

Supporting Information

H₂O-regulated chemoselectivity in oxa- versus aza-Michael reactions

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1. General Information

All chemical reagents were of analytical grade, obtained from commercial sources and used as supplied without further purification unless indicated.

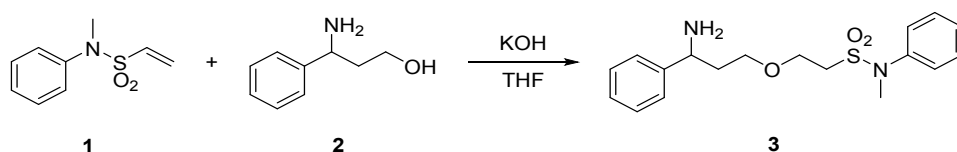
NMR spectra were recorded on a Bruker-500 (500 MHz) instrument. The deuterated solvents employed were purchased from Energy Chemical. Chemical shifts were given in ppm with respect to referenced solvent peaks. Spectra were analyzed with MestReNova. High-resolution mass spectra (HRMS-ESI) were obtained on an Agilent Technologies 6230 Accurate Mass TOF LC/MS instrument and Thermo fisher EASY1000-Fusion instrument. LC-MS² were recorded on Thermo fisher EASY1000-Fusion instrument and ABSciex 4600.

HPLC was performed using Waters 1525. Mobile phases are: 0.5% CF₃COOH on water (solvent A) and acetonitrile (solvent B). *Method A*: LC conditions: SunFire C18 column: 4.6X150 mm, 5 μm, column temperature: 30 °C, λ = 254 nm, gradient: 0-10 minutes 10-100% B, 10-12 minutes 100% B, flow rate: 1 mL /min.

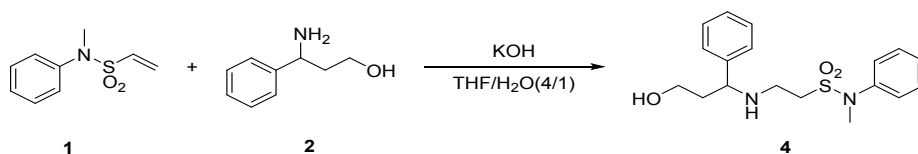
Method B: LC conditions: SunFire C18 column: 4.6X150 mm, 5 μm, column temperature: 30 °C, λ = 280 nm, gradient: 1-18 minutes 10-43% B, 18-19 minutes 43-100% B, 19-20 minutes 100% B, flow rate: 1 mL /min. HPLC was performed using SHIMADZU LC-30AD. Mobile phases are: 0.5% CF₃COOH on water (solvent A) and acetonitrile (solvent B). *Method*: LC conditions: Agela Technologies C18 column: 2.1X100 mm, 3 μm, column temperature: 30 °C, λ = 254 nm, gradient: 0-10 minutes 10-100% B, 10-12 minutes 100% B, flow rate: 0.4 mL /min.

LC-MS² was performed using ABSciex 4600. Mobile phases are: 0.1% HCOOH on water (solvent A) and acetonitrile (solvent B). *Method A*: LC conditions: Agela Technologies C18 column: 2.1X100 mm, 3 μm, column temperature: 30 °C, λ = 254 nm, gradient: 0-20 minutes 10-100% B, 20-23 minutes 100% B, 23-25 minutes 10% B, flow rate: 0.4 mL /min. *Method B*: LC conditions: GL Sciences C4 column: 2.1X150 mm, 5 μm, column temperature: 70 °C, λ = 254 nm, gradient: 0-5 minutes 15% B, 5-22 minutes 15-60% B, 22-25 minutes 60-90% B, 25-29 minutes 90% B, 29-32 minutes 15% B, flow rate: 0.2 mL /min.

Detailed synthetic method examples:



The compound 3-amino-3-phenyl-1-propanol **2** (1.2 mmol, 181.4 mg) and potassium hydroxide (2.0 mmol, 112.2 mg) were added to tetrahydrofuran (5 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **1** (1.0 mmol, 197.3 mg) was added. The resulting mixture was stirred at room temperature for 2 hours. The resulting crude mixture was purified by preparative HPLC (CH₃CN : H₂O = 10 ~ 100%, 0 ~ 20 min) after filtration. The signal of desired product was obtained at 12.1 min and afforded 320.6 mg (0.92 mmol, 92%) yield of **3** as a colorless oily liquid. ¹H NMR (500 MHz, DMSO) δ 8.48 (s, 2H), 7.51 – 7.35 (m, 9H), 7.31 (ddd, *J* = 9.5, 5.6, 2.6 Hz, 1H), 4.39 – 4.28 (m, 1H), 3.68 (dt, *J* = 11.7, 5.9 Hz, 1H), 3.64 – 3.57 (m, 1H), 3.38 (dt, *J* = 12.1, 4.0 Hz, 3H), 3.26 (s, 3H), 3.21 – 3.13 (m, 1H), 2.23 (ddt, *J* = 11.5, 8.3, 5.7 Hz, 1H), 1.99 (qd, *J* = 9.9, 5.0 Hz, 1H). ¹³C NMR (126 MHz, DMSO) δ 141.42, 137.35, 129.13, 128.82, 128.70, 127.38, 127.01, 126.38, 66.30, 64.01, 52.16, 48.72, 37.93, 34.06 ppm. ESI-HRMS calcd for C₁₈H₂₅N₂O₃S [(M+H)⁺]: 349.1586, found: 349.1461.

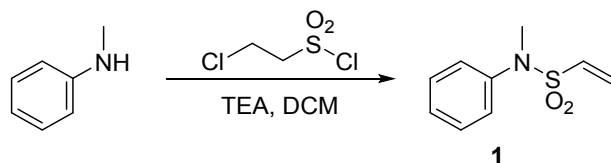


The compound 3-amino-3-phenyl-1-propanol **2** (1.2 mmol, 181.4 mg) and potassium hydroxide (2.0 mmol, 112.2 mg) were added to the mixture of tetrahydrofuran (4 mL) and H₂O (1 mL). And then compound **1** (1.0 mmol, 197.3 mg) was added. The resulting mixture was stirred at room temperature for 12 hours. The resulting crude mixture was purified by preparative HPLC (CH₃CN : H₂O = 10 ~ 100%, 0 ~ 20 min) after filtration. The signal of desired product was obtained at 11.8 min and afforded 313.6 mg (0.9 mmol, 90%) yield of **4** as a colorless oily liquid. ¹H NMR (500 MHz, DMSO) δ 9.54 (s, 1H), 7.54 – 7.35 (m, 7H), 7.35 – 7.28 (m, 3H), 4.62 – 4.36 (m, 2H), 3.61 (ddd, *J* = 13.7, 11.0, 5.2 Hz, 1H), 3.50 (ddd, *J* = 13.8, 10.9, 4.8 Hz, 1H), 3.35 (ddd,

$J = 10.6, 5.9, 4.7$ Hz, 1H), 3.21 (d, $J = 12.4$ Hz, 3H), 3.20 – 3.10 (m, 2H), 2.86 (td, $J = 11.7, 4.7$ Hz, 1H), 2.28 – 2.15 (m, 1H), 2.02 (ddt, $J = 14.6, 9.8, 4.8$ Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 140.71, 134.50, 129.32, 129.26, 129.10, 128.38, 127.54, 126.61, 59.57, 56.79, 44.90, 39.27, 38.11, 35.55 ppm. ESI-HRMS calcd for $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_3\text{S}$ [(M+H) $^+$]: 349.1586, found:349.1580.

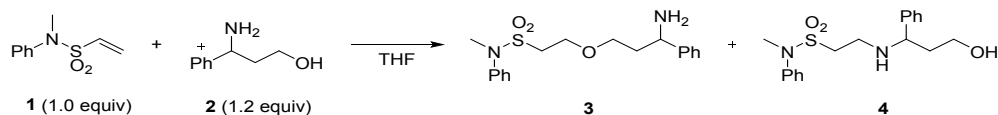
2. Experimental Procedures

2.1 Synthesis of *N*-methyl-*N*-phenylvinylsulfonamide **1**



To a stirred solution of *N*-methylaniline (2.14 g, 20 mmol) and trimethylamine (6.07 g, 60 mmol) in DCM (40 mL) was cooled to 0°C with ice-bath, 2-chloroethanesulfonyl chloride (3.91 g, 24 mmol) was added slowly. The resulting mixture was stirred at 0°C until the amine was consumed as determined by TLC. The reaction was quenched with water (20 mL) and the mixture was extracted with DCM (3 X 50 mL). The combined organic extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4 . The solvent was removed under vacuum and the residue was purified by column chromatography on a gradient from petroleum ether to 10% ethyl acetate in petroleum ether to afford 3.66 g (18.56 mmol, 93% yield) **1** as a white solid. ^1H NMR (500 MHz, THF) δ 7.37 – 7.29 (m, 4H), 7.22 (ddd, $J = 6.4, 3.6, 1.7$ Hz, 1H), 6.57 (dd, $J = 16.5, 10.0$ Hz, 1H), 6.01 (dd, $J = 33.6, 13.3$ Hz, 2H), 3.19 (s, 3H). ^{13}C NMR (126 MHz, THF) δ 143.12, 134.13, 129.71, 128.38, 127.71, 127.36, 38.18 ppm. ESI-HRMS calcd for $\text{C}_9\text{H}_{12}\text{NO}_2\text{S}$ [(M+H) $^+$]: 198.0589, found:198.0563.

2.2 Optimization of the reaction condition



In a 1.5 mL eppendorf tube, tetrahydrofuran (300 μL), 3-amino-3-phenyl-1-propanol **2** (1.2 equiv, 100 μL of a 0.6 M stock solution in tetrahydrofuran), *N*-methyl-*N*-phenylvinylsulfonamide **1** (1 equiv, 100 μL of a 0.5 M stock solution in tetrahydrofuran) and different bases (0.5 equiv, LiOH, NaOH, KOH, K_2CO_3 , Et_3N , DBU, DABCO, respectively) were vibrated on HulaMixer (Invitrogen) at room temperature for 2 hours or overnight. Then, 5 μL of each reaction solution were taken out and 500 μL of d^6 -DMSO was added for NMR analysis to obtain ^1H NMR. Yields were determined by ^1H NMR analysis of crude mixture.

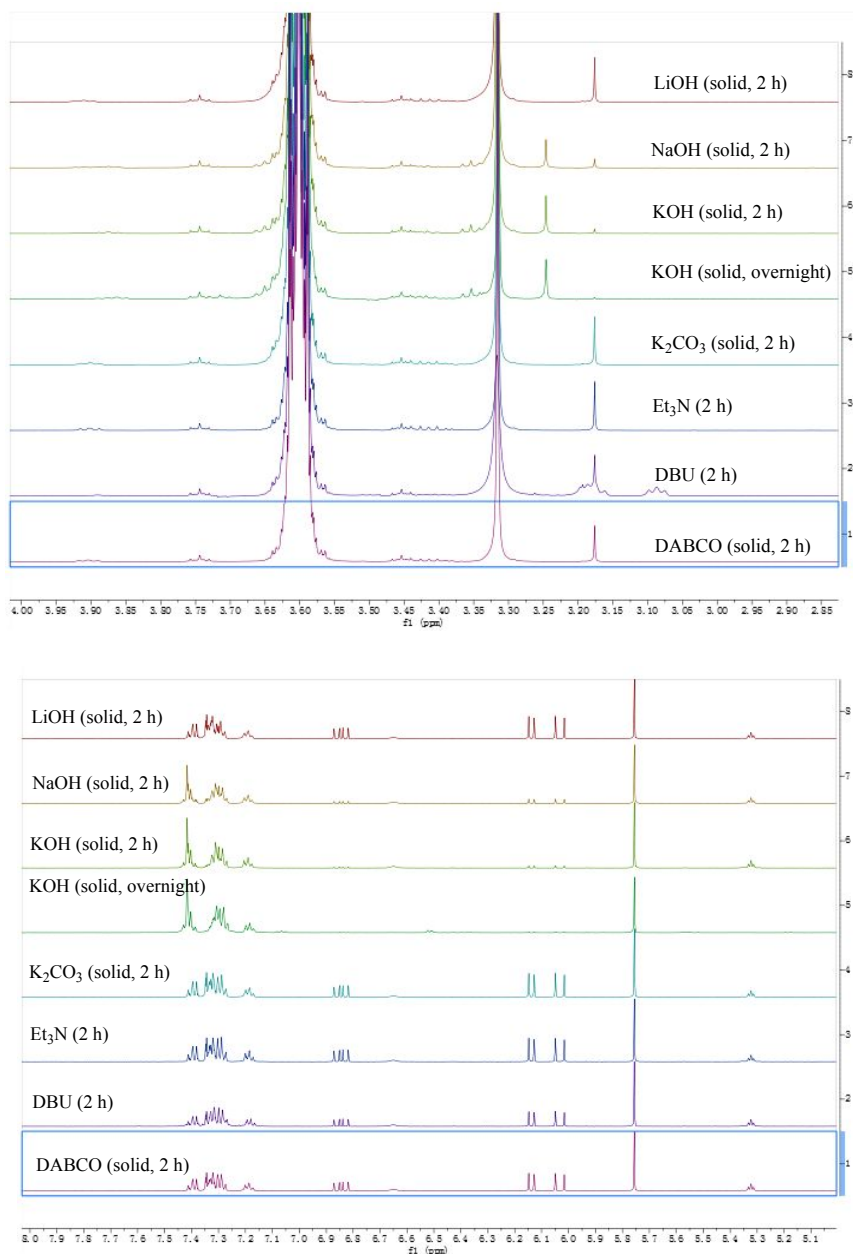
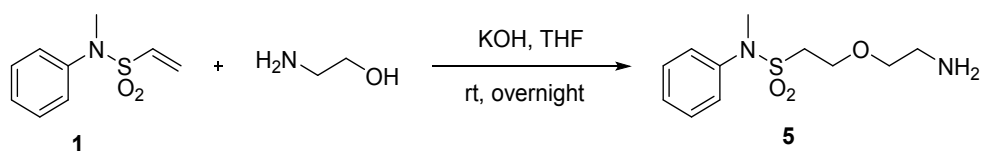


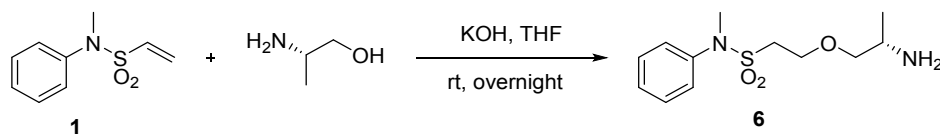
Figure S1. ^1H NMR analysis of crude mixture.

2.3 Substrate scope of aminoalcohols

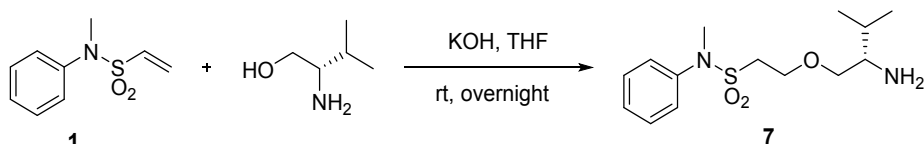


The compound ethanolamine (0.6 mmol, 36.65 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (8 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **1** (0.5 mmol, 98.63 mg) was added. The resulting mixture was stirred overnight at room temperature. The resulting crude mixture was purified by preparative HPLC ($\text{CH}_3\text{CN} : \text{H}_2\text{O} = 10 \sim 100\%$, 0 ~ 20 min) after filtration. The signal of desired product was obtained at 10.0 min and afforded 92 mg (0.357 mmol, 72%) yield of **5** as a colorless oily liquid. ^1H NMR (500 MHz, DMSO) δ 8.10 (m, 2H), 7.45 –

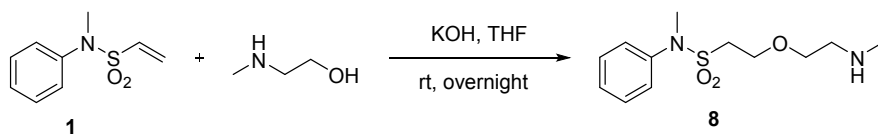
7.38 (m, 4H), 7.33 – 7.28 (m, 1H), 3.76 (t, $J = 6.3$ Hz, 2H), 3.61 (t, $J = 5.3$ Hz, 2H), 3.44 (t, $J = 6.3$ Hz, 2H), 3.26 (s, 3H), 2.94 (dd, $J = 10.0, 4.9$ Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 141.36, 129.12, 127.05, 126.48, 66.41, 63.95, 48.54, 38.22, 37.97 ppm. **ESI-HRMS** calcd for $\text{C}_{11}\text{H}_{19}\text{N}_2\text{O}_3\text{S}$ [(M+H) $^+$]: 259.1116, found:259.1135.



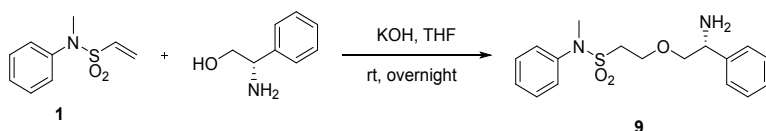
The compound L-alaninol (0.6 mmol, 45.07 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (3 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **1** (0.5 mmol, 98.63 mg) was added. The resulting mixture was stirred overnight at room temperature. The resulting crude mixture was purified by preparative HPLC ($\text{CH}_3\text{CN} : \text{H}_2\text{O} = 10 \sim 100\%$, 0 ~ 20 min) after filtration. The signal of desired product was obtained at 10.2 min and afforded 127.8 mg (0.47 mmol, 94%) yield of **6** as a colorless oily liquid. ^1H NMR (500 MHz, DMSO) δ 8.02 (s, 2H), 7.47 – 7.38 (m, 4H), 7.30 (dt, $J = 8.4, 1.9$ Hz, 1H), 3.85 – 3.71 (m, 2H), 3.51 (dd, $J = 10.4, 4.3$ Hz, 1H), 3.44 (t, $J = 6.1$ Hz, 3H), 3.34 (s, 1H), 3.26 (s, 3H), 1.13 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 141.39, 129.14, 127.07, 126.46, 71.27, 64.33, 48.46, 46.13, 37.94, 14.94 ppm. **ESI-HRMS** calcd for $\text{C}_{12}\text{H}_{21}\text{N}_2\text{O}_3\text{S}$ [(M+H) $^+$]: 273.1273, found:273.1294.



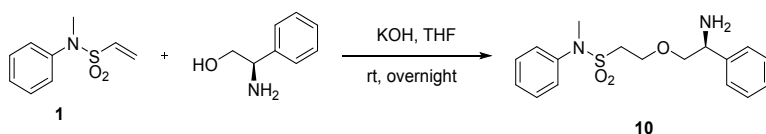
The compound D-valinol (0.6 mmol, 61.09 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (8 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **1** (0.5 mmol, 98.63 mg) was added. The resulting mixture was stirred overnight at room temperature. The resulting crude mixture was purified by preparative HPLC ($\text{CH}_3\text{CN} : \text{H}_2\text{O} = 10 \sim 100\%$, 0 ~ 20 min) after filtration. The signal of desired product was obtained at 10.7 min and afforded 141 mg (0.47 mmol, 94%) yield of **7** as a colorless oily liquid. ^1H NMR (500 MHz, DMSO) δ 8.01 (s, 2H), 7.46 – 7.37 (m, 4H), 7.32 – 7.27 (m, 1H), 3.87 – 3.71 (m, 2H), 3.61 (dd, $J = 10.6, 3.6$ Hz, 1H), 3.51 (dd, $J = 10.6, 7.3$ Hz, 1H), 3.46 (t, $J = 6.4$ Hz, 2H), 3.26 (s, 3H), 3.02 (s, 1H), 1.96 – 1.83 (m, 1H), 0.92 (dd, $J = 14.6, 6.9$ Hz, 6H). ^{13}C NMR (126 MHz, DMSO) δ 141.41, 129.14, 127.06, 126.44, 68.34, 64.38, 55.52, 48.43, 37.93, 27.79, 18.53, 18.07 ppm. **ESI-HRMS** calcd for $\text{C}_{14}\text{H}_{25}\text{N}_2\text{O}_3\text{S}$ [(M+H) $^+$]: 301.1586, found:301.1784.



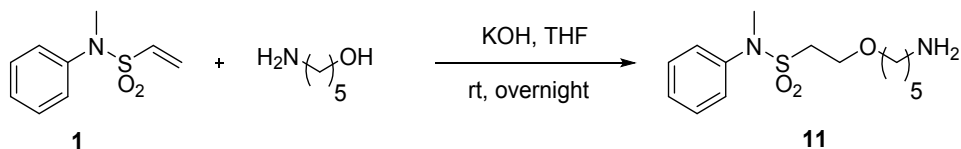
The compound 2-(methylamino)ethan-1-ol (0.6 mmol, 45.1 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (8 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **1** (0.5 mmol, 98.63 mg) was added. The resulting mixture was stirred overnight at room temperature. The resulting crude mixture was purified by preparative HPLC ($\text{CH}_3\text{CN} : \text{H}_2\text{O} = 10 \sim 100\%$, 0 ~ 20 min) after filtration. The signal of desired product was obtained at 9.8 min and afforded 118 mg (0.434 mmol, 87%) yield of **8** as a white solid. ^1H NMR (500 MHz, DMSO) δ 7.49 – 7.40 (m, 4H), 7.38 – 7.32 (m, 1H), 3.72 (t, $J = 5.0$ Hz, 4H), 3.50 (s, 2H), 3.30 (s, 5H), 2.84 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 140.85, 129.26, 127.56, 126.90, 56.96, 55.10, 49.19, 43.72, 39.66, 38.29 ppm. **ESI-HRMS** calcd for $\text{C}_{12}\text{H}_{21}\text{N}_2\text{O}_3\text{S}$ [(M+H) $^+$]: 273.1273, found:273.1369.



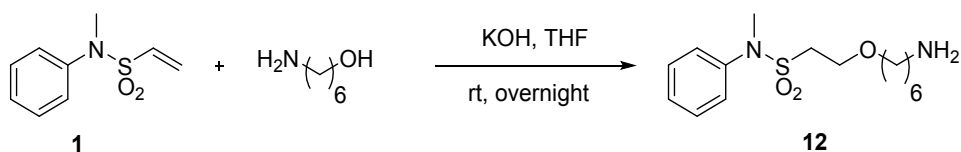
The compound (S)-(+)-2-Phenylglycinol (0.6 mmol, 82.3 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (8 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **1** (0.5 mmol, 98.63 mg) was added. The resulting mixture was stirred overnight at room temperature. The resulting crude mixture was purified by preparative HPLC (CH₃CN : H₂O = 10 ~ 100%, 0 ~ 20 min) after filtration. The signal of desired product was obtained at 11.4 min and afforded 76 mg (0.228 mmol, 46%) yield of **9** as a colorless oily liquid. **¹H NMR** (500 MHz, DMSO) δ 8.58 (s, 2H), 7.53 – 7.48 (m, 2H), 7.43 – 7.38 (m, 7H), 7.34 – 7.27 (m, 1H), 4.50 (s, 1H), 3.90 – 3.70 (m, 4H), 3.45 (t, *J* = 6.7 Hz, 2H), 3.21 (s, 3H). **¹³C NMR** (126 MHz, DMSO) δ 141.34, 134.98, 129.12, 128.86, 128.73, 127.60, 127.06, 126.48, 71.37, 64.43, 53.31, 48.56, 37.91 ppm. **ESI-HRMS** calcd for C₁₇H₂₃N₂O₃S [(M+H)⁺]: 335.1429, found:335.0486.



The compound D-phenylglycinol (0.6 mmol, 82.3 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (8 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **1** (0.5 mmol, 98.63 mg) was added. The resulting mixture was stirred overnight at room temperature. The resulting crude mixture was purified by preparative HPLC (CH₃CN : H₂O = 10 ~ 100%, 0 ~ 20 min) after filtration. The signal of desired product was obtained at 11.0 min and afforded 115 mg (0.344 mmol, 69%) yield of **10** as a colorless oily liquid. **¹H NMR** (500 MHz, DMSO) δ 8.63 (s, 2H), 7.51 (d, *J* = 6.8 Hz, 2H), 7.46 – 7.36 (m, 7H), 7.34 – 7.27 (m, 1H), 4.50 (dd, *J* = 7.2, 5.0 Hz, 1H), 3.85 (tdd, *J* = 12.9, 8.7, 4.2 Hz, 2H), 3.80 – 3.71 (m, 2H), 3.51 – 3.40 (m, 2H), 3.21 (s, 3H). **¹³C NMR** (126 MHz, DMSO) δ 141.35, 135.02, 129.12, 128.82, 128.72, 127.61, 127.06, 126.49, 71.38, 64.43, 53.31, 48.59, 37.91 ppm. **ESI-HRMS** calcd for C₁₇H₂₃N₂O₃S [(M+H)⁺]: 335.1429, found:335.0486.

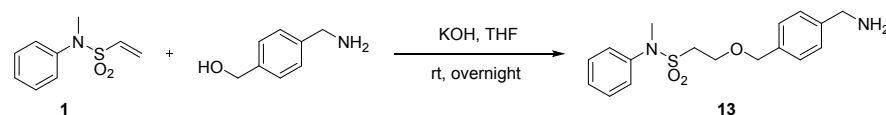


The compound 5-aminopentanol (0.6 mmol, 61.90 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (8 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **1** (0.5 mmol, 98.63 mg) was added. The resulting crude mixture was purified by preparative HPLC (CH₃CN : H₂O = 10 ~ 60%, 0 ~ 19 min) after filtration. The signal of desired product was obtained at 12.0 min and afforded 132 mg (0.44 mmol, 88%) yield of **11** as a colorless oily liquid. **¹H NMR** (500 MHz, MeOD) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 3.79 (t, *J* = 5.8 Hz, 2H), 3.48 (t, *J* = 6.2 Hz, 2H), 3.36 – 3.28 (m, 5H), 2.91 (t, *J* = 7.6 Hz, 2H), 1.74 – 1.55 (m, 4H), 1.53 – 1.39 (m, 2H). **¹³C NMR** (126 MHz, MeOD) δ 142.92 (s), 130.25 (s), 128.43 (s), 127.89 (s), 71.69 (s), 65.56 (s), 50.49 (s), 40.64 (s), 38.85 (s), 29.86 (s), 28.21 (s), 24.07 (s). **ESI-HRMS** calcd for C₁₄H₂₅N₂O₃S [(M+H)⁺]: 301.1586, found:301.1693.

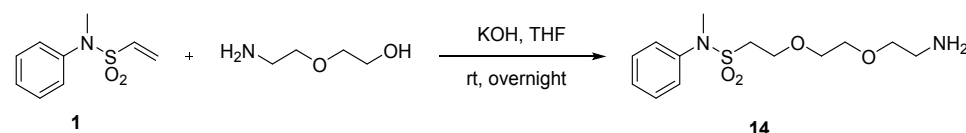


The compound 6-amino-1-hexanol (0.6 mmol, 70.32 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (8 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **1** (0.5 mmol, 98.63 mg) was added. The resulting crude mixture was purified by preparative HPLC (CH₃CN : H₂O = 10 ~ 60%, 0 ~ 19 min) after filtration. The signal of desired

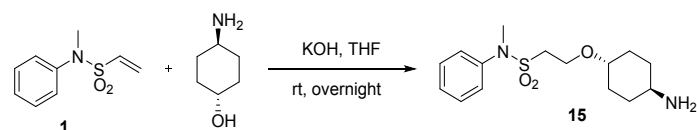
product was obtained at 12.5 min and afforded 121 mg (0.39 mmol, 78%) yield of **12** as a colorless oily liquid. **¹H NMR** (500 MHz, MeOD) δ 7.44 (dt, J = 8.6, 1.9 Hz, 2H), 7.41 – 7.35 (m, 2H), 7.32 – 7.27 (m, 1H), 3.78 (t, J = 5.9 Hz, 2H), 3.46 (t, J = 6.4 Hz, 2H), 3.34 – 3.28 (m, 5H), 2.95 – 2.88 (m, 2H), 1.71 – 1.55 (m, 4H), 1.46 – 1.36 (m, 4H). **¹³C NMR** (126 MHz, MeOD) δ 142.85 (s), 130.21 (s), 128.37 (s), 127.85 (s), 71.94 (s), 65.47 (s), 50.63 (s), 40.59 (s), 38.89 (s), 30.20 (s), 28.40 (s), 27.07 (s), 26.61 (s). **ESI-HRMS** calcd for C₁₅H₂₇N₂O₃S [(M+H)⁺]: 315.1742, found:315.1671.



The compound 4-hydroxymethylbenzylamine (0.6 mmol, 82.31 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (8 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **1** (0.5 mmol, 98.63 mg) was added. The resulting mixture was stirred overnight at room temperature. The resulting crude mixture was purified by preparative HPLC (CH₃CN : H₂O = 10 ~ 100%, 0 ~ 20 min) after filtration. The signal of desired product was obtained at 9.9 min and afforded 66 mg (0.198 mmol, 40%) yield of **13** as a colorless oily liquid. **¹H NMR** (500 MHz, DMSO) δ 8.3.6 (s, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.43 – 7.34 (m, 6H), 7.29 (ddd, J = 8.4, 5.7, 2.6 Hz, 1H), 4.51 (s, 2H), 4.04 (d, J = 5.0 Hz, 2H), 3.76 (t, J = 6.1 Hz, 2H), 3.44 (t, J = 6.1 Hz, 2H), 3.24 (s, 3H). **¹³C NMR** (126 MHz, DMSO) δ 141.42, 138.17, 133.38, 129.08, 128.85, 127.87, 126.94, 126.38, 71.60, 63.53, 49.02, 42.05, 37.95 ppm. **ESI-HRMS** calcd for C₁₇H₂₃N₂O₃S [(M+H)⁺]: 335.1429, found:335.1461.



The compound 2-(2-Aminoethoxy)ethanol (0.6 mmol, 63.09 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (8 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **1** (0.5 mmol, 98.63 mg) was added. The resulting mixture was stirred overnight at room temperature. The resulting crude mixture was purified by preparative HPLC (CH₃CN : H₂O = 10 ~ 100%, 0 ~ 20 min) after filtration. The signal of desired product was obtained at 10.0 min and afforded 94 mg (0.312 mmol, 63%) yield of **14** as a colorless oily liquid. **¹H NMR** (500 MHz, DMSO) δ 8.00 (s, 2H), 7.45 – 7.38 (m, 4H), 7.32 – 7.27 (m, 1H), 3.75 (t, J = 6.1 Hz, 2H), 3.60 (t, J = 5.3 Hz, 2H), 3.56 (s, 4H), 3.37 (t, J = 6.1 Hz, 2H), 3.25 (s, 3H), 2.96 (d, J = 4.2 Hz, 2H). **¹³C NMR** (126 MHz, DMSO) δ 141.46, 129.09, 126.96, 126.45, 69.56, 69.51, 66.68, 64.25, 49.10, 38.55, 37.97 ppm. **ESI-HRMS** calcd for C₁₃H₂₃N₂O₄S [(M+H)⁺]: 303.1379, found:303.1490



The compound trans-4-aminocyclohexanol (0.6 mmol, 69.1 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (8 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **1** (0.5 mmol, 98.63 mg) was added. The resulting mixture was stirred overnight at room temperature. The resulting crude mixture was purified by preparative HPLC (CH₃CN : H₂O = 10 ~ 100%, 0 ~ 20 min) after filtration. The signal of desired product was obtained at 11.2 min and afforded 97 mg (0.311 mmol, 63%) yield of **15** as a colorless oily liquid. **¹H NMR** (500 MHz, DMSO) δ 8.00 (s, 2H), 7.45 – 7.36 (m, 4H), 7.32 – 7.25 (m, 1H), 3.73 (t, J = 6.1 Hz, 2H), 3.32 (t, J = 6.0 Hz, 2H), 3.29 – 3.20 (m, 4H), 2.97 (dd, J = 9.2, 4.3 Hz, 1H), 1.95 (dd, J = 29.7, 10.5 Hz, 4H), 1.41 – 1.13 (m, 4H). **¹³C NMR** (126 MHz, DMSO) δ 141.47, 129.08, 126.92, 126.40, 76.05, 61.41, 49.55, 48.48, 38.03, 29.18, 28.06 ppm. **ESI-HRMS** calcd for C₁₅H₂₅N₂O₃S [(M+H)⁺]: 313.1586, found:313.1623.

2.4 Chemoselective conjugation to atenolol



Atenolol

16

CN(C)S(=O)(=O)C=C (1) + c1ccccc1CO (17a) + c1ccccc1CN (18a) $\xrightarrow[\text{rt, 2 h}]{\text{KOH, THF}}$ CN(C)S(=O)(=O)CCOCc1ccccc1 (19)

1

17a

18a

19

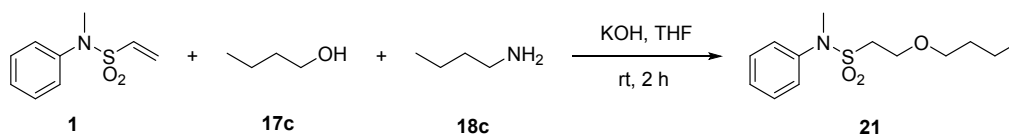


17b

18b

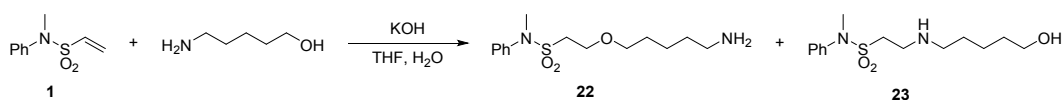
20

S8

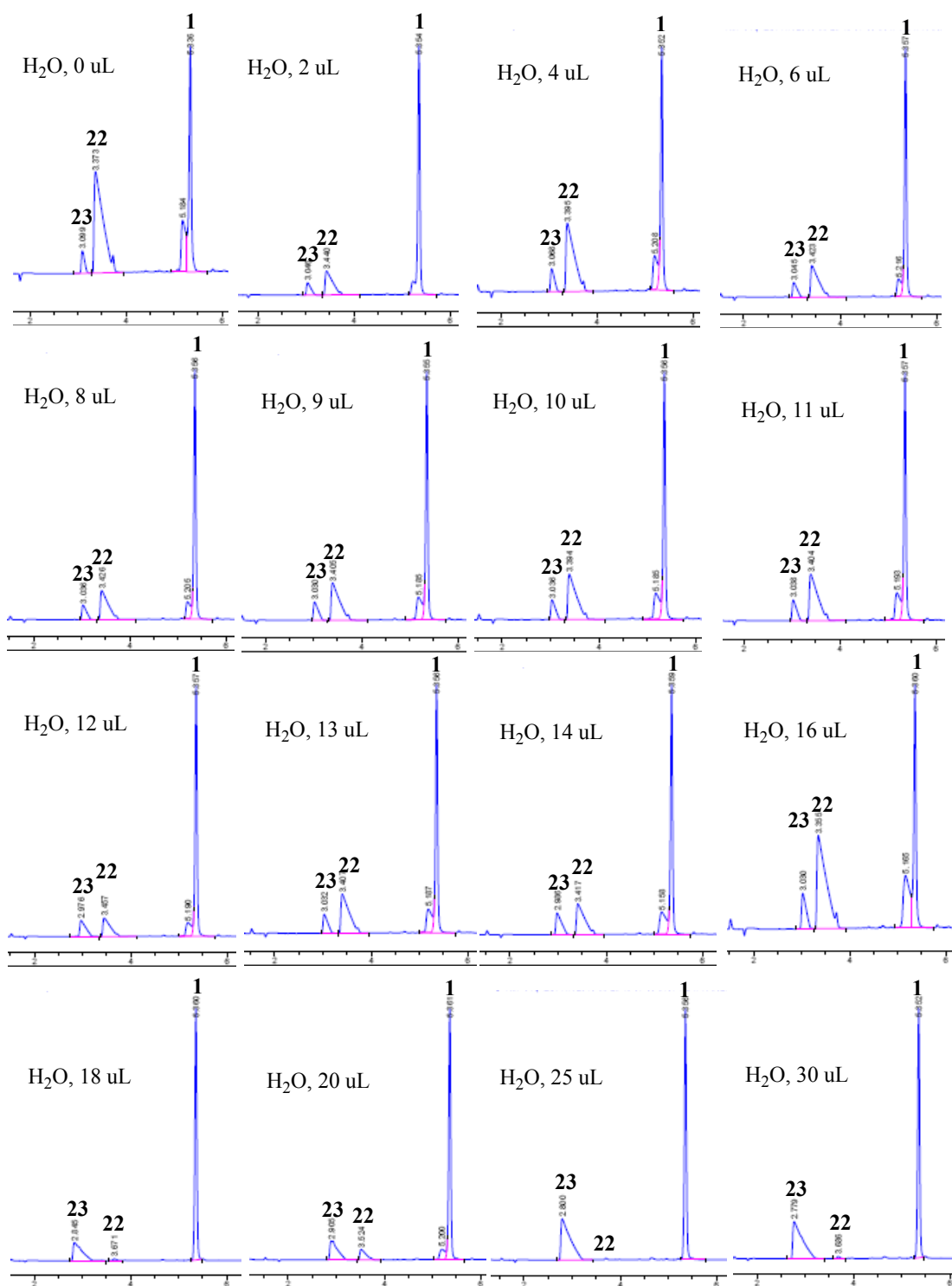


The compound 1-butanol **17c** (0.6 mmol, 44.47 mg), β -phenylethylamine **18c** (0.6 mmol, 43.88 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (8 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **1** (0.5 mmol, 98.63 mg) was added. The resulting mixture was stirred at room temperature for 48 hours. After filtering the reaction solution with a filter, the resulting crude mixture was purified by HPLC to afford 112 mg (0.42 mmol, 83%) yield of **21** as a light yellow oily liquid. $^1\text{H NMR}$ (500 MHz, DMSO) δ 7.45 – 7.37 (m, 4H), 7.32 – 7.27 (m, 1H), 3.68 (t, J = 6.1 Hz, 2H), 3.37 (m, 4H), 3.25 (s, 3H), 1.51 – 1.43 (m, 2H), 1.30 (ddd, J = 10.2, 9.4, 4.7 Hz, 2H), 0.86 (t, J = 7.4 Hz, 3H). $^{13}\text{C NMR}$ (126 MHz, DMSO) δ 141.4, 129.00, 126.84, 126.28, 69.98, 63.84, 49.09, 37.88, 31.08, 18.72, 13.70 ppm. **ESI-HRMS** calcd for $\text{C}_{13}\text{H}_{22}\text{NO}_3\text{S}$ [(M+H) $^+$]: 272.1320, found: 272.1314.

2.6 The effect of water on the reaction



In a 1.5 mL eppendorf tube, H_2O 0-200 μL , tetrahydrofuran 300-100 μL , 5-amino-1-pentanol (1.2 equiv, 100 μL of a 0.6 M stock solution in tetrahydrofuran), potassium hydroxide and compound **1** (1 equiv, 100 μL of a 0.5 M stock solution in tetrahydrofuran) were vibrated at room temperature for 4 hours. The yield of O-adduct **22** and N-adduct **23** was analyzed by RP-HPLC.



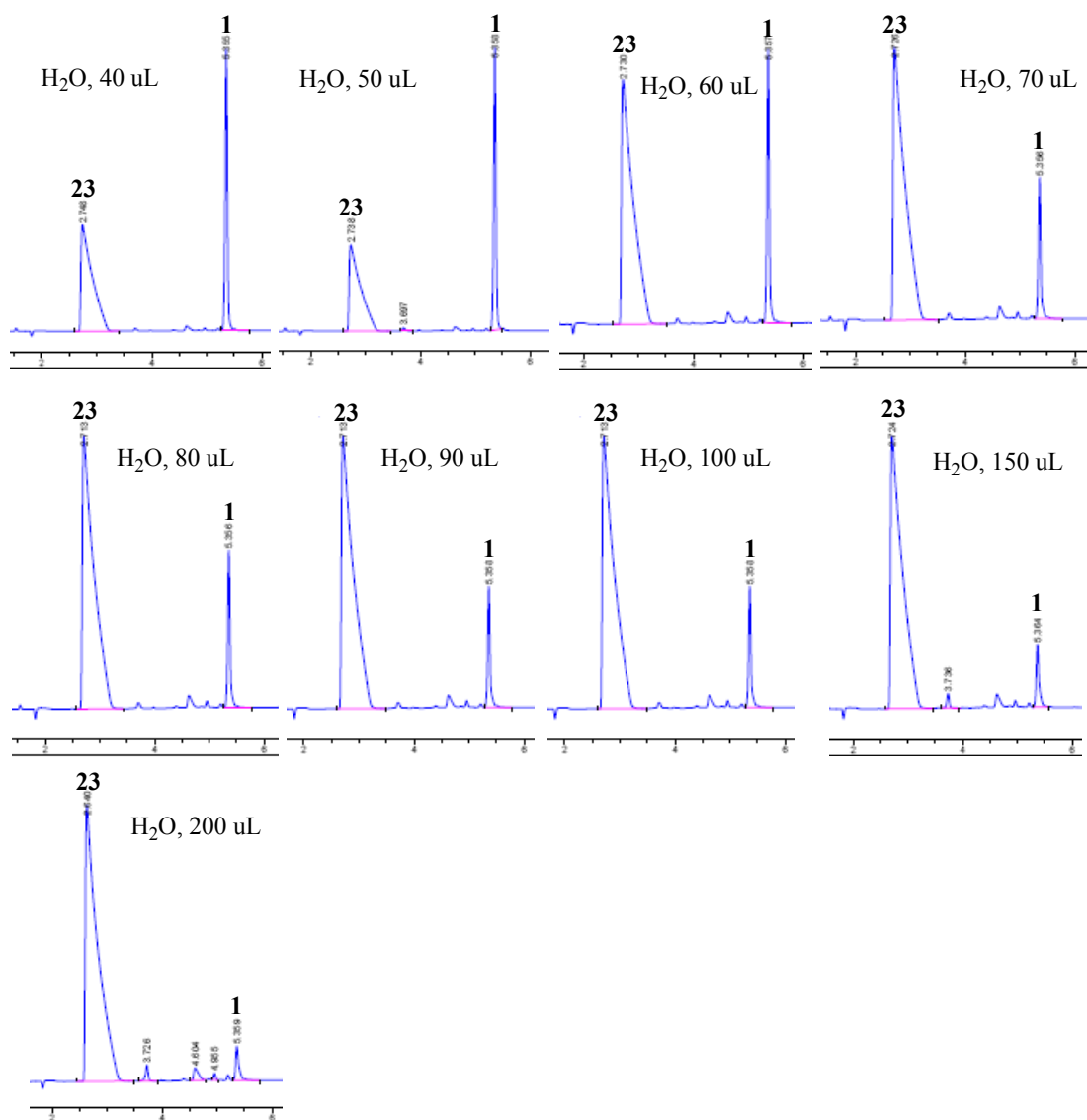
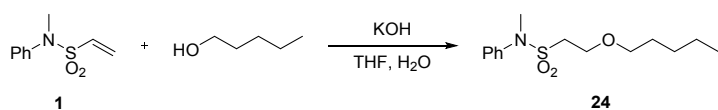
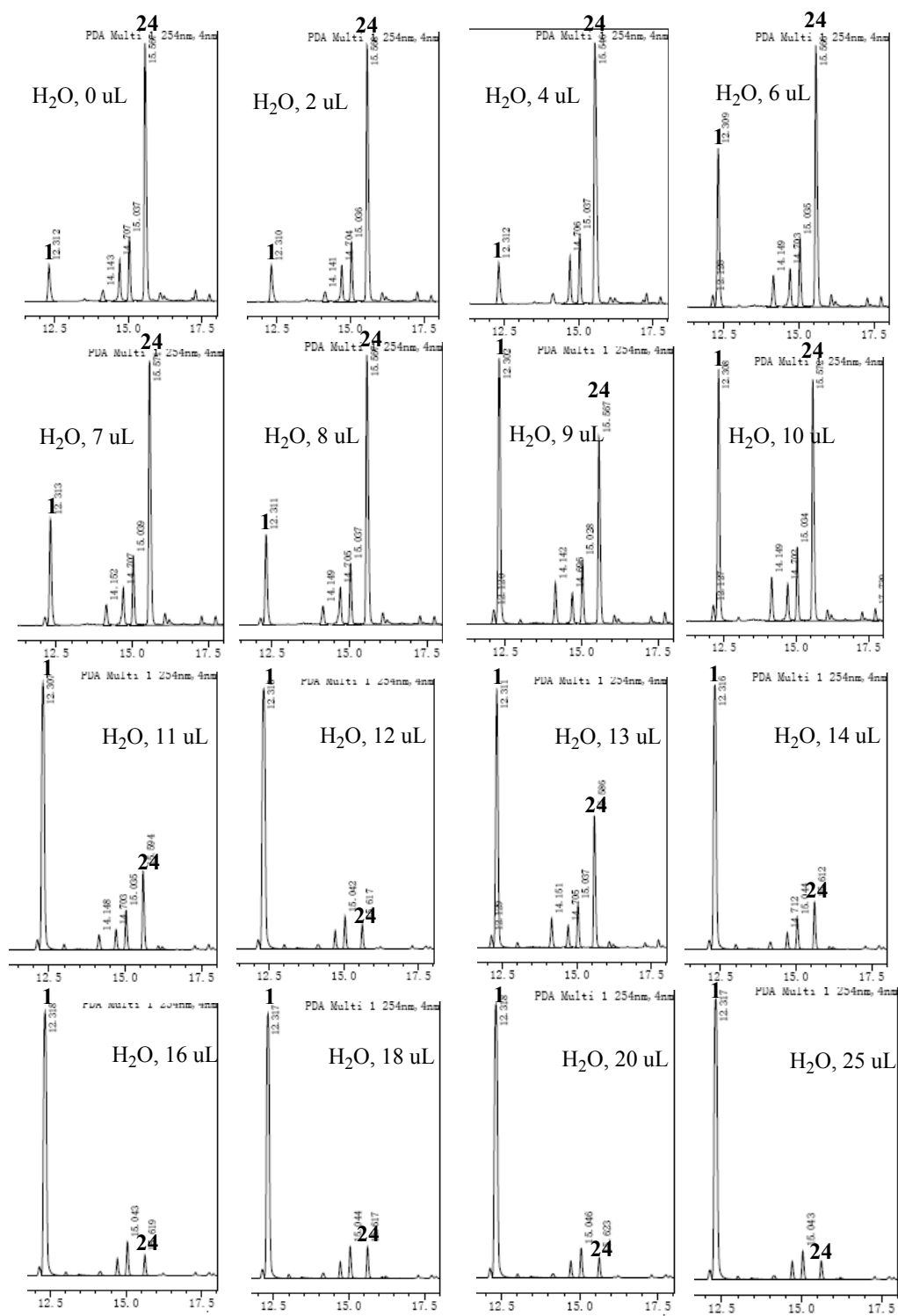


Figure S2. RP-HPLC analysis of the reaction.



In a 1.5 mL eppendorf tube, H₂O 0-30 μ L, tetrahydrofuran 300-270 μ L, pentylalcohol (1.2 equiv, 100 μ L of a 0.6 M stock solution in tetrahydrofuran), potassium hydroxide and compound **1** (1 equiv, 100 μ L of a 0.5 M stock solution in tetrahydrofuran) were vibrated at room temperature for 2 hours. The yield of oxa-addition product **24** was analyzed by RP-HPLC.



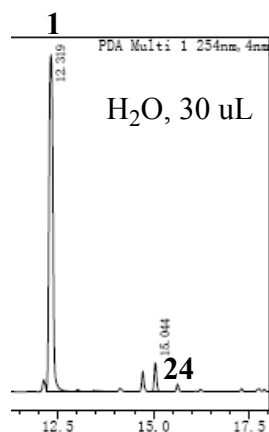
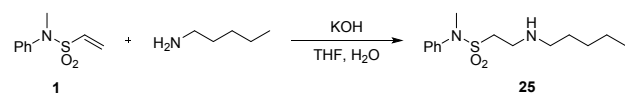


Figure s3. RP-HPLC spectrogram of the reaction.



In a 1.5 mL eppendorf tube, H₂O 0-200 μ L, tetrahydrofuran 300-100 μ L, pentylamine (1.2 equiv, 100 μ L of a 0.6 M stock solution in tetrahydrofuran), potassium hydroxide and compound **1** (1 equiv, 100 μ L of a 0.5 M stock solution in tetrahydrofuran) were vibrated at room temperature for 2 hours. The yield of aza-addition product **25** was analyzed by RP-HPLC.

