Structure-Activity Optimization of N-Arylindole GPR52 Agonists for Enhanced Antipsychotic Efficacy: Design, Synthesis, and Pharmacological Evaluation

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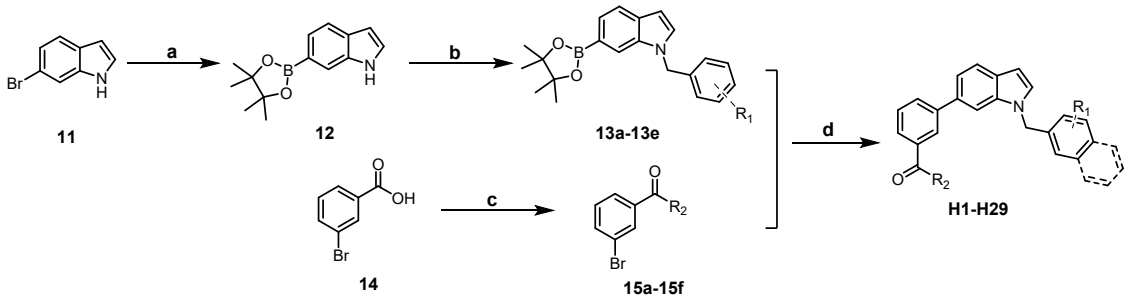
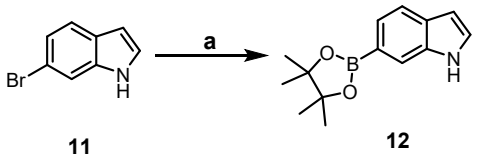
1. Synthesis of compounds H1-H29



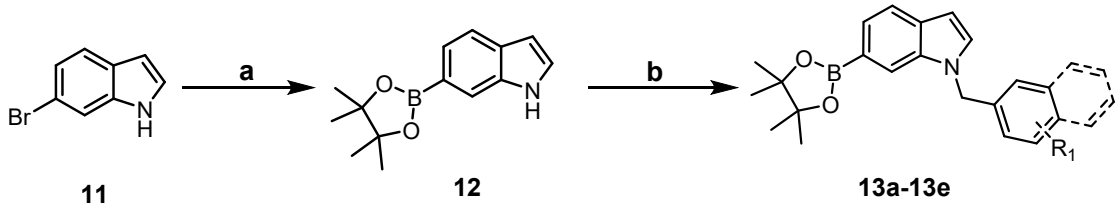
Scheme S1. Synthesis of compounds **H1** to **H29**. Reagents and conditions: a) $(Bpin)_2$, $Pd(dppf)Cl_2$, AcOK, 1,4-dioxane, N_2, 80 °C, 6 h. b) (bromomethyl)benzene, KOH, DMF, 50 °C, 2 h. c) (i) $(COCl)_2$, DCM, DMF, r.t., 3h; (ii) aminoethanol derivatives, Et_3N, DCM, 0 °C, 5 h. d) $Pd(PPh_3)_2Cl_2$, K_2CO_3, 1,4-Dioxane/H_2O, N_2, 80 °C, 6 h.

The synthetic procedure of compound 12



To a 250 mL reaction flask, 6-bromoindole (compound **11**, 12.5 g, 63.76 mmol), bis(pinacolato)diboron (32.4 g, 127.5 mmol), potassium acetate (18.8 g, 191.28 mmol), [1,1'-bis(diphenylphosphino)ferrocene] palladium(II) dichloride (2.33 g, 3.19 mmol), and 1,4-dioxane (150 mL) were added. The mixture was stirred and heated at 80 °C under N_2 protection for 8 hours. After TLC monitoring indicated the completion of the reaction, the solvent was removed under reduced pressure by rotary evaporation. The residue was washed with saturated brine (120 mL) and extracted with ethyl acetate (3 × 150 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether solution containing 10% ethyl acetate) to afford the white solid product **12**.

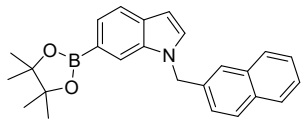
General procedures for the synthesis of compounds 13a-13e



Compound **12**, potassium hydroxide, (bromomethyl)benzene, and DMF

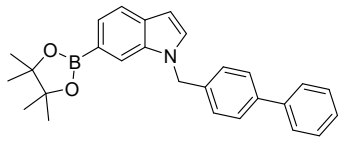
(40 mL) were added to a 250 mL reaction flask. The mixture was stirred at 50 °C for 2 hours. After the reaction was monitored by TLC, the mixture was diluted with saturated brine and extracted with ethyl acetate (3 × 120 mL). The organic phase was then washed with saturated brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether with 10% ethyl acetate) to afford the white solid product **13a-13e**.

Compound **13a**



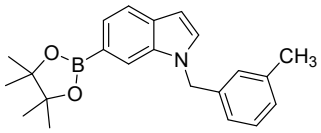
Compound **13a** was obtained by compound **12** (6.5 g, 26.7 mmol) and 2-(bromomethyl) naphthalene (8.3 g, 37.38 mmol)in 67.0% yield.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.83 – 7.77 (m, 2H), 7.75 – 7.69 (m, 2H), 7.62 (dd, J = 7.9, 0.9 Hz, 1H), 7.51 (s, 1H), 7.49 – 7.44 (m, 2H), 7.27 (s, 1H), 7.18 (d, J = 3.1 Hz, 1H), 6.60 (dd, J = 3.2, 0.9 Hz, 1H), 5.54 (s, 2H), 1.36 (s, 12H).^{13}C NMR (150 MHz, $CDCl_3$) δ 135.83, 134.59, 132.84, 132.30, 130.64, 128.85, 128.07, 127.80, 127.33, 127.19, 127.16, 125.77, 125.45, 125.36, 125.06, 125.04, 124.41, 119.81, 115.74, 109.25, 101.60, 83.02, 76.72, 76.51, 76.30, 49.21, 24.37.

Compound **13b**



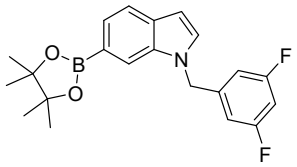
Compound **13b** was obtained by Compound 1**2** (7.0 g, 28.8 mmol) and 4-(bromomethyl)-1,1' -biphenyl (9.25 g, 37.44 mmol) in 68.6% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 1.0 Hz, 1H), 7.71 (dd, J = 7.9, 0.8 Hz, 1H), 7.63 (dd, J = 7.9, 0.9 Hz, 1H), 7.59 – 7.56 (m, 2H), 7.55 – 7.52 (m, 2H), 7.47 – 7.42 (m, 2H), 7.38 – 7.33 (m, 1H), 7.20 – 7.18 (m, 2H), 7.17 (d, J = 1.8 Hz, 1H), 6.61 (dd, J = 3.2, 0.9 Hz, 1H), 5.44 (s, 2H), 1.39 (s, 12H).^{13}C NMR (150 MHz, $CDCl_3$) δ 140.12, 140.03, 136.18, 135.77, 130.63, 128.80, 128.26, 126.94, 126.83, 126.77, 126.52, 125.04, 119.81, 115.72, 101.59, 83.02, 76.73, 76.52, 76.30, 48.79, 24.39.

Compound **13c**



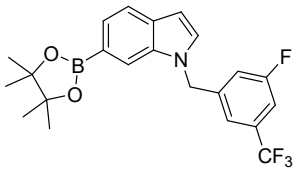
Compound **13c** was obtained by Compound **12** (7.0 g, 28.8 mmol) and 1-(bromomethyl) -3-methylbenzene (7.5 g, 40.32 mmol) in 67.9% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 1.0 Hz, 1H), 7.68 (dd, J = 8.0, 0.8 Hz, 1H), 7.59 (dd, J = 7.9, 0.9 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 3.2 Hz, 1H), 7.10 – 7.07 (m, 1H), 6.95 (t, J = 2.0 Hz, 1H), 6.92 – 6.89 (m, 1H), 6.56 (dd, J = 3.2, 0.9 Hz, 1H), 5.35 (s, 2H), 2.31 (s, 3H), 1.38 (s, 12H).^{13}C NMR (150 MHz, $CDCl_3$) δ 137.89, 137.05, 135.76, 130.57, 128.78, 128.10, 127.80, 127.10, 124.92, 124.90, 123.50, 119.72, 115.72, 115.70, 101.39, 101.37, 82.97, 76.70, 76.50, 76.48, 76.27, 49.00, 24.37, 24.36, 20.84.

Compound **13d**



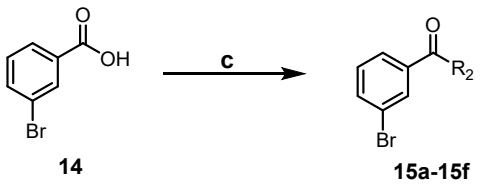
Compound **13d** was obtained by Compound **12** (7.0 g, 28.8 mmol) and 1-(bromomethyl)-3, 5-difluorobenzene (8.35 g, 40.32 mmol) in 82.7% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 0.9 Hz, 1H), 7.69 (dd, J = 7.9, 0.8 Hz, 1H), 7.61 (dd, J = 8.0, 0.9 Hz, 1H), 7.14 (d, J = 3.1 Hz, 1H), 6.72 – 6.67 (m, 1H), 6.61 (dd, J = 3.2, 0.9 Hz, 1H), 6.59 – 6.54 (m, 2H), 5.35 (s, 2H), 1.37 (s, 12H).^{13}C NMR (150 MHz, $CDCl_3$) δ 163.65, 163.56, 161.99, 161.91, 141.41, 135.51, 130.62, 128.61, 125.32, 119.94, 115.33, 108.97, 108.96, 108.92, 108.82, 108.79, 108.77, 102.64, 102.47, 102.31, 102.20, 83.06, 76.68, 76.47, 76.26, 48.33, 48.31, 48.30, 24.34.

Compound **13e**



Compound **13e** was obtained by compound **12** (3.7 g, 22mmol) and 1-(bromomethyl)-3-fluoro-5-(trifluoromethyl)benzene (5.03 g, 19.57 mmol) in 62.3% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 1.0 Hz, 1H), 7.69 (dd, J = 7.9, 0.8 Hz, 1H), 7.62 (dd, J = 7.9, 0.9 Hz, 1H), 7.26 (s, 1H), 7.23 (dt, J = 8.4, 2.0 Hz, 1H), 7.15 (d, J = 3.2 Hz, 1H), 6.82 (dt, J = 8.9, 2.1 Hz, 1H), 6.62 (dd, J = 3.2, 0.9 Hz, 1H), 5.42 (s, 2H), 1.37 (s, 12H).^{13}C NMR (150 MHz, $CDCl_3$) δ 163.17, 161.51, 141.35, 141.31, 135.45, 130.66, 128.44, 125.39, 120.01, 118.64, 118.62, 118.59, 116.64, 116.49, 115.27, 111.67, 111.65, 111.51, 111.49, 102.45, 83.08, 76.67, 76.46, 76.25, 48.28, 24.47, 24.31.

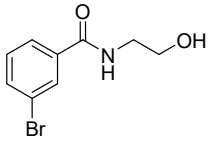
General procedures for the construction of compounds 15a-15f.



14 15a-15f

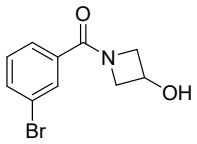
3-bromobenzoic acid (6.0 g, 30 mmol), DCM (50 mL), oxaloyl chloride (9.5 g, 75 mmol), and DMF (1 mL) were added to a 250 mL reaction flask. The mixed solution was stirred at room temperature for 3 hours and then vacuum-concentrated to obtain 3-bromobenzoyl chloride (a pale yellow oily substance). Then, at 0 ℃, the DCM solution of 3-bromobenzoyl chloride was dropped into the mixed solution of amino-1-alcohol (36 mmol), triethylamine (9.1 g, 90 mmol) and DCM (30 mL), and the mixture was stirred at room temperature for 5 hours. After the reaction was monitored by TLC, the excess solvent was evaporated by rotation, and water and ethyl acetate were added to treat the reaction. Then, the aqueous phase was extracted with ethyl acetate (3×100 mL), and the organic phase was combined. Subsequently, the combined organic phase was washed with saturated brine, dried with Na_2SO_4, filtered by suction, and vacuum-concentrated. The residue was purified by column chromatography (dichloromethane solution containing 3.5% methanol) to obtain a white solid product **15a-15f.**

Compound **15a**



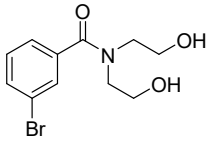
Compound **15a** was obtained by compound **14** (6.0 g，30 mmol) and 2-aminoethyl-1-alcohol (2.2 g, 36 mmol) in 62.3% yield. ^{1}H NMR (500 MHz, DMSO-*d6*) δ 7.77 (d, J = 2.0 Hz, 1H), 7.76 (d, J = 2.0 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.64 (d, J = 1.9 Hz, 1H), 3.49 (t, J = 6.2 Hz, 2H), 3.31 (t, J = 6.1 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.4, 137.1, 134.3, 131.0, 130.3, 126.8, 122.1, 59.3, 42.5.

Compound **15b**



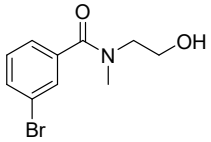
Compound **15b** was obtained by compound **14** (6.0 g，30 mmol) and 3-hydroxyazocyclic butane hydrochloride (2.6 g, 36 mmol) in 65.8% yield.1H NMR (500 MHz, DMSO-*d6*) *δ* 7.74 (t, *J* = 1.8 Hz, 1H), 7.72 – 7.68 (m, 1H), 7.59 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 5.76 (d, *J* = 6.0 Hz, 1H), 4.53 – 4.46 (m, 1H), 4.43 (t, *J* = 8.0 Hz, 1H), 4.24 (dd, *J* = 10.5, 6.8 Hz, 1H), 4.03 (dd, *J* = 9.3, 4.3 Hz, 1H), 3.78 (dd, *J* = 10.7, 4.4 Hz, 1H).^{13}C NMR (150 MHz, $CDCl_3$) δ 168.43, 134.58, 133.80, 130.53, 129.68, 125.93, 122.24, 76.88, 76.67, 76.46, 62.55, 61.30, 58.50

Compound **15c**



Compound **15c** was obtained by compound **14** (6.0 g，30 mmol) and diethanolamine (3.8 g, 36 mmol) in 60.0% yield. ^{1}H NMR (500 MHz, DMSO-d_6) *δ* 7.61 (q, *J* = 1.7 Hz, 1H), 7.60 (d, *J* = 1.8 Hz, 1H), 7.42 – 7.39 (m, 1H), 7.39 – 7.36 (m, 1H), 4.81 (dt, *J* = 17.9, 5.5 Hz, 2H), 3.61 (q, *J* = 5.9 Hz, 2H), 3.51 (t, *J* = 6.0 Hz, 2H), 3.45 (q, *J* = 5.8 Hz, 2H), 3.29 (t, *J* = 5.9 Hz, 2H).^{13}C NMR (150 MHz, DMSO-d_6) δ 169.83, 140.01, 132.14, 130.96, 129.98, 126.32, 121.86, 58.93, 58.76, 52.04, 47.80, 40.44, 40.30, 40.17, 40.03, 39.89, 39.75, 39.61.

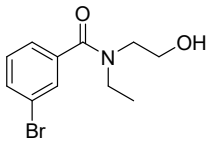
Compound **15d**



Compound **15d** was obtained by compound **14** (6.0 g，30 mmol) and 2-(methylamino) ethyl-1-alcohol (2.7 g, 36 mmol) in 64.7% yield. ^{1}H NMR (500 MHz, DMSO-d_6) *δ* 7.62 (d, *J* = 5.6 Hz, 1H), 7.60 (d, *J* = 4.0 Hz, 1H), 7.42 – 7.39 (m, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 4.85 – 4.77 (m, 1H), 3.62 (q, *J* = 5.8 Hz, 1H), 3.51 – 3.45 (m, 2H), 3.24 (t, *J* = 5.6 Hz, 1H), 3.00 – 2.88 (m, 3H).^{13}C NMR (150 MHz, DMSO-d_6) δ 169.71, 139.75, 132.66, 132.50, 132.21,

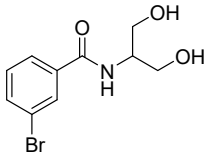
131.04, 130.92, 130.18, 129.90, 128.68, 126.45, 126.25, 121.89, 58.83, 58.23, 53.06, 50.15, 40.45, 40.31, 40.18, 40.04, 39.90, 39.76, 39.62, 38.71, 32.82.

Compound **15e**



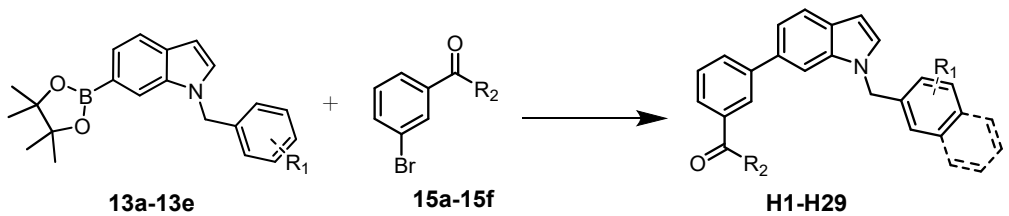
Compound **15e** was obtained by compound **14** (6.0 g，30 mmol) and 2-(ethylamino) ethyl-1-alcohol (3.2 g, 36 mmol) in 72.0% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.62 (t, J = 7.9 Hz, 1H), 7.57 (s, 1H), 7.39 (s, 1H), 7.37 (d, J = 3.9 Hz, 1H), 4.83 – 4.77 (m, 1H), 3.60 (q, J = 6.0 Hz, 1H), 3.46 (t, J = 7.1 Hz, 3H), 3.21 (q, J = 6.0 Hz, 2H), 1.17 – 0.97 (m, 3H).^{13}C NMR (150 MHz, DMSO-d_6) δ 169.23, 140.01, 132.49, 132.29, 132.15, 131.55, 131.15, 130.97, 129.94, 129.34, 126.24, 125.62, 62.79, 59.75, 59.01, 58.83, 51.15, 50.63, 47.22, 44.73, 43.48, 40.45, 40.32, 40.18, 40.04, 39.90, 39.80, 39.76, 39.62, 14.25, 12.97.

Compound **15f**



Compound **15f** was obtained by compound **14** (6.0 g，30 mmol) and 2-aminopropane-1, 3-diol (3.3g, 36 mmol) in 68.7% yield.1H NMR (500 MHz, DMSO-d_6) δ 8.13 (d, J = 8.1 Hz, 1H), 8.07 (t, J = 1.9 Hz, 1H), 7.86 (dt, J = 7.8, 1.3 Hz, 1H), 7.72 – 7.70 (m, 1H), 7.42 (t, J = 7.9 Hz, 1H), 4.66 (t, J = 5.6 Hz, 2H), 4.00 – 3.93 (m, 1H), 3.55 – 3.48 (m, 4H).^{13}C NMR (75 MHz, DMSO-d_6) δ 165.24, 137.42, 134.20, 130.88, 130.48, 127.05, 121.98, 60.82, 54.58, 40.80, 40.52, 40.24, 39.96, 39.69, 39.41, 39.13.

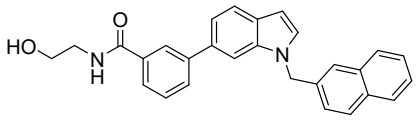
General procedures for the construction of compounds H1-H29.



Compound **15** (2.4 mmol), compound **13** (2.88 mmol), potassium carbonate

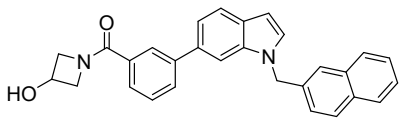
(993 mg, 7.2 mmol), and bis (triphenylphosphine) palladium dichloride (II) (170 mg, 0.24 mmol) were dissolved in 1, 4-dioxane/water (20 mL). In a volume ratio of 3:1), the mixture was heated and stirred at 80 °C under N_2 protection for 8 hours. After the reaction was monitored by TLC, the excess solvent was removed by rotary evaporation. The remaining mixture was washed with saturated brine (120 mL) and then extracted with ethyl acetate (3×150 mL) to combine the organic phase. The organic phase was dried with Na_2SO_4, filtered and vacuum-concentrated. The residue was purified by column chromatography (dichloromethane solution containing 2-2.5% methanol) to obtain the product **H1-H29**.

Compound **S2**



Compound **S2** was obtained by Compound **15a** (610 mg, 2.5 mmol) and compound 1**3a** (1.05 g, 2.75 mmol) in 62.5% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.87 (s, 1H), 7.85 – 7.78 (m, 4H), 7.75 (s, 2H), 7.67 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 3.2 Hz, 1H), 7.50 (t, J = 7.7 Hz, 1H), 7.47 – 7.43 (m, 2H), 7.41 (d, J = 8.3 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 6.56 (d, J = 3.1 Hz, 1H), 5.66 (s, 2H), 3.55 (t, J = 6.2 Hz, 2H), 3.38 (t, J = 6.2 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.9, 141.7, 136.7, 136.1, 135.3, 133.3, 133.0, 132.5, 130.4, 129.7, 129.1, 128.5, 128.3, 127.8(127.84), 127.8(127.81), 126.7, 126.3, 125.8(125.79), 125.8(125.76), 125.6, 121.3, 118.9, 108.6, 101.5, 59.9, 49.4, 42.3. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{28}H_{24}N_2O_2$, 443.1735; found, 443.1737.

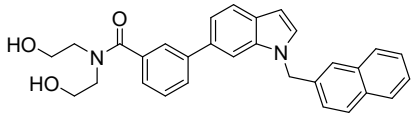
Compound **H1**



Compound **H1** was obtained by Compound **15b** (640 mg, 2.5 mmol) and compound **13a** (1.05 g, 2.75 mmol) in 60.3% yield.^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 – 7.82 (m, 4H), 7.83 – 7.77 (m, 3H), 7.67 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 3.2 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.50 – 7.45 (m, 2H), 7.41 (dd, J = 8.4, 1.8 Hz, 1H), 7.37 (dd, J = 8.2, 1.5 Hz, 1H), 6.57 (d, J = 3.1 Hz, 1H), 5.80 (d, J = 6.0 Hz, 1H), 5.70 (s, 2H), 4.56 – 4.49 (m, 1H), 4.47 (t, J = 8.5 Hz, 1H), 4.29 (dd, J = 10.5, 6.9 Hz, 1H), 4.08 (dd, J = 9.2,

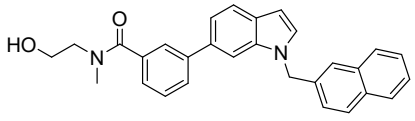
4.4 Hz, 1H), 3.84 (dd, *J* = 10.5, 4.4 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.0, 141.5, 136.5, 135.9, 133.9, 132.9, 132.8, 132.3, 130.3, 129.2, 128.9, 128.3, 128.1, 127.6(127.60), 127.6(127.57), 126.4, 126.0, 125.9, 125.8, 125.5, 125.4, 121.1, 118.5, 108.4, 101.1, 62.8, 60.5, 58.5, 49.2. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{29}H_{24}N_2O_2$, 455.1730; found, 455.1736.

Compound **H2**



Compound **H2** was obtained by Compound **15c** (692 mg, 2.4 mmol) and compound **13a** (1.01 g, 2.64 mmol) in 69.1% yield.^{1}H NMR (500 MHz, DMSO-d_6) δ 7.88 (d, *J* = 1.5 Hz, 1H), 7.85 (dd, *J* = 8.8, 3.3 Hz, 2H), 7.84 – 7.81 (m, 1H), 7.78 (s, 1H), 7.73 – 7.69 (m, 2H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 3.1 Hz, 1H), 7.50 – 7.44 (m, 3H), 7.39 (ddd, *J* = 13.7, 8.4, 1.7 Hz, 2H), 7.31 (dt, *J* = 7.6, 1.4 Hz, 1H), 6.55 (d, *J* = 3.0 Hz, 1H), 5.69 (s, 2H), 4.85 (dt, *J* = 19.6, 5.4 Hz, 2H), 3.66 (q, *J* = 5.9 Hz, 2H), 3.56 (t, *J* = 6.1 Hz, 2H), 3.49 (q, *J* = 5.8 Hz, 2H), 3.35 (d, *J* = 6.1 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.1, 141.3, 137.8, 136.5, 135.9, 133.0, 132.8, 132.3, 130.2, 128.8, 128.3, 128.0, 127.6(127.61), 127.6(127.57), 127.2, 126.4, 126.0, 125.6, 125.5, 125.0(125.01), 125.0(124.96), 121.0, 118.5, 108.3, 101.2, 58.6, 51.7, 49.2, 47.5. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{30}H_{28}N_2O_3$, 487.1992; found, 487.1993.

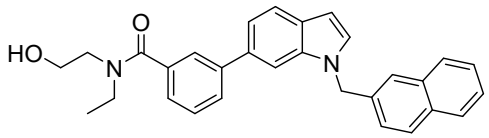
Compound **H3**



Compound **H3** was obtained by Compound 1**5d** (620 mg, 2.4 mmol) and compound **13a** (1.01 g, 2.64 mmol) in 67.1% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.83 – 7.80 (m, 1H), 7.78 (s, 1H), 7.75 – 7.64 (m, 3H), 7.60 (d, *J* = 3.1 Hz, 1H), 7.50 – 7.43 (m, 3H), 7.38 (t, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 1H), 6.55 (d, *J* = 3.1 Hz, 1H), 5.69 (s, 2H), 4.88 – 4.82 (m, 1H), 3.66 (q, *J* = 5.9 Hz, 1H), 3.56 – 3.47 (m, 2H), 3.30 (t, *J* = 5.8 Hz, 1H), 3.03 – 2.94 (m, 3H). ^{13}C

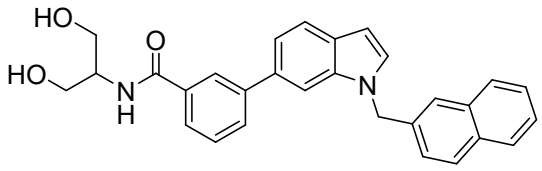
NMR (125 MHz, DMSO-d_6) δ 170.9, 141.2, 137.6, 136.5, 135.9, 132.9, 132.8, 132.2, 130.2, 128.7, 128.2, 128.0, 127.6(127.58), 127.6(127.56), 127.2, 126.4, 126.0, 125.5, 125.4, 125.1, 125.0, 121.0, 118.5, 108.4, 101.1, 58.1, 52.7, 49.1, 32.5. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{29}H_{26}N_2O_2$, 457.1886; found, 457.1885.

Compound **H4**



Compound **H4** was obtained by Compound **15e** (600 mg, 2.2 mmol) and compound **13a** (1.05 g, 2.75 mmol) in 62.1% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.83 – 7.80 (m, 1H), 7.78 (s, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.68 – 7.62 (m, 2H), 7.61 (d, J = 3.1 Hz, 1H), 7.50 – 7.44 (m, 3H), 7.38 (t, J = 8.6 Hz, 2H), 7.28 (t, J = 7.1 Hz, 1H), 6.55 (d, J = 3.1 Hz, 1H), 5.69 (s, 2H), 4.84 (q, J = 5.3 Hz, 1H), 3.64 (q, J = 6.0 Hz, 1H), 3.49 (t, J = 6.5 Hz, 3H), 3.27 (q, J = 7.3, 6.4 Hz, 2H), 1.20 – 0.96 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.5, 141.3, 137.9, 136.5, 135.9, 132.8, 132.2, 130.2, 128.8, 128.2, 128.0, 127.6(127.58), 127.6(127.55), 127.2, 126.4, 126.0, 125.6, 125.4, 124.9, 124.3, 124.2, 121.0, 118.5, 108.4, 101.1, 58.7, 50.2, 49.2, 44.3, 13.9. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{30}H_{28}N_2O_2$, 471.2043; found, 471.2047.

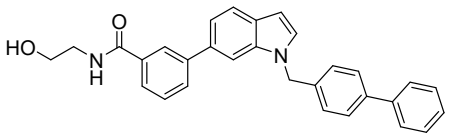
Compound **H5**



Compound **H5** was obtained by Compound **15f** (685 mg, 2.5 mmol) and compound **13a** (1.05 g, 2.75 mmol) in 63.0% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.14 (t, J = 1.8 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.90 (s, 1H), 7.86 (dd, J = 8.8, 4.0 Hz, 2H), 7.83 – 7.76 (m, 4H), 7.68 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 3.1 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.44 (dd, J = 8.2, 1.5 Hz, 1H), 7.40 (dd, J = 8.5, 1.8 Hz, 1H), 6.56 (d, J = 3.0 Hz, 1H), 5.69 (s, 2H), 4.69 (t, J = 5.8 Hz, 2H), 4.05 – 3.97 (m, 1H),

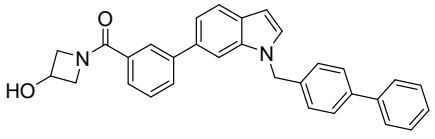
3.60 – 3.52 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.5, 141.4, 136.5, 135.9, 135.4, 133.2, 132.8, 132.3, 130.2, 129.4, 128.7, 128.3, 128.0, 127.6(127.64), 127.6(127.56), 126.4, 126.0, 125.7(125.72), 125.7(125.67), 125.5, 125.4, 121.0, 118.7, 108.4, 101.2, 60.4, 54.0, 49.1. HRMS (ESI, *m*/*z*): [M+Na]$^+$ calculated for $C_{29}H_{26}N_2O_3$, 473.1836; found, 473.1839。

Compound **H6**



Compound **H6** was obtained by Compound **15a** (660 mg, 2.7 mmol) and compound **13b** (1.22 g, 2.97 mmol) in 62.2% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (t, J = 5.6 Hz, 1H), 8.17 (t, J = 1.8 Hz, 1H), 7.88 (s, 1H), 7.84 (dt, J = 7.8, 1.5 Hz, 1H), 7.79 (dt, J = 7.9, 1.4 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.62 – 7.56 (m, 5H), 7.53 (t, J = 7.7 Hz, 1H), 7.46 – 7.38 (m, 3H), 7.35 – 7.30 (m, 3H), 6.55 (dd, J = 3.2, 0.8 Hz, 1H), 5.58 (s, 2H), 4.77 (t, J = 5.6 Hz, 1H), 3.55 (q, J = 6.0 Hz, 2H), 3.38 (q, J = 6.1 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.5, 141.4, 139.7, 139.3, 137.6, 136.5, 135.2, 133.1, 130.1, 129.4, 128.9, 128.8, 128.0, 127.6, 127.4, 126.9, 126.6, 125.6, 125.5, 121.0, 118.7, 108.4, 101.2, 59.8, 48.6, 42.3. HRMS (ESI, m/z): [M+Na]$^+$ calculated for $C_{30}H_{26}N_2O_2$, 469.1886; found, 469.1891.

