Supporting Information

SAR studies of sulfonylpiperazine analogs as novel negative allosteric modulators of human neuronal nicotinic receptors

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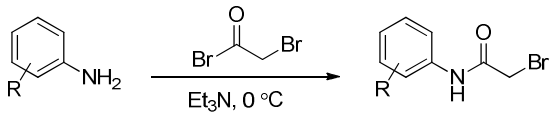
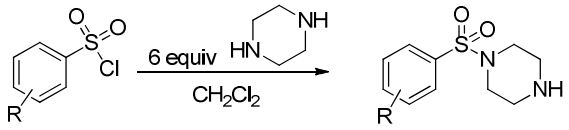
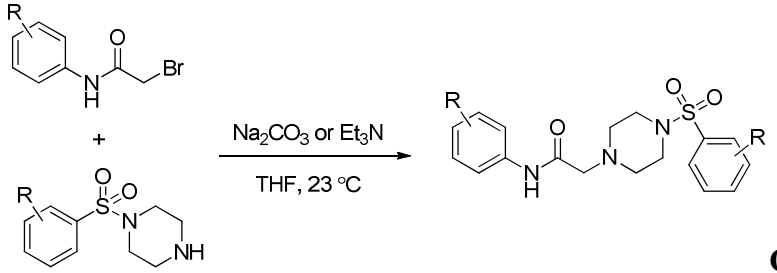


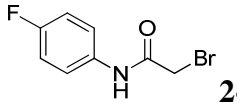
General Procedure A: Bromoacetyl bromide (10 mmol, 1 equiv) was added dropwise over 5 min to a solution of amine or alcohol (10 mmol, 1 equiv) and triethylamine (11 mmol, 1.1 equiv) in dichloromethane (50 mL, 0.2 M) at 0 ˚C. The reaction mixture was stirred at 0 ˚C for 20 min to 1 h, diluted with dichloromethane (50 mL), washed with saturated NH_4Cl (3 x 30 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford crude product. The crude product was purified by flash column chromatography, crystallization, or trituration to yield pure *N*-aryl-2-bromoacetamide (26% to 96%).



General Procedure B: Arylsulfonyl chloride (10 mmol, 1 equiv) was added in one portion to a solution of piperazine (60 mmol, 6 equiv) in CH_2Cl_2 (100 mL, 0.1 M) at 0 ˚C. The reaction mixture was stirred at 0 ˚C for 30 min, diluted with CH_2Cl_2 (200 mL), quenched by the addition of saturated $NaHCO_{3(aq)}$ (50 mL), washed with brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo* to provide crude product. The crude product was used directly, or purified by crystallization or trituration to yield pure arylsulfonylpiperazine (75% to quant).

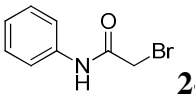


General Procedure C: Sodium carbonate (0.4 mmol, 2 equiv) or triethylamine (0.4 mmol, 2 equiv) was added to a solution of *N*-aryl-2-bromoacetamide (0.2 mmol, 1 equiv) and arylsulfonyl piperazine (0.2 mmol, 1 equiv) in THF (1 mL, 0.2 M) at 23 ˚C. The reaction mixture was allowed to stir for 16 h, diluted with CH_2Cl_2 (5 mL), filtered, and concentrated *in vacuo* to afford crude product. The crude product was purified by flash column chromatography to yield pure product (48% to 86%) which was converted to the HCl or MsOH salt for biological testing.

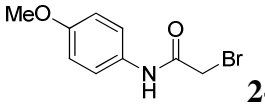


2-bromo-*N*-(4-fluorophenyl)acetamide (S1): Following general procedure A, the crude product was used directly as a brown solid (96%). Analytically pure material could be crystallized (EtOH) as a white crystal: ^{1}H NMR ($CDCl_3$, 500

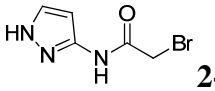
MHz) δ = 8.14 (br s, 1H), 7.45-7.53 (m, 2H), 6.98-7.10 (m, 2H), 4.02 (s, 2H); ^{13}C NMR ($CDCl_3$, 126MHz) δ = 163.5, 161.0, 159.0, 133.0, 133.0, 122.2, 122.1, 116.0, 115.9, 29.4; IR (neat) λ_{max} 3269, 2831, 1652, 1621, 1506, 1210, 836; HRMS (ESI) *m/z* calcd for $C_8H_7BrFNNaO$: 253.9587; found: 253.9559.



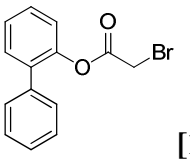
2-bromo-*N*-phenylacetamide (S2): Following general procedure A, the crude product, as an orange solid, was purified by passing through a plug of silica, followed by trituration (Et_2O) to provide pure **S2** as a white solid (58%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.20 (br s, NH), 7.53 (d, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.17 (br apparent t, 1H), 4.02 (s, 2H); ^{13}C NMR ($CDCl_3$, 101MHz) δ = 163.5, 137.0, 129.2, 125.3, 120.2, 29.6; IR (neat) λ_{max} 2919, 1652, 1556, 1337, 1112, 759; HRMS (ESI) *m/z* calcd for $C_8H_8BrNNaO$: 235.9681; found: 235.9682.



