activity,[26] the active conformation of dermorphin type opioid peptides binding to μ-opioid receptor also remains unclear. However, the primary structure of opioid receptors was recently elucidated[27—32] and knowledge of its steric structure is progressing. In future, more detailed information is expected from the results of SAR studies at the receptor level.

In conclusion, an investigation into compounds exhibiting potent analgesic activity after *p.o.* administration was carried out and 74 C-terminal analogues were synthesized based on the structure of ADAMB. Their analgesic activity was evaluated using the mouse-tail pressure test (s.c. and *p.o.*) and their SAR was investigated in detail. Although no analgesic activity superior to ADAMB after *p.o.* administration was observed, the results clearly demonstrated that participation of a β-amino acid residue with no side chain at the X-position, and a free carboxyl group at the C-terminal is more advantageous than that of ester or amide for improved analgesic activity. Moreover, *N*-methylation of the amide bond at the 4th position provided not only stability with regards to enzymic degradation but also suggested improved analgesic activity due to conformational factors. These results are summarized in Fig. 1.

In a recent report of ours, very strong and long-lasting analgesic activity of ADAMB after *p.o.* administration showed expression of a synergistic effect of amidination at N-terminal, *N*-methylation of the amide bond and homologation at the 4th position. The present results confirmed the fact that ADAMB has one of the most suitable structures for the expression of potent and long-lasting analgesic activity among the opioid peptides ever found. Future studies are needed to evaluate the relationship between *in vitro* affinity and selectivity to the opioid receptor and *in vivo* analgesic activity, which can lead to elucidation of the mechanism of analgesic action and the development of peptidergic analgesics.

Experimental

Chemistry Commercial amino acid derivatives and 1-hydroxybenzotriazole (HOBt) were obtained from Kokusan Chemical Works, Ltd., Tokyo, Japan. Other reagents and solvents were purchased from Aldrich Chemicals, WI, U.S.A. Boc-D-Arg(Cbz_2)-OH was prepared according to the procedure reported by Jetten *et al.*[33] Thin layer chromatography was performed on silica plates (0.25 mm; Merck, 60 F_{254}) using the following solvent systems: Rf_1, *n*-butanol/acetic acid/water (4 : 1 : 5, v/v/v, supernatant); Rf_2, *n*-butanol/acetic acid/water/pyridine (15 : 3 : 10 : 12, v/v/v/v). Purification of the final products was achieved by flash chromatography using a reverse phase silica gel Chromatorex ODS DM1020T, Fuji Silysia Chemical Ltd., Aichi, Japan, eluted by a stepwise gradient of acetonitrile (starting from 1—5% and stepwise by 1—2%) in 0.1 M acetic acid. An analytical high-pressure liquid chromatograph was on a Nucleosil 100 $5C_{18}$ column (4.6×150 mm) in an Agilent 1100 HPLC system. The products were analyzed with a linear gradient of 1—70% acetonitrile in 0.1% aqueous trifluoroacetic acid (TFA) over 20 min at a flow rate of 1 ml/min. The chromatogram was recorded by UV detection at 230 and 280 nm. ^{1}H-NMR spectra were recorded with a JEOL JMN-AL300 (300 MHz) spectrometer, using tetramethylsilane (TMS) as an internal standard. Mass spectra (FAB-MS) were obtained with JEOL mass spectrometer model JMS-700.

Method A (Coupling Procedure) To a solution of carboxy component (1 mmol), the amino component (1.1 eq), HOBt (1.1 eq) in *N*,*N*-dimethylformamide (DMF) (*ca.* 20 ml), and triethylamine (TEA) (1 eq if the amino component was in the protonated form) was added at 0 °C. Then, WSCI·HCl (1.2 eq) was added to the solution at −10 °C. This mixture was stirred for 30 min at −10 °C and overnight at room temperature. The reaction mixture was diluted with EtOAc. The solution or suspension was washed with 1 N-HCl, sat. $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was crystallized from appropriate solvents or purified by column chromatography.

Method B (Hydrogenation) Hydrogenation was performed in AcOH under H_2 atomospheric pressure and at room temperature in the presence of 5% Pd-C (catalyst to peptide ratio, 1 : 2, w/w). The reaction mixture was filtered through a Celite bed and evaporated to dryness.

Method C (Purification) The crude peptide was purified by ODS chromatography with a stepwise gradient of acetonitrile (starting from 1—5% and stepwise by 1—2%) in 0.1 N acetic acid as the eluting solvent and then lyophilized to give a white powder.

Preparation of N^{α}-(*N*,*N'*-bis-Cbz)amidino-Tyr(Bn)-D-Arg(Cbz_2)-Phe-OH (I) The starting material, Boc-Phe-OTce (237 g, 598 mmol), was treated with 4 N-HCl/EtOAc (1000 ml) to remove the Boc group for 30 min at room temperature. Ether was added to the solution and the precipitated solid was separated by filtration and dried in a vacuum desiccator over solid NaOH. This amine component was dissolved in DMF (1300 ml) on an ice bath. To this solution were added Boc-D-Arg(Cbz_2)-OH (295 g, 544 mmol) and HOBt (81 g, 599 mmol), the mixture was then neutralized with TEA (91 ml) followed by addition of WSCI·HCl (125 g, 652 mmol) at −10 °C. The reaction mixture was stirred for 1 h at the same temperature, then overnight at room temperature. The reaction mixture was diluted with EtOAc. The solution was washed with 1 N-HCl, sat. $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was solidified from EtOAc and hexane to give Boc-D-Arg(Cbz_2)-Phe-OTce, 339 g (76%) as white amorphous solid.

Boc-D-Arg(Cbz_2)-Phe-OTce (265 g, 323 mmol) was treated with 4 N-HCl/EtOAc (500 ml) to remove the Boc group for 30 min at room temperature. Ether was added to the solution and the precipitated solid was separated by filtration and dried in a vacuum desiccator over solid NaOH. This amine component was dissolved in DMF (800 ml) on an ice bath. To the solution were added Boc-Tyr(Bn)-OH (l09 g, 293 mmol) and HOBt (44 g, 326 mmol) and the mixture was then neutralized with TEA (45 ml) and WSCI·HCl (68 g, 352 mmol) was added at −10 °C. The reaction mixture was stirred for 1 h at the same temperature, then overnight at room temperature. The mixture was then diluted with EtOAc, and the solution was washed with 1 N-

HCl, sat. $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was solidified from EtOAc and hexane to give Boc-Tyr(Bn)-D-Arg(Cbz_2)-Phe-OTce, 262 g (83%) as white amorphous solid.

The Boc-Tyr(Bn)-D-Arg(Cbz_2)-Phe-OTce (240 g, 223 mmol) was treated with 4 N-HCl/EtOAc (500 ml) to remove the Boc group for 30 min at room temperature. Ether was added to the solution and the precipitated solid was separated by filtration and dried in a vacuum desiccator over solid NaOH. This amine component was dissolved in DMF (800 ml) on an ice bath. The solution was neutralized with TEA (34 ml), added with 1-(*N*,*N'*-bis(benzyloxycarbonyl)amidino)pyrazole (93 g, 245 mmol) and stirred overnight at room temperature. The reaction mixture was diluted with EtOAc. The solution was washed with 1 N-HCl, sat. $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was solidified from EtOAc and hexane to give N^{α}-(*N*,*N'*-bis-Cbz)amidino-Tyr(Bn)-D-Arg(Cbz_2)-Phe-OTce, 215 g (75%) as white amorphous solid.

This fully-protected peptide (200 g, 156 mmol) was dissolved in 90% AcOH (1000 ml). To this solution, zinc powder (50 g, 765 mmol) was added, and vigorous stirring followed for 2 h at room temperature. After the zinc powder was removed by filtration, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (1000 ml). The solution was washed with 1 N-HCl, sat. $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was solidified from EtOAc and hexane to give N^{α}-(*N*,*N'*-bis-Cbz)amidino-Tyr(Bn)-D-Arg(Cbz_2)-Phe-OH (**I**), 159 g (89%) as white amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 11.6 (1H, br s), 9.26 (1H, br s), 8.96 (1H, d, J=6.6 Hz), 7.50 (1H, br s), 7.37—7.05 (30H, m), 6.98 (2H, d, J=8.4 Hz), 6.74 (2H, d, J=8.4 Hz), 5.19—4.96 (8H, m), 4.90 (2H, s), 4.69 (1H, dd, J=12.8, 6.5 Hz), 4.52 (1H, t, J=6.6 Hz), 3.90 (1H, br s), 3.02 (3H, m), 1.67 (1H, br m), 1.48 (2H, br m). FAB-MS *m/z*: 1154 $(M+H)^+$.

