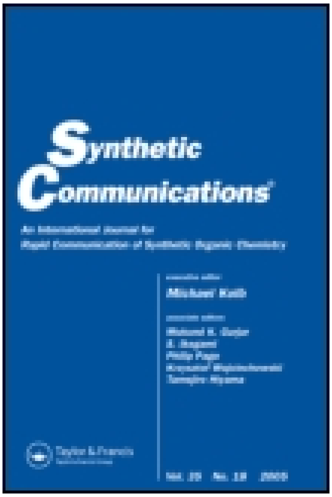

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Synthesis of Peptidyl Ureas Using p-Nitrophenyl-(9-fluorenylmethox Carbonylamino)methyl Carbamate Derivatives

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Synthesis of Peptidyl Ureas Using *p*-Nitrophenyl-(9-fluorenylmethoxy Carbonylamino)methyl Carbamate Derivatives

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ABSTRACT

An efficient synthesis of *p*-nitrophenyl-(9-fluorenylmethoxy carbonylamino) methyl carbamates using isocyanates derived from Fmoc-amino acid azides and *p*-nitrophenol in presence of an equimolar quantity of *N*-ethyldiisopropyl amine is described. All the carbamates have been isolated as crystalline solids and are fully characterized.

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Further, their utility for the synthesis of dipeptidyl ureas has been demonstrated.

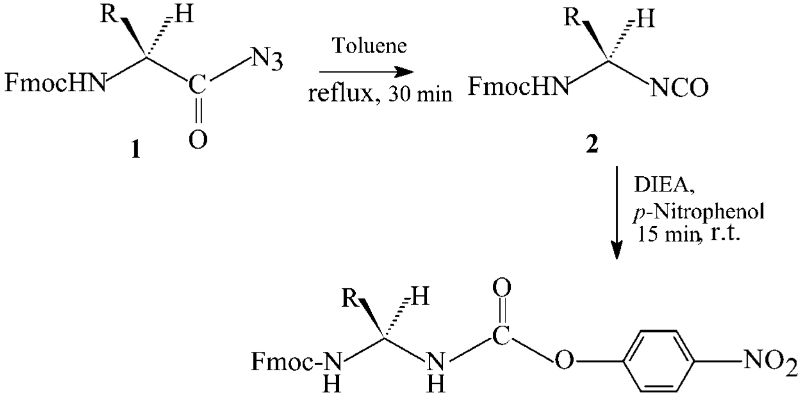
Key Words: Peptidyl ureas; *N*-Ethyldiisopropyl amine; Equimolar quantity; Isocyanate derivative.

INTRODUCTION

The peptide backbone provides a framework for constructing large folded polymers with a wide range of functions as well as smaller oligomeric agonists, antagonists, enzyme inhibitors, etc. The problems associated with the therapeutic utility of peptides have led to develop new oligomeric backbones (carbamates, peptoids, ureas, sulfonamides, azatides), which have improved pharmacokinetic properties relative to native peptides.[1]

The general procedures for the synthesis of peptidyl ureas involve the reaction of an isocyanate and primary amine. Isocyanates are usually prepared by bubbling phosgene gas through a solution of an amine at elevated temperature[2] or in the presence of a base at room temperature (r.t).[3] Although the use of triphosgene is a viable substitute,[4] its utility is reported to be not satisfactory in the case of isocyanate derivatives derived from N^{α}-protected amino acids.[5] Alternative methods for the preparation of peptidyl ureas are involve the use of a carbonic acid derivative. In general, the carbamates have been prepared using *p*-nitrophenyl chloroformate,[6] 2,4,5-trichlorophenyl chloroformate,[7] (phenoxycarbonyl) tetrazole,[8] *N*,*N*′-carbonyldiimidazole,[9] 1,1′-carbonylbisbenzotriazole,[10] etc., and mono protected diamines which have to be obtained in about four to five steps.[3a,11–13] The present communication describes the synthesis of *p*-nitrophenyl-(9-fluorenylmethoxy carbonylamino)methyl carbamate derivatives using *p*-nitrophenol and isocyanates derived from Fmoc-amino acid azides in presence of a base (Sch. 1) and their utility for the synthesis of several peptidyl ureas.

