Synthesis and biological evaluation of a novel class of β-carboline derivatives

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Table of contents

I. Experimental section of dipeptides and tripeptides S2

II. NMR Spectra S12

I. Experimental section of dipeptides and tripeptides

Boc-Trp-Trp-OBzl HOBt (1.87 g, 6.6 mmol) and DCC (1.48 g, 7.2 mmol) were added to a solution
of Boc-Trp-OH (2.84 g, 7.2 mmol) and HCl-Trp-OBzl (2.17 g, 6.6 mmol) in anhydrous THF (40 mL) at 0°C. The reaction mixture was adjusted to 8 with N-methylmorpholine. The reaction mixture obtained was kept at 0°C for 2 h followed by at room temperature for 24 h. DCU formed was removed by filtration. The filtrate was subject to evaporation under reduced pressure and the residue was dissolved in EtOAc (80 mL). The solution was washed successively with saturated NaHCO₃, 5% KHSO₄ and saturated NaCl, and the organic phase was collected and dried using Na₂SO₄. After filtration and evaporation under reduced pressure, purification of the residue by chromatography (30:1 CHCl₃-MeOH) provided the title compound as colorless powder (3.68 g, 6.3 mmol, 96% yield). mp 189-191°C. ¹HNR (300 MHz, CDCl₃): δ 7.90 (1H, s, N-H), 7.83 (1H, s, N-H), 7.67 (1H, d, J = 7.5 Hz, N-H), 7.37-7.12 (10H, m, Ar-H), 5.02 (2H, dd, J₁ = 28.2 Hz, J₂ = 12 Hz, CH₂Ph), 4.89 (1H, m, CH), 4.47 (1H, m, CH), 3.34-3.06 (4H, m, CH₂), 1.41 (9H, s, CH₃); ESIMS m/z 603 (M+Na).

Boc-Trp-Trp-OH At 0°C to the solution of Boc-Trp-Trp-OBzl (1.00 g, 1.72 mmol) in 10 ml of methanol 3 ml of aqueous NaOH (2 M) was added to adjust the solution to pH 12. The reaction mixture was stirred at 0°C for 30 min, and then was adjusted to pH 5.5 with hydrochloric acid (2 N). After filtration the filtrate was evaporated under reduced pressure. The residue was dissolved in 30 ml of methanol and the solution was filtrated. The filtrate was evaporated under reduced pressure and the residue was solidified in 10 ml of anhydrous ether to provide the title compound as colorless powder (0.76 g, 1.55 mmol, 90% yield). mp 200-202°C. ¹HNR (300 MHz, CDCl₃): δ 8.22 (1H, s, N-H), 8.12 (1H, s, N-H), 7.62 (1H, d, J = 7.2 Hz, N-H), 7.40-7.01 (10H, m, Ar-H), 4.78 (1H, m, CH), 4.50 (1H, m, CH), 3.31-3.09 (4H, m, CH₂), 1.42 (9H, s, CH₃); ESIMS m/z 491 (M+1).

Boc-Trp-Trp-Tyr-OBzl Using the same procedure as described for Boc-Trp-Trp-OBzl from Boc-Trp-Trp (490 mg, 1.0 mmol) and Tos-Tyr-OBzl (487 mg, 1.1 mmol) the title compound was obtained as
colorless powder (708 mg, 0.95 mmol, 95% yield). mp 220-222°C. ESIMS m/z 744 (M+1).

Boc-Trp-Trp-Glu(OBzl)-OBzl Using the same procedure as described for Boc-Trp-Trp-OBzl from Boc-Trp-Trp (490 mg, 1.0 mmol) and Tos-Glu(OBzl)-OBzl (549 mg, 1.1 mmol) the title compound was obtained as colorless powder (471 mg, 0.59 mmol, 59% yield). mp 202-204°C. ESIMS m/z 800 (M+1).

Boc-Trp-Trp-Thr-OBzl Using the same procedure as described for Boc-Trp-Trp-OBzl from Boc-Trp-Trp (490 mg, 1.0 mmol) and Tos-Thr-OBzl (419 mg, 1.1 mmol) the title compound was obtained as colorless powder (580 mg, 0.85 mmol, 85% yield). mp 190-192°C. ESIMS m/z 843 (M+1).

Boc-Trp-Trp-Lys(Nω-Z)-OBzl Using the same procedure as described for Boc-Trp-Trp-OBzl from Boc-Trp-Trp (490 mg, 1.0 mmol) and Tos-Lys(Nω-Z)-OBzl (596 mg, 1.1 mmol) the title compound was obtained as colorless powder (829 mg, 0.98 mmol, 98% yield). mp 201-203°C. ESIMS m/z 843 (M+1).

