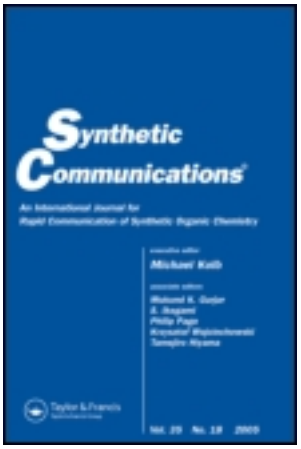

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SIMPLE AND MILD ONE-POT SYNTHESIS OF DIPEPTIDYL UREAS VIA CARBAMOYL AZIDES OF α-*N*-PROTECTED AMINO ACIDS

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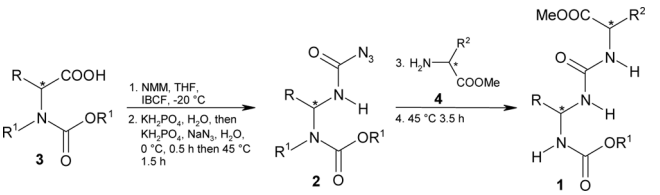
GRAPHICAL ABSTRACT



Abstract *A simple and mild one-pot synthesis of potentially bioactive* α-N-*protected dipeptidyl ureas is reported. The procedure involves the reaction between the carbamoyl azide of an* α-N-*protected amino acid and an* α-*amino acid methyl ester. The reaction is fast (3 h at 45 °C), regardless of the nature of both the reagents, and racemization free. The reported protocol represents a valid alternative to existing methods.*

Keywords Amino acid methyl esters; amino acids; carbamoyl azide; Curtius rearrangement; dipeptidyl ureas

INTRODUCTION

Over the years, intense research has been focused on chemical modifications of peptide backbone[1] in order to obtain bioactive mimetics with high metabolic stability, good bioavailability, high receptor affinity and selectivity, and minimal side effects. In the field of peptidomimetics, the urea linkage as a peptide bond surrogate (denoted ψ[. . . .])[1a] has attracted much attention in recent years[2] because of its metabolic stability and bonding properties. The first ureidopeptides with biological activity were synthesized and studied by Chipens and coworkers 30 years ago.[3] Since then, the urea moiety has been widely used as a structural element in the synthesis of a number of bioactive molecules such as [Leu]enkephalin analogs,[4] CCK-B receptors,[2f] endothelin[2e] and gastrin[5] antagonists, HIV-1 protease,[2a,6]

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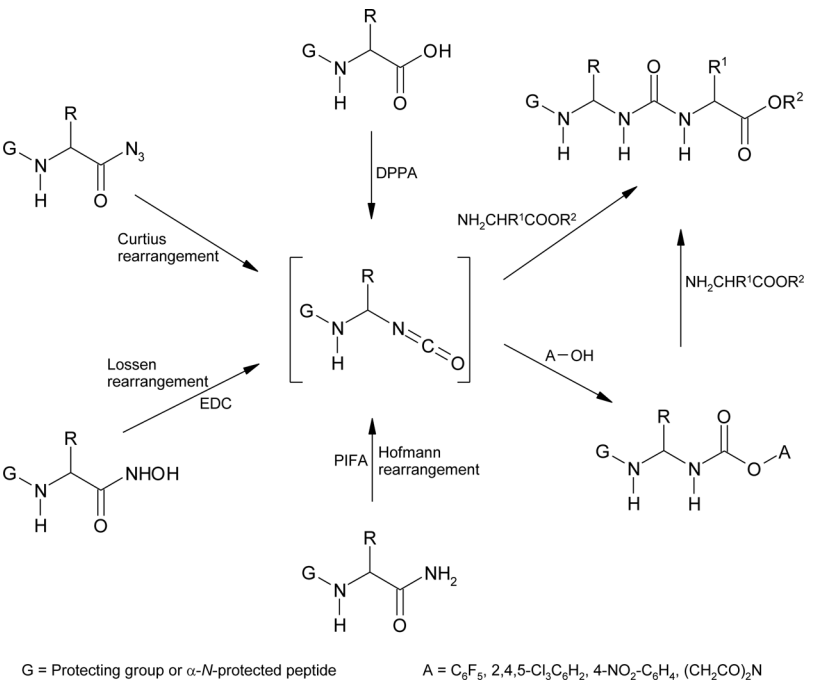
γ-secretase,[7] aspartic acid protease,[8] aspartic peptidase[9] and microbial alkaline proteinase[10] inhibitors, and growth hormone secretagog.[11] In this frame, the development of efficient, simplified synthetic procedures suitable to introduce a ureido connection between two neighboring α-amino acids is of particular interest.

Current strategies to synthesize ureidopeptides involve the corresponding amino acid isocyanate derivatives (Scheme 1). The most employed protocol involves the classical Curtius rearrangement of the pertinent α-*N*-protected amino acid azides, and the crude isocyanates prepared in this way can be subsequently trapped with pentafluorophenol,[12] 2,4,5-trichlorophenol,[13] 4-nitrophenol,[14] or *N*-hydroxysuccinimide[2o,2p,15] to give the corresponding stable carbamates, which react rapidly with suitably protected amino acid derivatives to afford the desired ureidopeptides. Sureshbabu et al. have reported that the isocyanates of α-*N*-[(9-fluorenylmethyl)oxy]carbonyl (Fmoc)[16] and 1,1-dioxobenzo[b]thiophene-2-ylmethyloxycarbonyl (Bsmoc)[17] protected amino acids and peptides are stable as such and directly usable in the synthesis of ureidopeptides and peptidyl ureas. More recently, the same authors have described the interesting and straightforward synthesis of α-*N*-Fmoc/Bsmoc/Boc/Z-protected ureido peptidomimetics starting from the α-*N*-protected amino acid or peptide acid in the presence of diphenylphosphoryl azide (DPPA) followed by the one-pot addition of the amino acid ester.[18] On the other hand, the suitable isocyanate intermediates can also be prepared through the oxidative Hofmann or Lossen rearrangements of the C-terminal of α-*N*-protected



Scheme 1. Overview of current approaches for the insertion of a ureido linkage ψ[NHCONH] between two neighboring α-amino acids.

amino and peptide amides[6e,19] or hydroxamic acids,[20] respectively (Scheme 1). Under these conditions, the amide C → N migration is usually promoted by bis(trifluoroacetoxy)iodobenzene (PIFA), whereas *N,N*-dicyclohexylcarbodiimide (DCC) or, better, the water-soluble 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) have been used with hydroxamic acids. The proposed isocyanate intermediates obtained from these rearrangements are directly intercepted by an amine nucleophile.