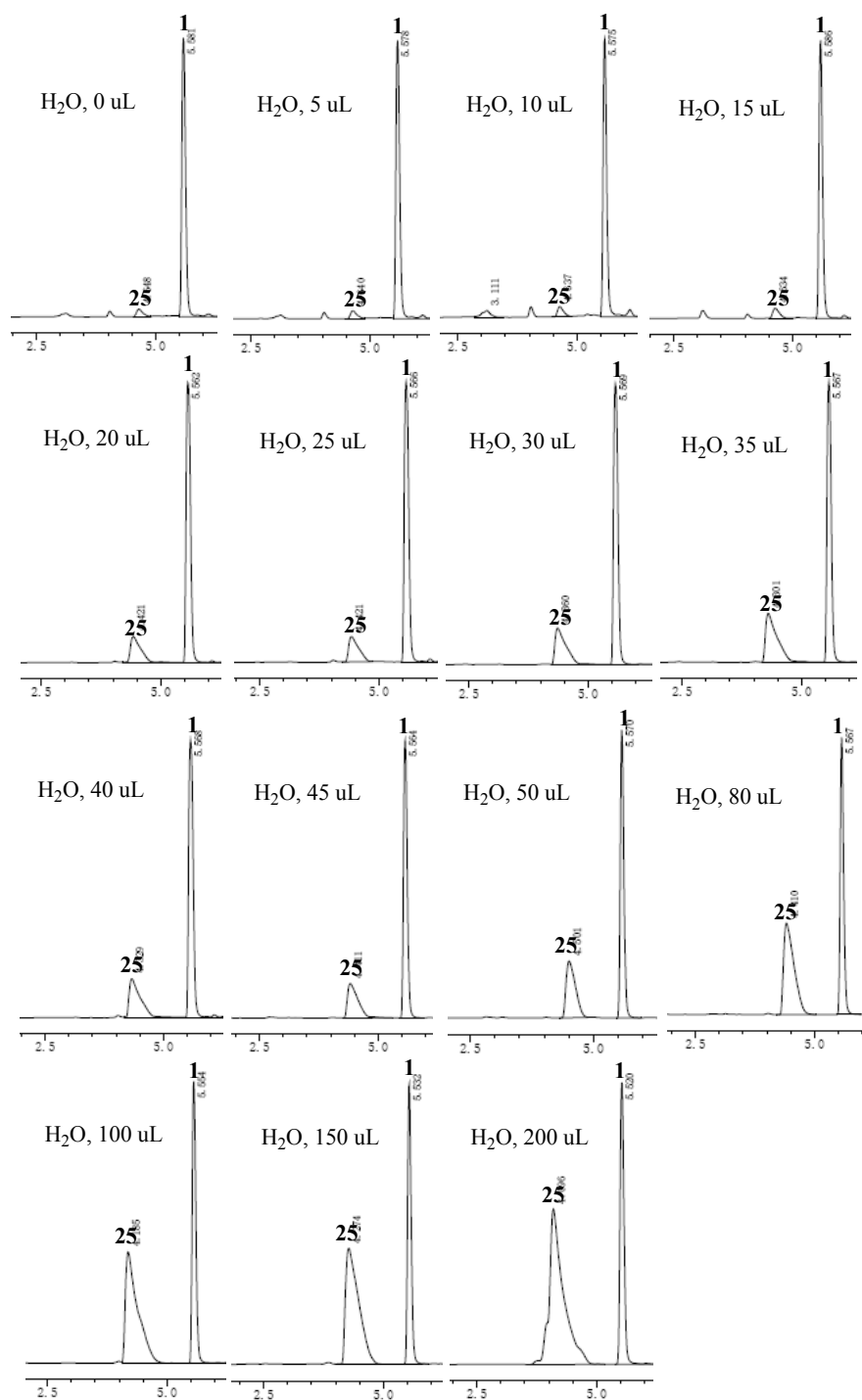
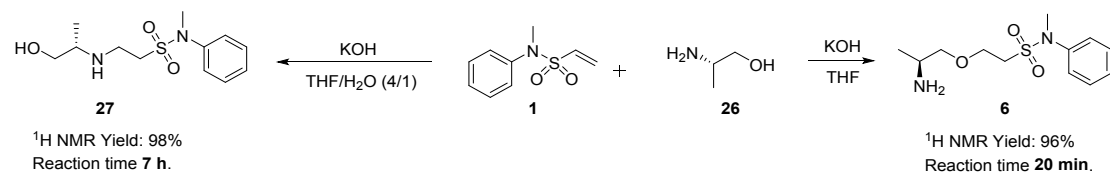
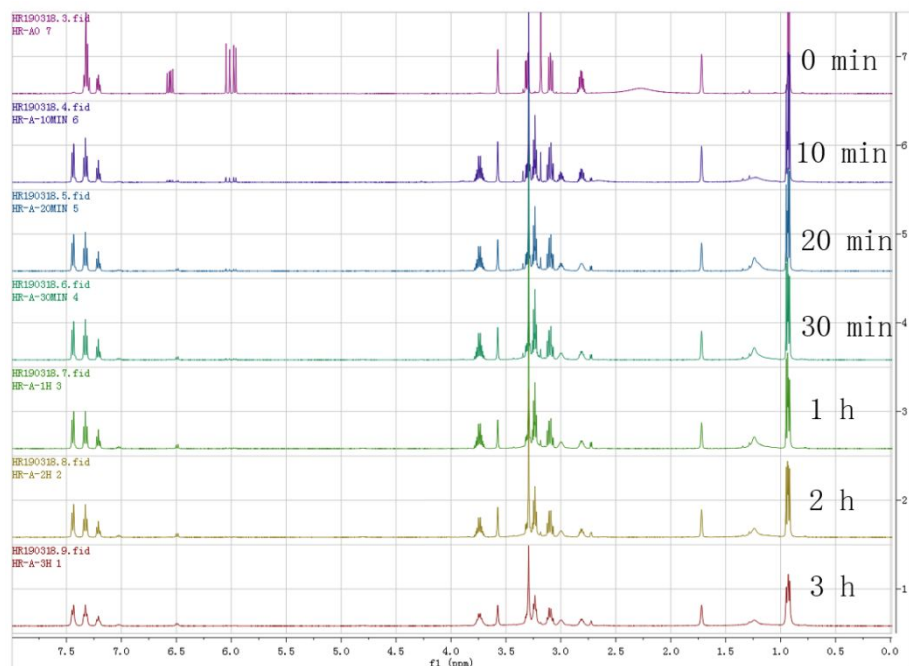


Figure S4. RP-HPLC spectrogram of the reaction.

2.7 The reaction time of O-adducts and N-adducts



Compound **1** (0.1 mmol, 19.73 mg), **26** (0.12 mmol, 9.0132 mg) and KOH (0.2 mmol, 11.22 mg) were dissolved in 500 μ L d^8 -THF, which was subjected to NMR analysis to obtain ^1H NMR.



Compound **1** (0.1 mmol, 19.73 mg), **26** (0.12 mmol, 9.0132 mg) and KOH (0.2 mmol, 11.22 mg) were dissolved in 400 μ L d^8 -THF and 100 μ L d^2 -H $_2$ O, which was subjected to NMR analysis to obtain ^1H NMR.

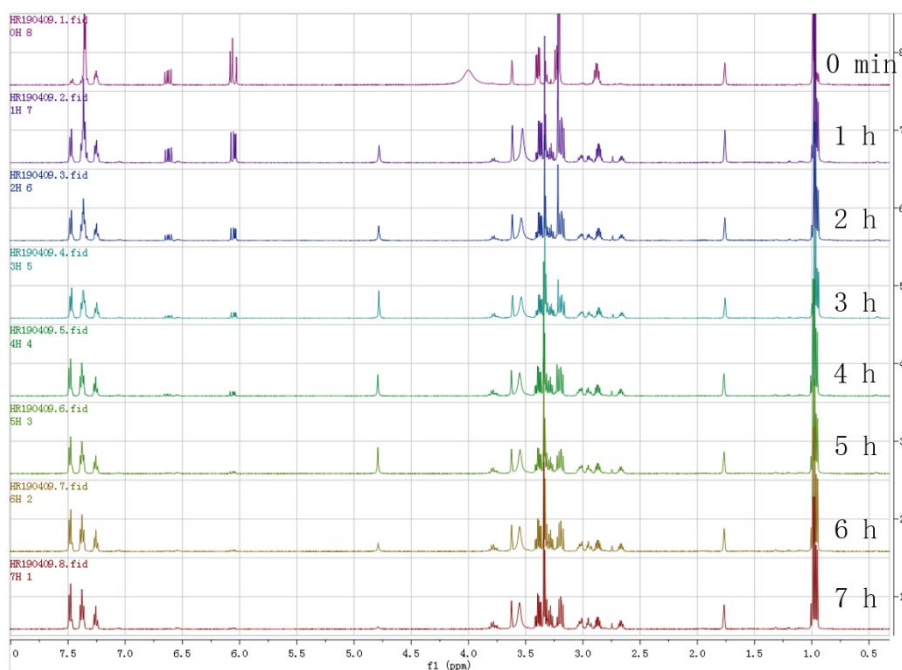
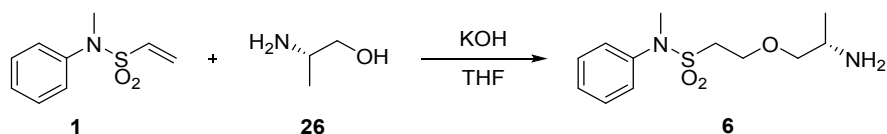
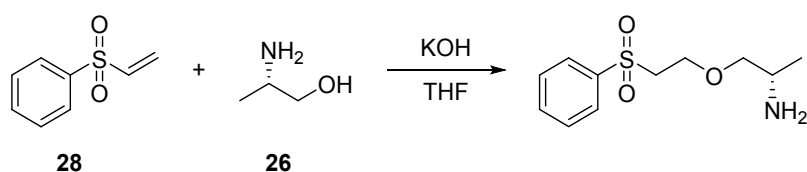


Figure S5. ^1H NMR spectra of oxa- and aza-Michael addition

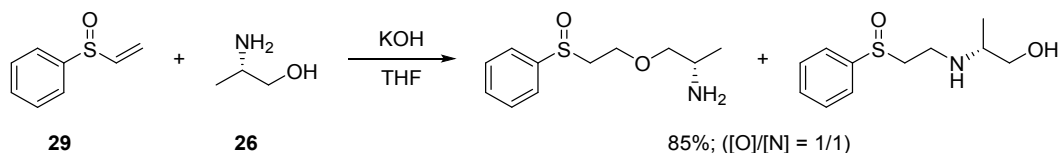
2.8 The effects of different Michael acceptors to the reaction



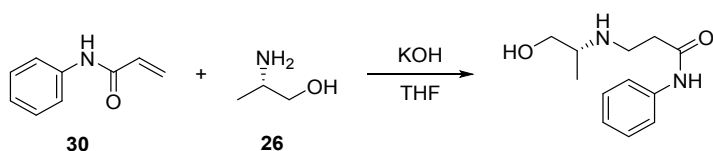
The compound L-(+)-alaninol **26** (0.6 mmol, 45.07 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (3 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **1** (0.5 mmol, 98.63 mg) was added. The resulting mixture was stirred overnight at room temperature. After filtering the reaction solution with a filter, the resulting crude mixture was purified by HPLC to afford 127.8 mg (0.47 mmol, 94%) yield of **6** as a colorless oily liquid. ¹H NMR (500 MHz, DMSO) δ 8.02 (s, 2H), 7.47 – 7.38 (m, 4H), 7.30 (dt, *J* = 8.4, 1.9 Hz, 1H), 3.85 – 3.71 (m, 2H), 3.51 (dd, *J* = 10.4, 4.3 Hz, 1H), 3.44 (t, *J* = 6.1 Hz, 3H), 3.34 (s, 1H), 3.26 (s, 3H), 1.13 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (126 MHz, DMSO) δ 141.39, 129.14, 127.07, 126.46, 71.27, 64.33, 48.46, 46.13, 37.94, 14.94 ppm. ESI-HRMS calcd for C₁₂H₂₁N₂O₃S [(M+H)⁺]: 273.1273, found:273.1294.



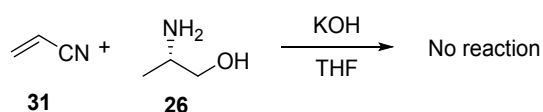
The compound L-(+)-alaninol **26** (0.6 mmol, 45.07 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (3 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound phenylvinylsulfonyl **28** (0.5 mmol, 84.11 mg) was added. The resulting mixture was stirred overnight at room temperature. The resulting crude mixture was purified by preparative HPLC (CH₃CN : H₂O = 10 ~ 100%, 0 ~ 20 min) after filtration. The signal of desired product was obtained at 4.4 min and afforded 120.5 mg (0.496 mmol, 98%) yield of O-addition product as a colorless oily liquid. ¹H NMR (500 MHz, MeOD) δ 7.90 – 7.84 (m, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 2H), 3.80 (td, *J* = 6.1, 2.5 Hz, 2H), 3.51 – 3.43 (m, 3H), 3.31 (dd, *J* = 10.1, 7.6 Hz, 1H), 3.27 – 3.19 (m, 1H), 1.10 (d, *J* = 6.7 Hz, 3H). ¹³C NMR (126 MHz, MeOD) δ 140.94 (s), 135.17 (s), 130.54 (s), 129.04 (s), 72.41 (s), 65.46 (s), 56.41 (s), 48.37 (s), 15.10 (s). ESI-HRMS calcd for C₁₁H₁₈NO₃S [(M+H)⁺]: 244.1007, found:244.0934.



The compound L-(+)-alaninol **26** (0.6 mmol, 45.07 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (3 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound phenylvinylsulphoxide **29** (0.5 mmol, 76.11 mg) was added. The resulting mixture was stirred overnight at room temperature. After filtering the reaction solution with a filter, the resulting crude mixture was purified by HPLC to afford 97.4 mg (0.42 mmol, 85%) yield of product (O-adduct/ N-adduct = 1:1) as a colorless oily liquid. ¹H NMR (500 MHz, DMSO) δ 9.24 (d, *J* = 172.6 Hz, 4H), 7.70 (dt, *J* = 3.5, 2.0 Hz, 4H), 7.66 – 7.57 (m, 6H), 3.60 (dt, *J* = 11.2, 3.8 Hz, 2H), 3.57 – 3.44 (m, 4H), 3.35 – 3.28 (m, 2H), 3.27 – 3.15 (m, 4H), 3.04 (ddd, *J* = 12.6, 10.0, 5.1 Hz, 2H), 1.16 (dt, *J* = 6.6, 3.3 Hz, 6H). ¹³C NMR (126 MHz, DMSO) δ 142.89, 142.79, 131.26, 129.49, 124.01, 123.99, 61.04, 61.00, 54.96, 54.93, 50.55, 50.43, 40.02, 39.85, 39.69, 39.52, 39.35, 39.19, 39.02, 37.93, 37.86, 13.26, 13.18. ESI-HRMS calcd for C₁₁H₁₈NO₂S [(M+H)⁺]: 228.1058, found:228.1172.

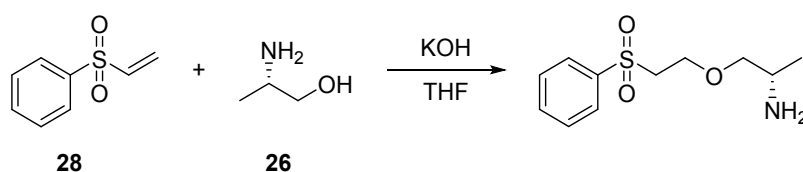


The compound L-(+)-alaninol **26** (0.6 mmol, 45.07 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (3 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **30** (0.5 mmol, 73.59 mg) was added. The resulting mixture was stirred overnight at room temperature. The resulting crude mixture was purified by preparative HPLC (CH₃CN : H₂O = 10 ~ 100%, 0 ~ 20 min) after filtration. The signal of desired product was obtained at 5.3 min and afforded 73.35 mg (0.33 mmol, 66%) yield of N-adduct as a colorless oily liquid. ¹H NMR (500 MHz, DMSO) δ 10.28 (s, 1H), 7.62 (dd, *J* = 27.5, 7.8 Hz, 2H), 7.33 – 7.21 (m, 2H), 7.00 (dd, *J* = 15.5, 8.1 Hz, 1H), 4.61 (s, 1H), 3.29 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.22 (dd, *J* = 10.4, 6.6 Hz, 1H), 2.85 (dt, *J* = 13.0, 6.6 Hz, 1H), 2.80 – 2.71 (m, 1H), 2.66 – 2.58 (m, 1H), 2.48 – 2.37 (m, 2H), 1.77 (d, *J* = 14.8 Hz, 1H), 0.92 (d, *J* = 6.4 Hz, 3H). ¹³C NMR (126 MHz, DMSO) δ 170.64, 139.34, 128.65, 122.93, 119.04, 65.41, 54.31, 42.85, 40.02, 39.85, 39.69, 39.52, 39.35, 39.19, 39.02, 37.25, 17.18. ESI-HRMS calcd for C₁₂H₁₉N₂O₂ [(M+H)⁺]: 223.1447, found: 223.1465.



The compound L-(+)-alaninol **26** (0.6 mmol, 45.07 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (3 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound acrylonitrile **31** (0.5 mmol, 21.04 mg) was added. The resulting mixture was stirred overnight at room temperature. No target product has been observed by mass spectrometry analysis.

2.9 The reaction of the electrophile **28** and compound **26**

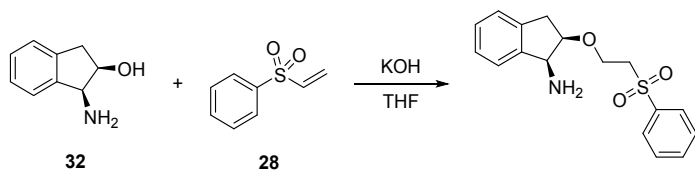


Compound **28** (0.1 mmol, 19.73 mg), **26** (0.12 mmol, 9.0132 mg) and KOH (0.2 mmol, 11.22 mg) were dissolved in 500 μL d⁸-THF, which was subjected to NMR analysis to obtain ¹H NMR.

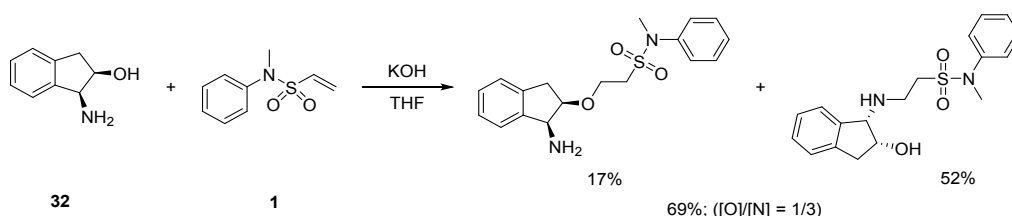


Figure s6. ^1H NMR spectra of the reaction between compound **28** and **26**

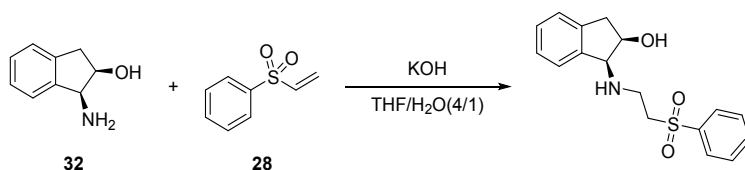
2.10 Reaction selectivity influenced by steric hindrance



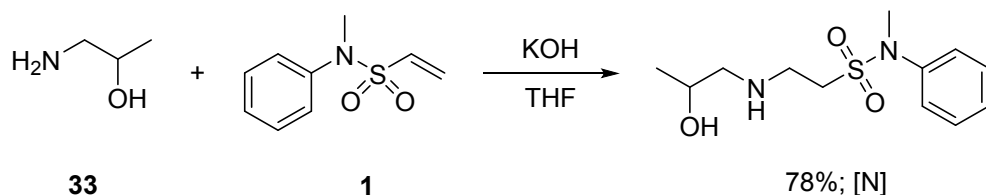
The compound (1S,2R)-(-)-cis-1-amino-2-indanol **32** (0.6 mmol, 89.51 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (3 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound phenylvinylsulfone **28** (0.5 mmol, 84.11 mg) was added. The resulting mixture was stirred at room temperature for 2 hours. The resulting crude mixture was purified by preparative HPLC ($\text{CH}_3\text{CN} : \text{H}_2\text{O} = 10 \sim 100\%$, $0 \sim 20$ min) after filtration. The signal of desired product was obtained at 3.4 min and afforded 114.3 mg (0.36 mmol, 72%) yield of O-adduct as a colorless oily liquid. **¹H NMR** (500 MHz, DMSO) δ 10.48 (s, 1H), 8.98 (s, 1H), 7.96 (d, $J = 7.4$ Hz, 2H), 7.83 (t, $J = 7.4$ Hz, 1H), 7.73 (dd, $J = 10.7, 4.7$ Hz, 3H), 7.37 – 7.19 (m, 3H), 4.70 – 4.58 (m, 2H), 4.07 (ddd, $J = 14.0, 11.5, 4.9$ Hz, 1H), 3.95 – 3.84 (m, 1H), 3.42 – 3.20 (m, 2H), 3.03 (qd, $J = 16.0, 3.4$ Hz, 2H). **¹³C NMR** (126 MHz, DMSO) δ 141.65, 138.09, 135.67, 134.59, 129.89, 129.38, 127.77, 126.65, 126.02, 125.39, 69.50, 62.96, 50.93, 40.02, 39.85, 39.69, 39.52, 39.35, 39.19, 39.02, 38.90. **ESI-HRMS** calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_3\text{S}$ [(M+H)⁺]: 318.1164, found: 318.1160.



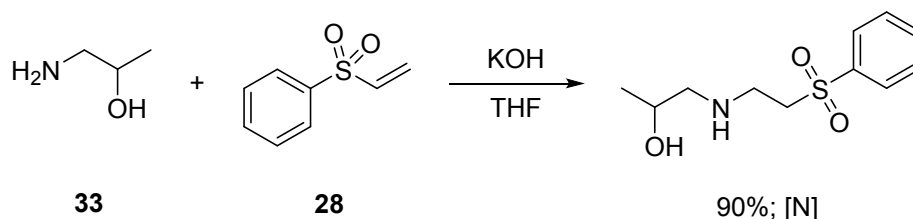
The compound (1S,2R)-(-)-cis-1-amino-2-indanol **32** (0.6 mmol, 89.51 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (3 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **1** (0.5 mmol, 98.63 mg) was added. The resulting mixture was stirred at room temperature for 2 hours. The resulting crude mixture was purified by preparative HPLC ($\text{CH}_3\text{CN} : \text{H}_2\text{O} = 10 \sim 100\%$, $0 \sim 20$ min) after filtration. The signal of desired product was obtained at 7.9 min and afforded 118 mg (0.34 mmol, 69%) yield of product (O-adduct/ N-adduct = 1:3) as a colorless oily liquid. **ESI-HRMS** calcd for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_3\text{S}$ [(M+H)⁺]: 347.1429, found: 347.1275.



The compound (1S,2R)-(-)-cis-1-amino-2-indanol **32** (0.6 mmol, 89.51 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (2.4 mL) and H_2O (0.6 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound phenylvinylsulfone **28** (0.5 mmol, 84.11 mg) was added. The resulting mixture was stirred at room temperature for 2 hours. The resulting crude mixture was purified by preparative HPLC ($\text{CH}_3\text{CN} : \text{H}_2\text{O} = 10 \sim 100\%$, $0 \sim 20$ min) after filtration. The signal of desired product was obtained at 3.4 min and afforded 106 mg (0.34 mmol, 67%) yield of N-adduct as a colorless oily liquid. **¹H NMR** (500 MHz, DMSO- d_6) δ 7.96 – 7.92 (m, 2H), 7.78 – 7.74 (m, 1H), 7.67 (dd, $J = 8.4, 7.1$ Hz, 2H), 7.19 – 7.10 (m, 4H), 4.75 (s, 1H), 4.34 (td, $J = 5.0, 2.7$ Hz, 1H), 3.85 (d, $J = 4.8$ Hz, 1H), 3.55 (t, $J = 7.2$ Hz, 2H), 3.04 (dt, $J = 12.4, 7.0$ Hz, 1H), 2.95 – 2.85 (m, 2H), 2.75 (dd, $J = 16.0, 2.7$ Hz, 1H), 2.31 (s, 1H). **¹³C NMR** (126 MHz, DMSO) δ 143.46, 140.75, 139.47, 133.76, 129.42, 127.70, 127.12, 125.96, 124.81, 124.37, 70.91, 65.33, 55.44, 41.16, 40.02, 39.85, 39.69, 39.52, 39.35, 39.19, 39.02. **ESI-HRMS** calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_3\text{S}$ [(M+H)⁺]: 318.1164, found: 318.1174.

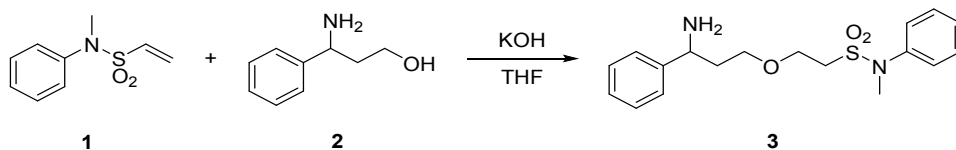


The compound 1-amino-2-propanol **33** (0.6 mmol, 45.066 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (5 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound phenylvinylsulfone **1** (0.5 mmol, 98.625 mg) was added. The resulting mixture was stirred at room temperature for 2 hours. The resulting crude mixture was purified by preparative HPLC ($\text{CH}_3\text{CN} : \text{H}_2\text{O} = 10 \sim 100\%$, $0 \sim 30$ min) after filtration. The signal of desired product was obtained at 17.4 min and afforded 107.2 mg (0.39 mmol, 78%) yield of N-adduct as a colorless oily liquid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.45 – 7.37 (m, 4H), 7.32 – 7.26 (m, 1H), 3.68 – 3.56 (m, 1H), 3.31 – 3.20 (m, 5H), 2.92 – 2.81 (m, 2H), 2.39 (dd, $J = 6.1, 2.0$ Hz, 2H), 1.01 (d, $J = 6.3$ Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 141.53, 129.07, 129.03, 126.89, 126.27, 65.32, 56.79, 48.80, 43.24, 40.02, 39.85, 39.69, 39.61, 39.52, 39.35, 39.19, 39.02, 37.87, 21.53. **ESI-HRMS** calcd for $\text{C}_{12}\text{H}_{21}\text{N}_2\text{O}_3\text{S}$ [(M+H) $^+$]: 273.1273, found: 273.1263.

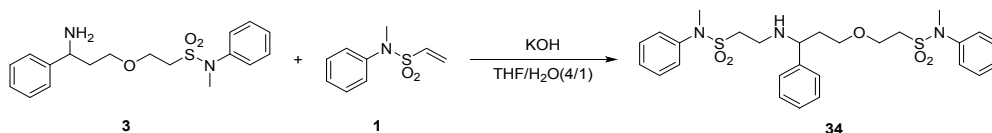


The compound 1-amino-2-propanol **33** (0.6 mmol, 45.066 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (5 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound phenylvinylsulfone **28** (0.5 mmol, 84.105 mg) was added. The resulting mixture was stirred at room temperature for 2 hours. The resulting crude mixture was purified by preparative HPLC ($\text{CH}_3\text{CN} : \text{H}_2\text{O} = 10 \sim 100\%$, $0 \sim 30$ min) after filtration. The signal of desired product was obtained at 17.4 min and afforded 109.5 mg (0.45 mmol, 90%) yield of N-adduct as a colorless oily liquid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.90 (dd, $J = 7.5, 1.7$ Hz, 2H), 7.79 – 7.71 (m, 1H), 7.66 (t, $J = 7.7$ Hz, 2H), 3.55 (td, $J = 6.6, 5.0$ Hz, 1H), 3.43 (dd, $J = 7.8, 6.3$ Hz, 2H), 2.83 – 2.71 (m, 2H), 2.32 (dd, $J = 6.0, 3.9$ Hz, 2H), 0.96 (d, $J = 6.3$ Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 139.38, 133.80, 129.44, 127.62, 65.21, 56.67, 54.96, 42.98, 40.02, 39.85, 39.69, 39.52, 39.35, 39.19, 39.02, 21.48. **ESI-HRMS** calcd for $\text{C}_{11}\text{H}_{18}\text{NO}_3\text{S}$ [(M+H) $^+$]: 244.1007, found: 244.1004.

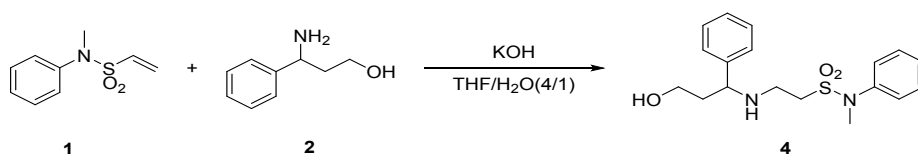
2.11 Chemoselectively stepwise conjugation to amine and alcohol



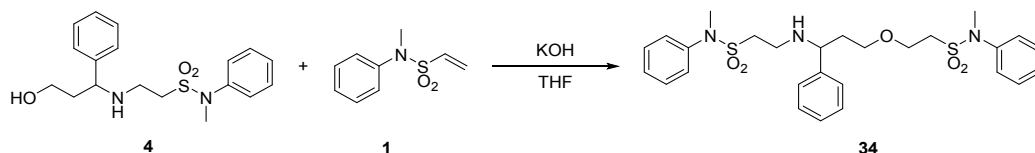
The compound 3-amino-3-phenyl-1-propanol **2** (0.6 mmol, 90.73 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (3 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **1** (0.5 mmol, 98.63 mg) was added. The resulting mixture was stirred at room temperature for 2 hours. The resulting crude mixture was purified by preparative HPLC ($\text{CH}_3\text{CN} : \text{H}_2\text{O} = 10 \sim 100\%$, $0 \sim 20$ min) after filtration. The signal of desired product was obtained at 12.1 min and afforded 160.3 mg (0.46 mmol, 92%) yield of **3** as a colorless oily liquid. ^1H NMR (500 MHz, DMSO) δ 8.48 (s, 2H), 7.51 – 7.35 (m, 9H), 7.31 (ddd, $J = 9.5, 5.6, 2.6$ Hz, 1H), 4.39 – 4.28 (m, 1H), 3.68 (dt, $J = 11.7, 5.9$ Hz, 1H), 3.64 – 3.57 (m, 1H), 3.38 (dt, $J = 12.1, 4.0$ Hz, 3H), 3.26 (s, 3H), 3.21 – 3.13 (m, 1H), 2.23 (ddt, $J = 11.5, 8.3, 5.7$ Hz, 1H), 1.99 (qd, $J = 9.9, 5.0$ Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 141.42, 137.35, 129.13, 128.82, 128.70, 127.38, 127.01, 126.38, 66.30, 64.01, 52.16, 48.72, 37.93, 34.06 ppm. **ESI-HRMS** calcd for $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_3\text{S}$ [(M+H) $^+$]: 349.1586, found: 349.1461.



The obtained compound **3** (0.2556 mmol, 88.94 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to the mixture of tetrahydrofuran (1.5 mL) and H₂O (0.375 mL). And then compound **1** (0.281 mmol, 55.45 mg) was added to the solution. The resulting mixture was stirred at room temperature for 2 hours. The resulting crude mixture was purified by preparative HPLC (CH₃CN : H₂O = 10 ~ 100%, 0 ~ 20 min) after filtration. The signal of desired product was obtained at 12.5 min and afforded 117 mg (0.215 mmol, 84%) yield of **32** as a colorless oily liquid. **¹H NMR** (500 MHz, MeOD) δ 7.48 – 7.44 (m, 3H), 7.44 – 7.28 (m, 12H), 4.49 (dd, J = 7.5, 5.0 Hz, 1H), 3.86 (qdd, J = 10.8, 6.2, 4.7 Hz, 2H), 3.57 (dt, J = 9.2, 4.4 Hz, 1H), 3.54 – 3.46 (m, 2H), 3.45 – 3.36 (m, 3H), 3.32 (d, J = 6.7 Hz, 3H), 3.29 (dt, J = 3.3, 1.6 Hz, 1H), 3.25 (s, 3H), 3.20 (ddd, J = 13.1, 8.9, 6.1 Hz, 1H), 3.02 (ddd, J = 13.1, 9.2, 5.7 Hz, 1H), 2.33 (dddd, J = 15.2, 9.0, 7.8, 4.1 Hz, 1H), 2.18 – 2.07 (m, 1H). **¹³C NMR** (126 MHz, MeOD) δ 142.62 (s), 142.11 (s), 134.87 (s), 131.04 (s), 130.77 (s), 130.55 (s), 130.50 (s), 129.01 (s), 128.98 (s), 128.83 (s), 128.09 (s), 130.77 (s), 127.95 (s), 69.04 (s), 66.06 (s), 63.79 (s), 49.54 (s), 46.15 (s), 41.44 (s), 39.02 (s), 38.86 (s), 34.20 (s). **ESI-HRMS** calcd for C₂₇H₃₆N₃O₅S₂ [(M+H)⁺]: 546.2096, found: 546.2086.



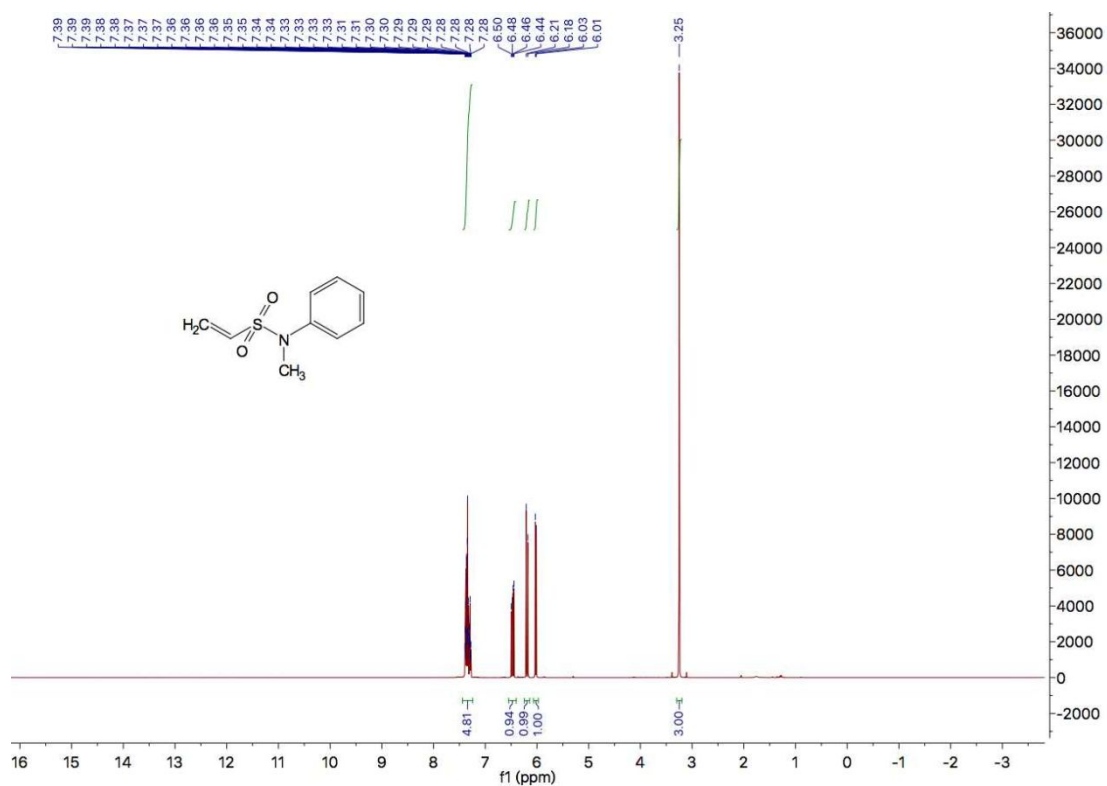
The compound 3-amino-3-phenyl-1-propanol **2** (0.6 mmol, 90.73 mg) and potassium hydroxide (0.25 mmol, 14.03 mg) were added to the mixture of tetrahydrofuran (2.4 mL) and H₂O (0.6 mL). And then compound **1** (0.5 mmol, 98.63 mg) was added. The resulting mixture was stirred at room temperature for 2 hours. The resulting crude mixture was purified by preparative HPLC (CH₃CN : H₂O = 10 ~ 100%, 0 ~ 20 min) after filtration. The signal of desired product was obtained at 11.8 min and afforded 156.8 mg (0.45 mmol, 90%) yield of **4** as a colorless oily liquid. **¹H NMR** (500 MHz, DMSO) δ 9.54 (s, 1H), 7.54 – 7.35 (m, 7H), 7.35 – 7.28 (m, 3H), 4.62 – 4.36 (m, 2H), 3.61 (ddd, J = 13.7, 11.0, 5.2 Hz, 1H), 3.50 (ddd, J = 13.8, 10.9, 4.8 Hz, 1H), 3.35 (ddd, J = 10.6, 5.9, 4.7 Hz, 1H), 3.21 (d, J = 12.4 Hz, 3H), 3.20 – 3.10 (m, 2H), 2.86 (td, J = 11.7, 4.7 Hz, 1H), 2.28 – 2.15 (m, 1H), 2.02 (ddt, J = 14.6, 9.8, 4.8 Hz, 1H). **¹³C NMR** (126 MHz, DMSO) δ 140.71, 134.50, 129.32, 129.26, 129.10, 128.38, 127.54, 126.61, 59.57, 56.79, 44.90, 39.27, 38.11, 35.55 ppm. **ESI-HRMS** calcd for C₁₈H₂₅N₂O₃S [(M+H)⁺]: 349.1586, found: 349.1580.



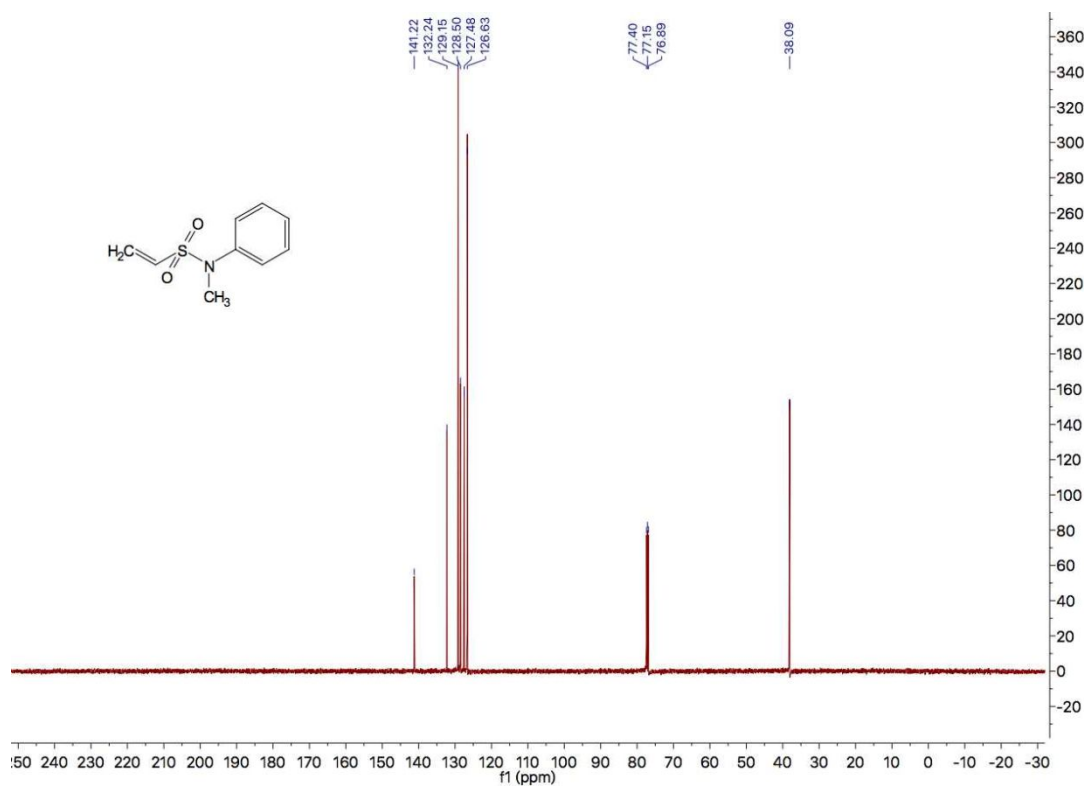
The obtained compound **4** (0.206 mmol, 71.68 mg) and potassium hydroxide (1.0 mmol, 56.11 mg) were added to tetrahydrofuran (1.5 mL). The undissolved solid potassium hydroxide was observed in the reaction mixture and then compound **1** (0.2266 mmol, 44.69 mg) was added to the solution. The resulting mixture was stirred at room temperature for 2 hours. The resulting crude mixture was purified by preparative HPLC (CH₃CN : H₂O = 10 ~ 100%, 0 ~ 20 min) after filtration. The signal of desired product was obtained at 12.5 min and afforded 96.6 mg (0.177 mmol, 86%) yield of **32** as a colorless oily liquid. **¹H NMR** (500 MHz, MeOD) δ 7.48 – 7.44 (m, 3H), 7.44 – 7.28 (m, 12H), 4.49 (dd, J = 7.5, 5.0 Hz, 1H), 3.86 (qdd, J = 10.8, 6.2, 4.7 Hz, 2H), 3.57 (dt, J = 9.2, 4.4 Hz, 1H), 3.54 – 3.46 (m, 2H), 3.45 – 3.36 (m, 3H), 3.32 (d, J = 6.7 Hz, 3H), 3.29 (dt, J = 3.3, 1.6 Hz, 1H), 3.25 (s, 3H), 3.20 (ddd, J = 13.1, 8.9, 6.1 Hz, 1H), 3.02 (ddd, J = 13.1, 9.2, 5.7 Hz, 1H), 2.33 (dddd, J = 15.2, 9.0, 7.8, 4.1 Hz, 1H), 2.18 – 2.07 (m, 1H). **¹³C NMR** (126 MHz, MeOD) δ 142.62 (s), 142.11 (s), 134.87 (s), 131.04 (s), 130.77 (s), 130.55 (s), 130.50 (s), 129.01 (s), 128.98 (s), 128.83 (s), 128.09 (s), 130.77 (s), 127.95 (s), 69.04 (s), 66.06 (s), 63.79 (s), 49.54 (s), 46.15 (s), 41.44 (s), 39.02 (s), 38.86 (s), 34.20 (s). **ESI-HRMS** calcd for C₂₇H₃₆N₃O₅S₂ [(M+H)⁺]: 546.2096, found: 546.2086.