Preparation of N^{α}-Amidino-Tyr-D-Arg-Phe-OH·2AcOH (1) Hydrogenation of N^{α}-(*N*,*N'*-bis-Cbz)amidino-Tyr(Bn)-D-Arg(Cbz_2)-Phe-OH (**I**) (1.15 g, 1.0 mmol) was carried out using method B, then purified using method C. Compound **1** was obtained after lyophilization in the form of a white powder (466 mg, 72%). HPLC t_R (min): 9.35. Rf_1 0.37. Rf_2 0.62. ^{1}H-NMR (CD_3OD) δ: 7.12 (5H, m), 6.97 (2H, d, J=8.6 Hz), 6.62 (2H, d, J=8.6 Hz), 4.54 (1H, dd, J=9.4, 4.4 Hz), 4.22 (2H, q), 2.87 (5H, m), 1.81 (6H, s), 1.41 (1H, br m), 1.30 (1H, br m), 1.06 (2H, m). FAB-MS *m/z*: 527 $(M+H)^+$.

Preparation of N^{α}-Amidino-Tyr-D-Arg-Phe-NHMe·2AcOH (2) According to method A, N^{α}-(*N*,*N'*-bis-Cbz)amidino-Tyr(Bn)-D-Arg(Cbz_2)-Phe-OH (**I**) (1.15 g, 1.0 mmol) was coupled with HCl·NHMe (74 mg, 1.1 mmol), yielding a fully-protected peptide, N^{α}-(*N*,*N'*-bis-Cbz)amidino-Tyr(Bn)-D-Arg(Cbz_2)-Phe-NHMe, which was deprotected according to method B. The crude compound was purified using method C and then lyophilized to give a white powder (495 mg, 75%). HPLC t_R (min): 9.03. Rf_1 0.45. Rf_2 0.67. ^{1}H-NMR (CD_3OD) δ: 7.15 (5H, m), 6.95 (2H, d, J=8.5 Hz), 6.62 (2H, d, J=8.5 Hz), 4.46 (1H, dd, J=10.6, 4.6 Hz), 4.25 (1H, t, J=7.7 Hz), 3.98 (1H, t, J=7.4 Hz), 2.97—2.56 (5H, m), 2.62 (3H, s), 1.81 (6H, s), 1.34 (2H, br m), 1.06 (1H, br m), 0.92 (1H, br m). FAB-MS *m/z*: 540 $(M+H)^+$.

Compounds **3**—**74** were prepared in the same manner from the corresponding amino acid derivatives, respectively.

N^{α}-Amidino-Tyr-D-Arg-Phe-NHEt·2AcOH (3) White powder (458 mg, 68%): HPLC t_R (min): 9.84. Rf_1 0.49. Rf_2 0.70. ^{1}H-NMR (CD_3OD) δ: 7.15 (5H, m), 6.95 (2H, d, J=8.4 Hz), 6.61 (2H, d, J=8.4 Hz), 4.46 (1H, dd, J=10.5, 4.8 Hz), 4.24 (1H, t, J=8.0 Hz), 4.00 (1H, t, J=7.2 Hz), 3.15 (2H, dd, J=16.2, 4.8 Hz), 3.03—2.65 (5H, m), 1.81 (6H, s), 1.35 (2H, br m), 1.10—0.80 (2H, br m), 0.98 (3H, t, J=7.2 Hz). FAB-MS *m/z*: 554 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-NH(*n*-Pr)·2AcOH (4) White powder (454 mg, 66%): HPLC t_R (min): 10.50. Rf_1 0.54. Rf_2 0.70. ^{1}H-NMR (CD_3OD) δ: 7.14 (5H, m), 6.96 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz), 4.47 (1H, dd, J=10.5, 4.8 Hz), 4.26 (1H, t, J= 7.1 Hz), 3.98 (1H, t, J=7.1 Hz), 3.03 (2H, t, J=7.2 Hz), 2.95—2.65 (5H, m), 1.84 (6H, s), 1.44—1.31 (4H, m), 1.06 (1H, br m), 0.95 (1H, br m), 0.76 (3H, t, J=7.4 Hz). FAB-MS *m/z*: 568 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-NH(*n*-Hex)·2AcOH (5) White powder (453 mg, 62%): HPLC t_R (min): 13.72. Rf_1 0.60. Rf_2 0.76. ^{1}H-NMR (CD_3OD) δ: 7.15 (5H, m), 6.96 (2H, d, J=8.7 Hz), 6.61 (2H, d, J=8.7 Hz), 4.47 (1H, dd, J=10.4, 5.4 Hz), 4.25 (1H, t, J=7.5 Hz), 4.01 (1H, t, J=7.2 Hz), 3.15 (2H, dd, J=15.4, 5.1 Hz), 3.05 (2H, t, J=7.2 Hz), 2.98—2.65 (5H, m), 1.81 (6H, s), 1.36 (2H, m), 1.17 (6H, m), 1.08 (1H, br m), 0.96 (1H, br m), 0.80 (3H, t, J=7.2 Hz). FAB-MS *m/z*: 610 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Gly-ol·2AcOH (6) White powder (504 mg, 73%): HPLC t_R (min) 8.69. Rf_1 0.45. Rf_2 0.69. ^{1}H-NMR (CD_3OD) δ: 7.15 (5H, m), 6.96 (2H, d, J=8.7 Hz), 6.62 (2H, d, J=8.7 Hz), 4.50 (1H, dd, J=10.8, 4.5 Hz), 4.27 (1H, t, J=7.5 Hz), 3.96 (1H, t, J=7.2 Hz), 3.49 (2H, m), 2.92—2.66 (6H, m), 1.82 (6H, s), 1.34 (2H, m), 1.07 (1H, br m), 0.90 (1H, br m). FAB-MS *m/z*: 570 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Sar-ol·2AcOH (7) White powder (387 mg, 55%): HPLC t_R (min): 9.26. Rf_1 0.42. Rf_2 0.68. ^{1}H-NMR (CD_3OD) δ: 7.14 (5H, m), 6.96 (2H, dd, J=8.6, 2.0 Hz), 6.62 (2H, dd, J=8.4, 1.5 Hz), 5.01 (1H, dt, J=32, 7.2 Hz), 4.29—4.23 (1H, m), 4.18—4.12 (1H, m), 3.54—3.47 (2H, m), 3.32 (1H, t, J=5.9 Hz), 3.01—2.76 (6H, m), 2.88 (1.5H, s), 2.82 (1.5H, s), 1.81 (6H,s), 1.48—1.06 (4H, br m). FAB-MS *m/z*: 584 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-NH(CH_2)$_2$OMe·2AcOH (8) White powder (500 mg, 71%): HPLC t_R (min): 9.68. Rf_1 0.47. Rf_2 0.70. ^{1}H-NMR (CD_3OD) δ: 7.15 (5H, m), 6.95 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz), 4.50 (1H, dd, J=10.2, 4.8 Hz), 4.24 (1H, t, J=7.5 Hz), 4.00 (1H, t, J=7.5 Hz), 3.31 (2H, m), 3.28—3.14 (2H, m), 2.97—2.66 (5H, m), 1.81 (6H, s), 1.35 (2H, m), 1.05 (1H, br m), 0.93 (1H, br m). FAB-MS *m/z*: 584 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Ala-ol·2AcOH (9) White powder (549 mg, 78%): HPLC t_R (min): 8.86. Rf_1 050. Rf_2 0.71. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.97 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz), 4.50 (1H, dd, J=10.8, 4.5 Hz), 4.26 (1H, t, J=7.5 Hz), 3.95 (1H, t, J=7.2 Hz), 3.84 (1H, dd, J=12.3, 5.7 Hz), 3.40—3.16 (3H, m), 2.97—2.66 (5H, m), 1.81 (6H, s), 1.35 (2H, m), 1.08 (4H, d, J=6.6 Hz), 0.88 (1H, br m). FAB-MS *m/z*: 584 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-D-Ala-ol·2AcOH (10) White powder (507 mg, 72%): HPLC t_R (min): 9.30. Rf_1 0.50. Rf_2 0.71. ^{1}H-NMR (CD_3OD) δ: 7.16 (5H, m), 6.96 (2H, d, J=8.7 Hz), 6.62 (2H, d, J=8.4 Hz), 4.47 (1H, dd, J=10.1, 5.3 Hz), 4.24 (1H, t, J=7.1 Hz), 3.98 (1H, t, J=7.2 Hz), 3.82 (1H, dd, J=12.6, 6.0 Hz), 3.44—3.40 (2H, m), 3.20—3.13 (1H, m), 2.98—2.68 (5H, m), 1.81 (6H, s), 1.37 (2H, br m), 1.08 (1H, br m), 0.94 (4H, d, J=6.9 Hz). FAB-MS *m/z*: 584 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-NH(CH_2)$_3$OH·2AcOH (11) White powder (500 mg, 71%): HPLC t_R (min): 8.97. Rf_1 0.49. Rf_2 0.70. ^{1}H-NMR (CD_3OD) δ: 7.16 (5H, m), 6.97 (2H, d, J=8.7 Hz), 6.62 (2H, d, J=8.4 Hz), 4.47 (1H, dd, J=10.8, 4.8 Hz), 4.28 (1H, t, J=7.2 Hz), 3.95 (1H, t, J=7.5 Hz), 3.44 (2H, m), 2.97—2.65 (5H, m), 1.82 (6H, s), 1.60 (2H, m), 1.36 (2H, br m), 1.08 (1H, m), 0.92 (1H, m). FAB-MS *m/z*: 584 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-NH(CH_2)$_4$OH·2AcOH (12) White powder (538 mg, 75%): HPLC t_R (min): 10.84. Rf_1 0.58. Rf_2 0.74. ^{1}H-NMR (CD_3OD) δ: 7.16 (5H, m), 6.99 (2H, d, J=8.4 Hz), 6.63 (2H, d, J=8.4 Hz), 4.47 (1H, dd, J=10.4, 4.8 Hz), 4.32 (1H, t, J=7.8 Hz), 4.00 (1H, t, J=7.2 Hz), 3.95 (2H, t, J=6.3 Hz), 3.17—3.09 (3H, m), 2.96—2.72 (5H, m), 1.82 (6H, s), 1.46 (6H, m), 1.12 (1H, m), 0.99 (1H, m). FAB-MS *m/z*: 598 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-NH(CH_2)$_2$$C_6H_5$·2AcOH (13) White powder (472 mg, 63%): HPLC t_R (min): 12.77. Rf_1 0.54. Rf_2 0.76. ^{1}H-NMR (CD_3OD) δ: 7.10 (10H, m), 6.96 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz), 4.46 (1H, dd, J=10.7, 5.1 Hz), 4.24 (1H, t, J=7.8 Hz), 4.02 (1H, t, J=7.5 Hz), 3.36 (2H, t, J=6.9 Hz), 3.15 (1H, m), 2.97—2.75 (4H, m), 2.69—2.60 (3H, m), 1.81 (6H, s), 1.33 (2H, m), 1.05 (1H, m), 0.90 (1H, m). FAB-MS *m/z*: 630 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe—N⟨⟩ ·2AcOH (14) White powder (471 mg, 66%): HPLC t_R (min): 11.79. Rf_1 0.49. Rf_2 0.76. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.97 (2H, d, J=8.1 Hz), 6.62 (2H, d, J=8.1 Hz), 4.98 (1H, t, J=7.8 Hz), 4.29 (1H, t, J=7.5 Hz), 4.16 (1H, dd, J=8.6, 5.1 Hz), 3.36 (3H, m), 3.14 (1H, m), 2.96—2.89 (4H, m), 2.83—2.76 (2H, m), 1.82 (6H, s), 1.49—1.36 (7H, m), 1.17 (2H, m), 1.05 (1H, m). FAB-MS *m/z*: 594 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe—N(H)⟨⟩ ·2AcOH (15) White powder (524 mg, 72%): HPLC t_R (min): 12.42. Rf_1 0.54. Rf_2 0.75. ^{1}H-NMR (CD_3OD) δ: 7.16 (5H, m), 6.97 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.7 Hz), 4.45 (1H, dd, J=10.2, 5.1 Hz), 4.24 (1H, t, J=7.1 Hz), 3.98 (1H, t, J=7.1 Hz), 3.50 (1H, br m), 3.15 (1H, dd, J=14.1, 5.1 Hz), 2.96—2.66 (5H, m), 1.85 (6H, s), 1.72—1.49 (5H, br m), 1.37 (2H, br m), 1.23—0.92 (7H, br m). FAB-MS *m/z*: 608 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe—N⟨⟩NH ·3AcOH (16) White powder (411 mg, 53%): HPLC t_R (min): 8.11. Rf_1 0.28. Rf_2 0.60. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.96 (2H, d, J=8.4 Hz), 6.61 (2H, d, J=8.4 Hz), 5.00 (1H, t,