Among the reported methods, some require multistep processes, high temperatures with potentially explosive substrates (e.g., acyl azides in the Curtius rearrangement), and the preliminary preparation of suitable reagents (e.g., amides or hydroxamic acids). Moreover, the reaction conditions employed can catalyze the hydrolysis of the formed isocyanates or the α-*N*-protecting group (PIFA)[19] as well as promote significant racemization (DPPA).

In this context, we recently proposed a fast and simple preparation of α-*N*-protected carbamoyl azides[21] and their use as suitable building blocks in the synthesis of unsymmetrical ureas.[22] In the present paper, we report an efficient use of carbamoyl azides in the one-pot, racemisation-free synthesis of α-*N*-protected ureidopeptides.

RESULTS AND DISCUSSION

The simple and convenient preparation of α-*N*-protected ureidopeptide esters **1** reported here has been successfully accomplished in a two-step, one-pot reaction sequence (Fig. 1, Table 1); the first step of the process consisted of the preparation of the α-*N*-protected carbamoyl azide **2**, promptly obtained as previously described.[22] In the second step, the free α-amino acid methyl ester **4** (1.4 equiv. with respect to **3**) was slowly added into the reaction mixture containing the crude carbamoyl azide **2**, and stirring was continued for 3 h at 45 °C. After separation of the organic phase and removal of tetrahydrofuran (THF), the obtained residue was thoroughly washed with water and crystallized from water/MeOH (80:20) to afford the pure α-*N*-protected dipeptidyl urea methyl ester **1** in 75–95% overall yield.

With the aid of electrospray ionization–mass spectrometry (ESI-MS) analysis, we observed that the reaction rate was not influenced by the nature of either the carbamoyl azide **2** or the α-amino acid methyl ester **4** involved. This circumstance might be explained by the high reactivity of the carbamoyl function as a result of

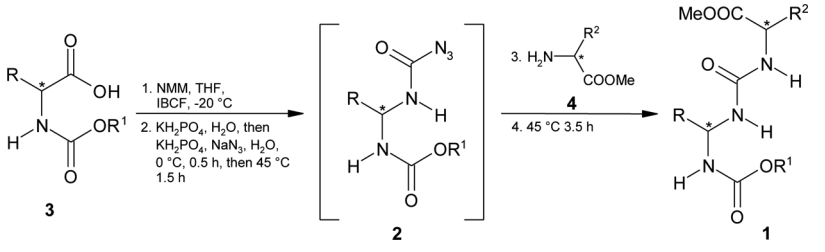
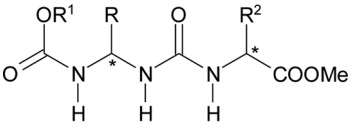


Figure 1. Synthesis of α-*N*-protected dipeptidyl urea methyl esters **1**.

Table 1. Analytical data of the synthesized α-*N*-protected dipeptidyl urea methyl esters **1**



1

1	R	R^1	R^2	Mp (°C)	$[\alpha]_D^{[20]}$ (*c*, solvent)
aae	$(CH_3)_2CH$	Et	HO-C_6H_4-CH_2	177–179	+13.6 (0.2, DMSO)
abe	$(CH_3)_2CH$	*t*-Bu	HO-C_6H_4-CH_2	137–139	−34.3 (0.3, DMSO)
ace	$(CH_3)_2CH$	Bn	HO-C_6H_4-CH_2	162–164	+27.8 (0.4, DMSO)
bad	$(CH_3)_2CHCH_2$	Et	$PhCH_2$	132–135	−58.8 (0.3, MeOH)
baf	$(CH_3)_2CHCH_2$	Et	1*H*-indole-3-CH_2	125–127	−26.7 (0.3, $CHCl_3$)
bbf	$(CH_3)_2CHCH_2$	*t*-Bu	1*H*-indole-3-CH_2	152–155	+37.5 (0.6, $CHCl_3$)
bcf	$(CH_3)_2CHCH_2$	Bn	1*H*-indole-3-CH_2	158–160	+16.4 (0.5, MeOH)
cad	Ph	Et	$PhCH_2$	127–129	+16.7 (0.3, MeOH)
cba	Ph	*t*-Bu	$(CH_3)_2CHCH_2$	100–101	+12.8 (0.4, DMSO)
cbd	Ph	*t*-Bu	$PhCH_2$	143–144	+40.7 (0.3, $CHCl_3$)
daa	$PhCH_2$	Et	$(CH_3)_2CHCH_2$	180–183	−28.0 (0.5, MeOH)
dab	$PhCH_2$	Et	$MeOOC(CH_2)_2$	138–140	−66.6 (0.3, DMSO)
dac	$PhCH_2$	Et	Ph	165–167	−46.7 (0.2, $CHCl_3$)
dba	$PhCH_2$	*t*-Bu	$(CH_3)_2CHCH_2$	154–156	−67.7 (0.3, $CHCl_3$)
dca	$PhCH_2$	Bn	$(CH_3)_2CHCH_2$	186–188	−28.0 (0.5, DMSO)

the presence of internally hydrogen-bonded conformations, which may favor the availability of the CON_3 group (Fig. 2).

This hypothesis was confirmed by comparison of the ^{1}H NMR spectra of *N*-ethoxycarbonyl-L-phenylalanine carbamoyl azide (**2da**) carried out at different concentrations in dimethylsulfoxide (DMSO-d_6; from 50 to 0.5 mg/mL): the chemical shift of all of the signals, and in particular the doublet ($J = 7.8$ Hz) at $\delta = 8.48$ ppm assigned to the $NHCON_3$ proton, as well as the broad singlet at $\delta = 7.56$ ppm corresponding to the NHCOOEt proton, remained unchanged. Moreover, a similar experiment carried out at different temperatures (from 40 °C to 90 °C) evidenced an upfield shift (ca. 0.5 ppm) effect involving just the two N-H signals, attributable to the weakening of intramolecular hydrogen bonds.[23]

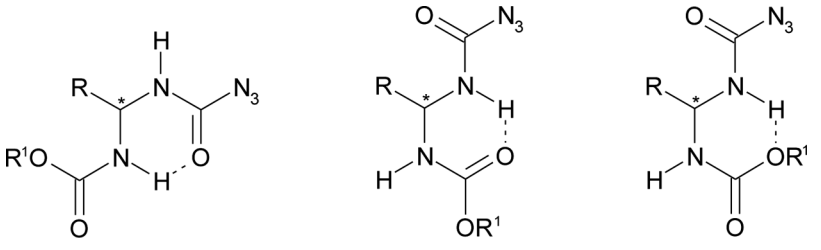


Figure 2. Possible conformations of **2** promoting the availability of the CON_3 group.