3. ^1H NMR, ^{13}C NMR, ^1H - ^{13}C HSQC, ^1H - ^{13}C HMBC and ^1H - ^1H COSY

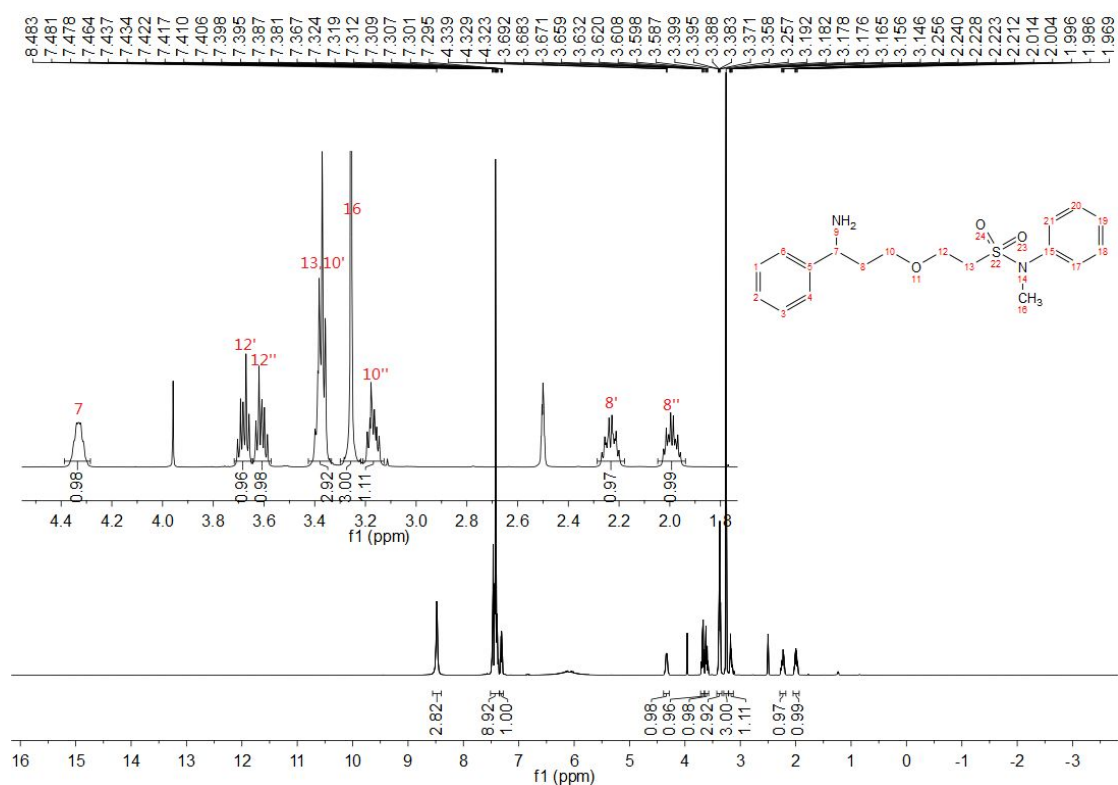
^1H NMR of compound 1



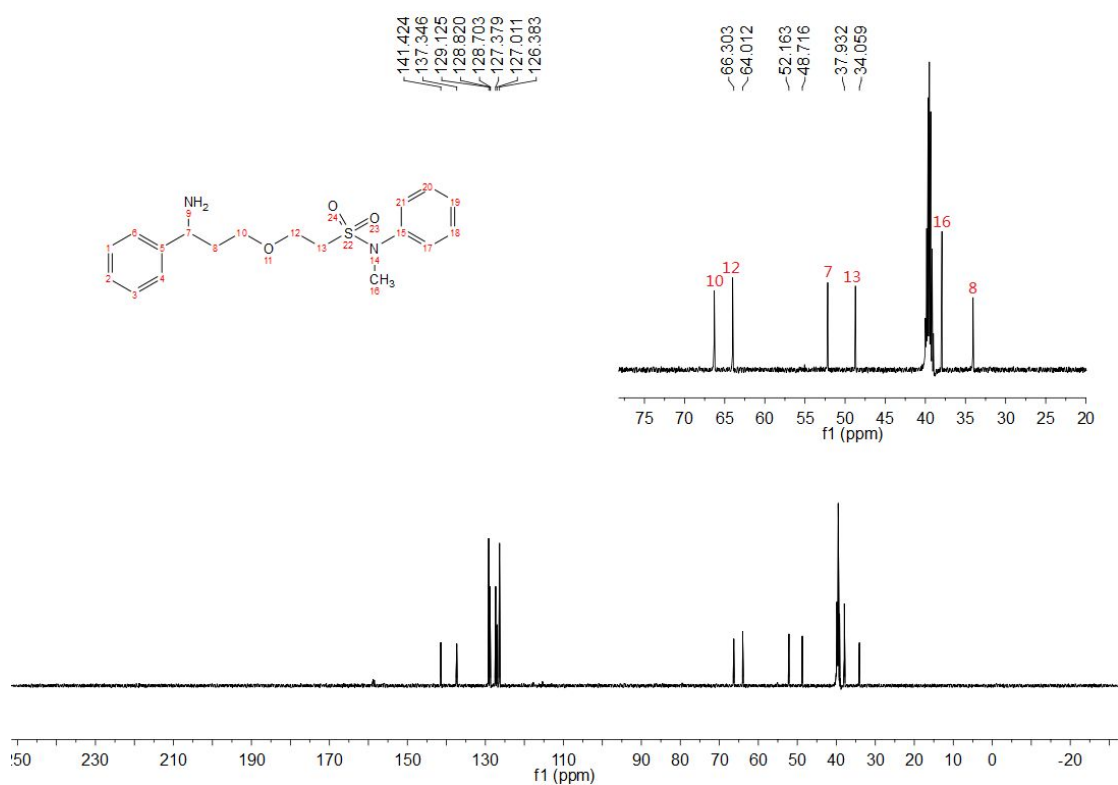
^{13}C NMR of compound 1



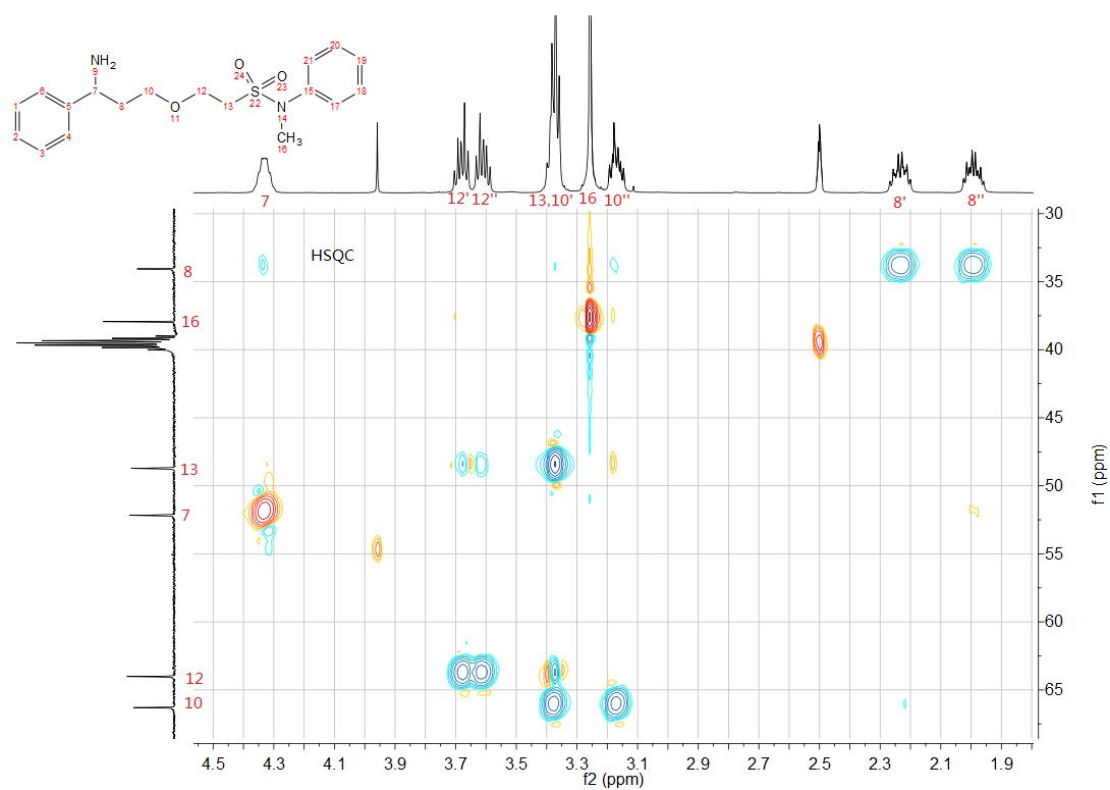
¹H NMR of compound 3



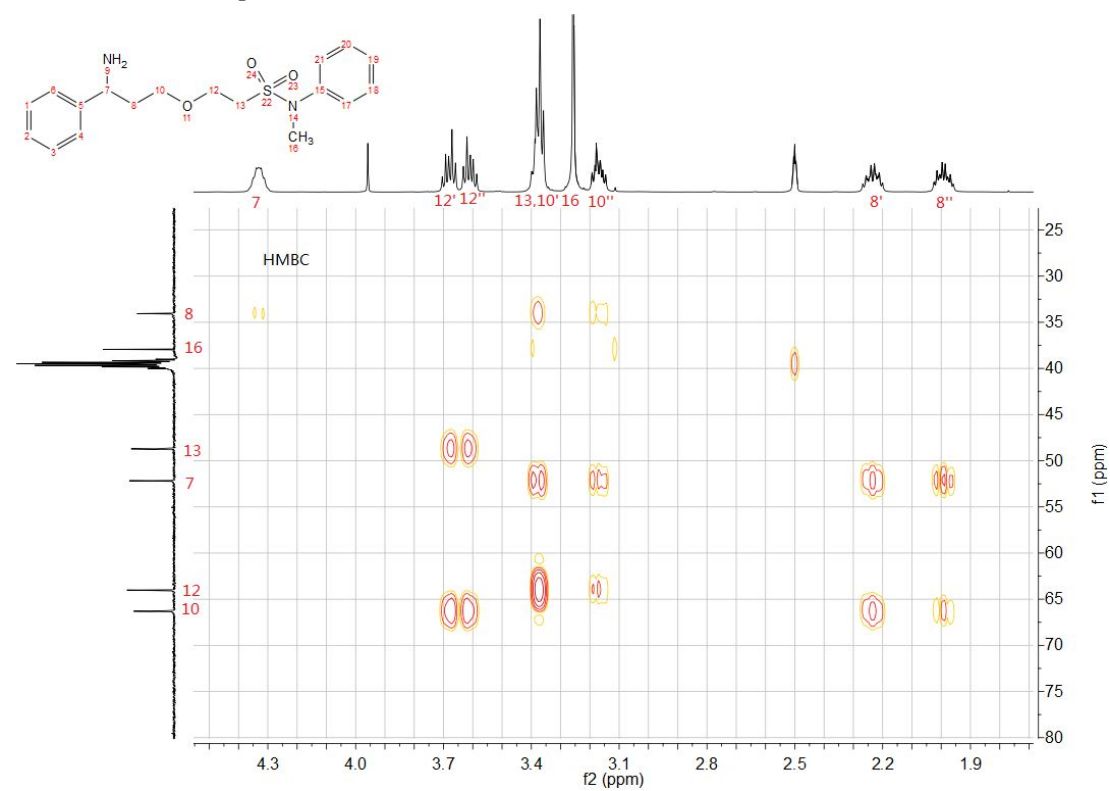
¹³C NMR of compound 3



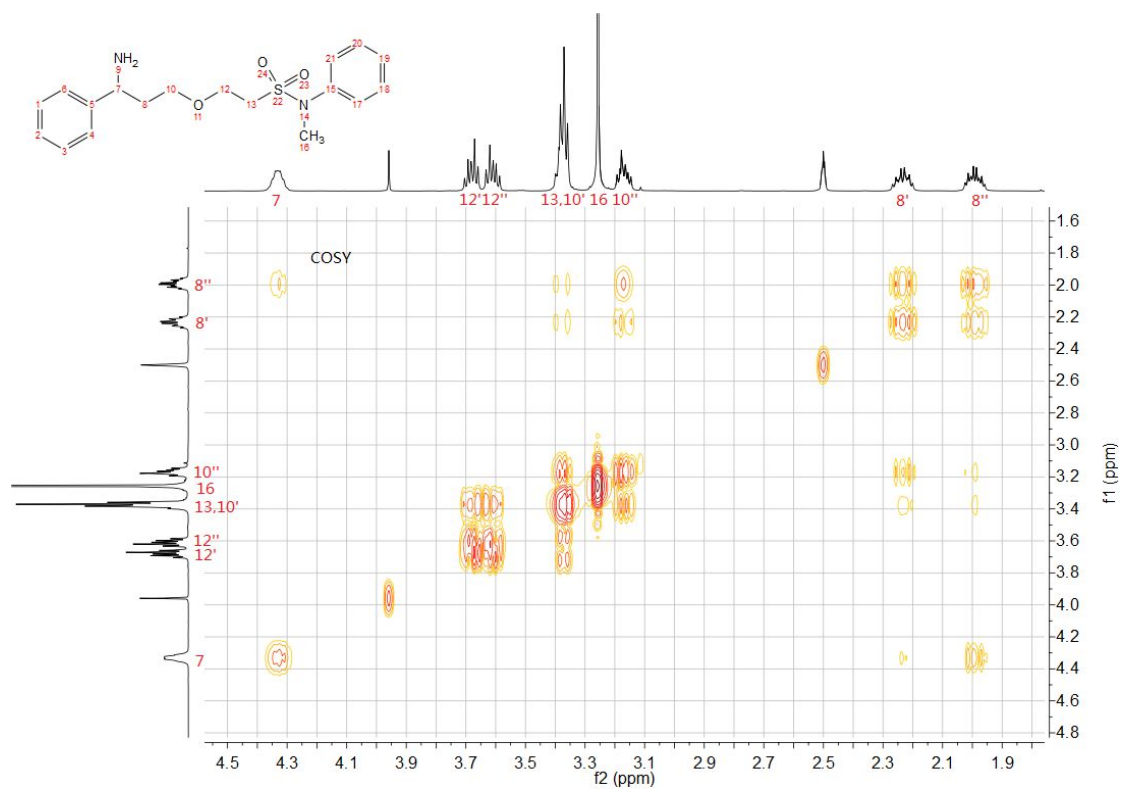
^1H - ^{13}C HSQC of compound 3



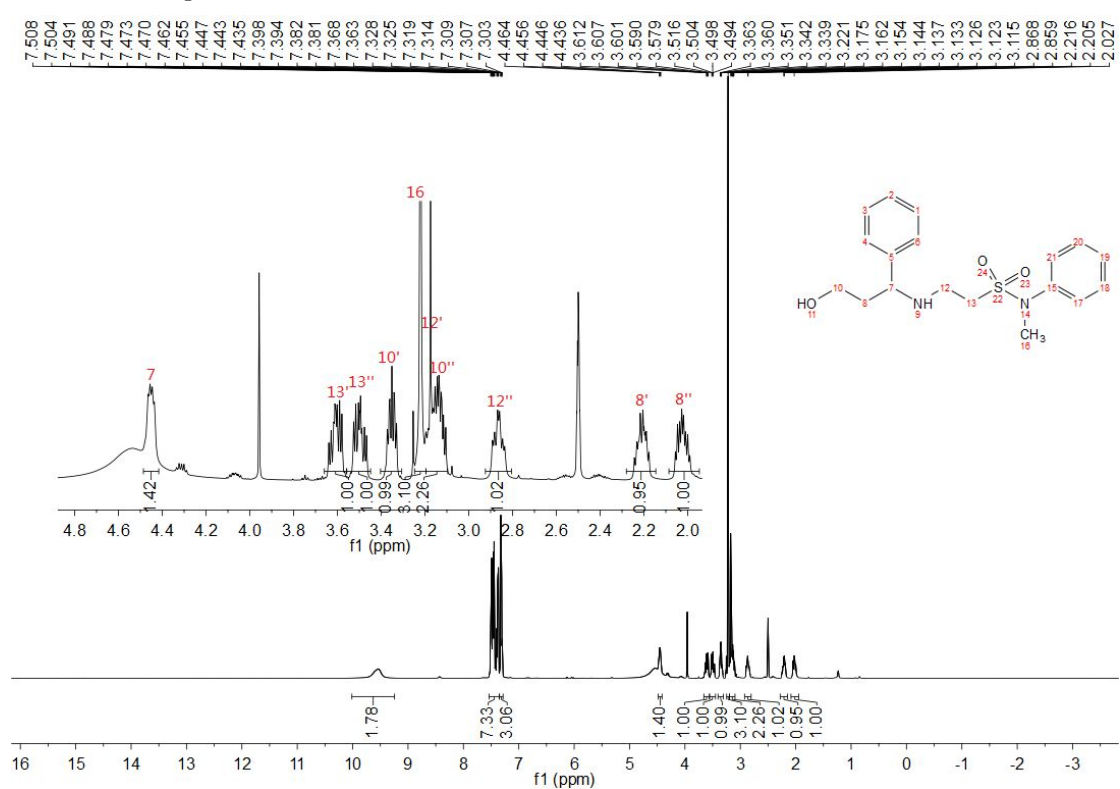
^1H - ^{13}C HMBC of compound 3



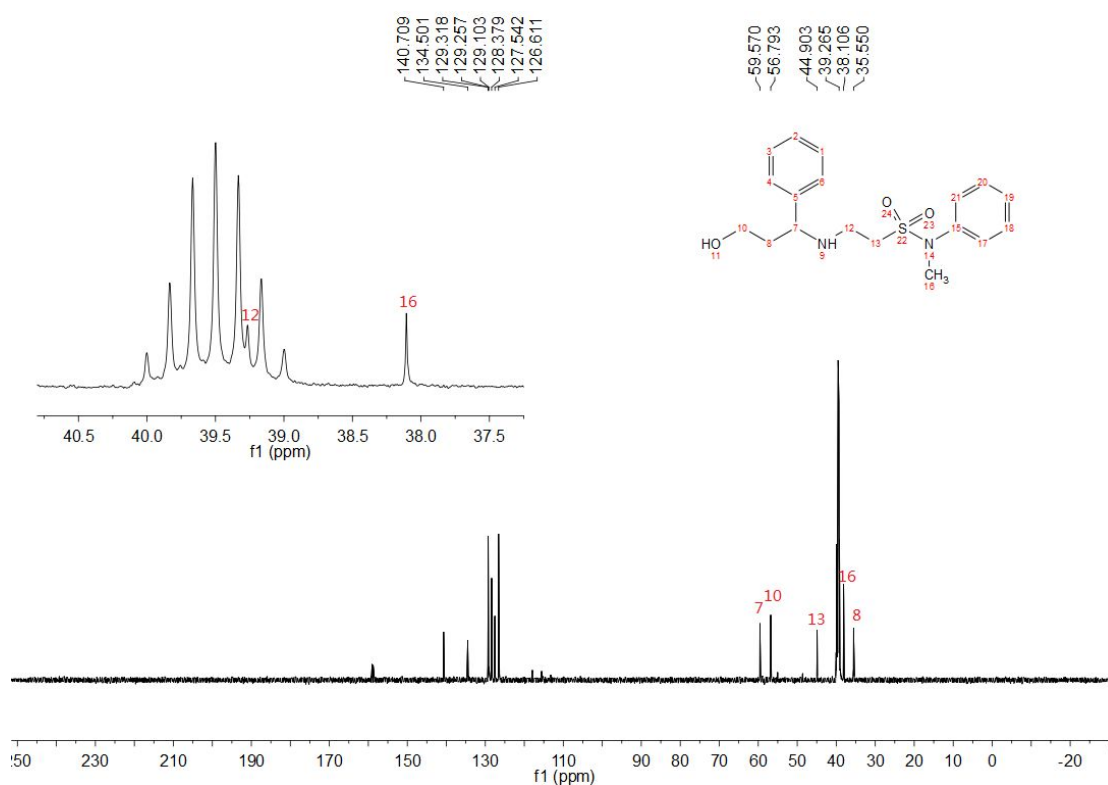
¹H-¹H COSY of compound 3



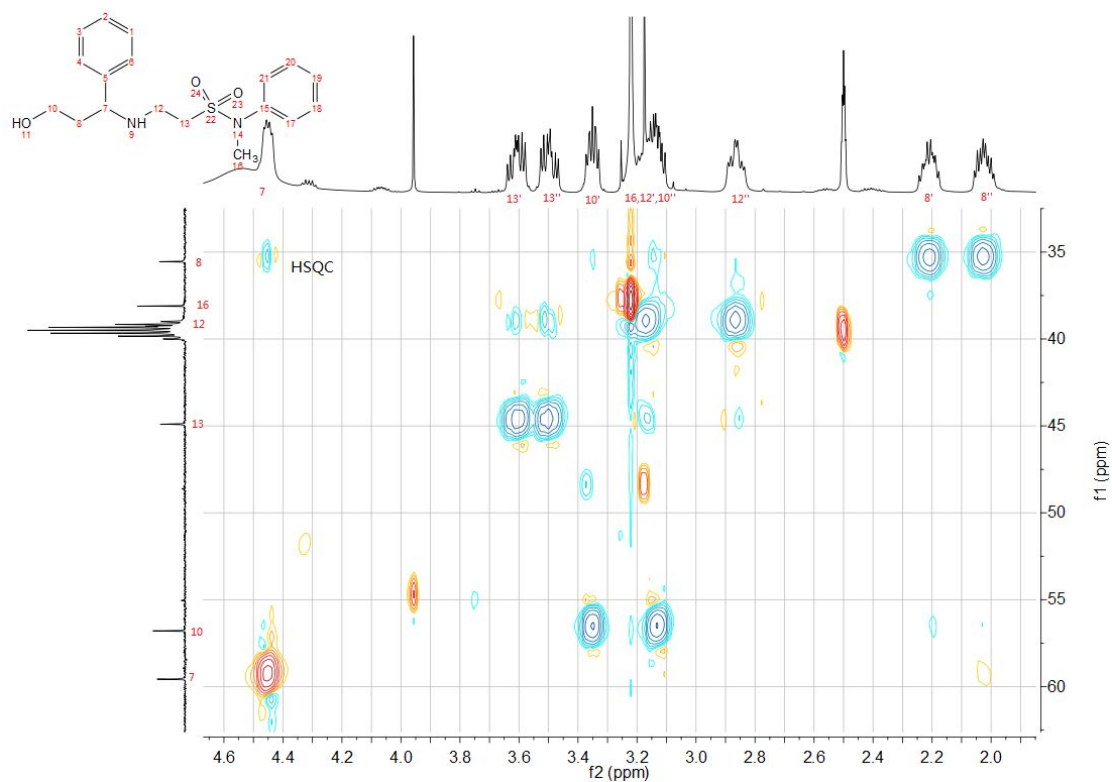
¹H NMR of compound 4



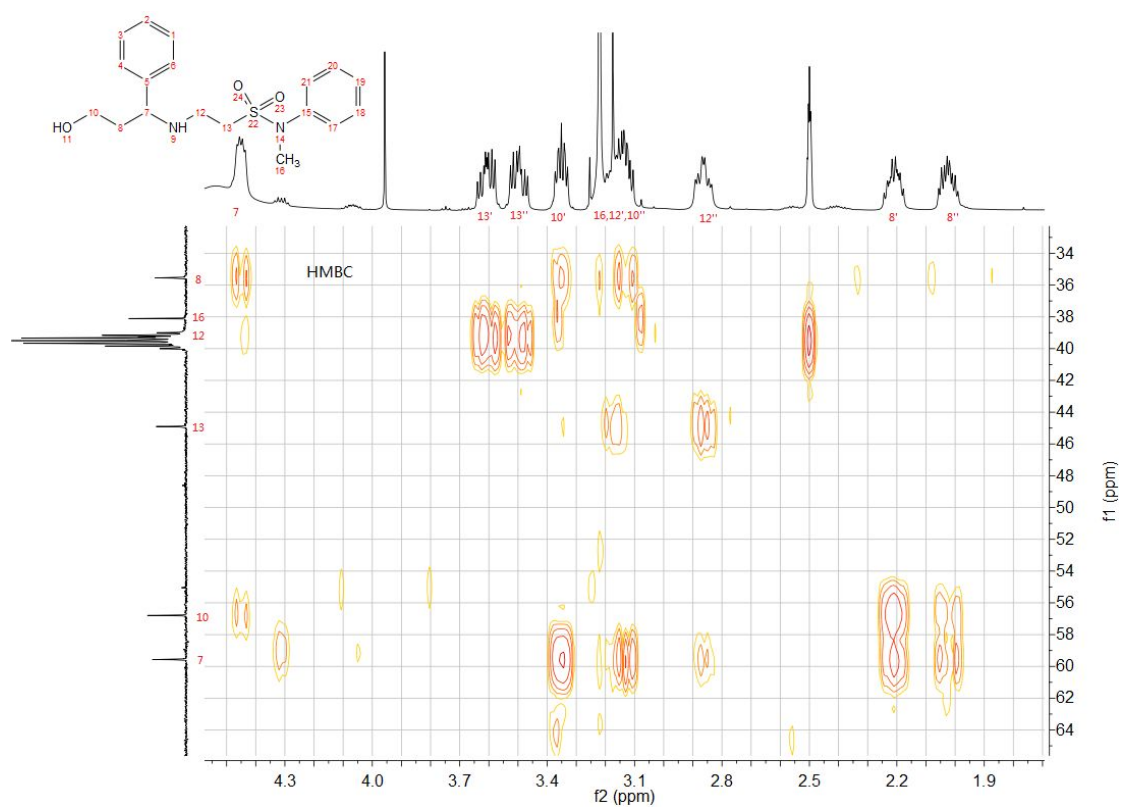
^{13}C NMR of compound 4



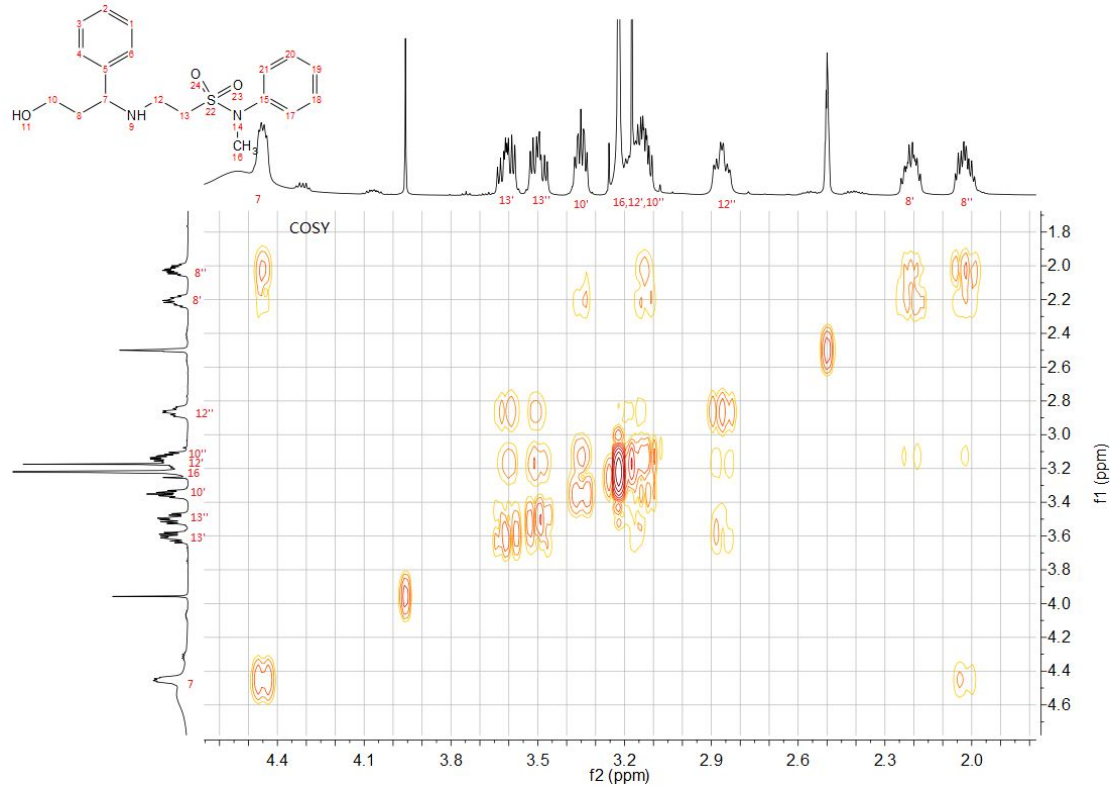
^1H - ^{13}C HSQC of compound 4



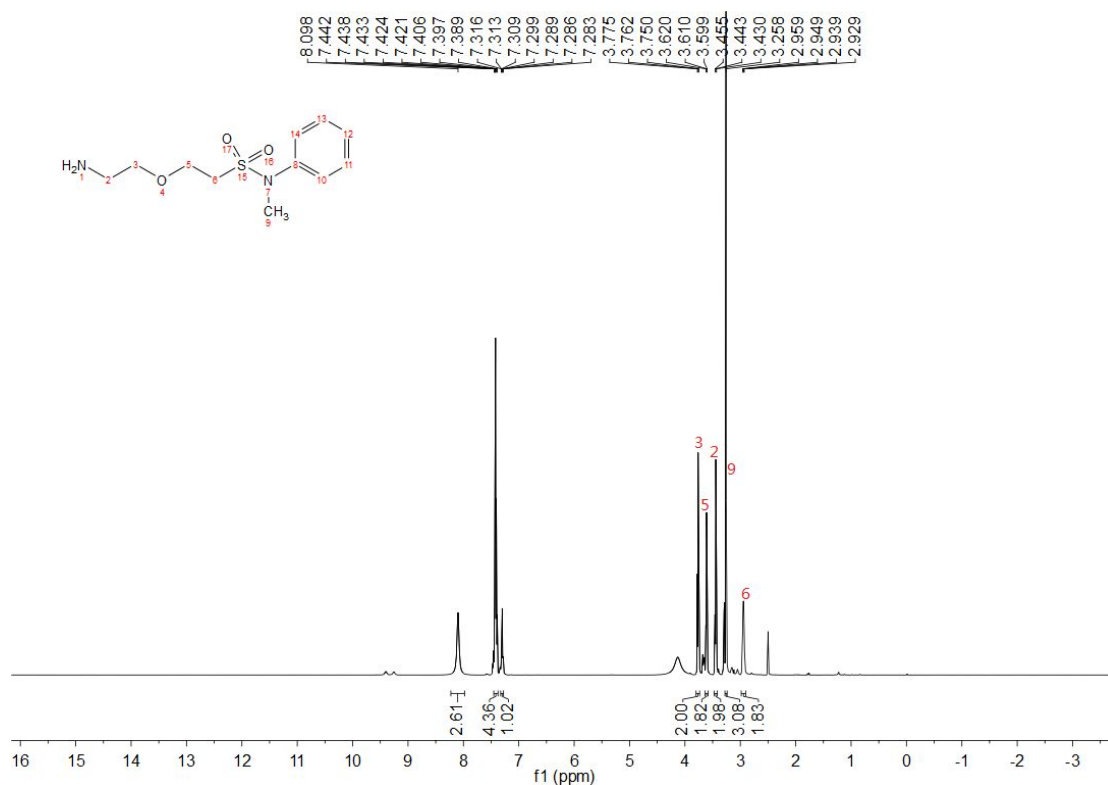
^1H - ^{13}C HMBC of compound 4



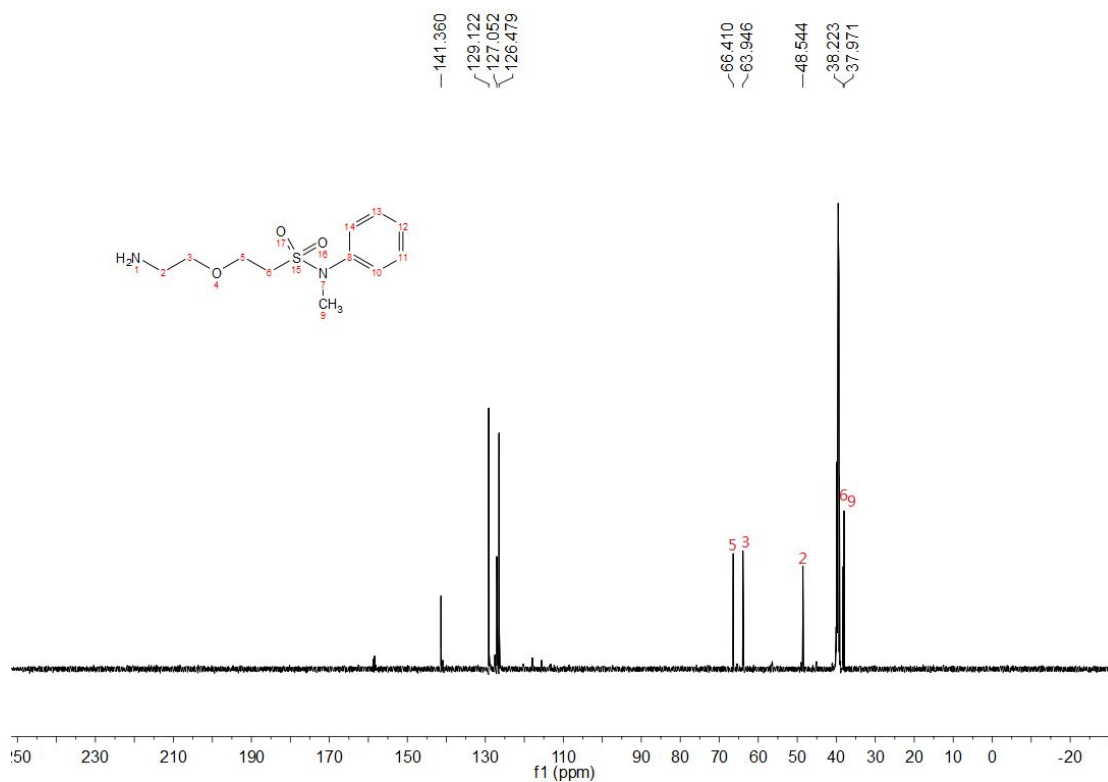
^1H - ^1H COSY of compound 4



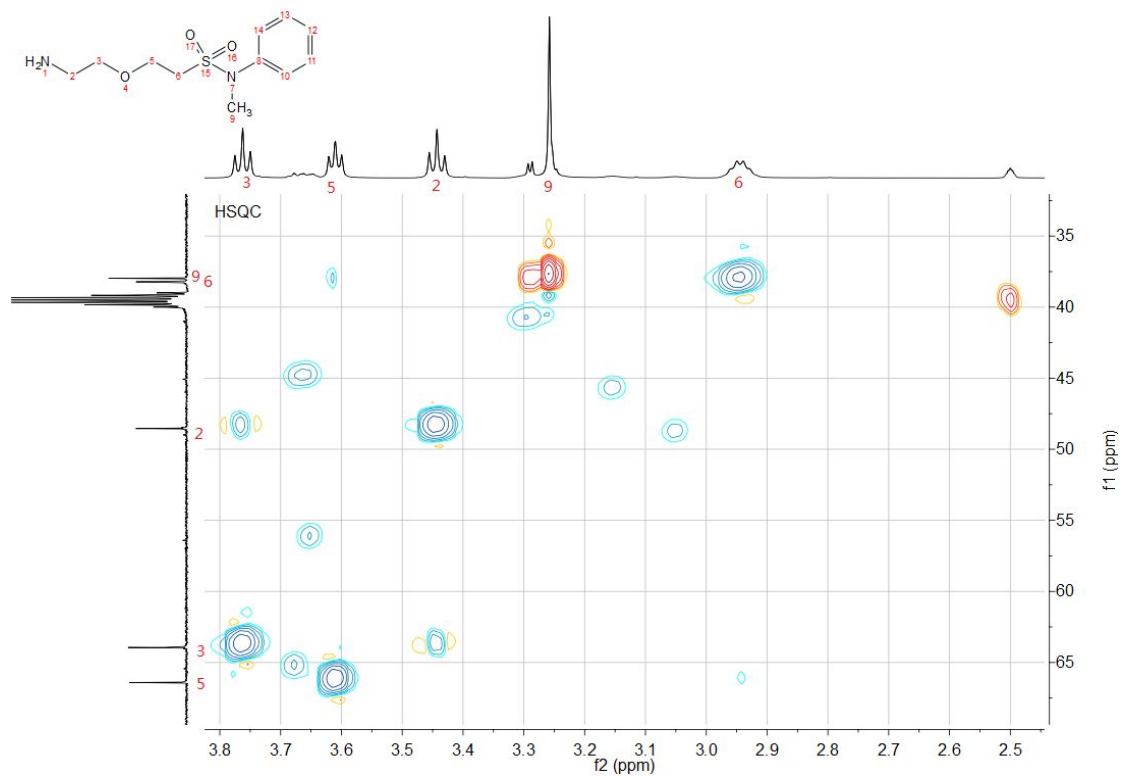
¹H NMR of compound 5



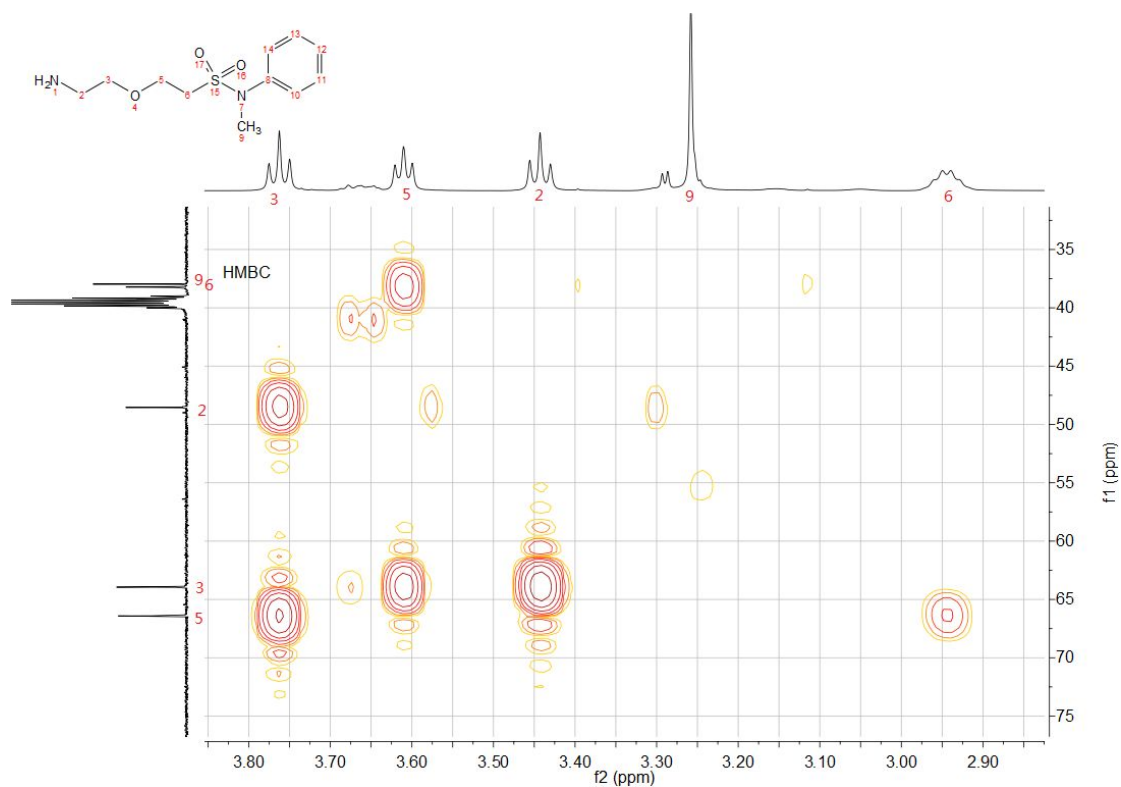
¹³C NMR of compound 5



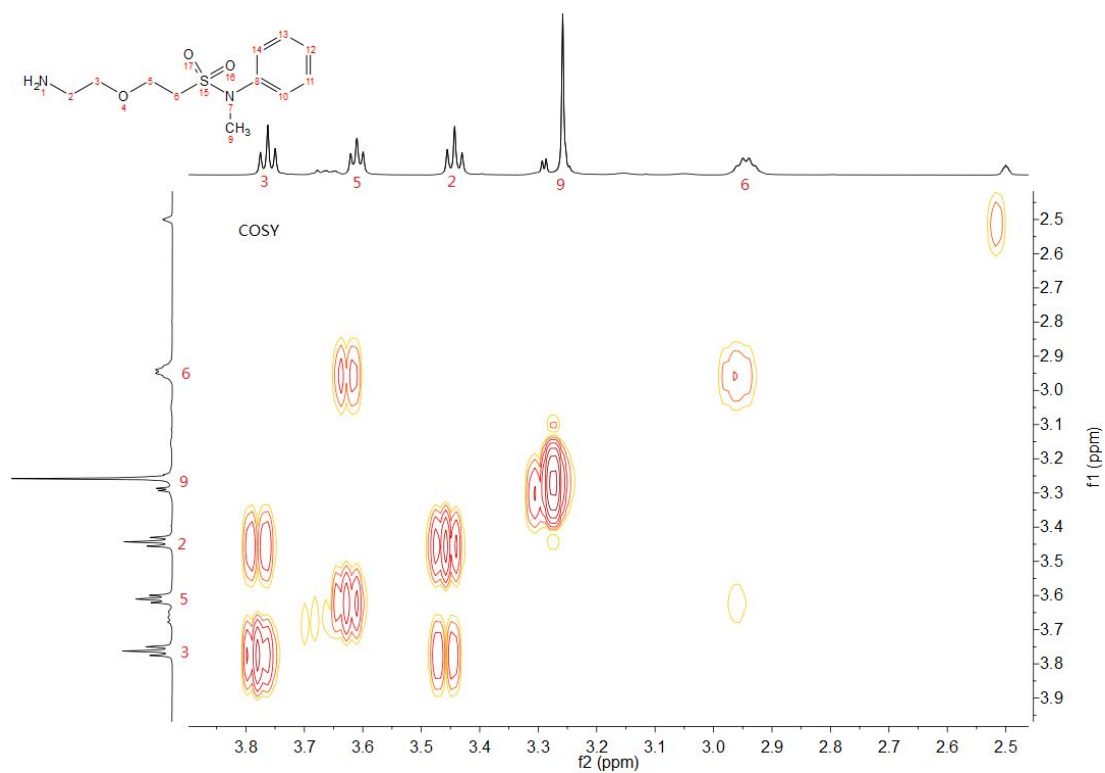
^1H - ^{13}C HSQC of compound 5



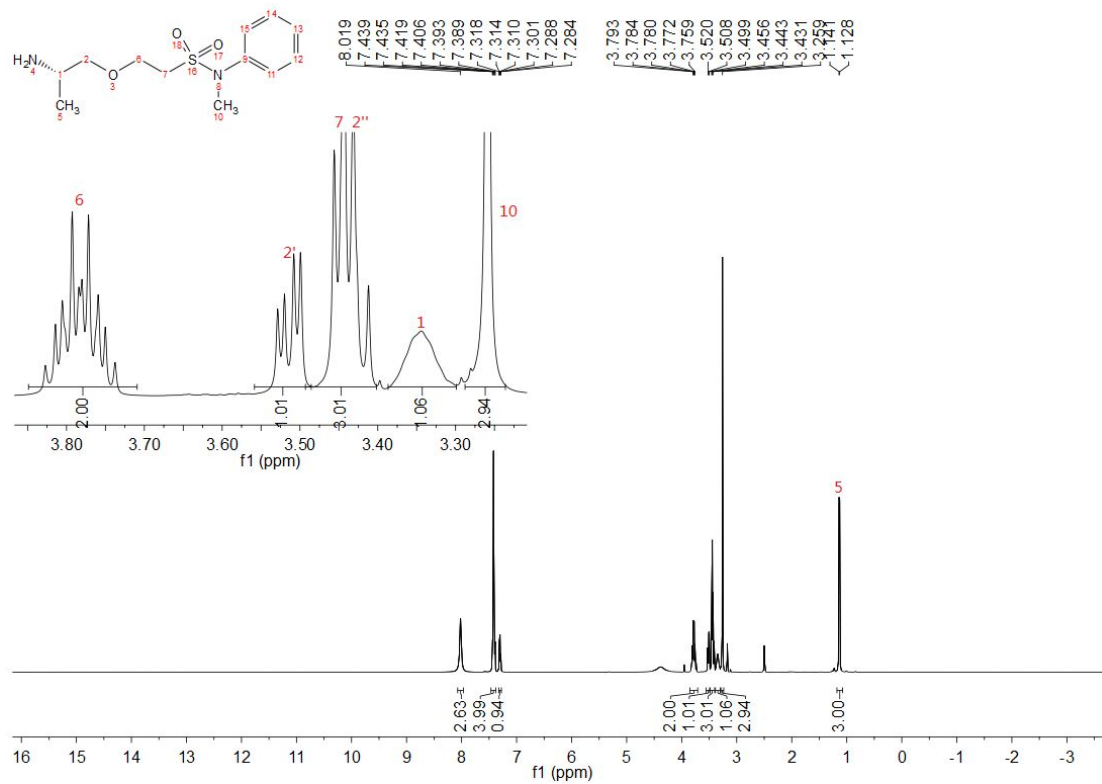
^1H - ^{13}C HMBC of compound 5



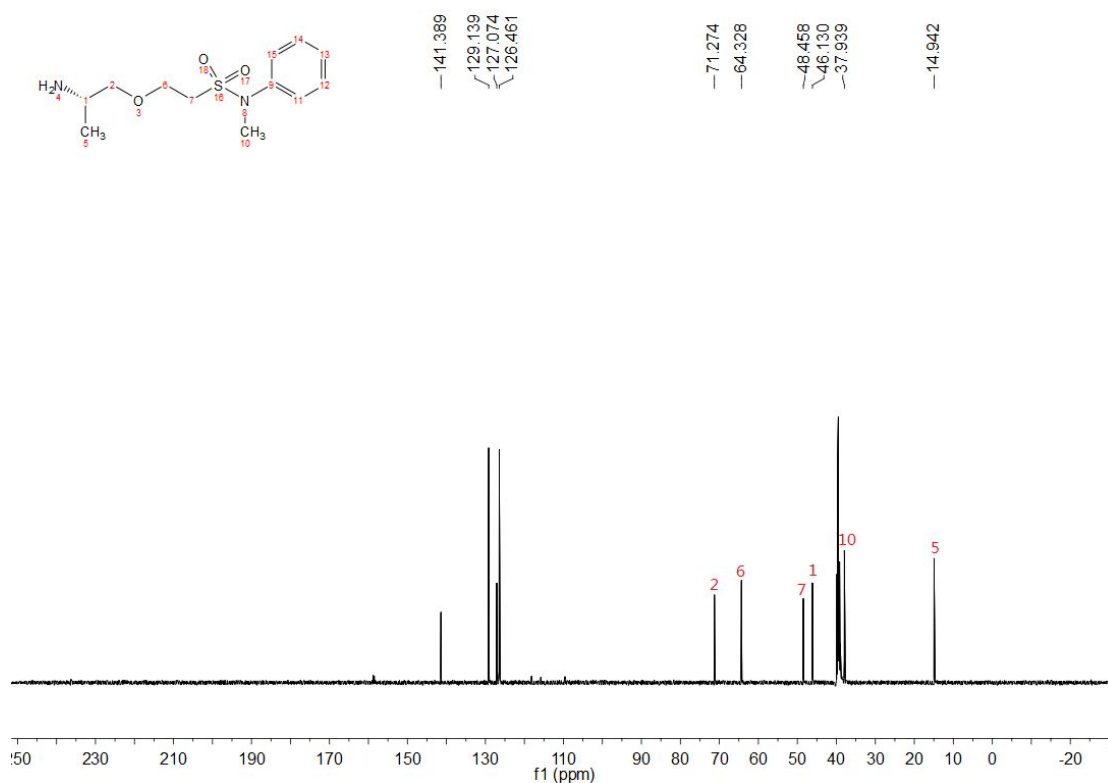
¹H-¹H COSY of compound 5



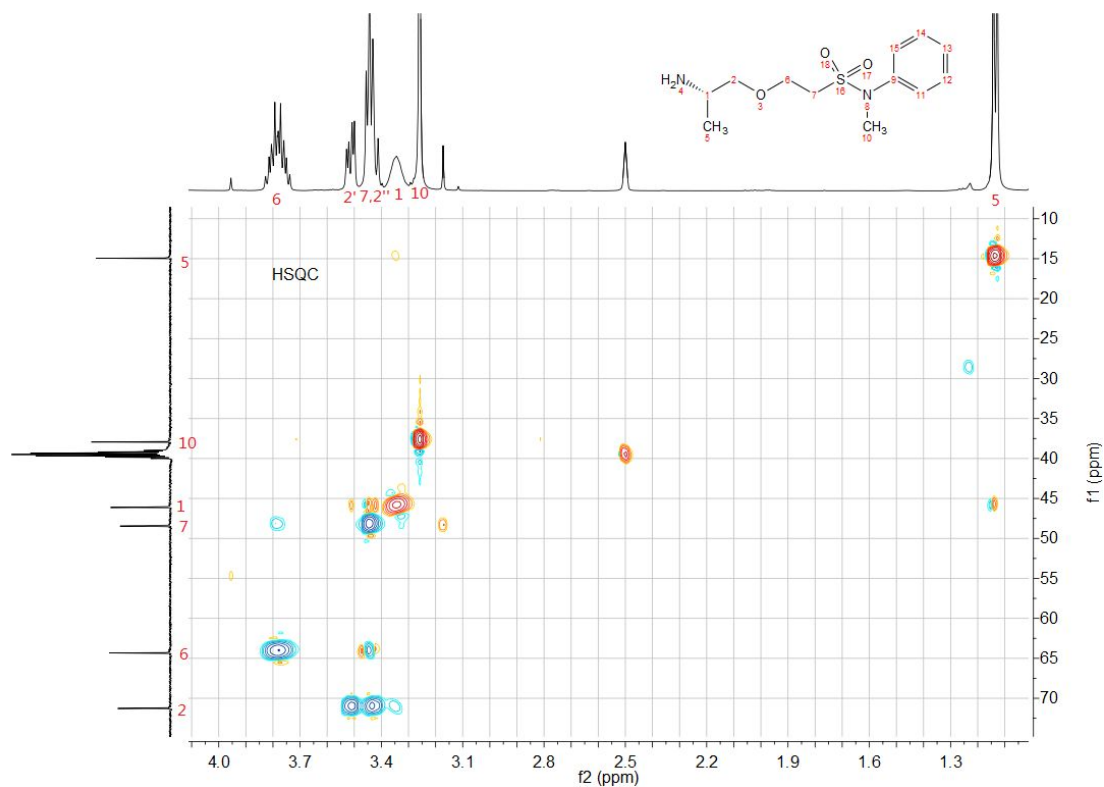
¹H NMR of compound 6



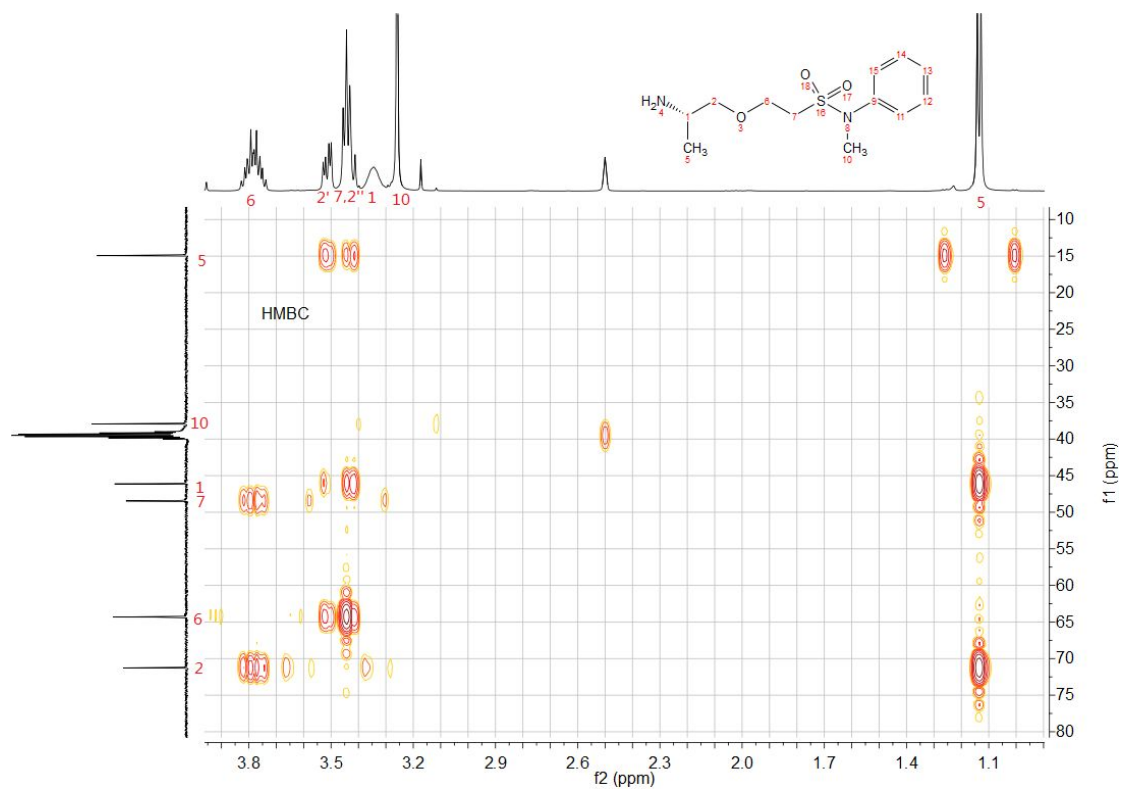
¹³C NMR of compound 6



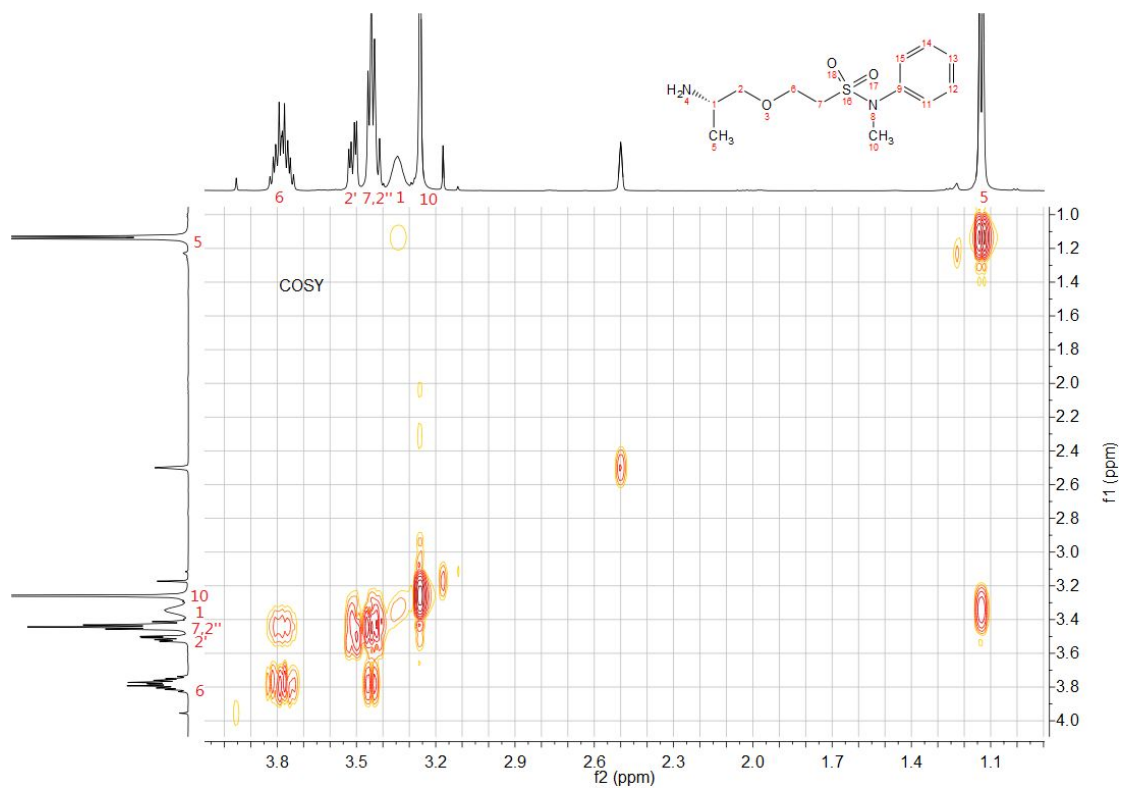
¹H-¹³C HSQC of compound 6



^1H - ^{13}C HMBC of compound 6



^1H - ^1H COSY of compound 6



Chemical structure of 2-methyl-2-sulfamoylpropanamide (SMILES: CC(C)(C)S(=O)(=O)NC=O) is shown with atom numbering 1-19. The ^1H NMR spectrum (DMSO- d_6) displays the following chemical shifts (ppm):

- 16.17 (broad singlet, 1H, NH)
- 8.014, 7.442, 7.434, 7.425, 7.422, 7.419, 7.405, 7.388, 7.316, 7.313, 7.309, 7.299, 7.288, 7.285, 7.282 (multiplet, 8H, aromatic protons)
- 3.797, 3.774, 3.606, 3.599, 3.516, 3.468, 3.456, 3.443, 3.264 (multiplet, 6H, methylene protons)
- 1.899, 1.885, 1.875, 1.859, 0.926, 0.910, 0.897 (multiplet, 6H, methyl protons)

The inset shows the region from 0.7 to 1.1 ppm, highlighting the methyl protons (1.899, 1.885, 1.875, 1.859, 0.926, 0.910, 0.897 ppm).