2-bromo-N-(4-methoxyphenyl)acetamide (S3): Following general procedure A, the crude product, as a brown solid, was purified by trituration (CH_2Cl_2) to provide pure **S3** as a white solid (50%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.11 (br s, NH), 7.37-7.45 (m, 2H), 6.81-6.91 (m, 2H), 4.00 (s, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 163.5, 157.2, 130.1, 122.2, 114.4, 55.6, 29.6; IR (neat) λ_{max} 3287, 2955, 1659, 1513, 1253, 1031, 830, 777, 710, 520; HRMS (ESI) *m/z* calcd for $C_9H_{10}BrNNaO_2$: 265.9787; found: 265.9781.

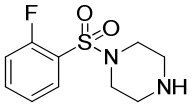


2-bromo-N-(1H-pyrazol-3-yl)acetamide (S4): Bromoacetyl bromide (0.150 mL, 1.72 mmol) was added to a solution of 3-aminopyrazole (142.5 mg, 1.72 mmol) and Na_2CO_3 (365 mg, 3.44 mmol) in THF (8.6 mL) at 0 ˚C. The reaction mixture was allowed to stir at 0 ˚C for 30 min, at which time the reaction mixture was filtered. Saturation of the organic layer with Et_2O (10 mL) led to precipitant that was collected by vacuum filtration to provide pure **S4** as a white solid (294 mg, 84%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.19 (br s, 1H), 11.10 (s, 1H), 7.74 (d, *J* = 2.2 Hz, 1H), 6.44 (d, *J* = 2.2 Hz, 1H), 4.05 (s, 2H); ^{13}C NMR (DMSO-d_6, 126 MHz) δ = 164.3, 145.3, 130.3, 96.0, 29.6; IR (neat) λ_{max} 3368, 2950, 1740, 1644, 1435, 1238, 1096, 1065, 998, 779; HRMS (ESI) *m/z* calcd for $C_5H_7BrN_3O$: 203.9767; found: 203.9758.

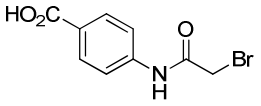


[1,1'-biphenyl]-2-yl 2-bromoacetate (S5): Following general procedure A, crude product **S5**, as a clear oil, was used without further purification: ^{1}H NMR ($CDCl_3$,

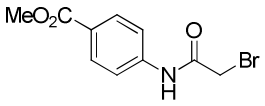
400 MHz) δ = 7.31-7.45 (m, 8H), 7.11-7.21 (m, 1H), 3.83 (s, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 165.5, 147.4, 136.9, 134.7, 131.0, 128.9, 128.6, 128.4, 127.6, 126.8, 122.3, 25.2; IR (neat) λ_{max} 1760, 1479, 1251, 1188, 1124, 745, 701; HRMS (ESI) *m/z* calcd for $C_{14}H_{11}BrNaO_2$: 312.9835; found: 312.9821.



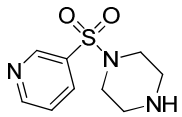
1-((2-fluorophenyl)sulfonyl)piperazine (S6): Following general procedure B, crude product was purified by trituration (Et_2O/hexanes) to provide **S6** as a white solid (75%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.77-7.88 (m, 1H), 7.49-7.64 (m, 1H), 7.26-7.33 (m, 1H), 7.21 (ddd, *J* = 9.9, 8.5, 1.0 Hz, 1H), 3.09-3.21 (m, 4H), 2.87-2.98 (m, 4H), 1.57 (br s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 160.2, 157.7, 135.1, 135.1, 131.3, 124.8, 124.6, 124.5, 124.4, 117.4, 117.2, 46.6, 45.4; IR (neat) λ_{max} 3338, 3099, 2855, 1599, 1582, 1173, 950, 583, 507; HRMS (ESI) *m/z* calcd for $C_{10}H_{14}FN_2O_2S$: 245.0755; found: 245.0744.



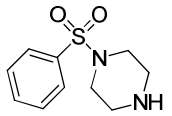
4-(2-bromoacetamido)benzoic acid (S7): Bromoacetyl bromide (0.903 mL, 10.4 mmol) was added to a solution of *p*-aminobenzoic acid (1.4 g, 10.4 mmol) and triethylamine (2.5 mL, 20.8 mmol) in CH_2Cl_2 (6 mL). The reaction mixture was stirred for 2 h, then filtered to provide crude product as a white solid. The filtrate was washed with saturated $NH_4Cl_{(aq)}$ upon where crude product precipitated. The combined crude product was triturated with CH_2Cl_2 to provide **S7** (820 mg, 31%) as a white solid with a minor inseparable impurity: ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 12.66 (br s, OH), 10.64 (br s, NH), 7.91 (d, *J* = 7.9 Hz, 2H), 7.66-7.72 (m, 2H), 4.05 (br s, 2H); ^{13}C NMR (DMSO-d_6 ,126 MHz) δ = 166.9, 165.4, 142.6, 130.5, 125.9, 118.7, 30.3; IR (neat) λ_{max} 3794, 1915, 1682, 1180, 857, 770, 548; HRMS (ESI) *m/z* calcd for $C_9H_8BrNNaO_3$: 279.9580; found: 279.9567.