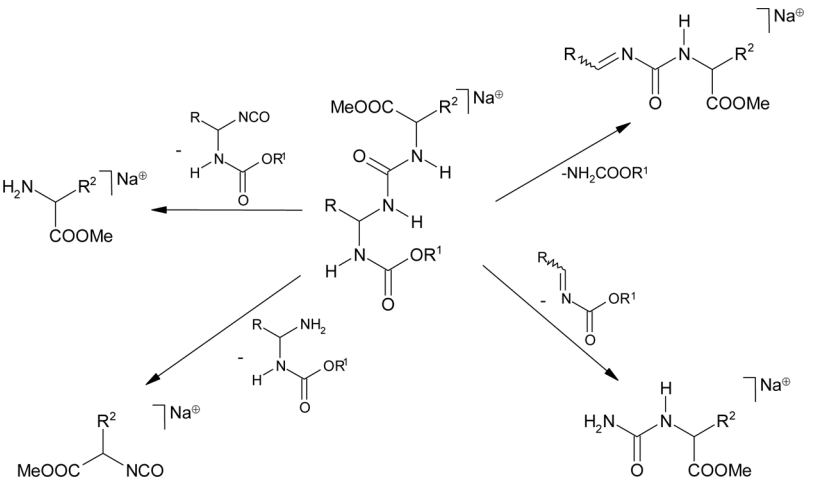
To rule out any incursion of racemization under our experimental conditions, Eoc-L-Phg-ψ[NHCONH]-L-Ph-OMe (**1cad**) was prepared by reaction of *N*-ethoxycarbonyl-L-phenylglycine (**3ca**) with L-phenylalanine methyl ester (**4d**), and its high-performance liquid chromatography (HPLC)–MS profile, as well as ^{1}H and ^{13}C NMR spectra, were compared with those obtained from the reaction of racemic *N*-ethoxycarbonyl-DL-phenylglycine (**rac-3ca**) with **4d**. The ESI-HPLC-MS analysis of the diastereoisomeric mixture of Eoc-D,L-Phg-ψ[NHCONH]-L-Ph-OMe (**diast-1cad**) obtained from **rac-3ca** evidenced two distinct peaks at $R_t = 12.1$ and 14.3 min of the same area and presented an identical MS^n fragmentation pattern. Both ESI HPLC-MS peaks evidenced the following features: (i) the sodium cationized molecule $[M + Na]^+$ at $m/z = 422$, (ii) the MS^2 spectrum of $[M + Na]^+$ was characterized by the presence of three ions at m/z 333, 245, and 228 due to the loss of NH_2COOEt (89 Da), Ph-CH=NCOOEt (177 Da), and $PhCH(NH_2)NHCOOEt$ (194 Da), respectively, and (iii) the fragmentation (MS^3) of the ion at $m/z = 333$ $[PhCH{=}NCONHCH(COOMe)CH_2Ph + Na]^+$ produced the peak at $m/z = 228$ $[PhCH_2CH(NCO)COOMe + Na]^+$. In addition, the ^{1}H and ^{13}C NMR spectra showed two sets of peaks for each proton and carbon signal, respectively. On the other hand, when we carried out the reaction with **3ca**, the corresponding ^{1}H and ^{13}C NMR spectra of **1cad** did not exhibit a similar complexity and the ESI-HPLC-MS analysis pointed out the presence of only one peak at $R_t = 12.1$ min. The analogous chromatographic and NMR behavior found in all the synthesized dipeptidyl ureas **1** confirmed that the present protocol proceeds with retention of configuration.

It is worth pointing out that when we attempted to synthesize Eoc-L-Phg-ψ[NHCONH]-L-Ph-OMe (**1cad**) following the DPPA method proposed by Sureshbabu et al.[18] the ESI-HPLC-MS analysis of the reaction mixture evidenced the presence of an equimolar mixture of the two epimers **1cad** and Eoc-D-Phg-ψ[NHCONH]-L-Ph-OMe (**epi-1cad**), demonstrating that a complete racemization had occurred. In addition, the same method employed in the reaction between *N*-Boc-L-phenylglycine (**3cb**) and **4d** afforded a mixture of Boc-L-Phg-ψ[NHCONH]-L-Ph-OMe (**1cbd**) and Boc-D-Phg-ψ[NHCONH]-L-Ph-OMe (**epi-1cbd**) in the approximate ratio of 70:30.

Some properties of dipeptidyl ureas **1** are reported in Table 1. All the products obtained were fully characterized by ^{1}H NMR, ^{13}C NMR, MS, and infrared (IR) spectra.

Taking into account the importance of mass spectrometry to elucidate the structure of peptides and peptidomimetics, we report some common features of the ESI-MS spectra of α-*N*-protected ureidopeptide esters **1**. In detail, the MS^2 spectra of sodium-cationized molecule $[M + Na]^+$ in the positive ion mode were characterized (Scheme 2), in addition to the intense ion (100% relative intensity) due to the loss of the carbamate moiety (NH_2COOR^1), by the presence of three additional peaks (10–40% relative intensity) corresponding to the urea, the isocyanate, and the α-amino methyl ester derived from the α-amino methyl ester moiety of **1**. Moreover, the MS^2 spectra of $[M + Na]^+$ for the *N*-Boc-derivatives **1abc**, **1bbf**, **1cba**, **1cbd** and **1dba** evidenced two fragment ions corresponding to the loss of isobutene and CO_2.[22]

In summary, we have developed an efficient, mild, and simple one-pot synthesis of ureidopeptide esters **1** starting from the carbamoyl azides of α-*N*-protected amino



Scheme 2. Fragmentation pattern of α-*N*-protected ureidopeptide esters **1**.

acids. The protocol proceeds with retention of configuration and represents a valid alternative to the DPPA method. Moreover, the study of ESI-MS^n spectra points out some common fragmentation pathways involving both the amino acid residues present in the ureidopeptide ester.