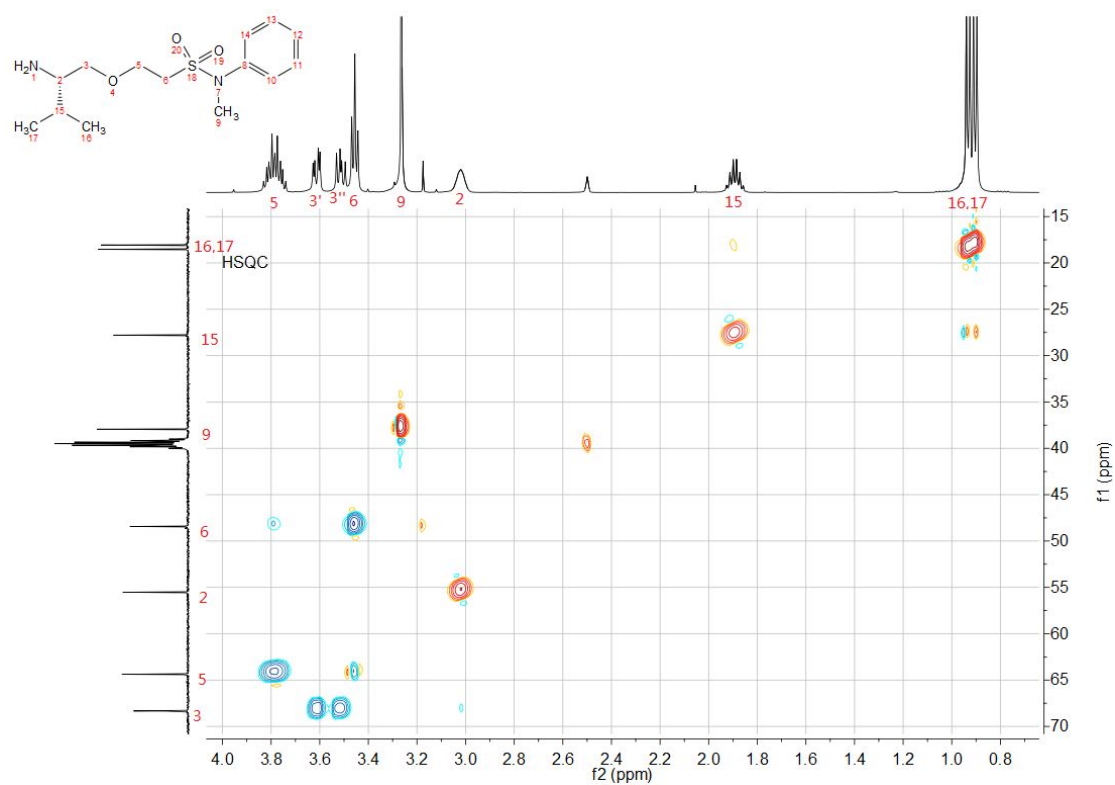
Chemical structure of the compound is shown above the spectrum. The structure is a substituted benzene ring with a sulfonamide group and a chiral center. The atoms are numbered 1 through 17, corresponding to the peaks in the spectrum.

The spectrum shows the following peaks (ppm):

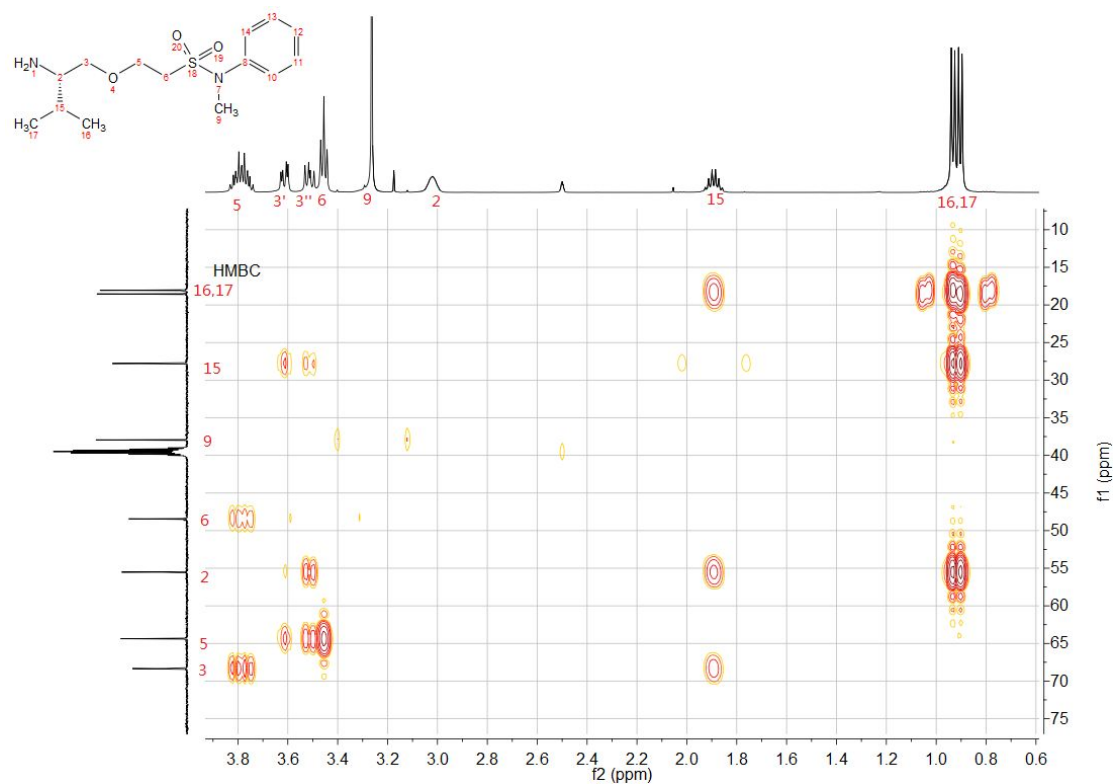
- 141.409
- 129.140
- 127.064
- 126.443
- 68.336
- 64.377
- 55.524
- 48.429
- 37.933
- 27.790
- 18.533
- 18.067

The spectrum also shows peaks labeled 3, 5, 2, 6, 9, 15, and 16,17, which correspond to the chemical structure.