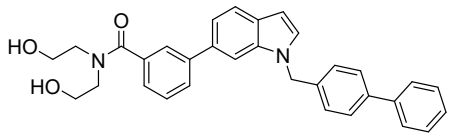
Compound **H7**



Compound **H7** was obtained by Compound **15b** (691 mg, 2.7 mmol) and compound **13b** (1.22 g, 2.97 mmol) in 62.2% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.88 (t, J = 1.8 Hz, 1H), 7.86 (s, 1H), 7.83 (dt, J = 7.2, 1.8 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.62 – 7.58 (m, 5H), 7.56 – 7.50 (m, 2H), 7.42 (dd, J = 8.4, 7.0 Hz, 2H), 7.37 (dd, J = 8.2, 1.6 Hz, 1H), 7.35 – 7.30 (m, 3H), 6.55 (d, J = 3.0 Hz, 1H), 5.79 (d, J = 5.9 Hz, 1H), 5.58 (s,

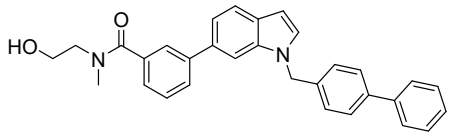
2H), 4.55 – 4.46 (m, 2H), 4.28 (dd, *J* = 10.1, 6.4 Hz, 1H), 4.13 – 4.05 (m, 1H), 3.83 (dd, *J* = 10.4, 3.6 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.0, 141.6, 139.7, 139.3, 137.6, 136.4, 133.9, 132.9, 130.2, 129.3, 128.9(128.94), 128.9(128.87), 128.0, 127.7, 127.4, 126.9, 126.6, 125.9, 125.8, 121.1, 118.5, 108.5, 101.1, 62.8, 60.5, 58.5, 48.7. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{31}H_{26}N_2O_2$, 481.1886; found, 481.1894.

Compound **H8**



Compound **H8** was obtained by Compound **15c** (764 mg, 2.65 mmol) and compound **13b** (1.2 g, 2.91 mmol) in 62.2% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.75 (d, *J* = 6.0 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 5H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.45 – 7.36 (m, 3H), 7.33 (d, *J* = 7.8 Hz, 4H), 6.55 (d, *J* = 3.1 Hz, 1H), 5.57 (s, 2H), 4.92 – 4.82 (m, 2H), 3.67 (q, *J* = 6.0 Hz, 2H), 3.57 (t, *J* = 6.1 Hz, 2H), 3.51 (q, *J* = 5.7 Hz, 2H), 3.38 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.1, 141.3, 139.8, 139.3, 137.8, 137.6, 136.5, 133.0, 130.1, 128.9, 128.8, 128.0, 127.7, 127.4, 127.2, 126.9, 126.6, 125.1, 125.0, 121.0, 118.5, 108.4, 101.1, 58.6, 51.7, 48.6, 47.5. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{32}H_{30}N_2O_3$, 513.2149; found, 513.2158.

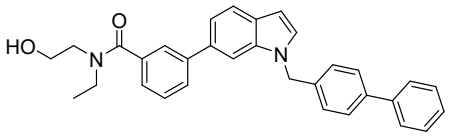
Compound **H9**



Compound **H9** was obtained by Compound **15d** (573 mg, 2.22 mmol) and compound **13b** (1.0 g, 2.44mmol) in 65.0% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.79 – 7.69 (m, 2H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 5H), 7.49 (q, *J* = 7.9 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.38 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.35 – 7.29 (m, 4H), 6.54 (d, *J* = 3.1 Hz, 1H), 5.57 (s, 2H), 4.86 (dd, *J* = 12.7, 7.4 Hz, 1H), 3.65 (q, *J* = 5.7 Hz, 1H), 3.57 – 3.47 (m, 2H), 3.32 (t, *J* = 5.9 Hz, 1H), 3.03 – 2.94 (m, 3H). ^{13}C

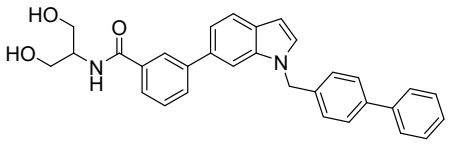
NMR (125 MHz, DMSO-d_6) δ 170.9, 141.2, 139.7, 139.2, 137.6, 137.5, 136.4, 132.9, 130.1, 128.9, 128.8, 128.0, 127.6, 127.4, 127.2, 126.9, 126.6, 125.2, 125.1, 121.0, 118.5, 108.4, 101.1, 58.1, 52.7, 48.6, 32.5. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{31}H_{28}N_2O_2$, 483.2043; found, 483.2046.

Compound **H10**



Compound **H10** was obtained by Compound **15e** (600 mg, 2.2 mmol) and compound **13b** (990 mg, 2.42 mmol) in 65.2% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.86 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.67 (t, J = 11.3 Hz, 2H), 7.62 – 7.56 (m, 5H), 7.53 – 7.45 (m, 1H), 7.41 (t, J = 7.7 Hz, 2H), 7.38 (d, J = 8.2 Hz, 1H), 7.35 – 7.26 (m, 4H), 6.54 (t, J = 2.6 Hz, 1H), 5.57 (s, 2H), 4.89 – 4.78 (m, 1H), 3.63 (t, J = 6.0 Hz, 1H), 3.50 (t, J = 6.5 Hz, 3H), 3.29 (t, J = 7.4 Hz, 2H), 1.20 – 0.94 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.5, 141.3, 139.7, 139.3, 137.9, 137.6, 136.4, 132.9, 130.2, 128.9, 128.8, 128.0, 127.6, 127.4, 127.3, 126.9, 126.6, 124.9, 124.3, 121.0, 118.5, 108.4, 101.1, 58.7, 50.2, 48.6, 44.3, 13.9. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{32}H_{30}N_2O_2$, 497.2199; found, 497.2202.

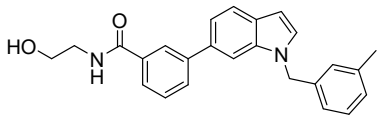
Compound **H11**



Compound **H11** was obtained by Compound **15f** (740 mg, 2.7 mmol) and compound **13b** (1.22 g, 2.97 mmol) in 60.6% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.17 (s, 1H), 8.12 (d, J = 8.1 Hz, 1H), 7.89 (s, 1H), 7.82 (dd, J = 16.7, 7.7 Hz, 2H), 7.69 (d, J = 8.2 Hz, 1H), 7.63 – 7.57 (m, 5H), 7.53 (t, J = 7.7 Hz, 1H), 7.47 – 7.39 (m, 3H), 7.33 (d, J = 7.7 Hz, 3H), 6.56 (d, J = 3.1 Hz, 1H), 5.58 (s, 2H), 4.70 (t, J = 5.7 Hz, 2H), 4.07 – 3.99 (m, 1H), 3.57 (t, J = 5.9 Hz, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.5, 141.4, 139.7, 139.3, 137.5, 136.5, 135.5, 133.2, 130.1, 129.4, 128.9, 128.7, 128.0,

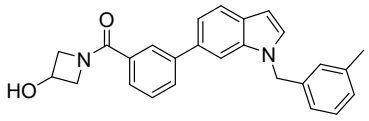
127.7, 127.4, 126.9, 126.6, 125.8, 125.7, 121.0, 118.7, 108.4, 101.2, 60.5, 54.0, 48.7. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{31}H_{28}N_2O_3$, 499.1992; found, 499.1991.

Compound **H12**



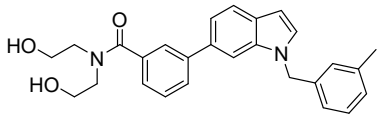
Compound **H12** was obtained by Compound **15a** (586 mg, 2.4 mmol) and compound **13c** (1.0 g, 2.88 mmol) in 63.0% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (t, J = 5.6 Hz, 1H), 8.17 (s, 1H), 7.85 – 7.79 (m, 3H), 7.67 (d, J = 8.2 Hz, 1H), 7.55 – 7.51 (m, 2H), 7.43 (dd, J = 8.2, 1.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.10 (s, 1H), 7.05 (d, J = 7.5 Hz, 1H), 7.01 (d, J = 7.7 Hz, 1H), 6.53 (d, J = 3.1 Hz, 1H), 5.48 (s, 2H), 4.79 (t, J = 5.6 Hz, 1H), 3.58 (q, J = 6.0 Hz, 2H), 3.40 (q, J = 6.1 Hz, 2H), 2.23 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.5, 141.5, 138.2, 137.7, 136.5, 135.3, 133.1, 130.1, 129.4, 128.8, 128.5, 128.0, 127.9, 127.7, 125.6, 125.5, 124.2, 120.9, 118.6, 108.4, 101.0, 59.8, 49.0, 42.3, 21.0. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{25}H_{24}N_2O_2$, 407.1730; found, 407.1737.

Compound **H13**



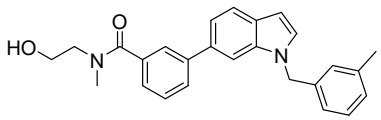
Compound **H13** was obtained by Compound **15b** (670 mg, 2.62 mmol) and compound **13c** (1.0 g, 2.88 mmol) in 64.5% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.86 (s, 1H), 7.83 – 7.78 (m, 2H), 7.65 (d, J = 8.2 Hz, 1H), 7.56 – 7.49 (m, 3H), 7.36 (dd, J = 8.3, 1.6 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.09 (s, 1H), 7.04 (dd, J = 14.4, 7.6 Hz, 2H), 6.52 (d, J = 3.1 Hz, 1H), 5.79 (d, J = 5.8 Hz, 1H), 5.48 (s, 2H), 4.56 – 4.51 (m, 1H), 4.48 (t, J = 7.7 Hz, 1H), 4.29 (t, J = 8.6 Hz, 1H), 4.08 (dd, J = 9.3, 4.1 Hz, 1H), 3.83 (dd, J = 10.7, 4.4 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.0, 141.6, 138.2, 137.7, 136.4, 133.9, 132.8, 130.2, 129.2, 129.0, 128.5, 128.0(128.02), 128.0(128.01), 127.7, 125.9, 125.8, 124.2, 121.0, 118.4, 108.5, 100.9, 62.8, 60.5, 58.5, 49.0, 21.0. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{26}H_{24}N_2O_2$, 419.1730; found, 419.1738.

Compound **H14**



Compound **H14** was obtained by Compound **15c** (750 mg, 2.6 mmol) and compound **13c** (1.0 g, 2.88 mmol) in 69.2% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (t, J = 1.7 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.63 (dt, J = 7.4, 1.8 Hz, 1H), 7.52 (s, 1H), 7.42 – 7.35 (m, 3H), 7.17 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 3.1 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H), 6.97 (s, 1H), 6.92 (d, J = 7.7 Hz, 1H), 6.56 (dd, J = 3.1, 0.8 Hz, 1H), 5.31 (s, 2H), 3.94 (t, J = 4.9 Hz, 2H), 3.72 – 3.63 (m, 4H), 3.45 (t, J = 5.0 Hz, 2H), 3.25 (s, 2H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 142.7, 138.6, 137.4, 137.0, 136.7, 134.2, 129.3, 128.9, 128.8, 128.6, 128.5, 128.4, 127.6, 126.2, 125.3, 124.0, 121.4, 119.4, 108.3, 101.7, 61.1, 60.5, 53.6, 50.0, 49.7, 21.5. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{27}H_{28}N_2O_3$, 451.1992; found, 451.1996.

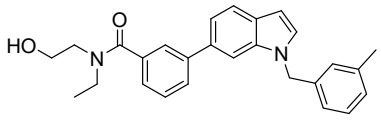
Compound **H15**



Compound **H15** was obtained by Compound **15d** (676 mg, 2.62 mmol) and compound **13c** (1.0 g, 2.88 mmol) in 62.0% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.80 (s, 1H), 7.76 – 7.66 (m, 2H), 7.64 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 3.1 Hz, 1H), 7.49 (q, J = 7.6 Hz, 1H), 7.36 (dd, J = 8.2, 1.6 Hz, 1H), 7.33 (dt, J = 7.5, 1.4 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.09 (s, 1H), 7.05 (d, J = 7.5 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.52 (d, J = 3.0 Hz, 1H), 5.47 (s, 2H), 4.88 – 4.81 (m, 1H), 3.66 (q, J = 6.0 Hz, 1H), 3.57 – 3.48 (m, 2H), 3.32 (t, J = 5.7 Hz, 1H), 3.04 – 2.96 (m, 3H), 2.23 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.0, 141.3, 138.2, 137.7, 137.6, 136.4, 132.8, 130.1, 128.8, 128.5, 128.0, 127.9, 127.7, 127.2, 125.2, 125.1, 124.2, 120.9, 118.4, 108.4, 100.9, 58.1, 52.7, 48.9, 32.5, 21.0. HRMS (ESI, m/z):

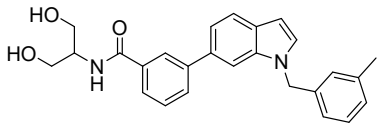
[M+Na]$^+$ calculated for $C_{26}H_{26}N_2O_2$, 421.1886; found, 421.1891.

Compound **H16**



Compound **H16** was obtained by Compound **15e** (713 mg, 2.62 mmol) and compound **13c** (1.0 g, 2.88 mmol) in 67.4% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.80 (s, 1H), 7.72 (d, J = 6.8 Hz, 1H), 7.68 – 7.59 (m, 2H), 7.53 (d, J = 3.1 Hz, 1H), 7.49 (q, J = 7.0 Hz, 1H), 7.36 (dd, J = 8.3, 1.6 Hz, 1H), 7.29 (s, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.09 (s, 1H), 7.04 (d, J = 7.5 Hz, 1H), 7.01 (d, J = 7.7 Hz, 1H), 6.52 (d, J = 3.1 Hz, 1H), 5.47 (s, 2H), 4.87 – 4.78 (m, 1H), 3.64 (q, J = 7.1 Hz, 1H), 3.51 (t, J = 6.7 Hz, 3H), 3.29 (t, J = 7.4 Hz, 2H), 2.23 (s, 3H), 1.21 – 1.00 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.5, 141.3, 138.2, 137.9, 137.7, 136.4, 132.8, 130.2, 128.8, 128.4, 128.0, 127.9, 127.7, 127.2, 124.9, 124.2, 120.9, 118.4, 108.4, 100.9, 58.7, 50.2, 49.0, 44.3, 21.0, 13.9. HRMS (ESI, m/z): [M+Na]$^+$ calculated for $C_{27}H_{28}N_2O_2$, 435.2043; found, 435.2047.

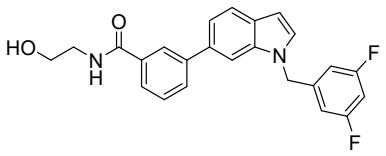
Compound **H17**



Compound **H17** was obtained by Compound **15f** (656 mg, 2.4 mmol) and compound **13c** (1.0 g, 2.88 mmol) in 60.3% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.62 (t, J = 8.0 Hz, 2H), 7.47 (s, 1H), 7.31 (t, J = 7.8 Hz, 2H), 7.21 (d, J = 7.7 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 3.1 Hz, 1H), 7.02 (d, J = 7.6 Hz, 1H), 6.92 (s, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.54 (d, J = 3.1 Hz, 1H), 5.24 (s, 2H), 4.14 – 4.08 (m, 1H), 3.84 (dd, J = 11.3, 4.4 Hz, 2H), 3.75 (dd, J = 11.3, 4.9 Hz, 2H), 2.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 143.0, 138.6, 137.4, 137.0, 134.4, 134.1, 130.8, 129.3, 129.0, 128.8, 128.5, 128.4, 127.6, 126.3, 125.1, 124.0, 121.4, 119.4, 108.3, 101.7, 62.4, 53.2, 49.9, 21.5.

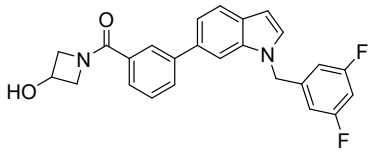
HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{26}H_{26}N_2O_3$, 437.1836; found, 437.1837.

Compound **H18**



Compound **H18** was obtained by Compound **15a** (719 mg, 2.95 mmol) and compound **13d** (1.2 g, 3.24 mmol) in 60.3% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (t, J = 5.6 Hz, 1H), 8.14 (s, 1H), 7.85 (s, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 3.1 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.45 (dd, J = 8.2, 1.5 Hz, 1H), 7.11 (tt, J = 9.4, 2.4 Hz, 1H), 6.93 – 6.88 (m, 2H), 6.57 (d, J = 3.1 Hz, 1H), 5.57 (s, 2H), 4.76 (t, J = 5.6 Hz, 1H), 3.55 (q, J = 6.0 Hz, 2H), 3.39 (q, J = 6.0 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.5, 162.5 (dd, J = 246.8, 13.1 Hz), 143.1 (t, J = 8.8 Hz), 141.3, 136.4, 135.3, 133.4, 130.1, 129.5, 128.8, 127.9, 125.6(125.65), 125.6(125.59), 121.1, 119.0, 110.1 (dd, J = 19.8, 6.0 Hz), 108.2, 102.9 (t, J = 25.9 Hz), 101.6, 59.8, 48.1, 42.3. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{24}H_{20}F_2N_2O_2$, 429.1385; found, 429.1394.

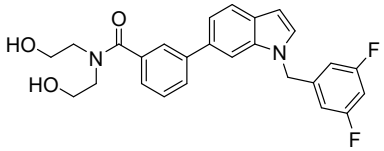
Compound **H19**



Compound **H19** was obtained by Compound **15b** (756 mg, 2.95 mmol) and compound **13d** (1.2 g, 3.24 mmol) in 62.3% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.85 (s, 1H), 7.83 (dt, J = 7.1, 1.9 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 3.2 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.39 (dd, J = 8.2, 1.6 Hz, 1H), 7.13 (tt, J = 9.4, 2.4 Hz, 1H), 6.96 – 6.90 (m, 2H), 6.57 (d, J = 3.0 Hz, 1H), 5.78 (d, J = 6.0 Hz, 1H), 5.58 (s, 2H), 4.57 – 4.46 (m, 2H), 4.29 (dd, J = 10.5, 6.6 Hz, 1H), 4.08 (dd, J = 9.2, 3.9 Hz, 1H), 3.83 (dd, J = 10.5, 4.1 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.0, 162.4 (dd, J = 246.9, 13.2 Hz), 143.1 (t, J = 8.8 Hz), 141.4, 136.4,

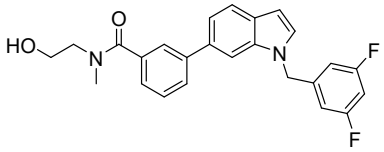
133.9, 133.1, 130.2, 129.3, 128.9, 128.0, 125.9(125.95), 125.9(125.89), 121.1, 118.8, 110.12 (dd, J = 19.7, 5.9 Hz), 108.3, 102.8 (t, J = 25.7 Hz), 101.5, 62.8, 60.4, 58.5, 48.0. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{25}H_{20}F_2N_2O_2$, 441.1385; found, 441.1386.

Compound **H20**



Compound **H20** was obtained by Compound **15c** (720 mg, 2.5 mmol) and compound **13d** (1.02 g, 2.75 mmol) in 71.0% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.61 (dt, J = 6.8, 2.1 Hz, 1H), 7.45 (s, 1H), 7.42 – 7.36 (m, 3H), 7.13 (d, J = 3.2 Hz, 1H), 6.67 (tt, J = 8.9, 2.4 Hz, 1H), 6.63 – 6.58 (m, 1H), 5.32 (s, 2H), 3.96 – 3.91 (m, 2H), 3.72 – 3.62 (m, 4H), 3.45 (t, J = 5.1 Hz, 2H), 3.33 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 163.4 (dd, J = 249.5, 12.6 Hz), 142.5, 141.8 (t, J = 8.6 Hz), 136.8, 136.7, 134.7, 129.1, 129.0, 128.6, 128.5, 126.2, 125.5, 121.6, 119.7, 109.6 (dd, J = 19.9, 6.0 Hz), 108.1, 103.2 (t, J = 25.3 Hz), 102.5, 61.0, 60.4, 53.6, 49.6, 49.3. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{26}H_{24}F_2N_2O_3$, 473.1647; found, 473.1657.

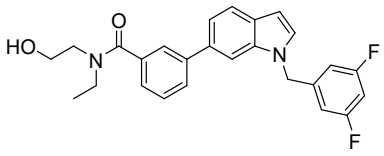
Compound **H21**



Compound **H21** was obtained by Compound **15d** (645 mg, 2.5 mmol) and compound **13d** (1.02 g, 2.75 mmol) in 64.7% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85 (s, 1H), 7.78 – 7.68 (m, 2H), 7.66 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 3.1 Hz, 1H), 7.50 (q, J = 7.5 Hz, 1H), 7.39 (dd, J = 8.2, 1.6 Hz, 1H), 7.33 (dt, J = 7.6, 1.4 Hz, 1H), 7.15 – 7.07 (m, 1H), 6.95 – 6.87 (m, 2H), 6.56 (d, J = 3.1 Hz, 1H), 5.57 (s, 2H), 4.88 – 4.80 (m, 1H), 3.66 (q, J = 5.9 Hz, 1H), 3.57 – 3.49 (m, 2H), 3.33 (t, J = 5.8 Hz, 1H), 3.04 – 2.96 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.0, 162.4 (dd, J = 246.7, 13.1 Hz), 143.1 (t, J = 8.8 Hz), 141.1, 137.6, 136.4, 133.2, 130.1,

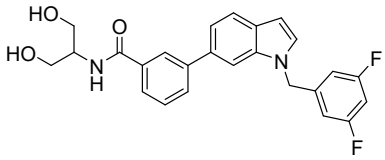
128.8, 127.9, 127.3, 125.2, 125.1, 121.1, 118.7, 110.1 (dd, J = 19.5, 6.0 Hz), 108.2, 103.04, 102.8 (t, J = 25.7 Hz), 58.1, 52.7, 48.0, 32.5. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{25}H_{22}F_2N_2O_2$, 443.1542; found, 443.1540.

Compound **H22**



Compound **H22** was obtained by Compound **15e** (544 mg, 2.0 mmol) and compound **13d** (812 mg, 2.2 mmol) in 65.0% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.84 (d, J = 1.5 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.58 (d, J = 3.2 Hz, 1H), 7.49 (q, J = 6.9 Hz, 1H), 7.39 (dd, J = 8.3, 1.5 Hz, 1H), 7.31 (t, J = 6.9 Hz, 1H), 7.16 – 7.07 (m, 1H), 6.96 – 6.87 (m, 2H), 6.56 (d, J = 3.0 Hz, 1H), 5.57 (s, 2H), 4.87 – 4.79 (m, 1H), 3.64 (q, J = 5.9 Hz, 1H), 3.50 (t, J = 6.7 Hz, 3H), 3.29 (t, J = 6.9 Hz, 2H), 1.19 – 0.98 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.5, 162.4 (dd, J = 246.8, 13.1 Hz), 143.1 (t, J = 8.8 Hz), 141.2, 137.9, 136.4, 133.2, 130.2, 128.9, 128.0, 127.3, 124.9, 124.3, 121.1, 118.7, 110.1 (dd, J = 19.6, 5.9 Hz), 108.2, 102.8 (t, J = 25.8 Hz), 101.5, 58.7, 50.2, 48.1, 44.3, 13.9. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{26}H_{24}F_2N_2O_2$, 457.1698; found, 457.1703.

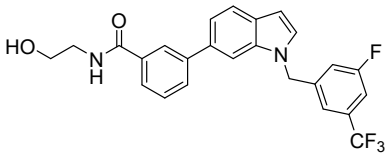
Compound **H23**



Compound **H23** was obtained by Compound **15f** (807 mg, 2.95 mmol) and compound **13d** (1.2 g, 3.24 mmol) in 65.3% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 7.8 Hz, 2H), 7.35 (s, 1H), 7.31 – 7.26 (m, 2H), 7.24 (t, J = 3.9 Hz, 1H), 7.06 (d, J = 3.1 Hz, 1H), 6.59 (tt, J = 8.8, 2.3 Hz, 1H), 6.54 (d, J = 3.2 Hz, 1H), 6.51 (d, J = 5.8 Hz, 2H), 5.21 (s, 2H), 4.11 – 4.05 (m, 1H), 3.80 (dd, J = 11.3, 4.4

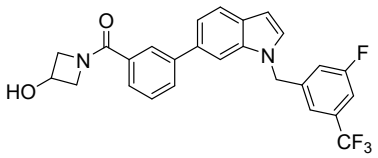
Hz, 2H), 3.71 (dd, J = 11.4, 5.0 Hz, 2H), 3.40 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 163.3 (dd, J = 249.7, 12.7 Hz), 142.7, 141.7 (t, J = 8.6 Hz), 136.7, 134.5, 134.4, 130.7, 129.1, 129.0, 128.5, 126.3, 125.2, 121.6, 119.8, 109.5 (dd, J = 19.9, 6.0 Hz), 108.0, 103.2 (t, J = 25.3 Hz), 102.5, 62.1, 53.2, 49.1. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{25}H_{22}F_2N_2O_3$, 459.1491; found, 459.1492.

Compound **H24**



Compound **H24** was obtained by Compound **15a** (355 mg, 1.45 mmol) and compound **13e** (670 mg, 1.6 mmol) in 60.5% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (t, J = 5.6 Hz, 1H), 8.15 (t, J = 1.9 Hz, 1H), 7.91 (s, 1H), 7.82 (dt, J = 7.7, 1.5 Hz, 1H), 7.79 (dt, J = 7.8, 1.4 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 3.2 Hz, 1H), 7.58 (dt, J = 8.8, 2.1 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.45 (dd, J = 8.3, 1.5 Hz, 1H), 7.33 (dt, J = 9.3, 1.9 Hz, 1H), 6.58 (d, J = 3.1 Hz, 1H), 5.66 (s, 2H), 3.55 (t, J = 6.3 Hz, 2H), 3.37 (q, J = 6.1 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.5, 162.1 (d, J = 247.1 Hz), 143.2 (d, J = 7.3 Hz), 141.3, 136.4, 135.3, 133.5, 131.1 (dd, J = 32.7, 8.6 Hz), 130.0, 129.4, 128.7, 127.9, 125.6, 123.2 (dd, J = 272.7, 3.0 Hz), 121.1, 112.0 (t, J = 3.5 Hz), 119.0, 118.1 (d, J = 21.8 Hz), 111.9 – 111.7 (m), 108.2, 101.7, 59.8, 47.9, 42.3. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{25}H_{20}F_4N_2O_2$, 479.1353; found, 479.1353.

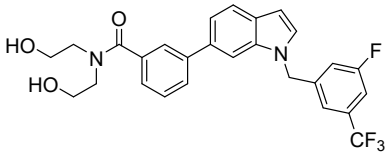
Compound **H25**



Compound **H25** was obtained by Compound **15b** (372 mg, 1.45 mmol) and compound **13e** (670 mg, 1.6 mmol) in 69.2% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 (d, J = 7.9 Hz, 2H), 7.83 (d, J = 7.3 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 3.2 Hz, 1H), 7.59 (d, J = 8.7 Hz, 1H), 7.57 – 7.50 (m, 3H), 7.40 (dd, J = 8.2, 1.5 Hz, 1H), 7.36 (d, J = 9.3 Hz,

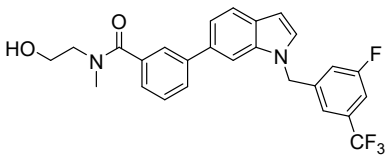
1H), 6.59 (d, J = 3.1 Hz, 1H), 5.78 (d, J = 5.8 Hz, 1H), 5.68 (s, 2H), 4.56 – 4.51 (m, 1H), 4.49 (t, J = 7.8 Hz, 1H), 4.29 (t, J = 8.4 Hz, 1H), 4.07 (dd, J = 9.1, 4.1 Hz, 1H), 3.84 (dd, J = 10.7, 4.3 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.1, 162.1 (d, J = 247.2 Hz), 143.2 (d, J = 7.5 Hz), 141.4, 136.4, 134.0, 133.2, 131.1 (dd, J = 32.8, 8.5 Hz), 130.1, 129.3, 128.9, 128.0, 125.9(125.94), 125.9(125.90), 123.2 (dd, J = 273.1, 2.9 Hz), 121.2, 120.0 – 119.9 (m), 118.8, 118.2 (d, J = 21.7 Hz), 111.9 – 111.7 (m), 108.2, 101.7, 62.7, 60.4, 58.5, 47.9. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{26}H_{20}F_4N_2O_2$, 491.1353; found, 491.1359.

Compound **H26**



Compound **H26** was obtained by Compound **15c** (420 mg, 1.45 mmol) and compound **13e** (670 mg, 1.6 mmol) in 60.7% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.61 (dt, J = 6.7, 2.2 Hz, 1H), 7.46 (s, 1H), 7.42 – 7.34 (m, 3H), 7.27 (s, 1H), 7.20 (dt, J = 8.4, 2.1 Hz, 1H), 7.13 (d, J = 3.2 Hz, 1H), 6.87 (dt, J = 9.1, 2.0 Hz, 1H), 6.61 (d, J = 3.1 Hz, 1H), 5.38 (s, 2H), 3.92 (t, J = 5.0 Hz, 2H), 3.66 (q, J = 4.9 Hz, 4H), 3.49 (s, 2H), 3.44 (t, J = 5.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 163.0 (d, J = 250.0 Hz), 142.4, 141.8 (d, J = 7.0 Hz), 136.8, 136.7, 134.8, 133.0 (dd, J = 33.4, 8.0 Hz), 129.0(129.00), 129.0(128.95), 128.6, 128.5, 126.2, 125.5, 123.2 (dd, J = 272.7, 3.0 Hz), 121.7, 119.8, 119.3 (t, J = 3.6 Hz), 117.3 (d, J = 22.1 Hz), 112.3 (dd, J = 24.6, 3.8 Hz), 108.0, 102.8, 60.9, 60.3, 53.6, 49.6, 49.1. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{27}H_{24}F_4N_2O_3$, 523.1615; found, 523.1625.