Boc-Trp-Trp-Val-OBzl Using the same procedure as described for Boc-Trp-Trp-OBzl from Boc-Trp-Trp (490 mg, 1.0 mmol) and Tos-Val-OBzl (432 mg, 1.1 mmol) the title compound was obtained as colorless powder (642 mg, 0.95 mmol, 95% yield). mp 210-212°C. 1H NMR (300 MHz, CDCl3): δ 8.03 (1H, brs, N-H), 7.38 (1H, m, Ar-H), 7.33 (14H, m, Ar-H), 5.13 (2H, m, CH2Ph), 4.72 (1H, m, CH), 4.69 (1H, m, CH), 3.61 (1H, m, CH), 3.43-3.10 (4H, m, CH2), 2.01 (1H, m, CH), 1.39 (9H, s, CH3), 0.77 (3H, d, J= 9.0 Hz, CH3), 0.72 (3H, d, J= 6.0 Hz, CH3); ESIMS m/z 680 (M+1).

Boc-Trp-Trp-Ile-OBzl Using the same procedure as described for Boc-Trp-Trp-OBzl from Boc-Trp-Trp (490 mg, 1.0 mmol) and Tos-Ile-OBzl (432 mg, 1.1 mmol) the title compound was obtained as colorless powder (687 mg, 0.99 mmol, 99% yield). mp 212-214°C. ESIMS m/z 694 (M+1).

Boc-Trp-Trp-Ala-OBzl Using the same procedure as described for Boc-Trp-Trp-OBzl from Boc-Trp-
Trp (490 mg, 1.0 mmol) and Tos-Ala-OBzl (386 mg, 1.1 mmol) the title compound was obtained as colorless powder (641 mg, 0.98 mmol, 98% yield). mp 202-204°C. 1H NMR (300 MHz, CDCl₃): δ 8.20 (1H, brs, N-H), 7.99 (1H, brs, N-H), 7.66 (1H, d, J = 9.0 Hz, Ar-H), 7.41-7.11 (12H, m, Ar-H), 6.99 (1H, s, Ar-H), 6.76 (1H, s, Ar-H), 5.14 (2H, m, CH₂Ph), 4.70 (1H, m, CH), 4.47 (1H, m, CH), 4.35 (1H, m, CH), 3.35 (2H, m, CH₂), 3.13 (1H, m, CH₂), 2.78 (1H, m, CH₂), 1.31 (3H, m, CH₃), 1.22 (9H, s, CH₃); 13C NMR (75 MHz, CDCl₃) δ 172.1, 171.6, 170.6, 155.5, 136.4, 136.1, 135.6, 128.6, 128.3, 128.1, 127.5, 127.4, 123.5, 123.3, 122.5, 122.2, 119.9, 119.6, 118.9, 118.5, 111.3, 111.2, 110.2, 109.9, 80.2, 66.9, 60.4, 53.6, 48.4, 28.0, 27.5, 27.0, 17.7; ESIMS m/z 652 (M+1).

**Boc-Trp-Trp-Asp(OBzl)-OBzl** Using the same procedure as described for Boc-Trp-Trp-OBzl from Boc-Trp-Trp (490 mg, 1.0 mmol) and Tos-Asp(OBzl)-OBzl (533 mg, 1.1 mmol) the title compound was obtained as colorless powder (473 mg, 0.60 mmol, 60% yield). mp 208-210°C. ESIMS m/z 786 (M+1).

**Boc-Trp-Trp-Pro-OBzl** Using the same procedure as described for Boc-Trp-Trp-OBzl from Boc-Trp-Trp (490 mg, 1.0 mmol) and Tos-Pro-OBzl (266 mg, 1.1 mmol) the title compound was obtained as colorless powder (654 mg, 0.96 mmol, 96% yield). mp 182-184°C. ESIMS m/z 678 (M+1).

**Boc-Trp-Trp-Gly-OBzl** Using the same procedure as described for Boc-Trp-Trp-OBzl from Boc-Trp-Trp (490 mg, 1.0 mmol) and Tos-Gly-OBzl (371 mg, 1.1 mmol) the title compound was obtained as colorless powder (414 mg, 0.65 mmol, 65% yield). mp 206-208°C. ESIMS m/z 638 (M+1).

**Boc-Trp-Trp-Trp-OBzl** Using the same procedure as described for Boc-Trp-Trp-OBzl from Boc-Trp-Trp (490 mg, 1.0 mmol) and Tos-Trp-OBzl (363 mg, 1.1 mmol) the title compound was obtained as colorless powder (664 mg, 0.87 mmol, 87% yield). mp 180-192°C. ESIMS m/z 767 (M+1).

**Boc-Trp-Trp-Phe-OBzl** Using the same procedure as described for Boc-Trp-Trp-OBzl from Boc-
Trp-Trp (490 mg, 1.0 mmol) and Tos-Phe-OBzl (470 mg, 1.1 mmol) the title compound was obtained as colorless powder (682 mg, 0.94 mmol, 94% yield). mp 200-202°C. ESIMS m/z 638 (M+1).

*Boc-Trp-Trp-Ser-OBzl* Using the same procedure as described for Boc-Trp-Trp-OBzl from Boc-Trp-Trp (490 mg, 1.0 mmol) and Tos∙Ser-OBzl (404 mg, 1.1 mmol) the title compound was obtained as colorless powder (563 mg, 0.84 mmol, 84% yield). mp 195-197°C. ESIMS m/z 668 (M+1).

