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

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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. ¹HNMR (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, *J*₁ = 28.2 Hz, *J*₂ = 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. ¹HNMR (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 682 (M+1).

Boc-Trp-Trp-Lys(N^ω-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(N^ω-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. ¹HNMR (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 (641mg, 0.98 mmol, 98% yield). mp 202-204°C. ¹HNMR (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); ¹³CNMR(75MHz, 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. ¹HNMR (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); 0.82 (6H, m, CH₃); ¹³CNMR (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. $[\alpha]_{\text{D}}^{20} + 9.77$ (c 1.1 in MeOH); $^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$): 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, CH_2Ph), 4.70 (2H, m, CH), 3.90 (1H, m, CH), 3.04 (6H, m, CH_2); $^{13}\text{C NMR}$ (125 MHz, $\text{DMSO-}d_6$) 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 $\text{C}_{38}\text{H}_{37}\text{N}_5\text{O}_5$: 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. $[\alpha]_{\text{D}}^{20} + 20.17$ (c 1.1 in MeOH); $^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$): 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, CH_2Ph), 4.68 (2H, m, CH), 3.82 (1H, m, CH), 3.07 (4H, m, CH_2), 2.56 (2H, m, CH_2), 2.06 (2H, m, CH_2); $^{13}\text{C NMR}$ (125 MHz, $\text{DMSO-}d_6$) 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 $\text{C}_{41}\text{H}_{41}\text{N}_5\text{O}_6$: 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. $[\alpha]_{\text{D}}^{20} + 6.10$ (c 1.2 in MeOH); $^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ 10.97 (2H, m, N-H), 7.32 (15H, m, Ar-H), 5.07 (2H, m, CH_2Ph), 4.66 (2H, m, CH), 3.62 (1H, m, CH),

3.40 (1H, m, CH), 3.13 (4H, m, CH₂), 1.15 (3H, m, CH₃); ¹³CNMR(125MHz, DMSO-*d*₆) 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 C₃₃H₃₅N₅O₅: C, 68.14; H, 6.07; N, 12.04. Found: C, 68.35; H, 6.22; N, 12.25.

Trp-Trp-Lys(N^ω-Z)-OBzl Using the same procedure as described for Trp-Trp-Tyr-OBzl from Boc-Trp-Trp-Lys(N^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]_D²⁰ +14.77 (c 1.2 in MeOH); ¹HNMR (500 MHz, DMSO-*d*₆): 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, CH₂); ¹³CNMR(125MHz, DMSO-*d*₆) 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]_D²⁰ +13.43 (c 1.4 in MeOH); ¹HNMR (500 MHz, DMSO-*d*₆): 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, *J*₁ = 13.5 Hz, *J*₂ = 5.4 Hz, CH), 4.62 (1H, dd, *J*₁ = 14.3 Hz, *J*₂ = 7.1 Hz, CH), 3.61 (1H, m, CH), 3.17 (4H, m, CH₂), 2.07 (1H, m, CH), 0.90 (6H, m, CH₃); ¹³CNMR(125MHz, DMSO-*d*₆) 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 $C_{34}H_{37}N_5O_4$: 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. $[\alpha]_D^{20} +17.00$ (c 1.2 in MeOH); $^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$): 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); $^{13}\text{C NMR}$ (125MHz, $\text{DMSO-}d_6$) 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 $C_{35}H_{39}N_5O_4$: 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. $[\alpha]_D^{20} +11.03$ (c 1.0 in MeOH); $^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$): 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); $^{13}\text{C NMR}$ (125MHz, $\text{DMSO-}d_6$) 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 $C_{32}H_{33}N_5O_4$: 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. $[\alpha]_{\text{D}}^{20} + 10.03$ (c 1.2 in MeOH); $^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$): 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, CH_2Ph), 4.65 (2H, m, CH), 3.36 (1H, m, CH), 3.17 (4H, m, CH_2), 2.92 (2H, m, CH_2); $^{13}\text{C NMR}$ (125 MHz, $\text{DMSO-}d_6$) 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 $\text{C}_{40}\text{H}_{39}\text{N}_5\text{O}_6$: 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. $[\alpha]_{\text{D}}^{20} + 16.73$ (c 1.3 in MeOH); $^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$): 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, CH_2Ph), 4.66 (2H, m, CH), 4.08 (1H, m, CH), 3.16 (6H, m, CH_2), 1.79 (4H, m, CH_2); $^{13}\text{C NMR}$ (125 MHz, $\text{DMSO-}d_6$) 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 $\text{C}_{34}\text{H}_{35}\text{N}_5\text{O}_4$: 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. $[\alpha]_{\text{D}}^{20} + 8.23$ (c 1.2 in MeOH); $^1\text{H NMR}$ (500 MHz, $\text{DMSO-}d_6$): 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, CH_2Ph), 4.70 (2H, m, CH), 3.16 (6H, m, CH_2); $^{13}\text{C NMR}$ (125 MHz, $\text{DMSO-}d_6$) 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 $C_{31}H_{31}N_5O_4$: 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. $[\alpha]_D^{20} + 6.73$ (c 1.2 in MeOH); $^1\text{HNMR}$ (500 MHz, $\text{DMSO-}d_6$): 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_2Ph), 3.43 (6H, m, CH_2); $^{13}\text{CNMR}$ (125MHz, $\text{DMSO-}d_6$) 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 $C_{40}H_{38}N_6O_4$: 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. $[\alpha]_D^{20} + 11.23$ (c 1.1 in MeOH); $^1\text{HNMR}$ (500 MHz, $\text{DMSO-}d_6$): 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_2Ph), 4.68 (2H, m, CH), 4.41 (1H, m, CH), 3.10 (6H, m, CH_2); $^{13}\text{CNMR}$ (125MHz, $\text{DMSO-}d_6$) 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 $C_{38}H_{37}N_5O_4$: C, 72.71; 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. $[\alpha]_D^{20} + 25.37$ (c 1.3 in MeOH); $^1\text{HNMR}$ (500 MHz, $\text{DMSO-}d_6$): 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); ¹³CNMR(125MHz, DMSO-*d*₆) 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; ESIMS *m/z* 568 (M+1); Anal. Calcd for C₃₂H₃₃N₅O₅: 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); ¹HNMR (500 MHz, DMSO-*d*₆): 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*₁ = 14.2 Hz, *J*₂ = 7.3 Hz, CH), 4.63 (1H, dd, *J*₁ = 14.2 Hz, *J*₂ = 7.3 Hz, CH), 3.19 (5H, m, CH, CH₂), 2.03 (3H, m, CH₃), 1.62 (4H, m, CH₂); ¹³CNMR(125MHz, DMSO-*d*₆) 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, 68.6, 54.9, 53.2, 34.5, 31.4, 30.6, 29.5, 17.8; ESIMS *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); ¹HNMR (500 MHz, DMSO-*d*₆): 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); ¹³CNMR(125MHz, DMSO-*d*₆) δ 172.9, 142.2, 136.8, 130.1, 127.8, 127.5, 127.1,

122.9, 122.2, 120.1, 119.2, 119.0, 111.3, 111.1, 110.9, 68.6, 54.8, 51.3, 43.6, 31.3, 30.6, 22.6, 22.0;

ESIMS m/z 594 (M+1); Anal. Calcd for $C_{35}H_{39}N_5O_4$: C, 70.80; H, 6.62; N, 11.80. Found: C, 70.98; H, 6.77; N, 12.03.

II. NMR Spectra

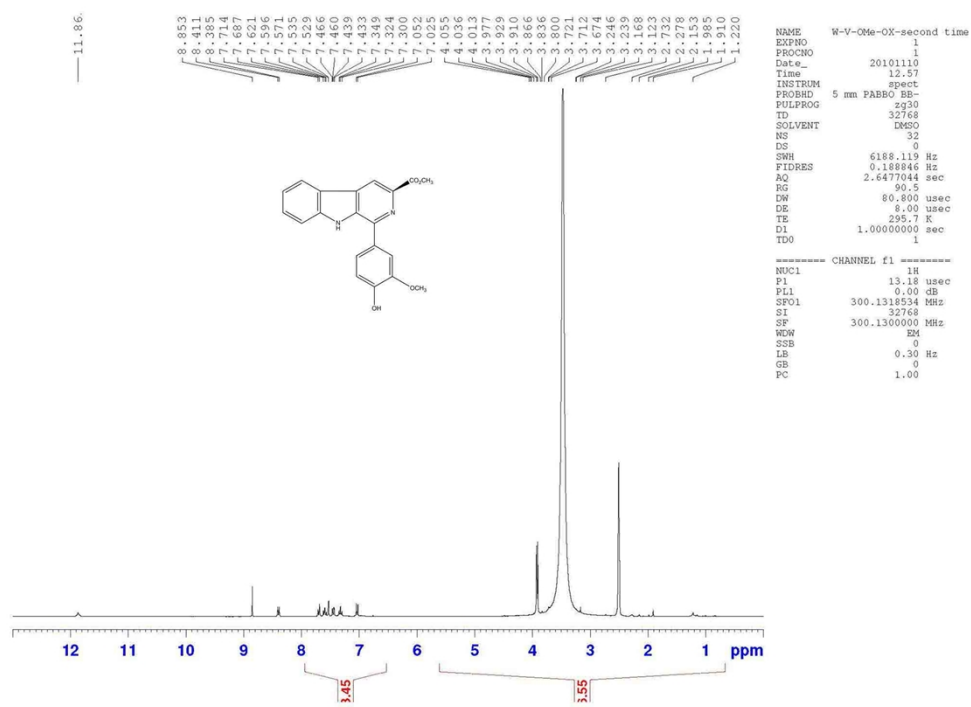


Figure S1 ^1H NMR spectrum of compound **5** in $\text{DMSO-}d_6$ recorded at 25°C

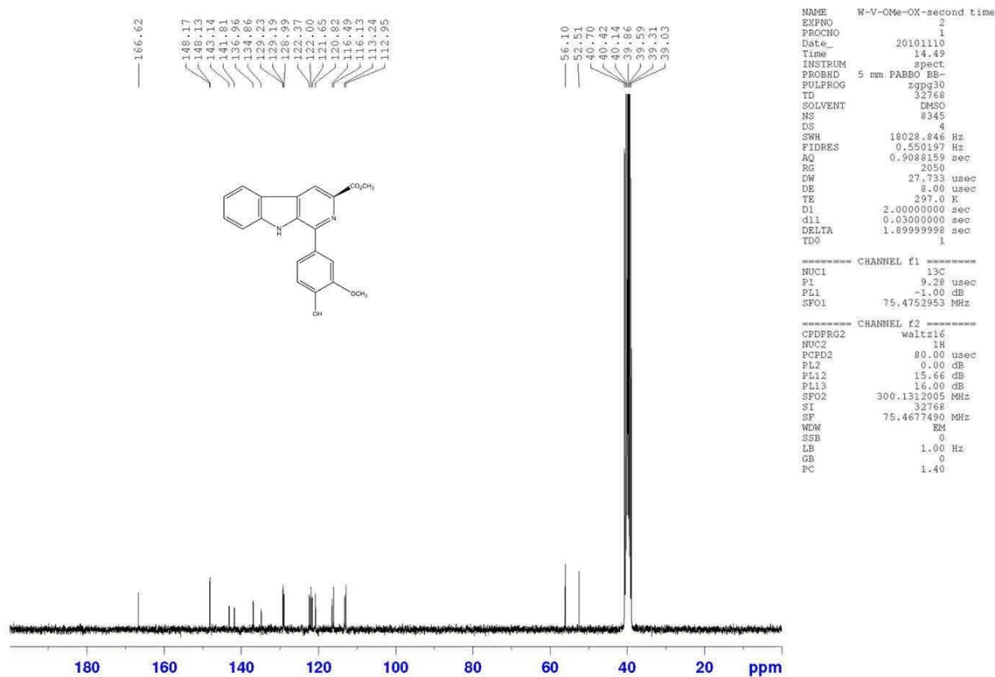


Figure S2 ^{13}C NMR spectrum of compound **5** in $\text{DMSO-}d_6$ recorded at 25 $^{\circ}\text{C}$