Fmoc protected amino acids were first converted to the corresponding azides **1** by the acid chloride method or by the mixed anhydride method using isobutyloxycarbonylchloride (IBC-Cl) and *N*-methyl morpholine (NMM) at 0°C (in the case of amino acids bearing acid labile side chain protecting groups).[14,15] The resulting acyl azides **1** were converted to the corresponding isocyanates **2** by the Curtius rearrangement (toluene, 65°C, 10 min), which were then reacted with *p*-nitrophenol (1 equiv.) in presence of *N*-ethyldiisopropylamine (DIEA, 1 equiv.) at r.t. to afford the carbamates **3** as crystalline solids in about 88–94% yield. All the carbamates **3** prepared have been separated as solids that were filtered and isolated. Their recrystallization using dimethylformamide (DMF)–dichloromethane (DCM) gave

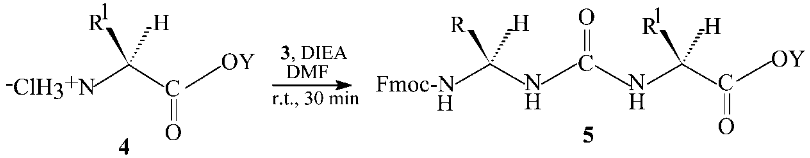


Scheme 1.

analytically pure samples. When stored at 4°C for long periods, neither noticeable degradation nor any change in their spectral behavior (^{1}H NMR recorded after several weeks of storage) has been observed.

The utility of the carbamates **3** has been demonstrated by the synthesis of a series of dipeptidyl ureas **5** (Sch. 2). The acylation of amino acid ester hydrochloride salt in presence of DIEA with the carbamate **3** in DCM at r.t. has resulted in the separation of the peptidyl ureas **5** as solids. As in the case with the carbamates **3**, the recrystallization of the peptidyl ureas **5** using dimethylsulfoxide (DMSO)–water mixture led to obtain analytically pure samples in about 90–96% of yield.

In summary, a simple method for the preparation of *p*-nitrophenyl-(9-fluorenylmethoxycarbonylamino)methyl carbamates and their utility for the synthesis of peptidyl ureas has been demonstrated. All the compounds prepared have been fully characterized.



Scheme 2.

EXPERIMENTAL

Melting points were determined using capillary method and are uncorrected. IR spectra were recorded on a Nicolet model impact 400D FT-IR spectrometer (KBr pellets, 3 cm^{-1} resolution). Specific rotations were recorded on Rudolf Research Autopol IV automatic polarimeter. Elementary analyses were carried out using Perkin Elmer Analyzer and the samples were dried for 24 hr under vacuum before analysis. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer. Mass spectra were recorded on MALDI-TOF (KRATOS) and PE-SCIEX 150 EX LCMS. All solvents were freshly distilled prior to use. Amino acid methyl ester hydrochlorides were prepared by using methanol and thionyl chloride. Fmoc-amino acid azides were prepared by the procedures reported by us.[14,15]

General Procedure for the Preparation of *p*-Nitrophenyl-(9-fluorenylmethoxy Carbonylamino)methyl Carbamate 3

The Fmoc-amino acid azide **1** (1 mmol) was converted to the respective isocyanate **2** by the Curtius rearrangement (in toluene at 65°C for 20 min). The solution was cooled to r.t. and *p*-nitrophenol (1 mmol) and DIEA (1 mmol) were added. It was stirred at r.t. till the completion of the reaction. The separated solid was filtered and washed with DCM and toluene to get the title compound as a solid in almost quantitative yield.

***p*-Nitrophenyl-{1-{[(9*H*-fluorenyl-9-ylmethoxy)carbonyl]amino}-methyl} carbamate 3a.** Yield: 91%; m.p.: 171°C; IR: 1734, 3328 cm^{-1}; ^{1}H NMR (δ, DMSO): 3.2 (2H, br), 4.2 (1H, t), 4.4 (2H, d), 6.7 (1H, s), 7.25–8.16 (13H, m); ^{13}C NMR (δ, DMSO): 41.5, 48.5, 66.6, 120.2, 122.5, 125.5, 126.0, 127.6, 128.5, 142.4, 145.4, 145.5, 154.2, 157.5, 157.6; MS (MALDI-TOF) m/z observed: 455.8 $[M+Na]^+$, 471.9 $[M+K]^+$; Anal. Calcd. for $C_{23}H_{19}N_3O_6$: C, 63.74; H, 4.42; N, 9.69. Found: C, 63.61; H, 4.35; N, 9.57.