*Boc-Trp-Trp-Met-OBzl* Using the same procedure as described for Boc-Trp-Trp-OBzl from Boc-Trp-Trp (490 mg, 1.0 mmol) and Tos∙Met-OBzl (452 mg, 1.1 mmol) the title compound was obtained as colorless powder (692 mg, 0.97 mmol, 97% yield). mp 218-220°C. ESIMS m/z 712 (M+1).

*Boc-Trp-Trp-Leu-OBzl* Using the same procedure as described for Boc-Trp-Trp-OBzl from Boc-Trp-Trp (490 mg, 1.0 mmol) and Tos∙Leu-OBzl (432 mg, 1.1 mmol) the title compound was obtained as colorless powder (675 mg, 0.97 mmol, 97% yield). mp 206-208°C. ¹H NMR (300 MHz, CDCl₃): δ 8.26 (1H, brs, N-H), 8.02 (1H, brs, N-H), 7.66 (1H, d, J = 6.0 Hz, Ar-H), 7.40-7.11 (12H, m, Ar-H), 6.96 (1H, s, Ar-H), 6.76 (1H, s, Ar-H), 5.13 (2H, s, CH₂Ph), 4.73 (1H, m, CH), 4.52 (1H, m, CH), 4.35 (1H, m, CH), 3.31 (2H, m, CH₂), 3.11 (1H, m, CH₂), 2.81 (1H, m, CH₂), 1.54 (1H, m, CH), 1.40 (2H, m, CH₂), 1.28 (9H, m, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 172.1, 171.7, 170.9, 136.4, 136.1, 135.7, 128.5, 128.3, 128.2, 127.5, 127.4, 123.5, 123.3, 122.5, 122.2, 119.9, 119.6, 118.9, 118.5, 111.4, 111.2, 110.1, 109.9, 80.2, 66.9, 60.3, 55.4, 53.7, 51.1, 40.9, 28.0, 27.5, 27.0, 24.5, 22.6, 21.9; ESIMS m/z 694 (M+1).

*Trp-Trp-Tyr-OBzl* To Boc-Trp-Trp-Tyr-OBzl (500 mg, 0.67 mmol) 7 ml of 4 M solution of hydrochloride in ethyl acetate was added. The reaction mixture was stirred at room temperature for 60 min and TLC (chloroform/methanol, 5:1) indicated the disappearance of Boc-Trp-Trp-Tyr-OBzl. The reaction mixture was evaporated under reduced pressure, the residue was dissolved in 40 ml of ethyl
acetate, the solution was again evaporated under reduced pressure and the residue was washed with anhydrous ether to provide the title compound as colorless powder (449 mg, 0.66 mmol 98% yield). mp 207-209 °C. [α]_D sup20 + 9.77 (c 1.1 in MeOH); ¹H NMR (500 MHz, DMSO-d₆): δ 10.89 (2H, m, N-H), 8.78 (1H, d, J = 7.3 Hz, N-H), 8.74 (1H, d, J = 8.2 Hz, N-H), 7.66 (1H, d, J = 8.0 Hz, Ar-H), 7.51 (1H, d, J = 7.9 Hz, Ar-H), 7.07 (17H, m, Ar-H), 5.02 (2H, m, CH₂Ph), 4.70 (2H, m, CH), 3.90 (1H, m, CH), 3.04 (6H, m, CH₂); ¹³C NMR (125MHz, DMSO-d₆) δ 172.6, 155.9, 142.2, 136.7, 132.2, 130.1, 129.0, 127.7, 127.5, 127.2, 122.9, 122.2, 120.1, 119.2, 119.0, 115.2, 111.3, 111.1, 110.9, 68.6, 54.8, 53.1, 40.6, 31.3, 30.8; ESIMS m/z 644 (M+1); Anal. Calcd for C₃₈H₃₇N₅O₅: C, 70.90; H, 5.79; N, 10.88. Found: C, 70.69; H, 5.63; N, 11.12.

Trp-Trp-Glu(OBzl)-OBzl Using the same procedure as described for Trp-Trp-Tyr-OBzl from Boc-Trp-Trp-Glu(OBzl)-OBzl (500 mg, 0.63 mmol) the title compound was obtained as colorless powder (455 mg, 0.62 mmol, 99% yield). mp 214-216 °C. [α]_D sup20 + 20.17 (c 1.1 in MeOH); ¹H NMR (500 MHz, DMSO-d₆): δ 10.93 (2H, m, N-H), 8.77 (1H, d, J = 7.2 Hz, N-H), 8.73 (1H, d, J = 7.7 Hz, N-H), 7.64 (1H, d, J = 7.8 Hz, Ar-H), 7.50 (1H, d, J = 7.8 Hz, Ar-H), 7.16 (18H, m, Ar-H), 5.03 (4H, m, CH₂Ph), 4.68 (2H, m, CH), 3.82 (1H, m, CH), 3.07 (4H, m, CH₂), 2.56 (2H, m, CH₂), 2.06 (2H, m, CH₂); ¹³C NMR (125MHz, DMSO-d₆) δ 173.3, 172.7, 142.5, 136.8, 130.1, 129.0, 127.7, 127.5, 127.2, 122.9, 122.2, 120.1, 119.2, 119.0, 111.3, 111.1, 110.9, 68.6, 54.8, 53.6, 31.3, 30.6, 29.2, 27.8. ESIMS m/z 700 (M+1); Anal. Calcd for C₄₁H₄₁N₅O₆: C, 70.37; H, 5.91; N, 10.01. Found: C, 70.16; H, 5.75; N, 10.24.