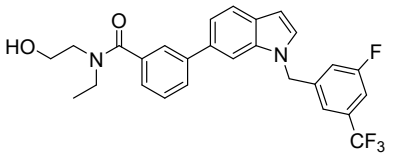
Compound **H27**



Compound **H27** was obtained by Compound **15d** (343 mg, 1.33 mmol) and compound **13e** (670 mg, 1.6 mmol) in 64.0% yield .^{1}H NMR (500

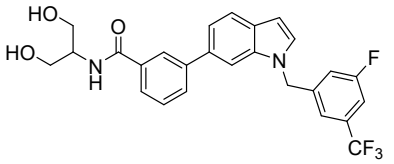
MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.77 – 7.68 (m, 2H), 7.66 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 3.2 Hz, 1H), 7.58 (dt, J = 8.7, 2.1 Hz, 1H), 7.53 (s, 1H), 7.49 (q, J = 7.6 Hz, 1H), 7.39 (dd, J = 8.2, 1.6 Hz, 1H), 7.36 – 7.31 (m, 2H), 6.57 (d, J = 3.1 Hz, 1H), 5.65 (s, 2H), 4.88 – 4.80 (m, 1H), 3.65 (q, J = 6.0 Hz, 1H), 3.56 – 3.47 (m, 2H), 3.32 (t, J = 5.9 Hz, 1H), 3.04 – 2.95 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 162.0 (d, J = 247.2 Hz), 143.2 (d, J = 7.3 Hz), 141.0, 137.6, 136.4, 133.2, 131.1 (dd, J = 32.7, 8.6 Hz), 130.0, 128.7, 128.0, 127.6, 127.2, 125.2, 123.2 (dd, J = 272.7, 3.0 Hz), 121.1, 120.0 (t, J = 3.5 Hz), 118.8, 118.2 (d, J = 21.7 Hz), 112.0 – 111.6 (m), 108.2, 101.7, 58.1, 52.7, 47.9, 32.5. HRMS (ESI, m/z): [M+Na]$^+$ calculated for $C_{26}H_{22}F_4N_2O_2$, 493.1510; found, 493.1516.

Compound **H28**



Compound **H28** was obtained by Compound **15e** (362 mg, 1.33 mmol) and compound **13e** (670 mg, 1.6 mmol) in 62.0% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.88 (d, J = 1.5 Hz, 1H), 7.73 (d, J = 6.9 Hz, 1H), 7.66 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 3.2 Hz, 1H), 7.58 (dt, J = 8.7, 2.1 Hz, 1H), 7.53 (s, 1H), 7.49 (q, J = 6.9 Hz, 1H), 7.39 (dd, J = 8.3, 1.5 Hz, 1H), 7.34 (d, J = 9.3 Hz, 1H), 7.30 (t, J = 7.0 Hz, 1H), 6.56 (d, J = 3.1 Hz, 1H), 5.65 (s, 2H), 4.86 – 4.79 (m, 1H), 3.63 (q, J = 5.6 Hz, 1H), 3.50 (t, J = 6.6 Hz, 3H), 3.28 (t, J = 6.7 Hz, 2H), 1.20 – 0.99 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.5, 162.0 (d, J = 247.1 Hz), 143.2 (d, J = 7.4 Hz), 141.2, 137.9, 136.3, 133.1, 131.1 (dd, J = 32.6, 8.4 Hz), 130.1, 128.9, 128.8, 128.0, 127.3, 124.9, 123.2 (dd, J = 272.9, 3.1 Hz), 121.1, 120.0 (t, J = 3.4 Hz), 118.8, 118.2 (d, J = 21.9 Hz), 112.0 – 111.7 (m) 108.2, 101.7, 58.7, 50.2, 47.9, 44.3, 13.9. HRMS (ESI, m/z): [M+Na]$^+$ calculated for $C_{27}H_{24}F_4N_2O_2$, 507.1666; found, 507.1673.

Compound **H29**



Compound **H29** was obtained by Compound **15f** (400 mg, 1.45 mmol) and compound **13e** (670 mg, 1.6 mmol) in 60.3% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.14 (t, J = 1.8 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.89 (s, 1H), 7.81 (td, J = 7.6, 1.6 Hz, 2H), 7.69 (d, J = 8.3 Hz, 1H), 7.62 (d, J = 3.2 Hz, 1H), 7.58 (dt, J = 8.8, 2.1 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.46 (dd, J = 8.2, 1.6 Hz, 1H), 7.33 (dt, J = 9.4, 2.0 Hz, 1H), 6.58 (d, J = 3.1 Hz, 1H), 5.66 (s, 2H), 4.69 (s, 2H), 4.05 – 3.96 (m, 1H), 3.55 (d, J = 5.9 Hz, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.5, 162.1 (d, J = 247.4 Hz), 143.2 (d, J = 7.3 Hz), 141.3, 136.4, 135.5, 133.5, 131.2 (dd, J = 32.7, 8.3 Hz), 130.0, 129.4, 128.7, 127.9, 125.8, 123.2 (dd, J = 272.5, 2.5 Hz), 121.1, 119.9 (t, J = 3.7 Hz), 119.1, 118.1 (d, J = 21.9 Hz), 111.9 – 111.7 (m), 108.2, 101.8, 60.4, 54.0, 47.9. HRMS (ESI, m/z): $[M+Na]^+$ calculated for $C_{26}H_{22}F_4N_2O_3$, 509.1459; found, 509.1465.

2. **Evaluation of GPR52 Agonistic Activities.**

Forskolin was used as the reference compound in this test and reported GPR52 agonist 4-(3-(3-fluoro-5-(trifluoromethyl)-benzyl)-5-methyl-1H-1,2,4-triazol-1-yl)-2-methylbenzamide (FTBMT, EC_{50} = 75 nM) was synthesized and used as the reference compound when screened in our assay in a 12-point concentration-response. Intracellular cAMP levels were quantified using a commercial cAMP TR-FRET kit (Shanghai VKEY Biotechnologies Co. Ltd.) according to the manufacturer's protocol.

After transfection for 48 h, CHO cells expressing human GPR52 were seeded at 12000 cells/well (0.2 ug/well GPR52 plasmid) and were incubated with test compounds (0.0126 nM-50000 nM, DMSO) for 30 min at 37 °C in the stimulation buffer (HBSS with 5mM HEPES, 0.5mM IBMX and 0.1% BSA (pH 7.4)). Following incubation, 5 μL of the Eu-labeled antibody working solution and 5 μL of the cAMP tracer complex were sequentially added to each well. The plate was sealed and incubated in the dark at room temperature for 60 minutes. The time-resolved fluorescence resonance energy transfer (TR-FRET) signal was then measured using a microplate reader (excitation at 320 nm, emission at 665 nm with a reference at 615 nm). The EC_{50} values were calculated with GraphPad Prism using a four-parameter nonlinear regression curve-fitting algorithm. Data were presented as Mean ± SEM. [1]

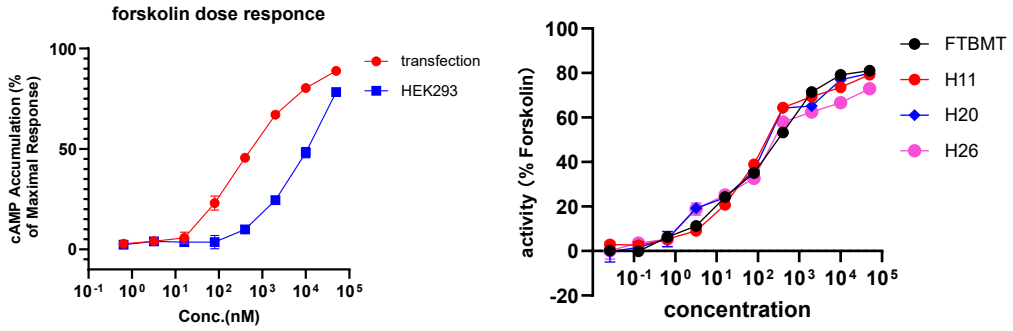


Fig. S3. Dose-Response Curves of the Reference Compound Forskolin, **H11**, **H20** and **H26**.

3. **MK-801-Induced Hyperlocomotion Test.**

Adult male ICR mice (22 ± 4 g) were purchased from Pizhou Oriental Breeding Co., Ltd. (Xuzhou, China) and housed under controlled conditions (21 ± 3 ^{o}C, 50 ± 20% humidity) with a 12-hour light/dark cycle (8 a.m. to 8 p.m.). The mice had free access to food and water and were randomly assigned to experimental groups (n = 8 per group) with individual cage housing. All procedures followed ethical guidelines to minimize animal suffering and reduce sample sizes, in compliance with the approved protocols (Project ID: 202300038) from the Ethics and Experimental Animal Committee of Jiangsu Ocean University.

The experiment was conducted in 20 × 20 cm^2 Plexiglas chambers under standardized environmental conditions. Male mice were grouped (8 mice in each group), weighed (20 – 25 g), labeled (solvent group, model group and drug administration group), and placed in a laboratory box in the field for an hour of acclimatization. Then, the mice were orally given corresponding compound in appropriate concentration and settled into the open field. After 30 minutes, 0.02 mg/ml of MK-801 (Dizocilpine) solution was intraperitoneally injected, and mice were immediately put back to the open field. The activity of the mice was monitored after the injection and continued for 60 minutes. After the recording, the recorded distance is analyzed using Prism 8.0. Data were presented as Mean ± SEM and statistically analyzed using one-way variance. When the P value is less than 0.05, it indicates statistical significance between groups.[2]

4. **Molecular Docking**

Molecular docking studies were performed using Discovery Studio 2019 (DS) to investigate the binding modes of synthesized compounds with GPR52.[3] The workflow consisted of the following steps: First, compound structures were drawn in ChemDraw 20.0 and prepared using the Small Molecules module in DS with default parameters. The crystal structure of GPR52 (PDB ID: 6LI0, resolution 2.20 Å) was retrieved from the Protein Data Bank and processed in the Prepare Protein module, including hydrogen addition, charge assignment, and removal of water molecules and native ligands.

The binding site was defined as a sphere centered at coordinates X = 33.9597, Y = 71.1931, Z = 66.6059 with a 10 Å radius. Semi-flexible docking was conducted using the CDOCKER module, with the Pose Cluster Radius parameter set to 0.5 (all other parameters at default settings). Resulting protein-ligand complexes were analyzed for key interactions in the DS visualization panel, with subsequent graphical rendering and analysis performed using PyMOL software.

5. ADMET Prediction

In this study, the ADMET properties of the designed compounds were predicted using the online servers SwissADME (http://www.swissadme.ch/) and pkCSM (http://www.biosig.lab.uq.edu.au/pkcsm/).[3] As summarized in Table S1, the predicted ADMET parameters include solubility (Log S), Caco-2 permeability, blood-brain barrier (BBB) penetration, central nervous system (CNS) activity, among others. In addition, the drug-likeness of these compounds was evaluated, with the results presented in Table S2.

Table S1 Analysis of drug-like properties of these new compounds

Compound	MW	Log $P_{o/w}$（<5）	RB	HBA	HBD
H1	432.52	4.46	4	3	1
H2	464.57	4.32	8	4	2
H3	434.54	4.68	6	3	1
H4	448.57	4.92	7	3	1
H5	450.54	4.06	7	4	3
H6	446.55	4.94	7	3	2
H7	458.56	4.81	5	3	1
H8	490.60	4.71	9	4	2
H9	460.58	5.12	7	3	1
H10	474.60	5.45	8	3	1
H11	476.58	4.40	8	4	3
H12	384.48	4.00	6	3	2
H13	396.49	3.97	4	1	3
H14	428.53	3.78	8	4	2
H15	398.51	4.17	6	3	1
H16	412.53	4.46	7	3	1
H17	414.51	3.57	7	4	3
H18	406.43	4.30	6	3	2
H19	418.44	4.23	4	3	1
H20	450.49	4.04	8	4	2
H21	420.46	4.49	6	3	1
H22	434.49	4.78	7	3	1
H23	436.46	3.76	7	4	3
H24	456.44	5.03	6	3	2
H25	468.45	4.88	4	3	1
H26	500.49	4.76	8	4	2
H27	470.47	5.19	6	3	1
H28	484.49	5.47	7	3	1
H29	486.47	4.62	7	4	3

Table S2 ADMET prediction results of the new compounds

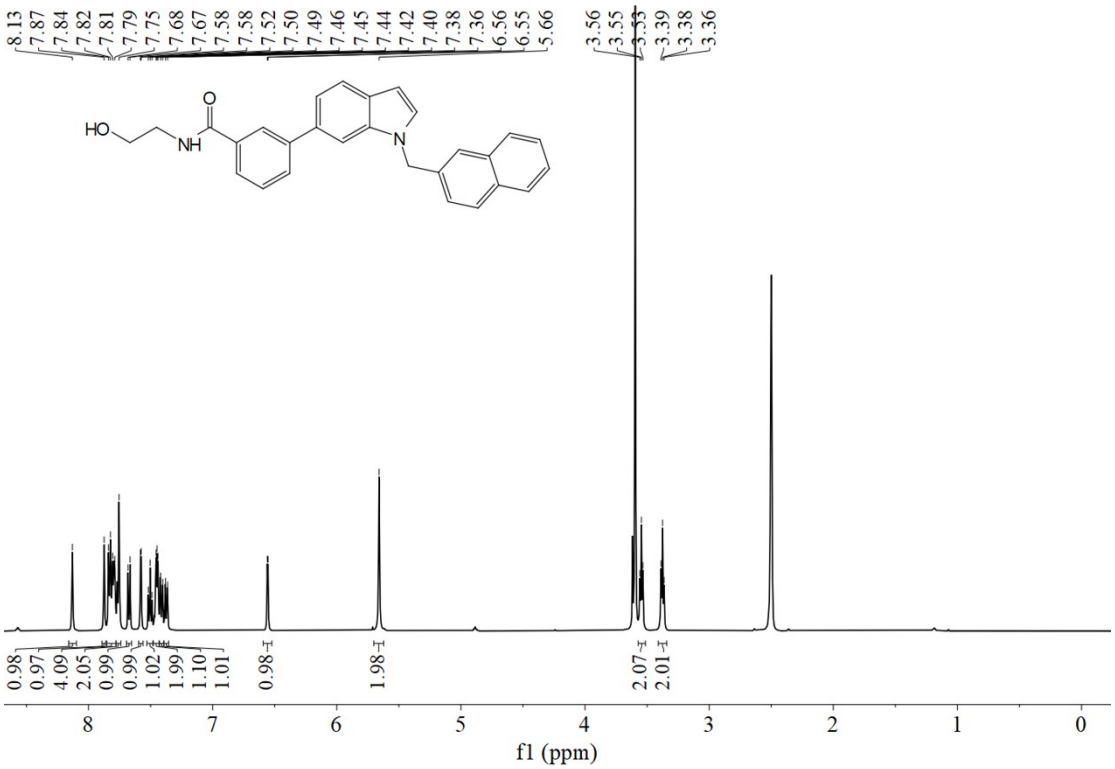
Compound	Log *S*	Caco2 permeability	BBB	CNS	CYP3A4	Total clearance	hERG I inhibitor	hERG II inhibitor	LD_{50}	Skin sensitization
H1	-5.141	1.004	Yes	Yes	Yes	0.566	No	Yes	2.379	No
H2	-4.779	0.775	Yes	Yes	Yes	0.705	No	Yes	2.776	No
H3	-5.481	1.003	Yes	Yes	Yes	0.673	No	Yes	2.348	No
H4	-5.475	0.990	Yes	Yes	Yes	0.709	No	Yes	2.336	No
H5	-4.672	0.811	Yes	Yes	Yes	0.549	No	Yes	2.800	No
H6	-5.467	0.976	Yes	Yes	Yes	0.609	No	Yes	2.515	No
H7	-5.174	0.983	Yes	Yes	Yes	0.590	No	Yes	2.549	No
H8	-4.698	0.724	Yes	Yes	Yes	0.731	No	Yes	2.888	No
H9	-5.469	0.982	Yes	Yes	Yes	0.697	No	Yes	2.509	No
H10	-5.424	0.970	Yes	Yes	Yes	0.734	No	Yes	2.500	No
H11	-4.610	0.760	Yes	Yes	Yes	0.574	No	Yes	2.905	No
H12	-4.718	1.006	Yes	Yes	Yes	0.620	No	Yes	2.658	No
H13	-4.537	1.013	Yes	Yes	Yes	0.595	No	Yes	2.683	No
H14	-4.544	0.915	Yes	Yes	Yes	0.741	No	Yes	2.895	No
H15	-4.828	1.012	Yes	Yes	Yes	0.708	No	Yes	2.656	No
H16	-4.921	1.000	Yes	Yes	Yes	0.744	No	Yes	2.648	No
H17	-4.440	0.751	Yes	Yes	Yes	0.584	No	Yes	2.921	No
H18	-5.052	1.055	Yes	Yes	Yes	0.441	No	Yes	2.955	No
H19	-4.741	1.062	Yes	Yes	Yes	0.407	No	Yes	3.003	No
H20	-5.030	0.952	Yes	Yes	Yes	0.493	No	Yes	3.206	No
H21	-5.169	1.061	Yes	Yes	Yes	0.520	No	Yes	2.958	No
H22	-5.313	1.049	Yes	Yes	Yes	0.558	No	Yes	2.948	No
H23	-4.910	0.568	Yes	Yes	Yes	0.356	No	Yes	3.218	No
H24	-5.079	1.021	Yes	Yes	Yes	0.297	No	Yes	2.751	No
H25	-4.749	1.028	Yes	Yes	Yes	0.269	No	Yes	2.783	No
H26	-4.944	0.889	Yes	Yes	Yes	0.420	No	Yes	2.965	No
H27	-5.182	1.027	Yes	Yes	Yes	0.386	No	Yes	2.753	No
H28	-5.293	1.015	Yes	Yes	Yes	0.422	No	Yes	2.746	No
H29	-4.846	0.925	Yes	Yes	Yes	0.262	No	Yes	2.986	No

Note: BBB: Blood brain barrier penetration; CNS: Central nervous system

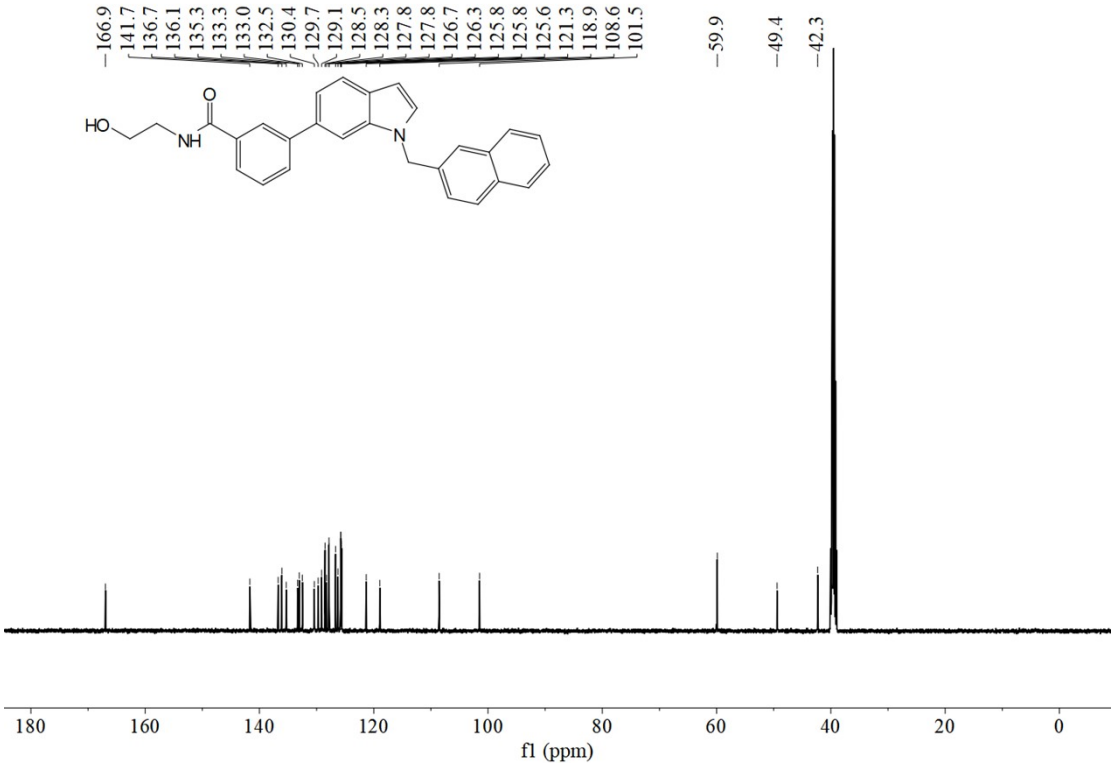
6. The ^{1}H NMR and ^{13}C NMR spectra of the new compounds

Compound **S2**:

^{1}H NMR (500 MHz, DMSO-d_6)

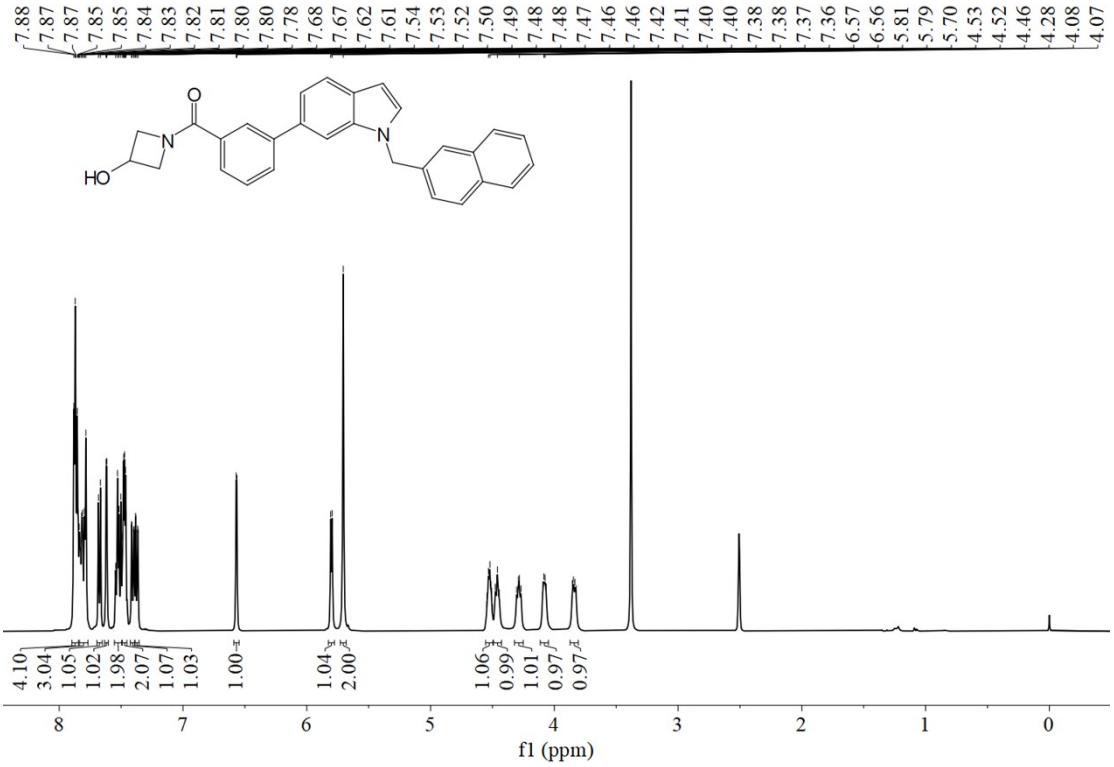


^{13}C NMR (125 MHz, DMSO-d_6)

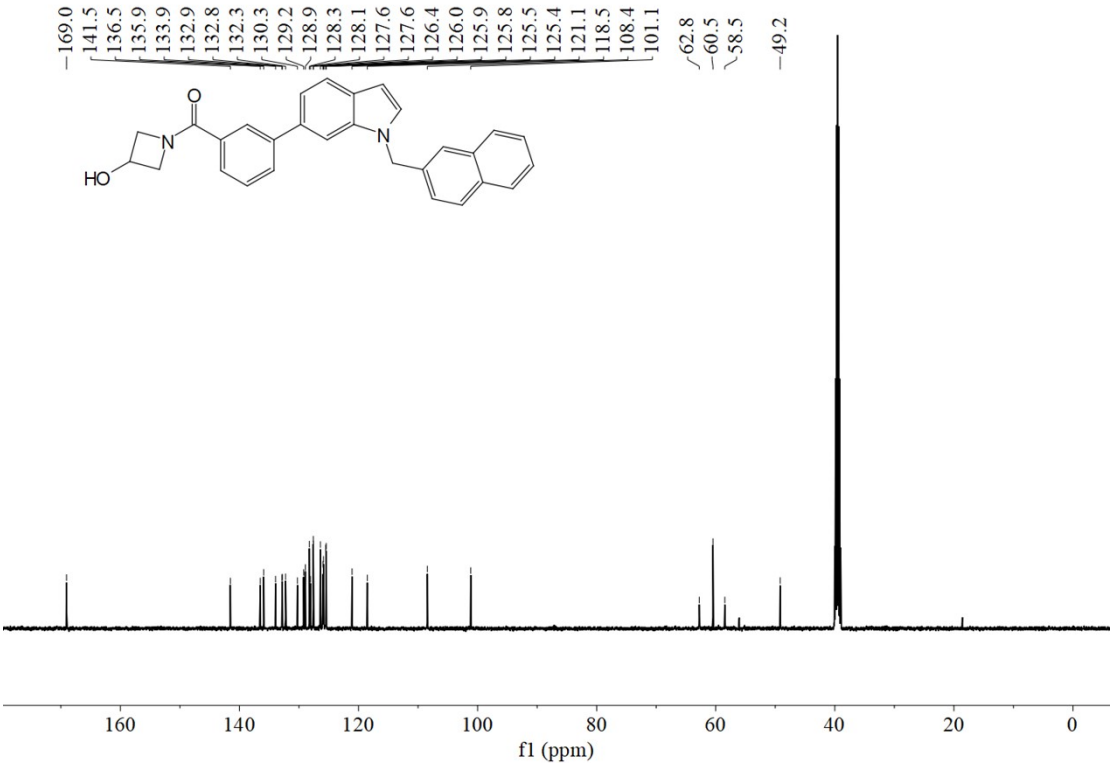


Compound **H1**:

^{1}H NMR (500 MHz, DMSO-d_6)

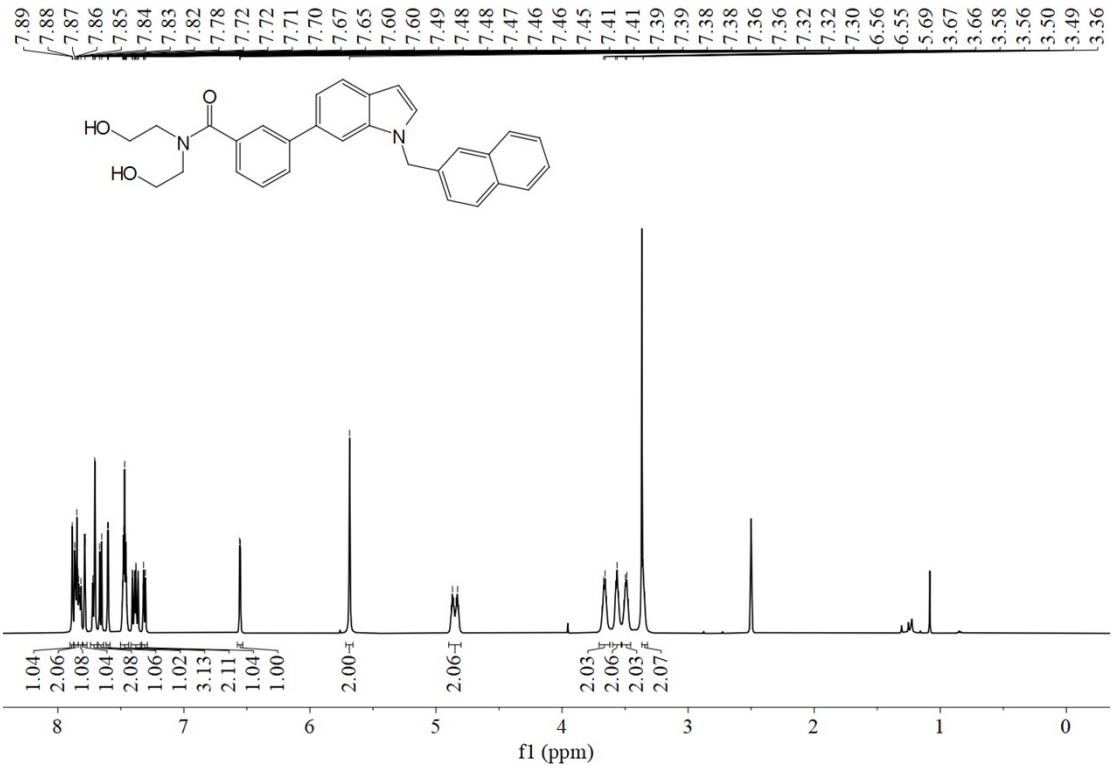


^{13}C NMR (125 MHz, DMSO-d_6)

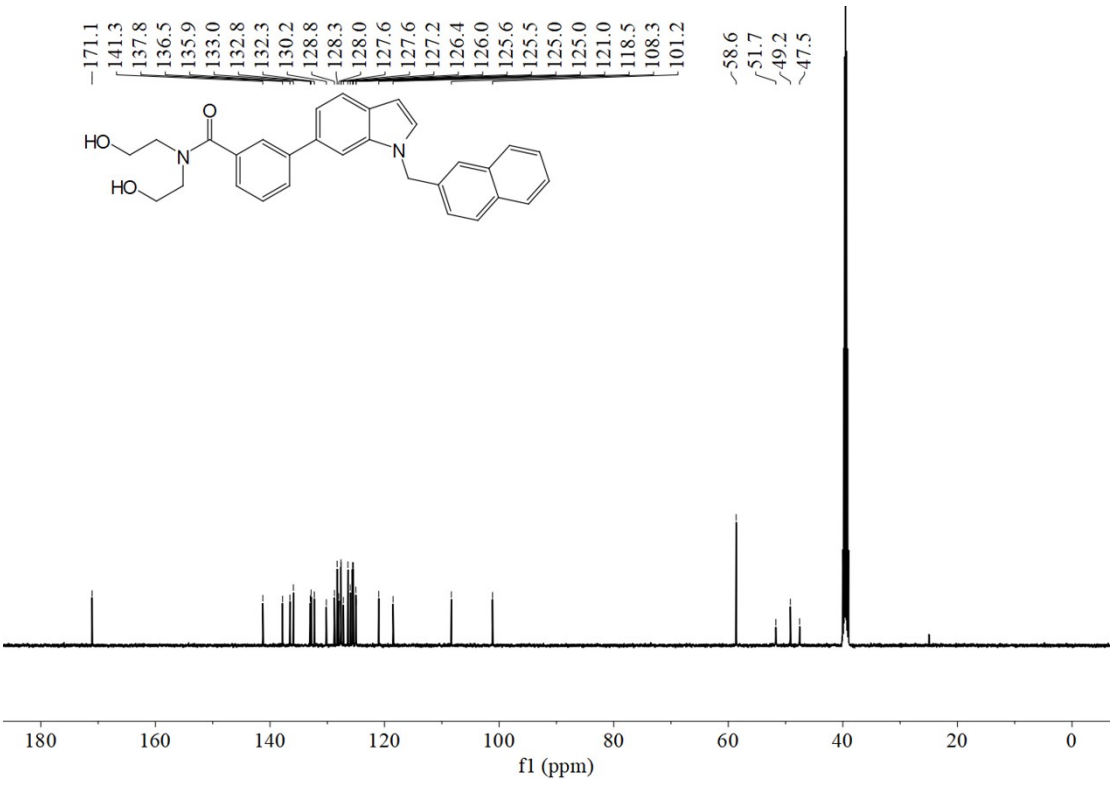


Compound **H2**:

^{1}H NMR (500 MHz, DMSO-d_6)

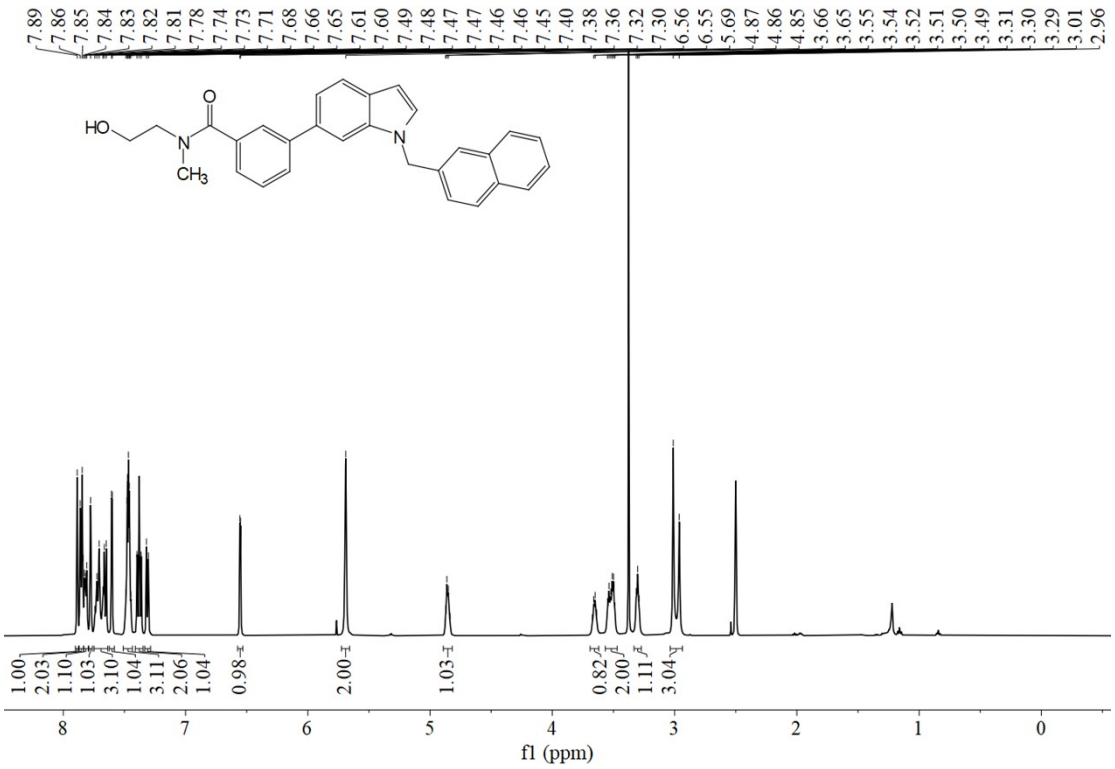


^{13}C NMR (125 MHz, DMSO-d_6)

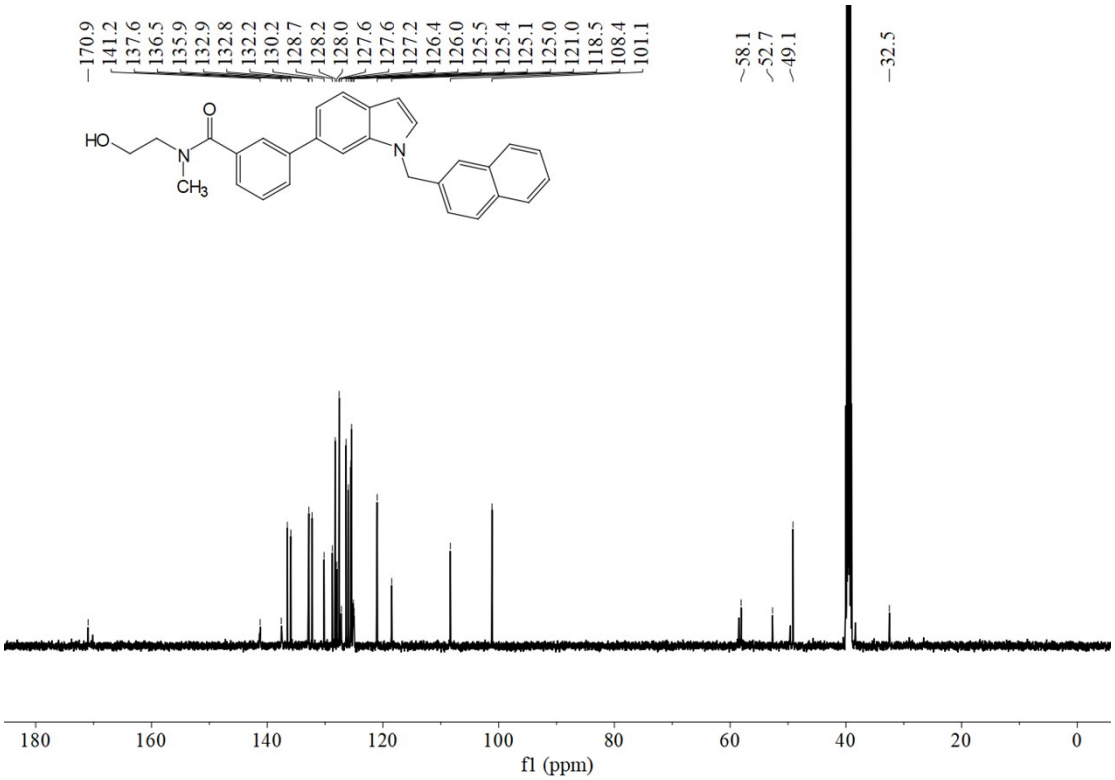


Compound **H3**:

^{1}H NMR (500 MHz, DMSO-d_6)

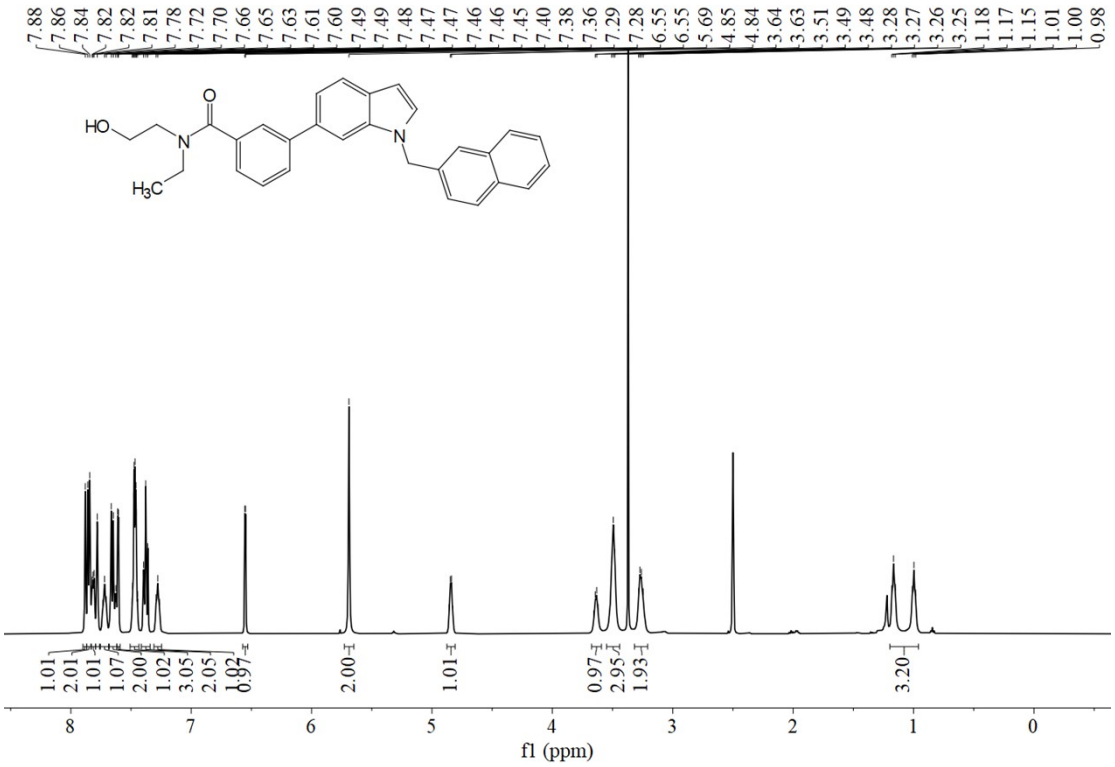


^{13}C NMR (125 MHz, DMSO-d_6)

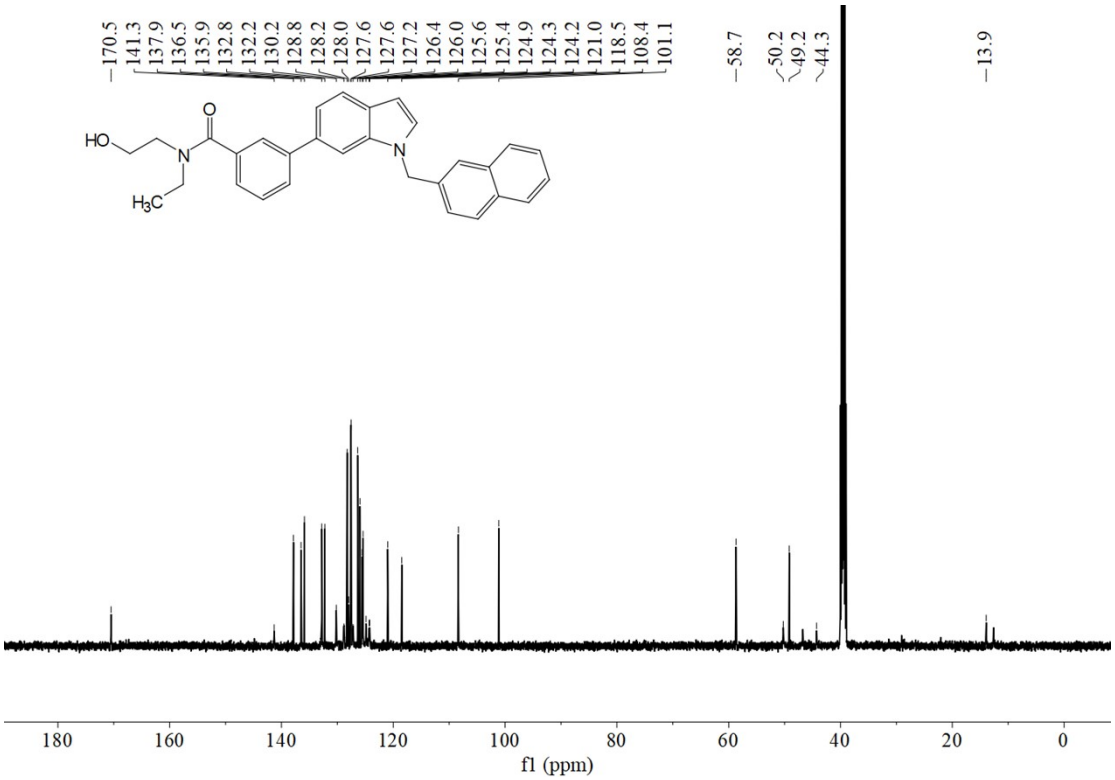


Compound **H4**:

^{1}H NMR (500 MHz, DMSO-d_6)

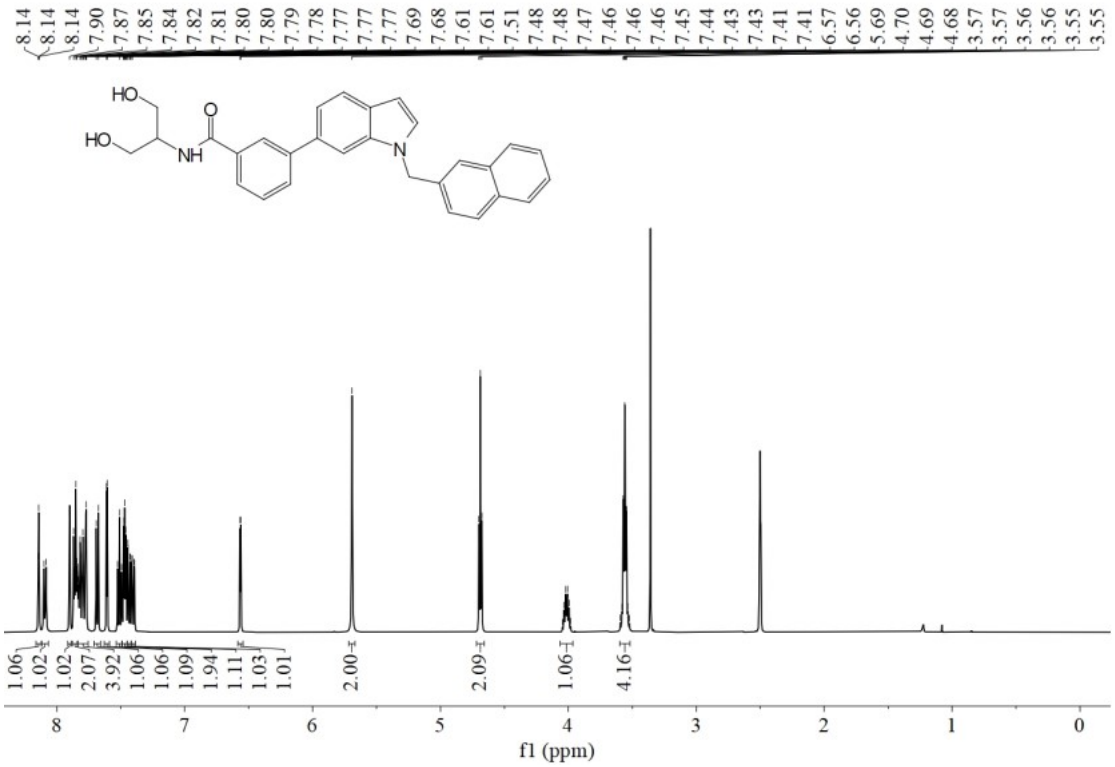


^{13}C NMR (125 MHz, DMSO-d_6)

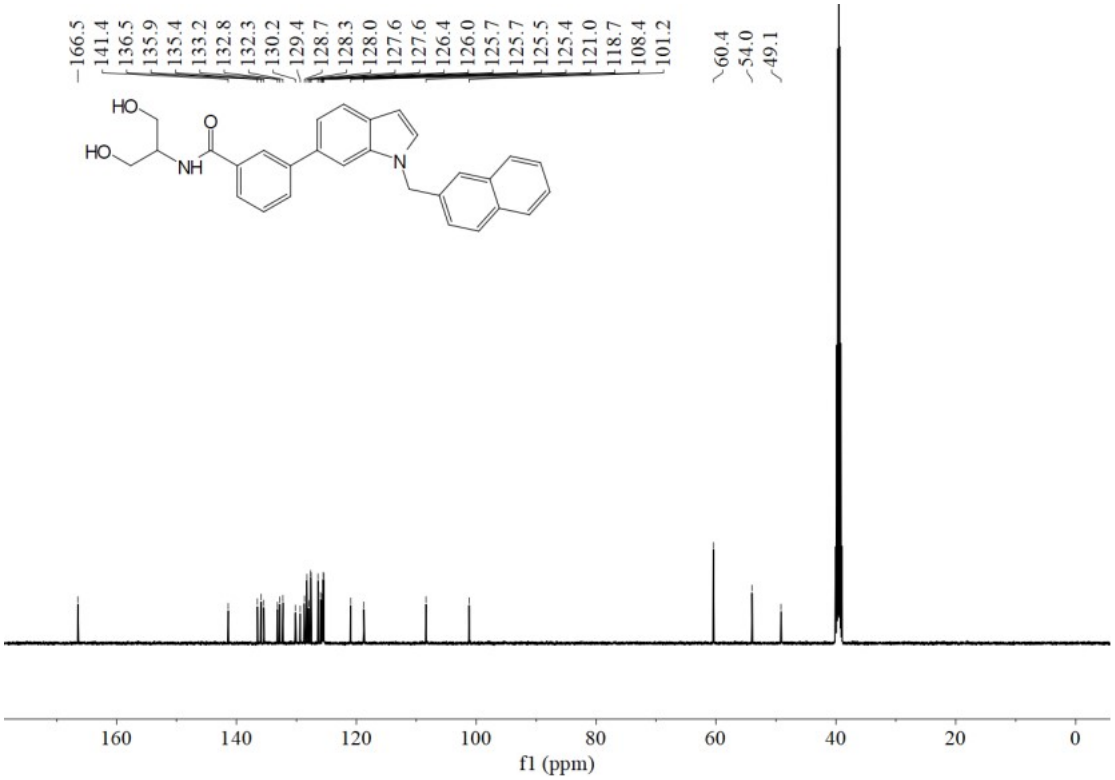


Compound **H5**:

^{1}H NMR (500 MHz, DMSO-d_6)

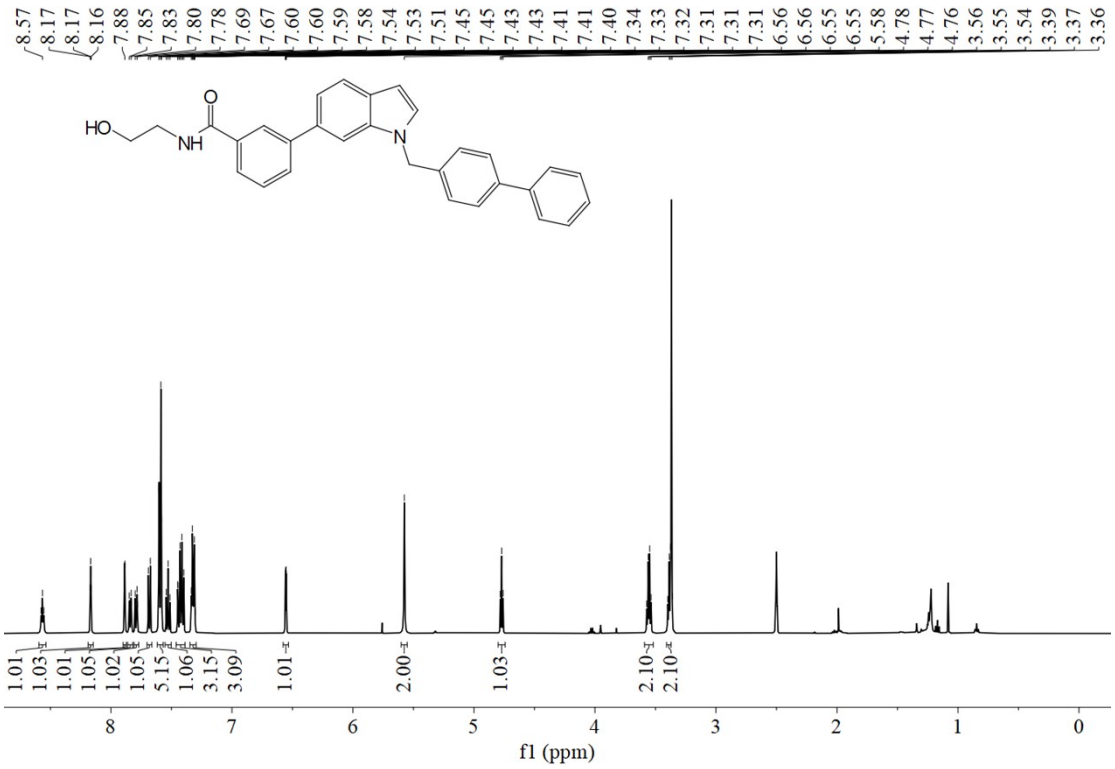


^{13}C NMR (125 MHz, DMSO-d_6)

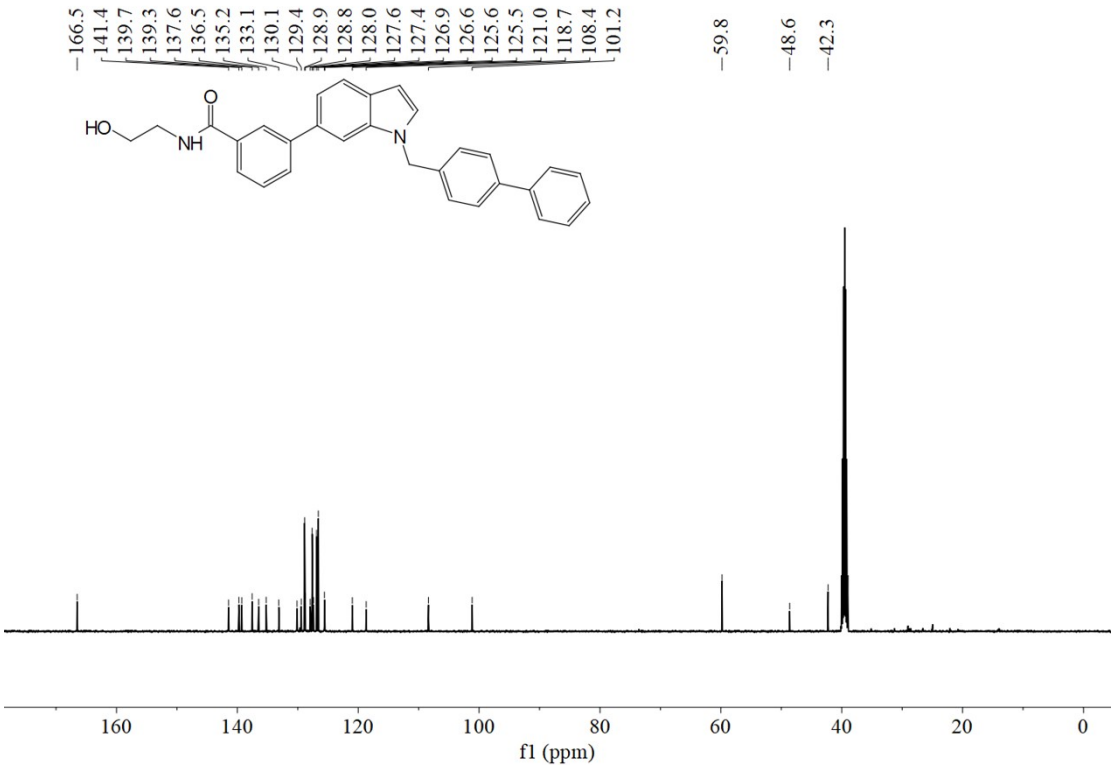


Compound **H6**:

^{1}H NMR (500 MHz, DMSO-d_6)

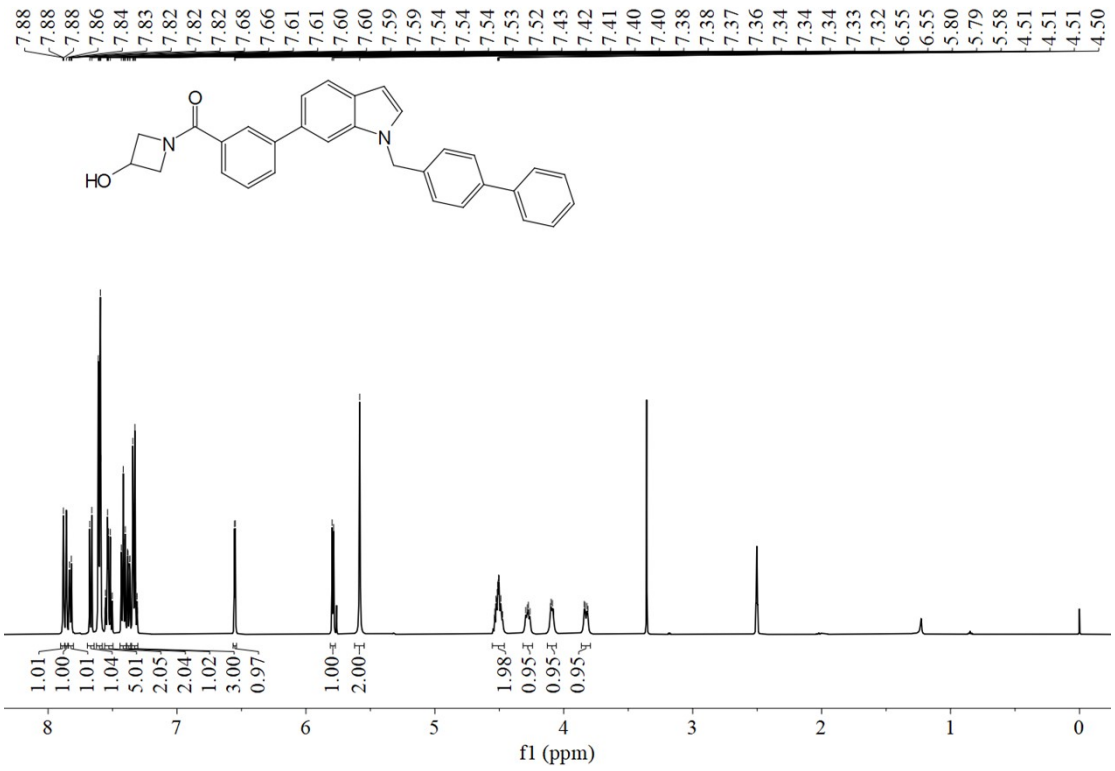


^{13}C NMR (125 MHz, DMSO-d_6)

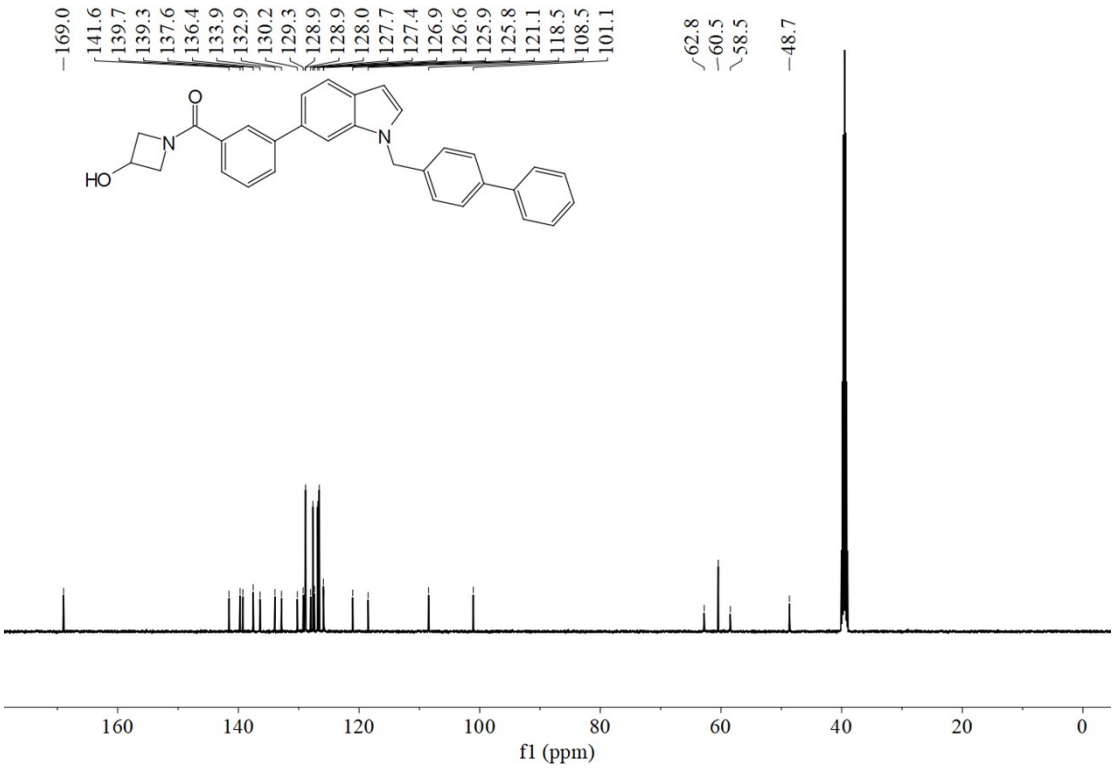


Compound **H7**:

^{1}H NMR (500 MHz, DMSO-d_6)

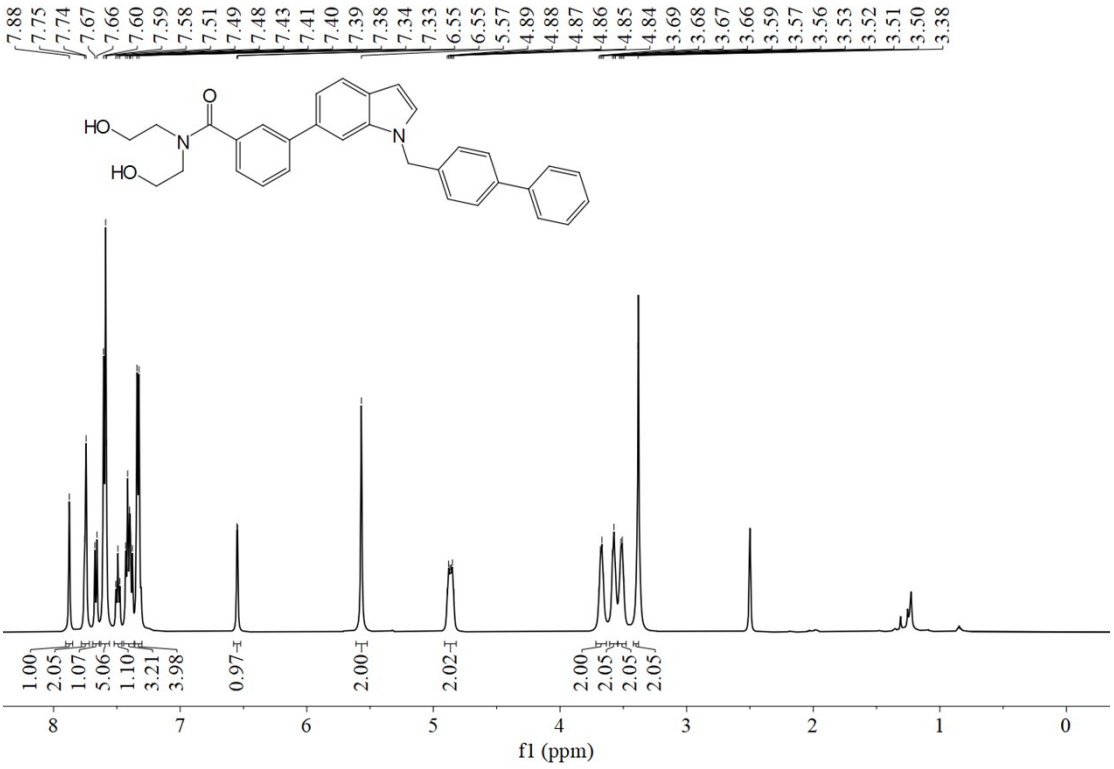


^{13}C NMR (125 MHz, DMSO-d_6)