***p*-Nitrophenyl-{1-{[(9*H*-fluorenyl-9-ylmethoxy)carbonyl]amino}-ethyl} carbamate 3b.** Yield: 92%; m.p.: 119°C; IR: 1734, 3317 cm^{-1}; $[\alpha]_D^{25}$ ($c = 1$, DMSO), −12.4; ^{1}H NMR (δ, DMSO): 1.14 (3H, d), 3.85 (1H, m), 4.2 (1H, t), 4.35 (2H, m), 6.6 (1H, d), 7.2–8.1 (13H, m); ^{13}C NMR (δ, DMSO): 18.3, 48.0, 48.5, 66.6, 120.2, 122.4, 125.6, 125.8, 127.6, 128.2, 141.9, 145.1, 145.7, 154.5, 157.1, 157.9; MS (MALDI-TOF) m/z observed: 469.8 $[M+Na]^+$, 485.8 $[M+K]^+$; Anal. Calcd. for $C_{24}H_{21}N_3O_6$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.31; H, 4.68; N, 9.29.

***p*-Nitrophenyl-{1-{[(9*H*-fluorenyl-9-ylmethoxy)carbonyl]amino}-2-methylpropyl} carbamate 3c.** Yield: 93%; m.p.: 139°C; IR: 1734, 3312 cm^{-1}; $[\alpha]_D^{25}$ ($c = 1$, DMSO), -4.5; ^{1}H NMR (δ, DMSO): 0.95 (7H, m), 3.8 (1H, m), 4.2 (1H, t), 4.4 (2H, m), 6.4 (1H, d), 7.3–8.15 (13H, m); ^{13}C NMR (δ, DMSO): 18.2, 19.5, 30.6, 47.4, 56.8, 66.9, 120.1, 121.9, 124.8, 125.0, 127.2, 127.9, 141.5, 143.8, 144.7, 153.8, 155.9, 157.5; MS (MALDI-TOF) m/z observed: 497.7 $[M + Na]^+$, 514.0 $[M + K]^+$; Anal. Calcd. for $C_{26}H_{25}N_3O_6$: C, 65.67; H, 5.30; N, 8.84. Found: C, 65.53; H, 5.21; N, 8.72.

***p*-Nitrophenyl-{1-{[(9*H*-fluorenyl-9-ylmethoxy)carbonyl]amino}-3-methylbutyl} carbamate 3d.** Yield: 92%; m.p.: 116°C; IR: 1733, 3320 cm^{-1}; $[\alpha]_D^{25}$ ($c = 1$, DMSO), -32.2; ^{1}H NMR (δ, DMSO): 0.95 (6H, m), 1.25–1.4 (3H, m), 3.8 (1H, m), 4.12 (1H, t), 4.35 (2H, m), 6.45 (1H, d), 7.25–8.12 (13H, m); ^{13}C NMR (δ, DMSO): 22.0, 23.2, 24.8, 41.9, 47.4, 49.9, 66.6, 120.0, 121.9, 125.0, 125.1, 127.1, 127.9, 141.4, 143.6, 144.8, 153.7, 155.9, 157.1; MS (MALDI-TOF) m/z observed: 511.9 $[M + Na]^+$, 528.1 $[M + K]^+$; Anal. Calcd. for $C_{27}H_{27}N_3O_6$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.12; H, 5.41; N, 8.45.

***p*-Nitrophenyl-{1-{[(9*H*-fluorenyl-9-ylmethoxy)carbonyl]amino}-2-methylbutyl} carbamate 3e.** Yield: 94%; m.p.: 159°C; IR: 1734, 3322 cm^{-1}; $[\alpha]_D^{25}$ ($c = 1$, DMSO), -14.7; ^{1}H NMR (δ, DMSO): 0.95 (6H, m), 1.2–1.5 (3H, m), 3.75 (1H, m), 4.2 (1H, t), 4.35 (2H, m), 6.5 (1H, d), 7.25–8.1 (13H, m); ^{13}C NMR (δ, DMSO): 11.5, 15.8, 26.1, 37.9, 48.4, 56.5, 66.6, 120.2, 122.6, 125.7, 125.9, 127.6, 128.2, 142.3, 144.5, 144.6, 153.7, 156.2, 157.3; MS (MALDI-TOF) m/z observed: 512.1 $[M + Na]^+$, 528.0 $[M + K]^+$; Anal. Calcd. for $C_{27}H_{27}N_3O_6$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.14; H, 5.43; N, 8.48.