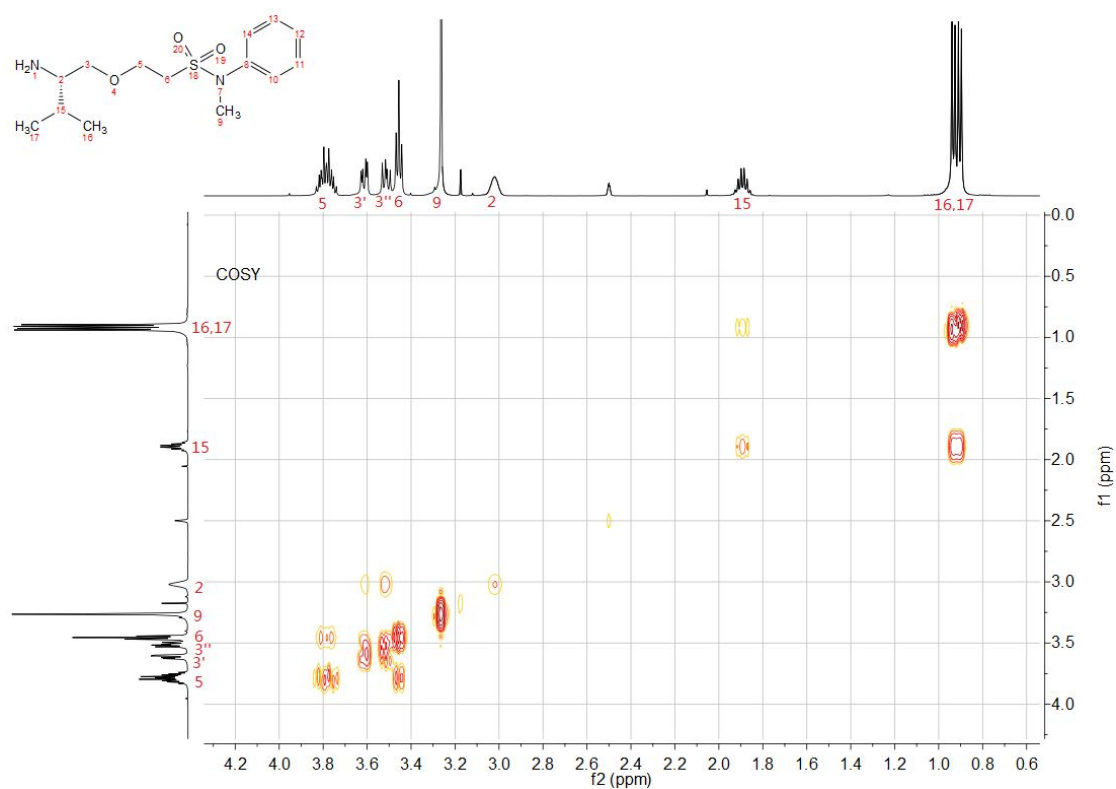
^1H - ^{13}C HSQC of compound 7



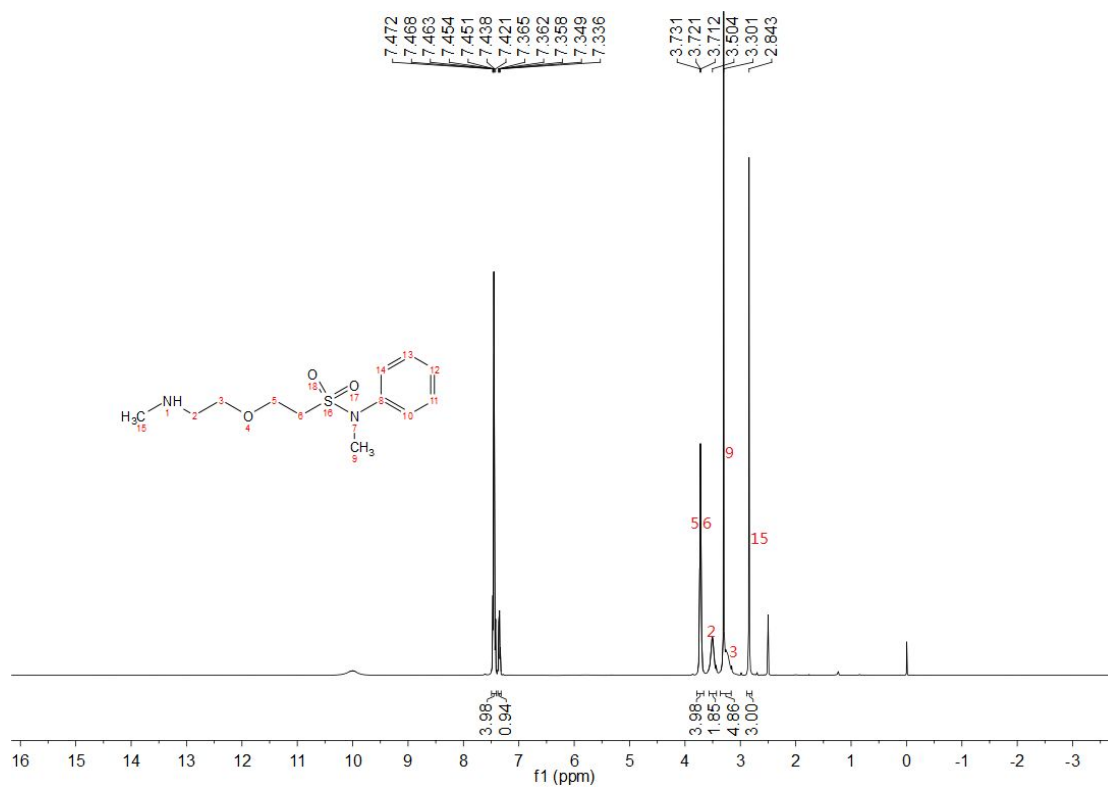
^1H - ^{13}C HMBC of compound 7



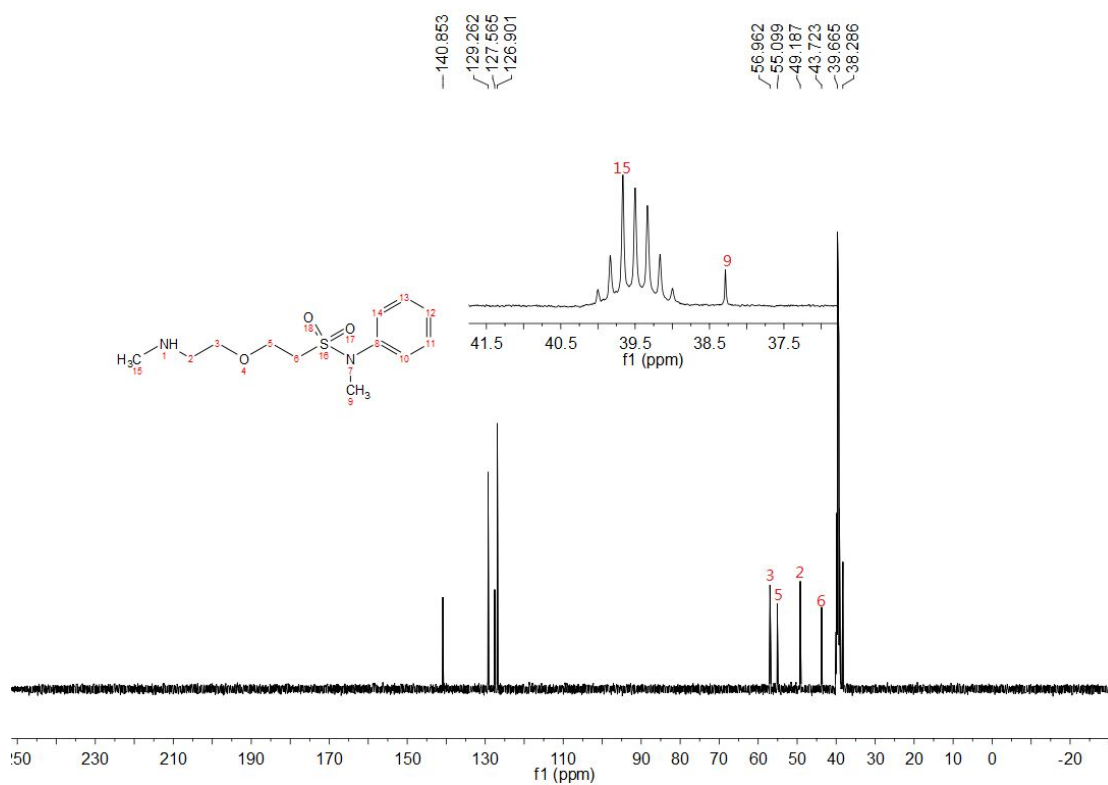
¹H-¹H COSY of compound 7



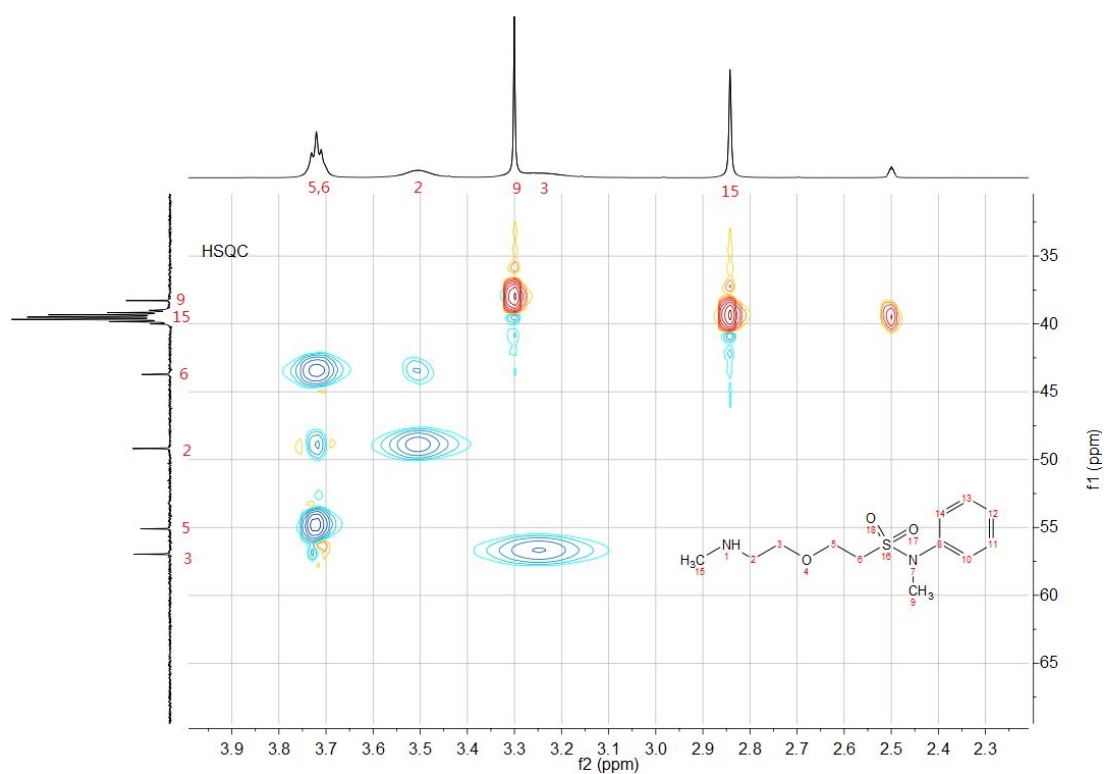
¹H NMR of compound 8



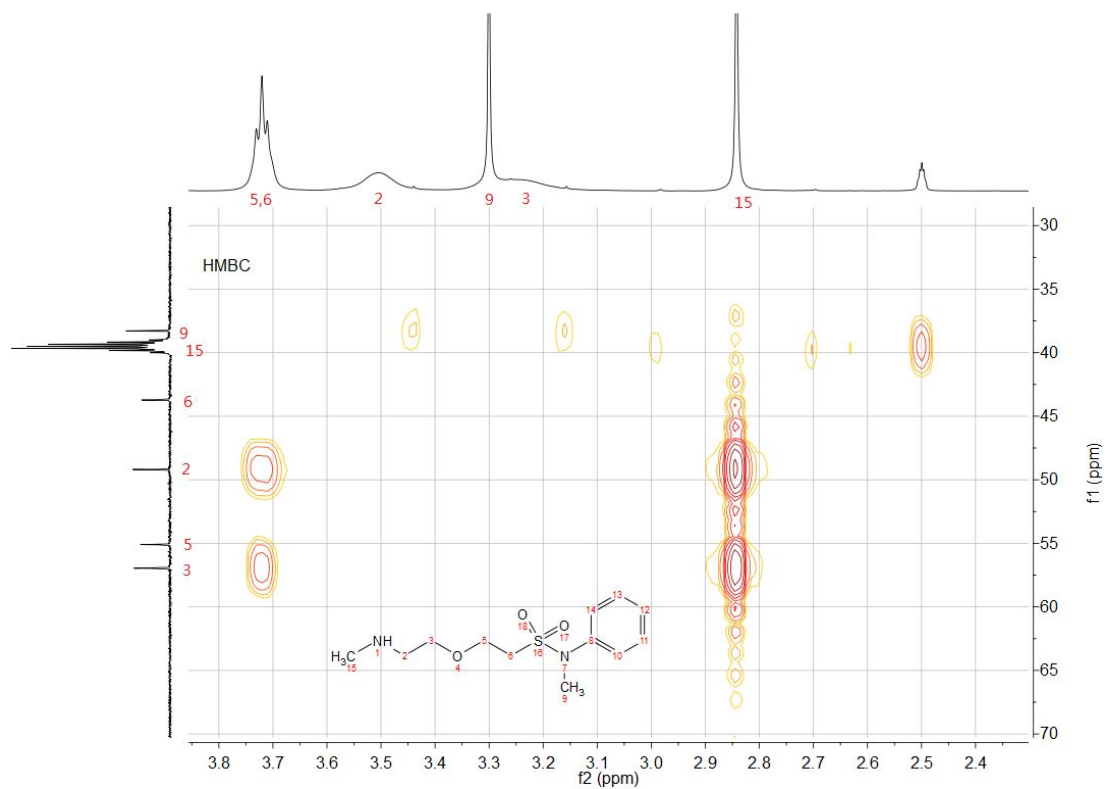
^{13}C NMR of compound 8



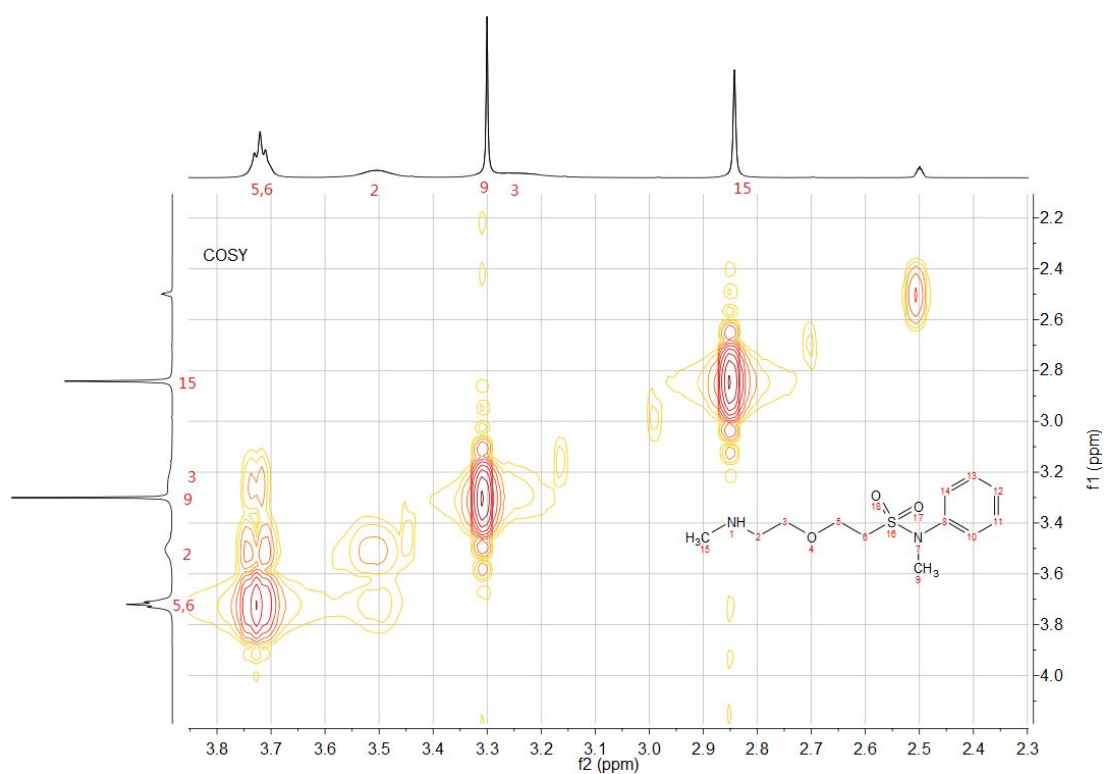
^1H - ^{13}C HSQC of compound 8



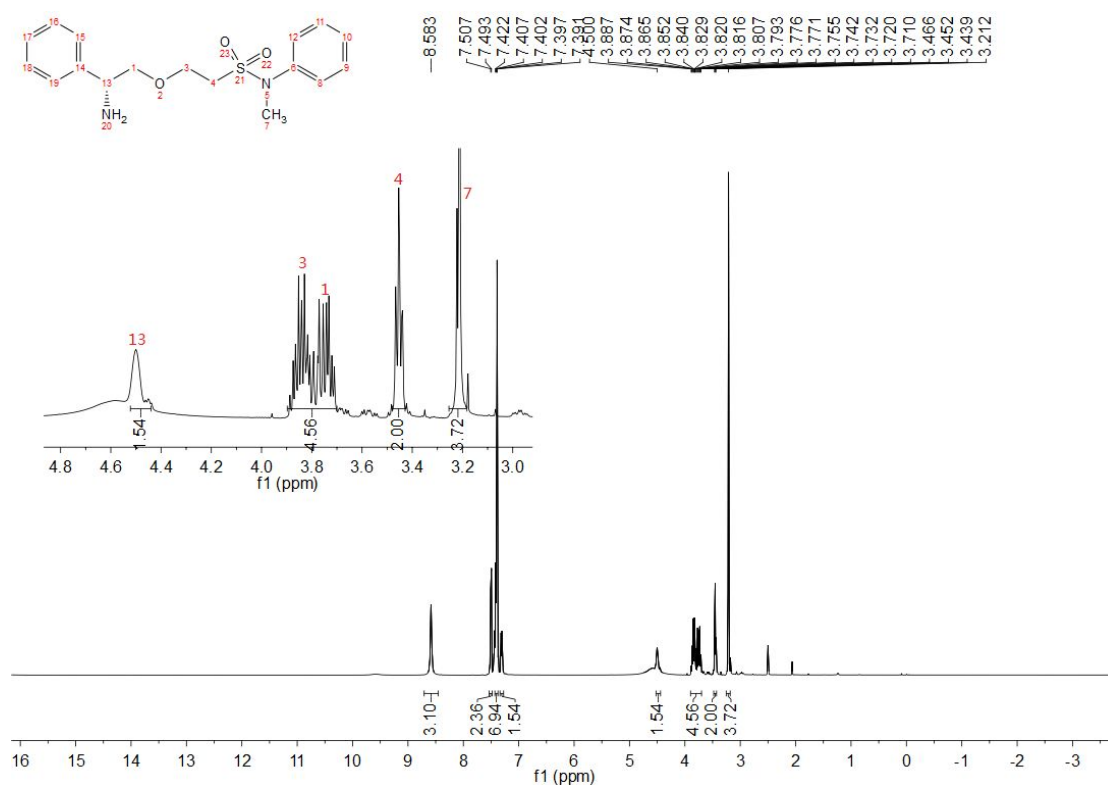
^1H - ^{13}C HMBC of compound 8



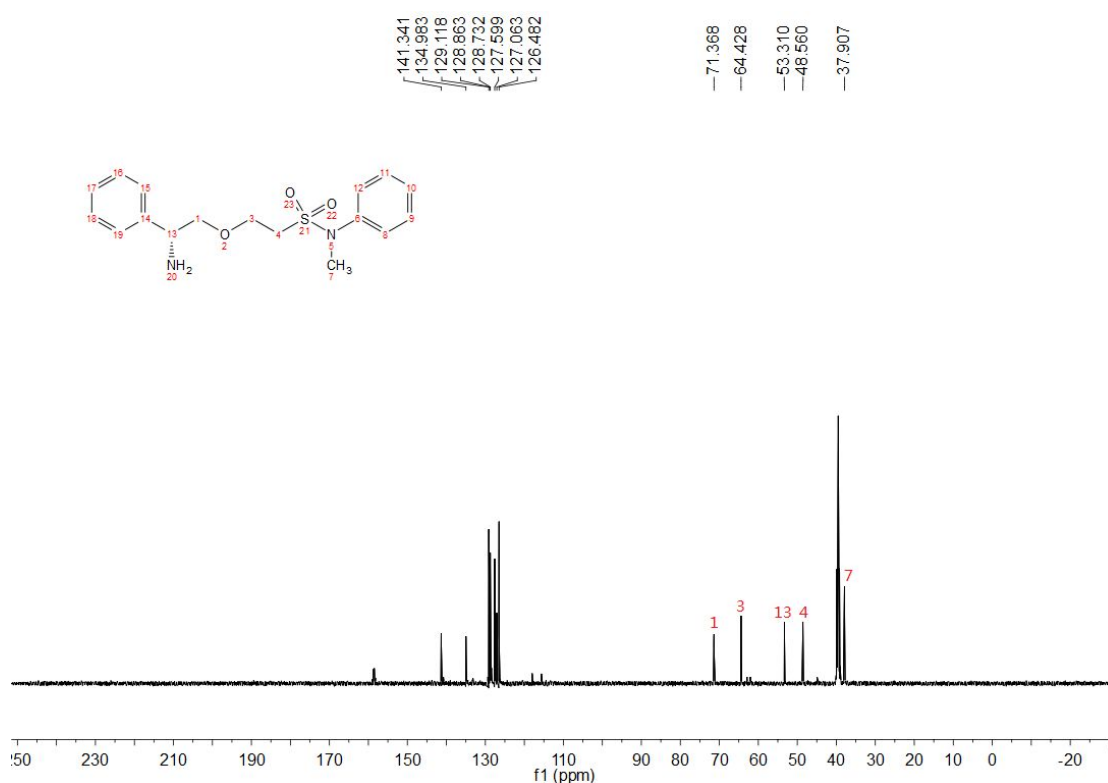
^1H - ^1H COSY of compound 8



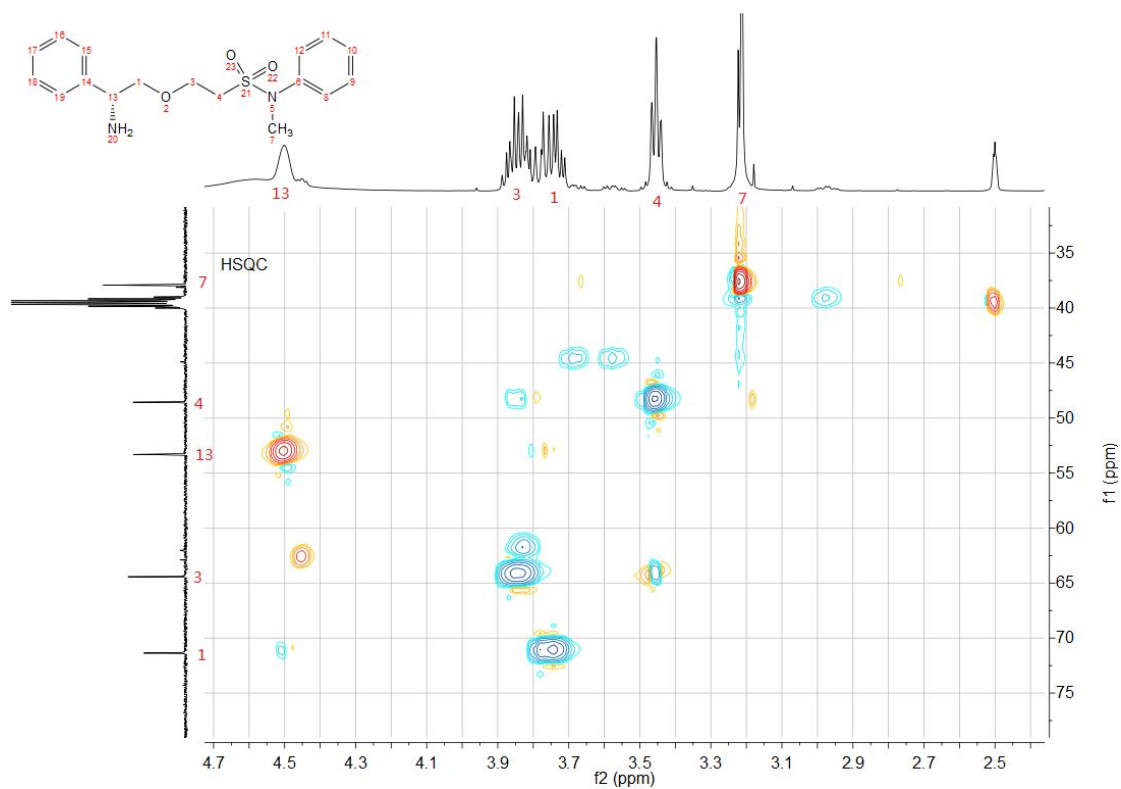
¹H NMR of compound 9



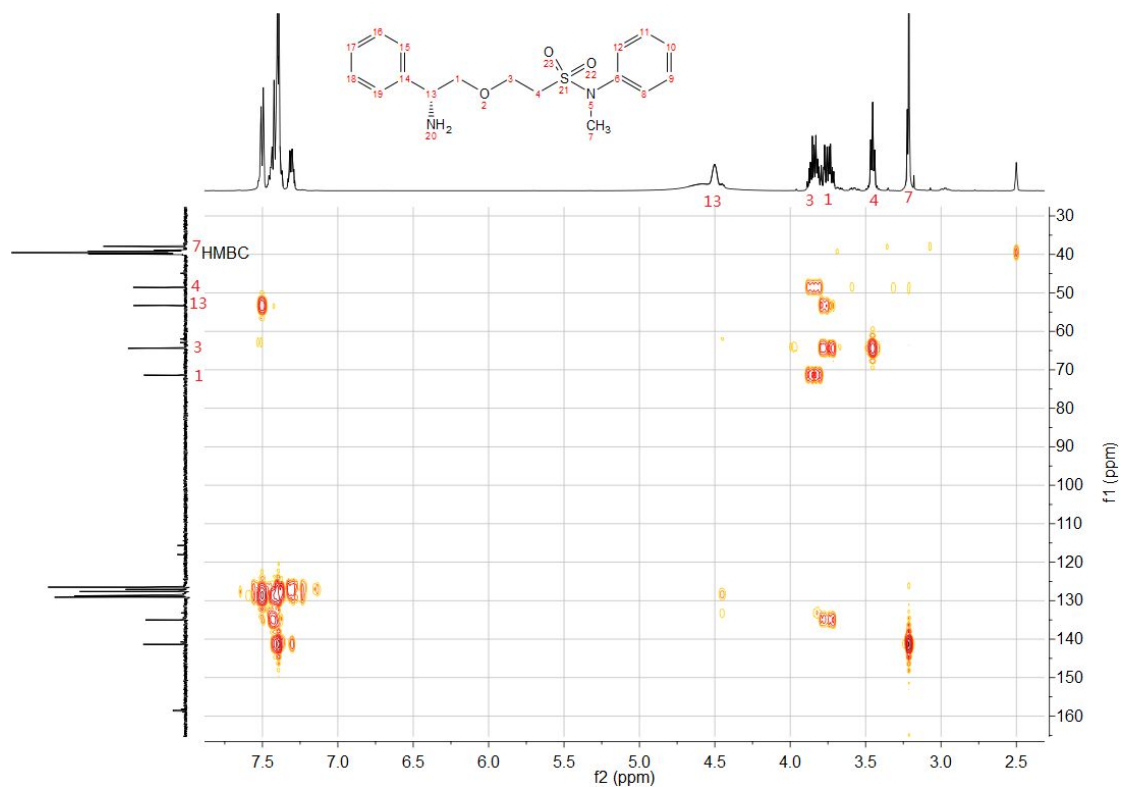
¹³C NMR of compound 9



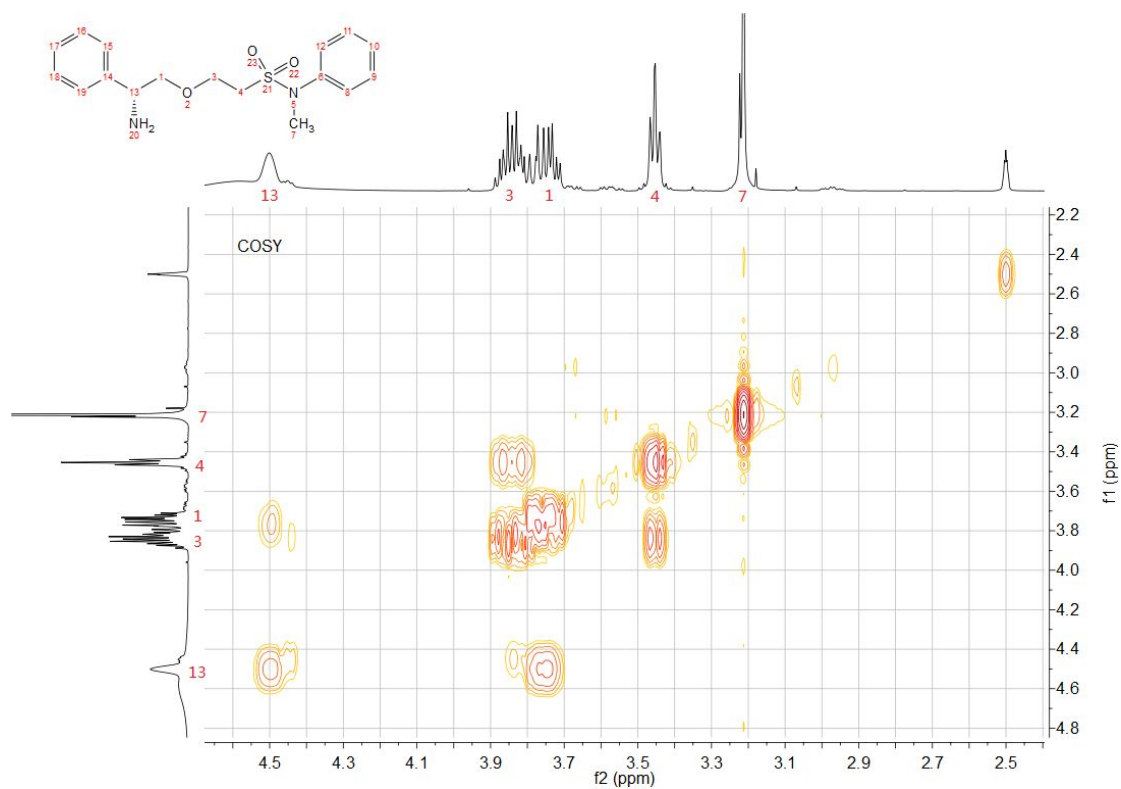
^1H - ^{13}C HSQC of compound 9



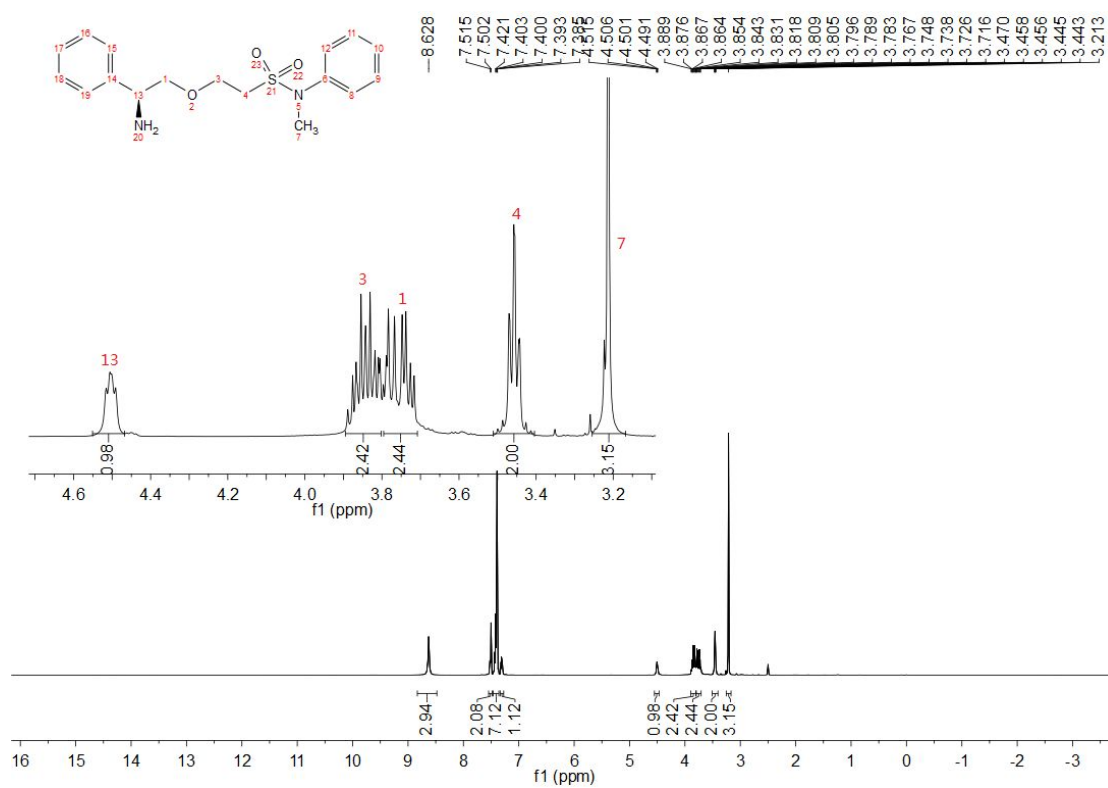
^1H - ^{13}C HMBC of compound 9



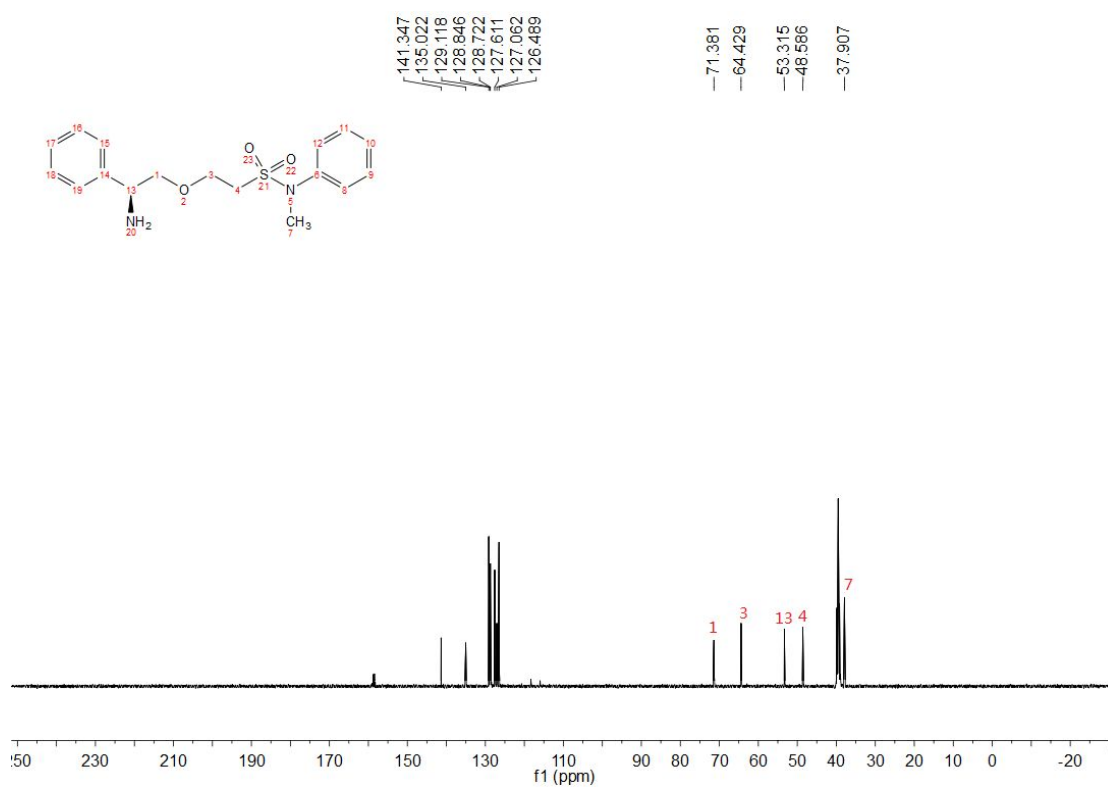
¹H-¹H COSY of compound 9



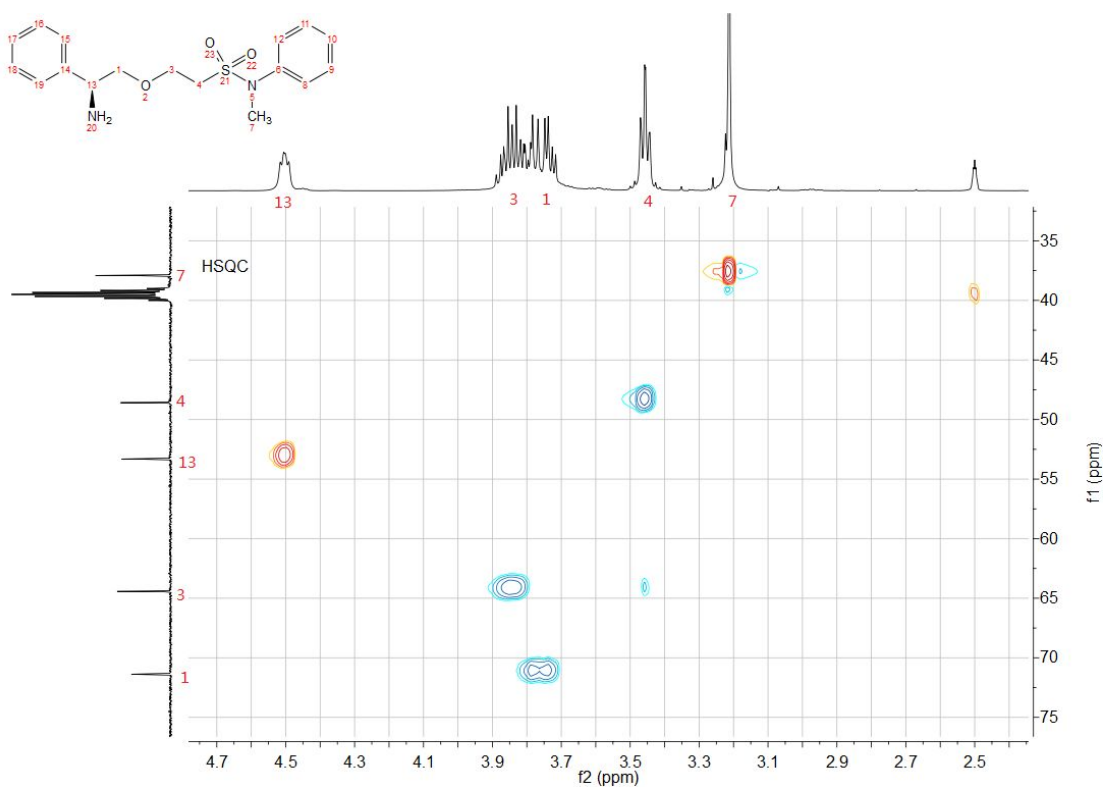
¹H NMR of compound 10



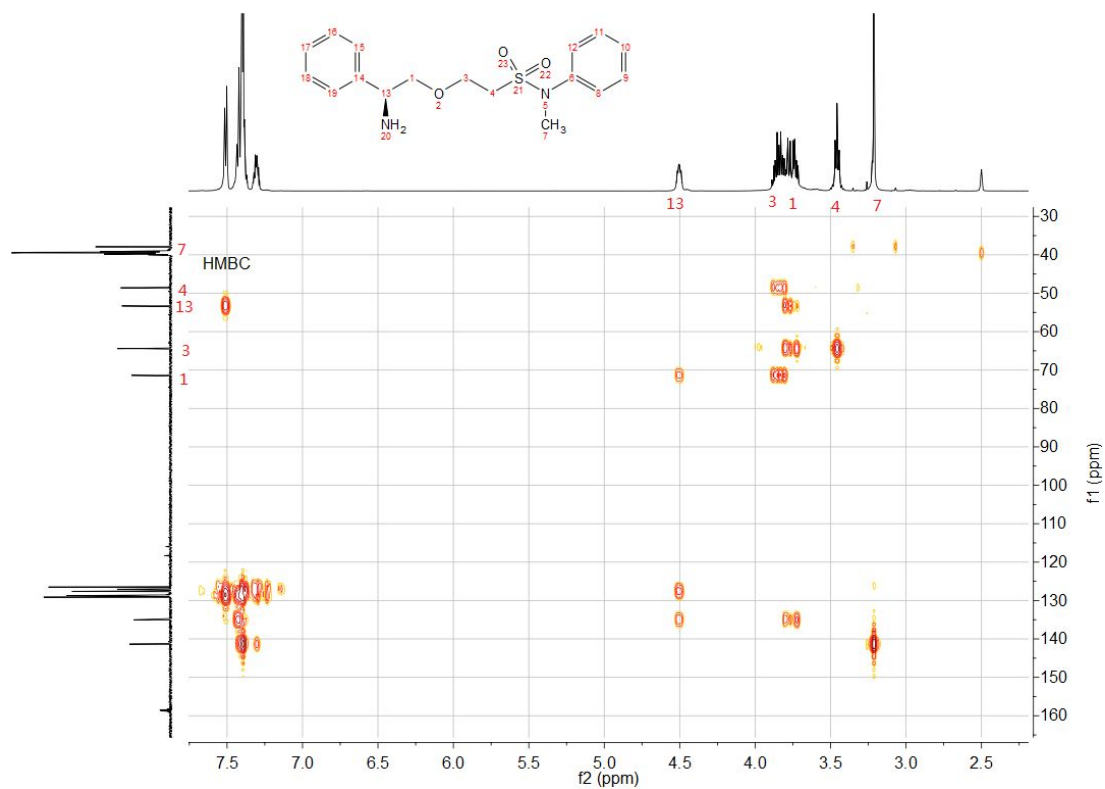
^{13}C NMR of compound 10



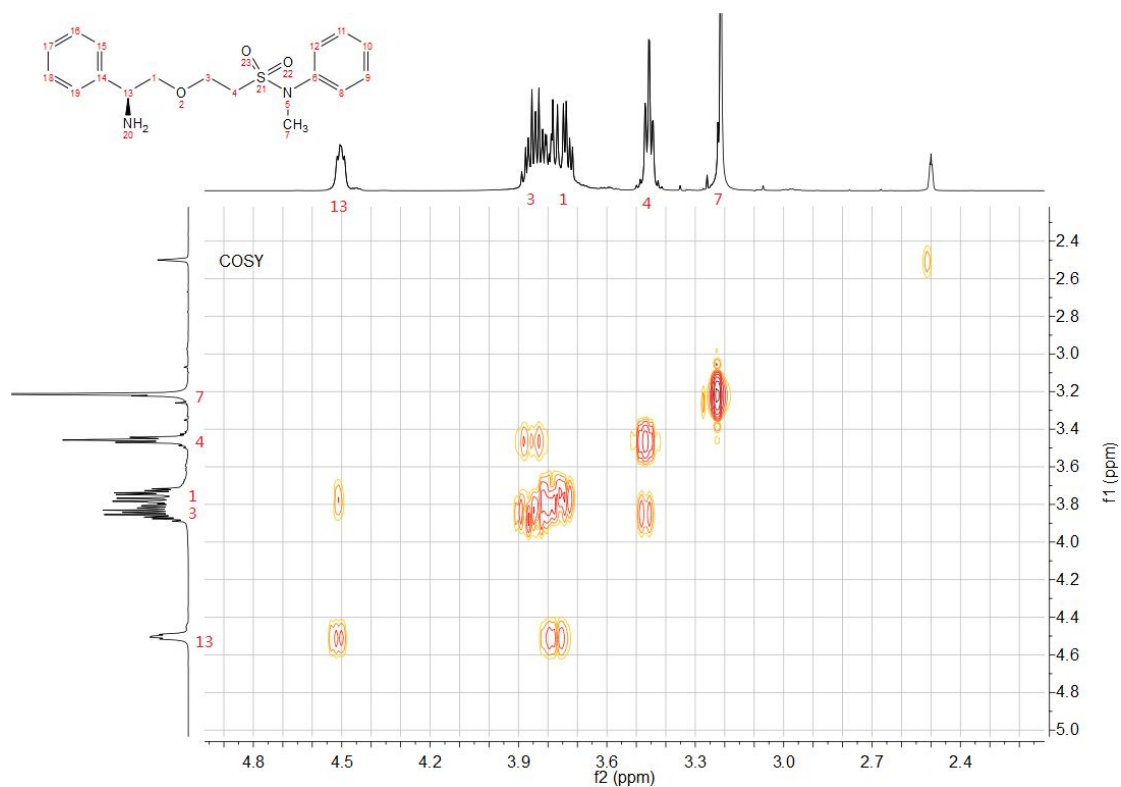
^1H - ^{13}C HSQC of compound 10



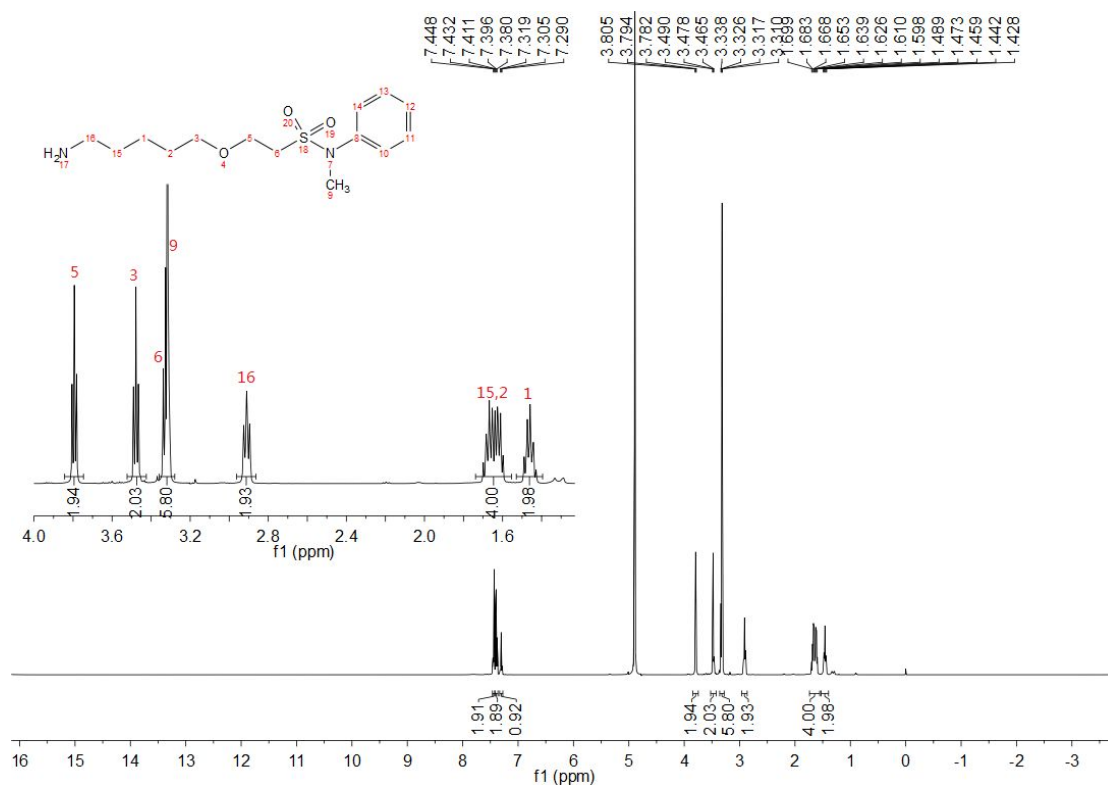
^1H - ^{13}C HMBC of compound 10



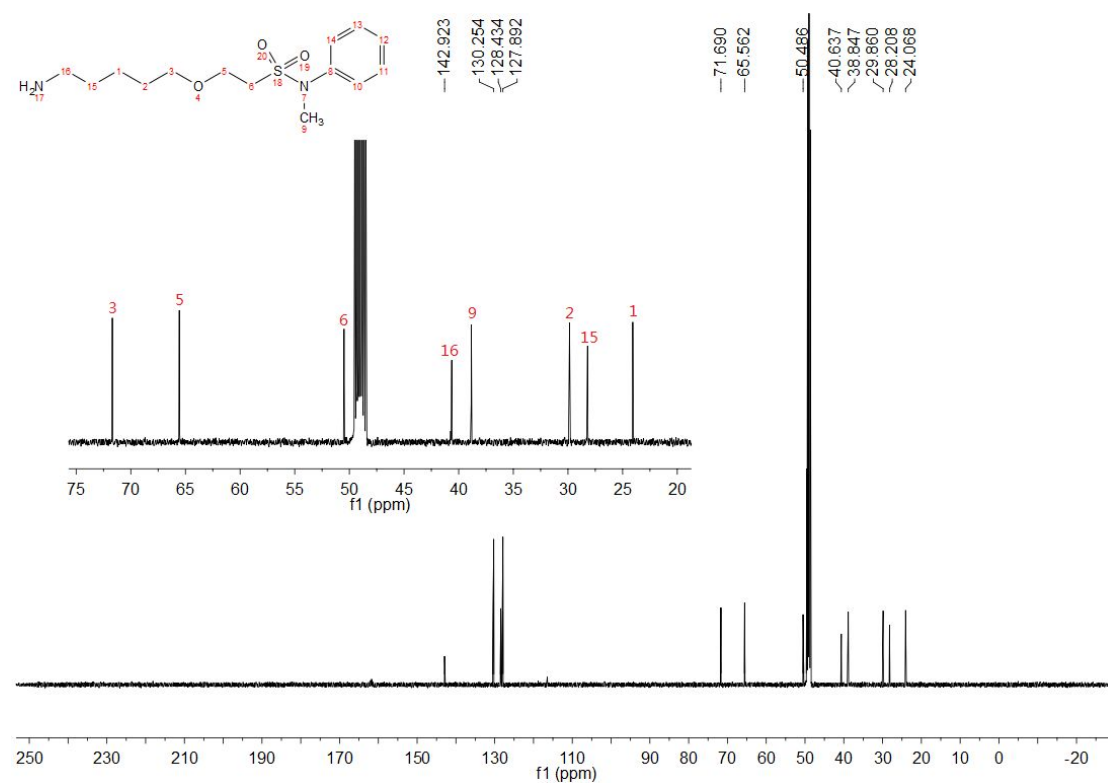
^1H - ^1H COSY of compound 10



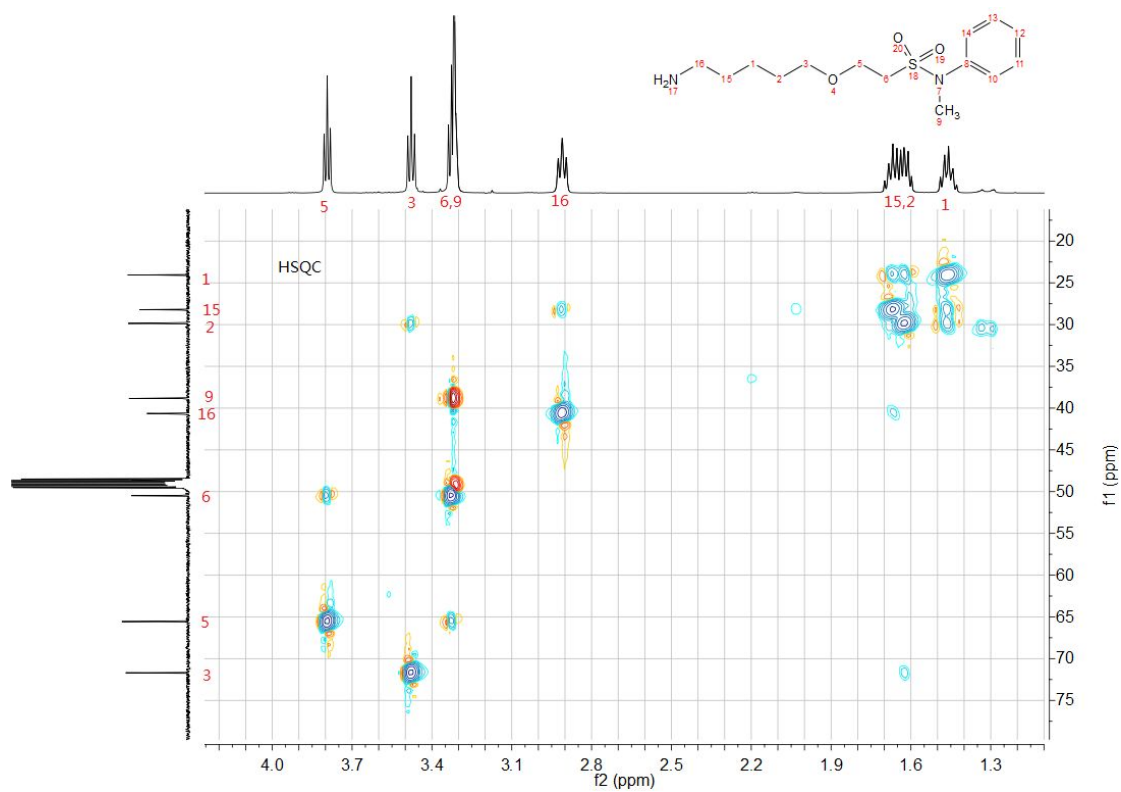
¹H NMR of compound 11



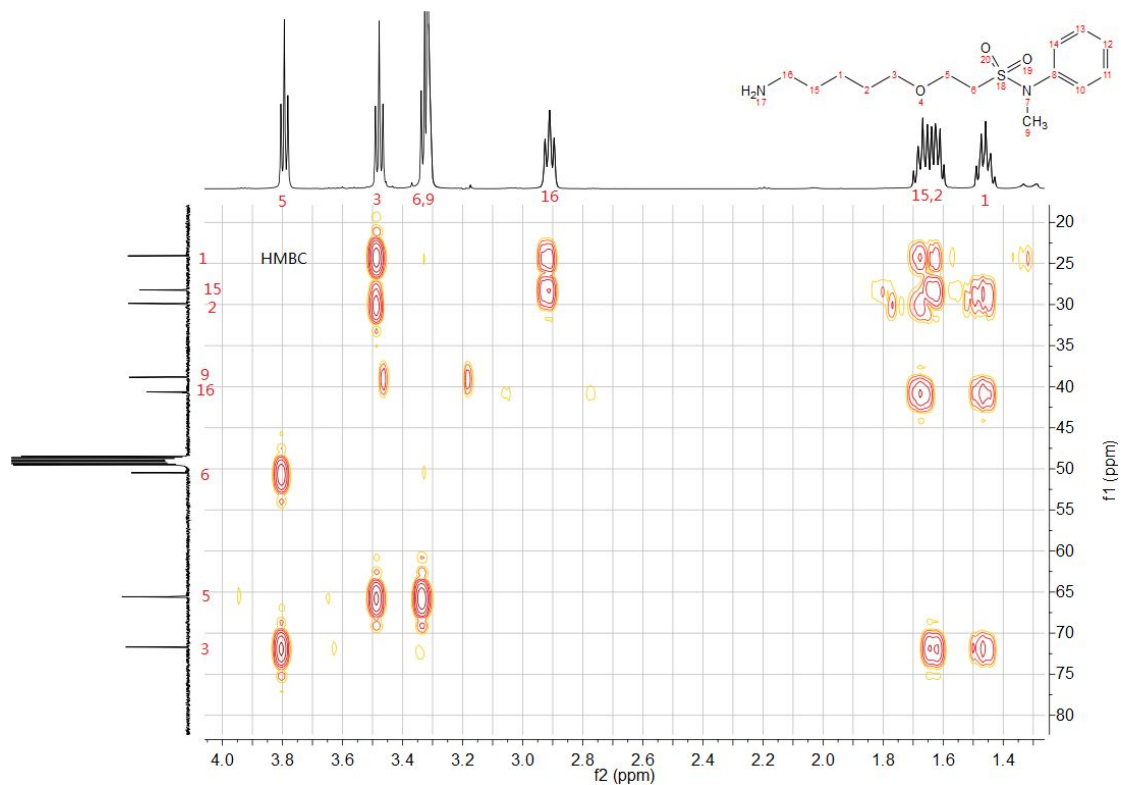
¹³C NMR of compound 11



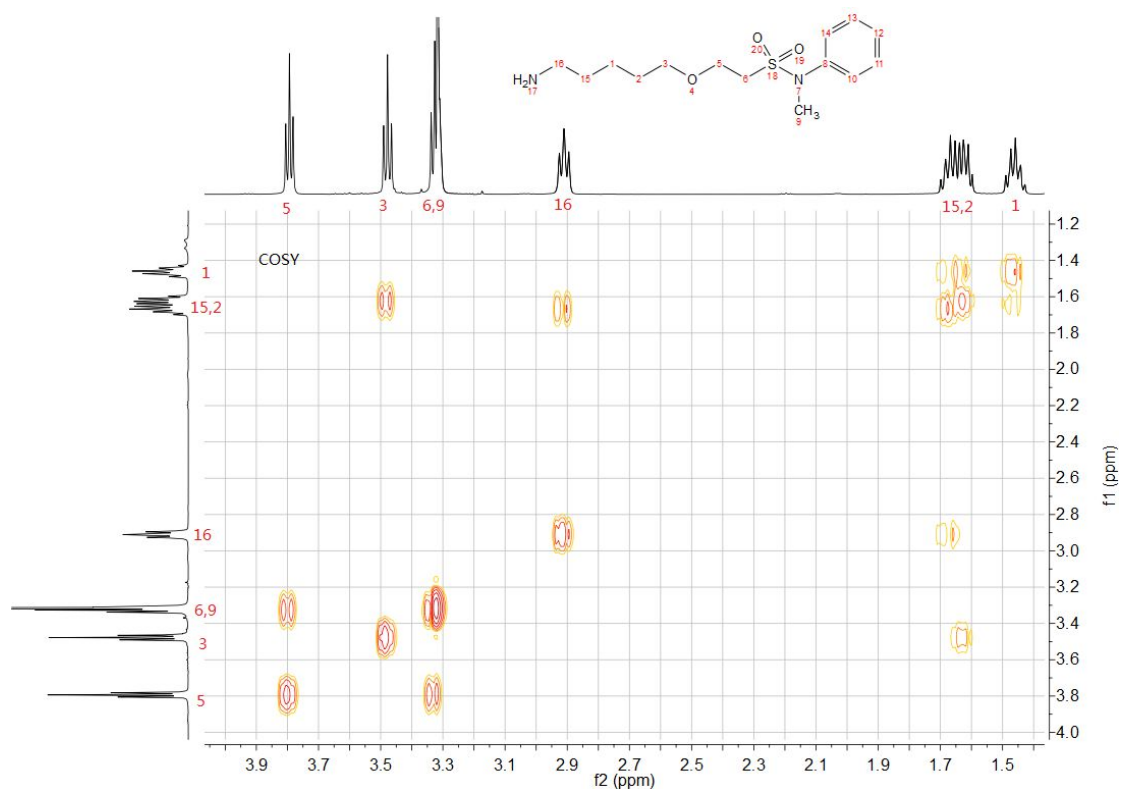
^1H - ^{13}C HSQC of compound 11



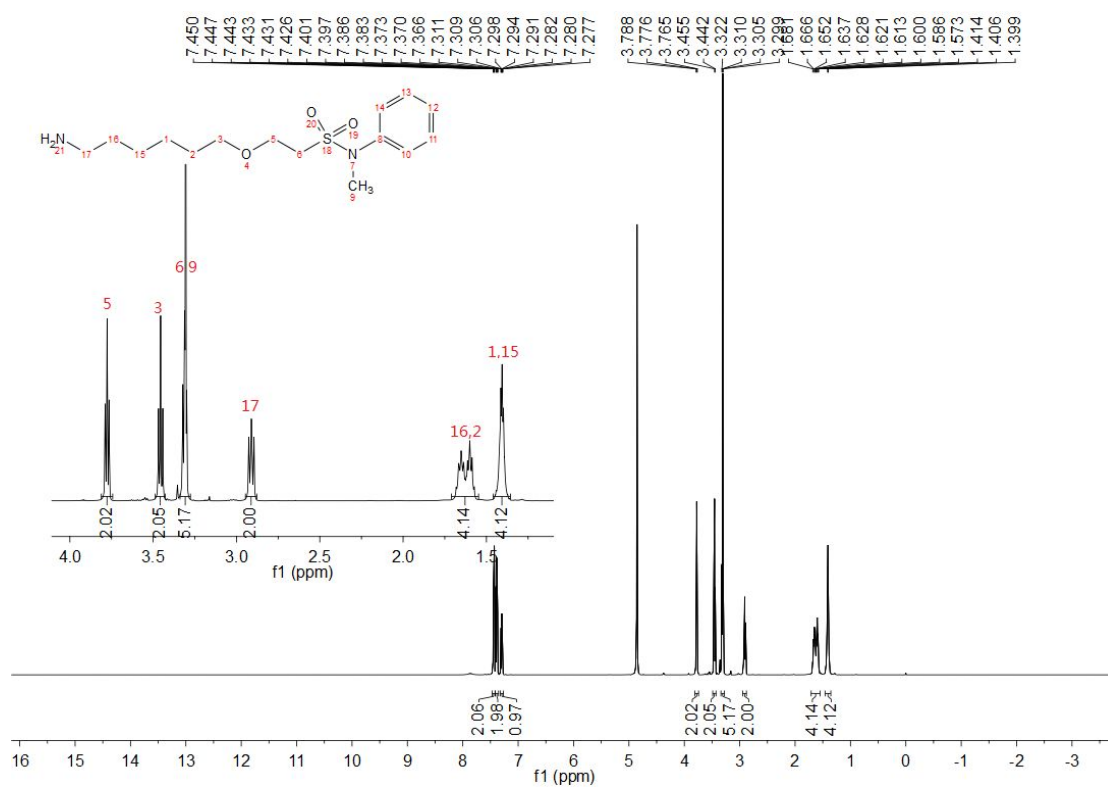
^1H - ^{13}C HMBC of compound 11



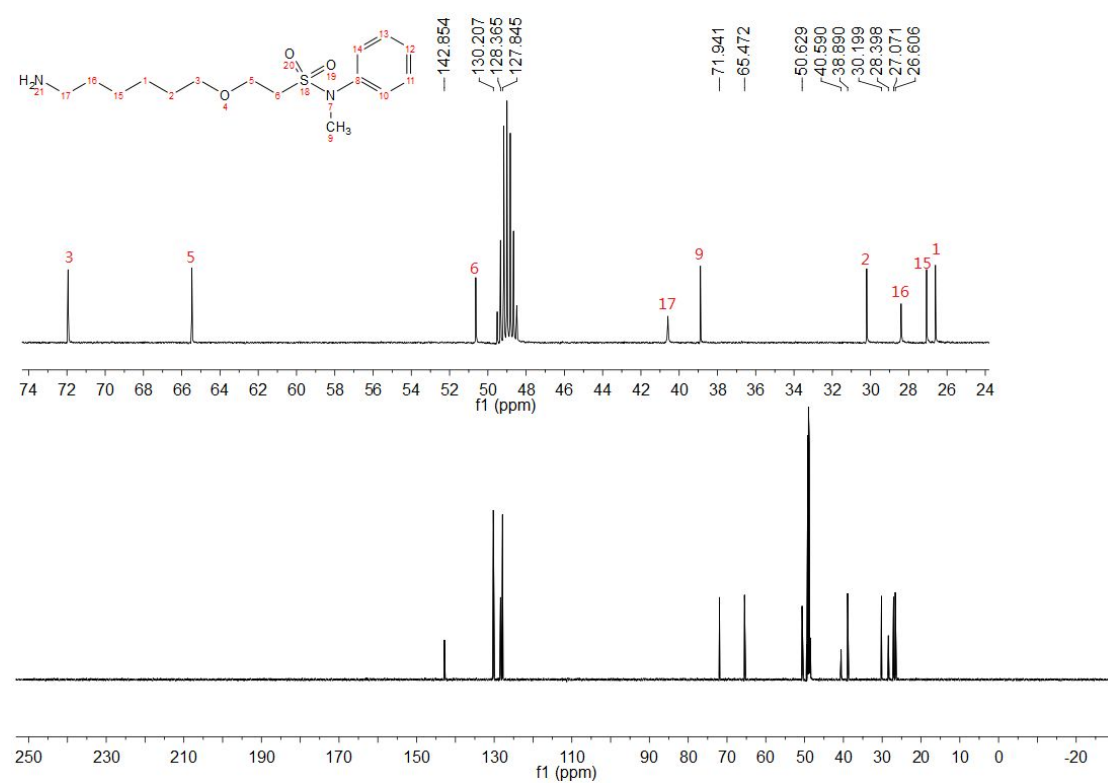
¹H-¹H COSY of compound 11



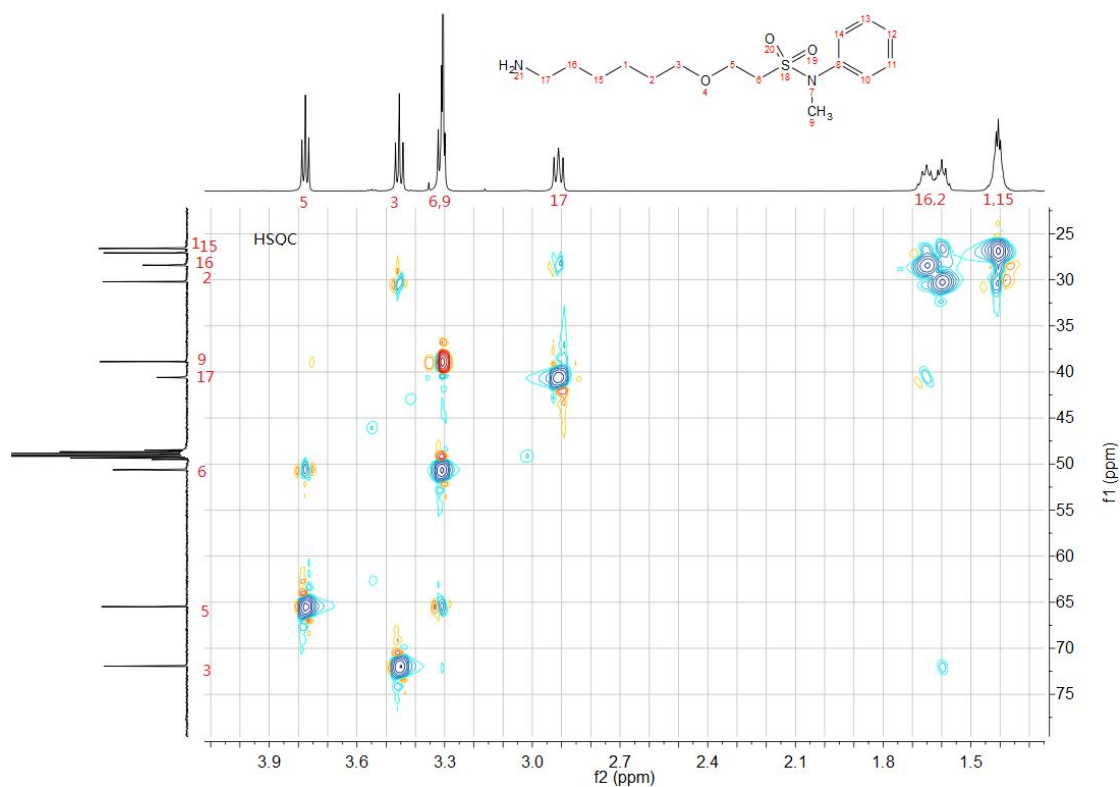
¹H NMR of compound 12



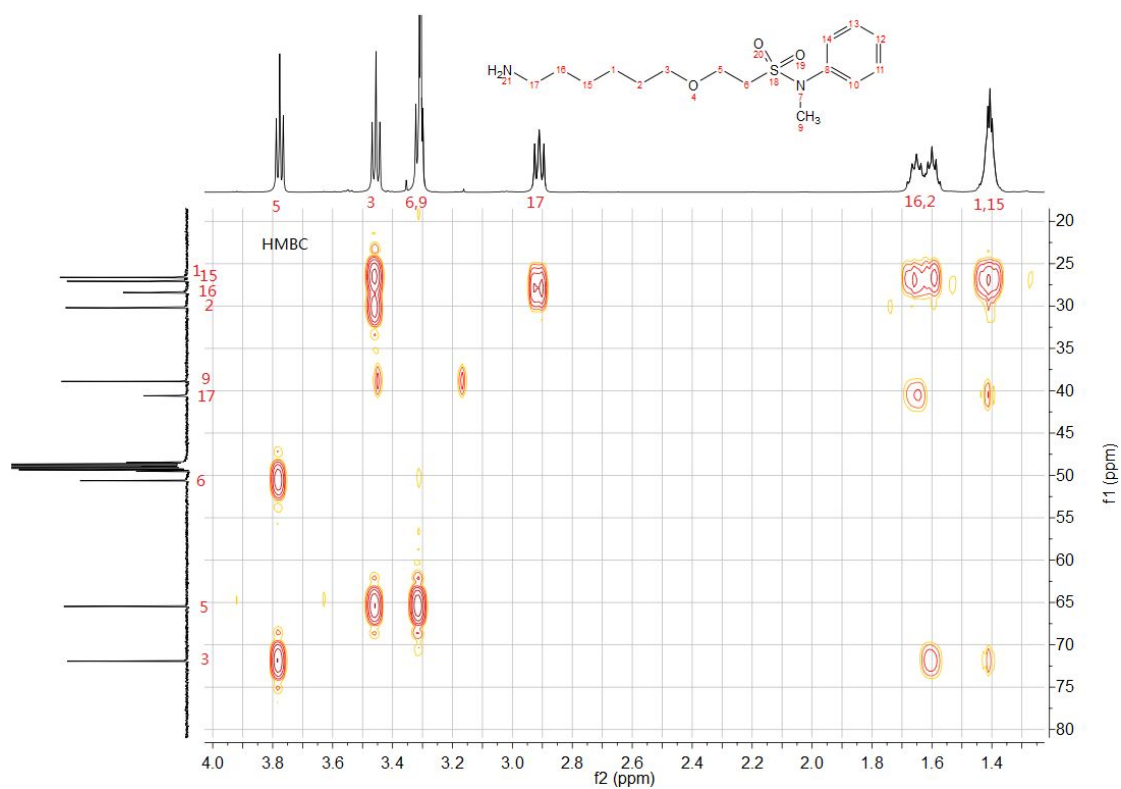
^{13}C NMR of compound 12



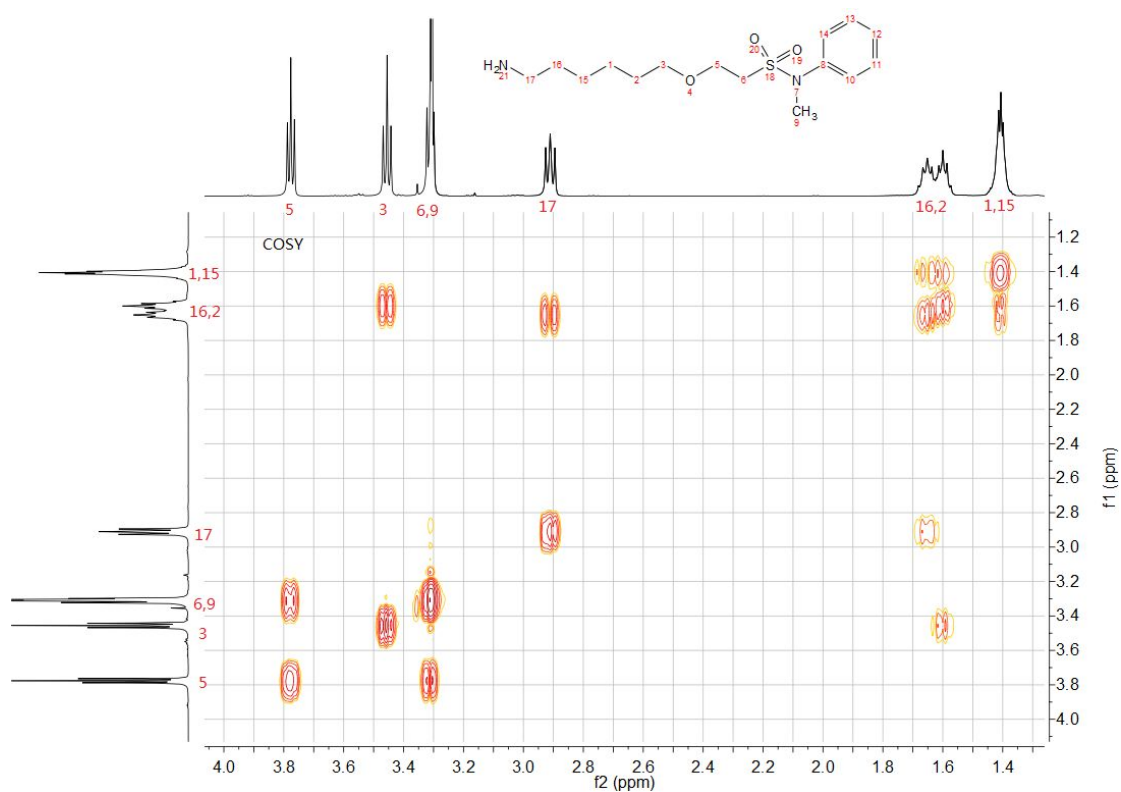
^1H - ^{13}C HSQC of compound 12



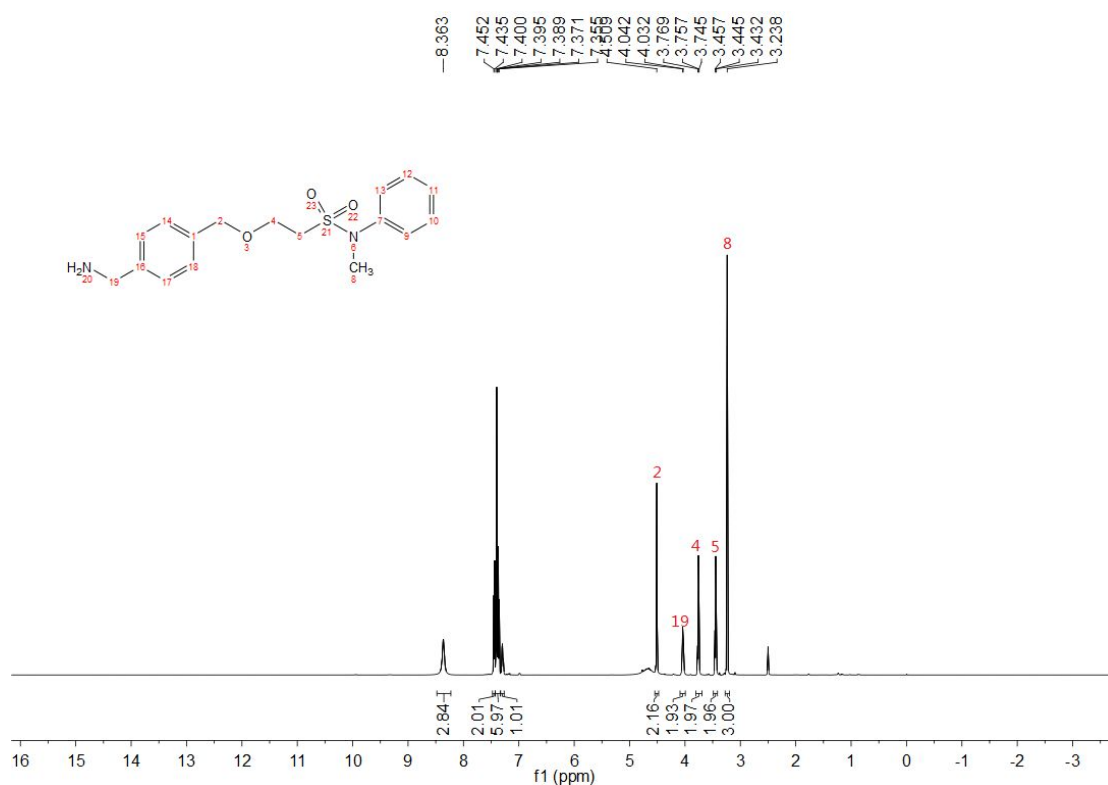
^1H - ^{13}C HMBC of compound 12



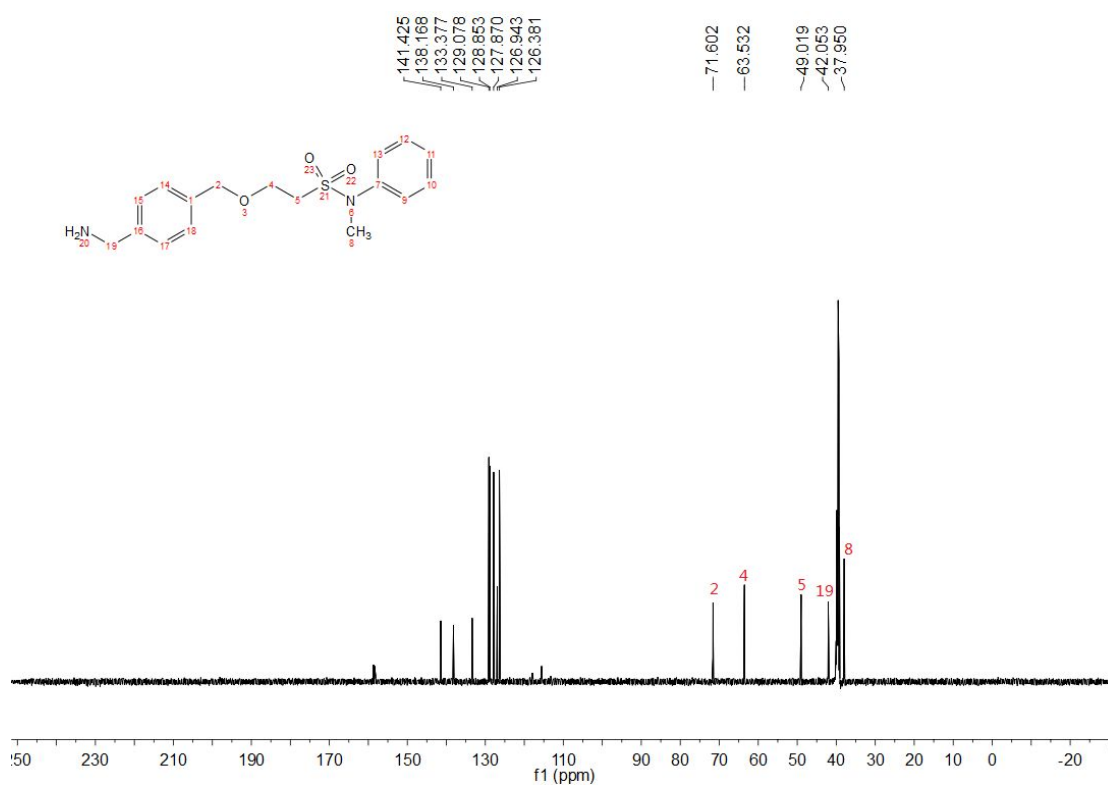
^1H - ^1H COSY of compound 12



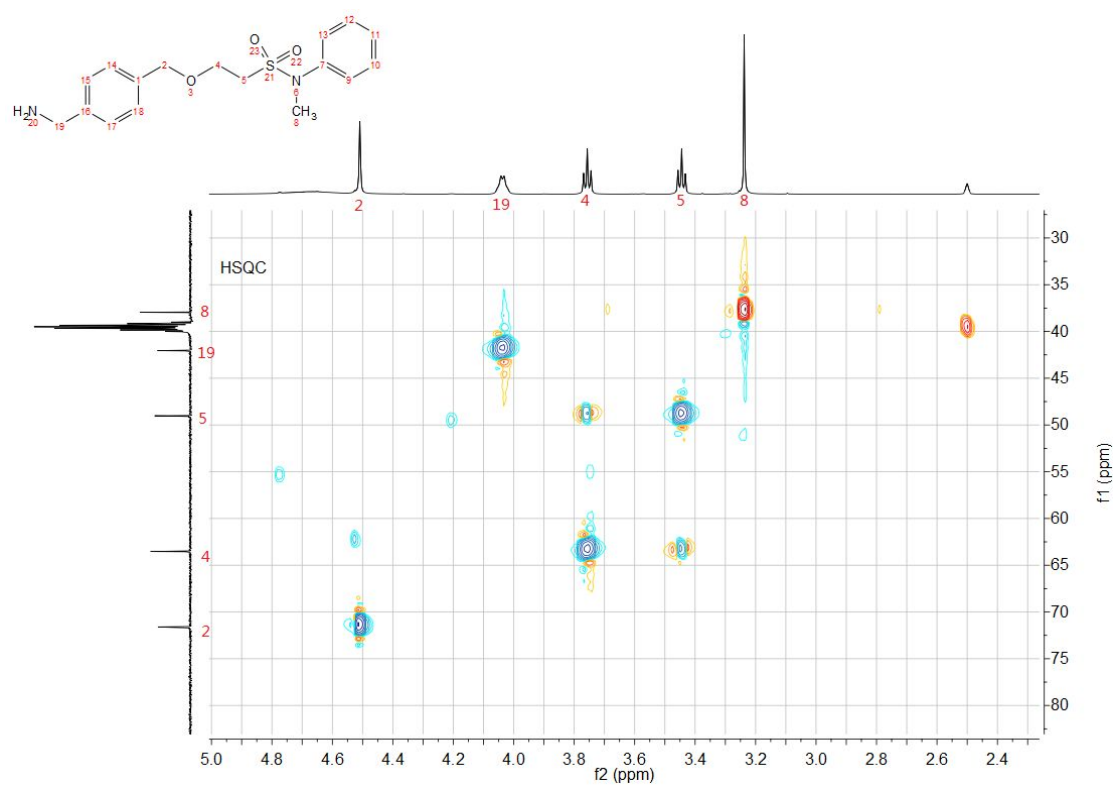
¹H NMR of compound 13



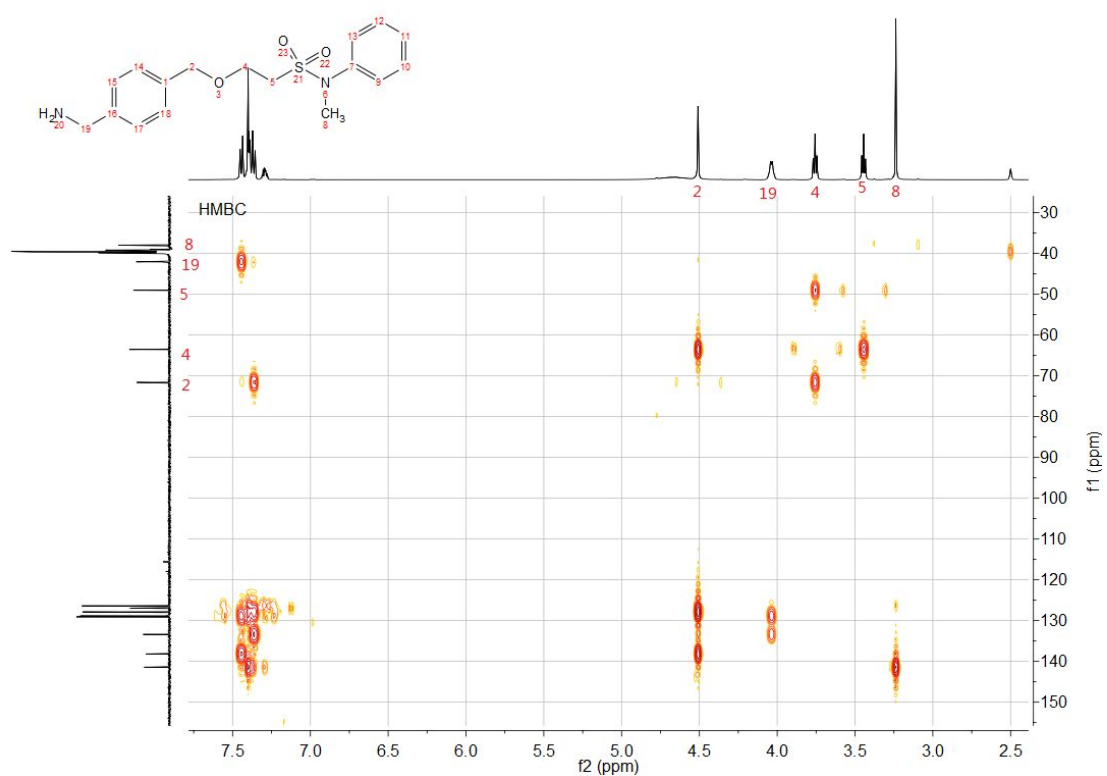
¹³C NMR of compound 13



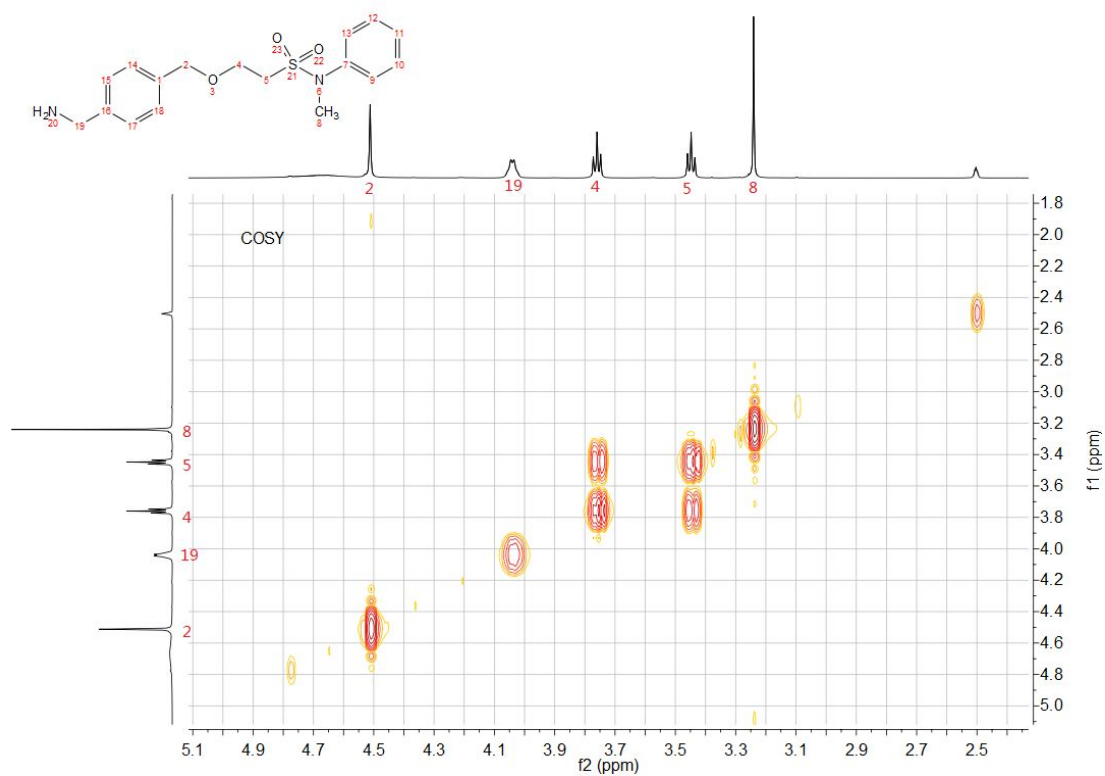
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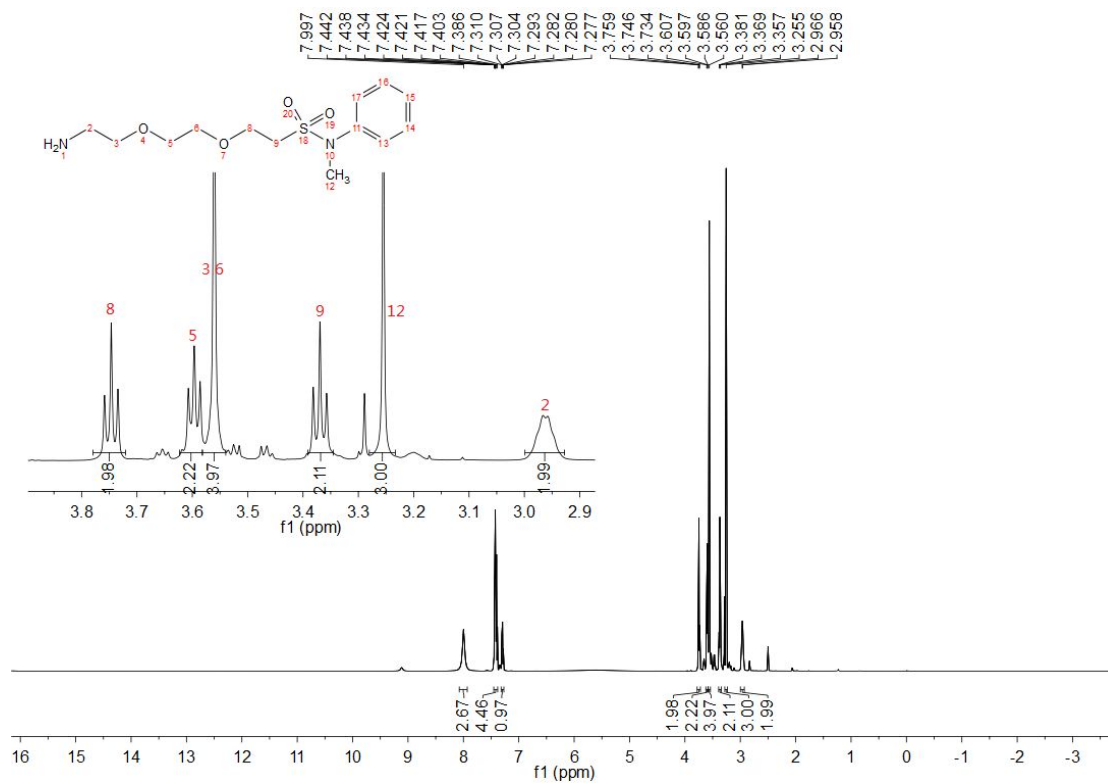
^1H - ^{13}C HMBC of compound 13