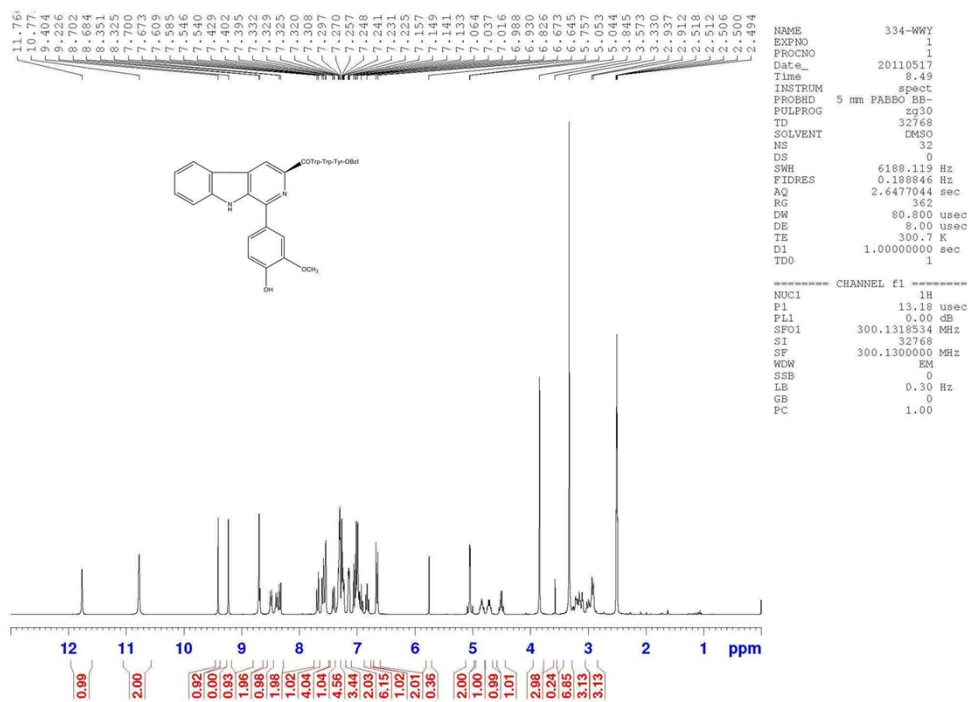


Figure S3 ¹H NMR spectrum of compound 7 in DMSO-*d*₆ recorded at 25 °C

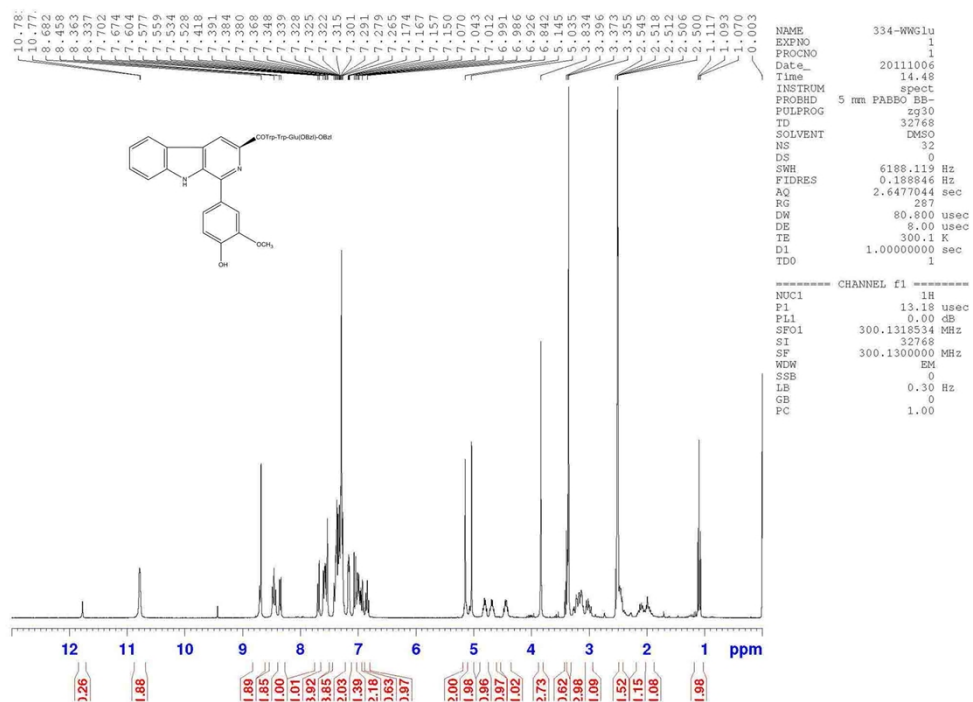


Figure S5 ¹H NMR spectrum of compound 8 in DMSO-*d*₆ recorded at 25 °C

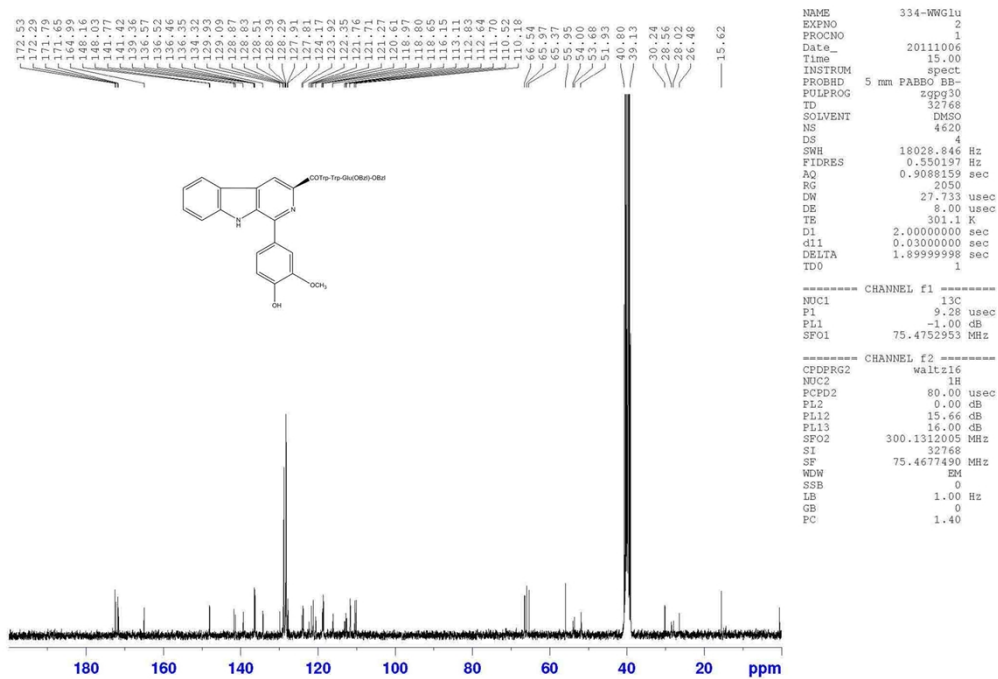


Figure S6 ^{13}C NMR spectrum of compound **8** in $\text{DMSO-}d_6$ recorded at 25 $^{\circ}\text{C}$

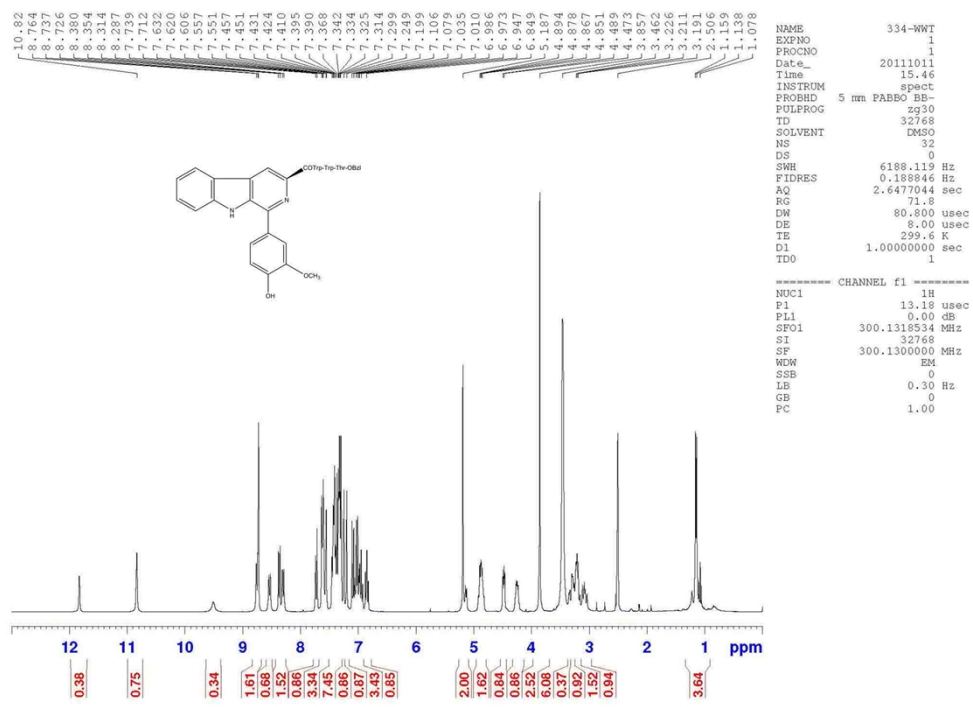


Figure S7 ^1H NMR spectrum of compound 9 in $\text{DMSO-}d_6$ recorded at 25°C

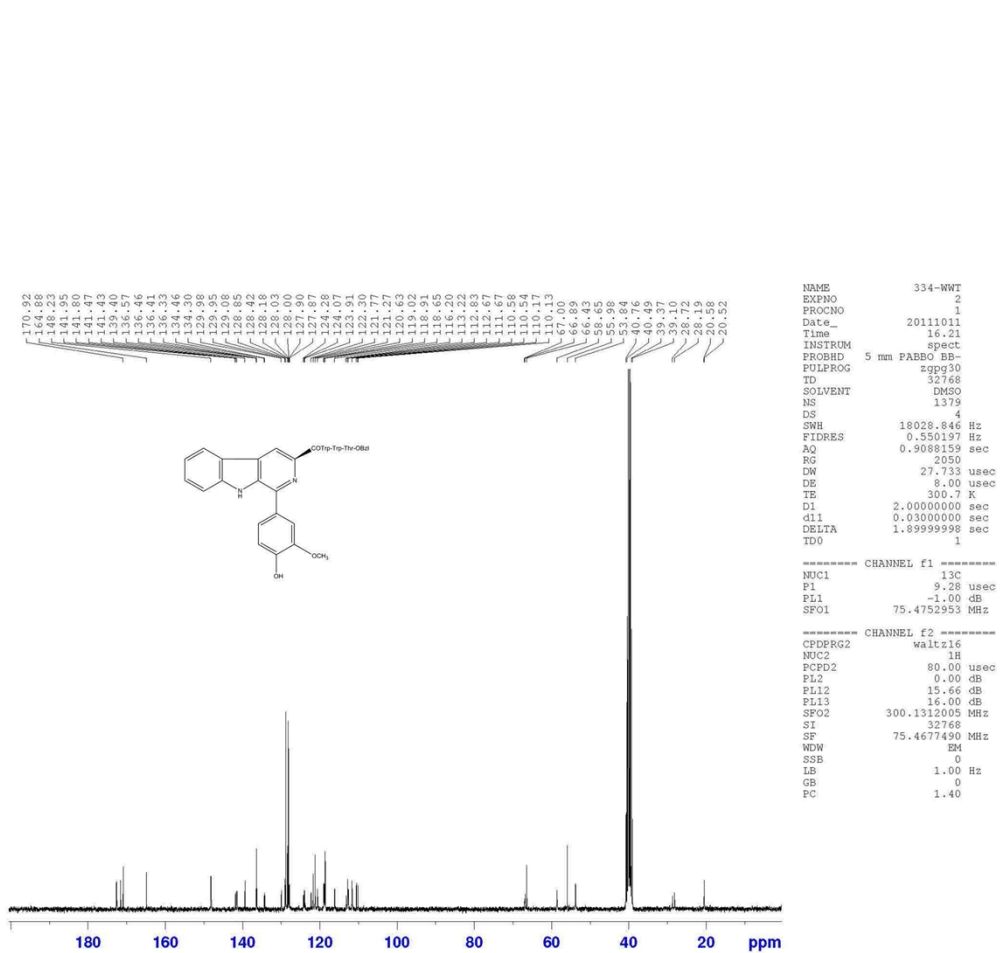


Figure S8 ^{13}C NMR spectrum of compound **9** in $\text{DMSO-}d_6$ recorded at $25\text{ }^\circ\text{C}$