***p*-Nitrophenyl-{1-{[(9*H*-fluorenyl-9-ylmethoxy)carbonyl]amino}-2-phenylethyl} carbamate 3f.** Yield: 93%; m.p.: 143°C; IR: 1734, 3317 cm^{-1}; $[\alpha]_D^{25}$ ($c = 1$, DMSO), -5.4; ^{1}H NMR (δ, DMSO): 2.85 (2H, d), 4.1 (1H, t), 4.25–4.45 (3H, m), 6.58 (1H, d), 7.1–8.15 (18H, m); ^{13}C NMR (δ, DMSO): 38.8, 47.2, 52.6, 66.6, 120.1, 121.9, 125.0, 125.1, 127.1, 127.2, 127.8, 128.7, 129.2, 136.9, 141.2, 143.5, 144.5, 53.7, 155.8, 156.4; MS (MALDI-TOF) m/z observed: 545.9 $[M + Na]^+$, 562.1 $[M + K]^+$; Anal. Calcd. for $C_{30}H_{25}N_3O_6$: C, 68.82; H, 4.81; N, 8.02. Found: C, 68.71; H, 4.70; N, 7.89.

***p*-Nitrophenyl-{1-{[(9*H*-fluorenyl-9-ylmethoxy)carbonyl]amino}-1-phenylethyl} carbamate 3g.** Yield: 89%; m.p.: 164°C; IR: 1735, 3319 cm^{-1}; $[\alpha]_D^{25}$ ($c = 1$, DMSO), -11.2; ^{1}H NMR (δ, DMSO): 4.2 (1H, t), 4.3–4.45 (3H, m), 6.6 (1H, d), 7.1–8.16 (18H, m); ^{13}C NMR (δ, DMSO): 47.2, 54.1, 66.6, 120.0, 122.0, 125.0, 125.1, 126.9, 127.2, 127.8, 128.7, 129.3, 136.8, 141.2, 143.9, 144.5, 153.8, 155.9, 156.6; MS (MALDI-TOF) m/z observed: 531.8 $[M + Na]^+$, 547.9 $[M + K]^+$; Anal. Calcd. for $C_{29}H_{23}N_3O_6$: C, 68.36; H, 4.55; N, 8.25. Found: C, 68.23; H, 4.44; N, 8.16.

***p*-Nitrophenyl-{D-1-{[(9*H*-fluorenyl-9-ylmethoxy)carbonyl]amino}-1-phenylmethyl} carbamate 3g*.** Yield: 88%; m.p.: 161°C; IR: 1734, 3318 cm^{-1}; $[\alpha]_D^{25}$ ($c = 1$, DMSO), +11.3; ^{1}H NMR (δ, DMSO): 4.1 (1H, t), 4.25–4.35 (3H, m), 6.65 (1H, d), 7.15–8.1 (18H, m); ^{13}C NMR (δ, DMSO): 47.3, 54.1, 66.5, 119.9, 122.1, 125.0, 125.2, 127.0, 127.2, 127.7, 128.8, 129.2, 136.7, 141.2, 143.8, 144.6, 153.8, 155.9, 156.6; MS (MALDI-TOF) m/z observed: 531.9 $[M+Na]^+$, 547.9 $[M+K]^+$; Anal. Calcd. for $C_{29}H_{23}N_3O_6$: C, 68.36; H, 4.55; N, 8.25. Found: C, 68.25; H, 4.47; N, 8.13.

***p*-Nitrophenyl-{1-{[(9*H*-fluorenyl-9-ylmethoxy)carbonyl]amino}-2-[(*tert*-butoxy)carbonyl]ethyl} carbamate 3h.** Yield: 87%; m.p.: 136°C; IR: 1734, 3316 cm^{-1}; $[\alpha]_D^{25}$ ($c = 1$, DMSO), −10.7; ^{1}H NMR (δ, DMSO): 1.45 (9H, s), 2.45 (2H, m), 4.2–4.35 (4H, m), 6.65 (1H, d), 7.2–8.14 (13H, m); ^{13}C NMR (δ, DMSO): 28.0, 37.9, 47.3, 49.1, 66.7, 81.6, 120.1, 121.8, 125.1, 125.3, 127.0, 127.7, 141.4, 143.8, 144.6, 153.7, 155.6, 156.8, 171.3; MS (MALDI-TOF) m/z observed: 570.0 $[M+Na]^+$, 586.2 $[M+K]^+$; Anal. Calcd. for $C_{29}H_{29}N_3O_8$: C, 63.61; H, 5.34; N, 7.67. Found: C, 63.52; H, 5.22; N, 7.56.