EXPERIMENTAL

All *N*-protected amino acids **3** were prepared by reported procedures.[24] All solvents and reagents were purchased from Aldrich Chemical Company and were used without further purification. Direct inlet mass spectra (DI-MS) and MS^n experiments were conducted with a Thermo Scientific Polaris Q ion trap mass spectrometer, working in the positive-ion 70-eV electron-impact mode. Spectra were recorded in the range 35–450 u, and temperatures between 100 and 180 °C were suitable to vaporize all the compounds into the ion source. The reactions were monitored by ESI-MS in the positive-ion mode with a Finnigan LXQ (linear trap) by simply diluting the intact reaction mixture with MeCN and directly infusing the obtained solution into the ion source with the aid of a syringe pump. HPLC-ESI-MS analyses were performed with the same instrument coupled with a Finnigan Surveyor LC Pump Plus and equipped with a Finnigan Surveyor Autosampler Plus. The LC separations were performed on a Zorbax SB C18 column (150 mm × 2.1 mm, 3.5 μm) operating at 30 °C and isocratically at 0.2 mL/min with the mobile phase was composed of $MeOH/H_2O$ (57:43, v/v). IR spectra were obtained with a Bruker Vector 22 spectrophotometer using the KBr technique for solids and recorded in the range 4000–400 cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-F 200 spectrometer at 200 and 50 MHz, respectively, using DMSO-d_6 at 40 °C as solvent. NMR peak locations are reported as δ values from TMS. Some ^1H multiplets are characterized by the term *app* (apparent): this refers only to their appearance and may be an oversimplification. Optical rotations were determined on suitable

solutions (g/100 mL) at 20 °C using an AP-300 automatic polarimeter purchased from Atago (Japan). Elemental analyses were performed with a Carlo Erba Mod. 1106 elemental analyzer. Melting points were determined with an automatic Mettler (Mod. FP61) melting-point apparatus and are not corrected.

General Procedure for the Synthesis of Dipeptidyl Ureas 1

N-Methylmorpholine (NMM, 0.30 mL, 2.73 mmol) was slowly added into a stirred solution of α-*N*-protected amino acid **3** (2.50 mmol) in THF (15 mL). After 5 min, isobutyl chloroformate (IBCF, 0.36 mL, 2.73 mmol) was slowly added into the reaction mixture, previously cooled to −20 °C, and stirring was continued for 20 min at the same temperature. The reaction mixture was subsequently warmed to 0 °C, and a solution of KH_2PO_4 (0.17 g, 1.25 mmol) in H_2O (1 mL) was added in one lot, followed after 5 min by a solution of KH_2PO_4 (1.70 g, 12.50 mmol) and NaN_3 (0.41 g, 6.25 mmol) in H_2O (9 mL). After stirring for 30 min at 0 °C, the mixture was warmed to 45 °C for 1.5 h, the free amino acid ester **4** (3.5 mmol) was slowly added, and the resulting mixture was stirred for an additional 3 h at the same temperature. THF was finally removed under reduced pressure, and the crude residue was washed with water and crystallized from water/MeOH (80:20), affording the product in a 75–95% overall yield.

Spectral Data of α-*N*-Protected Dipeptidyl Urea Methyl Esters 1

Eoc-L-Val-ψ[NHCONH]-L-Tyr-OMe (1aae). Yield: 80%; IR ν_{max} (cm^{-1}): 3368 (br), 3293 (br), 2954, 1756, 1687, 1634, 1539, 1513, 1459, 1254, 1154, 1038, 817, 614; ^{1}H NMR: δ 0.80 and 0.81 [2 d, $J = 6.7$, 6.7, 6 H, $(CH_3)_2CH$], 1.15 (t, $J = 7.3$, 3 H, CH_3CH_2), 1.85 [*app* sext, $J = 6.4$, 1 H, $(CH_3)_2CH$], 2.74 and 2.84 (AB of ABX, $J = 14.1$, 5.9, 5.6, 2 H, Ar-CH_2), 3.58 (s, 3 H, OCH_3), 3.96 (q, $J = 7.3$, 2 H, OCH_2), 4.35 (*app* q, $J = 6.7$, 1 H, *CHCOO), 4.81 (*app* q, $J = 9.1$, 1 H, NH*CHNH), 6.33 (br t, $J = 9.1$, 2 H, NHCONH), 6.65 (*app* d, $J = 8.2$, 2 H, Ar-H), 6.92 (*app* d, $J = 8.2$, 2 H, Ar-H), 7.24 (br s, 1 H, NHCOO), 9.23 (br s, 1 H, OH); ^{13}C NMR: δ 15.5, 18.9, 19.2, 33.3, 38.0, 52.4, 54.9, 60.3, 63.8, 115.9, 127.7, 130.9, 156.1, 156.9, 157.1, 173.8; EI-MS *m/z*: 293 (13), 292 (10), 249 (70), 233 (9), 196 (29), 178 (52), 147 (22), 144 (100), 116 (23), 107 (47), 98 (6), 72 (48); ESI-MS *m/z*: 404 $[M + Na]^+ \rightarrow (MS^2)$ 315, 261, 244, 218. Anal. calcd. for $C_{18}H_{27}N_3O_6$ (381.43): C, 56.68; H, 7.13; N, 11.02. Found: C, 56.43; H, 7.00; N, 11.12.

Boc-L-Val-ψ[NHCONH]-L-Tyr-OMe (1abe). Yield: 75%; IR ν_{max} (cm^{-1}): 3364 (br), 3291 (br), 2978, 1749, 1688, 1654, 1563, 1515, 1450, 1368, 1247, 1208, 1015, 780; ^{1}H NMR: δ 0.78 and 0.80 [2 d, $J = 6.5$, 6.5, 6 H, $(CH_3)_2CH$], 1.37 [s, 9 H, $(CH_3)_3C$], 1.79 [*app* sext, $J = 6.5$, 1 H, $(CH_3)_2CH$], 2.73 and 2.83 (AB of ABX, $J = 13.2$, 6.7, 6.5, 2 H, Ar-CH_2), 3.57 (s, 3 H, OCH_3), 4.34 (*app* q, $J = 6.8$, 1 H, *CHCOO), 4.75 (*app* q, $J = 8.2$, 1 H, NH*CHNH), 6.28 (br d, $J = 9.1$, 1 H, NHCONH), 6.42 (br d, $J = 7.6$, 1 H, NHCONH), 6.65 (*app* d, $J = 8.5$, 2 H, Ar-H), 6.92 (*app* d, $J = 8.5$, 2 H, Ar-H), 7.02 (br s, 1 H, NHCOO), 9.19 (br s, 1 H, OH); ^{13}C NMR: δ 18.9, 19.2, 29.0, 33.2, 38.0, 52.3, 54.9, 63.9, 79.9, 115.8,

127.7, 130.8, 155.5, 156.9, 157.1, 173.9; EI-MS *m/z*: 366 (3), 293 (10), 292 (15), 233 (8), 196 (25), 178 (100), 172 (10), 147 (39), 116 (16), 107 (89), 98 (10), 72 (40), 56 (34); ESI-MS *m/z*: 432 $[M + Na]^+ \rightarrow (MS^2)$ 376, 332, 315, 261, 244, 218. Anal. calcd. for $C_{20}H_{31}N_3O_6$ (409.48): C, 58.66; H, 7.63; N, 10.26. Found: C, 58.77; H, 7.54; N, 10.20.