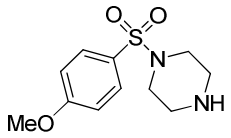
methyl 4-(2-bromoacetamido)benzoate (S8): Bromoacetyl bromide (0.335 mL, 3.86 mmol) was added to a solution of methyl-4-aminobenzoate (584 mg, 3.86 mmol) and triethylamine (0.95 mL, 7.7 mmol) in CH_2Cl_2 (1.9 mL) at 0 ˚C. The reaction was stirred 2 h, diluted with CH_2Cl_2 (10 mL), washed with saturated $NH_4Cl_{(aq)}$, dried (Na_2SO_4), and concentrated *in vacuo* to afford the crude product as a black oil. The crude product was purified by flash column chromatography (silica, 1:1 Et_2O/hexanes) to provide **S8** as an off white solid (80%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.26 (br s, 1H), 7.97-8.12 (m, *J* = 8.8 Hz, 2H), 7.58-7.67 (m, *J* = 8.8 Hz, 2H), 4.04 (s, 2H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 166.6, 164.3, 141.3, 130.9, 126.4, 119.3, 52.2, 29.4; IR (neat) λ_{max} 3816, 1921, 1716, 1674, 1603, 1278, 1111, 963, 853, 769; HRMS (ESI) *m/z* calcd for $C_{10}H_{10}BrNNaO_3$: 293.9736; found: 293.9728.



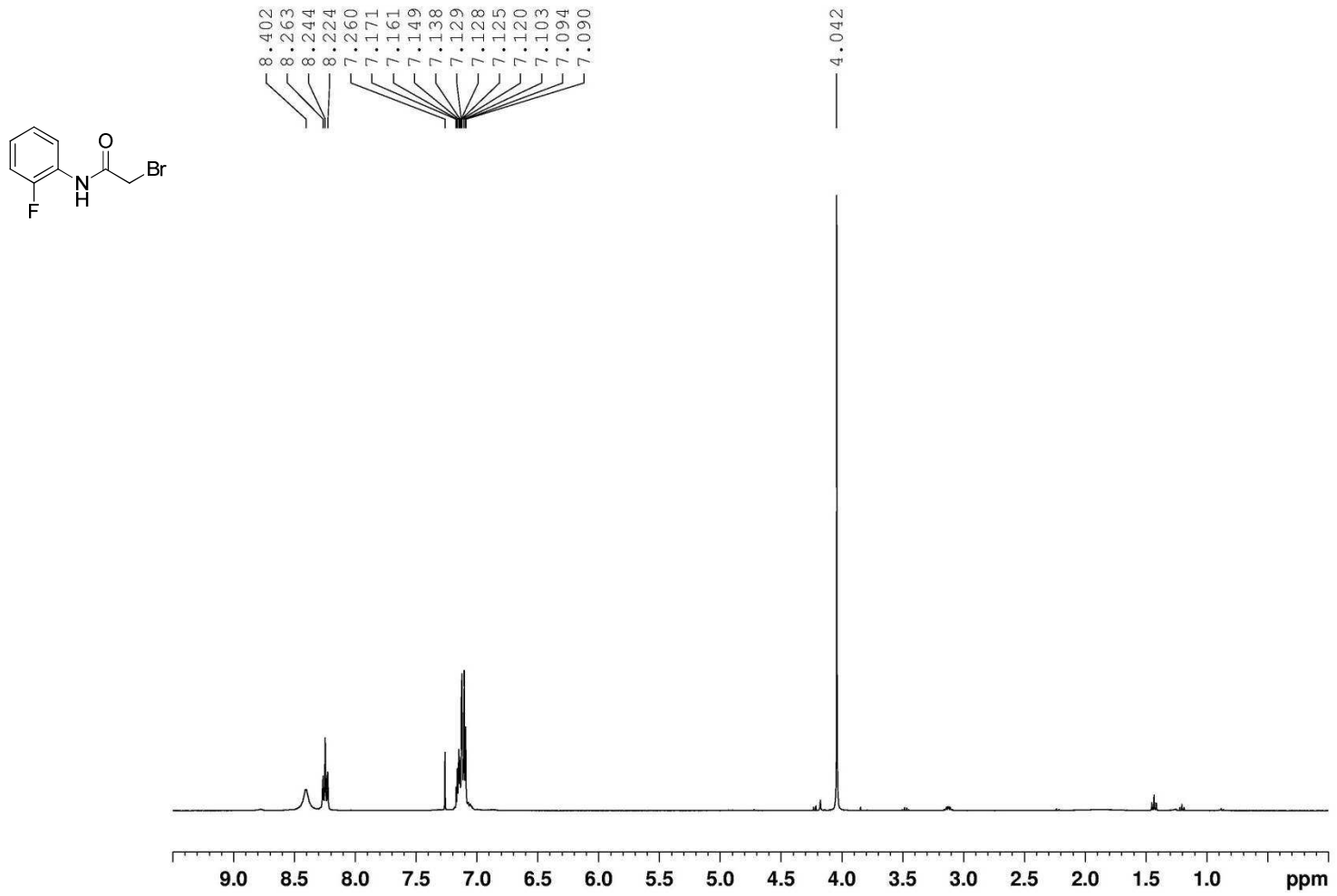
1-(pyridin-3-ylsulfonyl)piperazine (S9): Following general procedure B, crude **S9** (80%) was isolated, and used without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.92 (d, *J* = 1.9 Hz, 1H), 8.77 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.99 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.45 (dd, *J* = 8.0, 4.3 Hz, 1H), 2.93-3.04 (m, 4H), 2.82-2.93 (m, 4H), 2.47 (t, *J* = 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 153.4, 148.5, 135.3, 132.5, 123.7, 46.7, 45.2; IR (neat) λ_{max} 3436, 2853, 1574, 1174, 949, 756, 582; HRMS (ESI) *m/z* calcd for $C_9H_{14}N_3O_2S$: 228.0801; found: 228.0790.