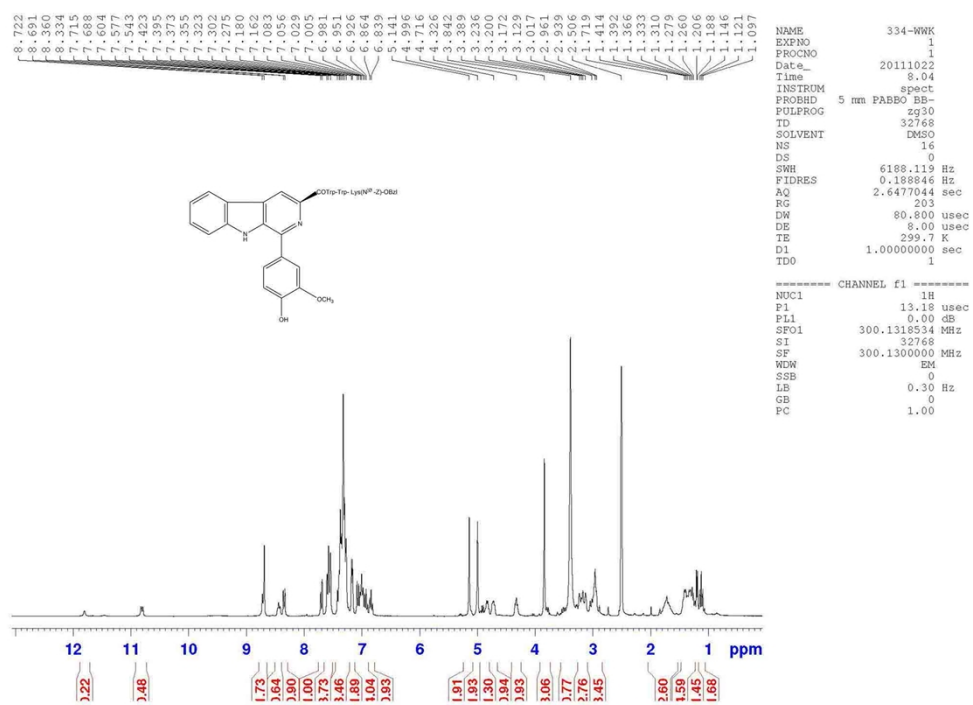


Figure S9 ¹H NMR spectrum of compound **10** in DMSO-*d*₆ recorded at 25 °C

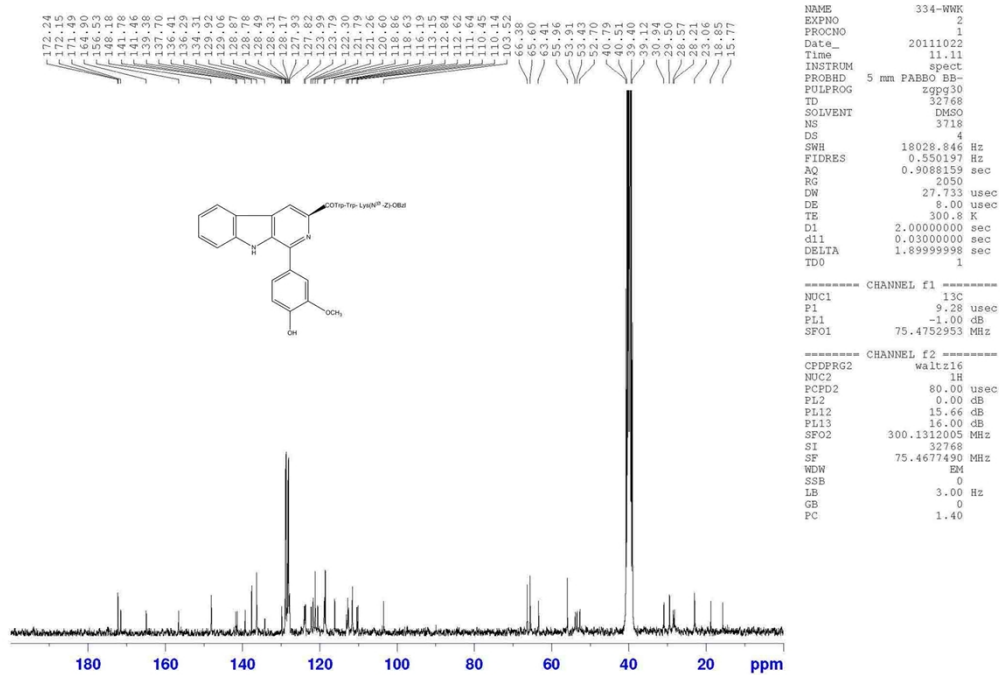


Figure S10 ^{13}C NMR spectrum of compound **10** in $\text{DMSO-}d_6$ recorded at $25\text{ }^\circ\text{C}$

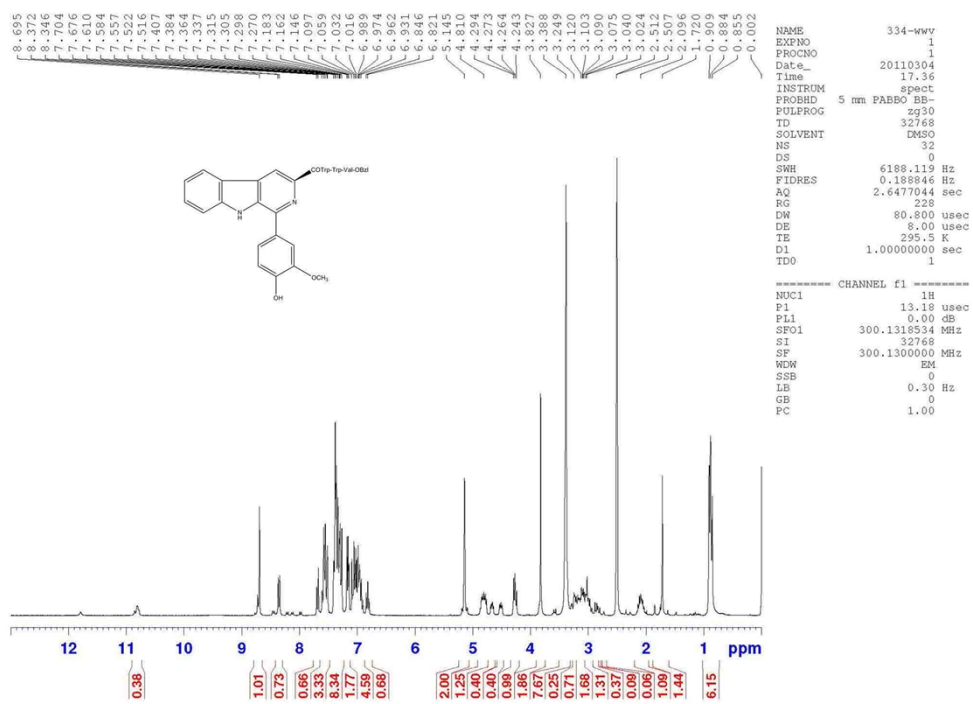


Figure S11 ^1H NMR spectrum of compound 11 in $\text{DMSO-}d_6$ recorded at 25°C

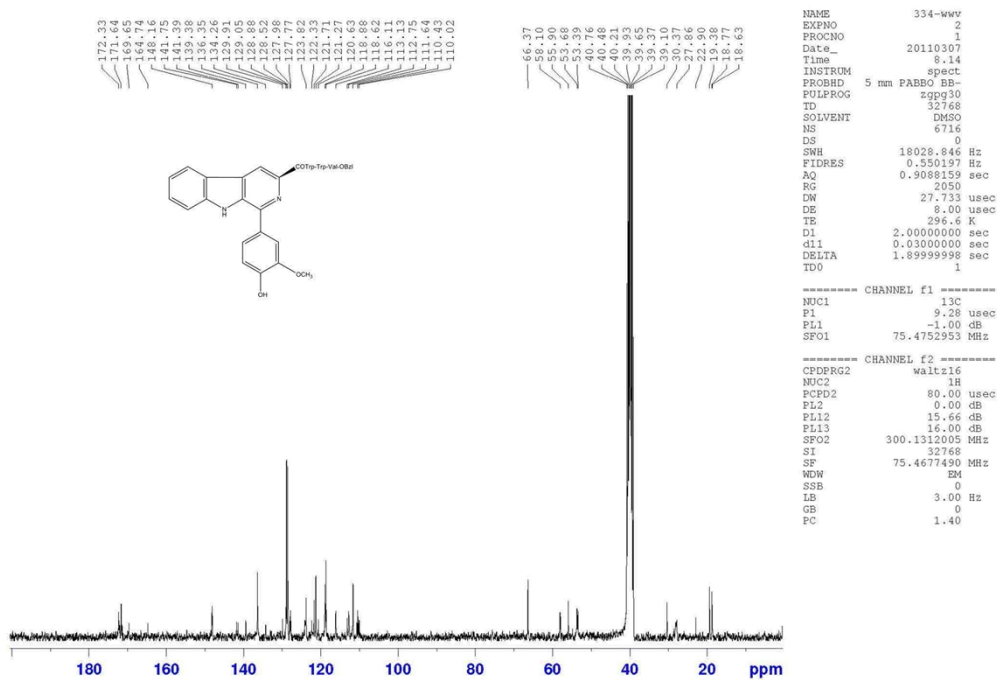


Figure S12 ^{13}C NMR spectrum of compound 11 in $\text{DMSO-}d_6$ recorded at 25 $^{\circ}\text{C}$