Trp-Trp-Thr-OBzl Using the same procedure as described for Trp-Trp-Tyr-OBzl from Boc-Trp-Trp-Thr-OBzl (500 mg, 0.73 mmol) the title compound was obtained as colorless powder (429 mg, 0.69 mmol, 95% yield). mp 195-197 °C. [α]_D sup20 + 6.10 (c 1.2 in MeOH); ¹H NMR (500 MHz, DMSO-d₆): δ 10.97 (2H, m, N-H), 7.32 (15H, m, Ar-H), 5.07 (2H, m, CH₂Ph), 4.66 (2H, m, CH), 3.62 (1H, m, CH),
3.40 (1H, m, CH), 3.13 (4H, m, CH₃), 1.15 (3H, m, CH₃); ^1^H NMR (125 MHz, DMSO-d₆) δ 172.9, 142.3, 136.8, 130.1, 127.7, 127.5, 127.2, 122.9, 122.2, 120.1, 119.2, 119.0, 111.4, 111.1, 110.9, 71.0, 68.6, 65.8, 54.6, 31.3, 30.8, 19.2; ESIMS m/z 582 (M+1); Anal. Calcd for C₃₅H₃₅N₅O₅: C, 68.14; H, 6.07; N, 12.04. Found: C, 68.35; H, 6.22; N, 12.25.

Trp-Trp-Lys(ω-Z)-OBzl Using the same procedure as described for Trp-Trp-Tyr-OBzl from Boc-Trp-Trp-Lys(ω-Z)-OBzl (500 mg, 0.59 mmol) the title compound was obtained as colorless powder (459 mg, 0.58 mmol, 99% yield). mp 193-195 °C. [α]_D^20 +14.77 (c 1.2 in MeOH); ^1^H NMR (500 MHz, DMSO-d₆) δ 10.99 (2H, m, N-H), 8.97 (1H, d, J = 7.9 Hz, N-H), 8.66 (1H, d, J = 7.3 Hz, N-H), 8.26 (1H, d, J = 7.1 Hz, N-H), 7.78 (1H, d, J = 7.9 Hz, Ar-H), 7.64 (1H, d, J = 7.9 Hz, Ar-H), 7.17 (18H, m, Ar-H), 5.01 (4H, m, CH₂Ph), 4.72 (1H, m, CH), 4.33 (1H, m, CH), 3.36 (1H, m, CH), 3.04 (6H, m, CH₂), 1.50 (6H, m, CH₃); ^1^3CNMR (125 MHz, DMSO-d₆) δ 172.9, 156.1, 142.2, 141.1, 136.7, 130.1, 129.3, 127.7, 127.5, 127.2, 122.9, 122.2, 120.1, 119.2, 119.0, 111.3, 111.1, 110.9, 68.6, 65.5, 54.8, 54.1, 42.2, 34.6, 31.3, 30.5, 29.6; ESIMS m/z 743 (M+1); Anal. Calcd for C₄₃H₄₆N₆O₆: C, 69.52; H, 6.24; N, 11.31. Found: C, 69.30; H, 6.10; N, 11.54.

Trp-Trp-Val-OBzl Using the same procedure as described for Trp-Trp-Tyr-OBzl from Boc-Trp-Trp-Val-OBzl (500 mg, 0.74 mmol) the title compound was obtained as colorless powder (440 mg, 0.72 mmol, 97% yield). mp 200-202 °C. [α]_D^20 +13.43 (c 1.4 in MeOH); ^1^H NMR (500 MHz, DMSO-d₆) δ 10.90 (2H, m, N-H), 8.72 (1H, d, J = 7.3 Hz, N-H), 8.58 (1H, d, J = 7.9 Hz, N-H), 7.63 (1H, d, J = 7.9 Hz, Ar-H), 7.49 (1H, d, J = 7.9 Hz, Ar-H), 7.17 (13H, m, Ar-H), 5.03 (2H, m, CH₂Ph), 4.71 (1H, dd, J₁ = 13.5 Hz, J₂ = 5.4 Hz, CH), 4.62 (1H, dd, J₁ = 14.3 Hz, J₂ = 7.1 Hz, CH), 3.61 (1H, m, CH), 3.17 (4H, m, CH₂), 2.07 (1H, m, CH), 0.90 (6H, m, CH₃); ^1^3CNMR (125 MHz, DMSO-d₆) δ 172.9, 142.1, 136.7, 130.0, 127.7, 127.5, 127.2, 122.9, 122.2, 120.1, 119.2, 119.0, 111.3, 111.1, 110.9, 68.5, 59.7, 54.8, 33.6,
31.2, 30.7, 17.4; ESIMS m/z 580 (M+1); Anal. Calcd for C_{34}H_{37}N_{5}O_{4}: C, 70.45; H, 6.34; N, 12.08. Found: C, 70.26; H, 6.20; N, 11.89.