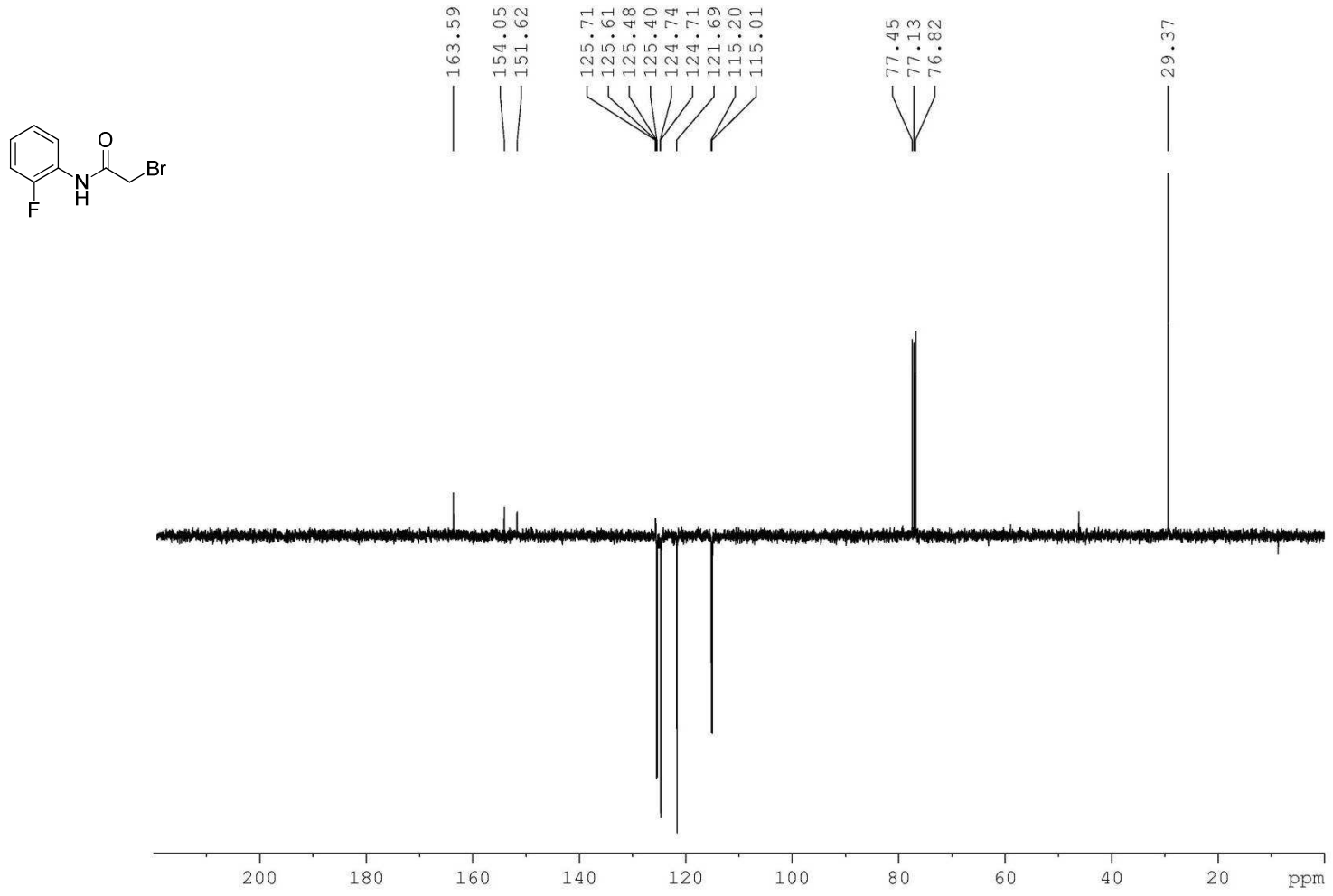
1-(phenylsulfonyl)piperazine (S10): Following general procedure B, pure **S10** (quant) was isoloated, and used without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.71-7.80 (m, 2H), 7.47-7.66 (m, 3H), 2.97-2.99 (m, 4H), 2.84-2.95 (m, 4H), 1.51 (br s, NH); ^{13}C NMR ($CDCl_3$,126 MHz) δ = 135.5, 132.8, 129.0, 127.7, 46.8, 45.2; IR (neat) λ_{max} 2860, 1917, 1448, 1170, 947, 693, 577; HRMS (ESI) *m/z* calcd for $C_{10}H_{15}N_2O_2S$: 227.0849; found 227.0841.