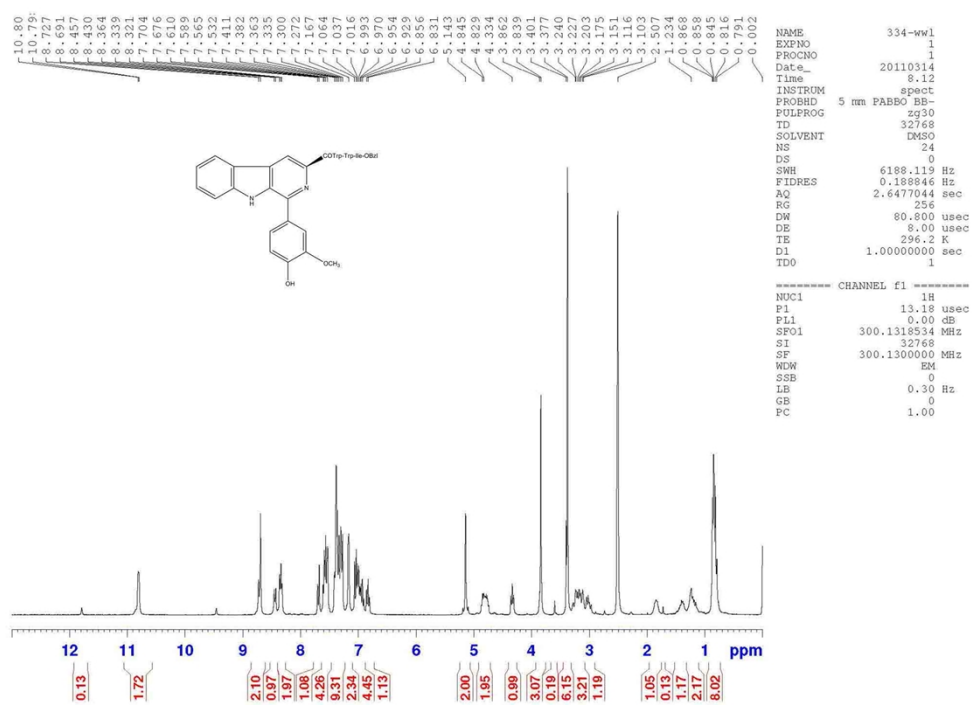


Figure S13 ^1H NMR spectrum of compound 12 in $\text{DMSO-}d_6$ recorded at 25°C

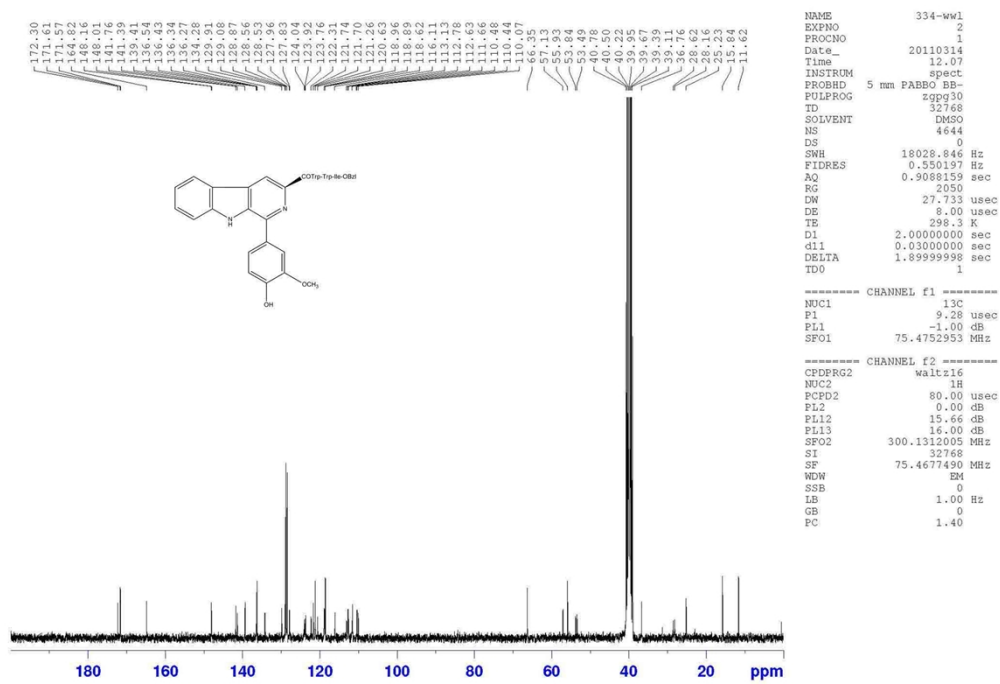
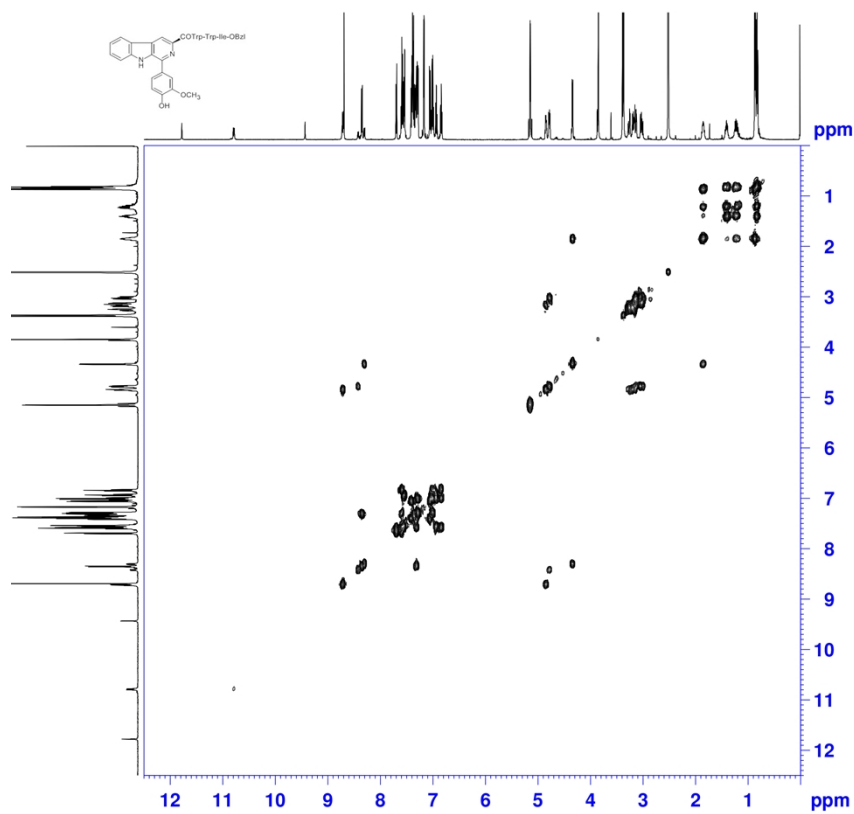


Figure S14 ^{13}C NMR spectrum of compound **12** in $\text{DMSO-}d_6$ recorded at 25 $^\circ\text{C}$



```

NAME          334-WWI
EXPNO         2
PROCNO        1
Date_         20110322
Time          9.57
INSTRUM       spect
PROBHD        5 mm PABBO BB-
PULPROG       cosygpmfqf
TD            1024
SOLVENT       DMSO
NS            8
DS            8
SWH           6684.492 Hz
FIDRES        6.527824 Hz
AQ            0.0766452 sec
RG            2050
DW            74.800 usec
DE            8.00 usec
TE            300.1 K
D0            0.00000300 sec
D1            2.00000000 sec
d13           0.00000400 sec
D16           0.00020000 sec
IN0           0.00014960 sec

===== CHANNEL f1 =====
NUC1          1H
P1            9.58 usec
PL1           -1.00 dB
SFO1          500.133069 MHz

===== GRADIENT CHANNEL =====
GPNAM1        SINE.100
GPNAM2        SINE.100
GPNAM3        SINE.100
GPZ1          16.00 %
GPZ2          12.00 %
GPZ3          40.00 %
F16           1000.00 usec
ND0           1
TD            128
SFO1          500.133 MHz
FIDRES        52.222595 Hz
SW            13.365 ppm
FnMODE        QF
SI            1024
SF            500.1300000 MHz
WDW           SINE
SSB           0
LB            0.00 Hz
GB            0
PC            1.40
SI            1024
MC2           QF
SF            500.1300000 MHz
WDW           SINE
SSB           0
LB            0.00 Hz
GB            0