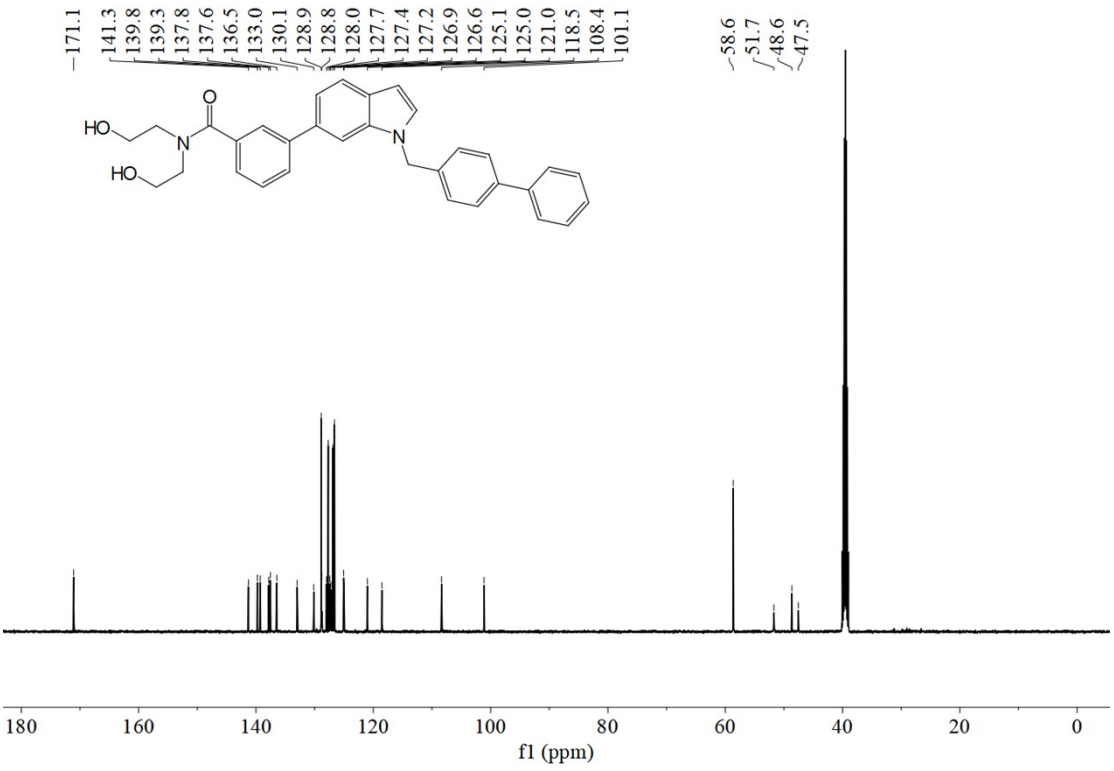


Compound **H8**:

^{1}H NMR (500 MHz, DMSO-d_6)

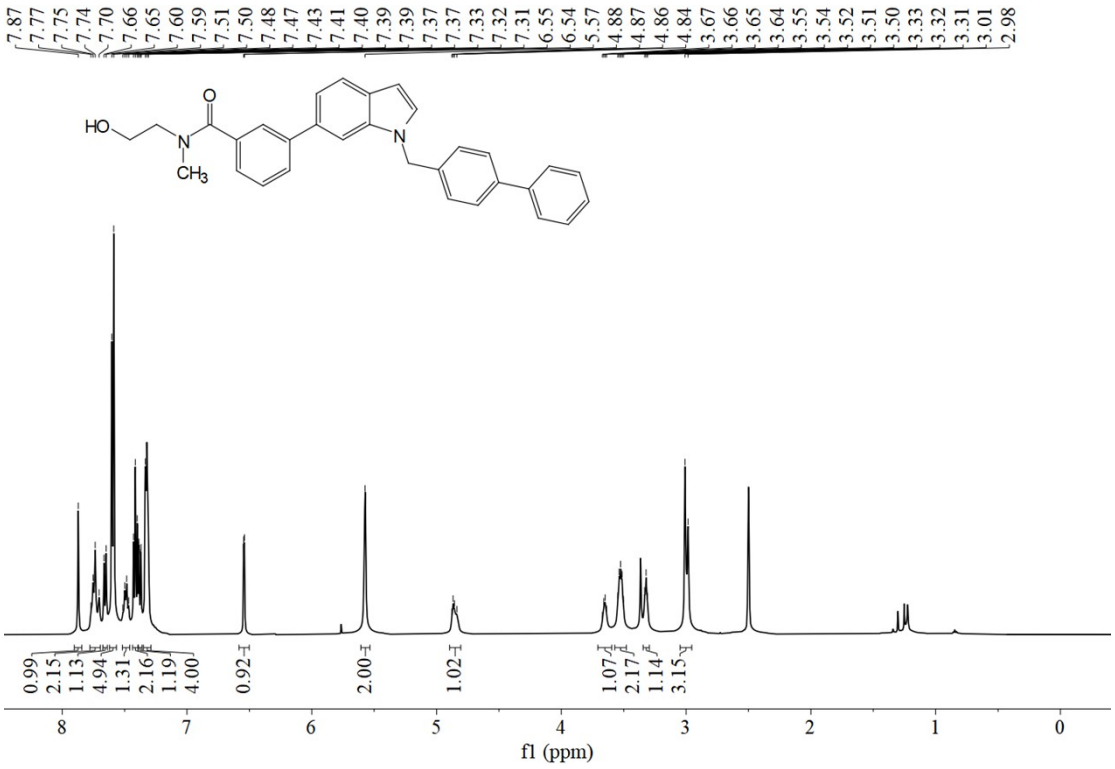


^{13}C NMR (125 MHz, DMSO-d_6)

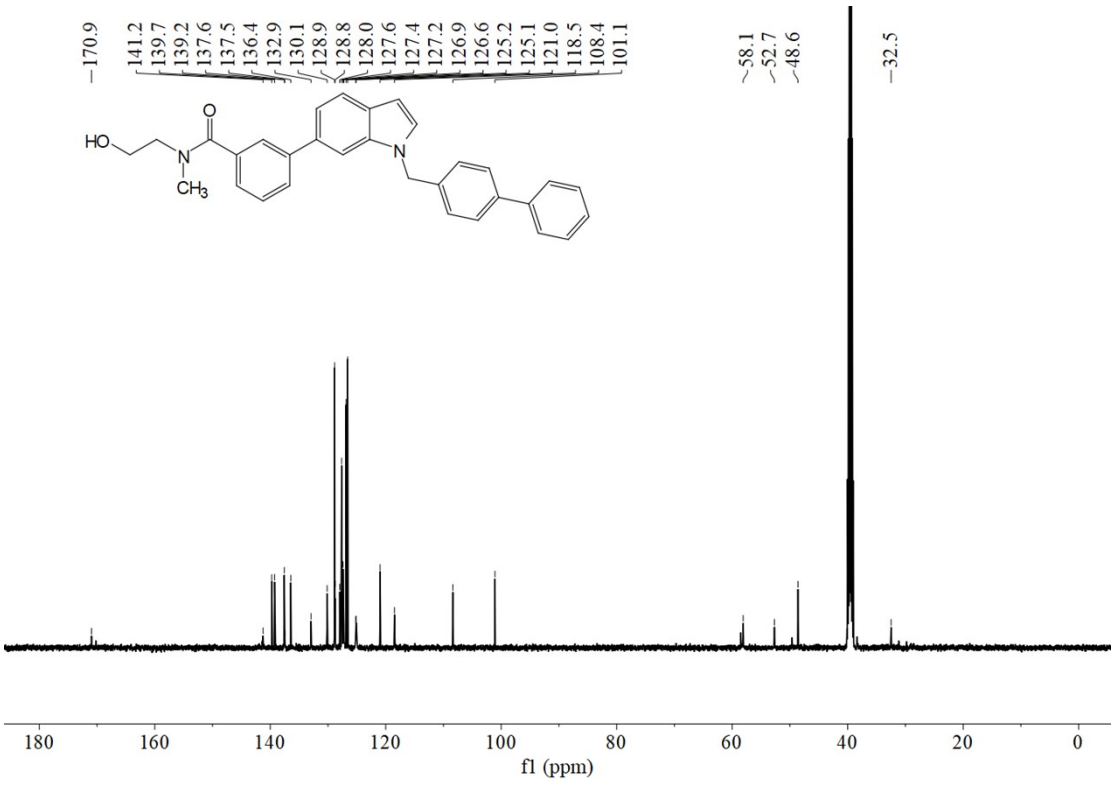


Compound **H9**:

^{1}H NMR (500 MHz, DMSO-d_6)

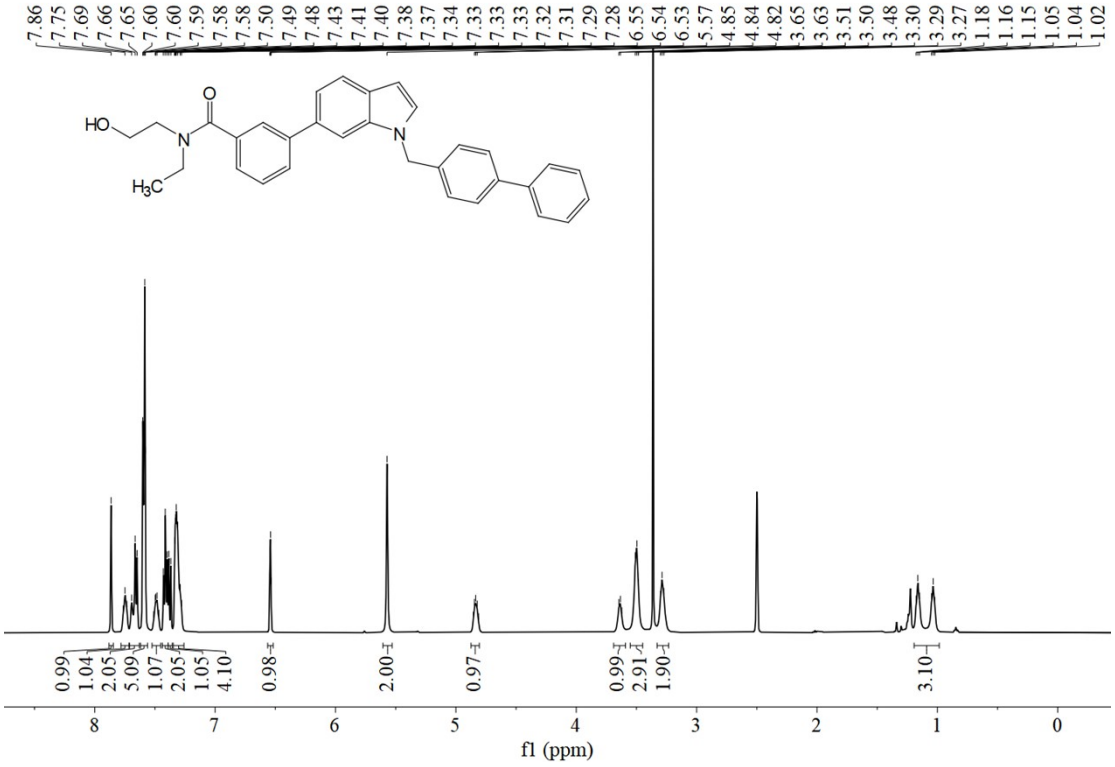


^{13}C NMR (125 MHz, DMSO-d_6)

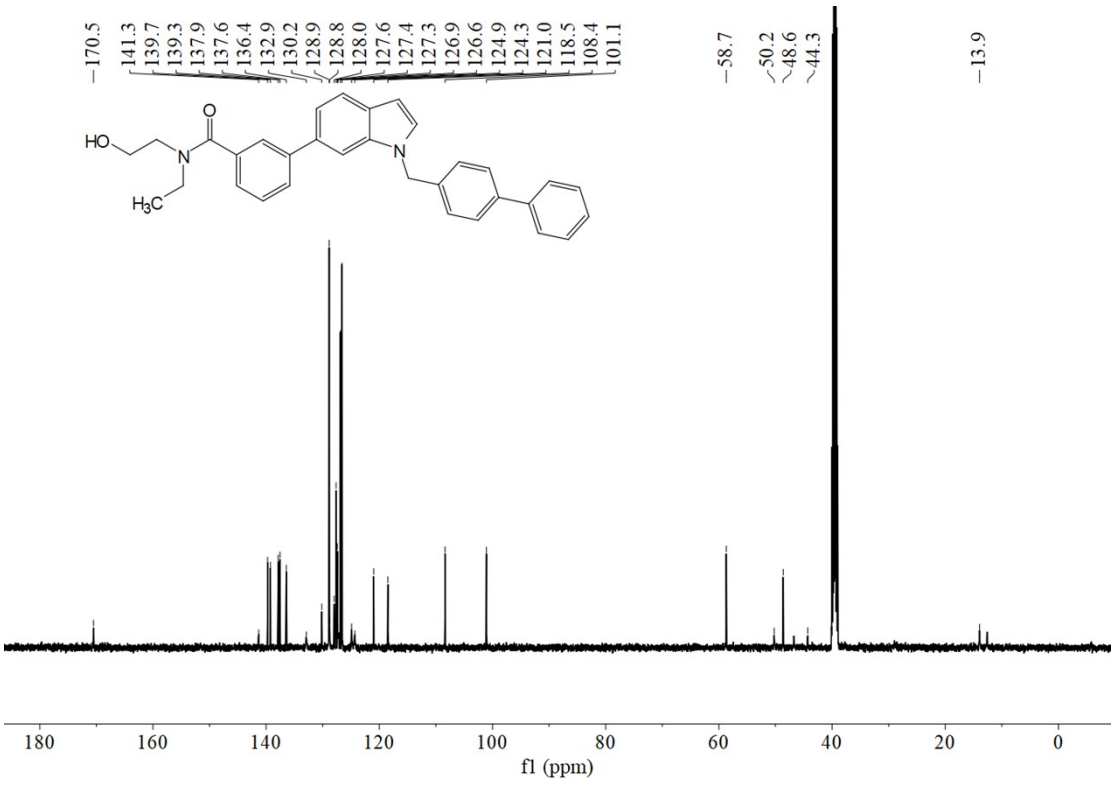


Compound **H10**:

^{1}H NMR (500 MHz, DMSO-d_6)

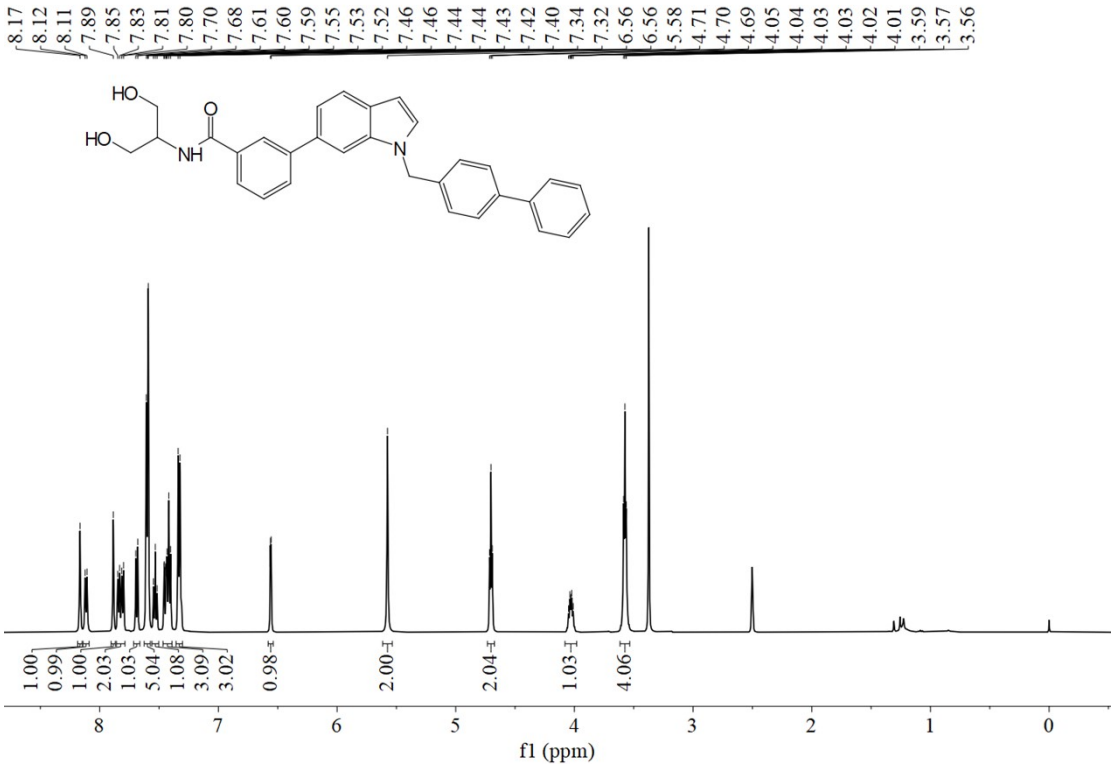


^{13}C NMR (125 MHz, DMSO-d_6)

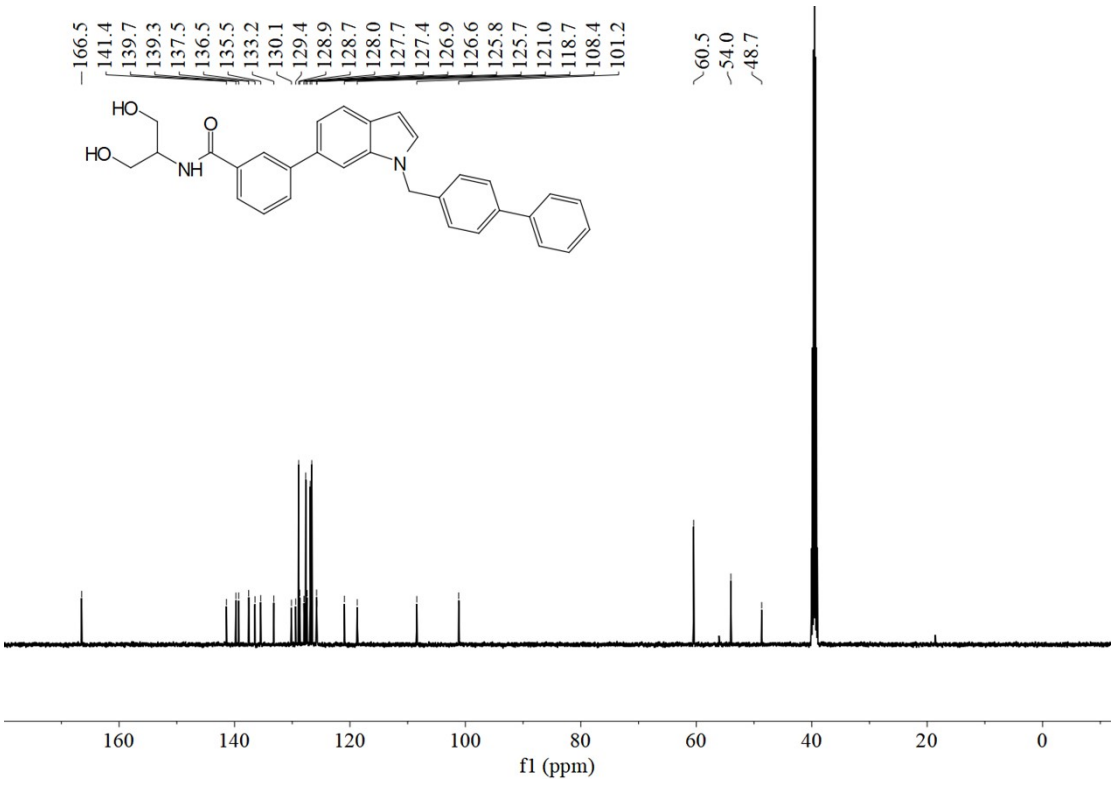


Compound **H11**:

^{1}H NMR (500 MHz, DMSO-d_6)

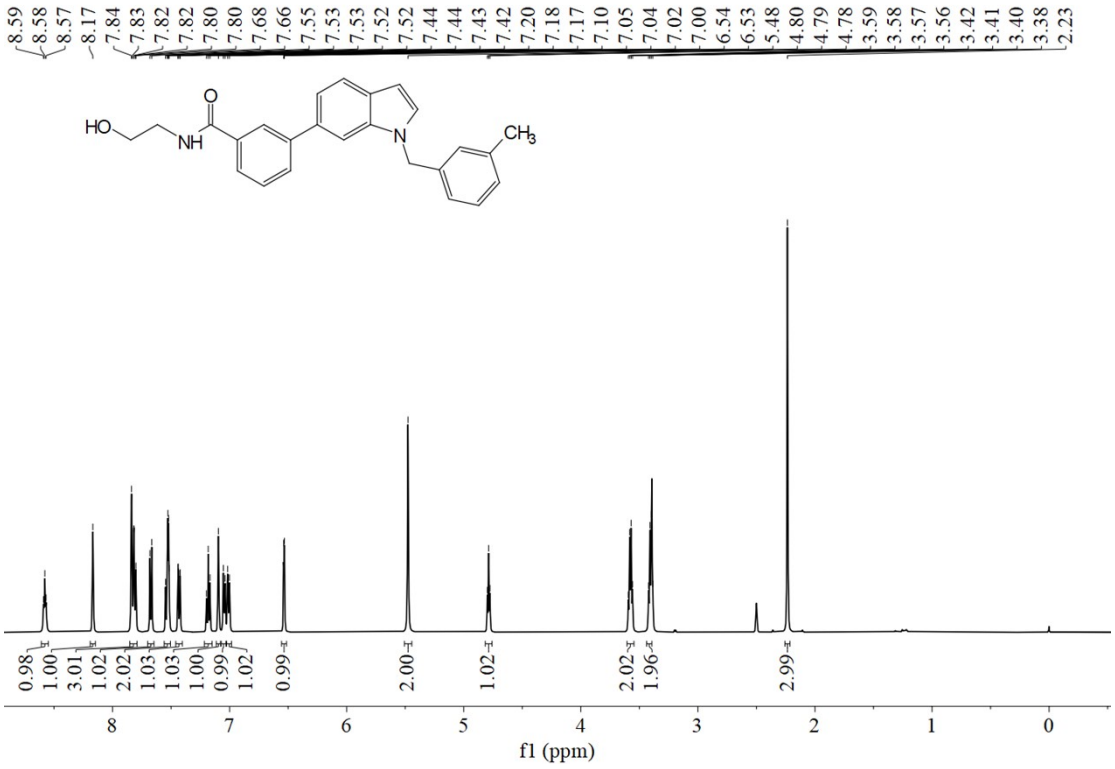


^{13}C NMR (125 MHz, DMSO-d_6)

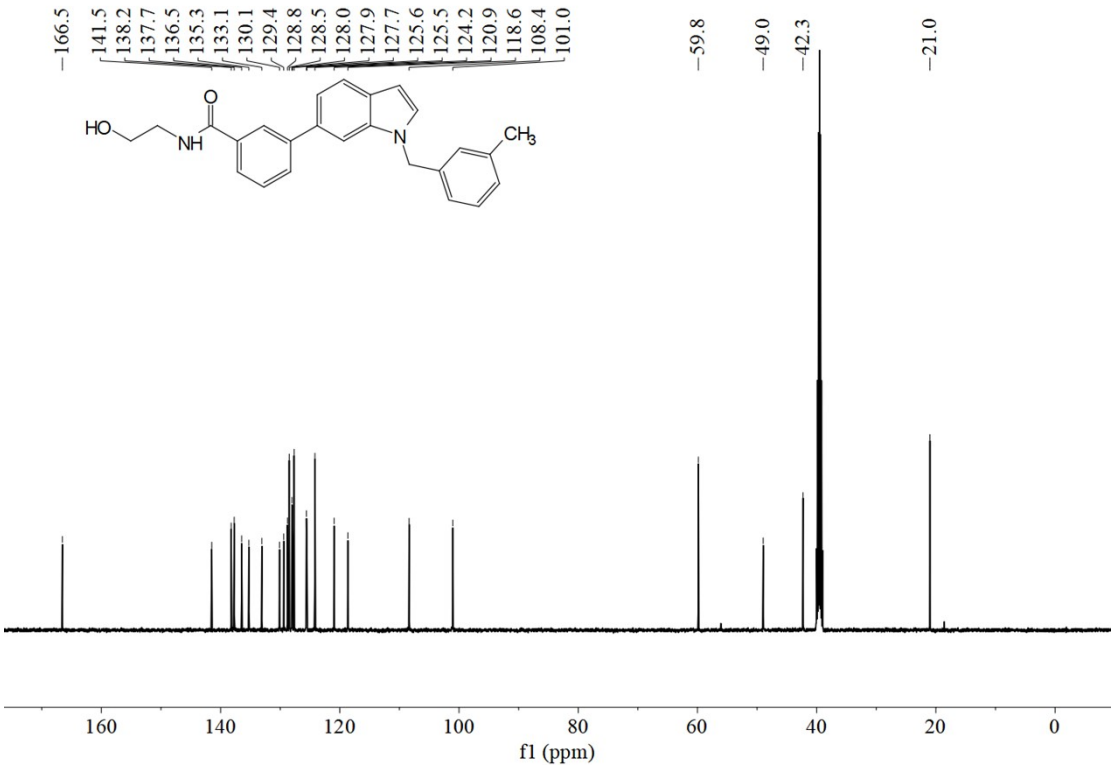


Compound **H12**:

^{1}H NMR (500 MHz, DMSO-d_6)

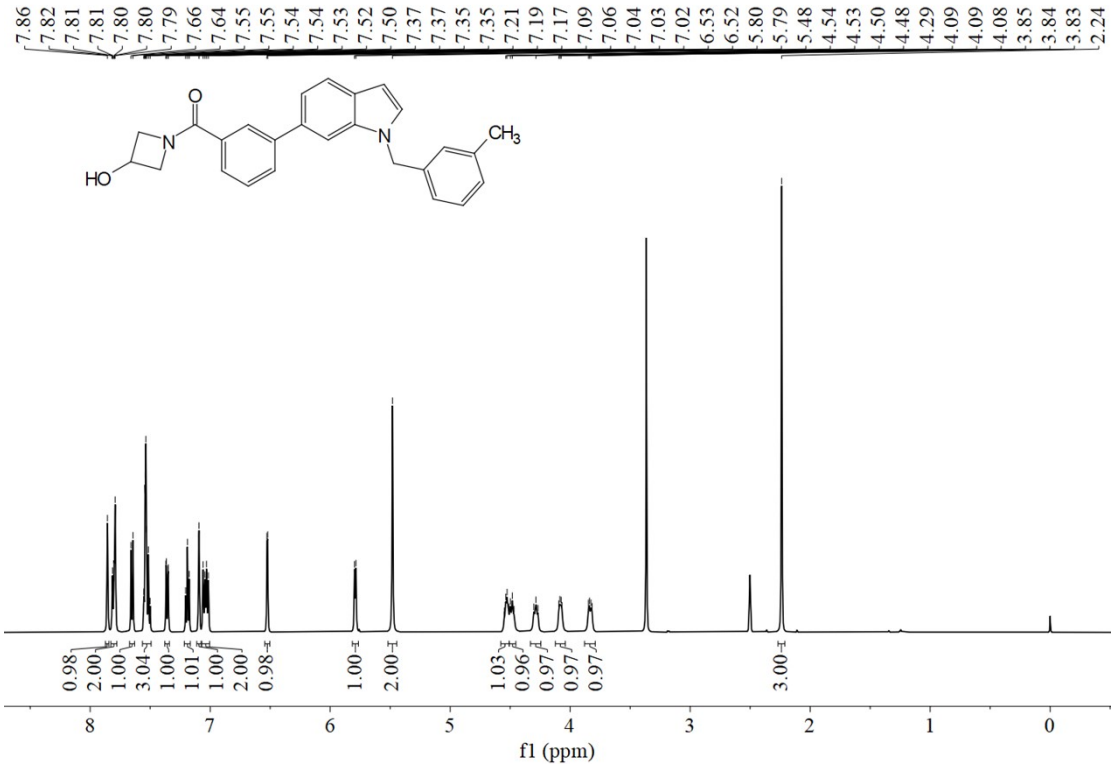


^{13}C NMR (125 MHz, DMSO-d_6)