1-((4-methoxyphenyl)sulfonyl)piperazine (S11): Following general procedure B, pure **S11** (99%) was isolated, and used without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.56-7.62 (m, 2H), 6.87-6.96 (m, 2H), 3.79 (s, 3H), 2.77-2.91 (m, 8H), 1.81 (s, NH); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 163.0, 129.8, 114.1, 55.6, 46.7, 45.1; IR (neat) λ_{max} 2845, 1911, 1597, 1162, 732, 559; HRMS (ESI) *m/z* calcd for $C_{11}H_{17}N_2O_3S$: 257.0954; found: 257.0961.

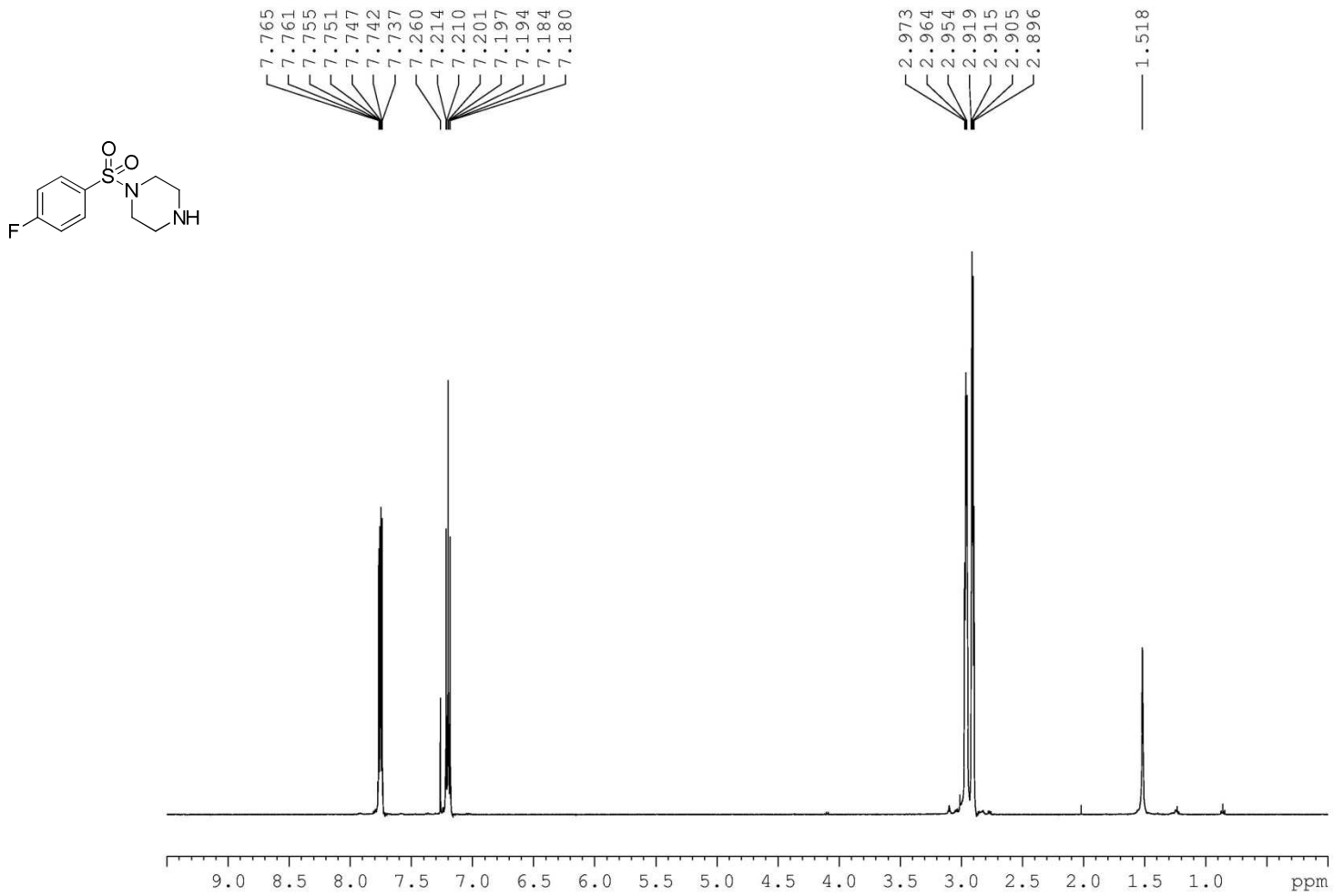


^{1}H NMR ($CDCl_3$, 400 MHz) of **2**.