J=8.2 Hz), 4.26 (1H, t, J=7.2 Hz), 4.04 (1H, dd, J=8.4, 5.4 Hz), 3.31 (3H, m), 3.14 (1H, m), 3.10—2.92 (4H, m), 2.88—2.65 (6H, m), 1.82 (9H, s), 1.34 (2H, br m), 1.07 (1H, br m), 0.95 (1H, br m). FAB-MS m/z: 595 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Gly-OH·2AcOH (17) White powder (535 mg, 76%): HPLC t_R (min): 8.80. Rf_1 0.35. Rf_2 0.62. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.96 (2H, d, J=8.7 Hz), 6.61 (2H, d, J=8.7 Hz), 4.58 (1H, dd, J=11.0, 4.5 Hz), 4.23 (1H, t, J=7.2 Hz), 4.01 (1H, t, J=7.2 Hz), 3.67 (2H, dd, J=27.2, 17.1 Hz), 2.97—2.69 (5H, m), 1.81 (6H, s), 1.35 (2H, br m), 1.05 (1H, br m), 0.91 (1H, br m). FAB-MS m/z: 584 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Gly-OMe·2AcOH (18) White powder (531 mg, 74%): HPLC t_R (min): 9.66. Rf_1 0.45. Rf_2 0.74. ^{1}H-NMR (CD_3OD) δ: 7.16 (5H, m), 6.95 (2H, d, J=8.4 Hz), 6.61 (2H, d, J=8.4 Hz), 4.58 (1H, dd, J=10.8, 4.5 Hz), 4.25 (1H, t, J=7.5 Hz), 4.01 (1H, t, J=7.2 Hz), 3.85 (2H, dd, J=30.1, 17.4 Hz), 3.62 (3H, s), 2.98—2.68 (5H, m), 1.81 (6H, s), 1.33 (2H, br m), 1.05 (1H, br m), 0.90 (1H, br m). FAB-MS m/z: 598 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Gly-NH2·2AcOH (19) White powder (499 mg, 71%): HPLC t_R (min): 8.40. Rf_1 0.38. Rf_2 0.68. ^{1}H-NMR (CD_3OD) δ: 7.16 (5H, m), 6.95 (2H, d, J=8.4 Hz), 6.61 (2H, d, J=8.4 Hz), 4.50 (1H, dd, J=10.7, 4.5 Hz), 4.26 (1H, t, J=7.2 Hz), 3.98 (1H, t, J=7.2 Hz), 3.75 (2H, dd, J=20.3, 16.8 Hz), 2.94—2.71 (5H, m), 1.82 (6H, s), 1.36 (2H, br m), 1.09 (1H, br m), 0.96 (1H, br m). FAB-MS m/z: 583 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Gly-NHMe·2AcOH (20) White powder (437 mg, 61%): HPLC t_R (min): 8.86. Rf_1 0.41. Rf_2 0.71. ^{1}H-NMR (CD_3OD) δ: 7.16 (5H, m), 6.97 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz), 4.48 (1H, dd, J=10.5, 4.8 Hz), 4.32 (1H, t, J=7.2 Hz), 3.99 (1H, t, J=7.5 Hz), 3.73 (2H, dd, J=30.5, 16.8 Hz), 2.96—2.75 (5H, m), 2.62 (3H, s), 1.82 (6H, s), 1.38 (2H, br m), 1.12 (1H, br m), 1.01 (1H, br m). FAB-MS m/z: 597 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Sar-OH·2AcOH (21) White powder (467 mg, 65%): HPLC t_R (min): 8.49. Rf_1 0.34. Rf_2 0.63. ^{1}H-NMR (CD_3OD) δ: 7.11 (5H, m), 6.97 (2H, d, J=8.7 Hz), 6.62 (2H, dd, J=8.6, 2.1 Hz), 5.03 (0.5H, dd, J=8.1, 6.0 Hz), 4.92 (0.5H, dd, J=8.9, 5.2 Hz), 4.27 (1H, dd, J=15.3, 8.1 Hz), 4.18 (0.5H, dd, J=8.1, 5.4 Hz), 4.13 (0.5H, dd, J=7.2, 6.6 Hz), 4.02 (0.5H, d, J=16.5 Hz), 3.81 (1H, d, J=2.4 Hz), 3.49 (0.5H, d, J=16.5 Hz), 3.03—2.74 (6H, m), 2.89 (1.5H, s), 2.83 (1.5H, s), 1.82 (6H, s), 1.49—1.06 (4H, br m). FAB-MS m/z: 598 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Sar-OMe·2AcOH (22) White powder (490 mg, 67%): HPLC t_R (min): 10.48. Rf_1 0.41. Rf_2 0.70. ^{1}H-NMR (CD_3OD) δ: 7.15 (5H, m), 6.96 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz), 5.03 (0.5H, dd, J=8.4, 6.3 Hz), 4.27 (1H, t, J=7.8 Hz), 4.17—4.10 (1H, m), 3.99 (2H, dd, J=42.4, 17.1 Hz), 3.63 (1H s), 3.60 (2H, s), 3.04—2.73 (6H, m), 2.97 (2H, s), 2.83 (1H, s), 1.82 (6H, s), 1.47 (1H, br m), 1.33 (1H, br m), 1.12 (2H, br m). FAB-MS m/z: 612 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-EtGly-OH·2AcOH (23) White powder (424 mg, 58%): HPLC t_R (min): 9.99. Rf_1 0.36. Rf_2 0.65. ^{1}H-NMR (CD_3OD) δ: 7.12 (5H, m), 6.97 (2H, d, J=8.4 Hz), 6.62 (2H, dd, J=8.7, 2.1 Hz), 5.01—4.85 (1H, m), 4.24 (1H, dd, J=15.6, 7.8 Hz), 4.14 (1H, t, J=6.6 Hz), 3.73 (1H, dd, J=25.7, 18.0 Hz), 3.53—3.37 (2H, m), 3.12—2.72 (7H, m), 1.81 (6H, s), 1.32 (2H, br m), 1.15 (1H, br m), 1.07 (1H, br m), 0.96—0.88 (1H, br m). FAB-MS m/z: 612 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-(*n*-Pr)Gly-OH·2AcOH (24) White powder (403 mg, 54%): HPLC t_R (min): 10.94. Rf_1 0.42. Rf_2 0.68. ^{1}H-NMR (CD_3OD) δ: 7.12 (5H, m), 6.97 (2H, d, J=8.1 Hz), 6.62 (2H, dd, J=8.4, 2.7 Hz), 5.00—4.87 (1H, m), 4.27—3.96 (2H, m), 3.74 (1H, s), 3.49—3.25 (1H, m), 3.06—2.75 (7H, m), 1.82 (6H, s), 1.70—1.00 (6H, m), 0.71 (3H, dd, J=13.4, 7.2 Hz). FAB-MS m/z: 626 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Ala-OH·2AcOH (25) White powder (481 mg, 67%): HPLC t_R (min): 9.19. Rf_1 0.40. Rf_2 0.68. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.97 (2H, d, J=8.4 Hz), 6.60 (2H, d, J=8.4 Hz), 4.53 (1H, dd, J=11.1, 3.9 Hz), 4.26—4.15 (2H, m), 3.98 (1H, t, J=7.0 Hz), 2.87—2.67 (5H, m), 1.84 (6H, s), 1.34 (2H, br m), 1.30 (3H, d, J=7.2 Hz), 1.05 (1H, m), 0.88 (1H, br m). FAB-MS m/z: 598 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Ala-OMe·2AcOH (26) White powder (505 mg, 69%): HPLC t_R (min): 10.22. Rf_1 0.51. Rf_2 0.75. ^{1}H-NMR (CD_3OD) δ: 7.15 (5H, m), 6.96 (2H, d, J=8.1 Hz), 6.61 (2H, d, J=8.1 Hz), 4.57 (1H, dd, J=10.7, 4.2 Hz), 4.35—4.24 (2H, m), 4.01 (1H, t, J=7.5 Hz), 3.59 (3H, s), 2.96—2.67 (5H, m), 1.82 (6H, s), 1.37 (2H, br m), 1.32 (3H, d, J=7.2 Hz), 1.06 (1H, br m), 0.97 (1H, br m). FAB-MS m/z: 612 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Ala-NH_2·2AcOH (27) White powder (459 mg, 64%): HPLC t_R (min): 8.83. Rf_1 0.43. Rf_2 0.72. ^{1}H-NMR (CD_3OD) δ: 7.16 (5H, m), 6.96 (2H, d, J=8.4 Hz), 6.61 (2H, d, J=8.4 Hz), 4.50 (1H, dd, J=11.0, 4.1 Hz), 4.34 (1H, dd, J=14.4, 7.2 Hz), 4.25 (1H, t, J=7.1 Hz), 3.88 (1H, t, J=7.2 Hz), 3.27 (1H, dd, J=14.0, 4.1 Hz), 2.97—2.78 (4H, m), 2.70 (1H, dd, J=14.0, 11.3 Hz), 1.82 (6H, s), 1.33 (5H, d, J=7.2 Hz), 1.06 (1H, br m), 0.85 (1H, br m). FAB-MS m/z: 597$(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Ala-NHMe·2AcOH (28) White powder (504 mg, 69%): HPLC t_R (min): 9.26. Rf_1 0.47. Rf_2 0.71. ^{1}H-NMR (CD_3OD) δ: 7.16 (5H, m), 6.98 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz), 4.50 (1H, dd, J=11.3, 4.1 Hz), 4.35—4.25 (2H, m), 3.91 (1H, t, J=7.1 Hz), 3.25 (1H, dd, J=14.9, 4.7 Hz), 2.92—2.83 (5H, m), 2.73 (1H, dd, J=14.1, 11.4 Hz), 2.58 (3H, s), 1.84 (6H, s), 1.36 (2H, m), 1.31 (3H, d, J=7.2 Hz), 1.09 (1H, br m), 0.89 (1H, br m). FAB-MS m/z: 611 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-MeAla-OH·2AcOH (29) White powder (373 mg, 51%): HPLC t_R (min): 10.44. Rf_1 0.45. Rf_2 0.70. ^{1}H-NMR (CD_3OD) δ: 7.12 (5H, m), 6.99 (2H, d, J=8.1 Hz), 6.64 (2H, d, J=8.4 Hz), 5.00 (1H, m), 4.37 (1H, m), 4.19 (1H, m), 3.05—2.64 (9H, m), 1.83 (6H, s), 1.52 (2H, br m), 1.33 (1H, m), 1.24 (2H, d, J=7.2 Hz), 1.07 (3H, d, J=7.2 Hz). FAB-MS m/z: 612 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-D-Ala-OH·2AcOH (30) White powder (495 mg, 69%): HPLC t_R (min): 9.54. Rf_1 0.40. Rf_2 0.68. ^{1}H-NMR (CD_3OD) δ: 7.15 (5H, m), 6.96 (2H, d, J=8.4 Hz), 6.61 (2H, d, J=8.7 Hz), 4.58 (1H, dd, J=9.9, 5.1 Hz), 4.28 (1H, t, J=7.1 Hz), 4.08 (2H, m), 3.14 (1H, dd, J=13.8, 5.1 Hz), 3.89 (3H, m), 2.82—2.72 (2H, m), 1.83 (6H, s), 1.40 (2H, br m), 1.17 (3H, d, J=6.9 Hz), 1.13 (1H, br m), 1.02 (1H, br m). FAB-MS m/z: 598 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-D-Ala-OMe·2AcOH (31) White powder (476 mg, 65%): HPLC t_R (min): 10.56. Rf_1 0.51. Rf_2 0.77. ^{1}H-NMR (CD_3OD) δ: 7.15 (5H, m), 6.95 (2H, d, J=8.1 Hz), 6.61 (2H, d, J=6.9 Hz), 4.55 (1H, dd, J=10.7, 5.0 Hz), 4.28 (2H, m), 3.98 (1H, t, J=7.2 Hz), 3.60 (3H, s), 3.17 (1H, m), 2.97—2.68 (5H, m), 1.81 (6H, s), 1.36 (2H, br m), 1.36 (2H, br m), 1.23 (3H, d, J=6.9 Hz), 1.08 (1H, br m), 0.92 (1H, br m). FAB-MS m/z: 612 $(M+H)^+$.