**Trp-Trp-Ile-OBzl** Using the same procedure as described for Trp-Trp-Tyr-OBzl from Boc-Trp-Trp-Ile-OBzl (500 mg, 0.72 mmol) the title compound was obtained as colorless powder (429 mg, 0.71 mmol, 99% yield). mp 228-230 °C. [α]_D^{20} +17.00 (c 1.2 in MeOH); ^1^HNMR (500 MHz, DMSO- d_6): δ 10.96 (2H, m, N-H), 8.70 (1H, d, J= 7.2 Hz, N-H), 8.65 (1H, d, J= 8.0 Hz, N-H), 7.25 (13H, m, Ar-H), 6.82 (2H, s, Ar-H), 5.04 (2H, m, CH_2Ph), 4.68 (2H, m, CH), 3.47 (1H, m, CH), 3.11 (4H, m, CH_2), 1.25 (1H, m, CH), 1.08 (2H, m, CH_2), 0.83 (6H, m, CH_3); ^13^CNMR(125MHz, DMSO-d_6) δ 172.9, 142.1, 136.6, 130.0, 127.8, 127.5, 127.2, 122.8, 122.2, 120.1, 119.2, 119.0, 111.3, 111.1, 110.9, 68.6, 57.1, 54.8, 39.5, 31.2, 30.6, 24.9, 14.6, 10.9; ESIMS m/z 594 (M+1); Anal. Calcd for C_{35}H_{39}N_{5}O_{4}: C, 70.80; H, 6.62; N, 11.80. Found: C, 71.01; H, 6.78; N, 11.58.

**Trp-Trp-Ala-OBzl** Using the same procedure as described for Trp-Trp-Tyr-OBzl from Boc-Trp-Trp-Ala-OBzl (500 mg, 0.78 mmol) the title compound was obtained as colorless powder (449 mg, 0.76 mmol, 98% yield). mp 205-207 °C. [α]_D^{20} +11.03 (c 1.0 in MeOH); ^1^HNMR (500 MHz, DMSO-d_6): δ 10.90 (2H, m, N-H), 8.66 (1H, d, J = 7.3 Hz, N-H), 8.59 (1H, d, J = 8.1 Hz, N-H), 7.63 (1H, d, J = 7.8 Hz, Ar-H), 7.49 (1H, d, J = 7.8 Hz, Ar-H), 7.14 (13H, m, Ar-H), 5.02 (2H, m, CH_2Ph), 4.66 (2H, m, CH), 4.60 (1H, m, CH), 3.10 (4H, m, CH_2), 1.49 (3H, m, CH_3); ^13^CNMR(125MHz, DMSO-d_6) δ 172.9, 142.3, 136.7, 130.1, 127.7, 127.5, 127.2, 122.9, 122.2, 120.1, 119.2, 119.0, 111.3, 111.1, 110.9, 68.5, 54.6, 48.7, 31.4, 30.7, 20.5; ESIMS m/z 552 (M+1); Anal. Calcd for C_{32}H_{33}N_{5}O_{4}: C, 69.67; H, 6.03; N, 12.70. Found: C, 69.88; H, 6.17; N, 12.91.

**Trp-Trp-Asp(OBzl)-OBzl** Using the same procedure as described for Trp-Trp-Tyr-OBzl from Boc-Trp-Trp-Asp(OBzl)-OBzl (500 mg, 0.64 mmol) the title compound was obtained as colorless powder
(450 mg, 0.63 mmol, 98% yield). mp 210-212 °C. [α]_D^{20} + 10.03 (c 1.2 in MeOH); ¹H NMR (500 MHz, DMSO-d₆): δ 10.98 (2H, m, N-H), 8.77 (1H, d, J = 7.9 Hz, N-H), 7.72 (1H, d, J = 7.3 Hz, N-H), 7.30 (20H, m, Ar-H), 5.08 (4H, m, CH₂Ph), 4.65 (2H, m, CH), 3.36 (1H, m, CH), 3.17 (4H, m, CH₂), 2.92 (2H, m, CH₂); ¹³C NMR (125 MHz, DMSO-d₆) δ 173.4, 172.9, 142.3, 141.1, 136.8, 130.2, 129.1, 127.8, 127.6, 127.3, 122.9, 122.2, 120.1, 119.2, 119.0, 111.3, 111.1, 110.9, 68.7, 54.5, 49.3, 41.0, 31.3, 30.2; ESIMS m/z 686 (M+1); Anal. Calcd for C₄₀H₃₉N₅O₆: C, 70.06; H, 5.73; N, 10.21. Found: C, 70.25; H, 5.90; N, 10.43.