```

Figure S15 H-H Cosy spectrum of compound **12** in DMSO-*d*₆ recorded at 25 °C

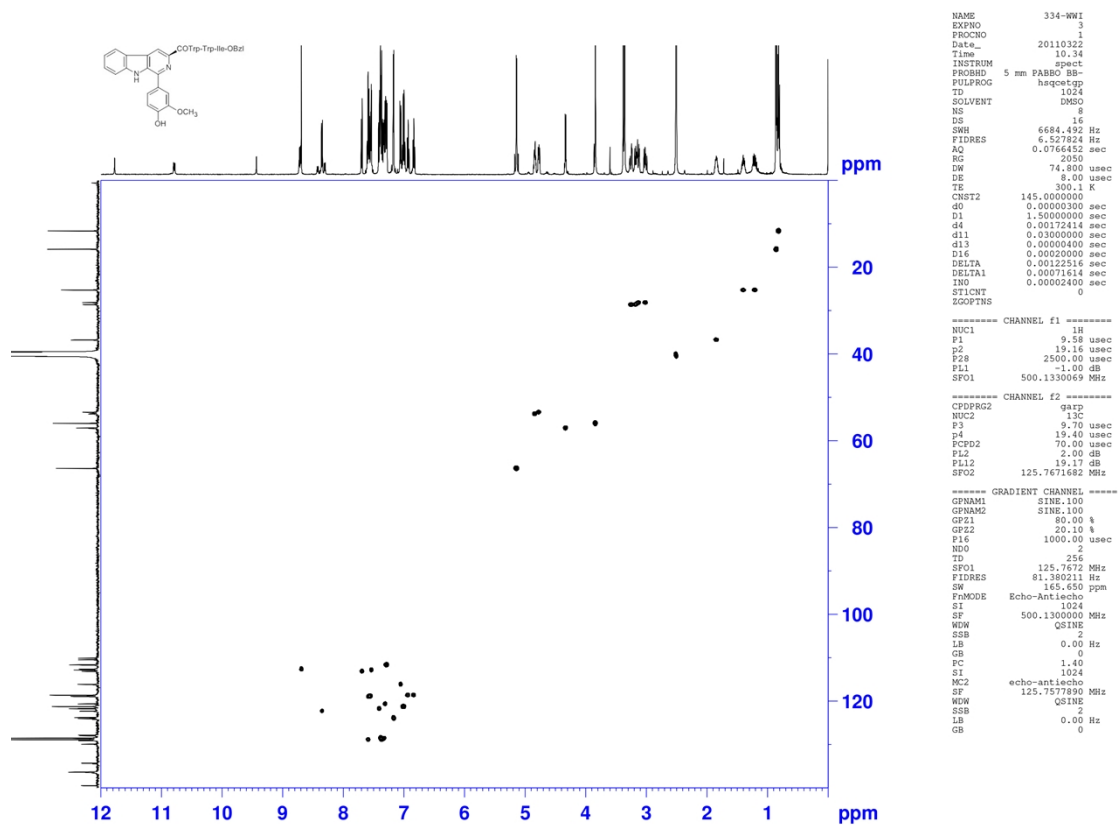


Figure S16 HMQC spectrum of compound **12** in DMSO-*d*₆ recorded at 25 °C

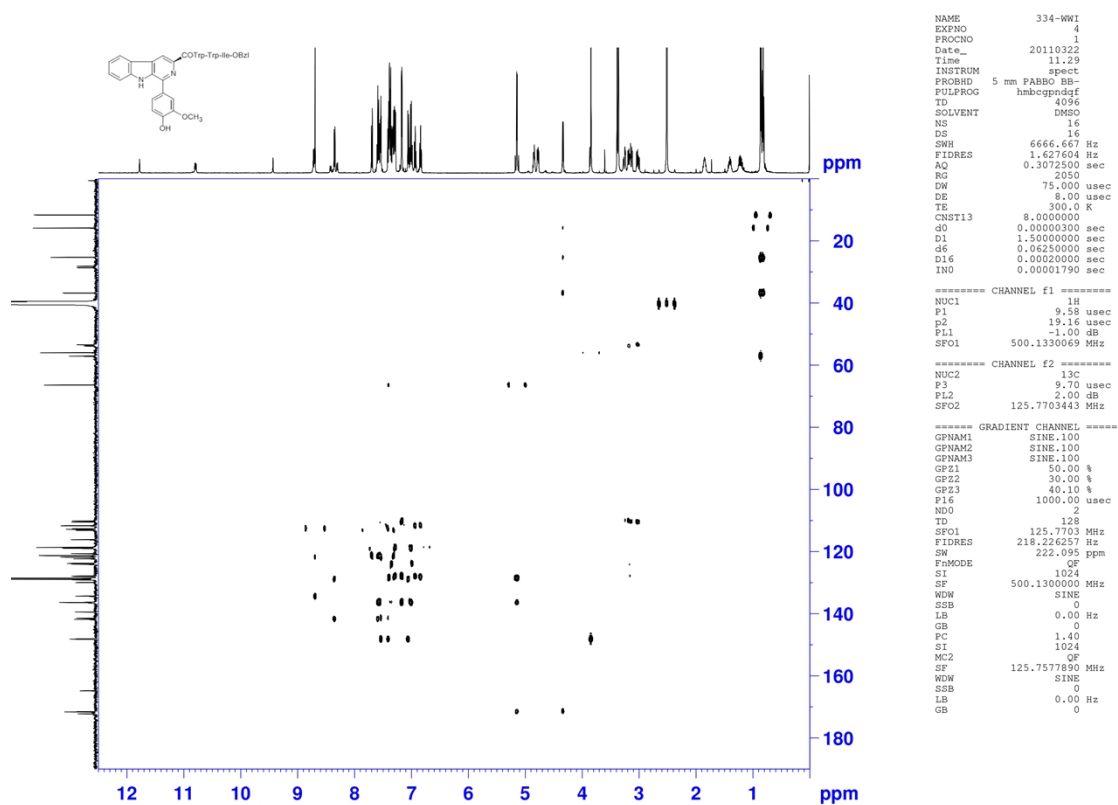


Figure S17 HMBC spectrum of compound **12** in DMSO-*d*₆ recorded at 25 °C

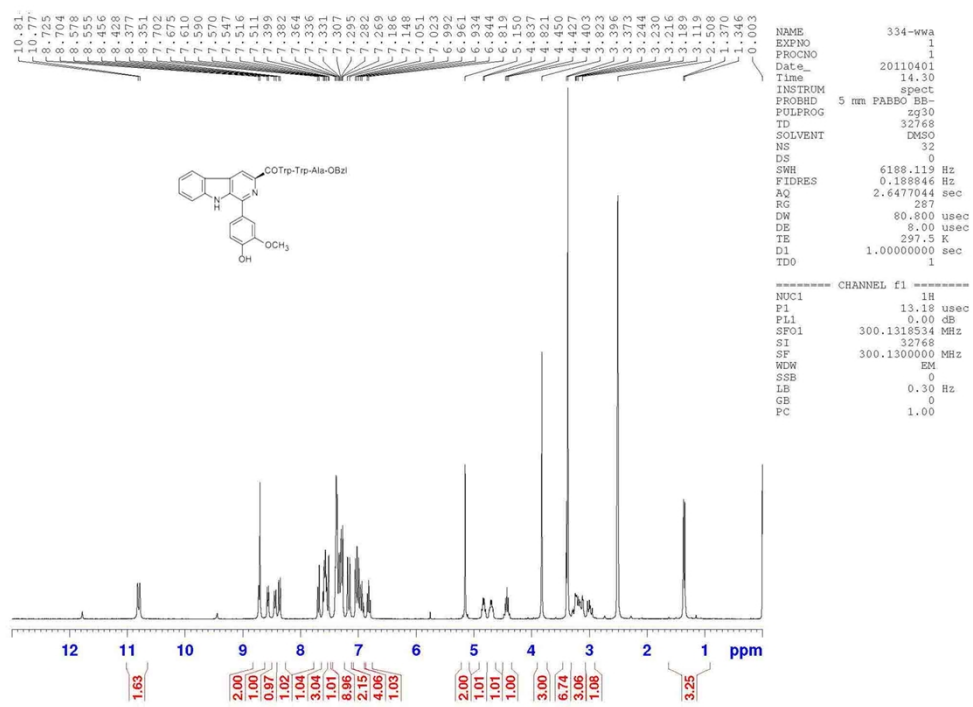


Figure S18 ^1H NMR spectrum of compound **13** in $\text{DMSO-}d_6$ recorded at 25 °C

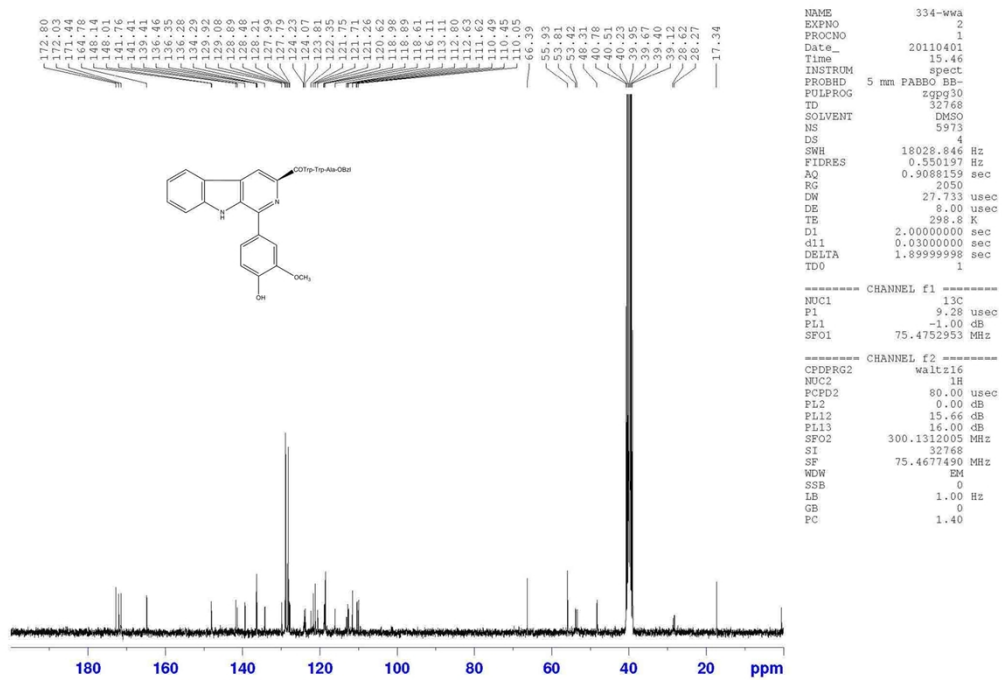


Figure S19 ^{13}C NMR spectrum of compound **13** in $\text{DMSO-}d_6$ recorded at 25°C

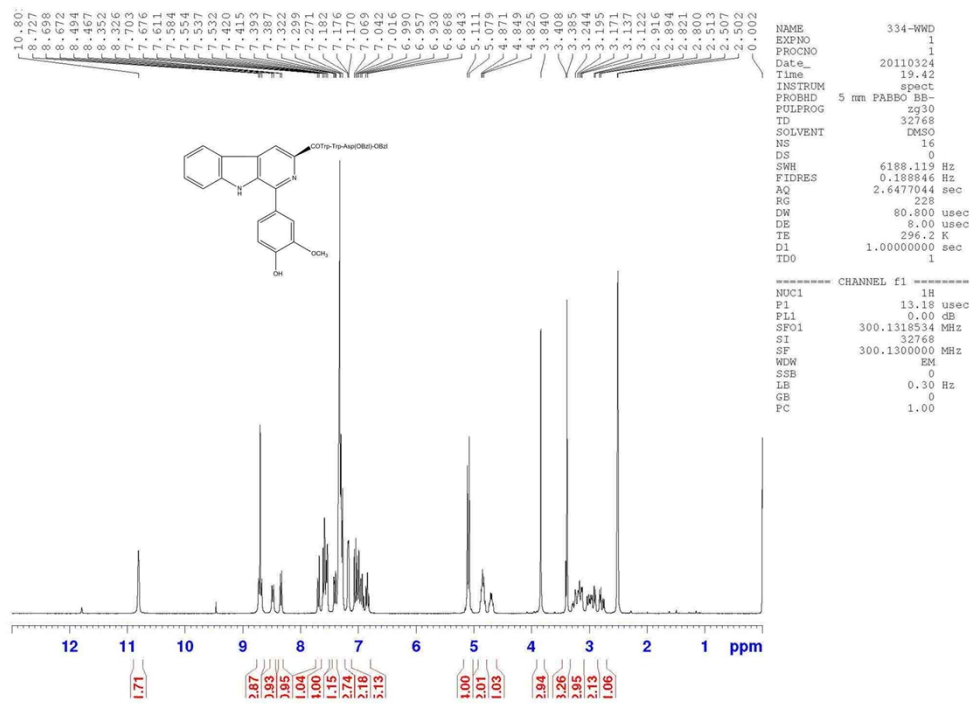


Figure S20 ¹H NMR spectrum of compound 14 in DMSO-*d*₆ recorded at 25 °C

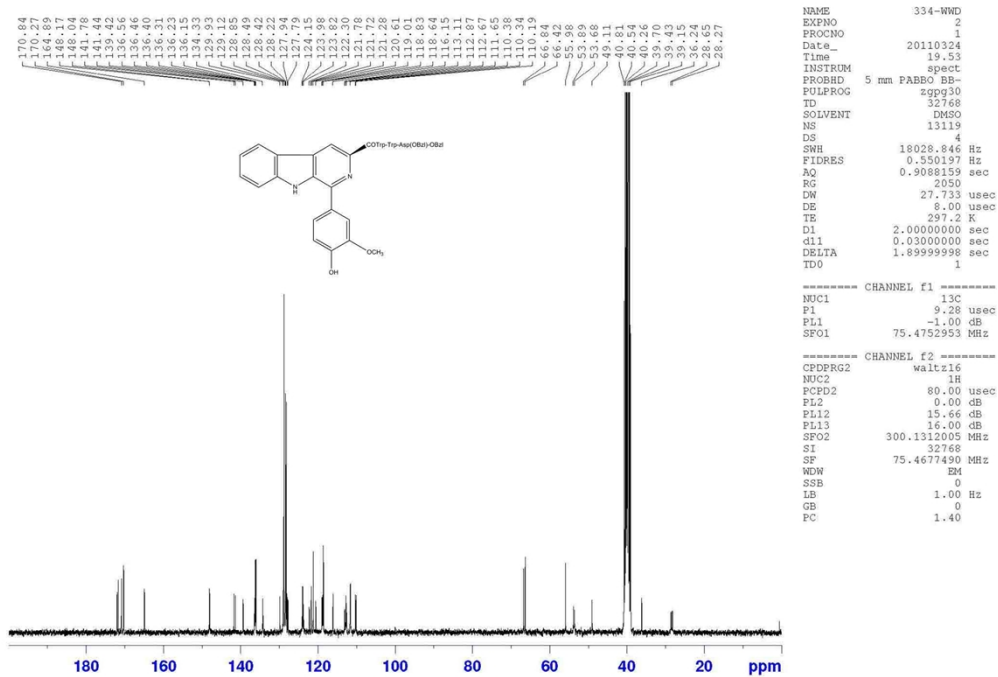


Figure S21 ^{13}C NMR spectrum of compound **14** in $\text{DMSO-}d_6$ recorded at 25°C