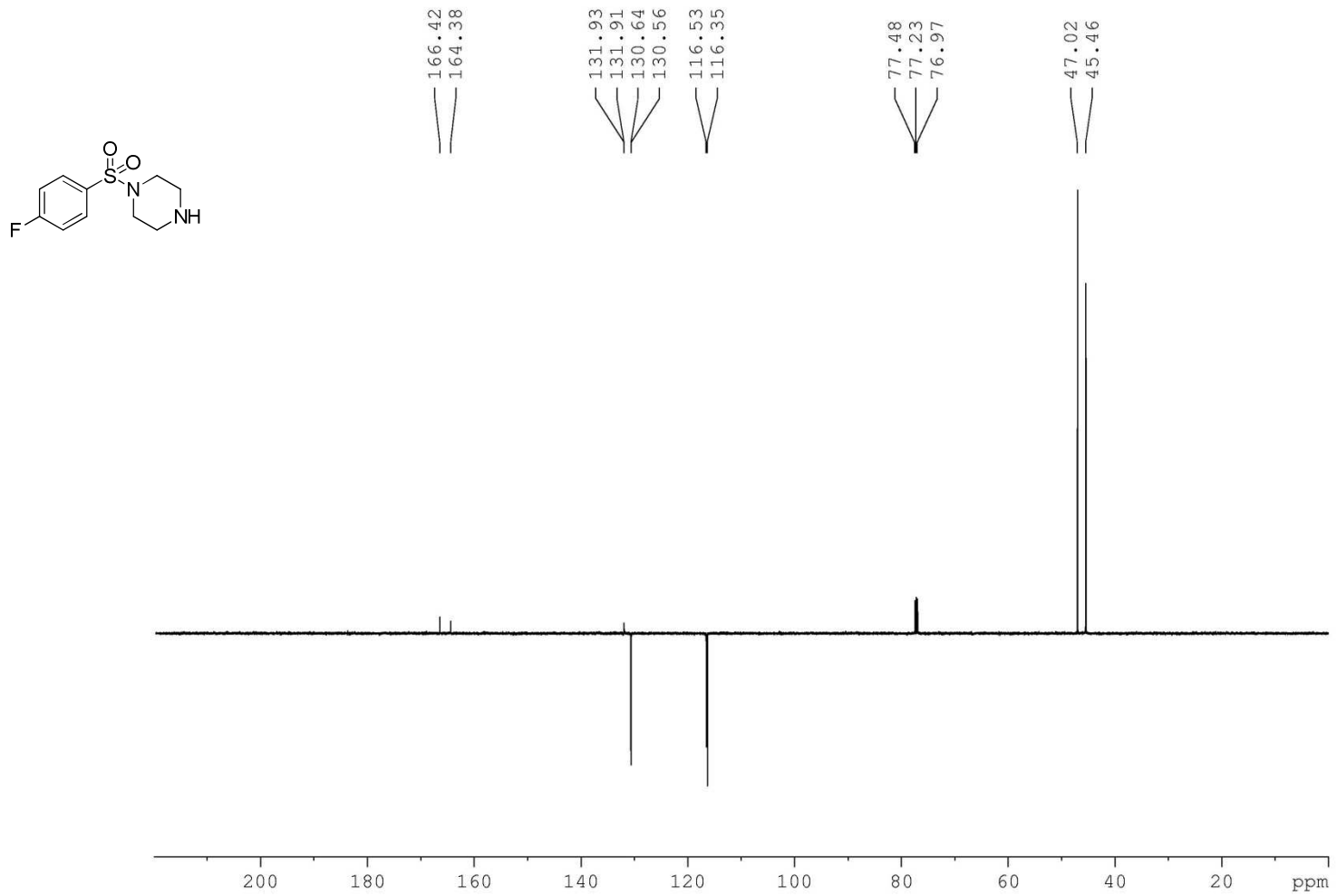


^{13}C NMR ($CDCl_3$, 101 MHz) of **2**.