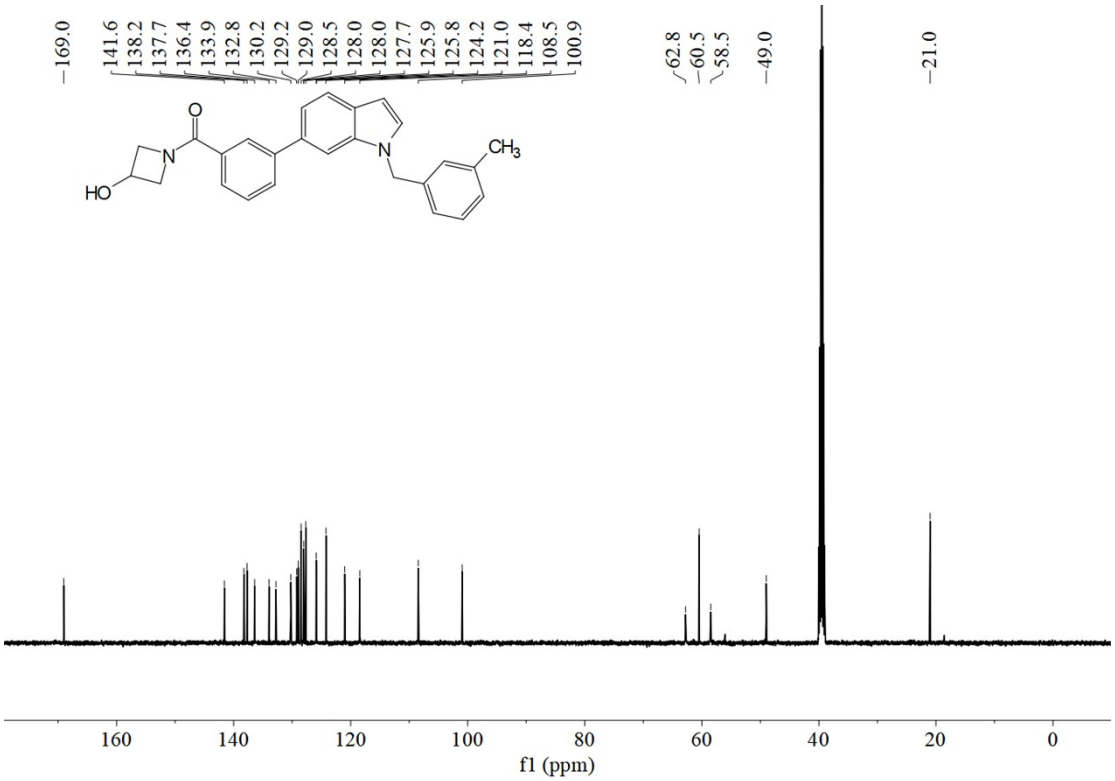


Compound **H13**:

^{1}H NMR (500 MHz, DMSO-d_6)

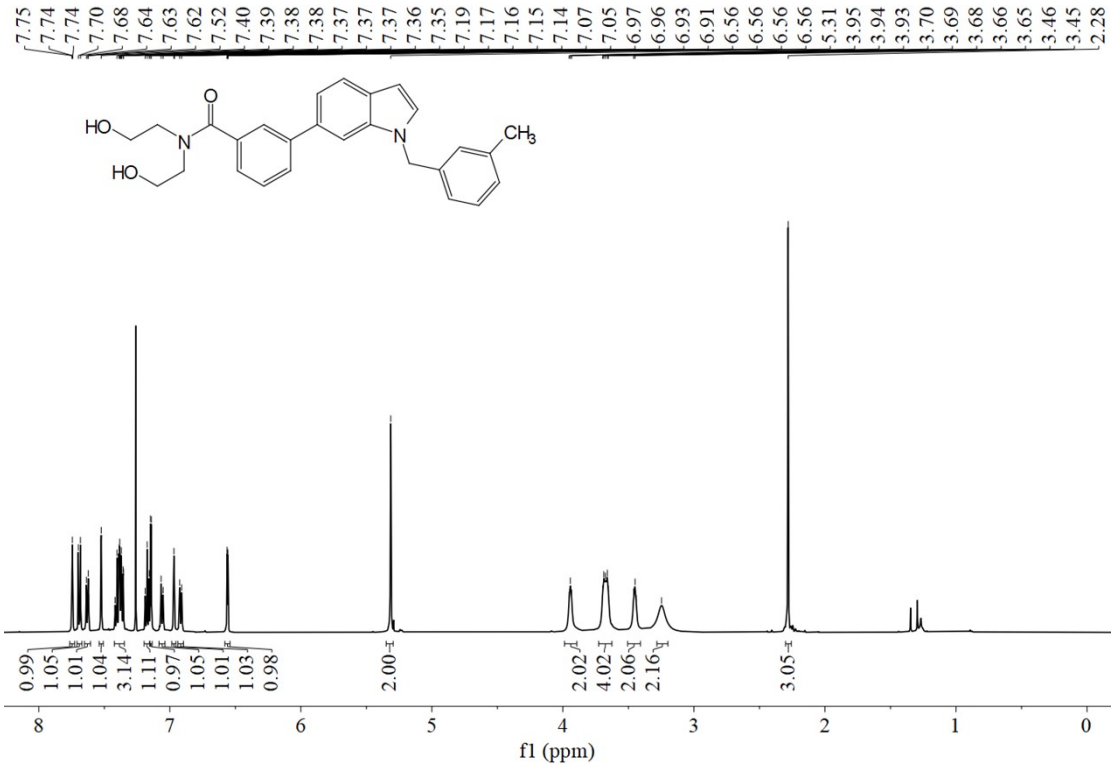


^{13}C NMR (125 MHz, DMSO-d_6)

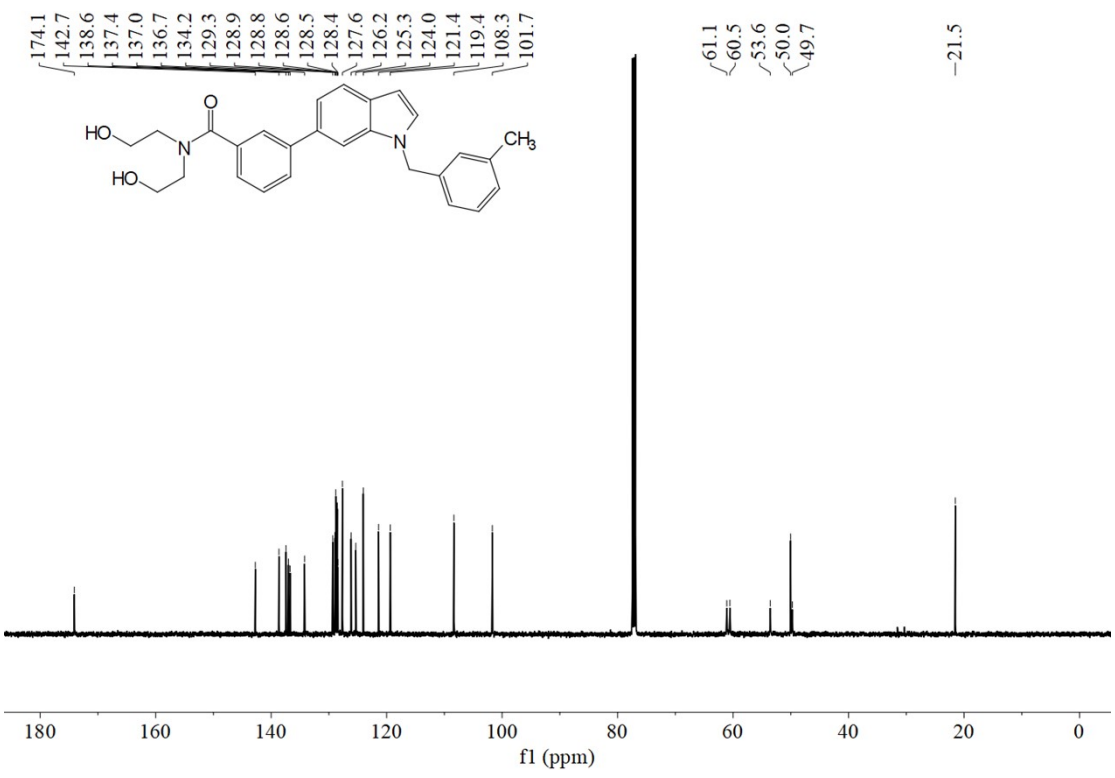


Compound **H14**:

^{1}H NMR (500 MHz, $CDCl_3$)

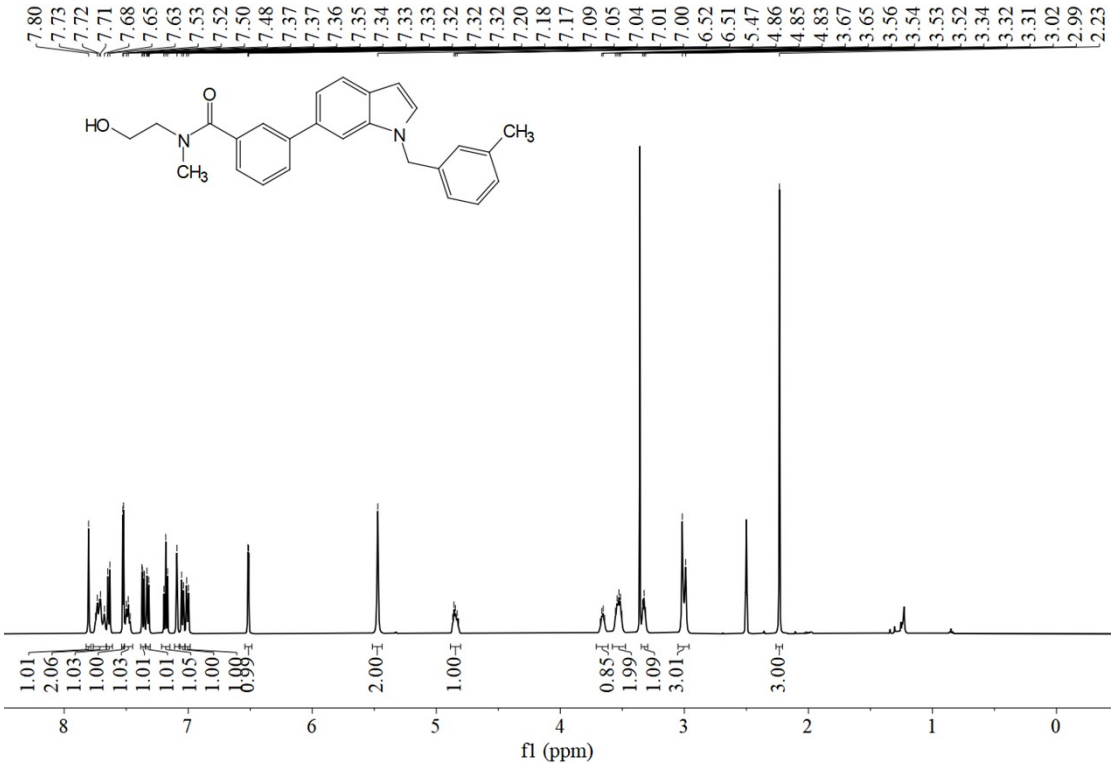


^{13}C NMR (125 MHz, $CDCl_3$)

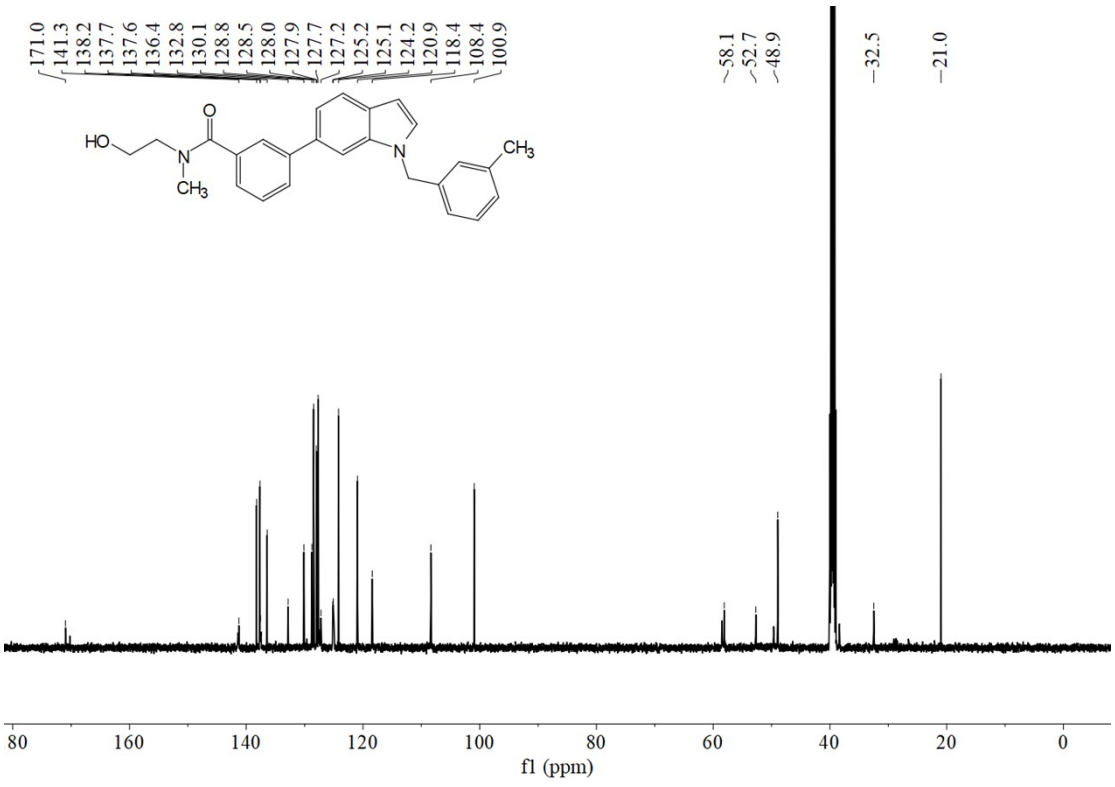


Compound **H15**:

^{1}H NMR (500 MHz, DMSO-d_6)

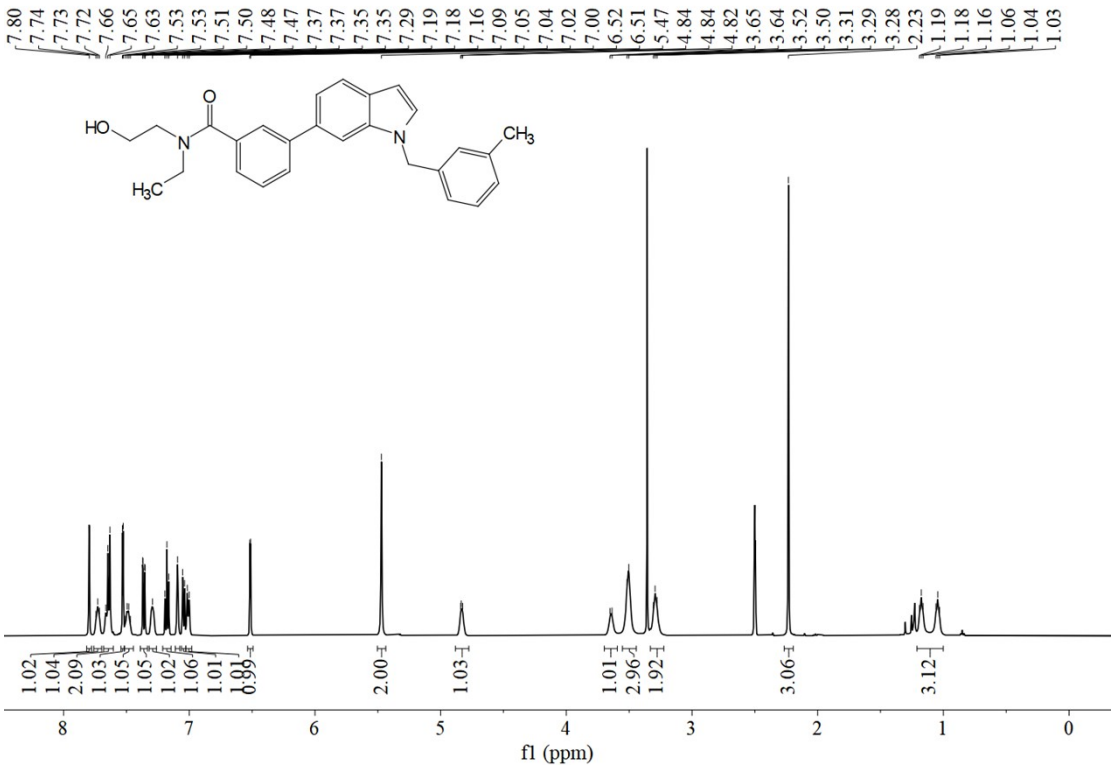


^{13}C NMR (125 MHz, DMSO-d_6)

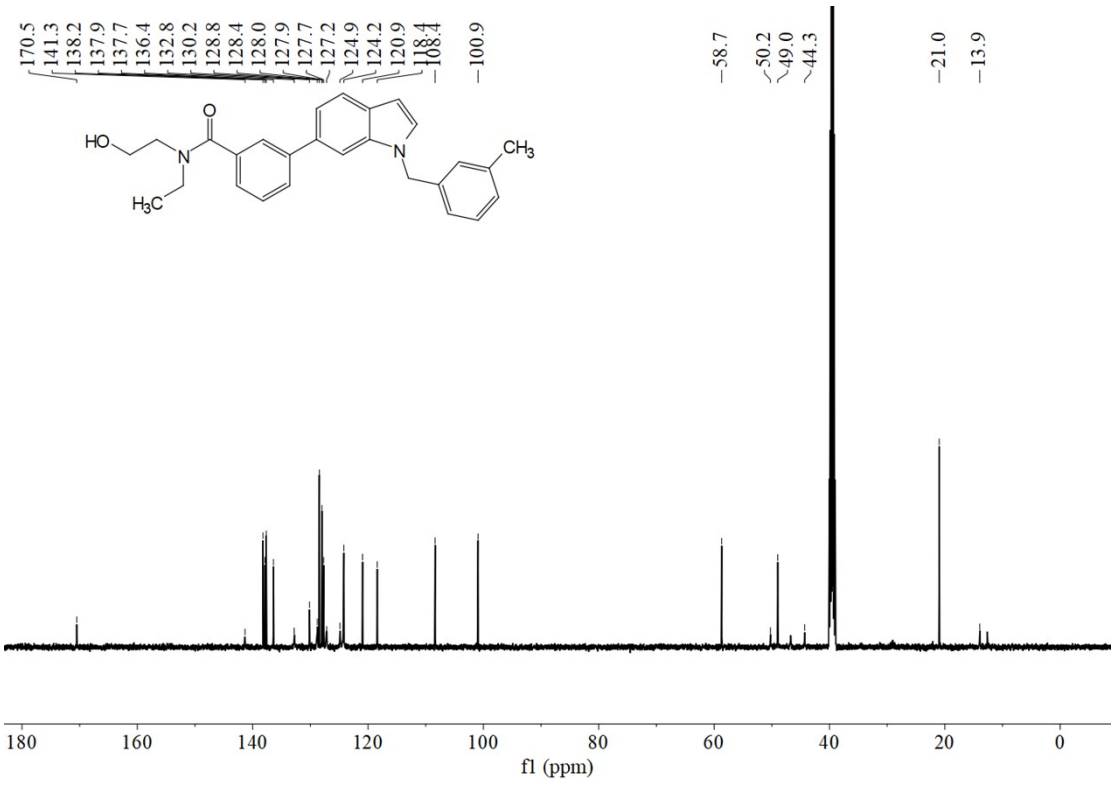


Compound **H16**:

^{1}H NMR (500 MHz, DMSO-d_6)

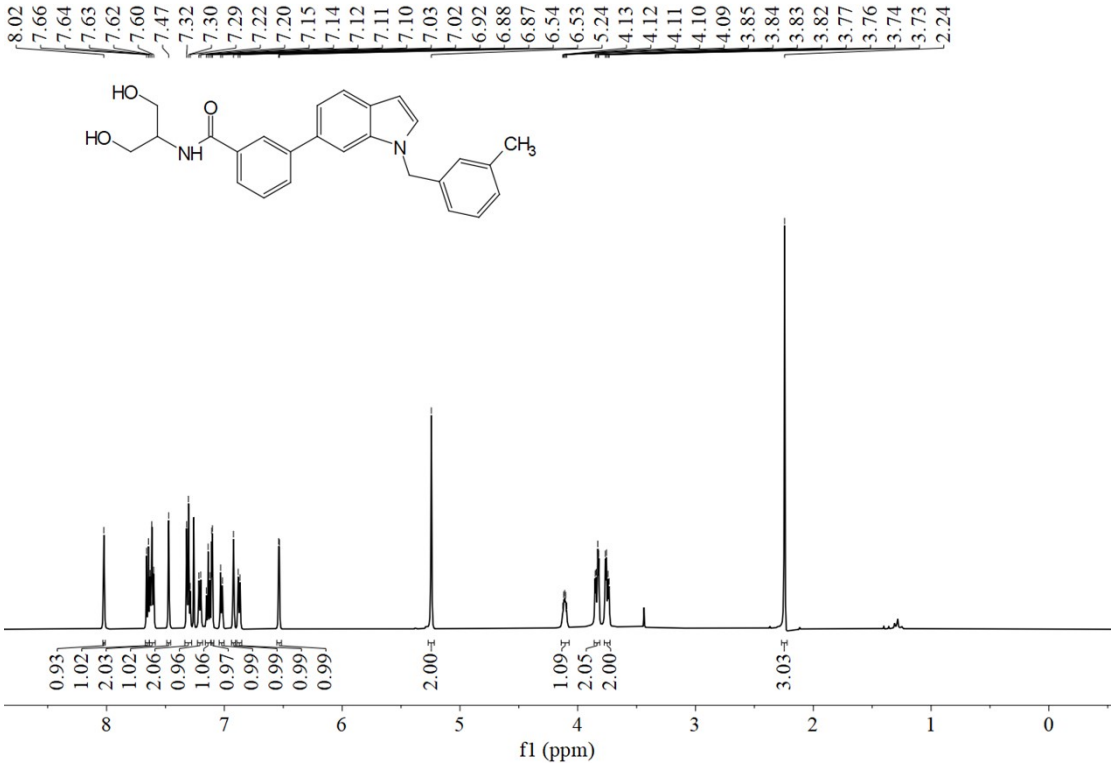


^{13}C NMR (125 MHz, DMSO-d_6)

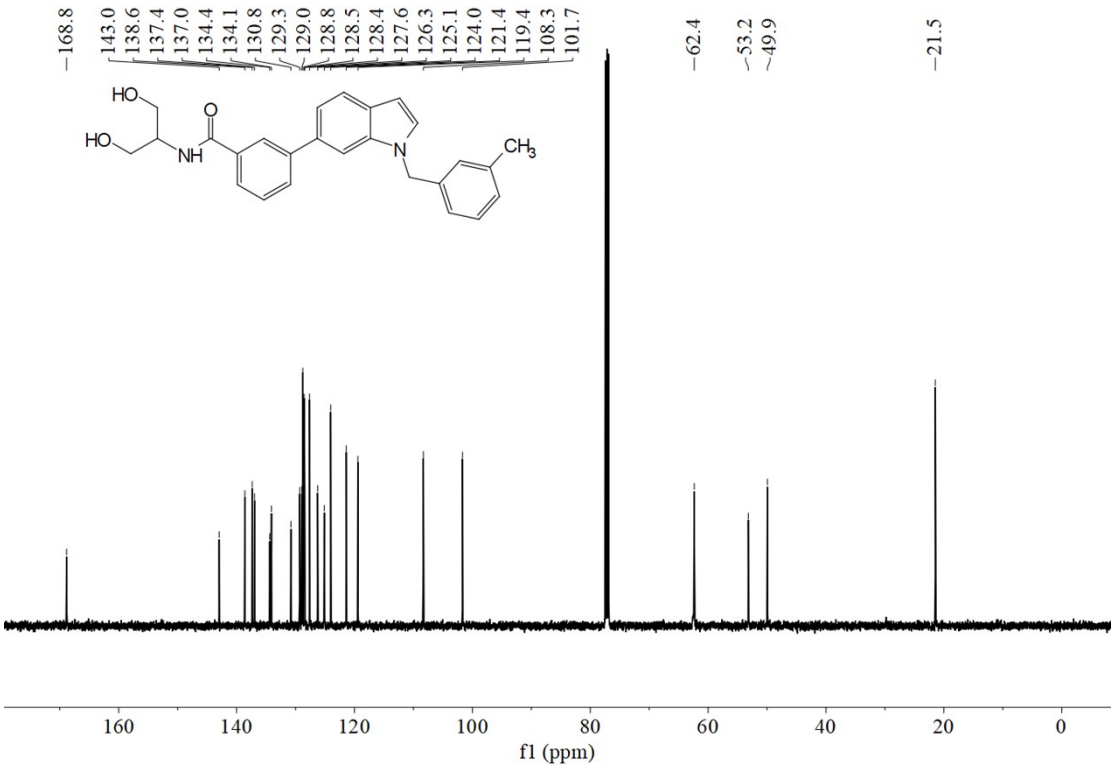


Compound **H17**:

^{1}H NMR (500 MHz, $CDCl_3$)

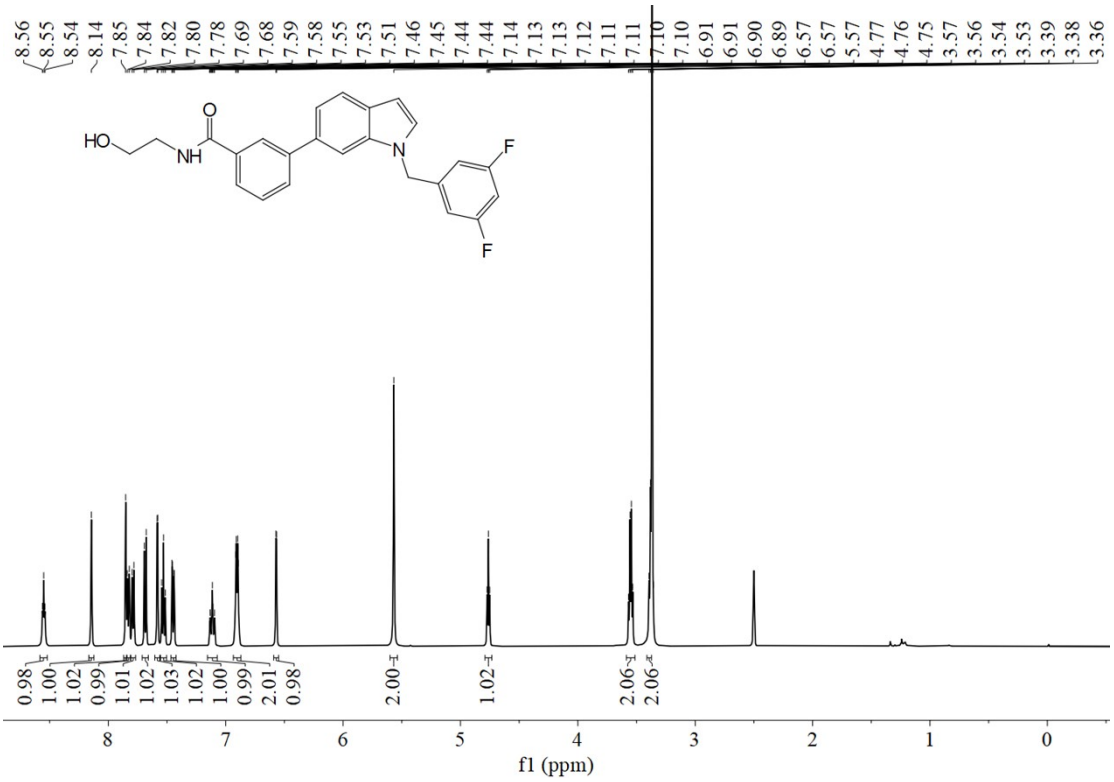


^{13}C NMR (125 MHz, $CDCl_3$)

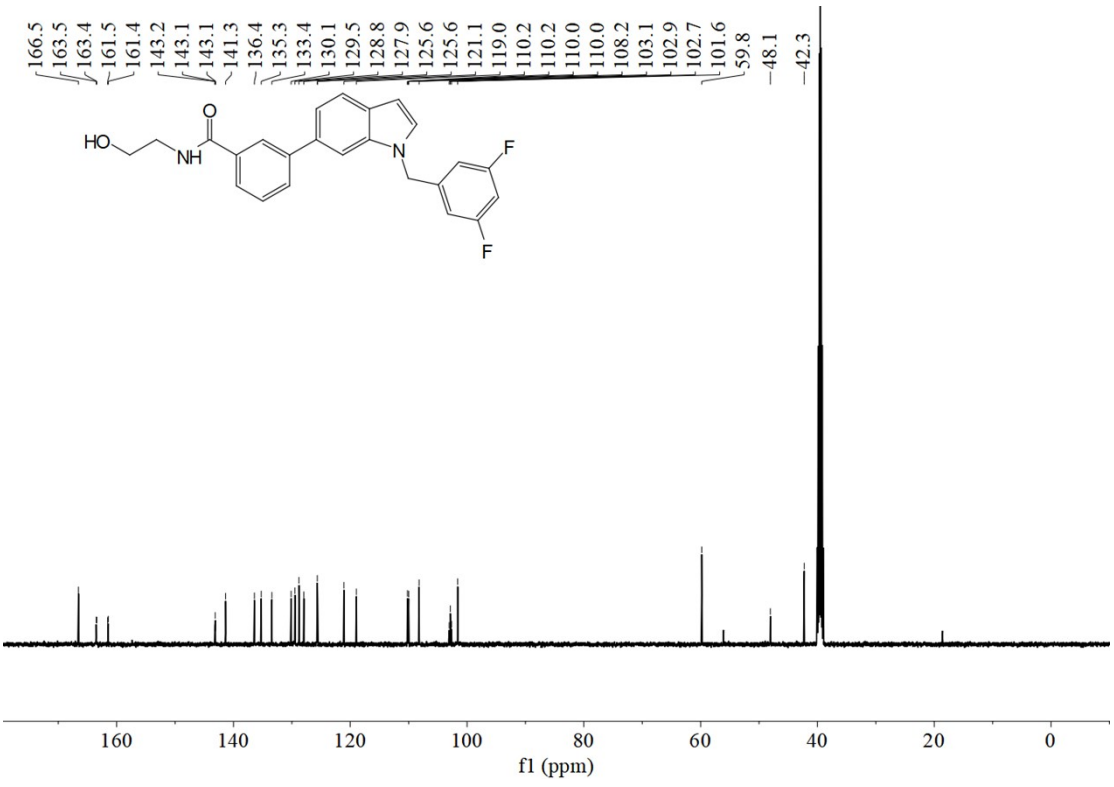


Compound **H18**:

^{1}H NMR (500 MHz, DMSO-d_6)