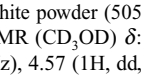
N^{α}-Amidino-Tyr-D-Arg-Phe-D-Ala-NH_2·2AcOH (32) White powder (437 mg, 61%): HPLC t_R (min): 9.04. Rf_1 0.44. Rf_2 0.72. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.96 (2H, d, J=8.1 Hz), 6.62 (2H, d, J=8.4 Hz), 4.42 (1H, dd, J=9.6, 6.0 Hz), 4.28 (1H, t, J=7.1 Hz), 4.17 (1H, dd, J=14.4, 7.2 Hz), 4.00 (1H, t, J=7.1 Hz), 3.11 (1H, dd, J=13.7, 6.2 Hz), 2.89 (3H, br m), 2.80 (2H, m), 1.82 (6H, s), 1.41 (2H, br m), 1.15 (4H, d, J=7.2 Hz), 1.04 (1H, br m). FAB-MS m/z: 597 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-D-Ala-NHMe·2AcOH (33) White powder (417 mg, 57%): HPLC t_R (min): 9.40. Rf_1 0.48. Rf_2 0.73. ^{1}H-NMR (CD_3OD) δ: 7.14 (5H, m), 6.95 (2H, d, J=9.0 Hz), 6.62 (2H, d, J=8.4 Hz), 4.41 (1H, dd, J=9.6, 6.0 Hz), 4.29 (1H, t, J=6.9 Hz), 4.15 (1H, dd, J=14.3, 7.1 Hz), 3.99 (1H, t, J=7.1 Hz), 3.11 (1H, dd, J=13.5, 6.0 Hz), 2.90 (3H, br m), 2.79 (2H, m), 2.60 (3H, s), 1.82 (6H, s), 1.42 (2H, br m), 1.12 (4H, d, J=7.2 Hz), 1.04 (1H, br m). FAB-MS m/z: 611 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-D-MeAla-OH·2AcOH (34) White powder (388 mg, 53%): HPLC t_R (min): 10.28. Rf_1 0.45. Rf_2 0.66. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.95 (2H, m), 6.64 (2H, m), 5.01 (1H, t, J=7.4 Hz), 4.26 (2H, m), 3.11—2.82 (6H, m), 2.77 (1H, s), 2.67 (2H, s), 1.86 (6H, s), 1.40 (2H, br m), 1.33—1.18 (3H, m), 1.09 (2H, d, J=7.2 Hz), 0.98 (1H, d, J=7.2 Hz). FAB-MS m/z: 612 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-D-MeAla-OMe·2AcOH (35) White powder (418 mg, 56%): HPLC t_R (min): 11.26. Rf_1 0.54. Rf_2 0.75. ^{1}H-NMR (CD_3OD) δ: 7.15 (5H, m), 6.94 (2H, m), 6.63 (2H, m), 4.98 (1H, m), 4.70 (1H, dd, J=14.7, 7.2 Hz), 4.28 (1H, t, J=7.4 Hz), 4.18 (1H, dd, J=8.5, 5.4 Hz), 3.60 (0.5H, s), 3.56 (2.5H, s), 2.97—2.90 (4H, m), 2.84—2.79 (2H, m), 2.77 (2.5H, s), 2.69 (0.5H, s), 1.83 (6H, s), 1.52 (1H, br m), 1.36 (1H, br m), 1.32 (1H, d, J=6.6 Hz), 1.16 (4H, d, J=7.2 Hz). FAB-MS m/z: 626 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-GABA-OH·2AcOH (36) White powder (498 mg, 68%): HPLC t_R (min): 9.26. Rf_1 0.50. Rf_2 0.70. ^{1}H-NMR (CD_3OD) δ: 7.12 (5H, m), 6.98 (2H, d, J=8.7 Hz), 6.62 (2H, d, J=8.4 Hz), 4.49 (1H, dd, J=10.5, 4.2 Hz), 3.95 (1H, t, J=7.1 Hz), 3.26 (1H, m), 3.08 (1H, m), 2.97—2.65 (5H, m), 2.16 (1H, t, J=6.6 Hz), 1.83 (6H, s), 1.72 (2H, m), 1.39 (2H, br m), 1.08 (1H, br m), 0.85 (1H, br m). FAB-MS m/z: 612 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe  **·2AcOH (37)** White powder