Z-L-Val-ψ[NHCONH]-L-Tyr-OMe (1ace). Yield: 77%; IR ν_{max} (cm^{-1}): 3377 (br), 3286 (br), 2958, 1744, 1692, 1634, 1571, 1537, 1257, 1047; ^1H NMR: δ 0.81 and 0.82 [2 d, $J = 6.7$, 6.5, 6 H, $(CH_3)_2CH$], 1.82 [*app* sext, $J = 6.5$, 1 H, $(CH_3)_2CH$], 2.74 and 2.84 (AB of ABX, $J = 12.9$, 7.3, 7.0, 2 H, Ar-CH_2), 3.58 (s, 3 H, OCH_3), 4.37 (*app* q, $J = 7.0$, 1 H, *CHCOO), 4.87 (*app* q, $J = 8.5$, 1 H, NH*C*HNH), 5.01 (*app* s, 2 H, $PhCH_2$), 6.41 (br d, $J = 8.2$, 2 H, NHCONH), 6.66 (*app* d, $J = 8.5$, 2 H, Ar-H), 6.93 (*app* d, $J = 8.8$, 2 H, Ar-H), 7.30–7.43 (m, 5 H, Ph-H), 7.53 (br s, 1 H, NHCOO), 9.21 (br s, 1 H, OH); ^{13}C NMR: δ 18.8, 19.2, 33.1, 38.0, 52.4, 54.9, 63.9, 65.9, 115.9, 127.6, 128.5, 129.0, 129.1, 130.8, 138.0, 155.9, 156.9, 157.1, 173.7; EI-MS *m/z*: 400 (5), 292 (7), 249 (23), 233 (5), 206 (15), 178 (52), 162 (27), 147 (21), 116 (10), 107 (100), 98 (3), 91 (90), 79 (31), 77 (30), 72 (19); ESI-MS *m/z*: 466 $[M + Na]^+ \rightarrow (MS^2)$ 315, 261, 244, 218. Anal. calcd. for $C_{23}H_{29}N_3O_6$ (443.50): C, 62.29; H, 6.59; N, 9.47. Found: C, 62.20; H, 6.68; N 9.36.

Eoc-L-Leu-ψ[NHCONH]-L-Phe-OMe (1bad). Yield: 84%; IR ν_{max} (cm^{-1}): 3354 (br), 3283 (br), 2985, 2956, 1749, 1696, 1658, 1562, 1530, 1467, 1359, 1241, 1210, 1046, 702; ^1H NMR: δ 0.90 [*app* d, $J = 5.9$, 6 H, $(CH_3)_2CH$], 1.18 (t, $J = 7.3$, 3 H, CH_2CH_3), 1.50–1.73 (m, 3 H, $CHCH_2$), 2.99 and 3.11 (AB of ABX, $J = 13.8$, 6.7, 6.5, 2 H, $PhCH_2$), 3.64 (s, 3 H, OCH_3), 4.00 (q, $J = 7.0$, 2 H, OCH_2), 4.71 (*app* q, $J = 6.5$, 1 H, *CHCOO), 5.13 (*app* quint, $J = 7.0$, 1 H, NH*C*HNH), 6.20 (br d, $J = 9.0$, 1 H, NHCONH), 6.40 (br d, $J = 7.1$, 1 H, NHCONH), 7.05–7.34 (m, 6 H, Ph-H + NHCOO); ^{13}C NMR: δ 14.8, 22.5, 22.6, 25.1, 38.7, 44.0, 52.3, 54.5, 58.2, 61.2, 127.0, 128.6, 129.6, 136.9, 156.7, 157.2, 173.4; EI-MS *m/z*: 322 (44), 291 (37), 290 (86), 247 (51), 231 (41), 199 (27), 180 (100), 162 (91), 158 (93), 130 (15), 120 (73), 117 (75), 91 (81); ESI-MS *m/z*: 402 $[M + Na]^+ \rightarrow (MS^2)$ 313, 245, 228, 202. Anal. calcd. for $C_{19}H_{29}N_3O_5$ (379.46): C, 60.14; H, 7.70; N, 11.07. Found: C, 60.18; H, 7.68; N, 11.15.

Eoc-L-Leu-ψ[NHCONH]-L-Trp-OMe (1baf). Yield: 85%; IR ν_{max} (cm^{-1}): 3369 (br), 3259 (br), 2958, 2928, 1753, 1693, 1643, 1531, 1440, 1372, 1341, 1240, 1020, 740; ^1H NMR: δ 0.86 [*app* d, $J = 5.6$, 6 H, $(CH_3)_2CH$], 1.15 (t, $J = 7.0$, 3 H, CH_2CH_3) 1.32–1.68 (m, 3 H, $CHCH_2$), 3.02 and 3.12 (AB of ABX, $J = 13.5$, 7.3, 5.9, 2 H, Ar-CH_2), 3.97 (q, $J = 7.1$, 2 H, OCH_2), 4.49 (*app* q, $J = 6.5$, 1 H, *CHCOO), 5.10 (*app* quint, $J = 7.9$, 1 H, NH*C*HNH), 6.37 (br d, $J = 7.3$, 1 H, NHCONH), 6.39 (br d, $J = 8.2$, 1 H, NHCONH), 6.87–7.19 (m, 3 H, Ar-H), 7.21–7.57 (m, 3 H, 2 × Ar-H + NHCOO), 10.87 (br s, 1 H, Ar-NH); ^{13}C NMR: δ 15.1, 23.1, 23.2, 25.2, 28.9, 45.1, 52.5, 54.3, 57.5, 60.3, 110.0, 112.2, 119.0, 119.2, 122.0, 124.5, 128.2, 137.0, 156.0, 156.9, 174.1; EI-MS *m/z*: 361 (2), 330 (4), 329 (8), 286 (5), 270 (8), 244 (3), 219 (7), 201 (49), 170 (8), 158 (7), 130 (100); ESI-MS *m/z*: 441 $[M + Na]^+ \rightarrow (MS^2)$ 352, 284, 267, 241. Anal. calcd. for $C_{21}H_{30}N_4O_5$ (418.49): C, 60.27; H, 7.23; N, 13.39. Found: C, 60.25; H, 7.28; N, 13.45.