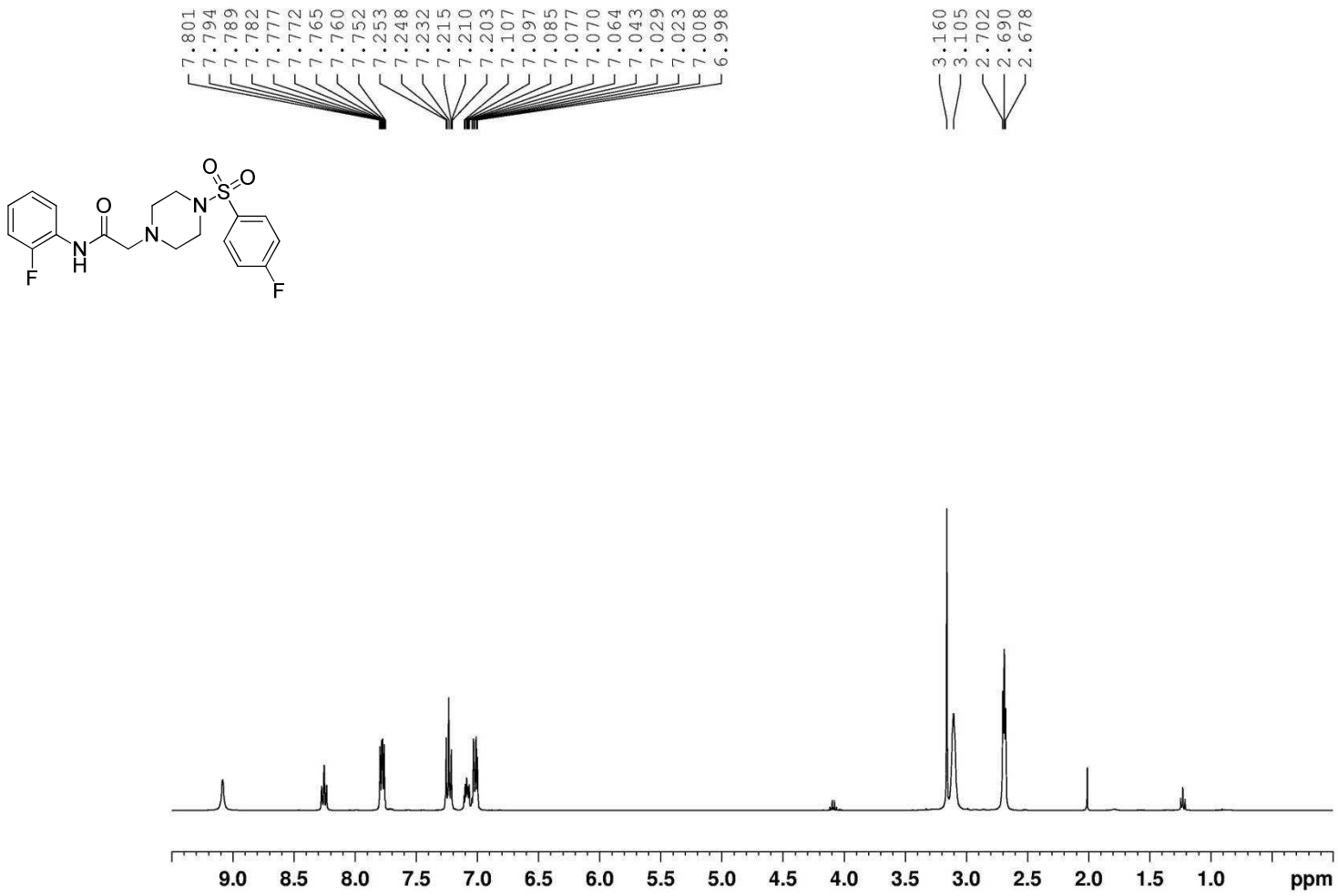
6S



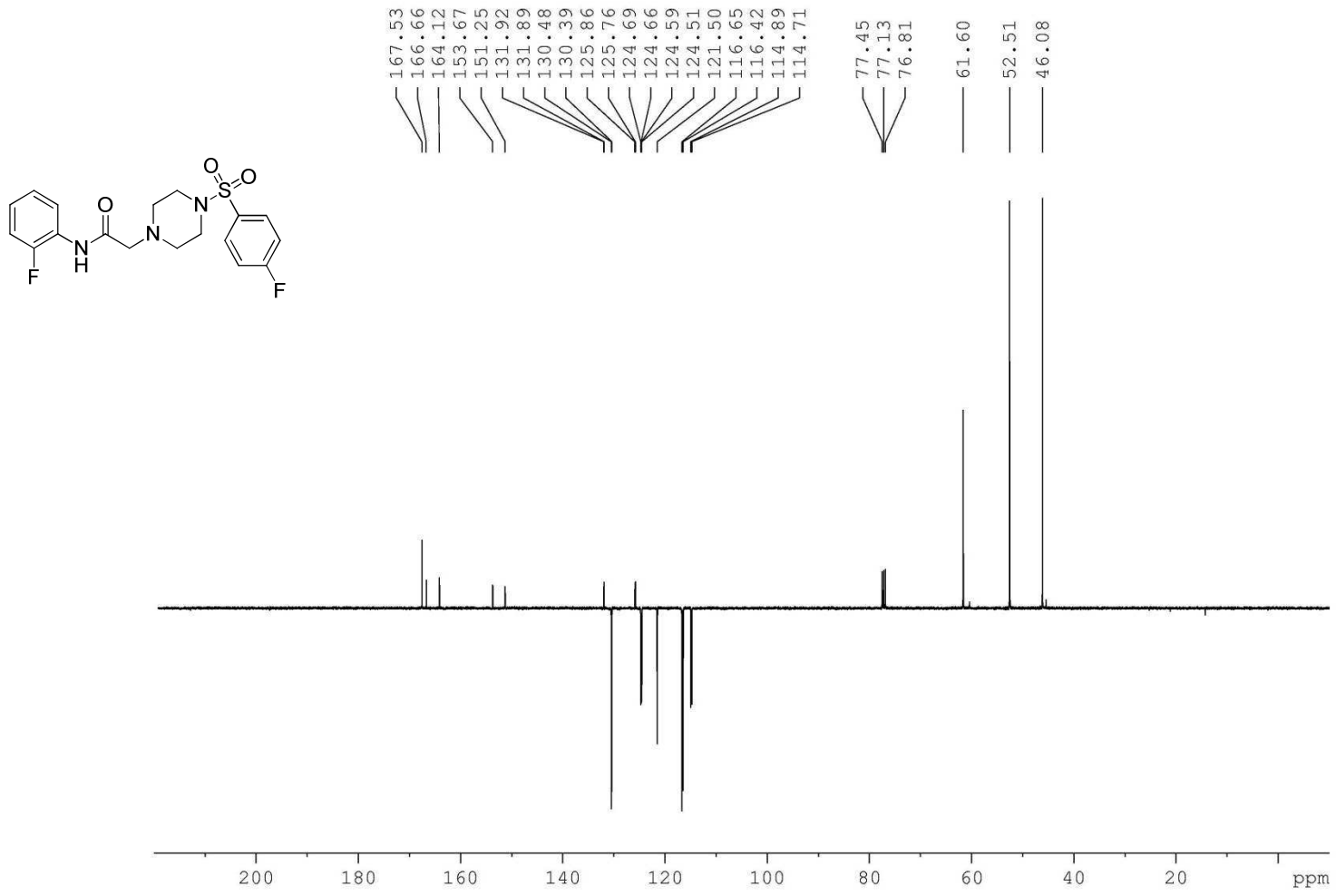
^{1}H NMR ($CDCl_3$, 500 MHz) of **3**.