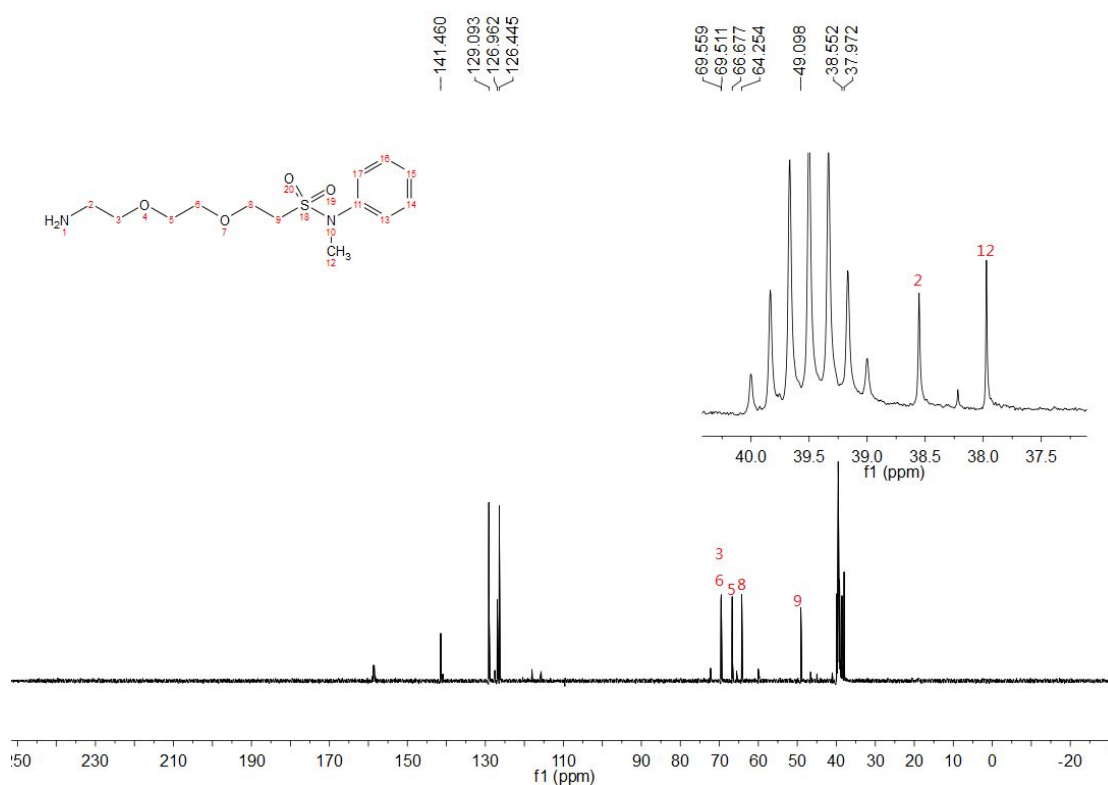
¹H-¹H COSY of compound 13



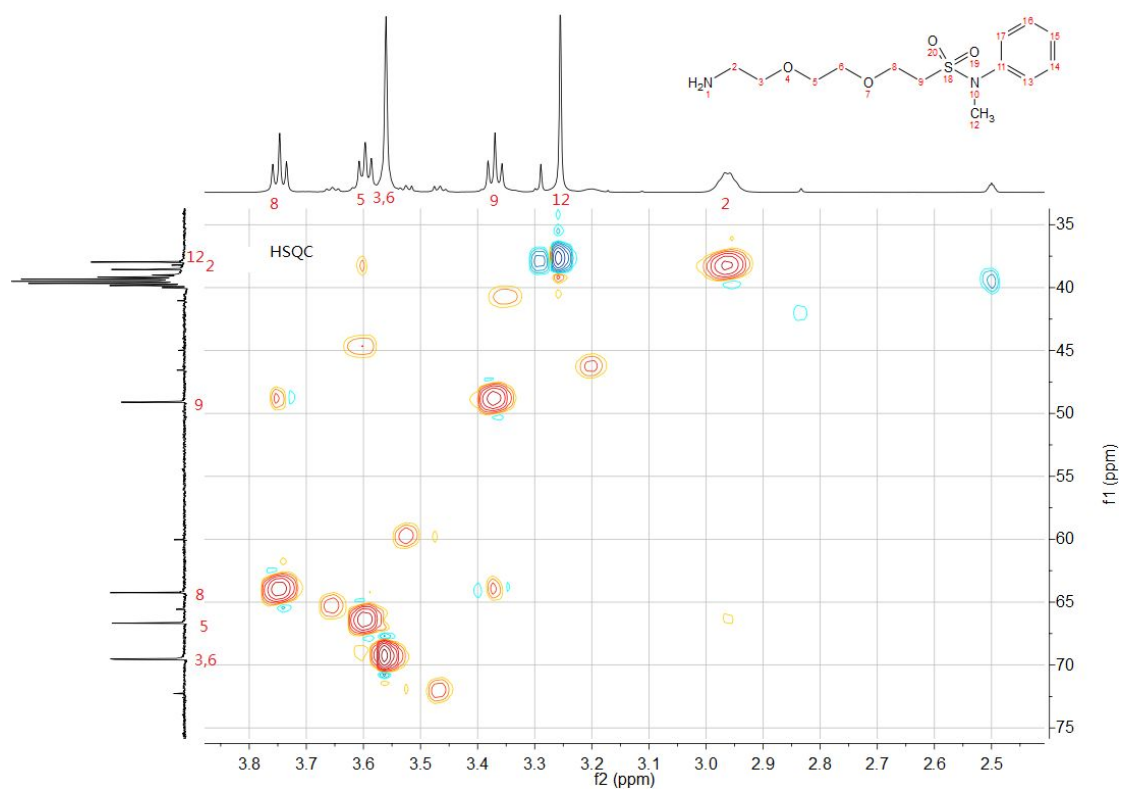
¹H NMR of compound 14



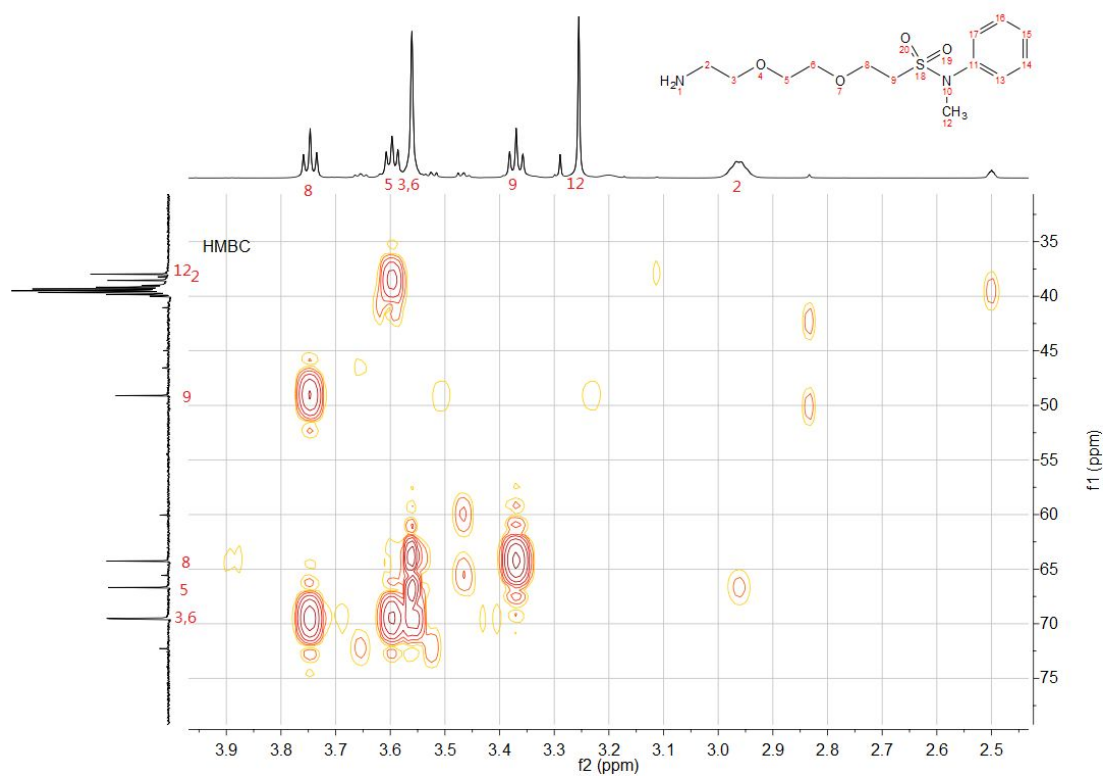
^{13}C NMR of compound 14



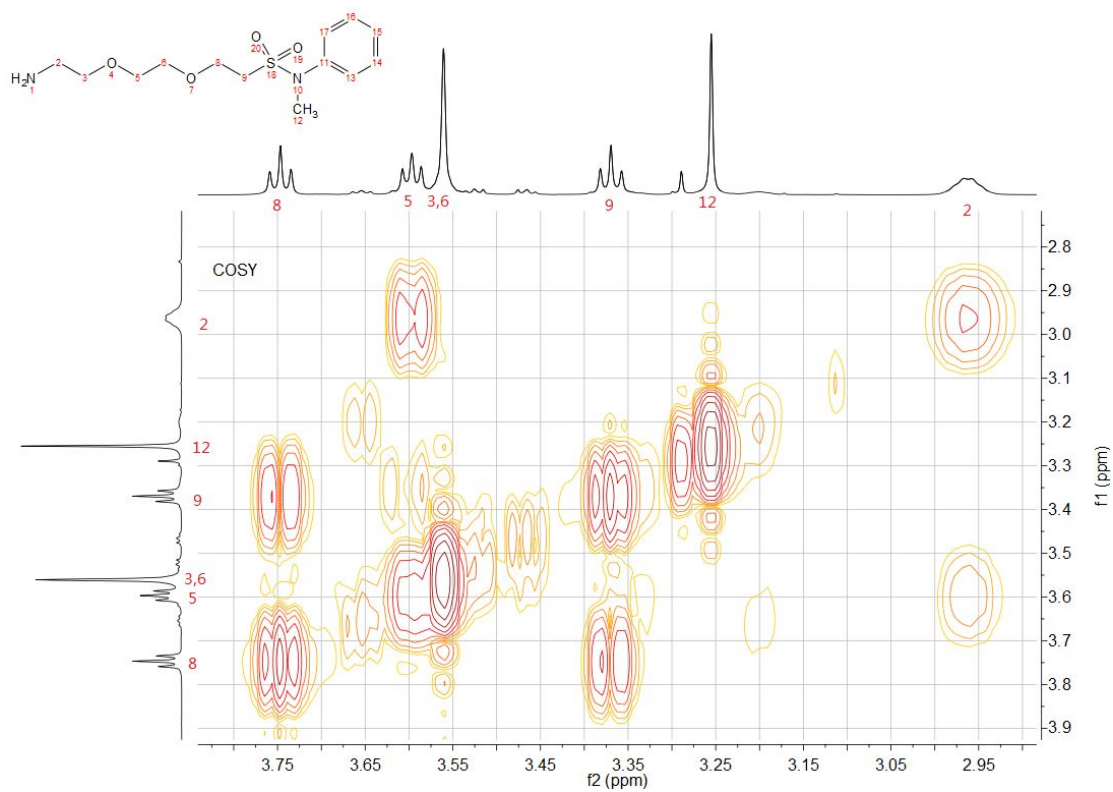
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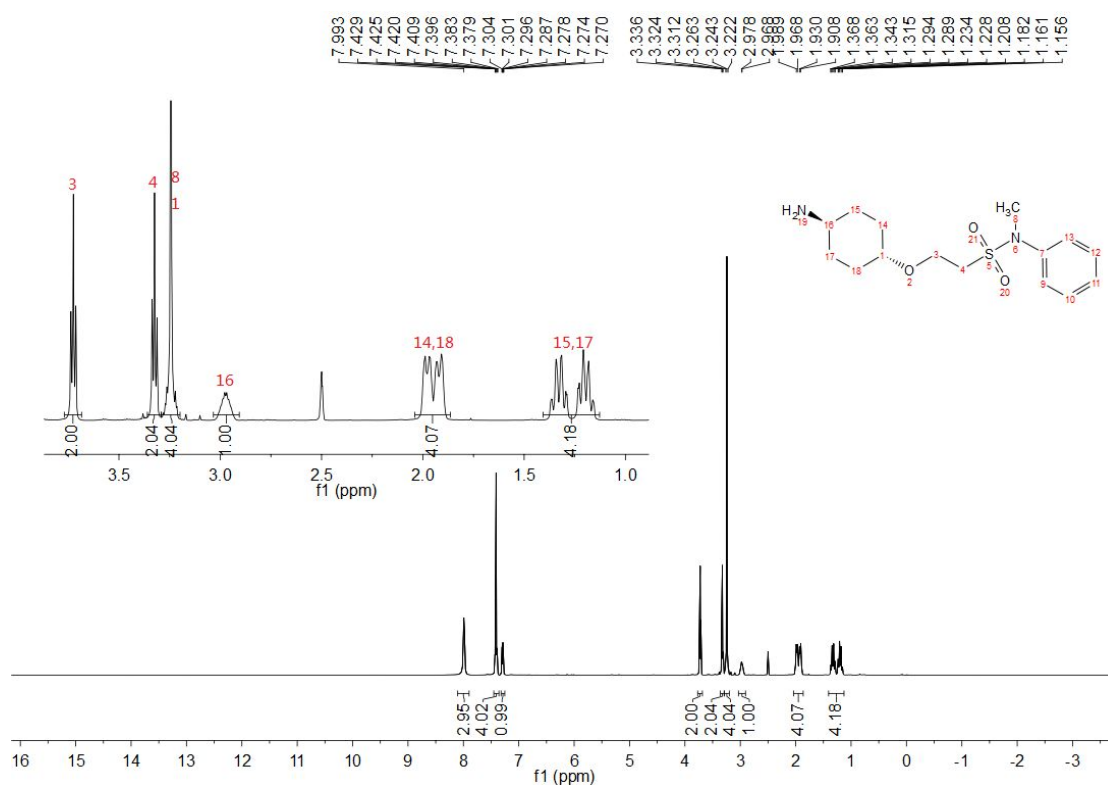
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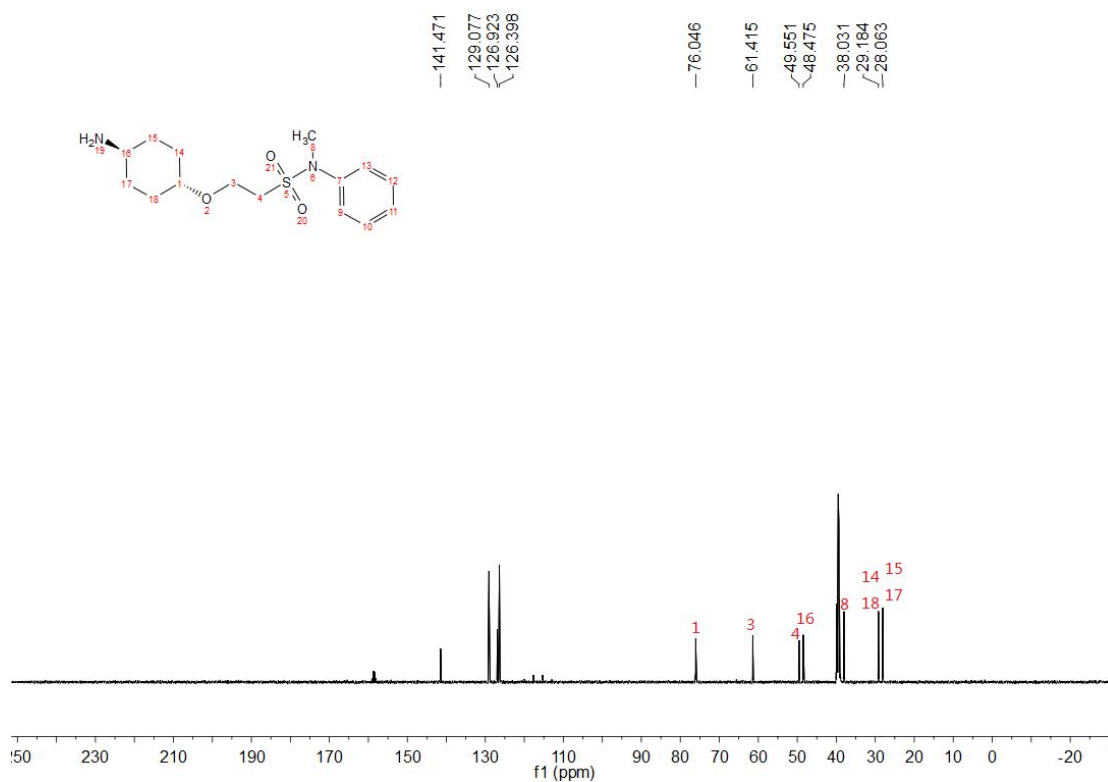
^1H - ^1H COSY of compound 14



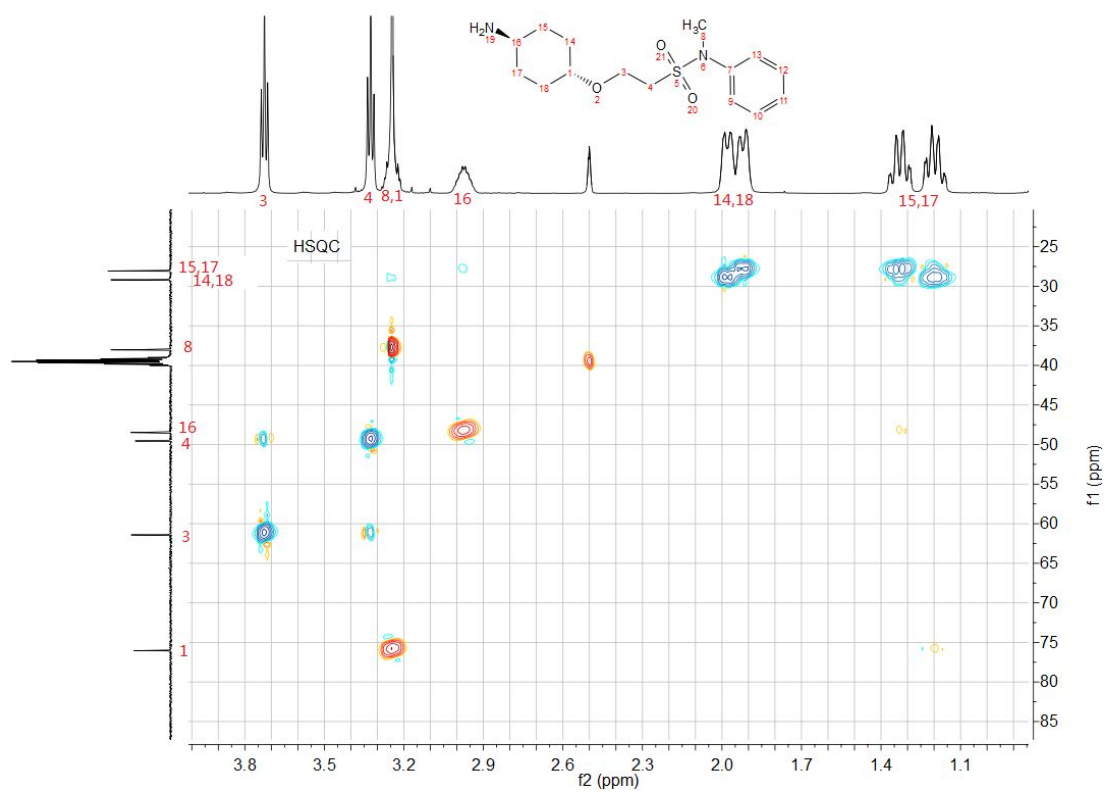
¹H NMR of compound 15



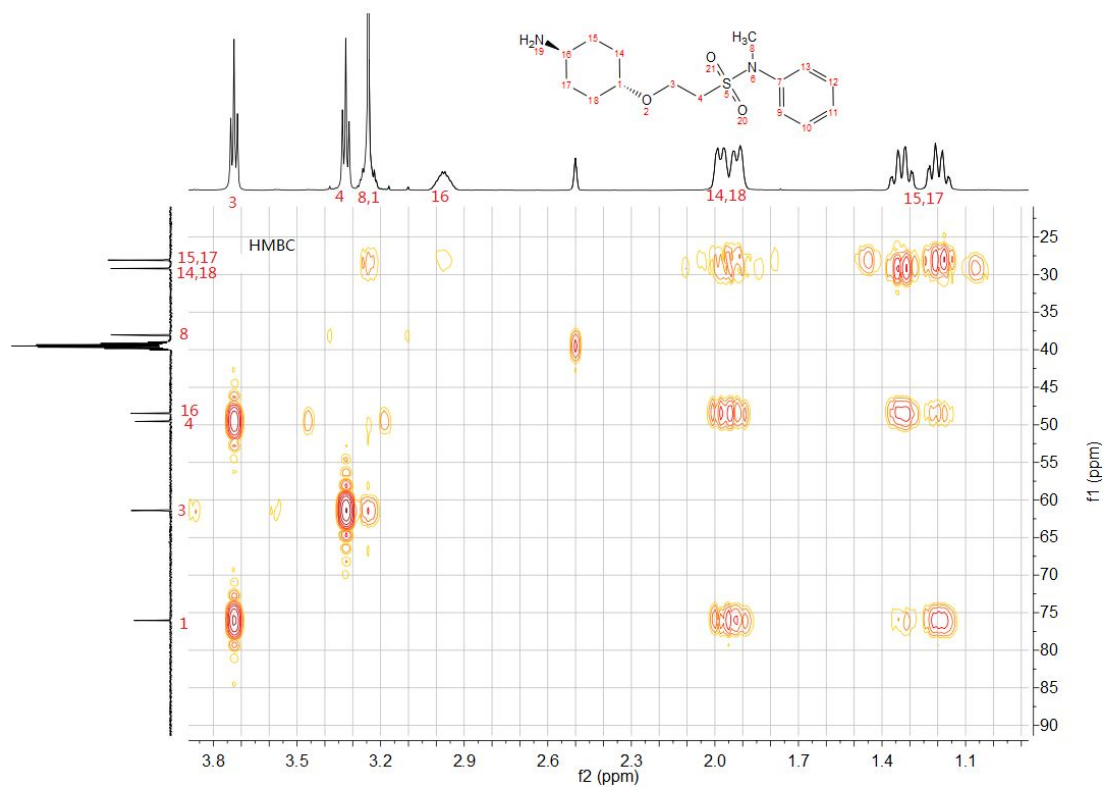
¹³C NMR of compound 15



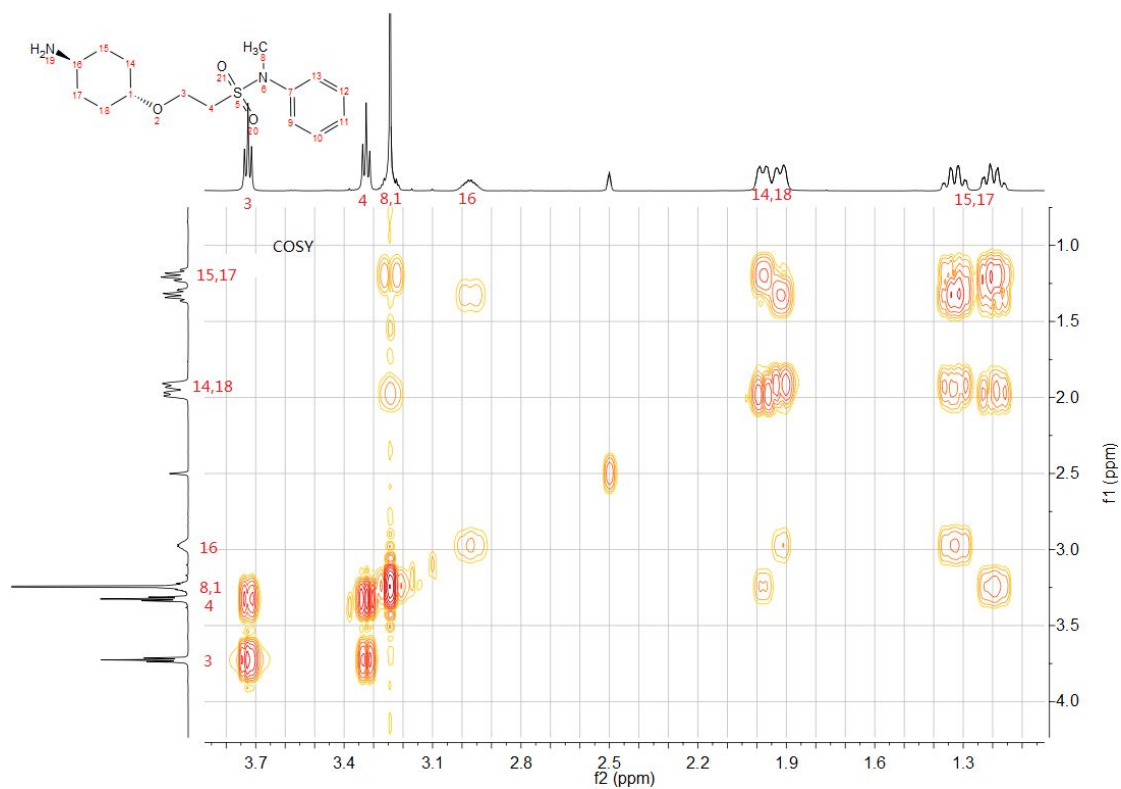
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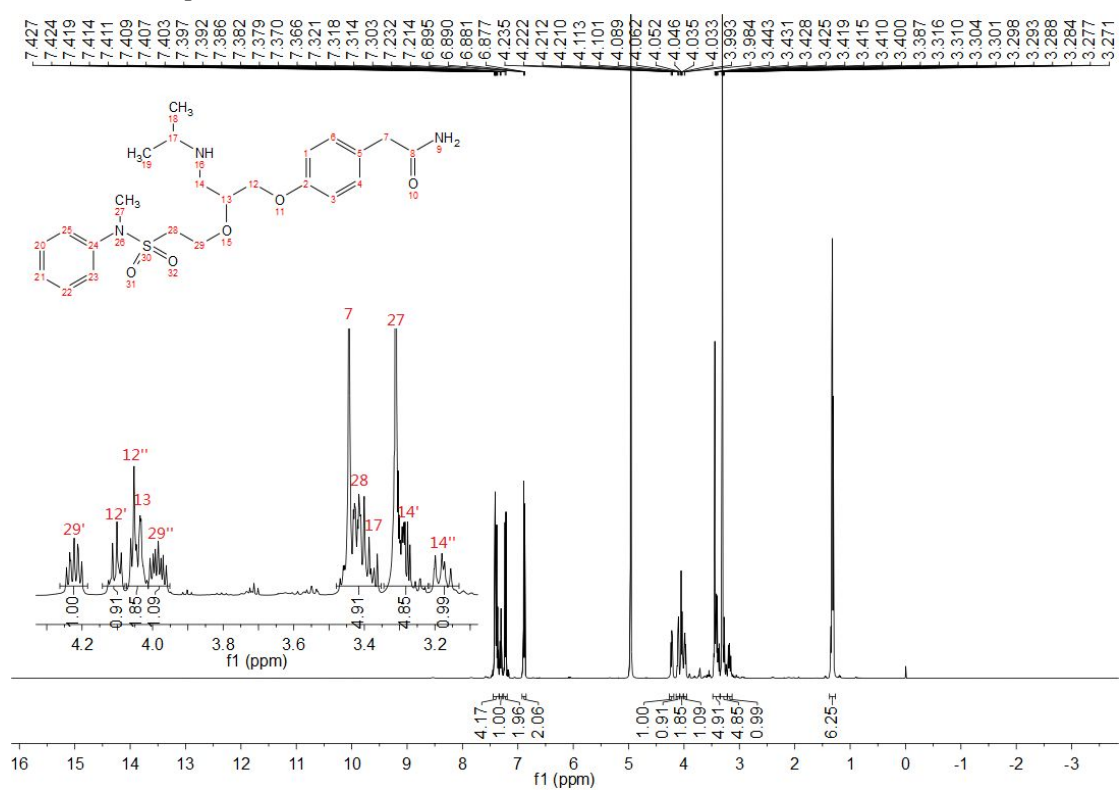
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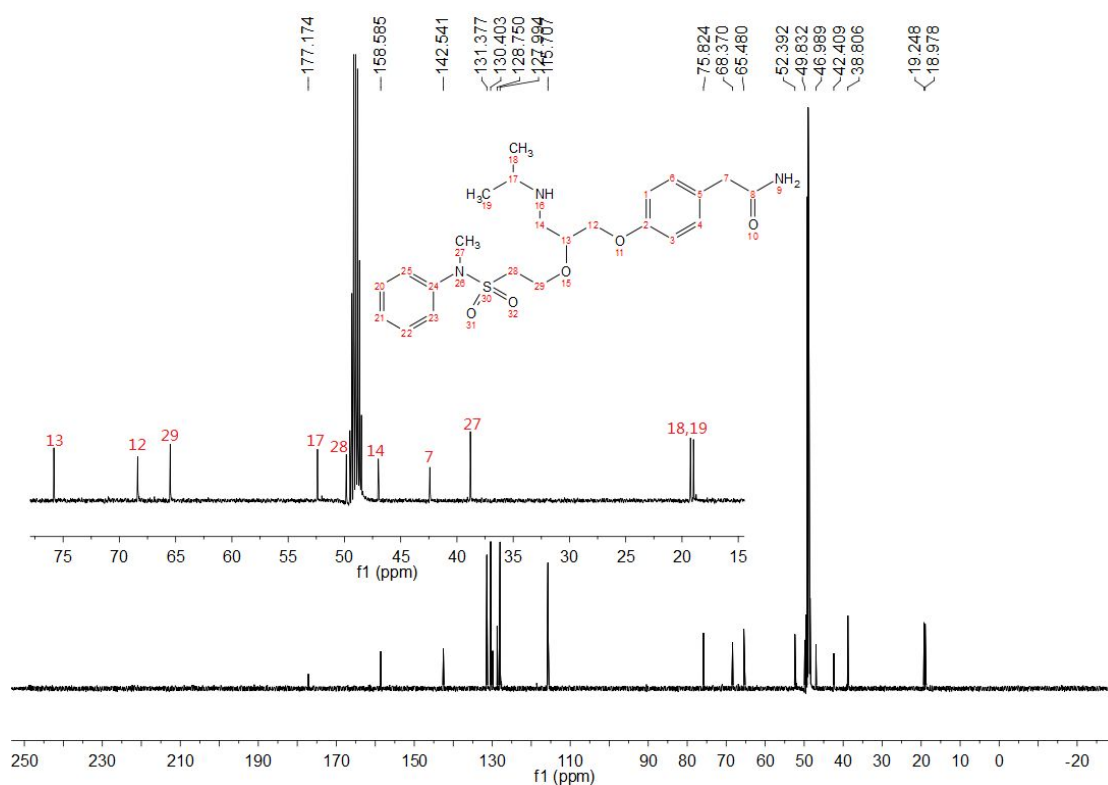
¹H-¹H COSY of compound 15



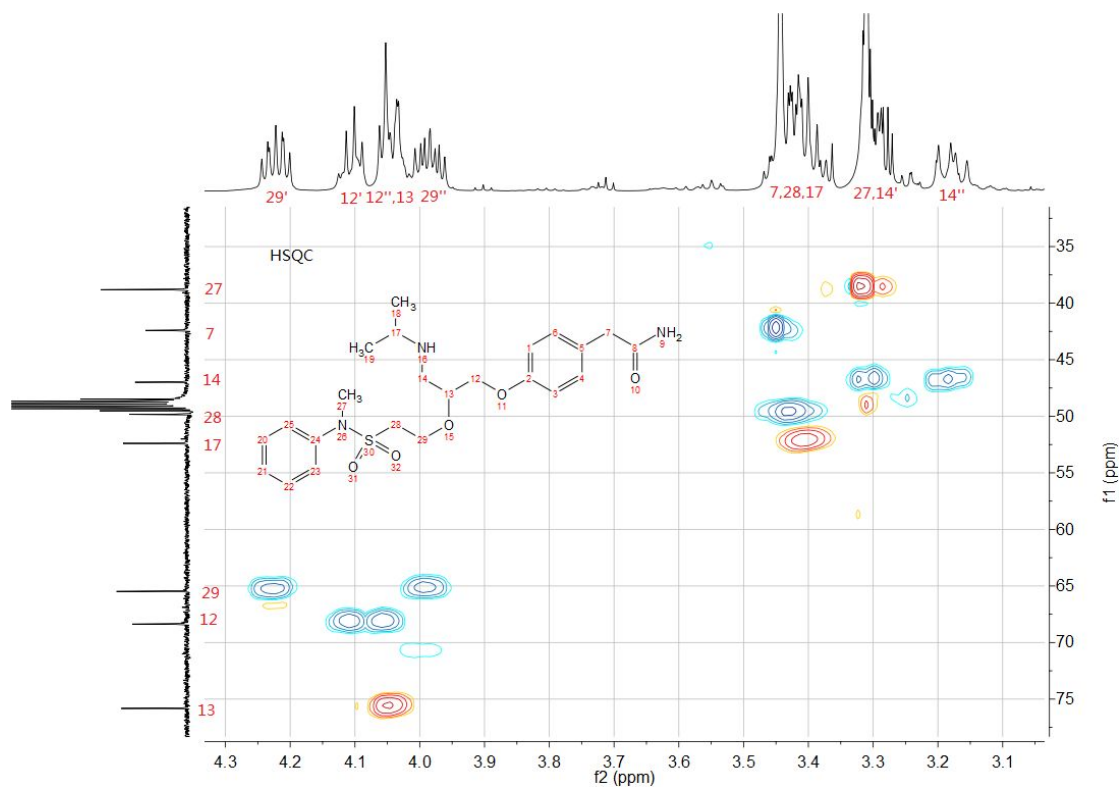
¹H NMR of compound 16



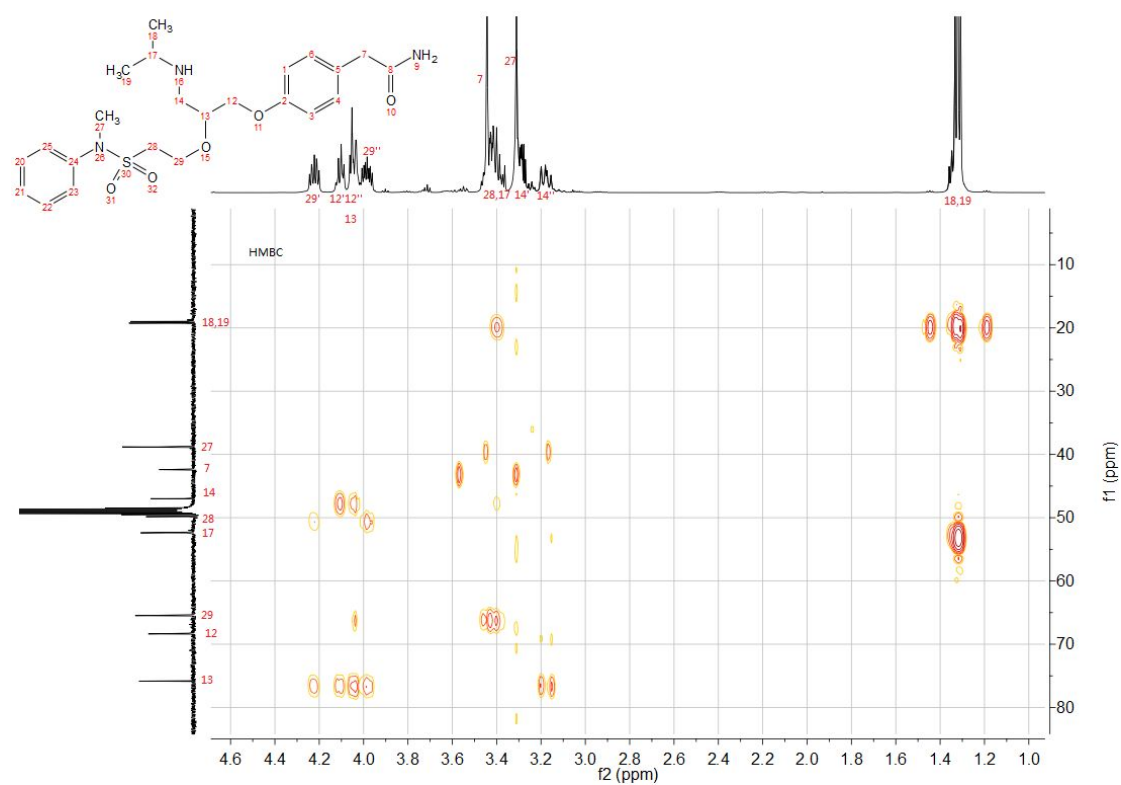
^{13}C NMR of compound 16



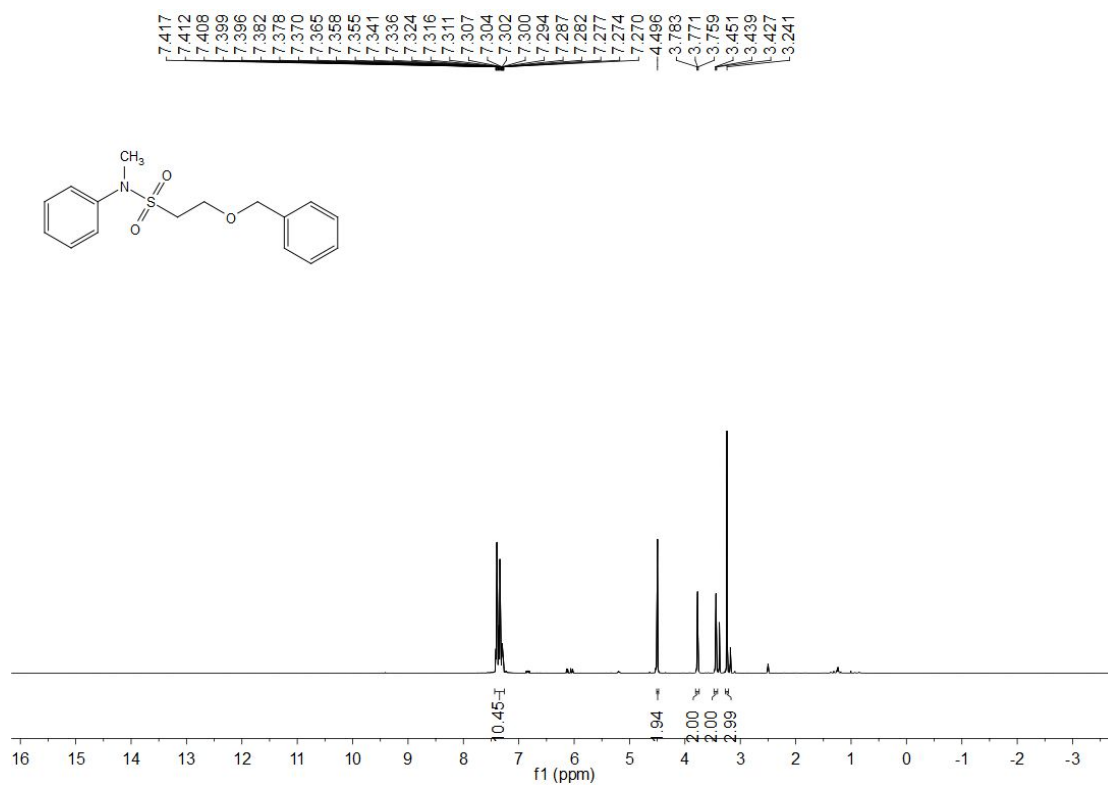
^1H - ^{13}C HSQC of compound 16



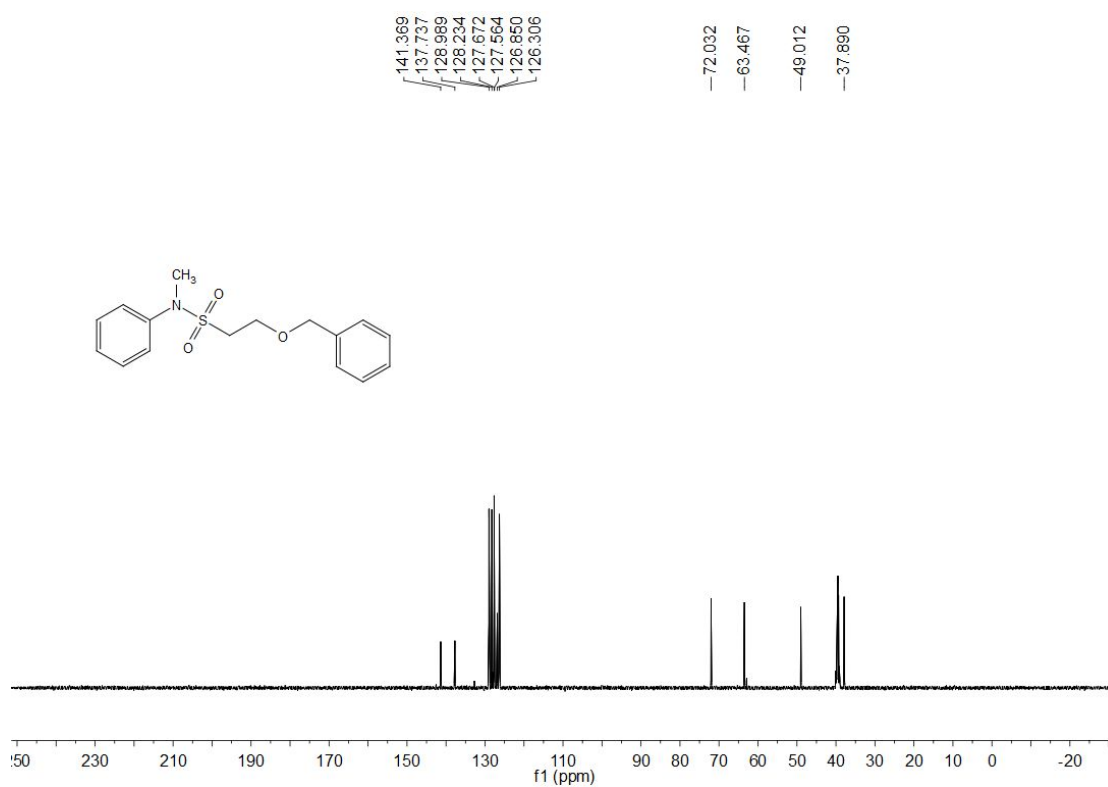
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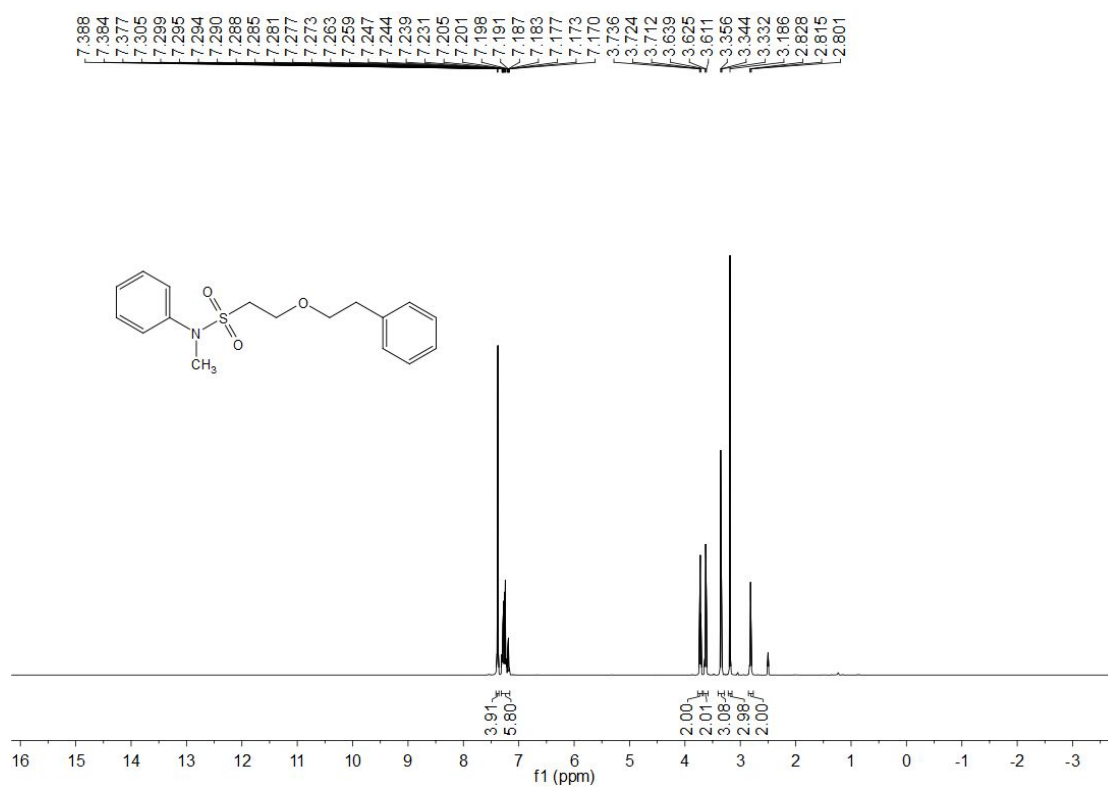
^1H NMR of compound 19



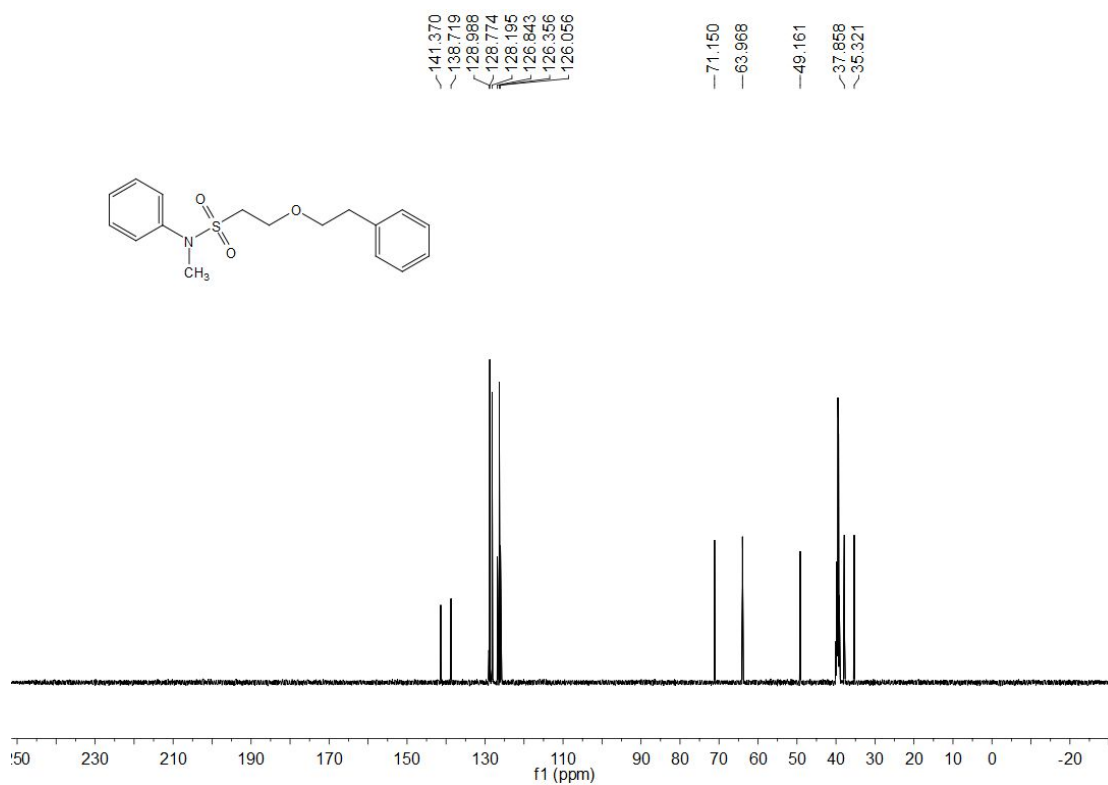
¹³C NMR of compound 19



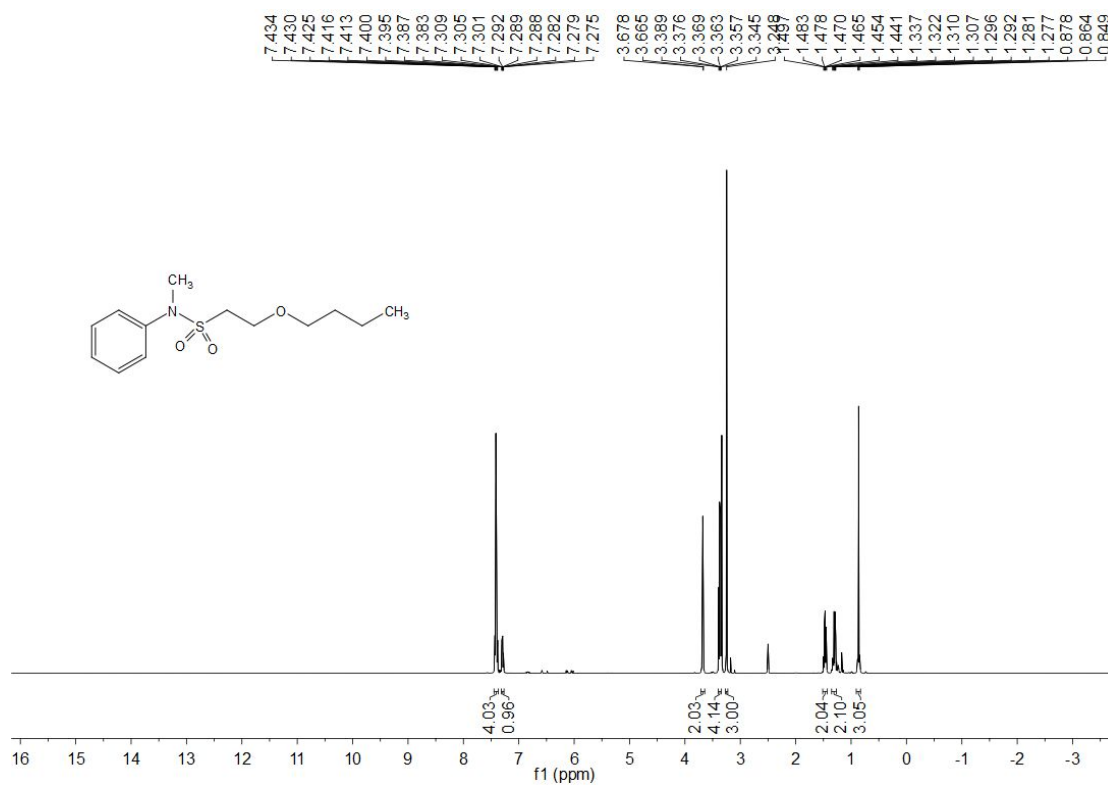
¹H NMR of compound 20



¹³C NMR of compound 20

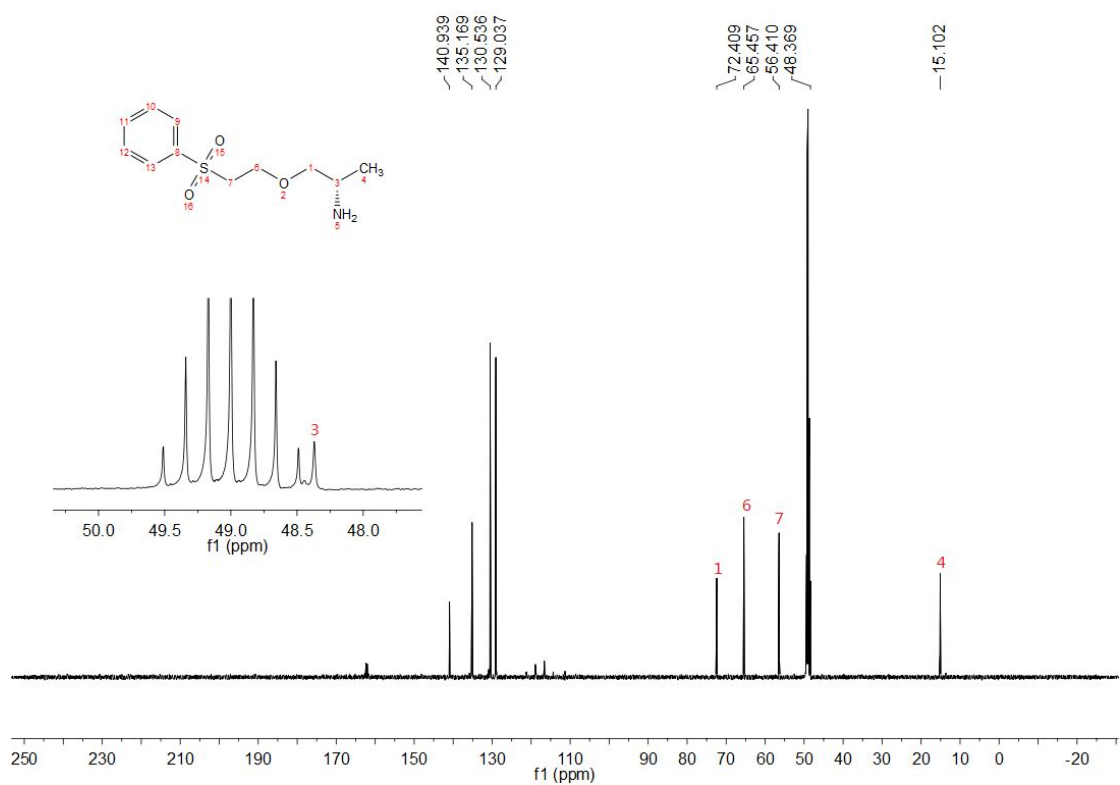


¹H NMR of compound 21

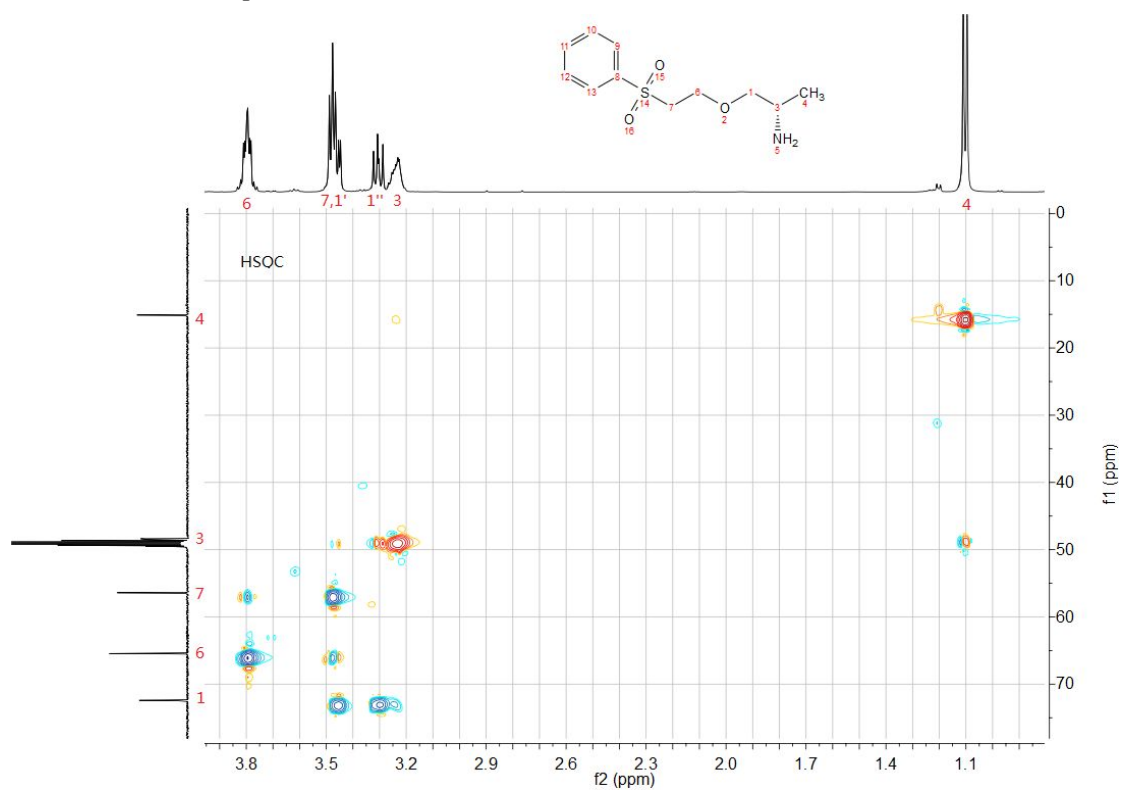


Chemical structure of 1-(4-ethoxyphenyl)ethan-1-yl phenyl sulfone (top) and its corresponding ¹³C NMR spectrum (bottom). The chemical structure is shown as a skeletal formula. The spectrum displays peaks at the following chemical shifts (ppm): 141.427, 129.002, 126.842, 126.283, 69.979, 63.839, 49.093, 37.876, 31.076, 18.725, and 13.697.