(414 mg, 54%): HPLC t_R (min): 12.45. $Rf_1$0.58. Rf_2 0.80.^{1}H-NMR (CD_3OD) δ: 8.48 (1H, t, J=9.2 Hz), 7.93 (1H, m), 7.30 (1H, m), 7.15 (6H, m), 6.98 (2H, t, J=8.6 Hz), 6.61 (2H, t, J=7.8 Hz), 4.66 (1H, m), 4.37 (1H, m), 4.23 (1H, dt, J=24.0, 6.6 Hz), 3.30 (1H, m), 3.05 (1H, m), 2.92 (3H, m), 2.84—2.72 (1H, m), 1.87 (1H, br m), 1.80 (6H, s), 1.59 (2H, br m), 1.15 (2H, br m). FAB-MS m/z: 646 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Leu-OH·2AcOH (38) White powder (509

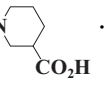
mg, 67%): HPLC t_R (min): 11.41. Rf_1 0.50. Rf_2 0.77. ^{1}H-NMR (CD_3OD) δ: 7.15 (5H, m), 6.98 (2H, d, J=8.1 Hz), 6.61 (2H, d, J=8.4 Hz), 4.48 (1H, dd, J=11.4, 3.6 Hz), 4.28 (1H, t, J=6.9 Hz), 4.13 (1H, t, J=7.2 Hz), 3.89 (1H, t, J=7.4 Hz), 3.31 (1H, dd, J=14.3, 3.5 Hz), 2.79 (4H, m), 2.64 (1H, dd, J=13.8, 11.7 Hz), 1.81 (6H, s), 1.58 (3H, m), 1.26 (2H, br m), 0.97 (1H, br m), 0.85 (6H, dd, J=6.0, 2.1 Hz), 0.75 (1H, br m). FAB-MS m/z: 640 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Nva-OH·2AcOH (39) White powder (530 mg, 71%): HPLC t_R (min): 10.66. Rf_1 0.49. Rf_2 0.77. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.96 (2H, d, J=8.1 Hz), 6.60 (2H, d, J=8.1 Hz), 4.52 (1H, dd, J=11.1, 3.6 Hz), 4.21 (2H, t, J=6.3 Hz), 3.96 (1H, t, J=7.2 Hz), 3.27 (1H, dd, J=14.3, 3.8 Hz), 2.83 (4H, t, J=6.8 Hz), 2.71 (1H, dd, J=14.0, 11.3 Hz), 1.84 (6H, s), 1.78—1.55 (2H, m), 1.34—1.27 (4H, m), 1.03 (1H, br m), 0.85 (3H, t, J=7.2 Hz), 0.80 (1H, br m). FAB-MS m/z: 626 $(M+H)^+$.

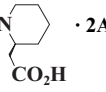
N^{α}-Amidino-Tyr-D-Arg-Phe-Phe-OH·2AcOH (40) White powder (508 mg, 64%): HPLC t_R (min): 11.91. Rf_1 0.47. Rf_2 0.76. ^{1}H-NMR (CD_3OD) δ: 7.14 (10H, m), 6.98 (2H, d, J=8.4 Hz), 6.61 (2H, d, J=8.4 Hz), 4.42 (2H, m), 4.16 (1H, t, J=7.5 Hz), 4.00 (1H, t, J=7.1 Hz), 3.15 (2H, m), 3.00—2.71 (5H, m), 2.54 (1H, t, J=12.9 Hz), 1.81 (6H, s), 1.35 (1H, br m), 1.24 (1H, br m), 0.99 (1H, br m), 0.80 (1H, br m). FAB-MS m/z: 674 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Pro-OH·2AcOH (41) White powder (424 mg, 57%): HPLC t_R (min): 9.94. Rf_1 0.40. Rf_2 0.68. ^{1}H-NMR (CD_3OD) δ: 7.12 (5H, m), 6.98 (2H, t, J=7.7 Hz), 6.62 (2H, dd, J=8.7, 6.6 Hz), 4.70 (1H, dd, J=8.3, 6.3 Hz), 4.29 (1H, dd, J=8.7, 6.6 Hz), 4.22 (1H, t, J=6.6 Hz), 4.13 (1H, br m), 3.65 (1H, br m), 3.45 (1H, br m), 2.98—2.71 (5H, m), 2.06—1.89 (2H, br m), 1.85 (6H, s), 1.67—1.45 (3H, br m), 1.23 (1H, br m), 1.11 (1H, br m). FAB-MS m/z: 624 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Pro-OMe·2AcOH (42) White powder (440 mg, 58%): HPLC t_R (min): 11.22. Rf_1 0.49. Rf_2 0.78. ^{1}H-NMR (CD_3OD) δ: 7.17 (5H, m), 6.97 (2H, d, J=8.0 Hz), 6.63 (2H, t, J=6.8 Hz), 4.30 (2H, m), 4.12 (1H, dd, J=8.4, 5.4 Hz), 3.63 (1H, m), 3.61 (3H, s), 3.36 (1H, br m), 3.06—2.73 (6H, m), 2.11 (1H, br m), 1.82 (6H, s), 1.60 (1H, br m), 1.42 (1H, br m), 1.33 (1H, br m), 1.12 (1H, br m). FAB-MS m/z: 638 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe—  ·**2AcOH (43)** White powder (477 mg, 63%): HPLC t_R (min): 10.39. Rf_1 0.48. Rf_2 0.73. ^{1}H-NMR (CD_3OD) δ: 7.12 (5H, m), 6.97 (2H, d, J=8.4 Hz), 6.61 (2H, dd, J=8.0, 3.5 Hz), 4.51 (1H, br m), 4.26 (1H, br m), 4.10 (1H, m), 3.73 (1H, br m), 3.53 (1H, br m), 2.94 (7H, br m), 2.49 (1H, br m), 2.04 (2H, br m), 1.81 (6H, s), 1.53—1.14 (7H, br m). FAB-MS m/z: 638 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-(R,S)βPro-OH·2AcOH (44) White powder (491 mg, 66%): HPLC t_R (min): 9.84. Rf_1 0.43. Rf_2 0.70. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.97 (2H, d, J=9.0 Hz), 6.62 (2H, d, J=8.4 Hz), 4.70 (1H, m), 4.24 (1H, m), 4.13 (1H, m), 3.72 (1H, m), 3.56 (2H, m), 3.44—3.25 (2H, m), 2.92 (4H, br m), 2.81 (3H, br m), 2.68 (1H, br m), 2.13—1.93 (3H, m), 1.86 (6H, s), 1.44 (2H, br m), 1.13 (2H, br m). FAB-MS m/z: 624 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe—  ·**2AcOH (45)** White powder (523 mg, 69%): HPLC t_R (min): 10.12. Rf_1 0.46. Rf_2 0.70. ^{1}H-NMR (CD_3OD) δ: 7.12 (5H, m), 6.97 (2H, d, J=8.4 Hz), 6.61 (2H, d, J=8.4 Hz), 4.50 (1H, dd, J=10.8, 4.5 Hz), 4.27 (1H, m), 4.10 (1H, m), 3.36 (1H, t, J=5.9 Hz), 3.40—3.16 (3H, m), 2.95 (1H, d, J=15.1 Hz), 2.33 (1H, dd, J=15.1, 8.4 Hz), 2.05—1.65 (4H, m), 1.81 (6H, s), 1.35 (2H, m), 1.08 (1H, br m), 0.88 (1H, br m). FAB-MS m/z: 638 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-αAib-OH·2AcOH (46) White powder (527 mg, 72%): HPLC t_R (min): 9.97. Rf_1 0.45. Rf_2 0.73. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.97 (2H, d, J=8.4 Hz), 6.61 (2H, d, J=8.7 Hz), 4.42 (1H, dd, J=10.2, 4.5 Hz), 4.24 (1H, dd, J=8.1, 6.3 Hz), 4.24 (1H, t, J=7.1 Hz), 3.15 (1H, dd, J=14.1, 4.5 Hz), 2.97—2.87 (3H, m), 2.80—2.69 (2H, m), 1.81 (6H, s), 1.49 (2H, br m), 1.39 (6H, s), 1.13 (1H, br m), 1.05 (1H, br m). FAB-MS m/z: 612 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-(R,S)βAib-OH·2AcOH (47) White powder (512 mg, 70%): HPLC t_R (min): 9.50. Rf_1 0.47. Rf_2 0.75. ^{1}H-NMR (CD_3OD) δ: 7.14 (5H, m), 6.98 (2H, dd, J=8.7, 2.7 Hz), 6.61 (2H, dd, J=8.4, 1.5 Hz), 4.52 (2H, br m), 4.48 (1H, t, J=4.1 Hz), 4.21 (1H, m), 3.93 (1H, dt, J=38.5, 7.4 Hz), 3.32 (1H, dd, J=13.8, 3.9 Hz), 3.10 (1H, m), 2.98 (1H, m), 2.82 (3H, m), 2.67 (1H, dd, J=24.9, 12.9 Hz), 2.38 (1H, br m), 1.81 (6H, s), 1.32 (2H, br m), 1.02 (4H, dd, J=7.1, 4.4 Hz), 0.80 (1H, br m), 0.71 (1H, br m). FAB-MS m/z: 612 $(M+H)^+$.