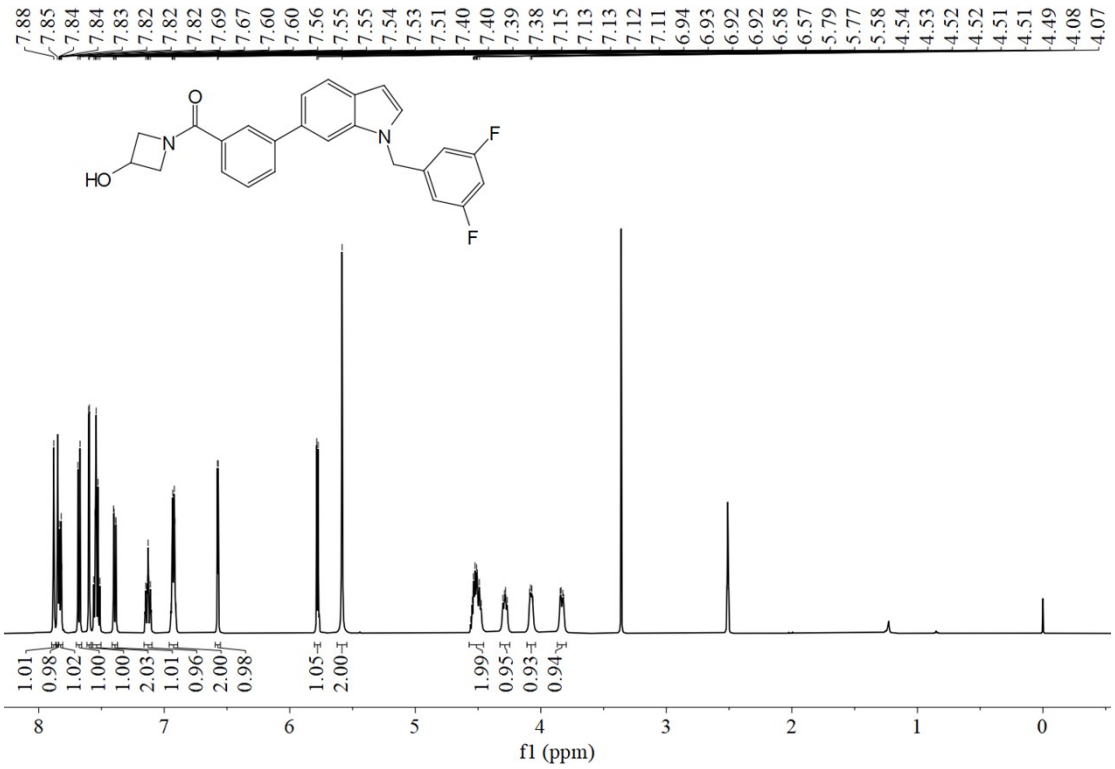


^{13}C NMR (125 MHz, DMSO-d_6)

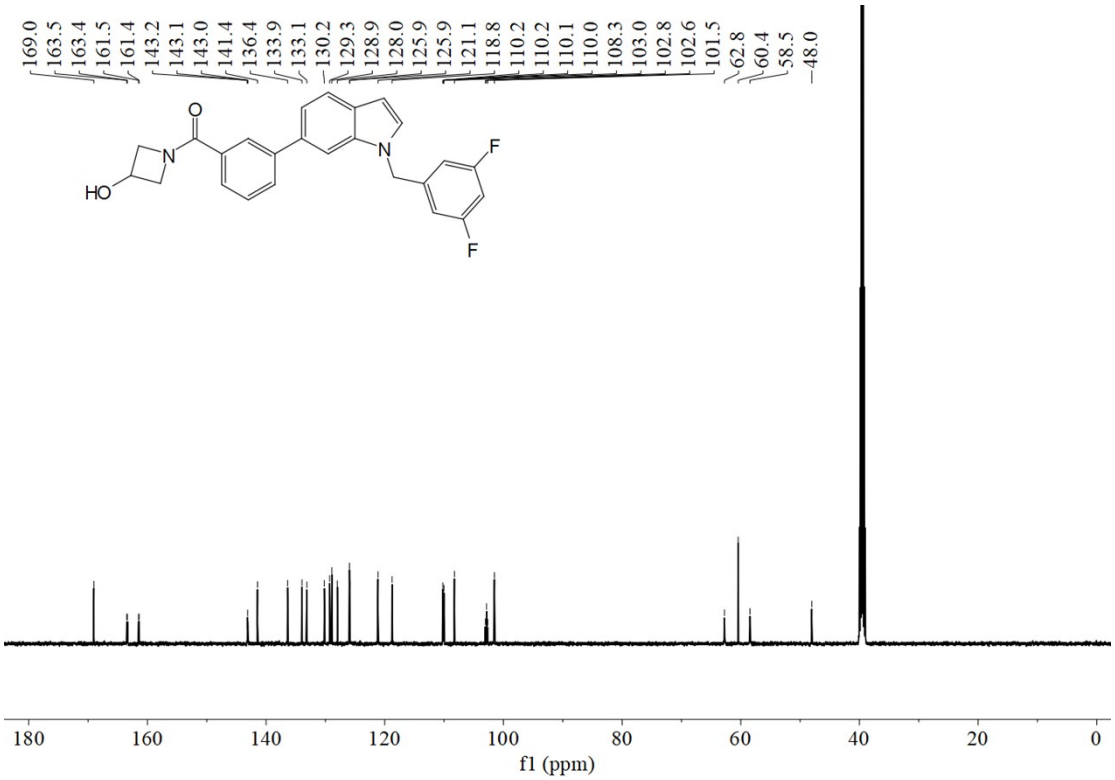


Compound **H19**:

^{1}H NMR (500 MHz, DMSO-d_6)

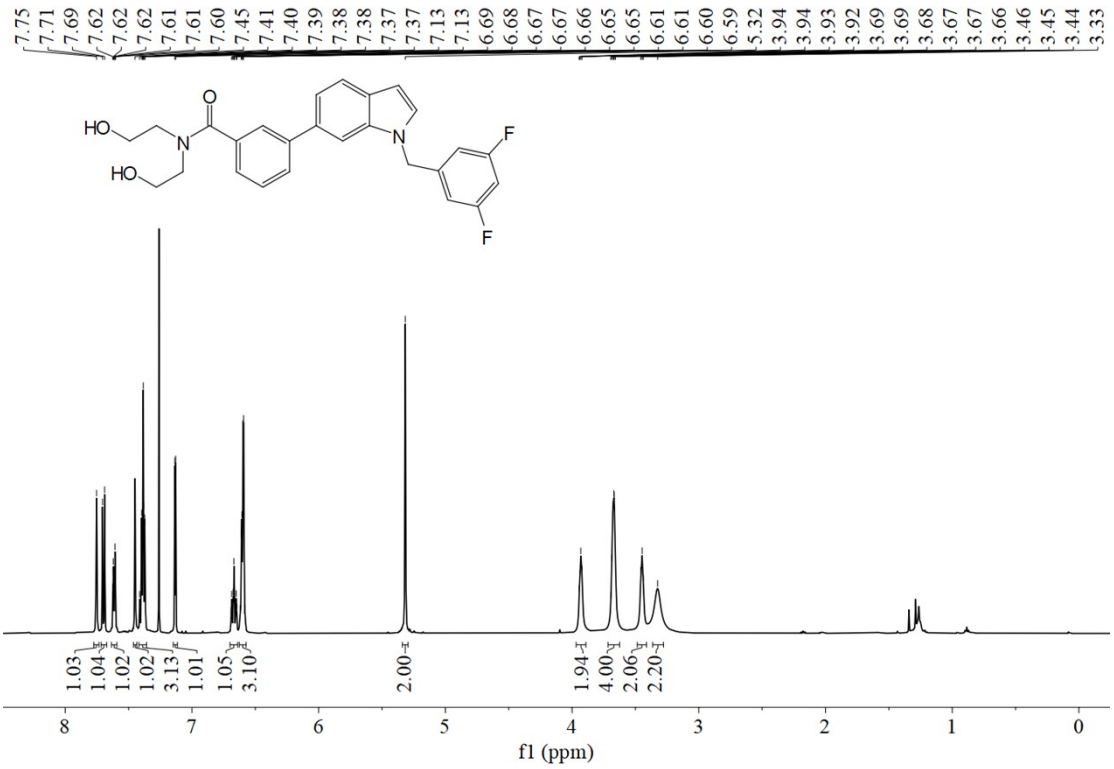


^{13}C NMR (125 MHz, DMSO-d_6)

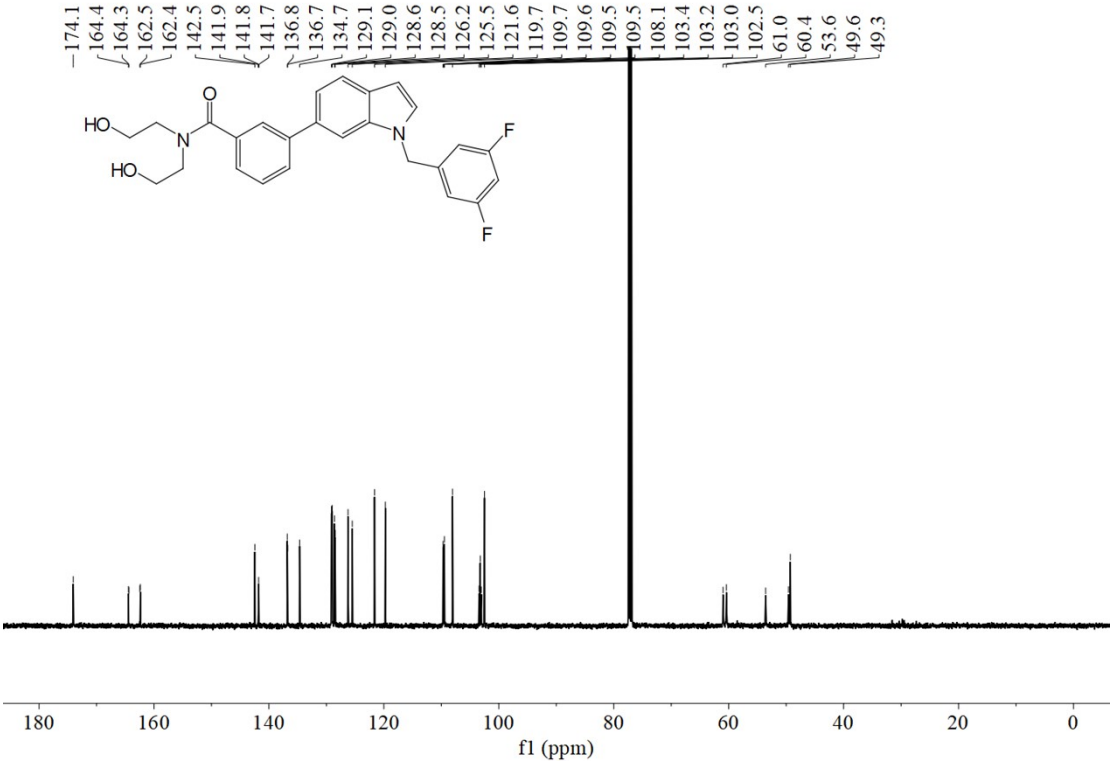


Compound **H20**:

^{1}H NMR (500 MHz, $CDCl_3$)

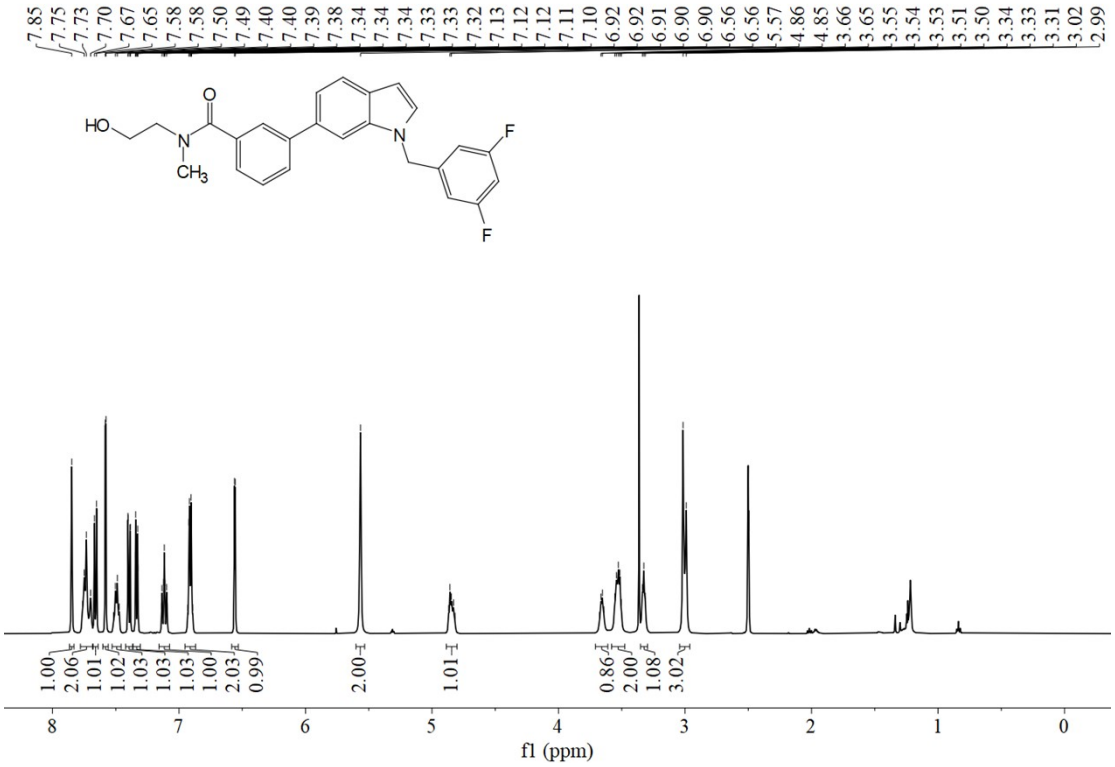


^{13}C NMR (125 MHz, $CDCl_3$)

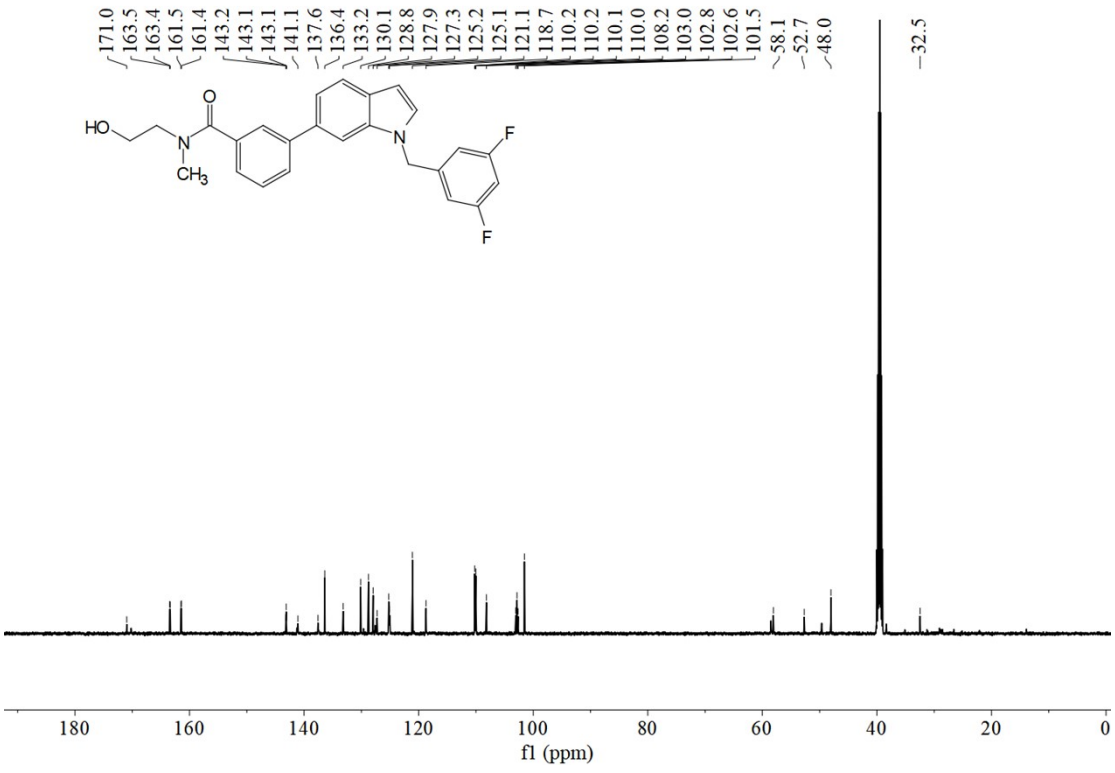


Compound **H21**:

^{1}H NMR (500 MHz, DMSO-d_6)

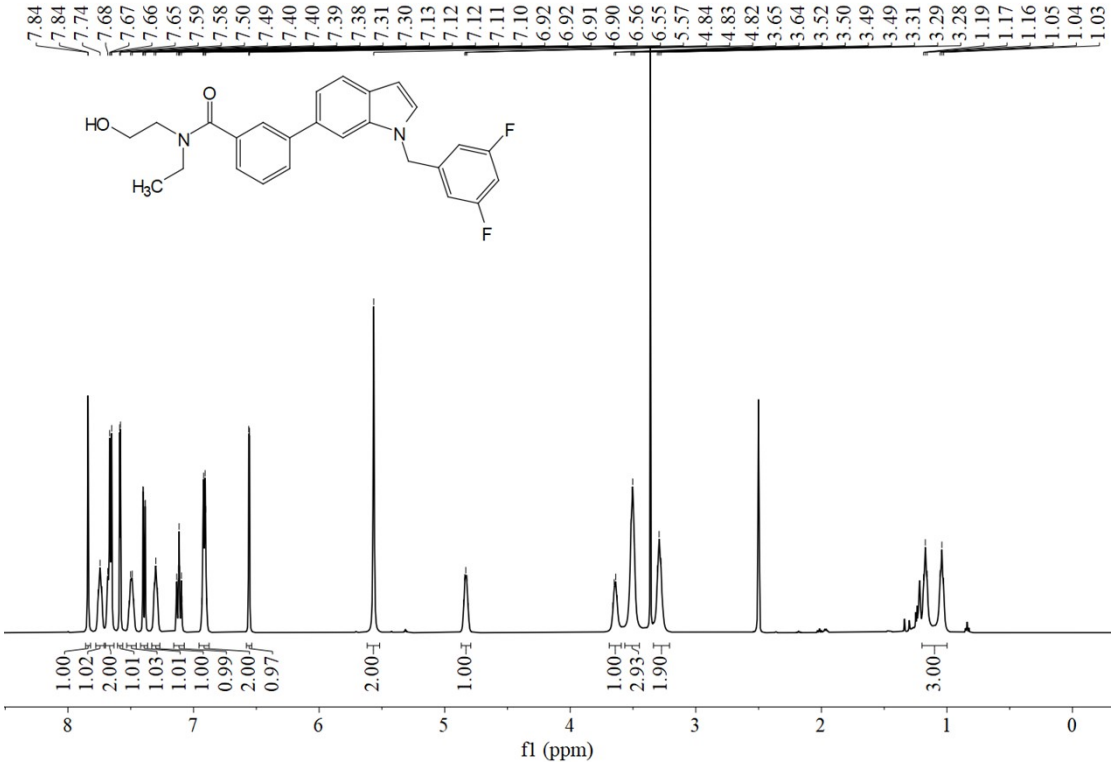


^{13}C NMR (125 MHz, DMSO-d_6)

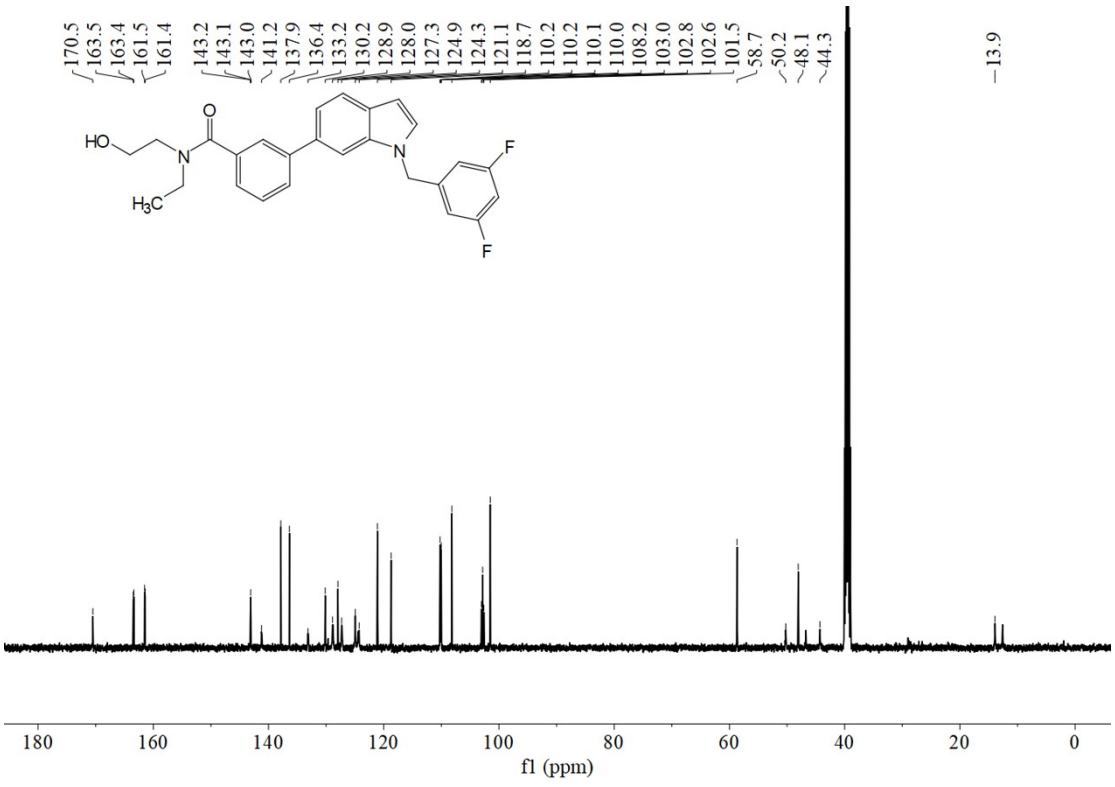


Compound **H22**:

^{1}H NMR (500 MHz, DMSO-d_6)

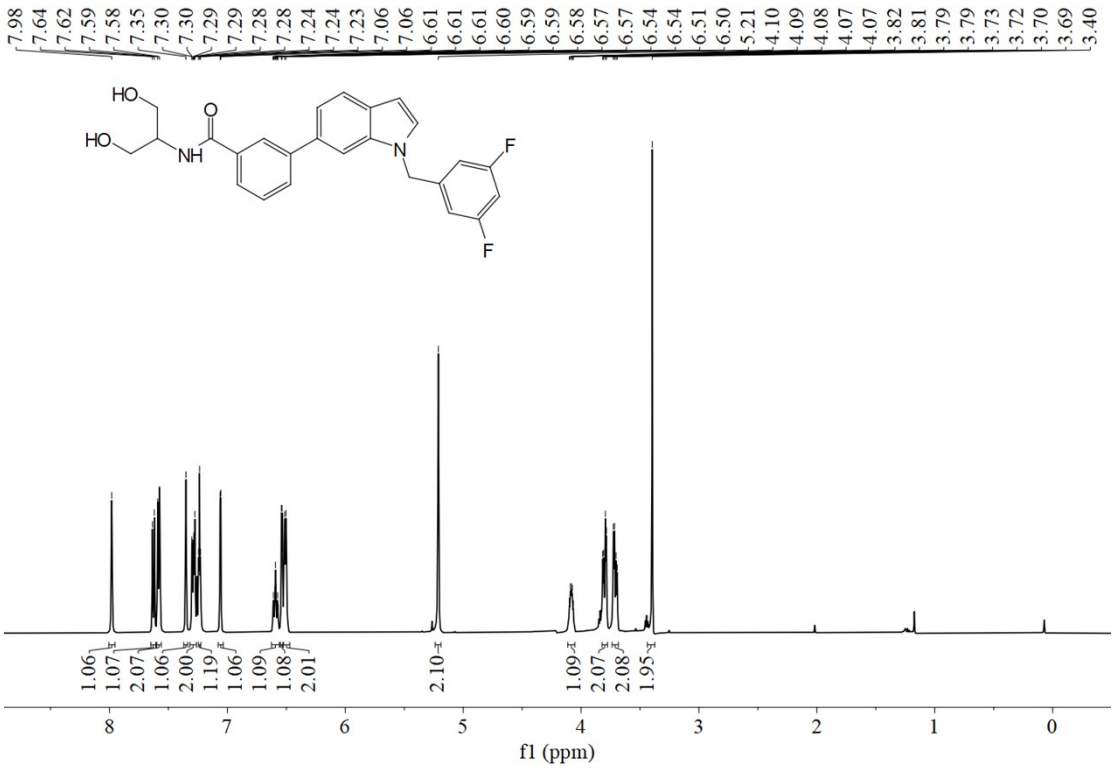


^{13}C NMR (125 MHz, DMSO-d_6)

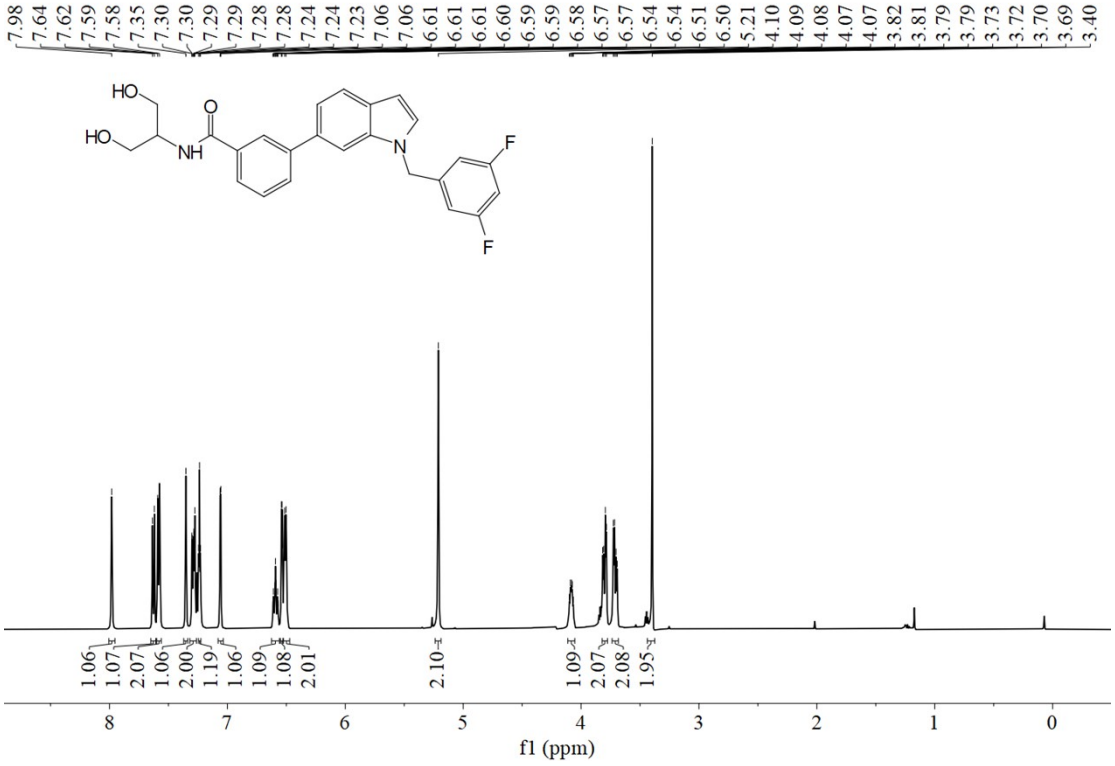


Compound **H23**:

^{1}H NMR (500 MHz, $CDCl_3$)

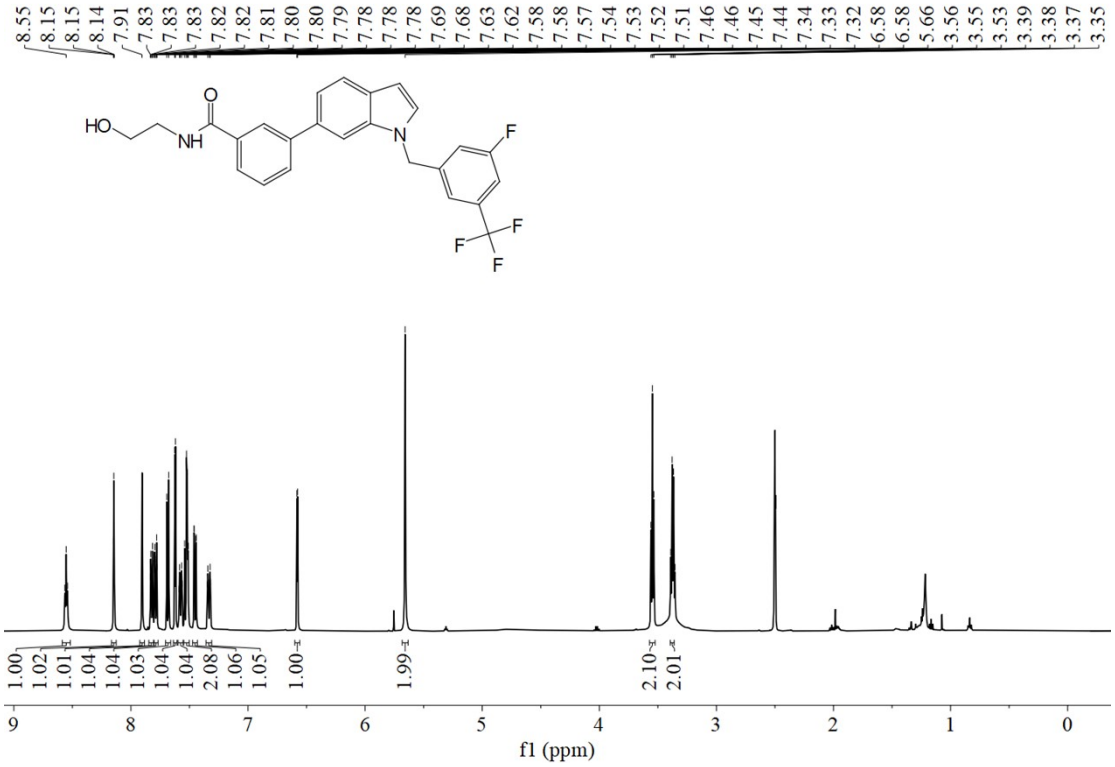


^{13}C NMR (125 MHz, $CDCl_3$)