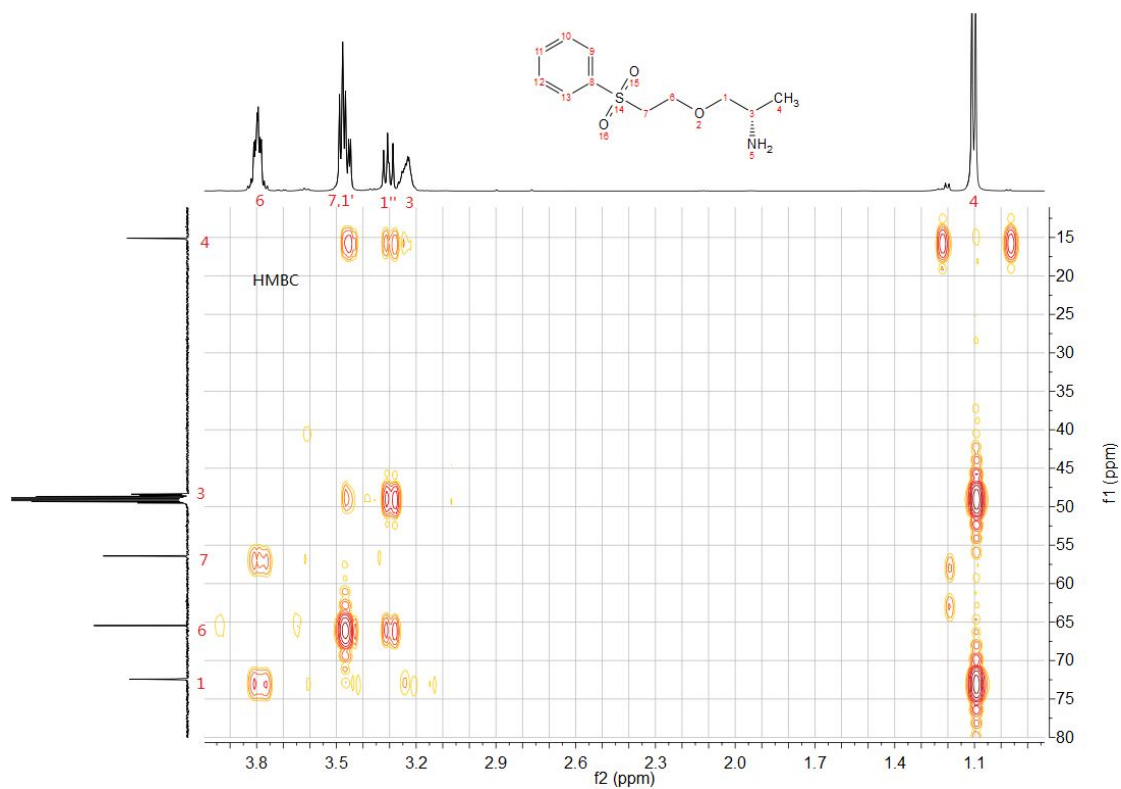
S61



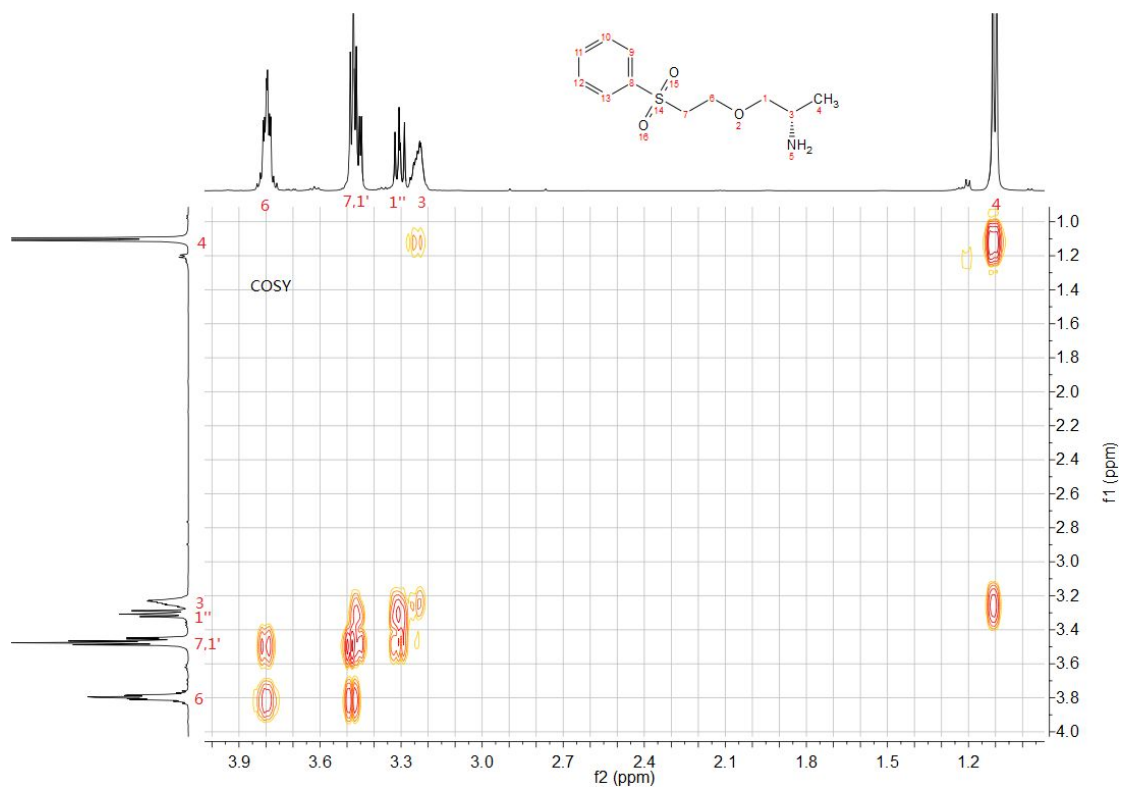
¹H-¹³C HSQC of compound 26-28-O-adduct



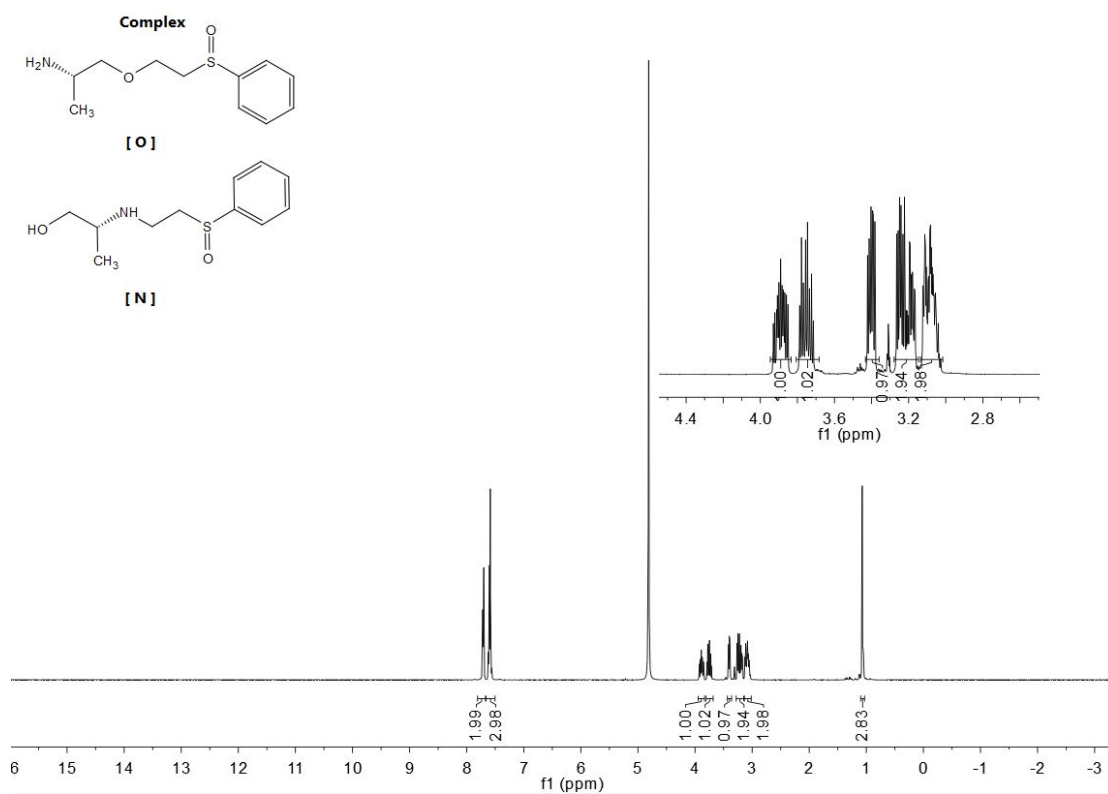
^1H - ^{13}C HMBC of compound 26-28-O-adduct



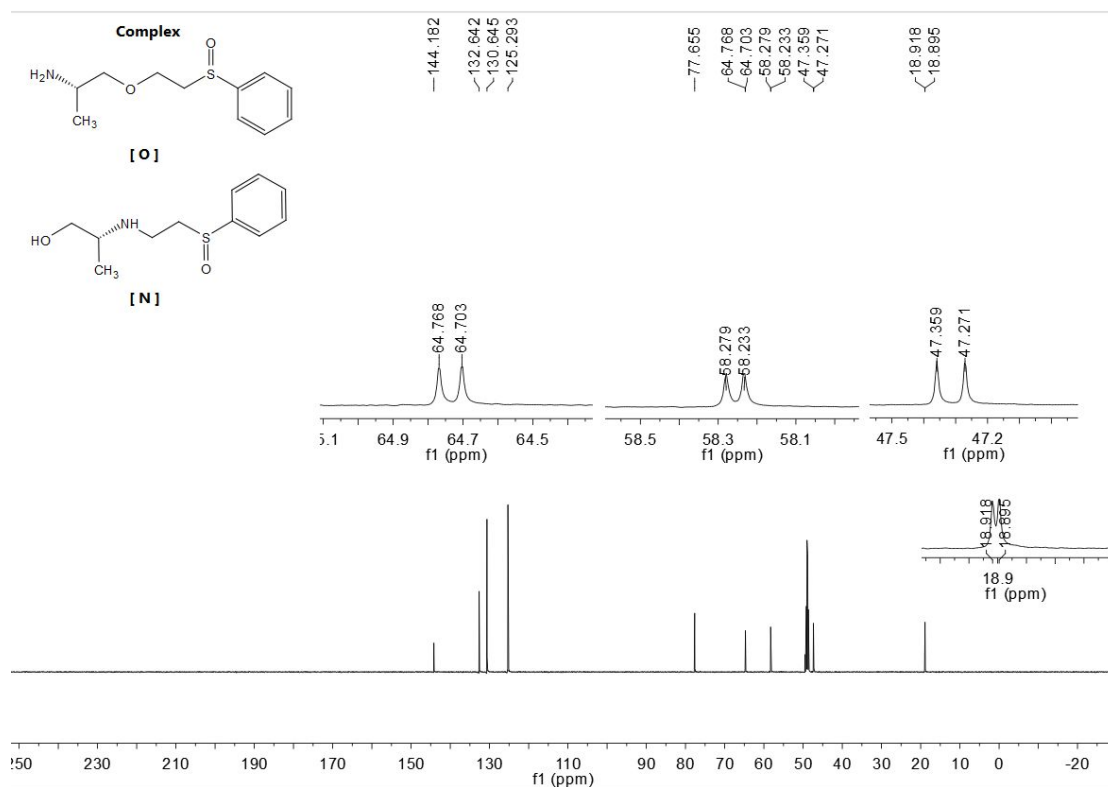
^1H - ^1H COSY of compound 26-28-O-adduct



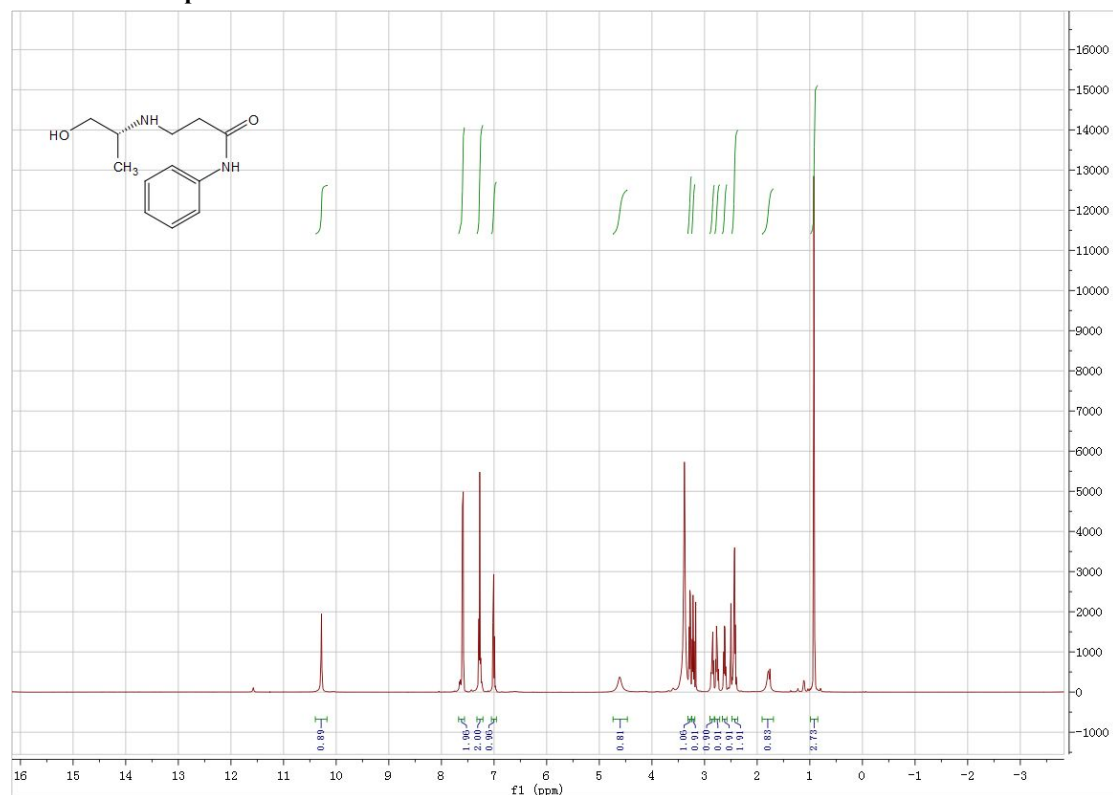
¹H NMR of compound 26-29-complex



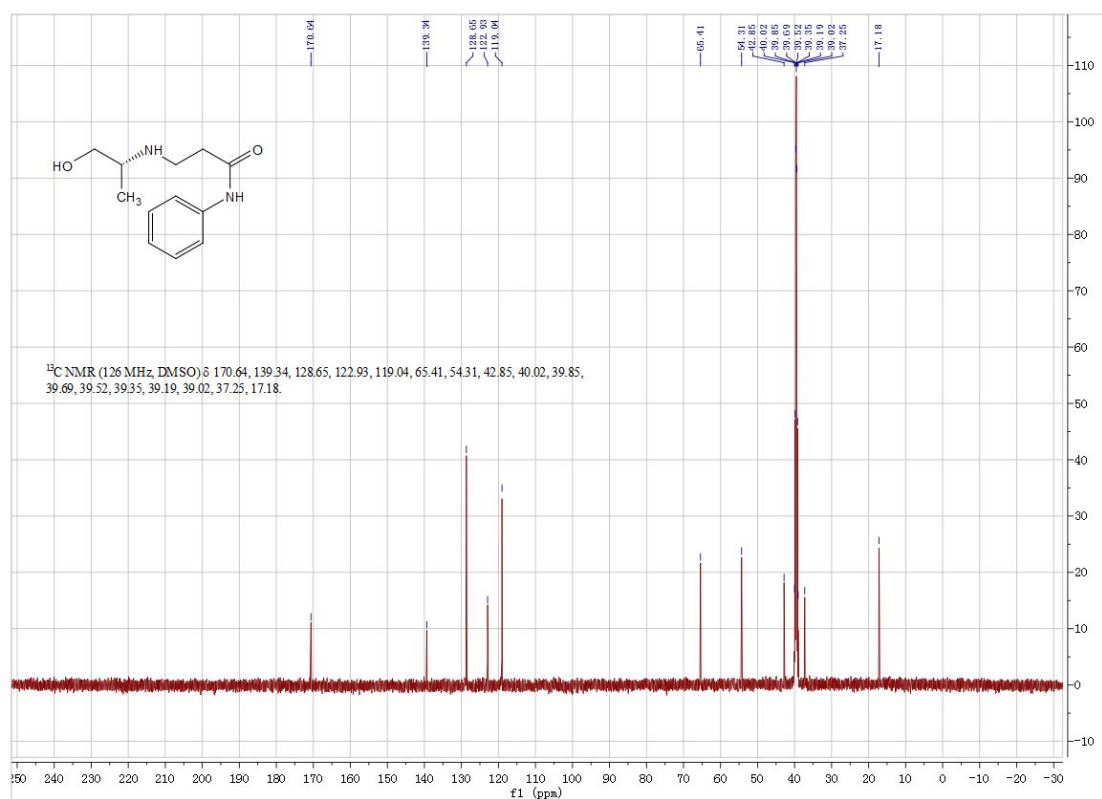
¹³C NMR of compound 26-29-complex



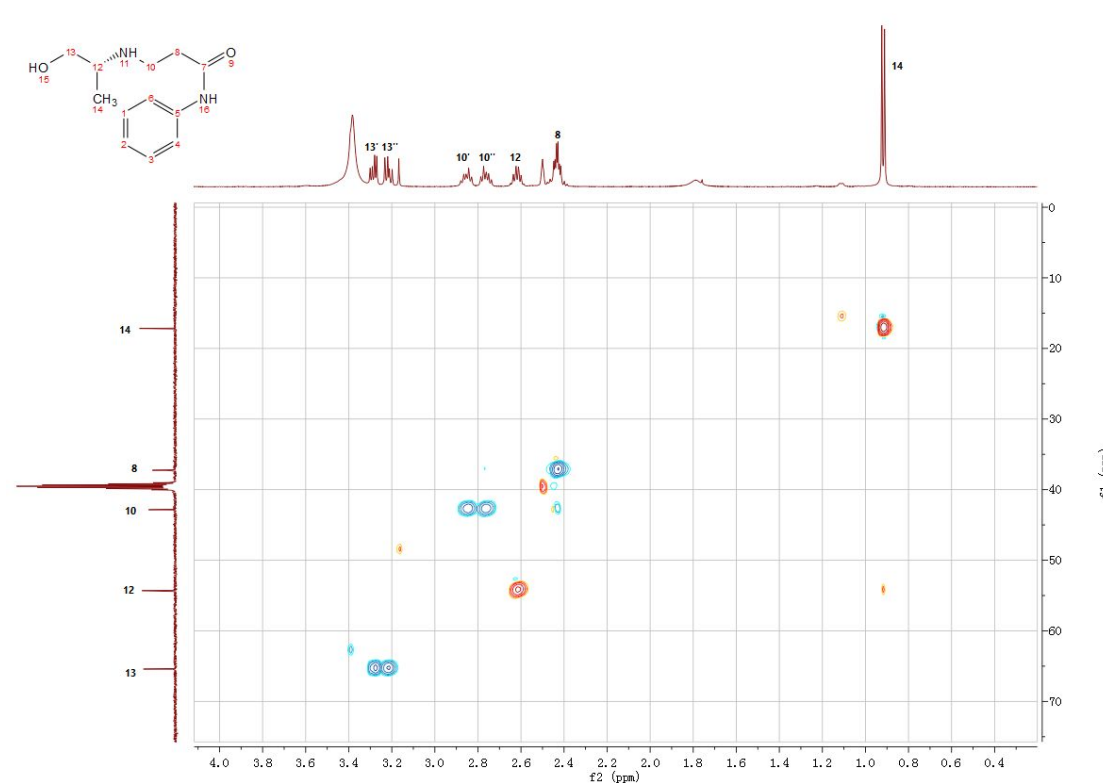
¹H NMR of compound 26-30-N-adduct



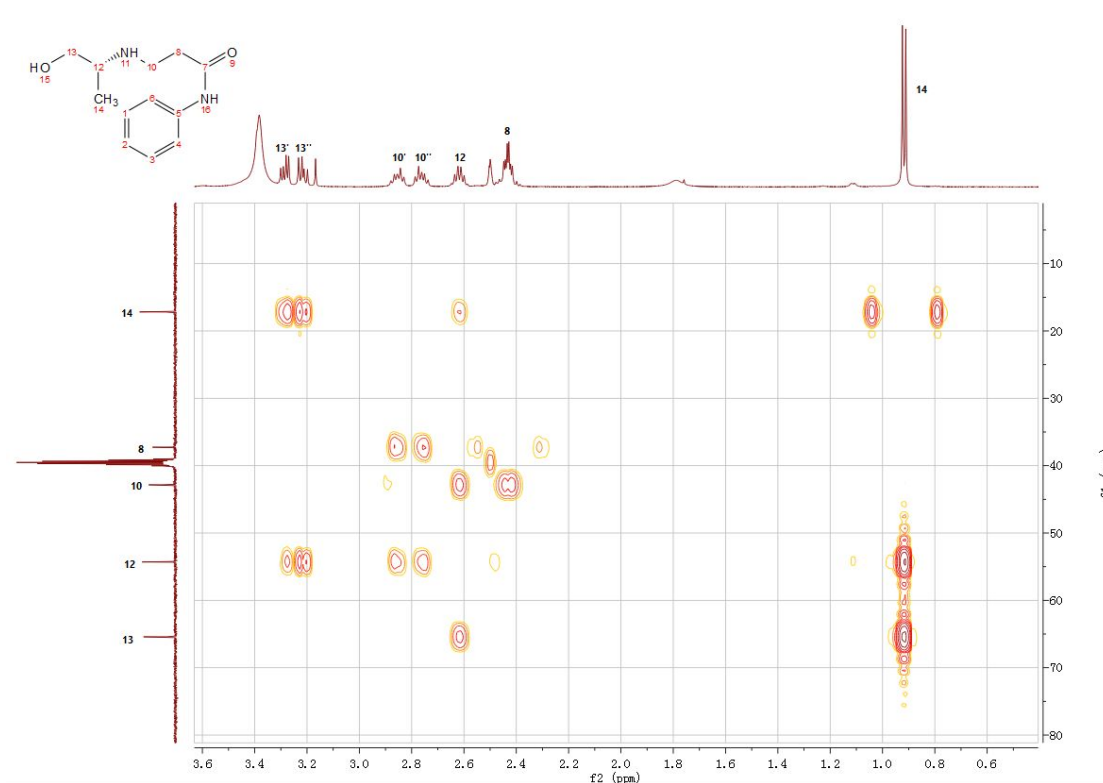
¹³C NMR of compound 26-30-N-adduct



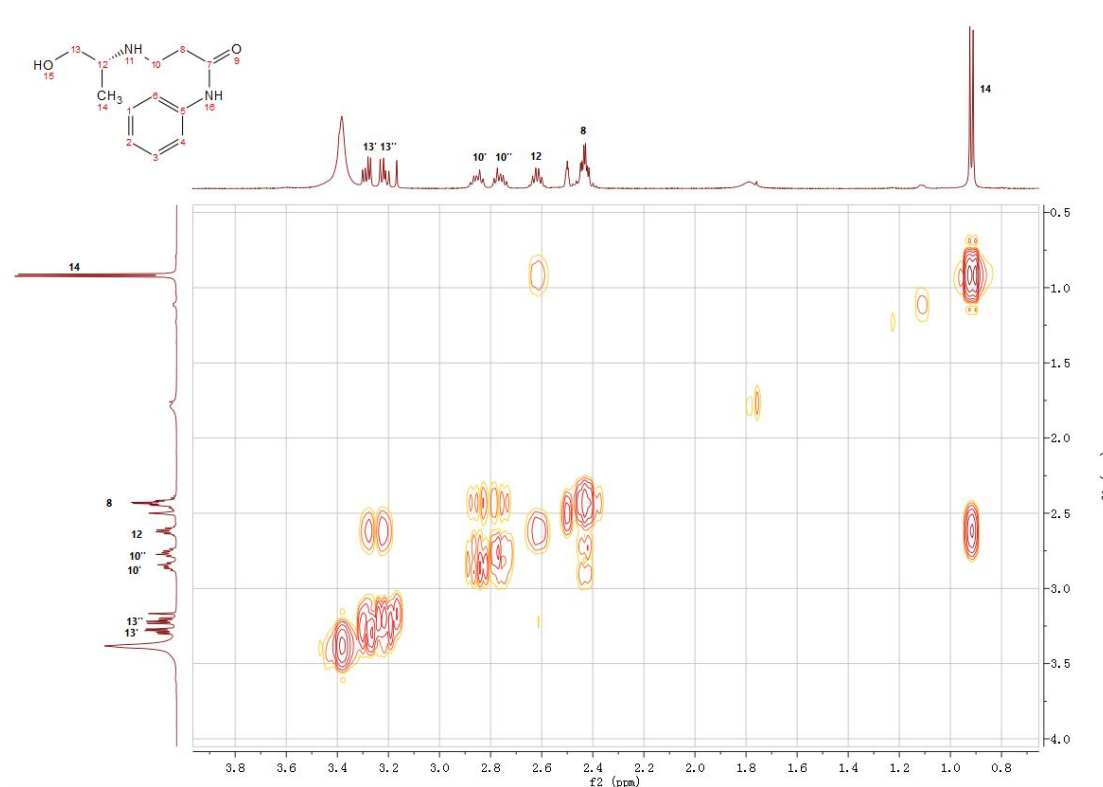
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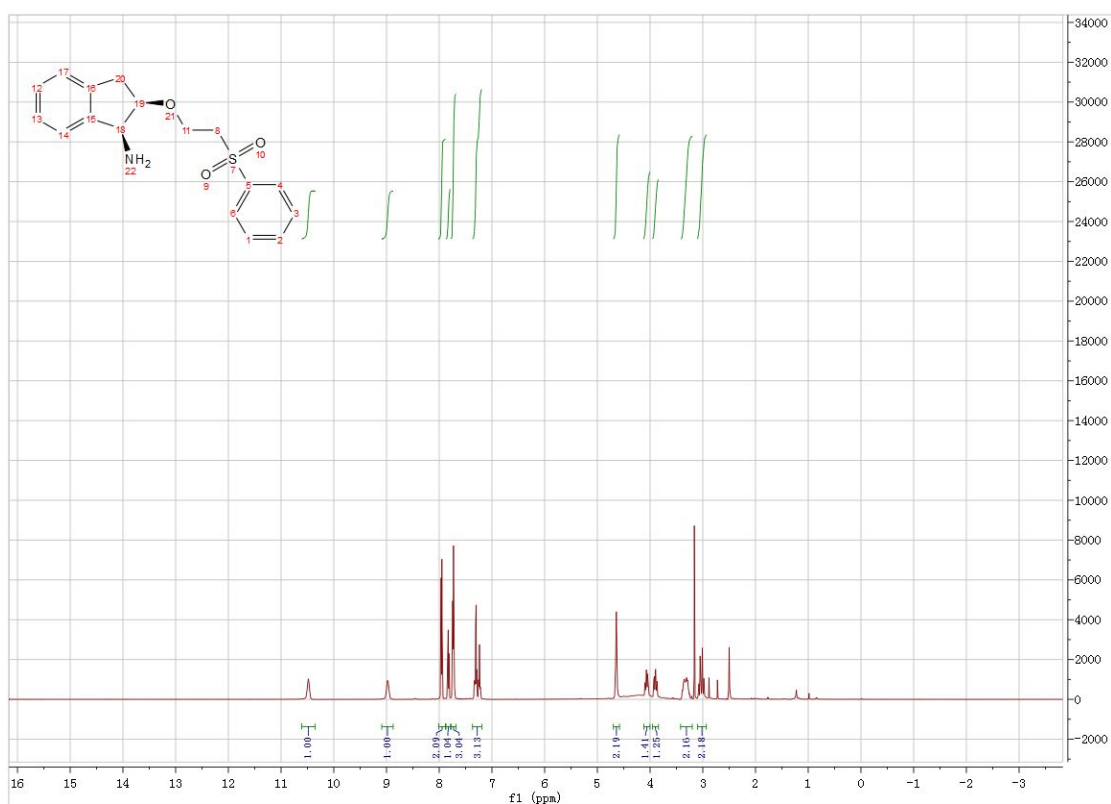
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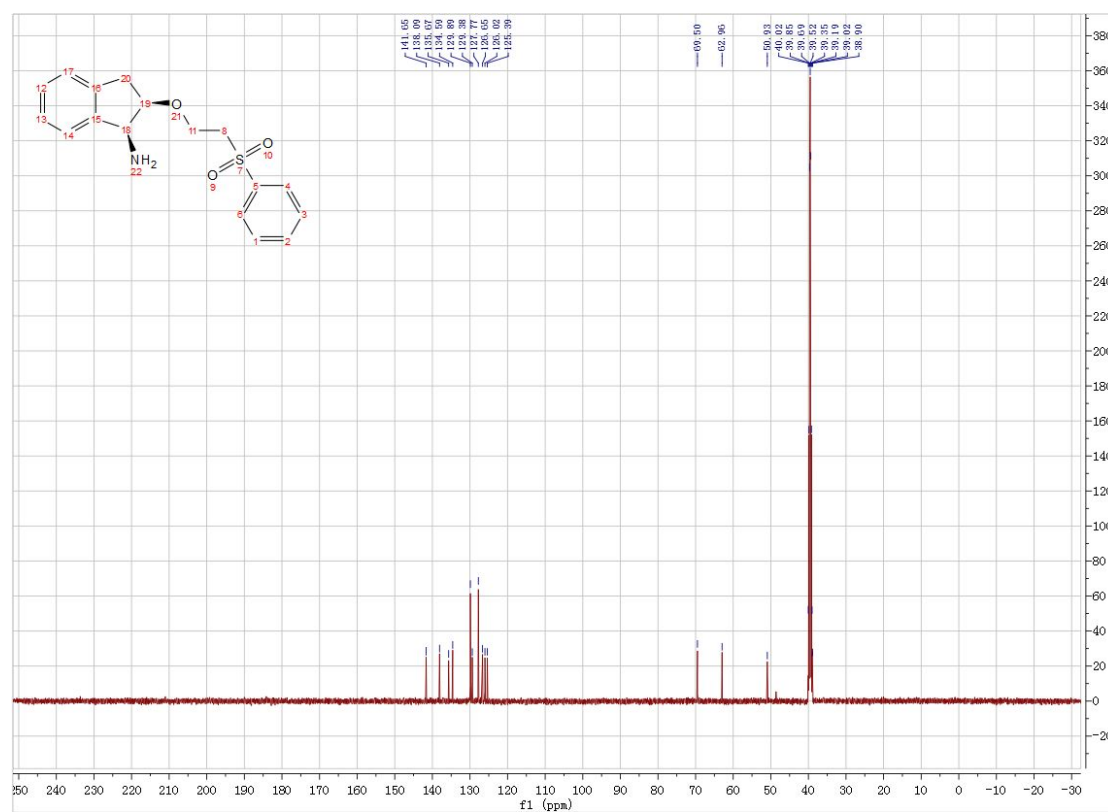
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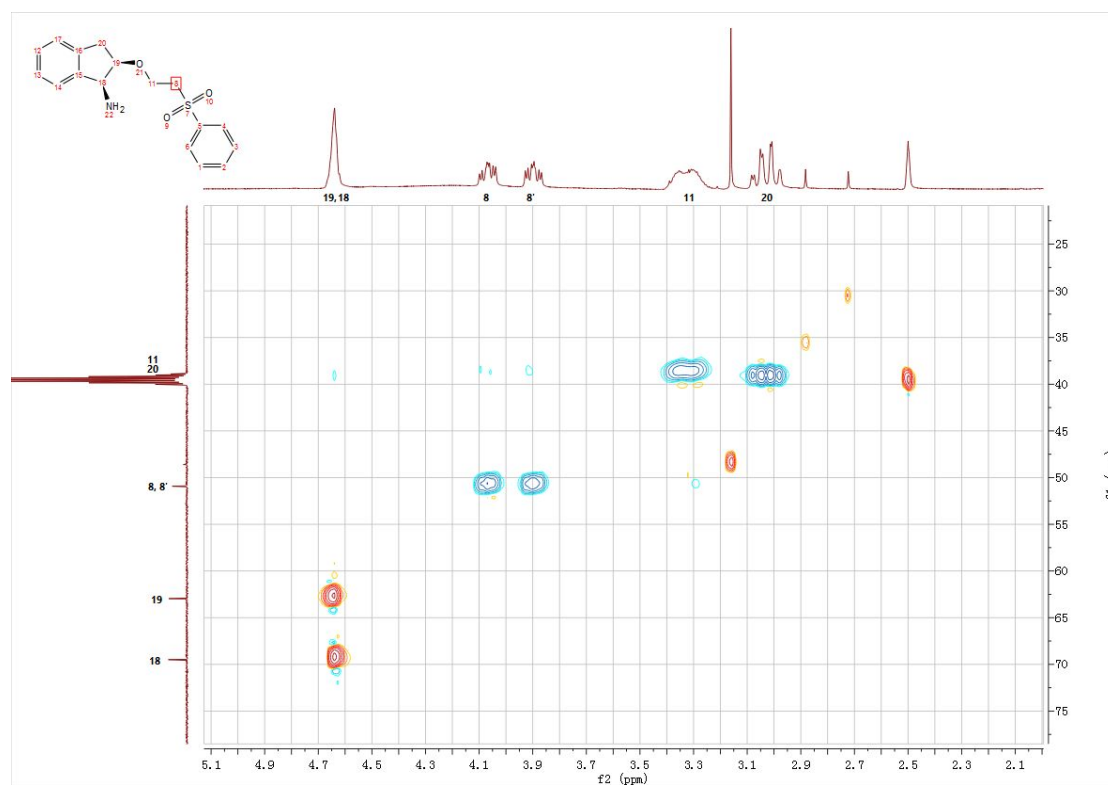
¹H NMR of compound 28-32-O-adduct



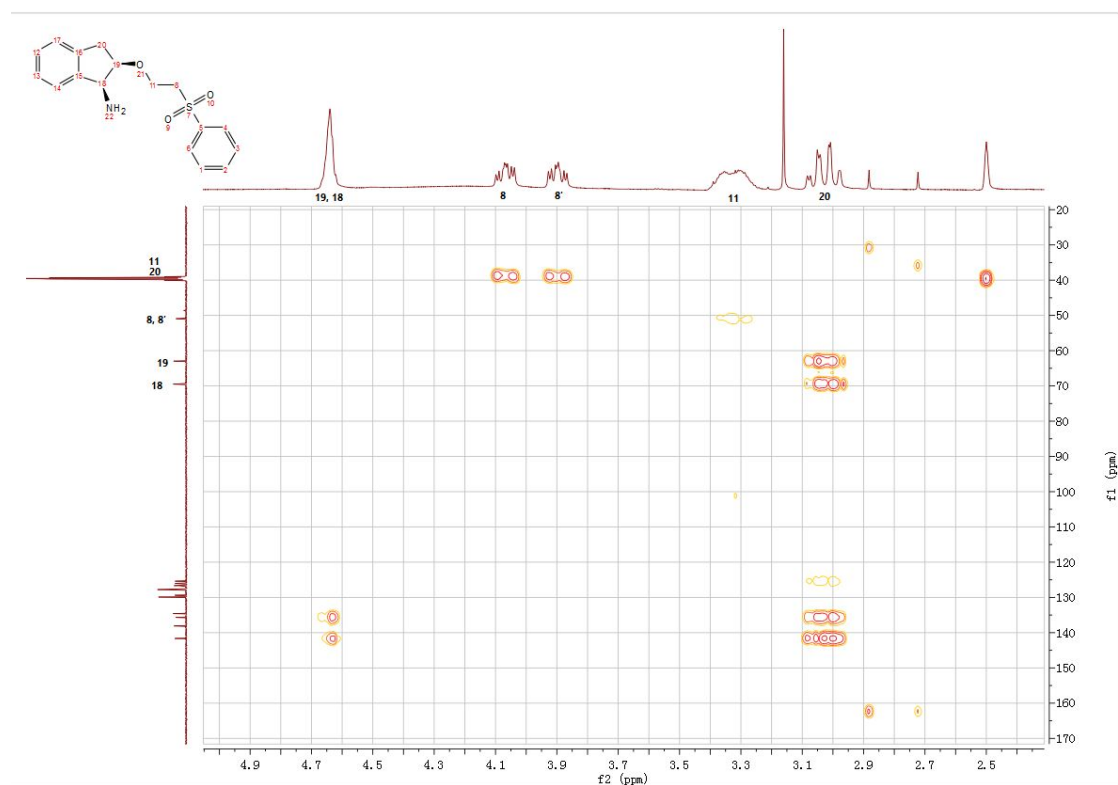
^{13}C NMR of compound 28-32-O-adduct



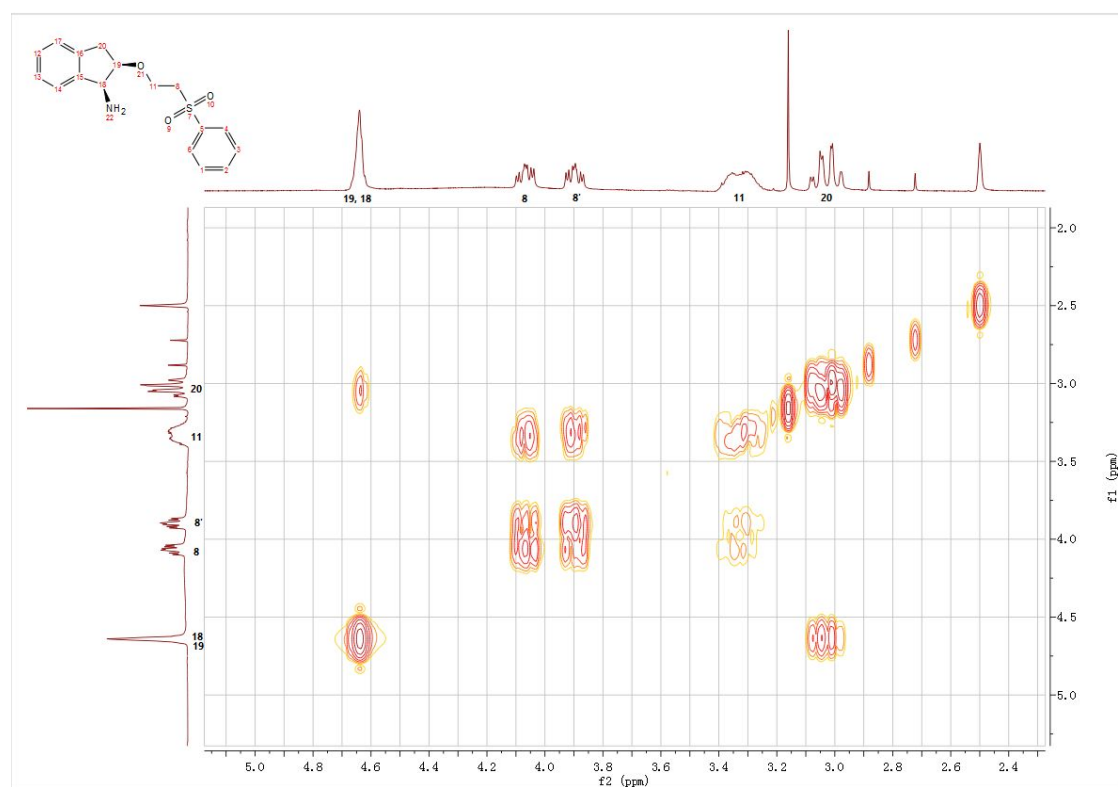
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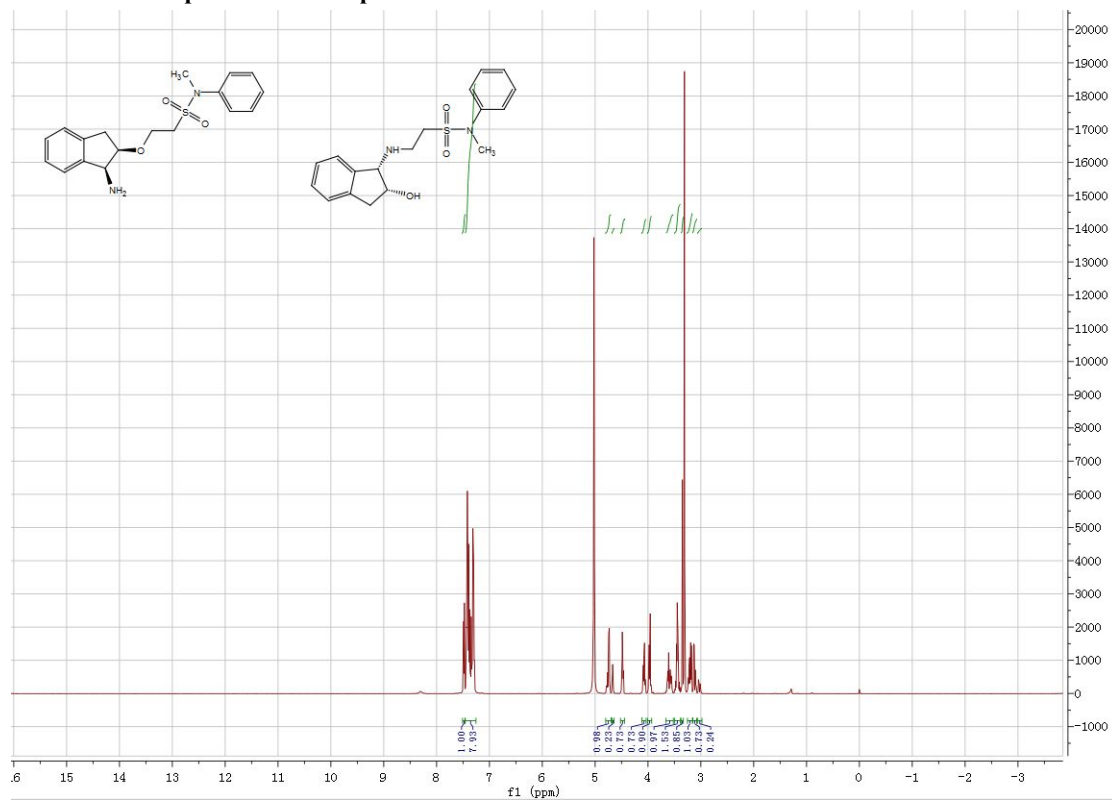
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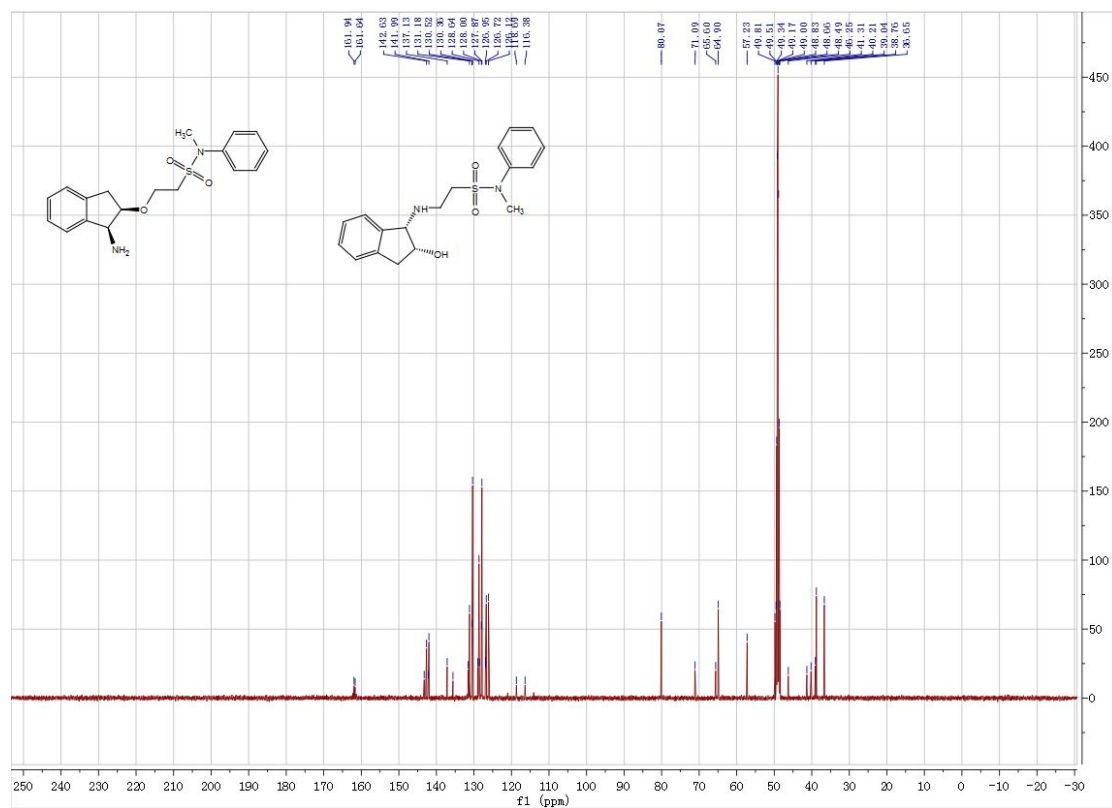
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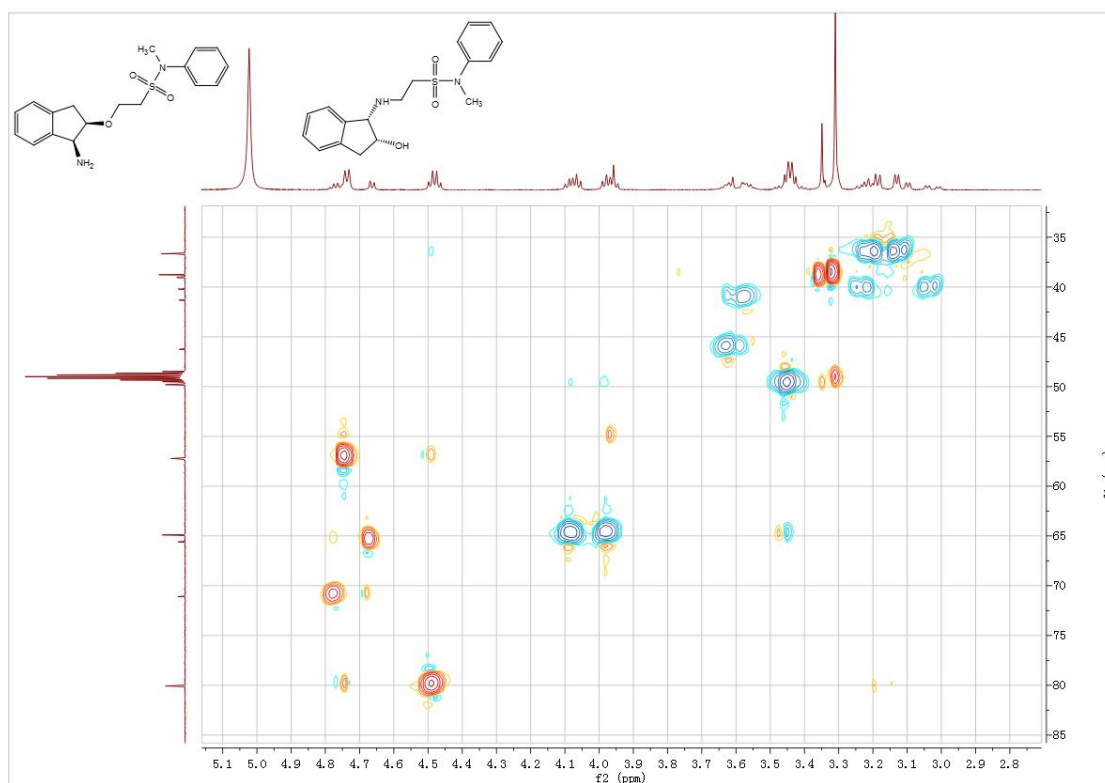
¹H NMR of compound 1-32-complex