***p*-Nitrophenyl-{1-{[(9*H*-fluorenyl-9-ylmethoxy)carbonyl]amino}-3-[(*tert*-butoxy)carbonyl]ethyl} carbamate 3i.** Yield: 89%; m.p.: 140°C; IR: 1734, 3319 cm^{-1}; $[\alpha]_D^{25}$ ($c = 1$, DMSO), −12.3; ^{1}H NMR (δ, DMSO): 1.5 (9H, s), 2.3–2.6 (4H, m), 4.2–4.4 (4H, m), 6.68 (1H, d), 7.1–8.1 (13H, m); ^{13}C NMR (δ, DMSO): 28.0, 31.0, 37.8, 47.3, 48.7, 66.7, 81.6, 120.1, 121.8, 125.1, 125.3, 127.0, 127.7, 141.4, 143.8, 144.6, 153.7, 155.6, 156.8, 171.1; MS (MALDI-TOF) m/z observed: 583.8 $[M+Na]^+$, 599.8 $[M+K]^+$; Anal. Calcd. for $C_{30}H_{31}N_3O_8$: C, 64.16; H, 5.56; N, 7.48. Found: C, 64.03; H, 5.42; N, 7.39.

***p*-Nitrophenyl-{1-{[(9*H*-fluorenyl-9-ylmethoxy)carbonyl]amino}-2-[4-(*tert*-butoxy)phenyl]ethyl} carbamate 3j.** Yield: 88%; m.p.: 144°C; IR: 1736, 3314 cm^{-1}; $[\alpha]_D^{25}$ ($c = 1$, DMSO), −13.8; ^{1}H NMR (δ, DMSO): 1.3 (9H, s), 2.8 (2H, d), 3.95–4.35 (4H, m), 6.55 (1H, d), 7.1–8.16 (17H, m); ^{13}C NMR (δ, DMSO): 28.8, 38.2, 47.3, 52.7, 66.6, 78.6, 120.0, 122.0, 124.5, 125.0, 125.1, 127.2, 127.7, 129.6, 131.4, 141.5, 143.6, 144.6, 153.8, 154.5, 155.8, 156.8; MS (MALDI-TOF) m/z observed: 618.0 $[M+Na]^+$, 634.1 $[M+K]^+$; Anal. Calcd. for $C_{34}H_{33}N_3O_7$: C, 68.56; H, 5.58; N, 7.05. Found: C, 68.42; H, 5.43; N, 6.89.

***p*-Nitrophenyl-{1-{[(9*H*-fluorenyl-9-ylmethoxy)carbonyl]amino}-2-[benzyloxy]ethyl} carbamates 3k.** Yield: 91%; m.p.: 129°C; IR: 1734, 3317 cm^{-1}; $[\alpha]_D^{25}$ ($c = 1$, DMSO), −4.2; ^{1}H NMR (δ, DMSO): 2.85 (2H, s), 3.35 (2H, d), 3.85 (1H, m), 4.2 (1H, t), 4.35 (2H, m), 6.5 (1H, d), 7.15–8.15 (18H, m); ^{13}C NMR (δ, DMSO): 38.6, 47.2, 50.7, 61.5, 66.8, 120.0, 121.8, 124.9, 125.0, 127.0, 127.1, 127.7, 128.8, 129.3, 136.8, 141.3, 143.8, 144.7, 153.6, 155.9, 156.8; MS (MALDI-TOF) m/z observed: 576.1 $[M+Na]^+$, 591.9 $[M+K]^+$; Anal. Calcd. for $C_{31}H_{27}N_3O_7$: C, 67.26; H, 4.91; N, 7.59. Found: C, 62.13; H, 4.80; N, 7.47.

General Procedure for the Synthesis of Dipeptidyl Ureas 5

To a stirred solution of amino acid methyl ester hydrochloride salt **4** (1 mmol) in DMF (5 mL) and DIEA (2 mmol), carbamate **3** (1 mmol) was added and stirred at r.t. till the completion of the reaction. The separated solid was filtered and crystallized using DMSO and water (70 : 30) to get the dipeptidyl urea **5** as a crystalline off-white solid.