N^{α}-amidino-Tyr-D-Arg-Phe-(R)αAbu-OH·2AcOH (48) White powder (505 mg, 69%): HPLC t_R (min): 10.24. Rf_1 0.42. Rf_2 0.70. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.97 (2H, d, J=8.7 Hz), 6.61 (2H, d, J=8.4 Hz), 4.65 (1H, dd, J=9.6, 5.4 Hz), 4.29 (1H, t, J=7.2 Hz), 4.09 (2H, dd, J=14.9, 7.4 Hz), 3.13 (1H, dd, J=14.0, 5.6 Hz), 2.90 (3H, m), 2.83—2.73 (2H, m), 1.83 (6H, s), 1.70 (6H, m), 1.57 (1H, m), 1.41 (2H, br m), 1.11 (1H, br m), 1.02 (1H, br m), 0.67 (3H, t, J=7.2 Hz). FAB-MS m/z: 612 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-(S)αAbu-OH·2AcOH (49) White powder (476 mg, 65%): HPLC t_R (min): 9.65. Rf_1 0.44. Rf_2 0.79. ^{1}H-NMR (CD_3OD) δ: 7.14 (5H, m), 6.96 (2H, d, J=8.4 Hz), 6.60 (2H, d, J=8.4 Hz), 4.51 (1H, dd, J=11.3, 3.8 Hz), 4.18 (2H, m), 3.99 (1H, t, J=7.2 Hz), 3.28 (1H, dd, J=14.1, 3.9 Hz), 2.83 (4H, m), 2.71 (1H, dd, J=14.1, 11.4 Hz), 1.81 (6H, s), 1.35 (2H, m), 1.78—1.63 (2H, m), 1.33 (2H, br m), 1.02 (1H, br m), 0.84 (1H, t, J=7.4 Hz). FAB-MS m/z: 612 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-(R,S)βAbu-OH·2AcOH (50) White powder (520 mg, 71%): HPLC t_R (min): 9.29, 9.60. Rf_1 0.44. Rf_2 0.74. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.97 (2H, d, J=8.4 Hz), 6.61 (2H, dd, J=8.4, 2.4 Hz), 4.45 (1H, m), 4.27 (1H, br m), 4.12 (1H, br m), 3.99 (1H, br m), 3.20 (1H, br m), 2.96—2.67 (5H, br m), 2.28 (2H, m), 1.84 (6H, s), 1.36 (2H, br m), 1.13 (2H, d, J=6.6 Hz), 1.07 (1H, br m), 1.00 (1H, d, J=6.6 Hz), 0.86 (1H, br m). FAB-MS m/z: 612 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Arg-NH_2·3AcOH (51) White powder (543 mg, 63%): HPLC t_R (min): 8.21. Rf_1 0.25. Rf_2 0.70. ^{1}H-NMR (CD_3OD) δ: 7.16 (5H, m), 6.96 (2H, d, J=8.7 Hz), 6.61 (2H, d, J=8.7 Hz), 4.50 (1H, dd, J=11.3, 4.4 Hz), 4.33 (1H, dd, J=9.2, 5.0 Hz), 4.25 (1H, t, J=7.1 Hz), 3.88 (1H, t, J=7.4 Hz), 3.26 (1H, m), 3.12 (2H, t, J=7.4 Hz), 2.85 (4H, t, J=7.1 Hz), 2.75 (1H, dd, J=14.1, 11.1 Hz), 1.81 (6H, s), 1.72 (1H, br m), 1.58 (1H, br m), 1.34 (1H, br m), 1.07 (1H, br m), 0.88 (1H, br m). FAB-MS m/z: 682 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-D-Arg-NH_2·3AcOH (52) White powder (526 mg, 61%): HPLC t_R (min): 8.24. Rf_1 0.22. Rf_2 0.67. ^{1}H-NMR (CD_3OD) δ: 7.15 (5H, m), 6.96 (2H, d, J=8.7 Hz), 6.62 (2H, d, J=8.4 Hz), 4.44 (1H, dd, J=8.9, 7.1 Hz), 4.29 (1H, t, J=6.8 Hz), 4.16 (1H, dd, J=9.6, 4.5 Hz), 4.05 (1H, t, J=7.1 Hz), 3.08 (1H, m), 2.99—2.79 (7H, m), 1.81 (9H, s), 1.74 (1H, br m), 1.44 (3H, br m), 1.22 (1H, br m), 1.06 (1H, br m). FAB-MS m/z: 682 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Asp-OH·2AcOH (53) White powder (480 mg, 63%): HPLC t_R (min): 8.65. Rf_1 0.31. Rf_2 0.57. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.98 (2H, d, J=8.4 Hz), 6.61 (2H, d, J=8.4 Hz), 4.56 (1H, dd, J=11.0, 4.1 Hz), 4.46 (1H, t, J=5.7 Hz), 4.24 (1H, t, J=7.4 Hz), 4.00 (1H, t, J=6.9 Hz), 2.97—2.76 (4H, m), 2.70 (3H, br m), 1.83 (6H, s), 1.38 (2H, br m), 1.07 (1H, br m), 0.88 (1H, br m). FAB-MS m/z: 642 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Asu-OH·2AcOH (54) White powder (556 mg, 68%): HPLC t_R (min): 10.26. Rf_1 0.49. Rf_2 0.72. ^{1}H-NMR (CD_3OD) δ: 7.12 (5H, m), 6.91 (2H, d, J=10.2 Hz), 6.60 (2H, d, J=8.7 Hz), 4.47 (1H, dd, J=11.1, 3.9 Hz), 4.20 (1H, t, J=7.4 Hz), 4.14 (1H, dd, J=7.1, 4.7 Hz), 3.98 (1H, t, J=7.2 Hz), 3.21 (1H, dd, J=11.1, 4.2 Hz), 2.84—2.64 (6H, m), 2.11 (2H, t, J=7.2 Hz), 1.82 (6H, s), 1.70 (2H, br m), 1.47 (2H, br m), 1.36 (2H, br m), 1.24 (4H, br m), 1.04 (1H, br m), 0.92 (1H, br m). FAB-MS m/z: 698 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-Taurine·2AcOH (55) White powder (415 mg, 55%): HPLC t_R (min): 8.27. Rf_1 0.39. Rf_2 0.69. ^{1}H-NMR (CD_3OD) δ: 7.11 (5H, m), 6.96 (2H, d, J=8.1 Hz), 6.60 (2H, d, J=8.4 Hz), 4.45 (1H, dd, J=10.8, 4.2 Hz), 4.29 (1H, t, J=6.9 Hz), 3.93 (1H, t, J=6.8 Hz), 3.49 (2H, t, J=6.5 Hz), 2.86 (6H, br m), 2.70 (1H, m), 1.81 (6H, s), 1.32 (2H, br m), 1.03 (1H, br m), 0.90 (1H, br m). FAB-MS m/z: 634 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-$NHCH_2SO_3H$·2AcOH (56) White powder (429 mg, 58%): HPLC t_R (min): 8.01. Rf_1 0.35. Rf_2 0.64. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.97 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz), 4.55 (3H, m), 4.26 (1H, t, J=7.5 Hz), 2.86 (6H, br m), 2.73 (1H, m), 1.82 (6H, s), 1.35 (2H, br m), 1.00 (1H, br m), 0.92 (1H, br m). FAB-MS m/z: 620 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-MeβAla-OMe·2AcOH (57) White powder (530 mg, 71%): HPLC t_R (min): 10.89. Rf_1 0.48. Rf_2 0.77. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.96 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz), 4.95 (1H, dt, J=27.9, 7.4 Hz), 4.50 (1H, br s), 4.25 (1H, t, J=7.1 Hz), 4.17 (1H, dd, J=8.1, 6.0 Hz), 3.55 (3H, s), 3.50—3.33 (2H, m), 2.92 (4H, m), 2.82 (3H, m), 2.75 (2H, m), 2.38 (2H, t, J=7.2 Hz), 1.81 (6H, s), 1.46 (1H, br m), 1.37 (1H, br m), 1.16 (2H, br m). FAB-MS m/z: 626 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-MeβAla-OEt·2AcOH (58) White powder (555 mg, 73%): HPLC t_R (min): 11.77. Rf_1 0.51. Rf_2 0.77. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.96 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz),