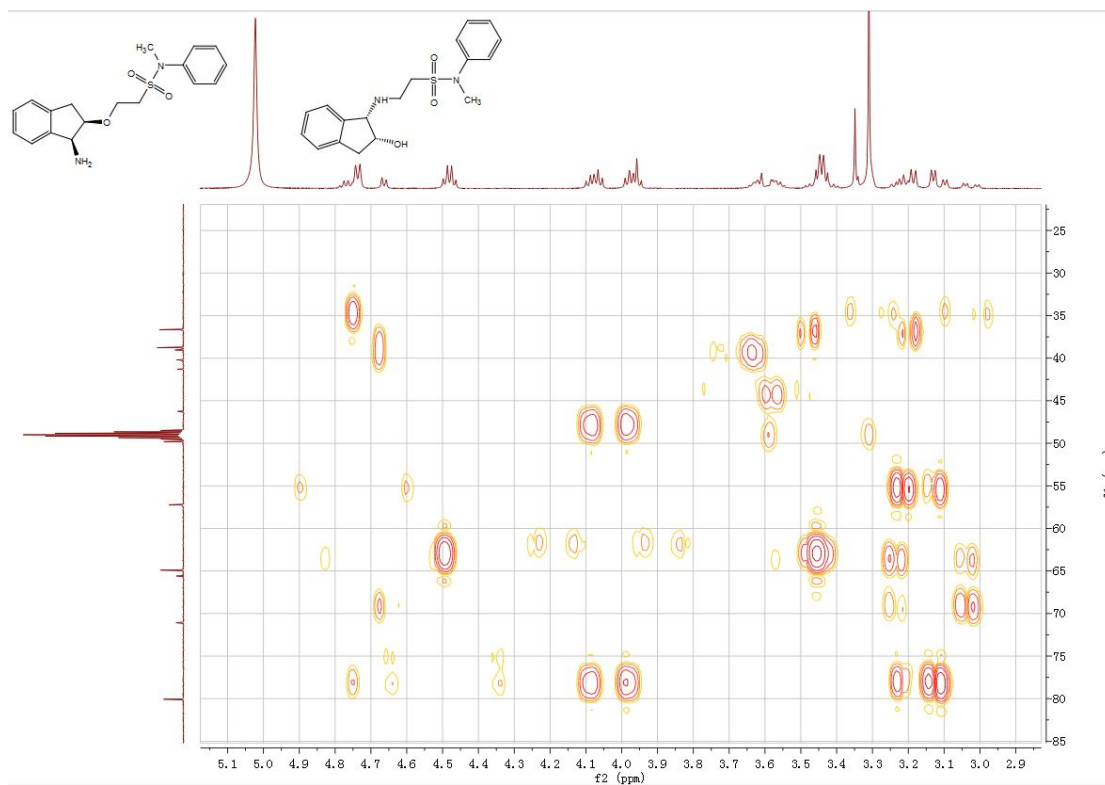
¹³C NMR of compound 1-32-complex



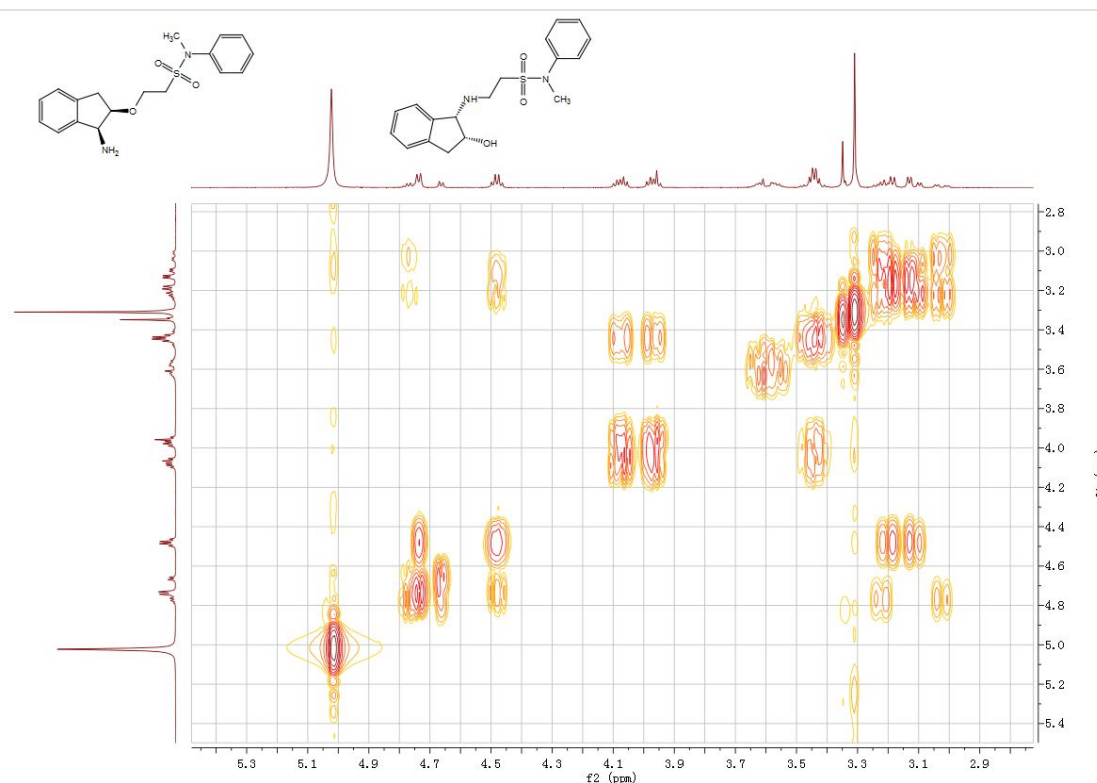
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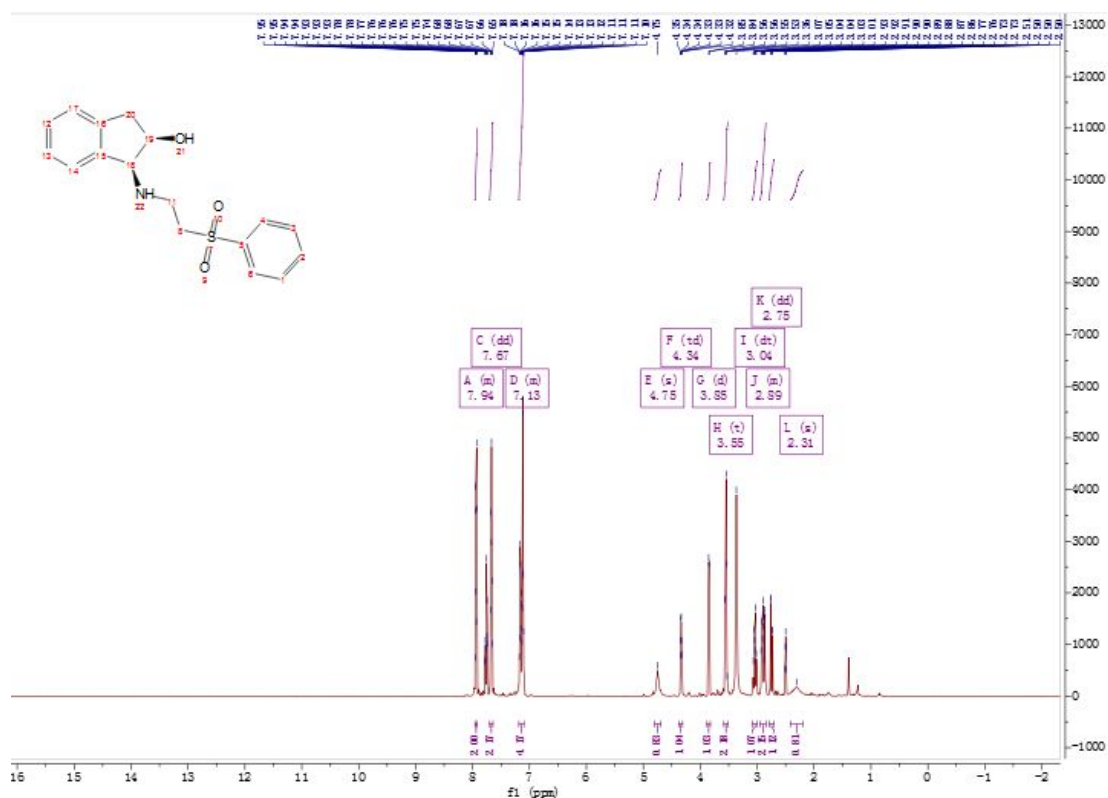
^1H - ^{13}C HMBC of compound 1-32-complex



¹H-¹H COSY of compound 1-32-complex



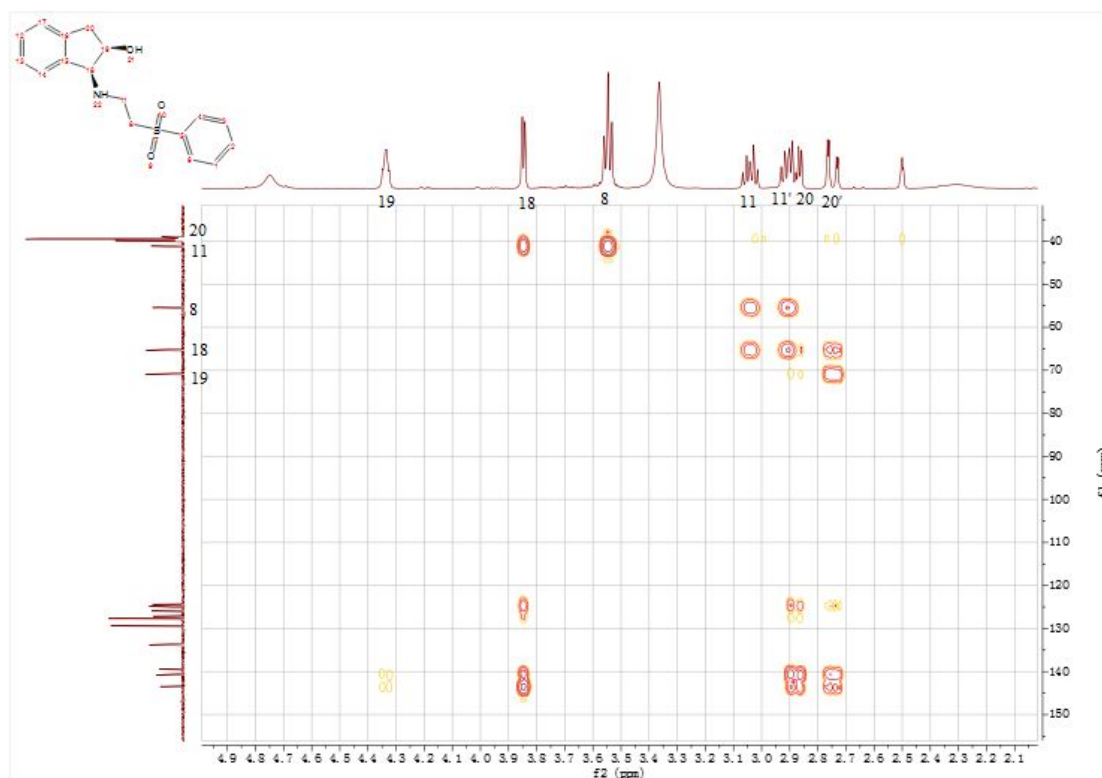
¹H NMR of compound 28-32-N-adduct



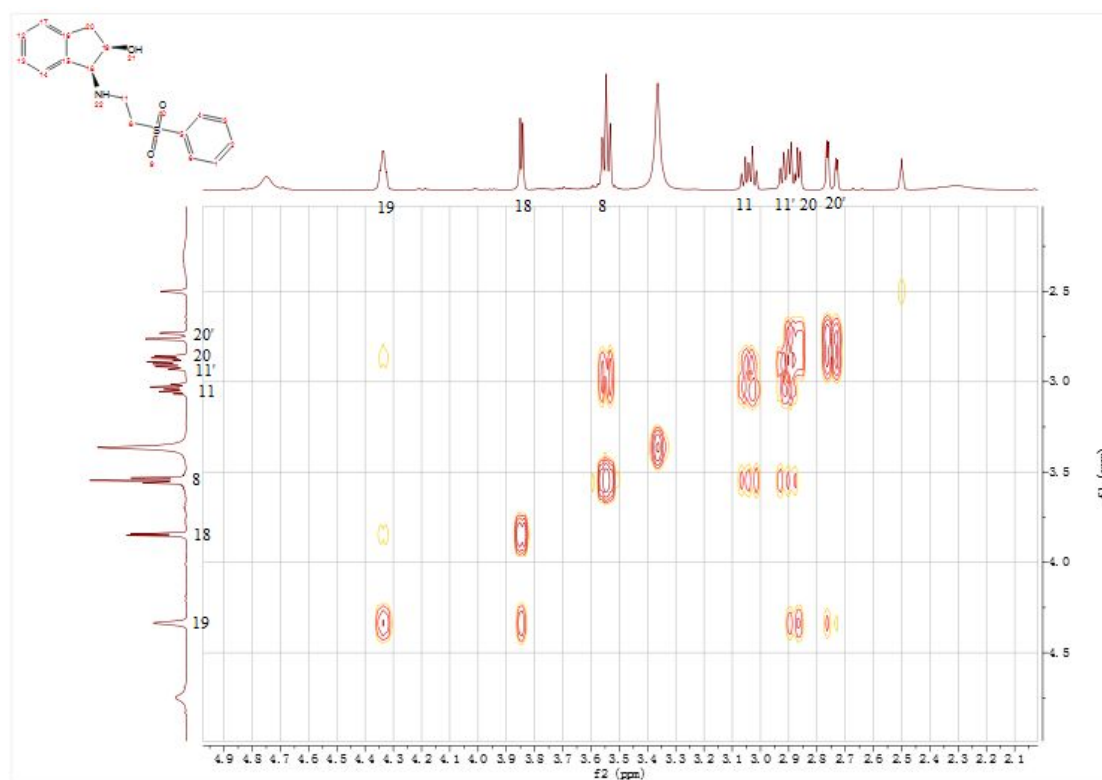
Chemical structure of compound 10 is shown in the top left. The ¹H NMR spectrum (CDCl₃) is displayed below, with peaks labeled by their chemical shifts (ppm):

- 143.46, 141.75, 139.36, 138.42, 137.70, 137.02, 135.46, 134.81, 134.37
- 70.91, 65.33, 55.44
- 41.16, 40.02, 39.29, 38.56, 37.83, 36.69, 35.29, 34.52, 33.79, 33.06, 32.29, 31.02, 30.29

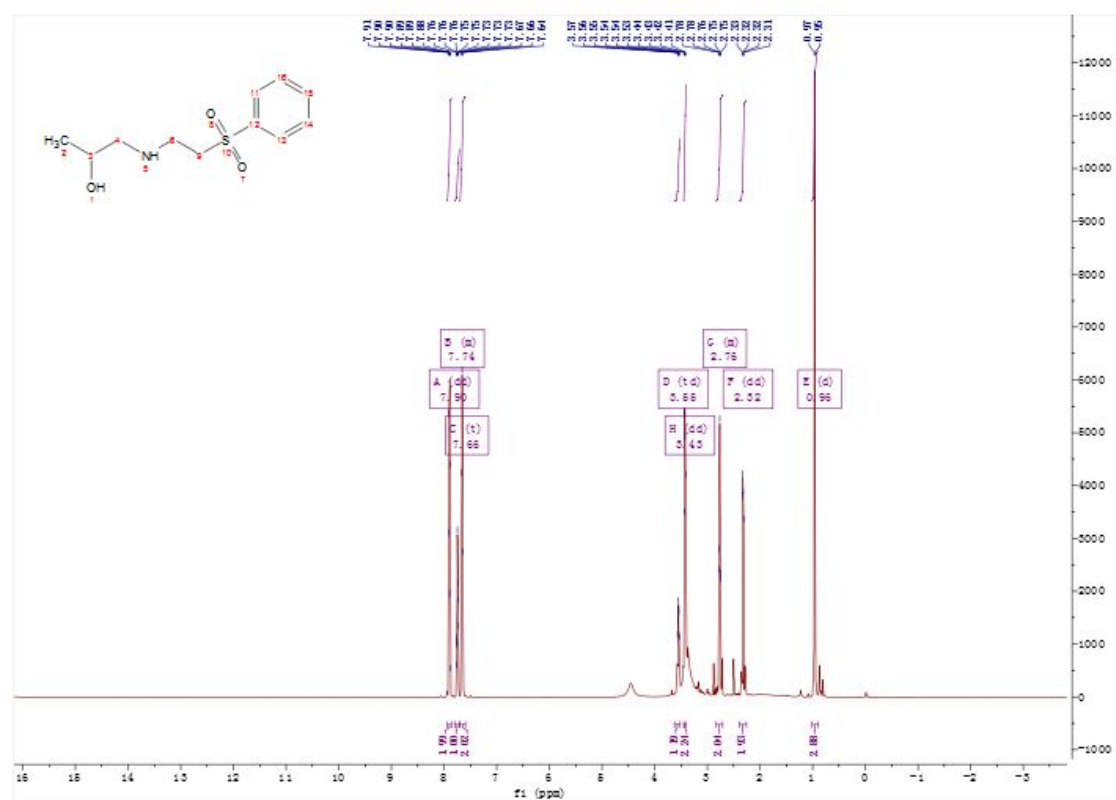
^1H - ^{13}C HMBC of compound 28-32-N-adduct



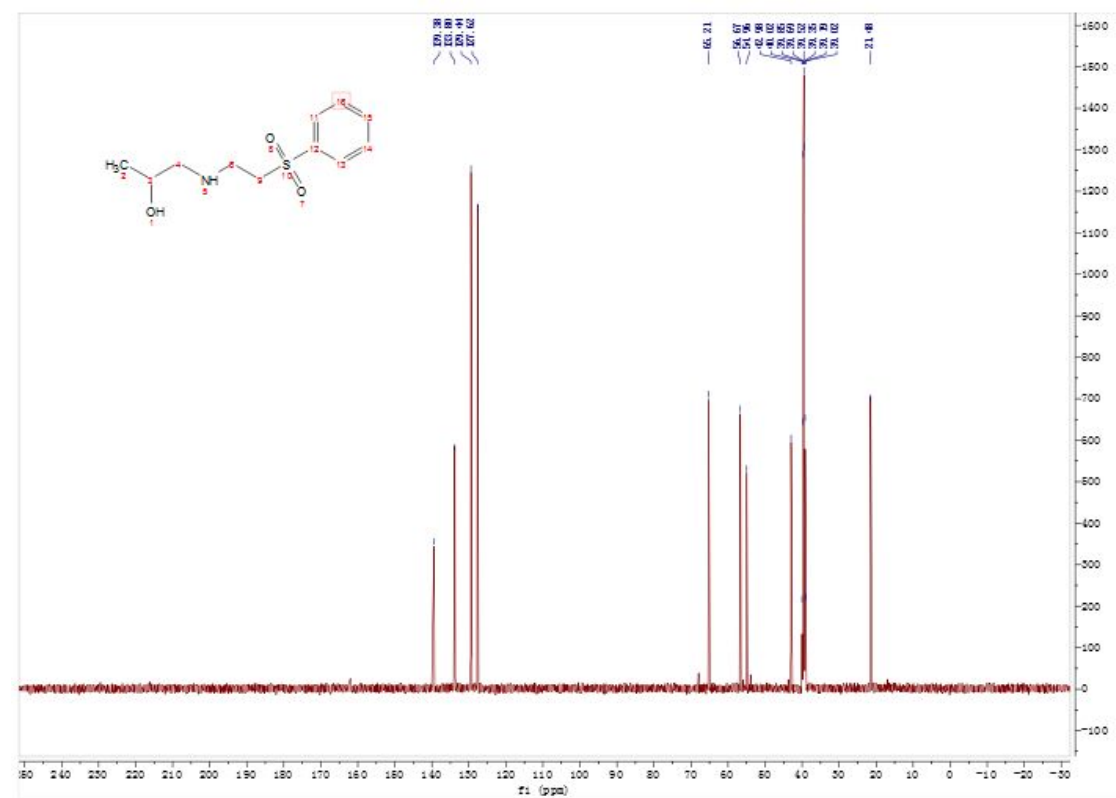
^1H - ^1H COSY of compound 28-32-N-adduct



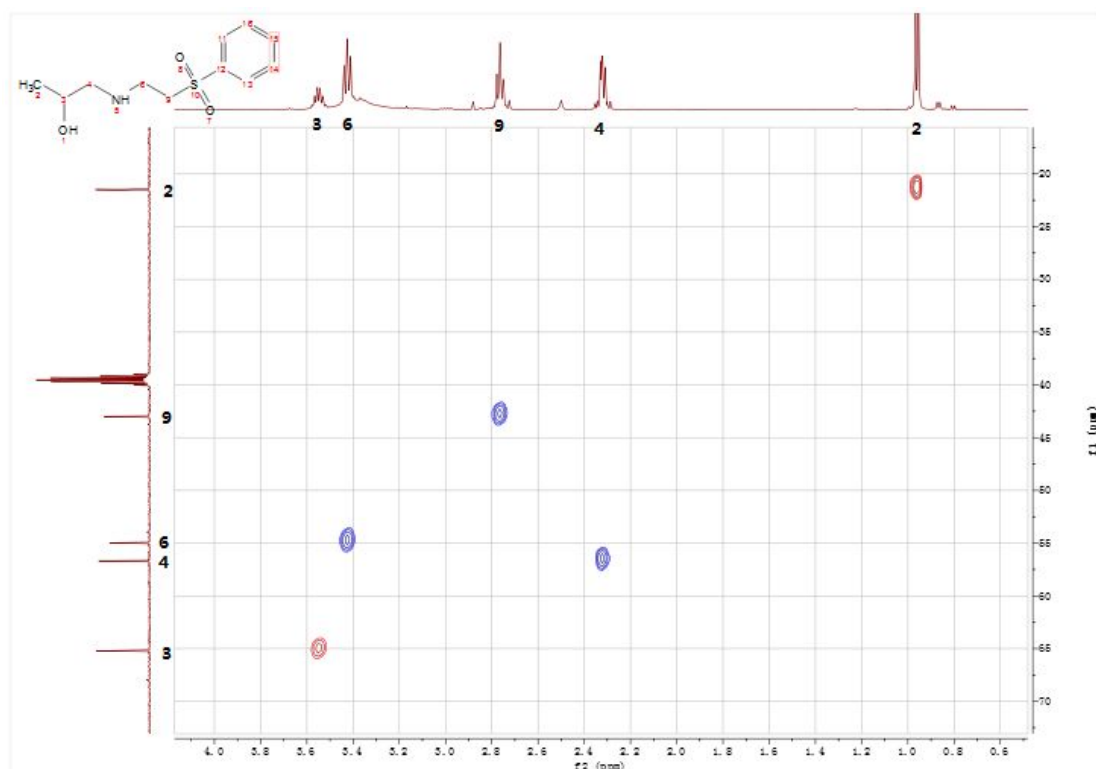
¹H NMR of compound 28-33-N-adduct



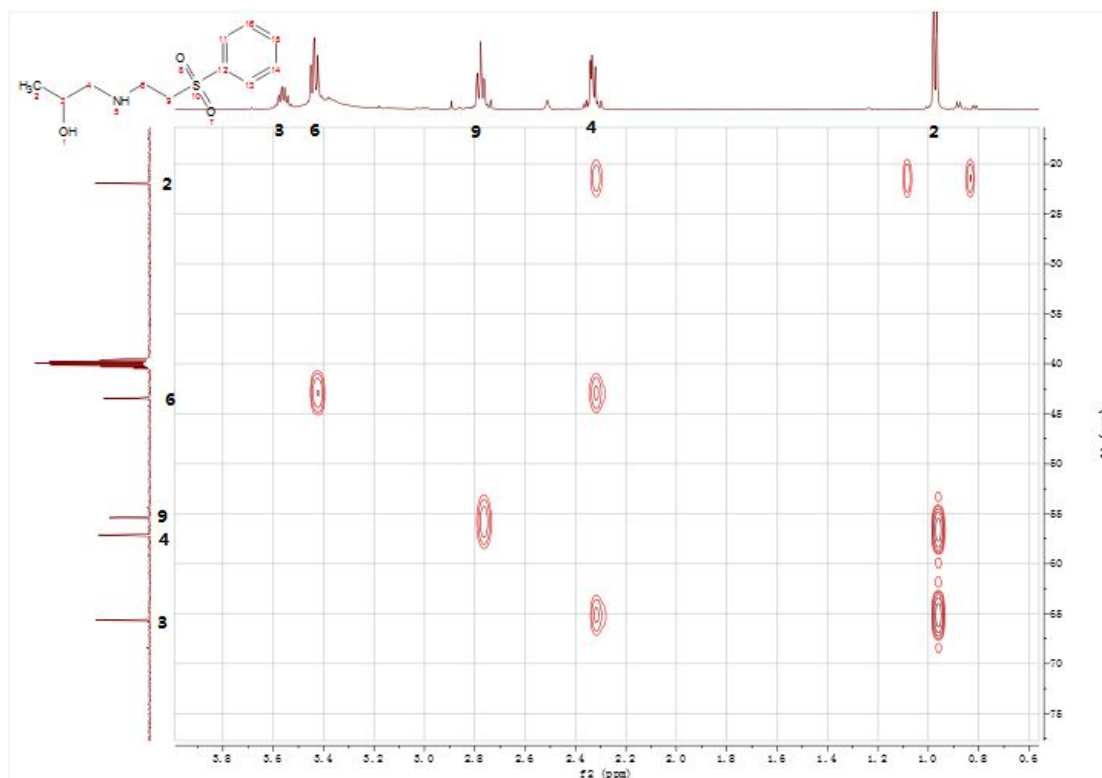
¹³C NMR of compound 28-33-N-adduct



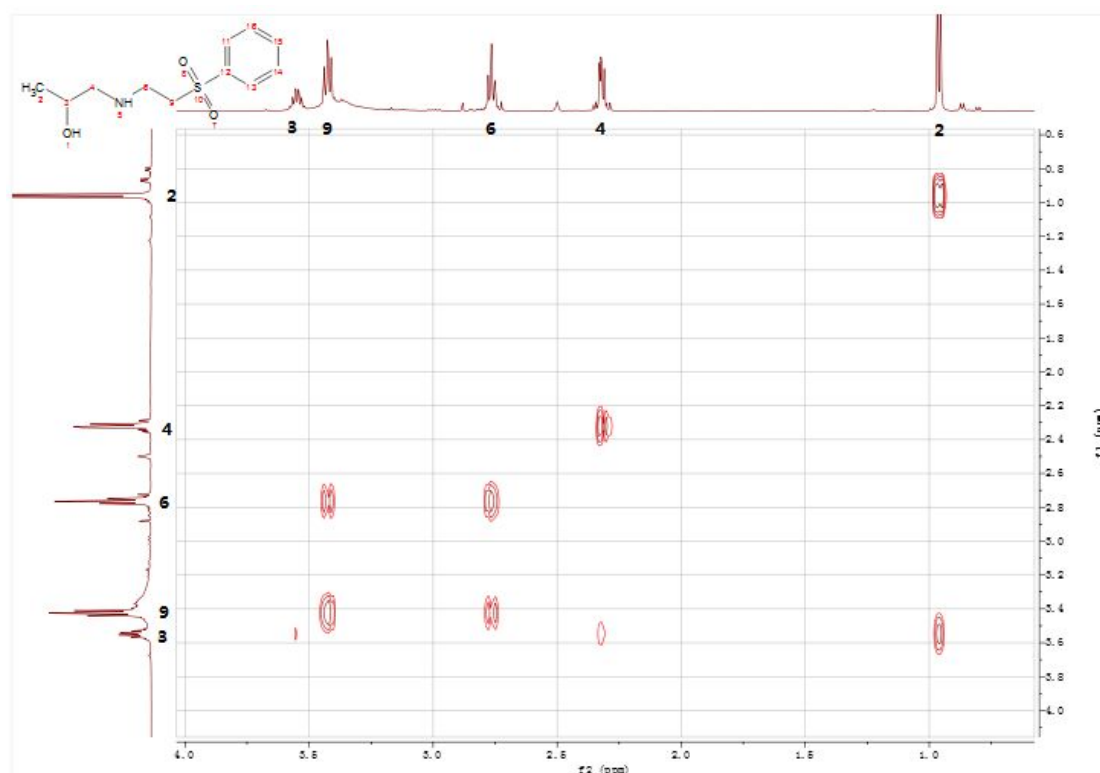
^1H - ^{13}C HSQC of compound 28-33-N-adduct



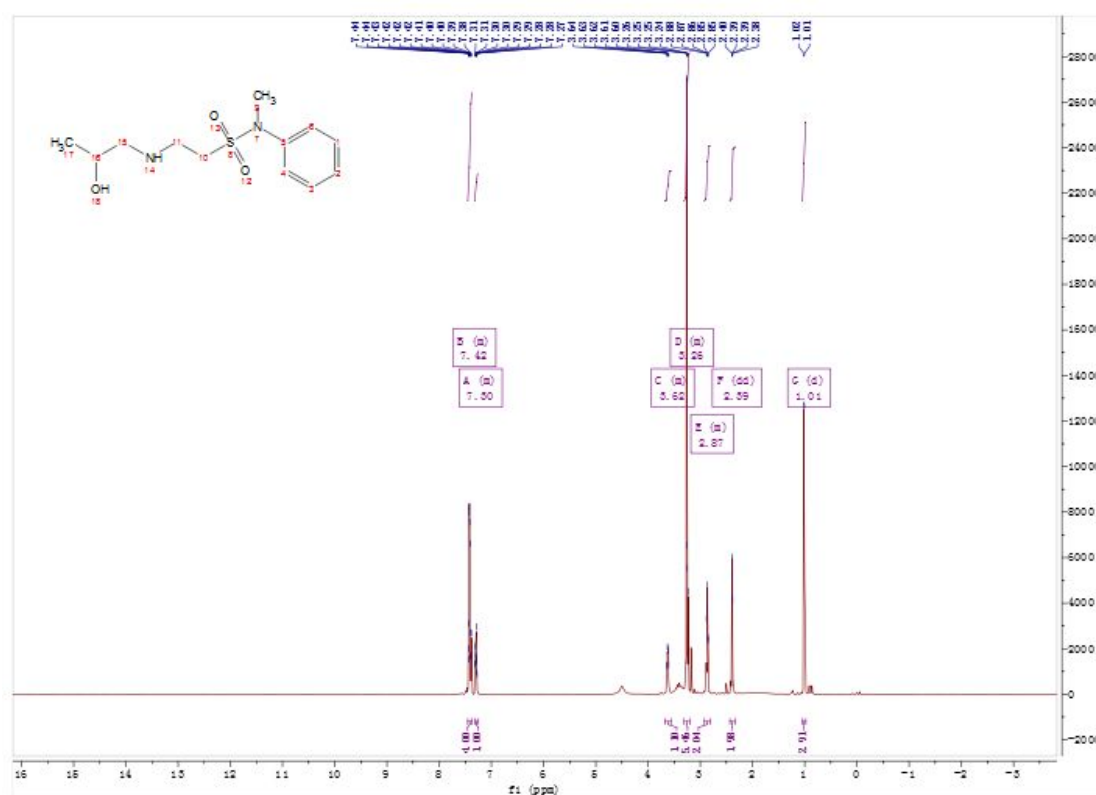
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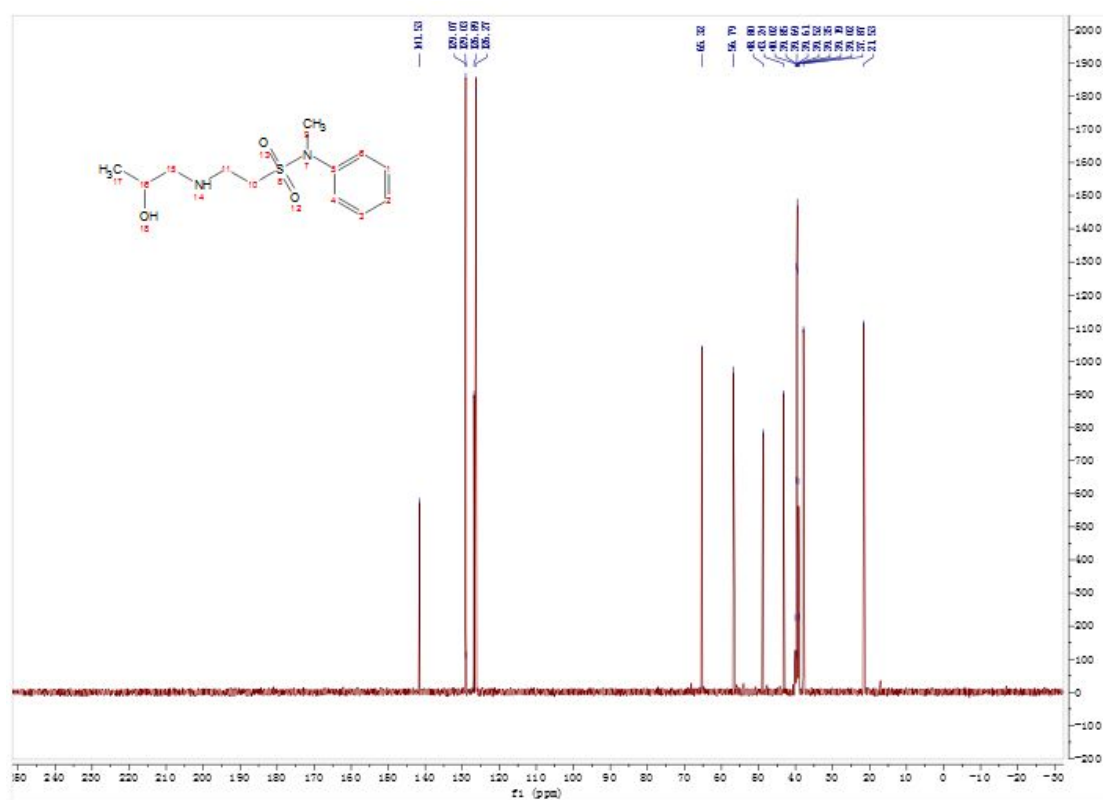
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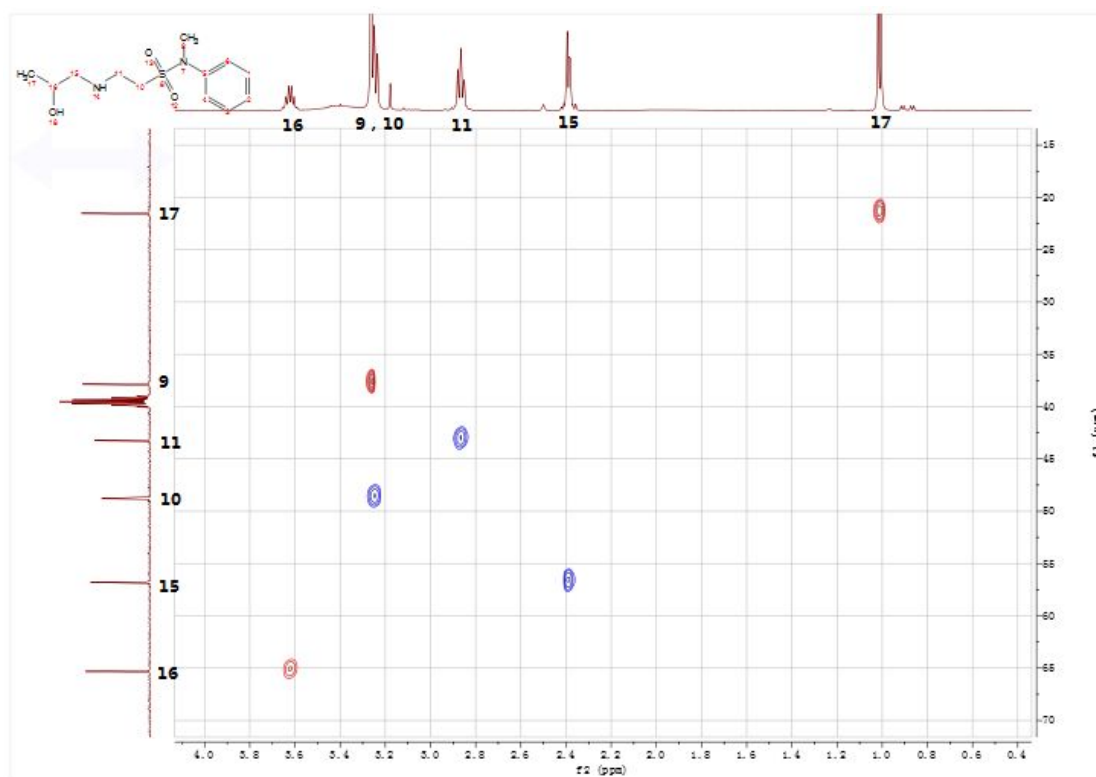
¹H NMR of compound 1-33-N-adduct



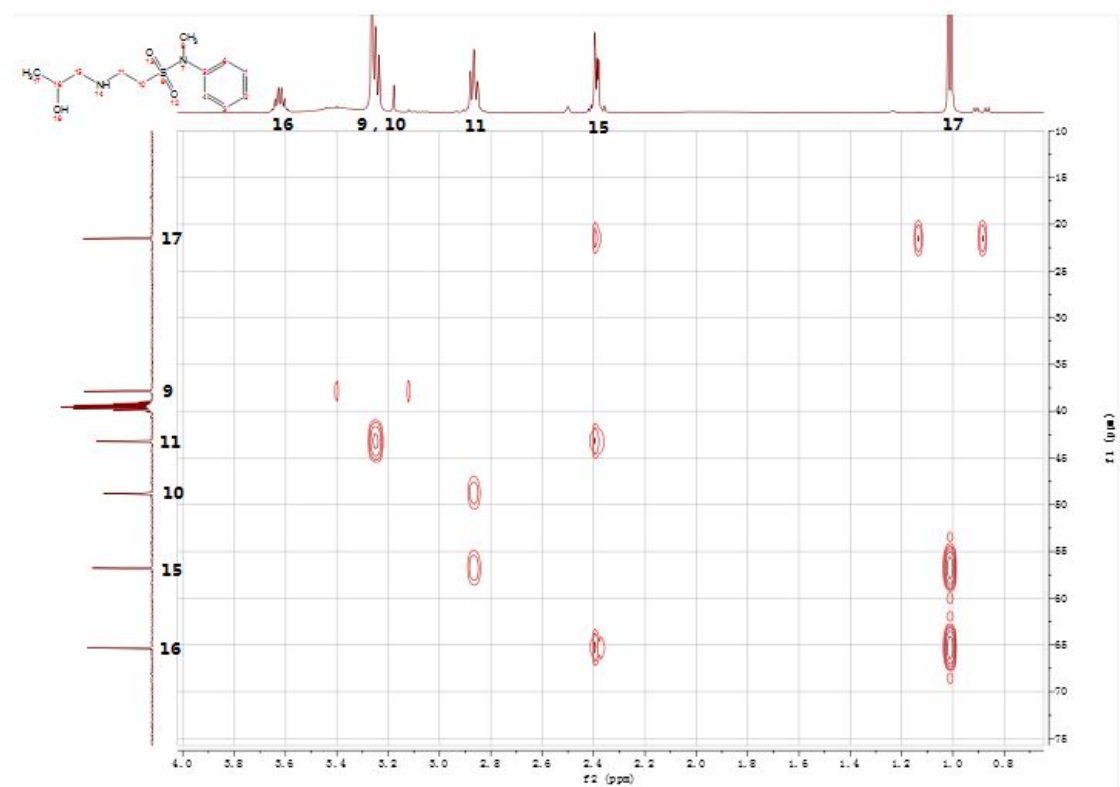
^{13}C NMR of compound 1-33-N-adduct



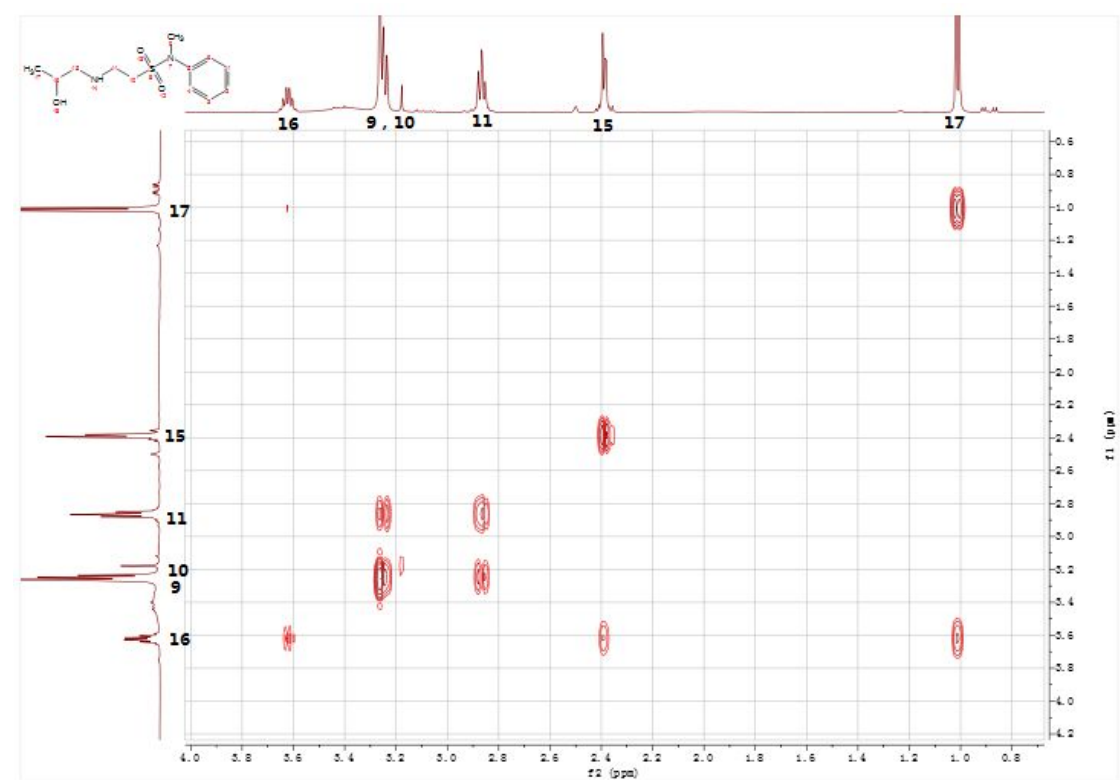
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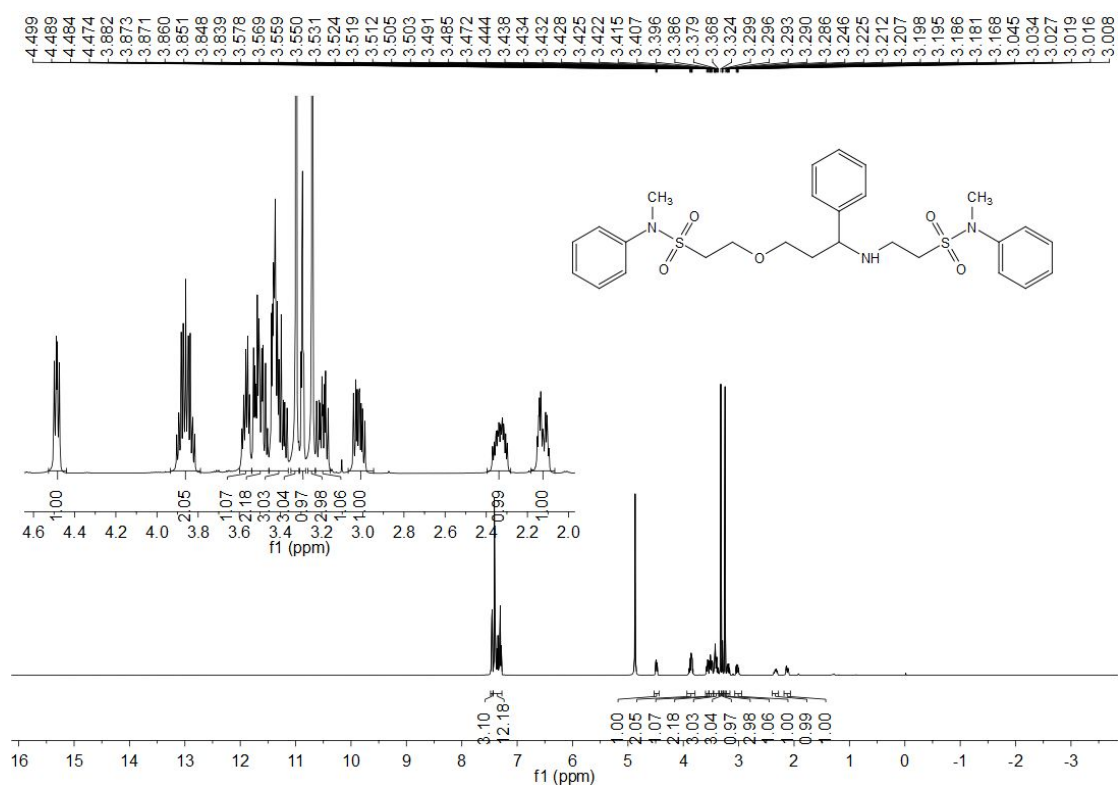
^1H - ^{13}C HMBC of compound 1-33-N-adduct



^1H - ^1H COSY of compound 1-33-N-adduct



¹H NMR of compound 34



¹³C NMR of compound 34