Fmoc-Ile^u-Gly-Ome (5a). Yield: 96%; m.p.: 143°C; ^{1}H NMR (δ, DMSO): 0.8 (6H, m), 1.1–1.65 (3H, m), 2.5 (2H, m), 3.6 (3H, s), 3.8 (1H, m), 4.2–4.4 (3H, m), 5.0 (1H, d), 6.3–6.5 (2H, m), 7.3–7.9 (8H, m); ^{13}C NMR (δ, DMSO): 11.0, 14.3, 25.0, 40.4, 41.2, 46.7, 51.5, 61.5, 65.1, 120.0, 125.2, 127.0, 127.6, 140.7, 143.8, 155.0, 156.8, 171.5; ES MS m/z observed: 440.2; Anal. Calcd. for $C_{24}H_{29}N_3O_5$: C, 65.59; H, 6.65; N, 9.56. Found: C, 65.38; H, 6.52; N, 9.38.

Fmoc-Phe^u-Leu-OMe (5b). Yield: 94%; m.p.: 148°C; ^{1}H NMR (δ, DMSO): 0.95 (6H, d), 1.35 (2H, s), 1.6 (1H, m), 2.82 (2H, d), 3.65 (3H, m), 3.8 (1H, m), 4.1–4.4 (4H, m), 5.1 (1H, d), 6.5–6.7 (2H, m), 7.2–7.85 (13H, m); ^{13}C NMR (δ, DMSO): 22.0, 23.0, 24.5, 37.2, 47.3, 51.4, 54.2, 61.3, 66.6, 120.1, 125.0, 126.5, 127.0, 127.5, 128.5, 129.2, 137.5, 141.3, 144.0, 155.8, 156.5, 171.6; MS (MALDI-TOF) m/z observed: 552.6 $[M+Na]^+$, 568.7 $[M+K]^+$; Anal. Calcd. for $C_{31}H_{35}N_3O_5$: C, 70.30; H, 6.66; N, 7.93. Found: C, 70.18; H, 6.57; N, 7.81.

Fmoc-Phe^u-Phe-OMe (5c). Yield: 90%; m.p.: 184°C; ^{1}H NMR (δ, DMSO): 2.85 (4H, d), 3.65 (3H, s), 3.96–4.1 (2H, m), 4.2 (1H, t), 4.4 (2H, m), 6.0 (1H, d), 6.7–6.9 (2H, m), 7.1–7.85 (18H, m); ^{13}C NMR (δ, DMSO): 37.2, 37.3, 47.4, 54.1, 54.3, 61.3, 66.6, 120.1, 125.0, 126.5, 126.6, 127.0, 127.6, 128.4, 128.6, 129.1, 129.3, 137.5, 137.6, 141.2, 144.0, 155.8, 156.5, 171.1; MS (MALDI-TOF) m/z observed: 586.6 $[M+Na]^+$, 602.7 $[M+K]^+$; Anal. Calcd. for $C_{34}H_{33}N_3O_5$: C, 72.45; H, 5.90; N, 7.45. Found: C, 72.38; H, 5.81; N, 7.39.

Fmoc-Phg^u-Phe-OMe (5d). Yield: 91%; m.p.: 167°C; ^{1}H NMR (δ, DMSO): 2.85 (2H, d), 3.60 (3H, s), 3.95–4.1 (2H, m), 4.2 (1H, t), 4.4 (2H, m), 6.1 (1H, d), 6.6–6.9 (2H, m), 7.1–7.9 (18H, m); ^{13}C NMR (δ, DMSO): 37.2, 47.4, 54.1, 54.6, 61.3, 66.6, 120.1, 125.0, 126.7, 127.0, 127.2, 127.6, 128.2, 128.6, 129.0, 129.3, 137.5, 137.8, 141.3, 144.0, 155.4, 156.3, 171.1; MS (MALDI-TOF) m/z observed: 572.1 $[M+Na]^+$, 588.1 $[M+K]^+$; Anal. Calcd. for $C_{33}H_{31}N_3O_5$: C, 72.11; H, 5.68; N, 7.64. Found: C, 71.98; H, 5.57; N, 7.49.