Boc-L-Leu-ψ[NHCONH]-L-Trp-OMe (1bbf). Yield: 77%; IR ν_{max} (cm^{-1}): 3386 (br), 3326 (br), 3265 (br), 2930, 1718, 1687, 1663, 1577, 1522, 1459, 1365, 1303, 1258, 1170, 1044, 866, 757; ^{1}H NMR: δ 0.84 [*app* d, $J = 5.6$, 6 H, $(CH_3)_2CH$], 1.37 [s, 9 H, $(CH_3)_3C$], 1.38–1.59 (m, 3 H, $CHCH_2$), 3.06 and 3.91 (AB of ABX, $J = 13.8$, 7.3, 6.2, 2 H, Ar-CH_2), 3.56 (s, 3 H, OCH_3), 4.47 (*app* q, $J = 6.2$, 1 H, *CHCOO), 5.04 (*app* quint, $J = 7.6$, 1 H, NH*C*H*NH), 6.28 (br d, $J = 9.1$, 1 H, NHCON*H*), 6.36 (br d, $J = 7.9$, 1 H, N*H*CONH), 6.91–7.15 (m, 4 H, 3 × Ar-H + NHCOO), 7.32 (*app* d, $J = 7.9$, 1 H, Ar-H), 7.44 (*app* d, $J = 7.6$, 1 H, Ar-H), 10.85 (br s, 1 H, Ar-NH); ^{13}C NMR: δ 23.2, 23.3, 25.3, 28.9, 29.2, 45.2, 52.6, 54.3, 57.2, 78.6, 110.1, 112.3, 119.1, 119.3, 121.9, 124.6, 128.2, 137.0, 155.4, 157.0, 174.3; EI-MS *m/z*: 389 (2), 330 (4), 286 (3), 270 (8), 244 (7), 219 (4), 201 (67), 186 (4), 170 (8), 130 (100); ESI-MS *m/z*: 469 $[M + Na]^+ \rightarrow (MS^2)$ 413, 369, 352, 284, 267, 241. Anal. calcd. for $C_{23}H_{34}N_4O_5$ (446.55): C, 61.86; H, 7.67; N, 12.55. Found: C, 61.90; H, 7.65; N, 12.50.

Z-L-Leu-ψ[NHCONH]-L-Trp-OMe (1bcf). Yield: 87%; IR ν_{max} (cm^{-1}): 3408 (br), 3319 (br), 3293 (br), 2953, 1731, 1695, 1647, 1571, 1536, 1456, 1433, 1338, 1232, 738, 697; ^{1}H NMR: δ 0.85 [*app* d, $J = 5.6$, 6 H, $(CH_3)_2CH$], 1.31–1.67 (m, 3 H, $CHCH_2$), 3.02 and 3.11 (AB of ABX, $J = 13.4$, 7.1, 5.6, 2 H, Ar-CH_2), 3.56 (s, 3 H, OCH_3), 4.49 (*app* q, $J = 6.2$, 1 H, *CHCOO), 5.00 (*app* s, 2 H, $PhCH_2$), 5.13 (*app* quint, $J = 7.4$, 1 H, NH*C*H*NH), 6.33 (br d, $J = 7.7$, 1 H, NHCON*H*), 6.40 (br d, $J = 8.5$, 1 H, N*H*CONH), 6.91–7.12 (m, 3 H, Ar-H), 7.27–7.56 (m, 8 H, 2 × Ar-H + 5 × Ph-H + NHCOO), 10.85 (br s, 1 H, Ar-NH); ^{13}C NMR: δ 23.0, 23.1, 25.2, 28.9, 45.3, 52.5, 54.2, 57.6, 66.0, 110.0, 112.2, 119.0, 119.2, 121.8, 124.5, 128.2, 128.6, 129.0, 129.4, 137.0, 138.0, 155.8, 156.9, 174.0; EI-MS *m/z*: 423 (2), 329 (4), 286 (2), 270 (6), 244 (3), 220 (2), 219 (4), 201 (23), 170 (4), 130 (100), 91 (28); ESI-MS *m/z*: 503 $[M + Na]^+ \rightarrow (MS^2)$ 352, 284, 267, 241. Anal. calcd. for $C_{26}H_{32}N_4O_5$ (480.56): C, 64.98; H, 6.71; N, 11.66. Found: C, 64.88; H, 6.80; N, 11.71.

Eoc-L-Phg-ψ[NHCONH]-L-Phe-OMe (1cad). Yield: 92%; IR ν_{max} (cm^{-1}): 3392 (br), 3295 (br), 2982, 1731, 1697, 1641, 1566, 1528, 1259, 1068, 1037, 748, 696; ^{1}H NMR: δ 1.14 (t, $J = 6.8$, 3 H, CH_2CH_3), 2.88 and 3.01 (AB of ABX, $J = 13.5$, 8.2, 7.6, 2 H, Ph-CH_2), 3.62 (s, 3 H, OCH_3), 3.97 (q, $J = 7.0$, 2 H, OCH_2), 4.43 (*app* q, $J = 7.6$, 1 H, *CHCOO), 6.19 (t, $J = 8.5$, 1 H, NH*C*H*NH), 6.54 (br d, $J = 9.1$, 1 H, NHCON*H*), 6.83 (br d, $J = 8.8$, 1 H, N*H*CONH), 7.10–7.42 (m, 10 H, Ar-H), 7.97 (br s, 1 H, NHCOO); ^{13}C NMR: δ 15.5, 38.4, 52.7, 55.1, 60.7, 61.1, 126.9, 127.6, 128.3, 129.2, 129.3, 130.1, 137.9, 142.4, 157.1, 157.2, 173.8; EI-MS *m/z*: 311 (20), 310 (15), 267 (5), 266 (40), 251 (28), 250 (10), 219 (17), 208 (8), 180 (10), 178 (22), 162 (77), 150 (15), 132 (100), 106 (55), 91 (90), 77 (45); ESI-MS *m/z*: 422 $[M + Na]^+ \rightarrow (MS^2)$ 333, 245, 228, 202. Anal. calcd. for $C_{21}H_{25}N_3O_5$ (399.45): C, 63.15; H, 6.31; N, 10.52. Found: C, 63.05; H, 6.33; N, 10.47.