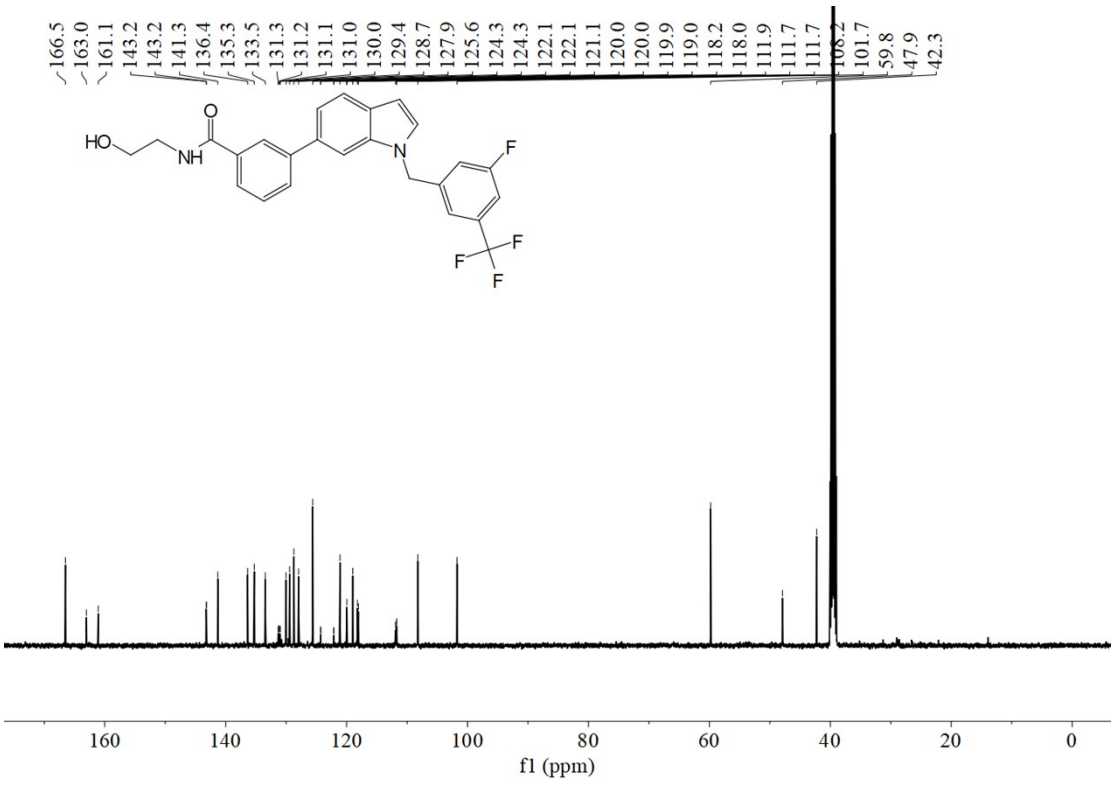


Compound **H24**:

^{1}H NMR (500 MHz, DMSO-d_6)

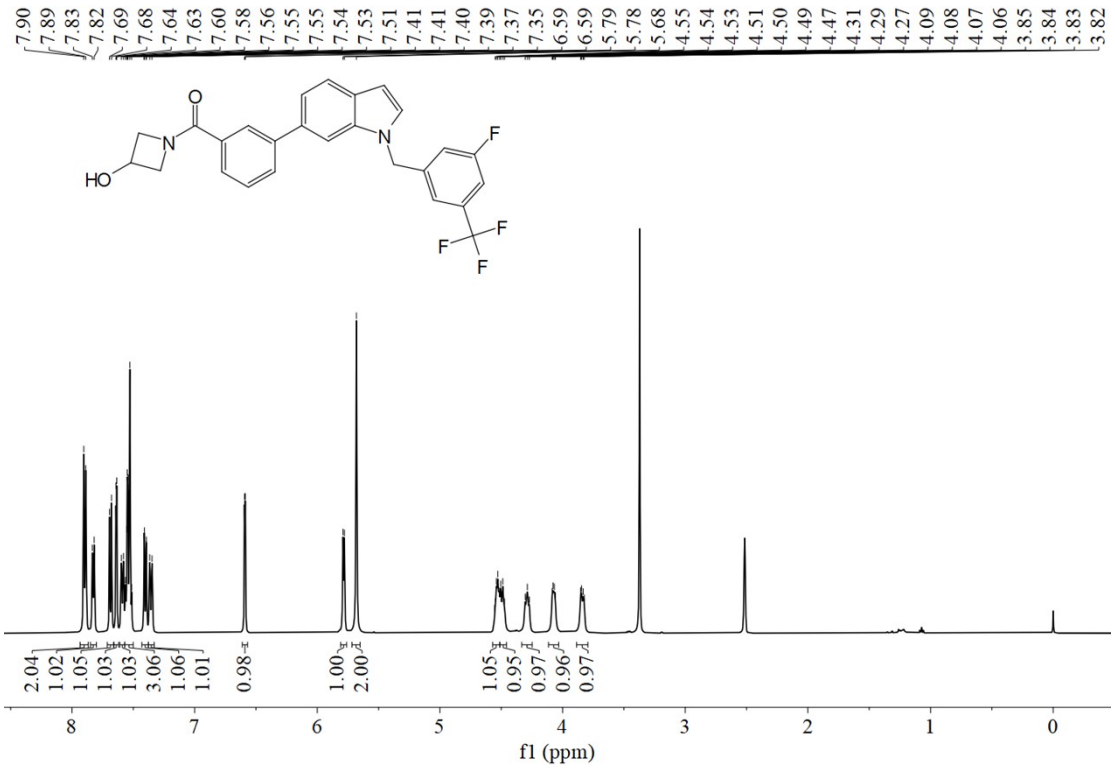


^{13}C NMR (125 MHz, DMSO-d_6)

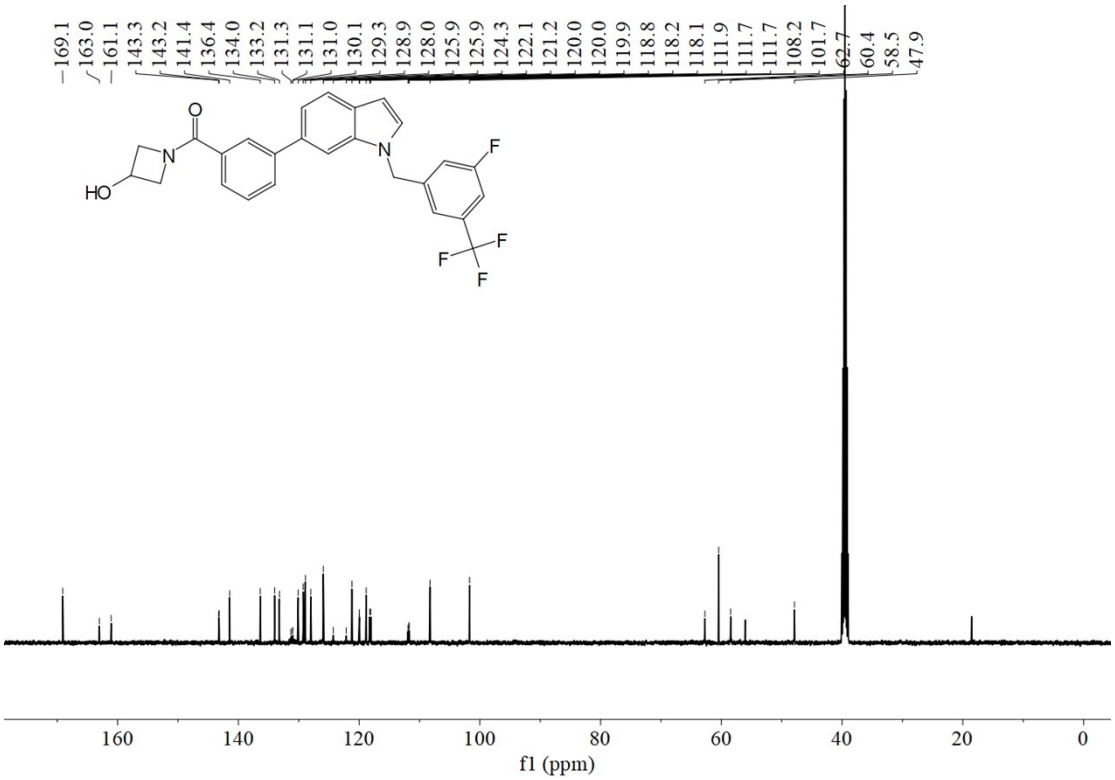


Compound **H25**:

^{1}H NMR (500 MHz, DMSO-d_6)

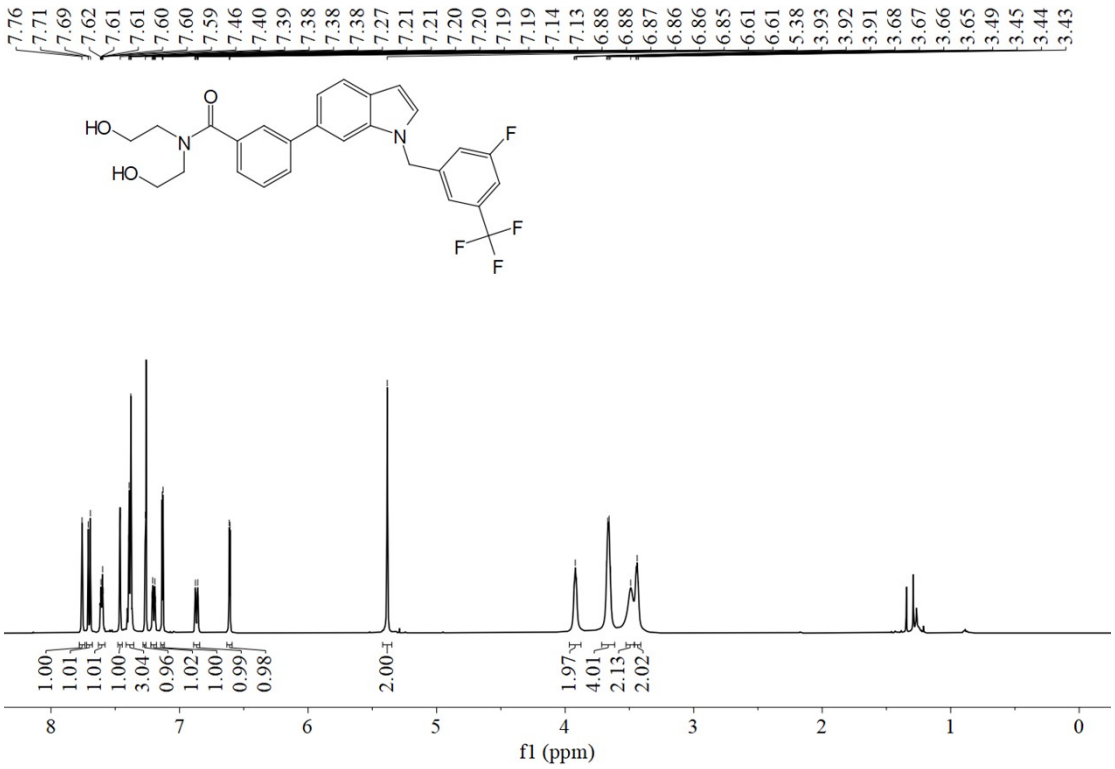


^{13}C NMR (125 MHz, DMSO-d_6)

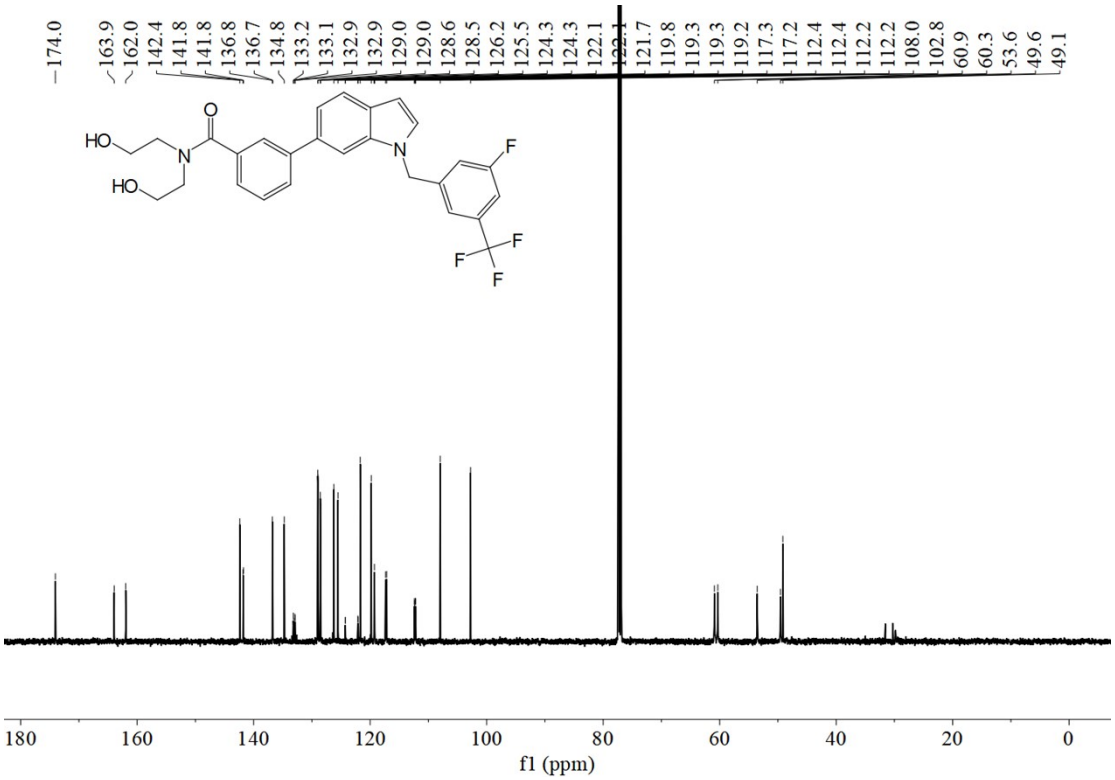


Compound **H26**:

^{1}H NMR (500 MHz, $CDCl_3$)

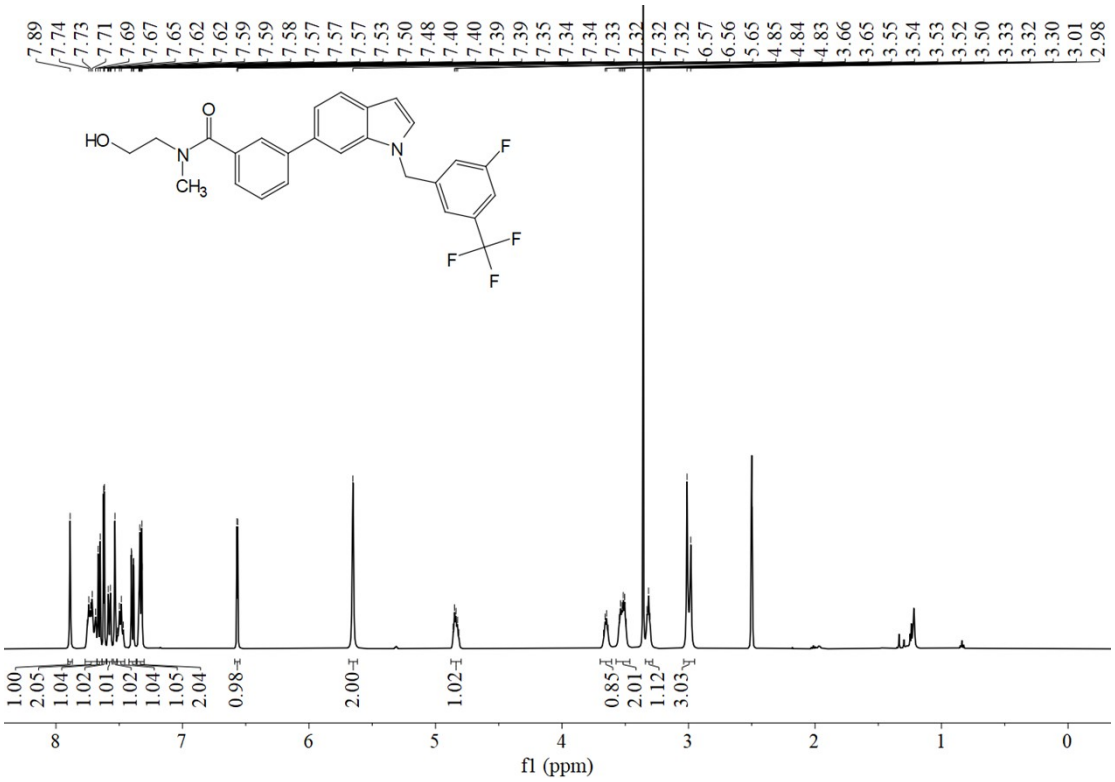


^{13}C NMR (125 MHz, $CDCl_3$)

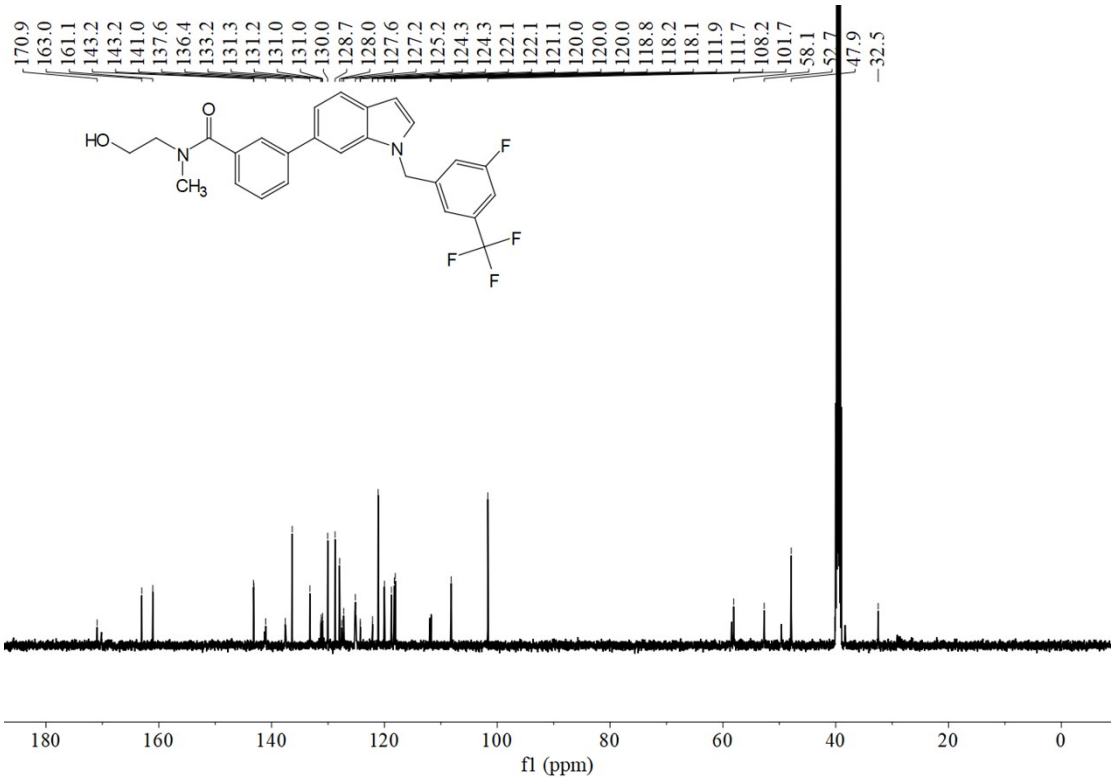


Compound **H27**:

^{1}H NMR (500 MHz, DMSO-d_6)

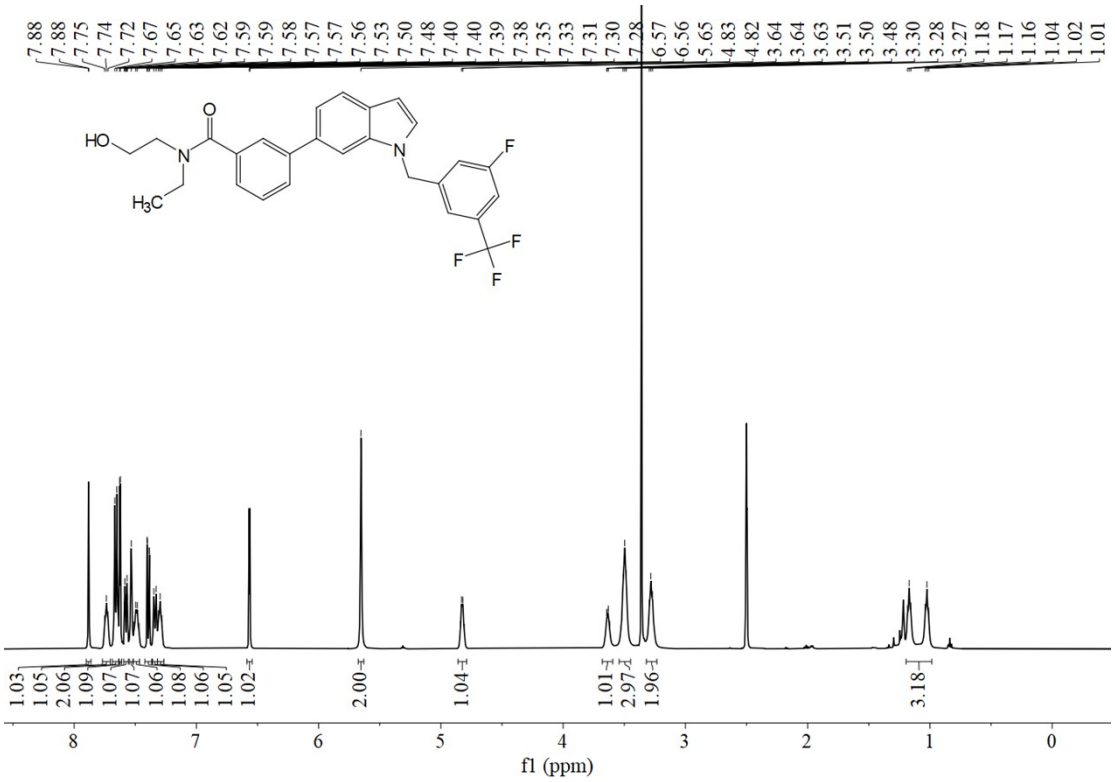


^{13}C NMR (125 MHz, DMSO-d_6)

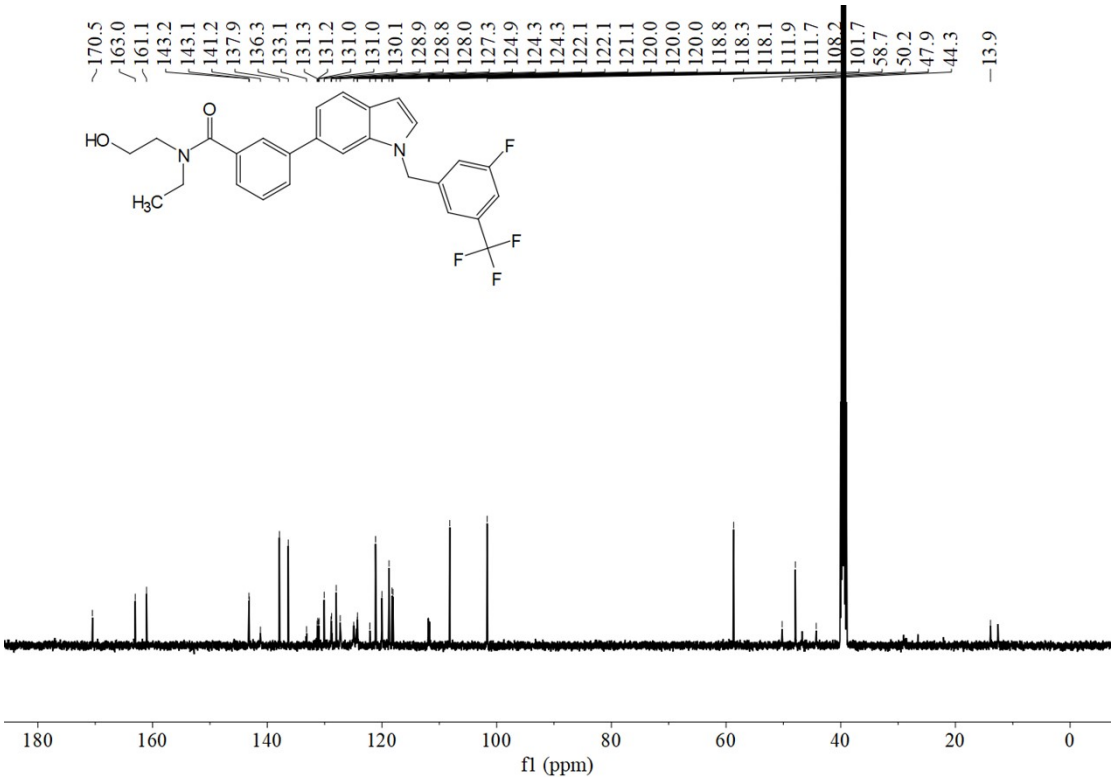


Compound **H28**:

^{1}H NMR (500 MHz, DMSO-d_6)

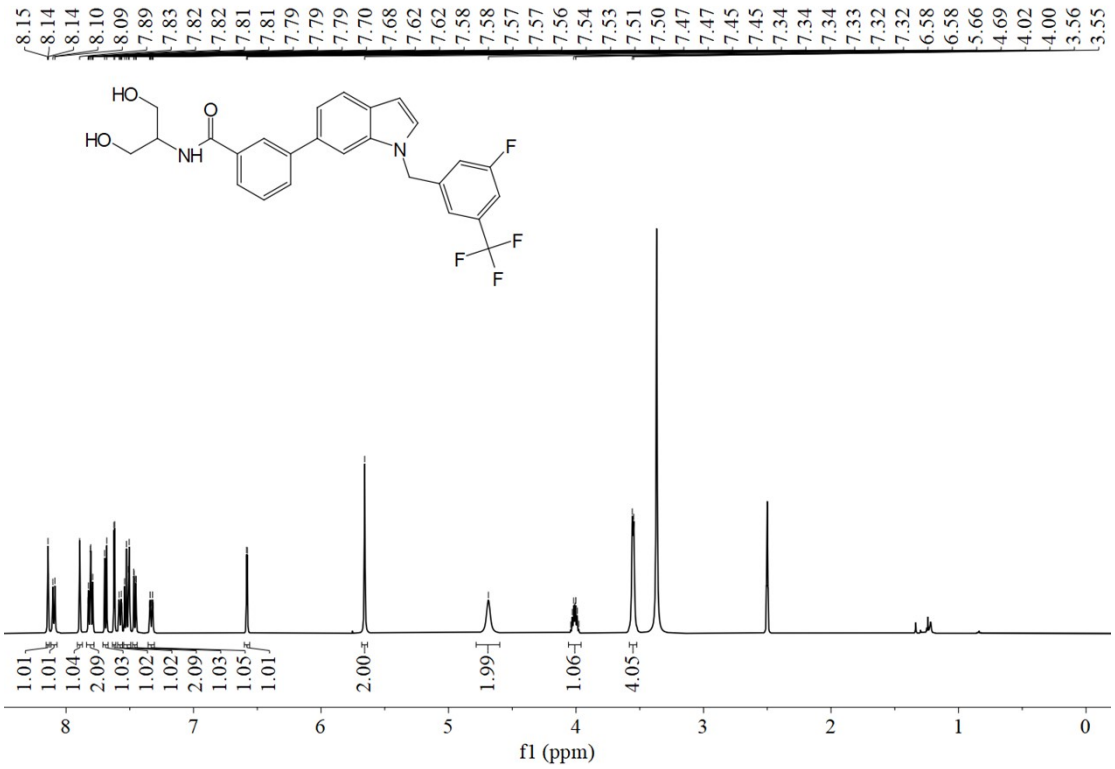


^{13}C NMR (125 MHz, DMSO-*d6*)

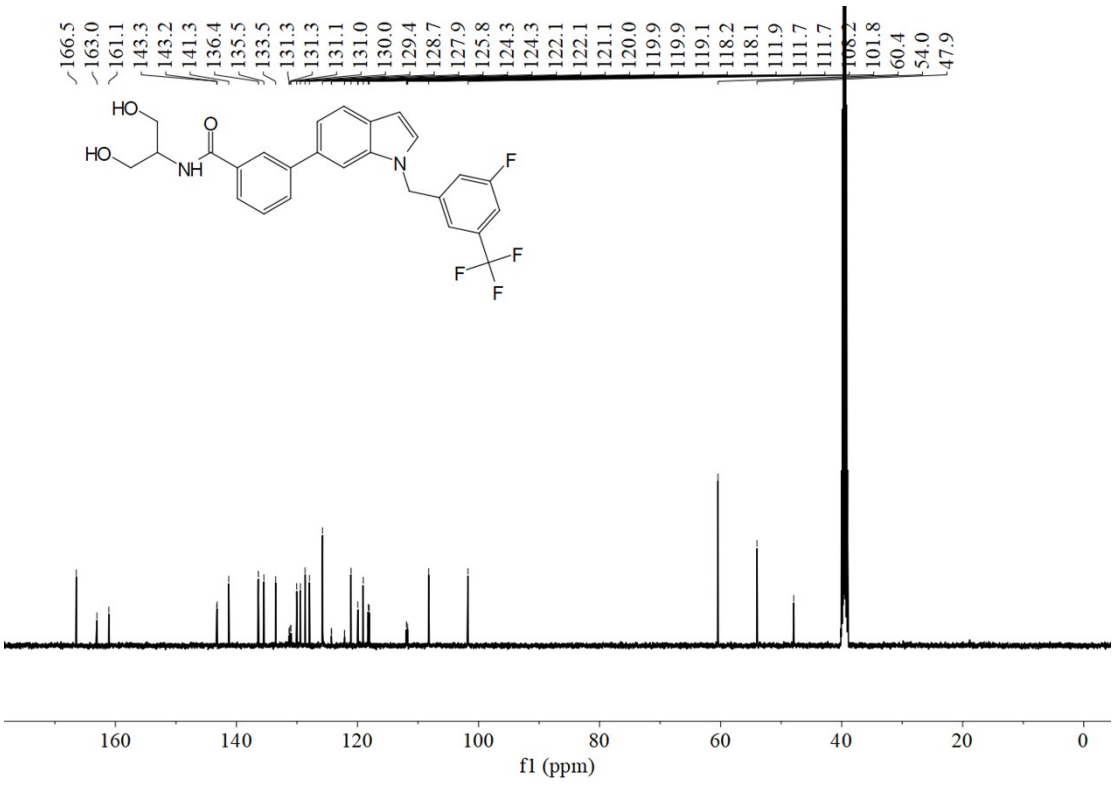


Compound **H29**:

^{1}H NMR (500 MHz, DMSO-d_6)



^{13}C NMR (125 MHz, DMSO-d_6)



7. **Reference**

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