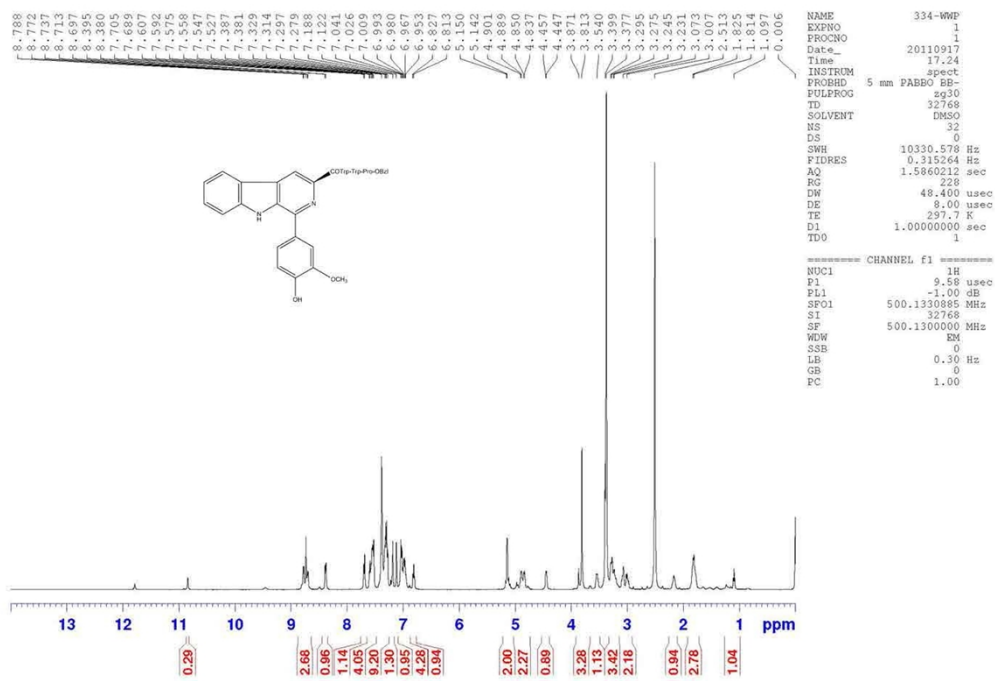


Figure S22 ¹H NMR spectrum of compound 15 in DMSO-*d*₆ recorded at 25 °C

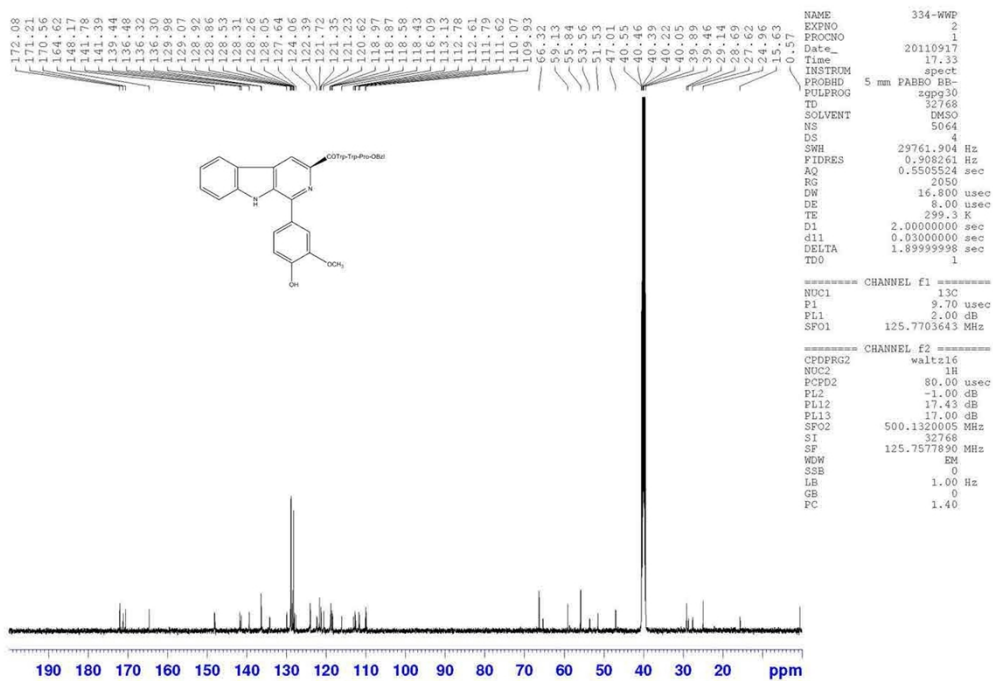


Figure S23 ¹³C NMR spectrum of compound 15 in DMSO-*d*₆ recorded at 25 °C

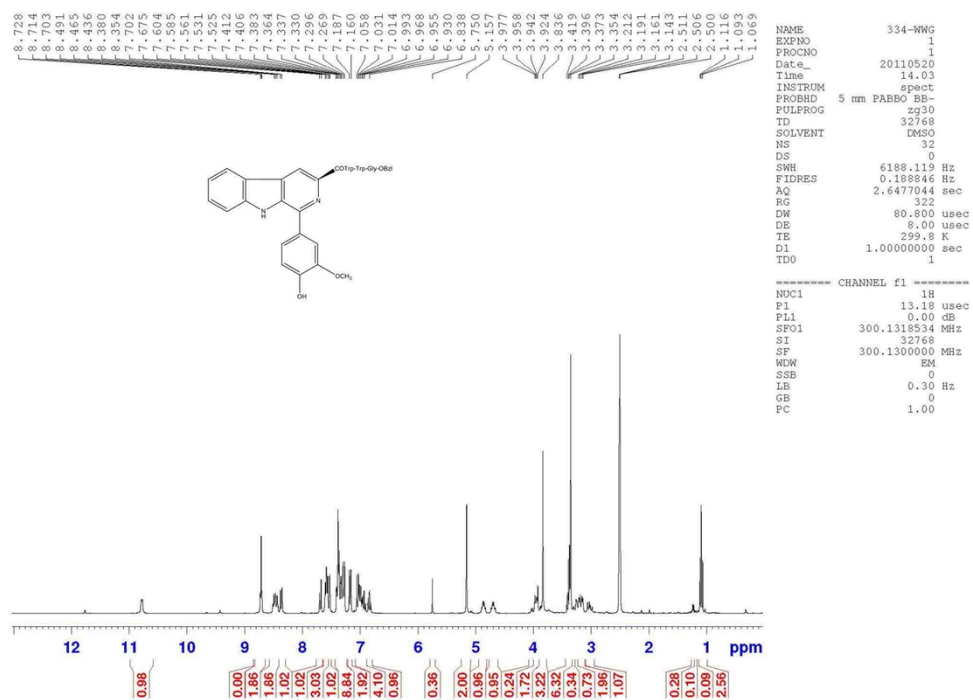


Figure S24 ^1H NMR spectrum of compound 16 in $\text{DMSO-}d_6$ recorded at 25°C

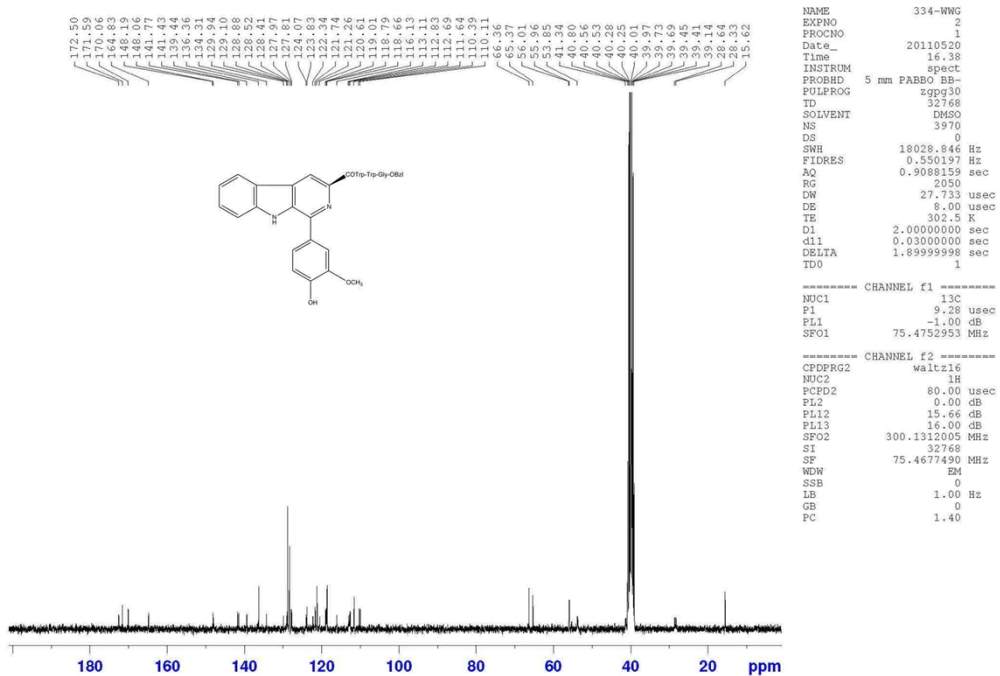


Figure S25 ¹³C NMR spectrum of compound 16 in DMSO-*d*₆ recorded at 25 °C

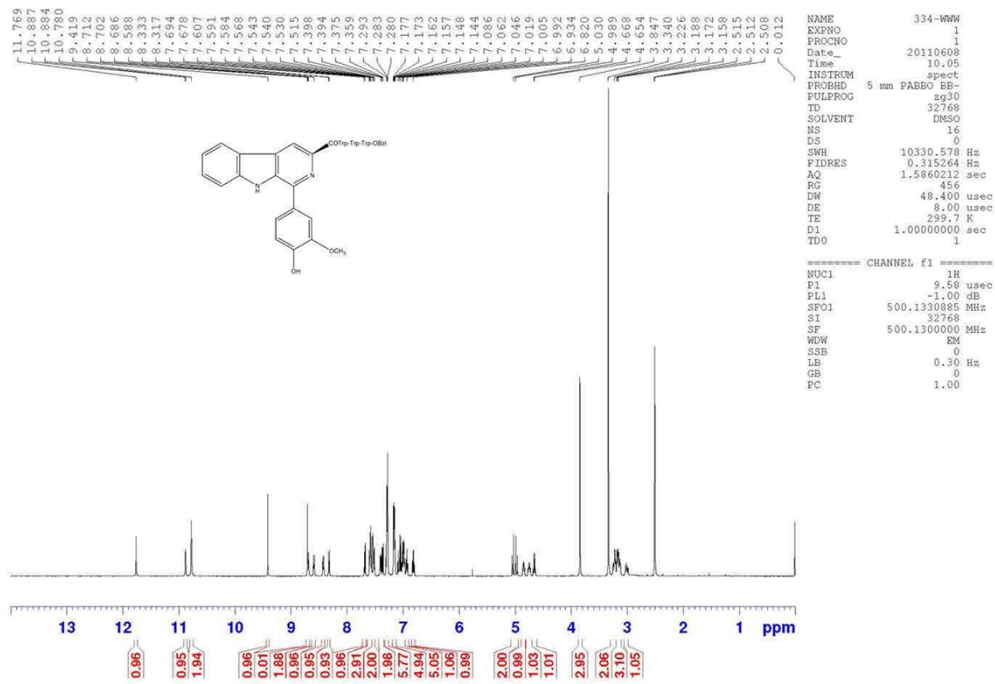