**Trp-Trp-Pro-OBzl** Using the same procedure as described for Trp-Trp-Tyr-OBzl from Boc-Trp-Trp-Pro-OBzl (500 mg, 0.74 mmol) the title compound was obtained as colorless powder (451 mg, 0.73 mmol, 99% yield). mp 182-184 °C. [α]_D^{20} + 16.73 (c 1.3 in MeOH); ¹H NMR (500 MHz, DMSO-d₆): δ 10.92 (1H, s, N-H), 10.87 (1H, s, N-H), 8.73 (2H, m, N-H), 7.64 (1H, d, J = 7.9 Hz, Ar-H), 7.50 (1H, d, J = 7.9 Hz, Ar-H), 7.18 (13H, m, Ar-H), 5.06 (2H, m, CH₂Ph), 4.66 (2H, m, CH), 4.08 (1H, m, CH), 3.16 (6H, m, CH₂), 1.79 (4H, m, CH₂); ¹³C NMR (125 MHz, DMSO-d₆) δ 172.7, 142.2, 136.6, 130.1, 127.8, 127.5, 127.2, 122.9, 122.2, 120.1, 119.2, 119.0, 111.3, 111.1, 110.9, 68.7, 60.5, 54.8, 45.7, 32.3, 31.2, 30.6, 24.9; ESIMS m/z 578 (M+1); Anal. Calcd for C₃₄H₃₅N₅O₄: C, 70.69; H, 6.11; N, 12.12. Found: C, 70.90; H, 6.27; N, 12.34.

**Trp-Trp-Gly-OBzl** Using the same procedure as described for Trp-Trp-Tyr-OBzl from Boc-Trp-Trp-Gly-OBzl (500 mg, 0.79 mmol) the title compound was obtained as colorless powder (446 mg, 0.78 mmol, 99% yield). mp 201-203 °C. [α]_D^{20} + 8.23 (c 1.2 in MeOH); ¹H NMR (500 MHz, DMSO-d₆): δ 10.96 (1H, s, N-H), 10.90 (1H, s, N-H), 8.80 (1H, d, J = 7.3 Hz, N-H), 8.67 (1H, d, J = 8.3 Hz, N-H), 7.60 (1H, d, J = 7.9 Hz, Ar-H), 7.52 (1H, d, J = 7.9 Hz, Ar-H), 7.17 (13H, m, Ar-H), 5.05 (2H, m, CH₂Ph), 4.70 (2H, m, CH), 3.16 (6H, m, CH₂); ¹³C NMR (125 MHz, DMSO-d₆) δ 172.9, 142.2, 136.7,
130.2, 127.7, 127.5, 127.2, 122.9, 122.2, 120.1, 119.2, 119.0, 111.3, 111.1, 110.9, 68.5, 54.6, 48.8, 43.1, 31.4, 30.6; ESIMS m/z 538 (M+1); Anal. Calcd for C$_{31}$H$_{31}$N$_5$O$_4$: C, 69.26; H, 5.81; N, 13.30. Found: C, 69.27; H, 5.95; N, 13.52.

Trp-Trp-Trp-OBzl Using the same procedure as described for Trp-Trp-Tyr-OBzl from Boc-Trp-Trp-Trp-OBzl (500 mg, 0.65 mmol) the title compound was obtained as colorless powder (416mg, 0.59 mmol, 91% yield). mp 212-214 °C. [α]$_{D}^{20}$ + 6.73 (c 1.2 in MeOH); $^1$HNMR (500 MHz, DMSO-$d_6$): δ 11.10 (3H, m, N-H), 8.03 (2H, m, N-H), 7.39 (20H, m, Ar-H), 4.57 (6H, m, CH, CH$_2$Ph), 3.43 (6H, m, CH$_2$); $^{13}$CNMR(125MHz, DMSO-$d_6$) δ 172.8, 142.2, 136.7, 136.3, 130.1, 127.7, 127.5, 127.2, 122.9, 122.2, 120.1, 119.2, 119.0, 111.3, 111.1, 110.9, 68.5, 55.0, 54.7, 34.1, 31.3, 30.7; ESIMS m/z 667 (M+1); Anal. Calcd for C$_{40}$H$_{38}$N$_6$O$_4$: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.86; H, 5.60; N, 12.82.