Boc-L-Phg-ψ[NHCONH]-L-Leu-OMe (1cba). Yield: 95%; IR ν_{max} (cm^{-1}): 3401 (br), 3315 (br), 2962, 1748, 1687, 1653, 1564, 1528, 1366, 1254, 1172, 698; ^{1}H NMR: δ 0.88 and 0.90 [2 d, $J = 6.5$, 6.7, 6 H, $(CH_3)_2CH$], 1.37 [s, 9 H, $(CH_3)_3C$], 1.40–1.74 (m, 3 H, $CHCH_2$), 3.62 (s, 3 H, OCH_3), 4.19 (*app* q, $J = 6.5$, 1 H, *CHCOO), 6.16 (t, $J = 8.8$, 1 H, NH*C*H*NH), 6.62 (br d, $J = 7.9$, 2 H, NHCONH),

7.22–7.38 (m, 5 H, Ar-H), 7.58 (br s, 1 H, NHCOO); ^{13}C NMR: δ 22.5, 23.5, 25.1, 29.0, 41.7, 51.9, 52.2, 60.6, 79.0, 126.7, 128.1, 128.9, 142.7, 157.0, 157.1, 174.8; EI-MS *m/z*: 277 (20), 276 (7), 233 (12), 217 (88), 206 (59), 174 (35), 165 (58), 150 (60), 146 (28), 132 (91), 128 (8), 106 (100), 57 (11); ESI-MS *m/z*: 416 $[M + Na]^+ \rightarrow (MS^2)$ 360, 316, 299, 211, 194, 168. Anal. calcd. for $C_{20}H_{31}N_3O_5$ (393.48): C, 61.05; H, 7.94; N, 10.68. Found: C, 61.19; H, 7.89; N, 10.65.

Boc-L-Phg-ψ[NHCONH]-L-Phe-OMe (1cbd). Yield: 86%; IR ν_{max} (cm^{-1}): 3387 (br), 3320 (br), 2985, 1735, 1699, 1646, 1568, 1521, 1447, 1362, 1254, 1215, 1165, 1096, 1068, 1027, 747, 699; ^{1}H NMR: δ 1.37 [s, 9 H, $(CH_3)_3C$], 2.87 and 3.00 (AB of ABX, $J = 13.5$, 7.9, 7.9, 2 H, Ph-CH_2), 3.60 (s, 3 H, OCH_3), 4.42 (*app* q, $J = 7.7$, 1 H, *CHCOO), 6.14 (t, $J = 8.2$, 1 H, NH*C*H*NH), 6.58 (br d, $J = 7.9$, 1 H, NHCON*H*), 6.76 (br d, $J = 8.5$, 1 H, N*H*CONH), 7.12–7.47 (m, 10 H, Ar-H), 7.67 (br s, 1 H, NHCOO); ^{13}C NMR: δ 29.1, 38.5, 52.7, 55.1, 60.5, 79.0, 126.9, 127.6, 128.2, 129.1, 129.2, 130.1, 137.9, 142.7, 157.1, 157.2, 173.8; EI-MS *m/z*: 311 (15), 310 (33), 267 (26), 266 (57), 251 (38), 250 (21), 219 (32), 206 (55), 180 (16), 162 (81), 150 (56), 132 (100), 106 (33), 91 (86); ESI-MS *m/z*: 450 $[M + Na]^+ \rightarrow (MS^2)$ 394, 350, 333, 245, 228, 202. Anal. calcd. for $C_{23}H_{29}N_3O_5$ (427.50): C, 64.62; H, 6.84; N, 9.83. Found: C, 64.64; H, 6.90; N, 9.80.

Eoc-L-Phe-ψ[NHCONH]-L-Leu-OMe (1daa). Yield: 80%; IR ν_{max} (cm^{-1}): 3398 (br), 3311 (br), 2960, 1723, 1693, 1644, 1568, 1523, 1298, 1265, 999, 757, 700; ^{1}H NMR: δ 0.80 and 0.85 [2 d, $J = 6.5$, 6.5, 6 H, $(CH_3)_2CH$], 1.11 (t, $J = 7.1$, 3 H, CH_2CH_3), 1.29–1.60 (m, 3 H, $CHCH_2$), 2.86 (br *app* d, $J = 6.8$, 2 H, Ph-CH_2), 3.60 (s, 3 H, OCH_3), 3.92 (q, $J = 7.0$, 2 H, OCH_2), 4.14 (*app* q, $J = 7.9$, 1 H, *CHCOO), 5.15 (*app* quint, $J = 7.7$, 1 H, NH*C*H*NH), 6.43 (br t, $J = 7.9$, 2 H, NHCONH), 7.08–7.32 (m, 5 H, Ar-H), 7.64 (br s, 1 H, NHCOO); ^{13}C NMR: δ 15.6, 22.5, 23.7, 25.1, 42.0, 42.2, 51.6, 52.6, 60.4, 127.1, 129.0, 130.1, 138.7, 156.7, 157.0, 175.0; EI-MS *m/z*: 291 (6), 290 (19), 288 (53), 258 (20), 247 (8), 231 (24), 202 (13), 192 (21), 191 (23), 146 (70), 145 (55), 128 (15), 120 (42), 119 (70), 118 (65), 117 (100), 91 (37), 89 (47); ESI-MS *m/z*: 402 $[M + Na]^+ \rightarrow (MS^2)$ 313, 211, 194, 168. Anal. calcd. for $C_{19}H_{29}N_3O_5$ (379.46): C, 60.14; H, 7.70; N, 11.07. Found: C, 60.28; H, 7.65; N, 11.19.

Eoc-L-Phe-ψ[NHCONH]-L-Glu-(OMe)$_2$ (1dab). Yield: 78%; IR ν_{max} (cm^{-1}): 3396 (br), 3304 (br), 2979, 1732, 1700, 1641, 1575, 1553, 1513, 1297, 1266, 1237, 1053, 951, 705; ^{1}H NMR: δ 1.11 (t, $J = 6.8$, 3 H, CH_2CH_3), 1.62–2.05 (m, 2 H, *$CHCH_2CH_2$), 2.28 (*app* t, $J = 7.3$, 2 H, CH_2COO), 2.89 (br *app* d, $J = 6.7$, 2 H, Ph-CH_2), 3.58 (s, 3 H, CH_2COOCH_3), 3.62 (s, 3 H, *$CHCOOCH_3$), 3.93 (q, $J = 7.0$, 2 H, OCH_2), 4.10–4.24 (m, 1 H, *CHCOO), 5.16 (*app* quint, $J = 7.6$, 1 H, NH*C*H*NH), 6.40 (br d, $J = 8.5$, 1 H, NHCON*H*), 6.47 (br d, $J = 8.2$, 1 H, N*H*CONH), 7.08–7.34 (m, 5 H, Ar-H), 7.46 (br s, 1 H, NHCOO); ^{13}C NMR: δ 15.4, 28.1, 30.3, 41.3, 52.2, 52.5, 60.4, 60.5, 61.8, 127.0, 128.9, 130.0, 138.7, 156.2, 156.9, 173.4, 173.9; EI-MS *m/z*: 321 (10), 320 (9), 318 (45), 286 (84), 277 (8), 261 (8), 246 (8), 192 (57), 191 (50), 176 (53), 158 (7), 145 (24), 144 (31), 120 (39), 119 (41), 118 (31), 117 (100), 91 (24), 89 (24); ESI-MS *m/z*: 432 $[M + Na]^+ \rightarrow (MS^2)$ 343, 241, 224, 198. Anal. calcd. for $C_{19}H_{27}N_3O_7$ (409.44): C, 55.74; H, 6.65; N, 10.26. Found: C, 55.70; H, 6.70; N, 10.36.