Figure S26 ^1H NMR spectrum of compound 17 in $\text{DMSO}-d_6$ recorded at 25°C

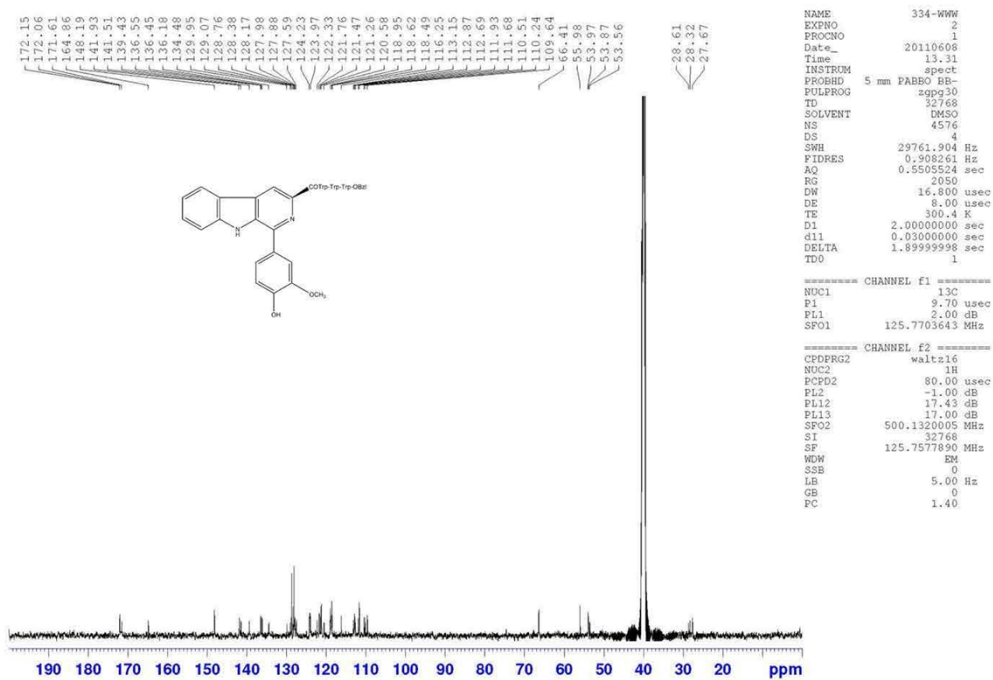


Figure S27 ^{13}C NMR spectrum of compound 17 in $\text{DMSO-}d_6$ recorded at 25 $^\circ\text{C}$

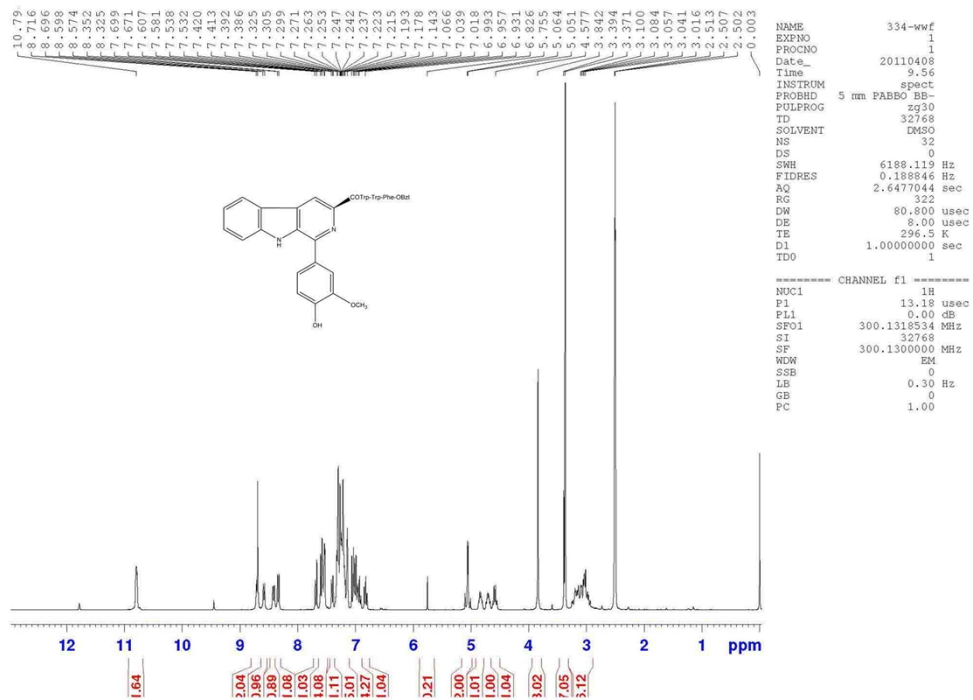


Figure S28 ¹H NMR spectrum of compound 18 in DMSO-*d*₆ recorded at 25 °C

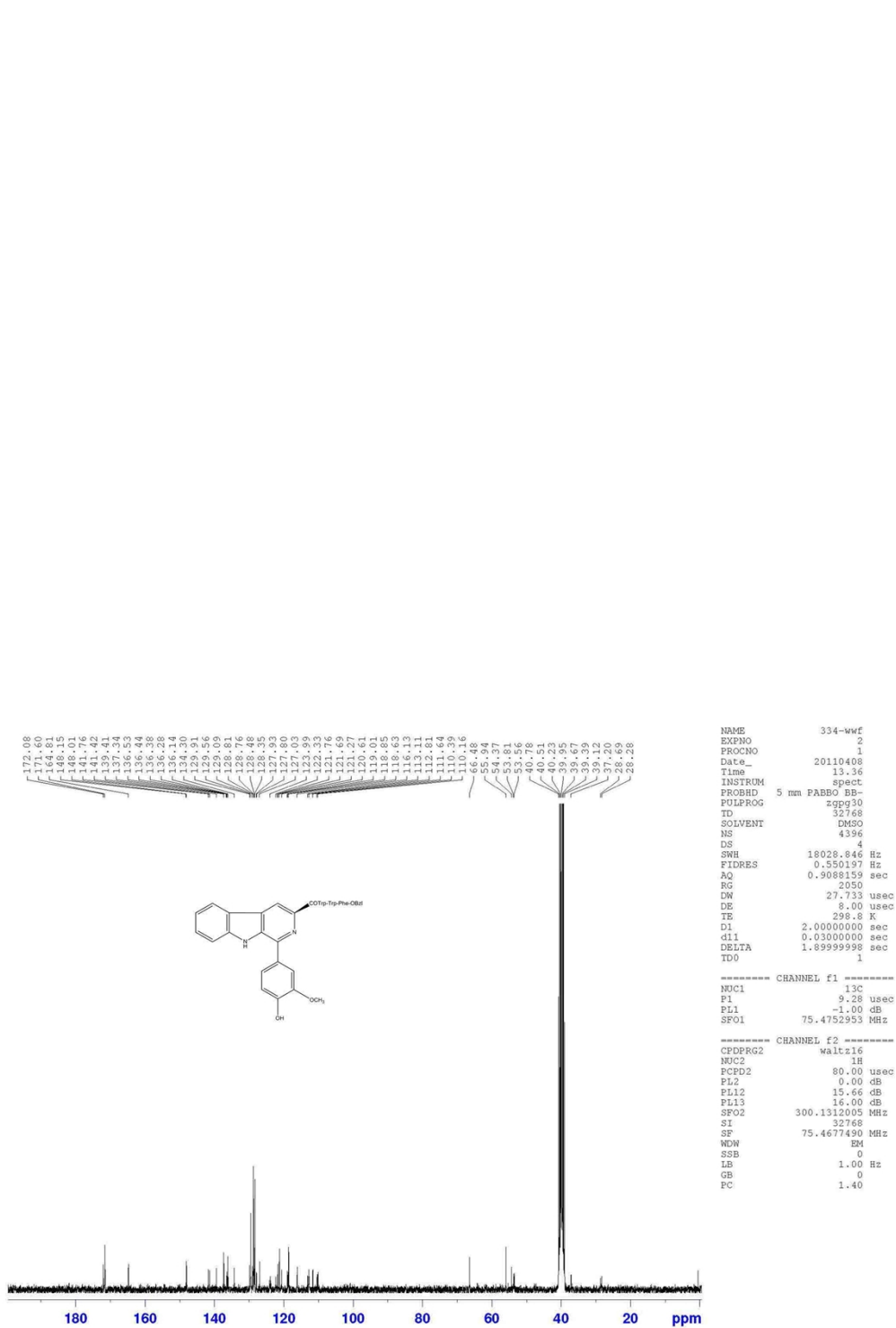


Figure S29 ^{13}C NMR spectrum of compound 18 in $\text{DMSO-}d_6$ recorded at 25°C

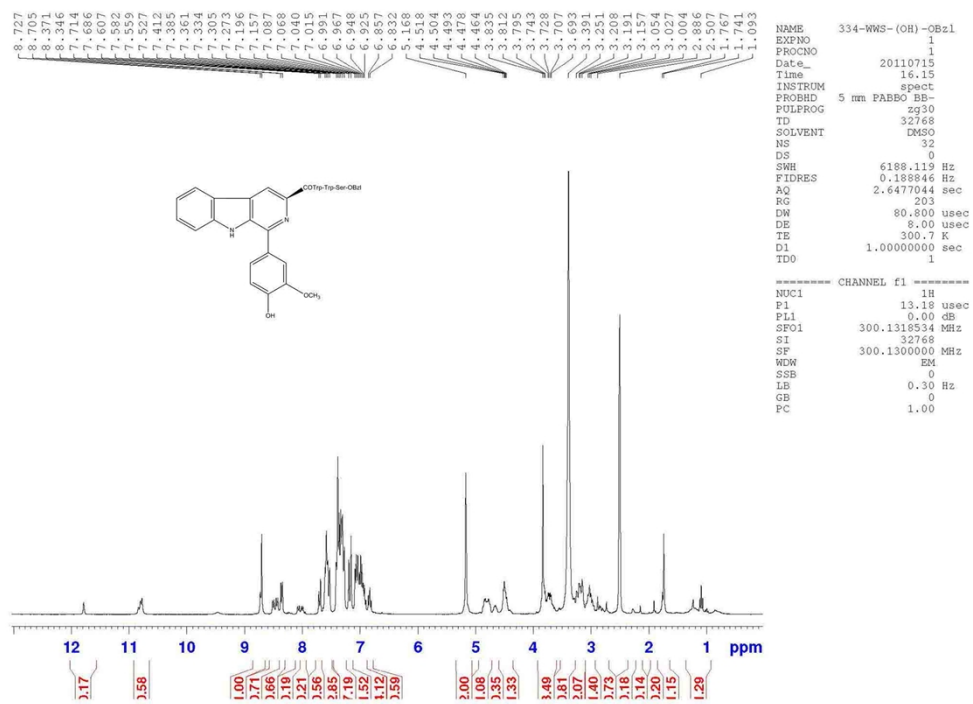
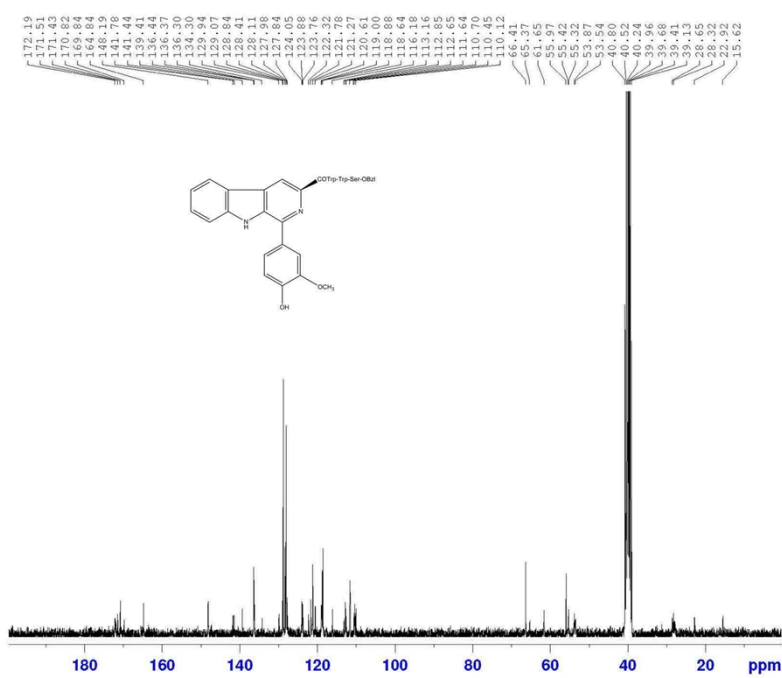