Fmoc-D-Phg^u-Phe-OMe (5e). Yield: 91%; m.p.: 181°C; ^{1}H NMR (δ, DMSO): 2.84 (2H, d), 3.6 (3H, s), 3.93–4.1 (2H, m), 4.2 (1H, t), 4.4 (2H, m), 6.1 (1H, d), 6.6–6.9 (2H, d), 7.2–7.9 (18H, m); ^{13}C NMR (δ, DMSO): 37.3, 47.4, 54.2, 54.6, 61.4, 66.6, 120.2, 125.1, 126.8, 127.1, 127.2, 127.6, 128.2, 128.6, 129.0, 129.4, 137.5, 137.9, 141.4, 144.0, 155.6, 156.4, 171.0; MS (MALDI-TOF) m/z observed: 572.1 $[M+Na]^+$, 588.1 $[M+K]^+$; Anal. Calcd. for $C_{33}H_{31}N_3O_5$: C, 72.11; H, 5.68; N, 7.64. Found: C, 72.01; H, 5.56; N, 7.46.

Fmoc-Asp(O^{t}Bu)^u-Gly-Ome (5f). Yield: 90%; m.p.: 157°C; ^{1}H NMR (δ, DMSO): 1.45 (9H, s), 1.9 (2H, d), 2.6 (2H, d), 3.65 (3H, s), 4.1 (1H, t), 4.3–4.4 (3H, m), 5.8 (1H, d), 6.5–6.7 (2H, m), 7.3–7.75 (8H, m); ^{13}C NMR (δ, DMSO): 27.9, 37.5, 41.5, 47.1, 50.0, 61.3, 66.8, 81.5, 120.0, 125.0, 127.5, 128.0, 141.0, 144.1, 155.5, 156.5, 170.8, 171.1; MS (MALDI-TOF) m/z observed: 519.8 $[M+Na]^+$, 536.0 $[M+K]^+$; Anal. Calcd. for $C_{26}H_{31}N_3O_7$: C, 62.76; H, 6.28; N, 8.44. Found: C, 62.66; H, 6.07; N, 8.29.

Fmoc-Val^u-Leu-OBzl (5g). Yield: 95%; m.p.: 184°C; ^{1}H NMR (δ, DMSO): 0.92 (12H, m), 1.32–1.85 (4H, m), 3.1 (2H, s), 3.7–3.8 (2H, m), 4.2 (1H, t), 4.42 (2H, m), 5.1 (1H, d), 6.6–6.7 (2H, m), 7.2–7.85 (13H, m); ^{13}C NMR (δ, DMSO): 18.5, 19.5, 22.0, 23.1, 24.5, 29.2, 37.2, 40.2, 47.2, 51.5, 59.0, 66.6, 120.0, 125.0, 126.5, 127.2, 128.0, 128.4, 129.3, 137.6, 141.2, 144.0, 155.4, 156.8, 176.4; MS (MALDI-TOF) m/z observed: 580.0 $[M+Na]^+$, 596.1 $[M+K]^+$; Anal. Calcd. for $C_{33}H_{39}N_3O_5$: C, 71.07; H, 7.05; N, 7.53. Found: C, 70.96; H, 6.89; N, 7.41.

Fmoc-Leu^u-Phe-OBzl (5h). Yield: 92%; m.p.: 145°C; ^{1}H NMR (δ, DMSO): 0.95 (6H, d), 1.35 (2H, s), 1.6 (1H, m), 2.85 (2H, d), 3.1 (2H, s), 3.8 (1H, m), 4.1–4.45 (4H, m), 5.1 (1H, d), 6.5–6.7 (2H, m), 7.2–7.85 (18H, m); ^{13}C NMR (δ, DMSO): 22.0, 23.0, 24.5, 37.2, 40.2, 47.3, 51.4, 54.2, 66.6, 120.1, 125.0, 126.5, 126.6, 127.0, 127.5, 128.5, 128.7, 129.1, 129.2, 137.5, 137.6, 141.3, 144.0, 155.8, 156.5, 171.6; MS (MALDI-TOF) m/z observed: 628.7 $[M+Na]^+$, 644.8 $[M+K]^+$; Anal. Calcd. for $C_{37}H_{39}N_3O_5$: C, 73.36; H, 6.49; N, 6.94. Found: C, 73.21; H, 6.37; N, 6.79.

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