Eoc-L-Phe-ψ[NHCONH]-L-Phg-OMe (1dac). Yield: 79%; IR ν_{max} (cm^{-1}): 3381 (br), 3306 (br), 2984, 1737, 1697, 1645, 1553, 1514, 1297, 1234, 1053, 699; ^1H NMR: δ 1.12 (t, $J = 7.0$, 3 H, $CHCH_3$), 2.90 (br *app* d, $J = 6.8$, 2 H, Ph-CH_2), 3.61 (s, 3 H, OCH_3), 3.92 (q, $J = 6.8$, 2 H, OCH_2), 5.19 (*app* quint, $J = 7.6$, 1 H, NH^*CHNH), 5.28 (d, $J = 7.6$, 1 H, $^*CHCOO$), 6.52 (br d, $J = 7.9$, 1 H, NHCONH), 6.96 (br d, $J = 7.6$, 1 H, NHCONH), 7.12–7.48 (m, 10 H, Ar-H), 7.55 (br s, 1 H, NHCOO); ^{13}C NMR: δ 15.3, 41.8, 52.9, 57.5, 60.4, 60.6, 127.0, 128.0, 128.9, 129.5, 129.6, 130.0, 138.2, 138.6, 156.0, 156.7, 172.7; EI-MS *m/z*: 340 (9), 311 (10), 310 (26), 308 (47), 278 (51), 276 (23), 267 (8), 251 (47), 192 (24), 191 (36), 166 (97), 145 (76), 120 (39), 119 (100), 118 (69), 117 (83), 91 (53), 89 (40); ESI-MS *m/z*: 422 $[M + Na]^+ \rightarrow (MS^2)$ 333, 231, 214, 188. Anal. calcd. for $C_{21}H_{25}N_3O_5$ (399.45): C, 63.15; H, 6.31; N, 10.52. Found: C, 63.18; H, 6.25, N, 10.50.

Boc-L-Phe-ψ[NHCONH]-L-Leu-OMe (1dba). Yield: 85%; IR ν_{max} (cm^{-1}): 3396 (br), 3323 (br), 2958, 1728, 1694, 1648, 1555, 1517, 1368, 1299, 1262, 1172, 1011, 701; ^1H NMR: δ 0.80 and 0.85 [2 d, $J = 6.2$, 6.5, 6 H, $(CH_3)_2CH$], 1.33 [s, 9 H, $(CH_3)_3C$], 1.32–1.65 (m, 3 H, $CHCH_2$), 2.86 (br *app* d, $J = 6.8$, 2 H, Ph-CH_2), 3.60 (s, 3 H, OCH_3), 4.13 (*app* q, $J = 7.3$, 1 H, $^*CHCOO$), 5.10 (*app* quint, $J = 7.6$, 1 H, NH^*CHNH), 6.40 (br d, $J = 7.6$, 1 H, NHCONH), 6.50 (br d, $J = 8.2$, 1 H, NHCONH), 7.07–7.38 (m, 5 H, Ar-H), 7.60 (br s, 1 H, NHCOO); ^{13}C NMR: δ 22.5, 23.6, 25.1, 29.1, 41.7, 41.9, 51.6, 52.6, 60.2, 78.8, 127.0, 128.9, 130.1, 138.7, 156.8, 157.1, 175.0; EI-MS *m/z*: 316 (10), 291 (7), 290 (7), 260 (38), 247 (5), 231 (18), 220 (8), 216 (100), 164 (11), 146 (92), 128 (8), 120 (44), 119 (34), 118 (23), 91 (18), 89 (12); ESI-MS *m/z*: 430 $[M + Na]^+ \rightarrow (MS^2)$ 374, 330, 313, 211, 194, 168. Anal. calcd. for $C_{21}H_{33}N_3O_5$ (407.51): C, 61.90; H, 8.16; N, 10.31. Found: C, 61.85; H, 8.10; N, 10.42.

Z-L-Phe-ψ[NHCONH]-L-Leu-OMe (1dca). Yield: 85%; IR ν_{max} (cm^{-1}): 3400 (br), 3318 (br), 2951, 1727, 1694, 1636, 1570, 1535, 1453, 1295, 1266, 1087, 1044, 1020, 745, 699; ^1H NMR: δ 0.81 and 0.85 [2 d, $J = 6.2$, 6.2, 6 H, $(CH_3)_2CH$], 1.30–1.68 (m, 3 H, $CHCH_2$), 2.89 (br *app* d, $J = 7.1$, 2 H, Ph-$CH_2{}^*CH$), 3.60 (s, 3 H, OCH_3), 4.16 (*app* q, $J = 7.9$, 1 H, $^*CHCOO$), 4.98 (*app* s, 2 H, $PhCH_2$), 5.20 (*app* quint, $J = 7.5$, 1 H, NH^*CHNH), 6.43 (br d, $J = 6.8$, 2 H, NHCONH), 7.07–7.45 (m, 10 H, Ar-H), 7.68 (br s, 1 H, NHCOO); ^{13}C NMR: δ 22.4, 23.5, 25.0, 41.3, 41.9, 51.5, 52.4, 60.5, 65.9, 127.0, 128.3, 128.5, 128.9, 129.1, 130.0, 137.9, 138.5, 156.7, 156.9, 174.8; EI-MS *m/z*: 350 (28), 291 (6), 290 (13), 258 (16), 254 (10), 247 (8), 231 (24), 179 (27), 146 (38), 145 (47), 128 (10), 120 (20), 119 (42), 118 (35), 91 (100); ESI-MS *m/z*: 464 $[M + Na]^+ \rightarrow (MS^2)$ 313, 211, 194, 168. Anal. calcd. for $C_{24}H_{31}N_3O_5$ (441.53): C, 65.29; H, 7.08; N, 9.52. Found: C, 65.35; H, 7.12; N, 9.40.

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