Figure S30 ^1H NMR spectrum of compound 19 in $\text{DMSO}-d_6$ recorded at 25°C



```

NAME          334-WWS-(OH)-OB21
EXPNO         2
PROCNO        1
Date_         20110715
Time          18.47
INSTRUM       spect
PROBHD        5 mm PABBO BB-
PULPROG       zgpg30
TD            32768
SOLVENT       DMSO
NS            4079
DS            4
SWH           18028.846 Hz
FIDRES        0.550197 Hz
AQ            0.9088159 sec
RG            2050
DM            27.733 usec
DE            8.00 usec
TE            302.2 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0           1

----- CHANNEL f1 -----
NUC1          13C
P1            9.28 usec
PL1           -1.00 dB
SFO1          75.4752953 MHz

----- CHANNEL f2 -----
CPDPRG2      waltz16
NUC2          1H
PCPD2        80.00 usec
PL2           0.00 dB
PL12         15.66 dB
PL13         16.00 dB
SFO2          300.1312005 MHz
SI            32768
SF            75.4677490 MHz
WDW           E4
SSB           0
LB            1.00 Hz
GB            0
FC            1.40

```

Figure S31 ^{13}C NMR spectrum of compound **19** in $\text{DMSO-}d_6$ recorded at 25 °C

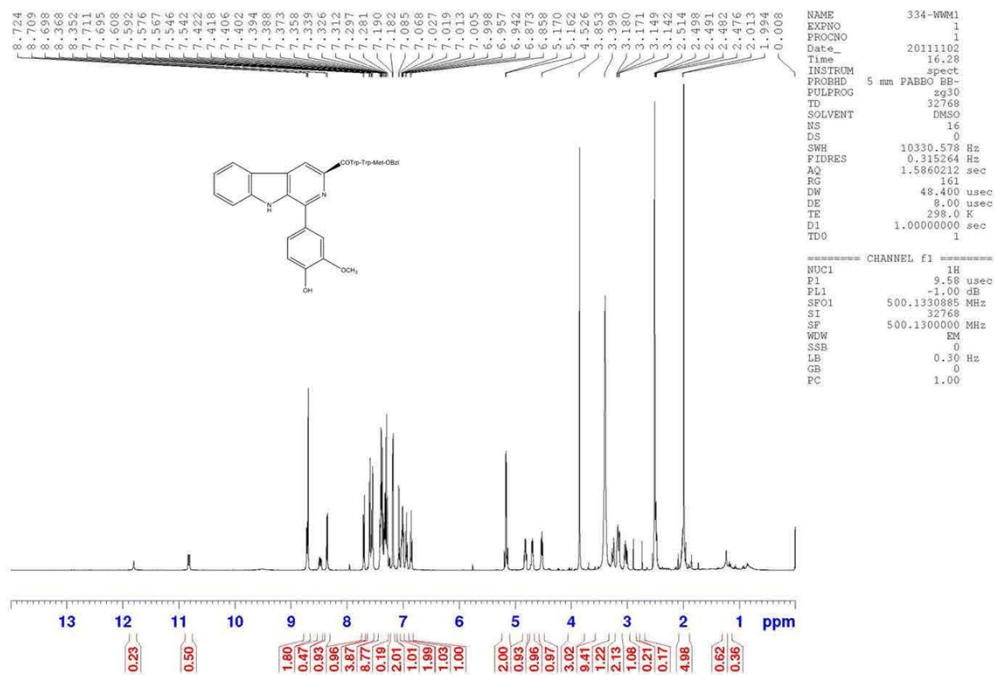


Figure S32 ¹H NMR spectrum of compound **20** in DMSO-*d*₆ recorded at 25 °C

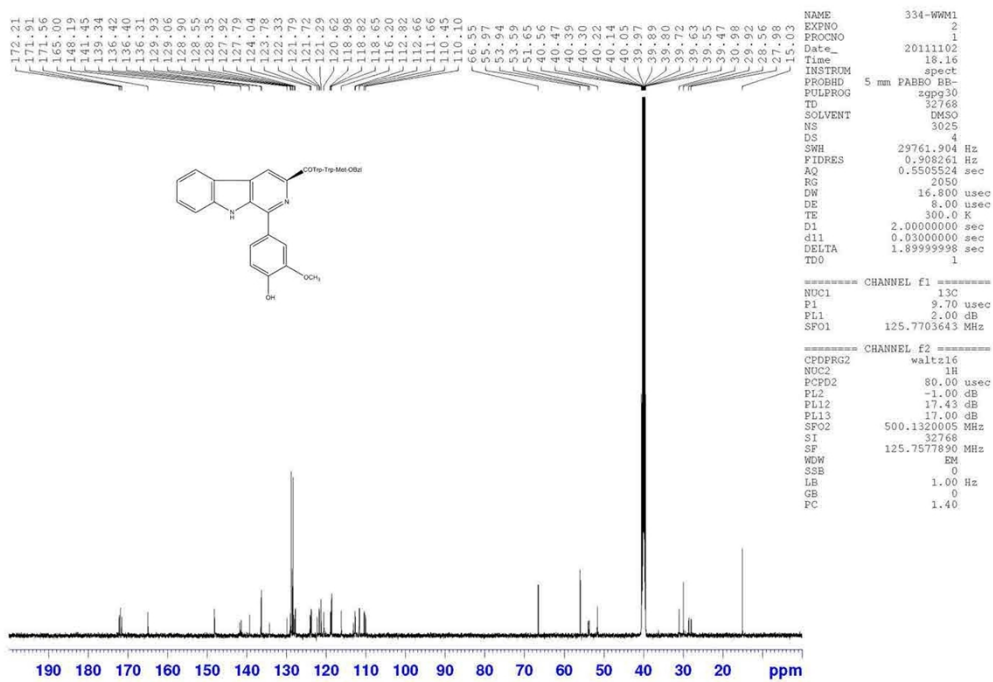


Figure S33 ^{13}C NMR spectrum of compound 20 in $\text{DMSO-}d_6$ recorded at 25 $^{\circ}\text{C}$

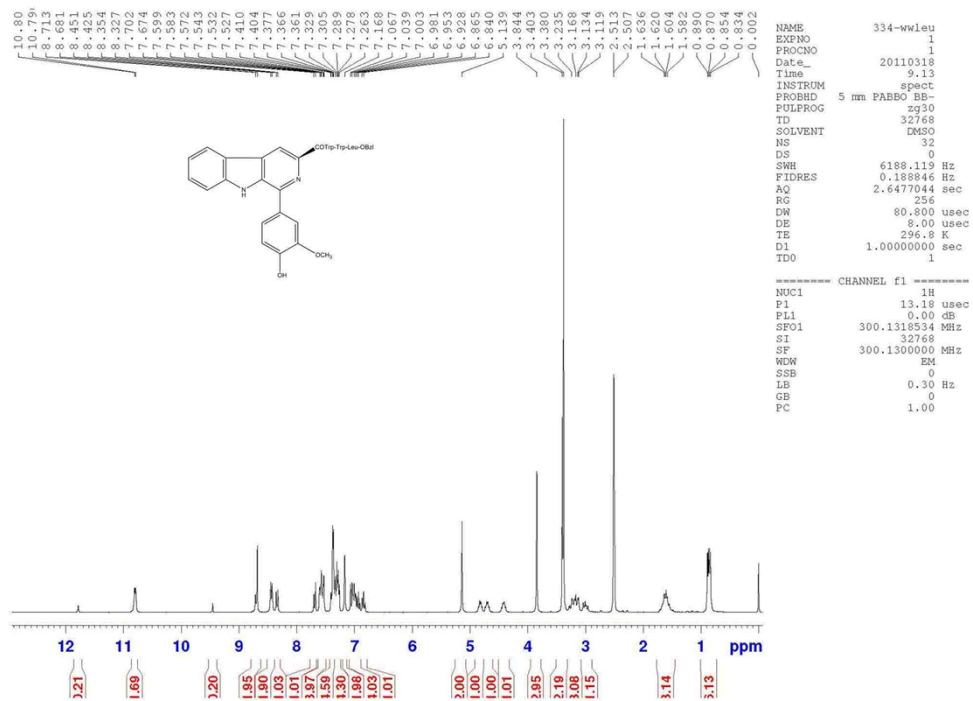


Figure S34 ¹H NMR spectrum of compound 21 in DMSO-*d*₆ recorded at 25 °C

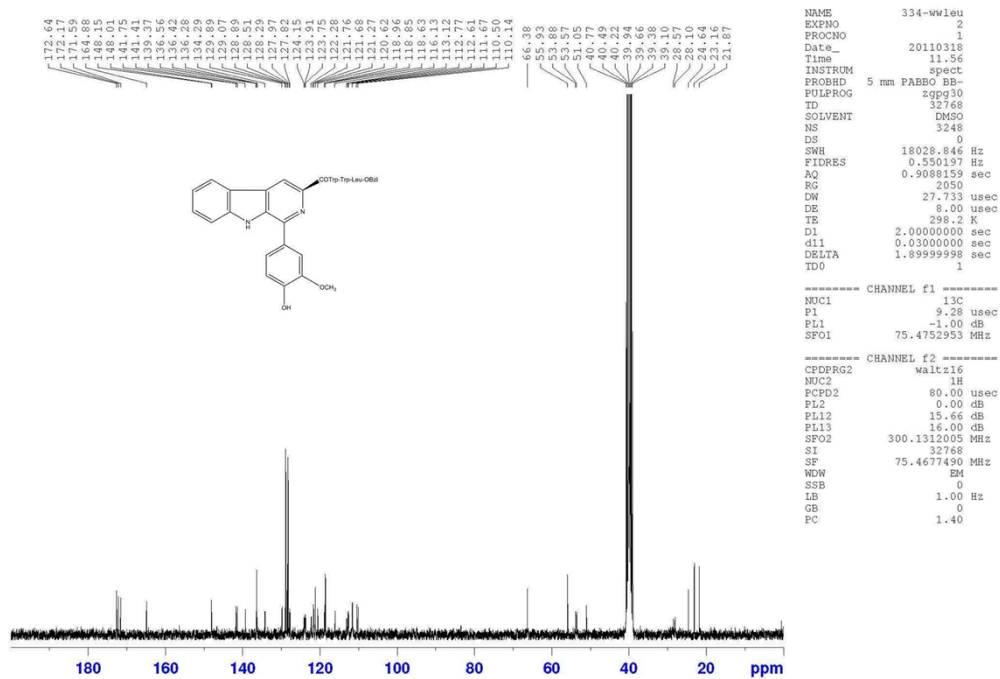


Figure S35 ^{13}C NMR spectrum of compound **21** in $\text{DMSO-}d_6$ recorded at 25°C