Trp-Trp-Phe-OBzl Using the same procedure as described for Trp-Trp-Tyr-OBzl from Boc-Trp-Trp-Phe-OBzl (500 mg, 0.69 mmol) the title compound was obtained as colorless powder (432mg, 0.67 mmol, 97% yield). mp 199-201 °C. [α]$_{D}^{20}$ + 11.23 (c 1.1 in MeOH); $^1$HNMR (500 MHz, DMSO-$d_6$): δ 10.98 (2H, m, N-H), 8.98 (1H, d, $J$ = 8.0 Hz, N-H), 8.82 (1H, d, $J$ = 7.2 Hz, N-H), 7.64 (1H, d, $J$ = 7.9 Hz, Ar-H), 7.53 (1H, d, $J$ = 11.4 Hz, Ar-H), 7.19 (18H, m, Ar-H), 5.03 (2H, m, CH$_2$Ph), 4.68 (2H, m, CH), 4.41 (1H, m, CH), 3.10 (6H, m, CH$_2$); $^{13}$CNMR(125MHz, DMSO-$d_6$) δ 172.9, 142.2, 139.6, 136.7, 130.0, 128.6, 127.8, 127.5, 127.2, 126.1, 122.9, 122.2, 120.1, 119.2, 119.0, 111.3, 111.1, 110.9, 68.6, 54.6, 53.7, 40.6, 31.2, 30.6; ESIMS m/z 628 (M+1); Anal. Calcd for C$_{38}$H$_{37}$N$_5$O$_4$: C, 72.05; H, 5.94; N, 11.16. Found: C, 72.50; H, 5.80; N, 11.39.

Trp-Trp-Ser-OBzl Using the same procedure as described for Trp-Trp-Tyr-OBzl from Boc-Trp-Trp-Ser-OBzl (500 mg, 0.75 mmol) the title compound was obtained as colorless powder (440 mg, 0.73 mmol, 97% yield). mp 218-220 °C. [α]$_{D}^{20}$ + 25.37 (c 1.3 in MeOH); $^1$HNMR (500 MHz, DMSO-$d_6$): δ
10.93 (2H, m, N-H), 8.72 (2H, m, N-H), 7.28 (15H, m, Ar-H), 5.09 (2H, m, CH₂Ph), 4.61 (2H, m, CH), 4.08 (2H, m, CH₂), 3.46 (1H, m, CH), 3.13 (4H, m, CH₂); ¹³C NMR (125 MHz, DMSO- d₆) δ 172.7, 142.1, 136.8, 130.1, 127.6, 127.5, 127.1, 122.9, 122.2, 120.1, 119.2, 119.0, 111.4, 111.1, 110.9, 68.6, 64.1, 56.8, 54.7, 31.4, 30.6; ESI MS m/z 568 (M+1); Anal. Calcd for C₃₂H₂₃N₅O₅: C, 67.71; H, 5.86; N, 12.34. Found: C, 67.50; H, 5.71; N, 12.11.

Trp-Trp-Met-OBzl Using the same procedure as described for Trp-Trp-Tyr-OBzl from Boc-Trp-Trp-Met-OBzl (500 mg, 0.70 mmol) the title compound was obtained as colorless powder (448 mg, 0.69 mmol, 98% yield). mp 215-217 °C. [α]D²₀ + 7.77 (c 1.4 in MeOH); ¹H NMR (500 MHz, DMSO- d₆): δ 10.96 (2H, m, N-H), 8.79 (1H, d, J = 7.3 Hz, N-H), 8.71 (1H, d, J = 7.9 Hz, N-H), 7.72 (1H, d, J = 7.8 Hz, Ar-H), 7.67 (1H, d, J = 7.8 Hz, Ar-H), 7.19 (13H, m, Ar-H), 5.03 (2H, m, CH₂Ph), 4.71 (1H, dd, J = 14.2 Hz, J = 7.3 Hz, CH), 4.63 (1H, dd, J = 14.2 Hz, J = 7.3 Hz, CH), 3.19 (5H, m, CH, CH₂), 2.03 (3H, m, CH₃), 1.62 (4H, m, CH₂); ¹³C NMR (125 MHz, DMSO- d₆) δ 172.9, 142.0, 136.9, 130.2, 127.7, 127.5, 127.2, 122.9, 122.2, 120.1, 119.2, 119.0, 111.3, 111.1, 110.8, 68.5, 54.9, 53.2, 34.5, 31.4, 30.6, 29.5, 17.8; ESI MS m/z 612 (M+1); Anal. Calcd for C₃₄H₃₇N₅O₄S: C, 66.75; H, 6.10; N, 11.45. Found: C, 66.94; H, 6.25; N, 11.23.