4.95 (1H, dt, J=27.3, 7.5 Hz), 4.53 (1H, br s), 4.26 (1H, t, J=7.2 Hz), 4.17 (1H, dd, J=8.3, 5.3 Hz), 4.01 (2H, dd, J=14.3, 7.1 Hz), 3.55—3.00 (3H, m), 2.91 (4H, m), 2.82 (3H, m), 2.75 (2H, m), 2.37 (2H, t, J=7.4 Hz), 1.81 (6H, s), 1.47 (1H, br m), 1.34 (1H, br m), 1.17 (2H, br m), 1.14 (3H, dt, J=2.4, 7.2 Hz). FAB-MS m/z: 640 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-MeβAla-O(n-Pr)·2AcOH (59) White powder (542 mg, 70%): HPLC t_R (min): 13.45. Rf_1 0.54. Rf_2 0.79. ^{1}H-NMR (CD_3OD) δ: 7.15 (5H, m), 6.97 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz), 4.94 (1H, dt, J=31.3, 7.5 Hz), 4.31 (1H, m), 4.13 (1H, m), 3.47 (1H, m), 3.38 (1H, m), 3.00 (2H, t, J=7.2 Hz), 2.91 (4H, m), 2.82 (3H, m), 2.76 (2H, m), 2.25 (2H, m), 1.82 (6H, s), 1.41 (4H, m), 1.17 (2H, m), 0.80 (3H, dt, J=3.0, 7.0 Hz). FAB-MS m/z: 654 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-MeβAla-O(n-Hex)·2AcOH (60) White powder (563 mg, 69%): HPLC t_R (min): 15.74. Rf_1 0.58. Rf_2 0.80. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.96 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.7 Hz), 4.94 (1H, dt, J=27.6, 7.5 Hz), 4.28 (1H, t, J=7.2 Hz), 4.15 (1H, dd, J=8.4, 5.1 Hz), 3.96 (2H, t, J=6.6 Hz), 3.53 (1H, m), 3.32 (1H, m), 2.91 (4H, m), 2.82 (3H, m), 2.75 (2H, m), 2.37 (2H, t, J=7.2 Hz), 1.82 (6H, s), 1.52 (3H, br m), 1.37 (1H, br m), 1.23 (8H, m), 0.81 (3H, t, J=6.8 Hz). FAB-MS m/z : 696 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-MeβAla-OPOM·2AcOH (61) White powder (524 mg, 62%): HPLC t_R (min): 14.95. Rf_1 0.57. Rf_2 0.63. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.97 (2H, dd, J=8.4, 4.5 Hz), 6.62 (2H, dd, J=8.7, 1.8 Hz), 5.75 (2H, s), 5.00 (1H, dt, J=61.3, 7.2 Hz), 4.26 (1H, dt, J=24.9, 7.2 Hz), 4.17 (1H, dd, J=13.2, 6.9 Hz), 3.75 (1H, m), 3.57 (1H, m), 2.94 (4H, m), 2.80 (3H, m), 2.73 (2H, m), 2.24 (2H, m), 1.83 (6H, s), 1.50 (1H, br m), 1.40 (1H, br m), 1.23 (9H, s), 1.11 (2H, br m). FAB-MS m/z: 726 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-MeβAla-NH_2·2AcOH (62) White powder (541 mg, 74%): HPLC t_R (min): 9.10. Rf_1 0.30. Rf_2 0.64. ^{1}H-NMR (CD_3OD) δ: 7.14 (5H, m), 6.96 (2H, d, J=8.4 Hz), 6.61 (2H, d, J=8.4 Hz), 4.90 (1H, dt, J=33.1, 7.2 Hz), 4.50 (1H, br s), 4.19 (1H, m), 4.05 (1H, m), 3.46—3.25 (2H, m), 2.92 (4H, m), 2.81 (3H, m), 2.20 (2H, m), 1.81 (6H, s), 1.44 (1H, br m), 1.35 (1H, br m), 1.03 (2H, br m). FAB-MS m/z: 611 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-MeβAla-NHMe·2AcOH (63) White powder (544 mg, 73%): HPLC t_R (min): 9.49. Rf_1 0.32. Rf_2 0.67. ^{1}H-NMR (CD_3OD) δ: 7.16 (5H, m), 6.96 (2H, d, J=8.1 Hz), 6.62 (2H, d, J=8.4 Hz), 4.94 (1H, dt, J=31.6, 7.4 Hz), 4.52 (1H, br s), 4.27 (1H, m), 4.15 (1H, m), 3.52—3.32 (2H, m), 2.92 (4H, m), 2.80 (3H, m), 2.59 (3H, s), 2.24 (2H, m), 1.82 (6H, s), 1.46 (1H, br m), 1.37 (1H, br m), 1.16 (2H, br m). FAB-MS m/z: 625 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-MeβAla-NHEt·2AcOH (64) White powder (539 mg, 71%): HPLC t_R (min): 10.00. Rf_1 0.41. Rf_2 0.70. ^{1}H-NMR (CD_3OD) δ: 7.16 (5H, m), 6.97 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz), 4.94 (1H, dt, J=31.0, 7.5 Hz), 4.53 (1H, br s), 4.28 (1H, m), 4.14 (1H, m), 3.07 (2H, dd, J=14.6, 7.4 Hz), 2.92 (4H, m), 2.82 (3H, m), 2.76 (2H, m), 2.24 (2H, m), 1.81 (6H, s), 1.46 (1H, br m), 1.37 (1H, br m), 1.16 (2H, br m), 1.00 (3H, dt, J=2.7, 7.2 Hz). FAB-MS m/z: 639 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-MeβAla-N$(Me)_2$·2AcOH (65) White powder (501 mg, 66%): HPLC t_R (min): 10.20. Rf_1 0.33. Rf_2 0.67. ^{1}H-NMR (CD_3OD) δ: 7.14 (5H, m), 6.96 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz), 4.92 (1H, m), 4.52 (1H, br s), 4.25 (1H, t, J=7.2 Hz), 4.17 (1H, dd, J=8.0, 5.3 Hz), 3.50 (1H, m), 3.33 (1H, m), 2.95 (3H, m), 2.92 (3H, s), 2.86 (2H, s), 2.83 (2H, s), 2.80 (3H, s), 2.76 (2H, s), 2.40 (1H, m), 1.81 (6H, s), 1.47 (1H, br m), 1.34 (1H, br m), 1.17 (1H, br m). FAB-MS m/z: 639 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-MeβAla-N$(Et)_2$·2AcOH (66) White powder (488 mg, 62%): HPLC t_R (min): 11.58. Rf_1 0.43. Rf_2 0.72. ^{1}H-NMR (CD_3OD) δ: 7.14 (5H, m), 6.96 (2H, d, J=8.7 Hz), 6.63 (2H, d, J=8.7 Hz), 4.93 (1H, m), 4.51 (1H, br s), 4.26 (1H, t, J=7.2 Hz), 4.17 (1H, dd, J=8.3, 5.3 Hz), 3.52 (1H, m), 3.26 (1H, m), 2.94 (4H, m), 2.83 (4H, s), 2.76 (1H, s), 2.38 (2H, m), 1.81 (6H, s), 1.47 (1H, br m), 1.37 (1H, br m), 1.17 (2H, br m), 1.04 (6H, dt, J=24.6, 7.1 Hz), . FAB-MS m/z: 667 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-MeβAla-NH(n-Hex)·2AcOH (67) White powder (546 mg, 67%): HPLC t_R (min): 13.83. Rf_1 0.55. Rf_2 0.73. ^{1}H-NMR (CD_3OD) δ: 7.16 (5H, m), 6.97 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz), 4.95 (1H, dt, J=33.4, 7.4 Hz), 4.29 (1H, m), 4.14 (1H, m), 3.52 (1H, m), 3.35 (1H, m), 3.04 (2H, t, J=6.5 Hz), 2.92 (4H, m), 2.81 (3H, m), 2.76 (2H, m), 2.24 (2H, m), 1.82 (6H, s), 1.37 (4H, m), 1.21 (8H, br s), 0.80 (3H, t, J=6.2 Hz). FAB-MS m/z: 695 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-MeβAla-NH(n-Pr)·2AcOH (68) White powder (541 mg, 70%): HPLC t_R (min): 10.80. Rf_1 0.47. Rf_2 0.70. ^{1}H-NMR (CD_3OD) δ: 7.15 (5H, m), 6.97 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz), 4.94 (1H, dt, J=31.3, 7.5 Hz), 4.31 (1H, m), 4.13 (1H, m), 3.38 (1H, m), 3.00 (2H, t, J=7.2 Hz), 2.94 (4H, m), 2.80 (4H, m), 2.76 (1H, s), 2.25 (2H, m), 1.82 (6H, s), 1.46—1.34 (4H, m), 1.17 (2H, m), 0.80 (3H, dt, J=3.0, 7.4 Hz). FAB-MS m/z: 653 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-βAla-OH·2AcOH (69) White powder (517 mg, 72%): HPLC t_R (min): 9.05. Rf_1 0.43. Rf_2 0.66. ^{1}H-NMR (CD_3OD) δ: 7.13 (5H, m), 6.97 (2H, d, J=8.4 Hz), 6.61 (2H, d, J=8.7 Hz), 4.49 (1H, dd, J=11.1, 4.2 Hz), 4.23 (2H, t J=7.2 Hz), 3.89 (1H, t, J=7.2 Hz), 3.38 (2H, m), 3.28 (2H, dd, J=14.1, 4.2 Hz), 2.94 (1H, m), 2.84 (3H, m), 2.67 (1H, dd, J=14.0, 11.3 Hz), 2.28 (2H, t, J=6.2 Hz), 1.82 (6H, s), 1.33 (2H, br m), 1.06 (1H, br m), 0.79 (1H, br m). FAB-MS m/z: 598 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-βAla-OMe·2AcOH (70) White powder (534 mg, 73%): HPLC t_R (min): 10.05. Rf_1 0.50. Rf_2 0.75. ^{1}H-NMR (CD_3OD) δ: 7.14 (5H, m), 6.95 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz), 4.46 (1H, dd, J=10.5, 4.8 Hz), 4.26 (2H, t, J=7.1 Hz), 3.97 (1H, t, J=7.2 Hz), 3.54 (3H, s), 3.34 (2H, dt, J=2.4, 6.9 Hz), 3.17 (1H, m), 2.95—2.76 (4H, m), 2.67 (1H, dd, J=14.0, 11.0 Hz), 2.42 (2H, t, J=6.9 Hz), 1.81 (6H, s), 1.36 (2H, br m), 1.08 (1H, br m), 0.90 (1H, br m). FAB-MS m/z: 612 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-EtβAla-OH·2AcOH (71) White powder (462 mg, 62%): HPLC t_R (min): 10.84. Rf_1 0.44. Rf_2 0.70. ^{1}H-NMR (CD_3OD) δ: 7.14 (5H, m), 6.95 (2H, d, J=8.7 Hz), 6.62 (2H, d, J=8.4 Hz), 4.96 (1H, m), 4.30 (1H, t, J=6.6 Hz), 4.23 (1H, dd, J=8.6, 4.9 Hz), 3.66—3.37 (2H, m), 3.05 (4H, m), 2.95—2.87 (2H, m), 2.61—2.30 (2H, m), 1.82 (6H, s), 1.57 (1H, br m), 1.48 (1H, br m), 1.25 (1H, br m), 1.05 (3H, m). FAB-MS m/z: 626 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-EtβAla-OMe·2AcOH (72) White powder (494 mg, 65%): HPLC t_R (min): 11.65. Rf_1 0.49. Rf_2 0.72. ^{1}H-NMR (CD_3OD) δ: 7.15 (5H, m), 6.96 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz), 4.96 (1H, m), 4.35 (1H, t, J=6.6 Hz), 4.26 (1H, dd, J=8.4, 5.2 Hz), 3.65 (3H, s), 3.62—3.40 (2H, m), 3.03 (4H, m), 2.93—2.85 (2H, m), 2.57—2.39 (2H, m), 1.81 (6H, s), 1.55 (1H, br m), 1.47 (1H, br m), 1.25 (1H, br m), 1.04 (3H, m). FAB-MS m/z: 640 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-(n-Pr)βAla-OH·2AcOH (73) White powder (479 mg, 63%): HPLC t_R (min): 11.18. Rf_1 0.51. Rf_2 0.74. ^{1}H-NMR (CD_3OD) δ: 7.14 (5H, m), 6.97 (2H, dd, J=8.4, 3.6 Hz), 6.62 (2H, d, J=7.8 Hz), 4.96 (1H, dt, J=60.7, 7.5 Hz), 4.27 (1H, dt, J=21.3, 7.4 Hz), 4.16 (1H, br s), 3.48 (1H, m), 3.32 (2H, m), 2.93 (4H, m), 2.87—2.72 (3H, m), 2.28 (2H, m), 1.83 (6H, s), 1.38 (3H, br m), 1.15 (3H, br m), 0.70 (3H, dt, J=9.9, 7.4 Hz). FAB-MS m/z: 640 $(M+H)^+$.