Trp-Trp-Leu-OBzl Using the same procedure as described for Trp-Trp-Tyr-OBzl from Boc-Trp-Trp-Leu-OBzl (500 mg, 0.72 mmol) the title compound was obtained as colorless powder (450 mg, 0.71 mmol, 99% yield). mp 222-224 °C. [α]D²₀ + 15.76 (c 1.3 in MeOH); ¹H NMR (500 MHz, DMSO- d₆): δ 10.92 (2H, m, N-H), 8.76 (1H, d, J = 8.1 Hz, N-H), 8.71 (1H, d, J = 7.2 Hz, N-H), 7.64 (1H, d, J = 7.9 Hz, Ar-H), 7.50 (1H, d, J = 7.9 Hz, Ar-H), 7.16 (13H, m, Ar-H), 6.85 (2H, s, N-H), 5.02 (2H, m, CH₂Ph), 4.63 (2H, m, CH), 3.75 (1H, m, CH), 3.15 (4H, m, CH₂), 2.01 (2H, m, CH₂), 1.59 (1H, m, CH), 0.89 (6H, m, CH₃); ¹³C NMR (125 MHz, DMSO- d₆) δ 172.9, 142.2, 136.8, 130.1, 127.8, 127.5, 127.1,
ESIMS m/z 594 (M+1); Anal. Calcd for C$_{35}$H$_{49}$N$_{5}$O$_{4}$: C, 70.80; H, 6.62; N, 11.80. Found: C, 70.98; H, 6.77; N, 12.03.

II. NMR Spectra
Figure S1  $^1$H NMR spectrum of compound 5 in DMSO-$d_6$ recorded at 25 °C
Figure S2. $^{13}$C NMR spectrum of compound 5 in DMSO-$d_6$ recorded at 25 °C.
Figure S3 ¹H NMR spectrum of compound 7 in DMSO-\textit{d}_6 recorded at 25 °C
Figure S4  $^{13}$C NMR spectrum of compound 7 in DMSO-$d_6$ recorded at 25 °C
Figure S5 $^1$H NMR spectrum of compound 8 in DMSO-$d_6$ recorded at 25 $^\circ$C
Figure S6  $^{13}$C NMR spectrum of compound 8 in DMSO-$d_6$ recorded at 25 °C
Figure S7  $^1$H NMR spectrum of compound 9 in DMSO-$d_6$ recorded at 25 °C
Figure S8  $^{13}$C NMR spectrum of compound 9 in DMSO-$d_6$ recorded at 25 °C
Figure S9  $^1$H NMR spectrum of compound 10 in DMSO-$d_6$ recorded at 25 °C
Figure S10  $^{13}$C NMR spectrum of compound 10 in DMSO-$d_6$ recorded at 25 °C
Figure S11  $^1$H NMR spectrum of compound 11 in DMSO-$d_6$ recorded at 25 $^\circ$C
Figure S12  $^{13}$C NMR spectrum of compound 11 in DMSO-$d_6$ recorded at 25 °C
Figure S13  $^1$H NMR spectrum of compound 12 in DMSO-$d_6$ recorded at 25 °C
Figure S14  $^{13}$C NMR spectrum of compound 12 in DMSO-$d_6$ recorded at 25 °C
Figure S15 H-H Cosy spectrum of compound 12 in DMSO-$_d_6$ recorded at 25 °C.
Figure S16  HMQC spectrum of compound 12 in DMSO-$d_6$ recorded at 25 °C
Figure S17  HMBC spectrum of compound 12 in DMSO-$d_6$ recorded at 25 °C
Figure S18  $^1$H NMR spectrum of compound 13 in DMSO-$d_6$ recorded at 25 °C
Figure S19  $^{13}$C NMR spectrum of compound 13 in DMSO-$d_6$ recorded at 25 °C
Figure S20  $^1$H NMR spectrum of compound 14 in DMSO-$d_6$ recorded at 25 °C
Figure S21  $^{13}$C NMR spectrum of compound 14 in DMSO-$d_6$ recorded at 25 °C
Figure S22  $^1$H NMR spectrum of compound 15 in DMSO-$d_6$ recorded at 25 °C
Figure S23  $^{13}$C NMR spectrum of compound 15 in DMSO-$d_6$ recorded at 25 °C
Figure S24 $^1$H NMR spectrum of compound 16 in DMSO-$d_6$ recorded at 25 °C.
Figure S25  $^{13}$C NMR spectrum of compound 16 in DMSO-$d_6$ recorded at 25 °C
Figure S26  $^1$H NMR spectrum of compound 17 in DMSO-$d_6$ recorded at 25 °C
Figure S27  $^{13}$C NMR spectrum of compound 17 in DMSO-$d_6$ recorded at 25 °C
Figure S28: $^1$H NMR spectrum of compound 18 in DMSO-$d_6$ recorded at 25 °C
Figure S29  $^{13}$C NMR spectrum of compound 18 in DMSO-$d_6$ recorded at 25 °C
Figure S30  $^1$H NMR spectrum of compound 19 in DMSO-$d_6$ recorded at 25 °C
Figure S31 $^{13}$C NMR spectrum of compound 19 in DMSO-$d_6$ recorded at 25 °C.
Figure S32  $^1$H NMR spectrum of compound 20 in DMSO-$d_6$ recorded at 25 °C
Figure S33  $^{13}$C NMR spectrum of compound 20 in DMSO-$d_6$ recorded at 25 °C
Figure S34: $^1$H NMR spectrum of compound 21 in DMSO-$d_6$ recorded at 25 °C
Figure S35  $^{13}$C NMR spectrum of compound 21 in DMSO-$d_6$ recorded at 25 °C