N^{α}-Amidino-Tyr-D-Arg-Phe-(Bn)βAla-OH·2AcOH (74) White powder (460 mg, 57%): HPLC t_R (min): 12.42. Rf_1 0.53. Rf_2 0.75. ^{1}H-NMR (CD_3OD) δ: 7.14 (7H, m), 6.96 (5H, m), 6.63 (2H, d, J=8.1 Hz), 5.02 (1H, dt, J=93.8, 7.2 Hz), 4.52 (1H, br s), 4.43—4.30 (2H, m), 4.21 (2H, m), 3.67 (1H, dm, J=110 Hz), 3.04—2.89 (3H, m), 2.84—2.78 (2H, m), 2.60 (1H, dm, J=96.2 Hz), 2.29 (1H, m), 1.82 (6H, s), 1.47 (1H, br m), 1.35 (1H, br m), 1.12 (2H, br m). FAB-MS m/z: 688 $(M+H)^+$.

Antinociceptive Assays Male mice of ddY strain weighing 10—32 g were used in the experiment. They were purchased from Japan SLC Inc. (Shizuoka, Japan) and housed in cages of 5—6 animals matched for weight and placed in a colony room. Animals were given standard food (MM-3, Japan SLC Inc.) and tap water *ad libitum* in an air-conditioned room at 23±2 °C and 55±20% relative humidity with a standard 12-h light–dark cycle (lights on 6 : 00—18 : 00). Antinociception was examined by the tail pressure test according to the reported method by Sakurada *et al.*[34] with a slight modification. Thus, mechanical pressure was applied to the base of the tail at a rate of 32 g/s using an automated tail-pressure unit (Ugo Basile, Italy). Biting or struggling behavior in mice was used as an indication of response threshold and only mice responding behaviorally to a tail-pressure of 100 to 300 g were selected for this experiment. The trials were terminated at the level of 500 g to prevent tail tissue damage. The mean±S.E.M. of the pressure level was plotted. To obtain the response curve, the dose was plotted against percentage of maximum possible effect (%MPE) as follows: $\%MPE=(P_2-P_1/500-P_1)\times100$, where P_1 is the response pressure before drug administration (g) and P_2 is the response pressure after drug administration (g). The peptides administered were dissolved in saline solution (Fuso Chemical Industries, Osaka, Japan). Saline solution was used as the control. ED_{50} values were obtained by the method of Litchfield and Wilcoxon[35] to compare their antinociceptive activities. These values were calculated from the values obtained at the time of peak effect after either peptide or morphine administration.

References and Notes

1) Symbols and abbreviations are in accordance with recommendations of IUPAC-IUB Joint Commission on Biochemical Nomenclature:

Nomenclature and Symbolism for Amino Acids and Peptides. *Biochem. J.*, **219**, 345—373 (1984). The other abbreviations are as follows: AcOH, acetic acid; Asu, L-α-aminosuberic acid; Bn, benzyl; Boc, tert-butyloxycarbonyl; Cbz, benzyloxycarbonyl; DMF, *N*,*N*-dimethylformamide; EtOAc, ethyl acetate; GABA, γ-aminobutylic acid; HOBt, 1-hydroxybenzotriazole; Tce, 2,2,2-trichloroethyl; TEA, triethylamine; WSCI·HCl, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride.

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