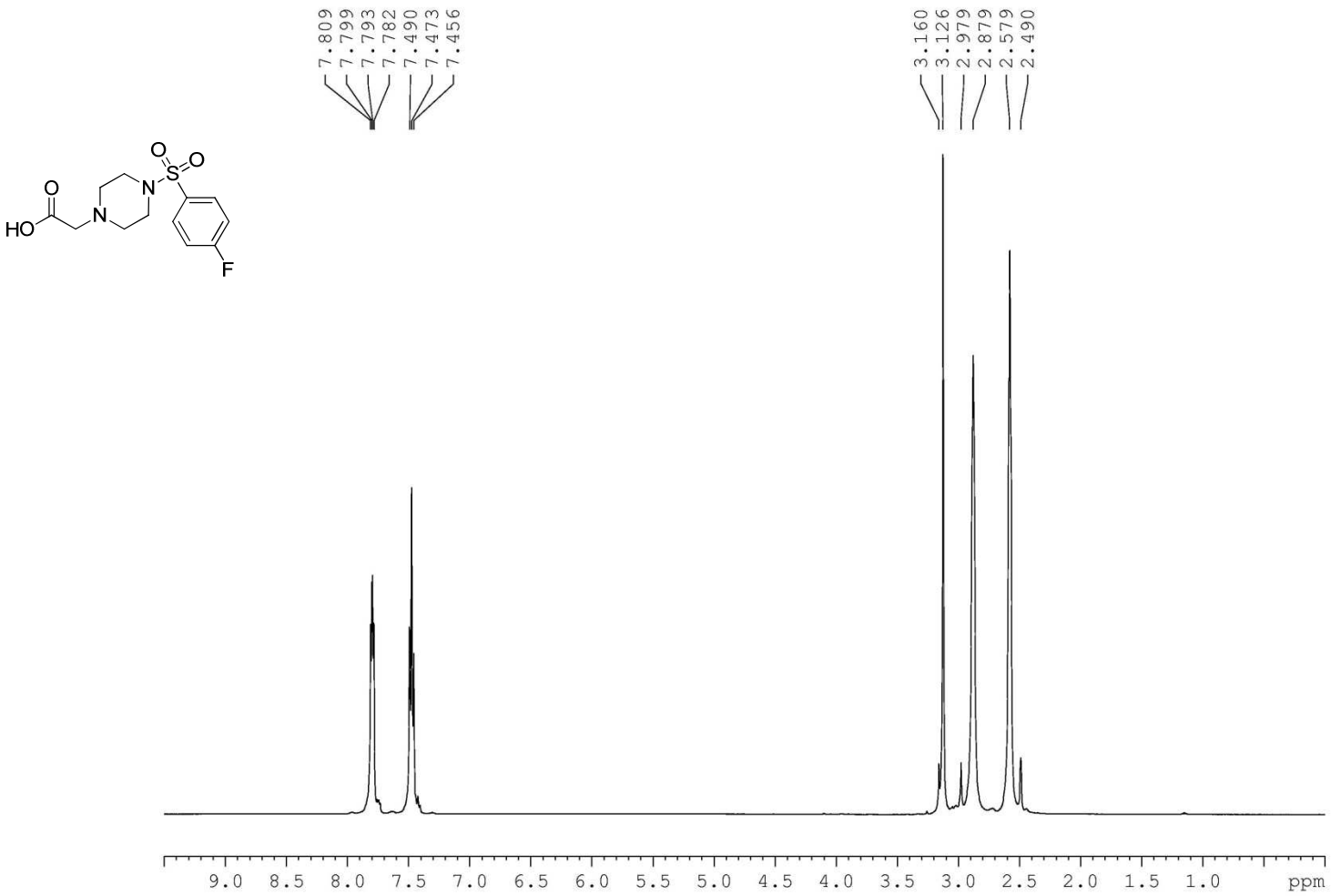
^{13}C NMR ($CDCl_3$, 126 MHz) of **3**.



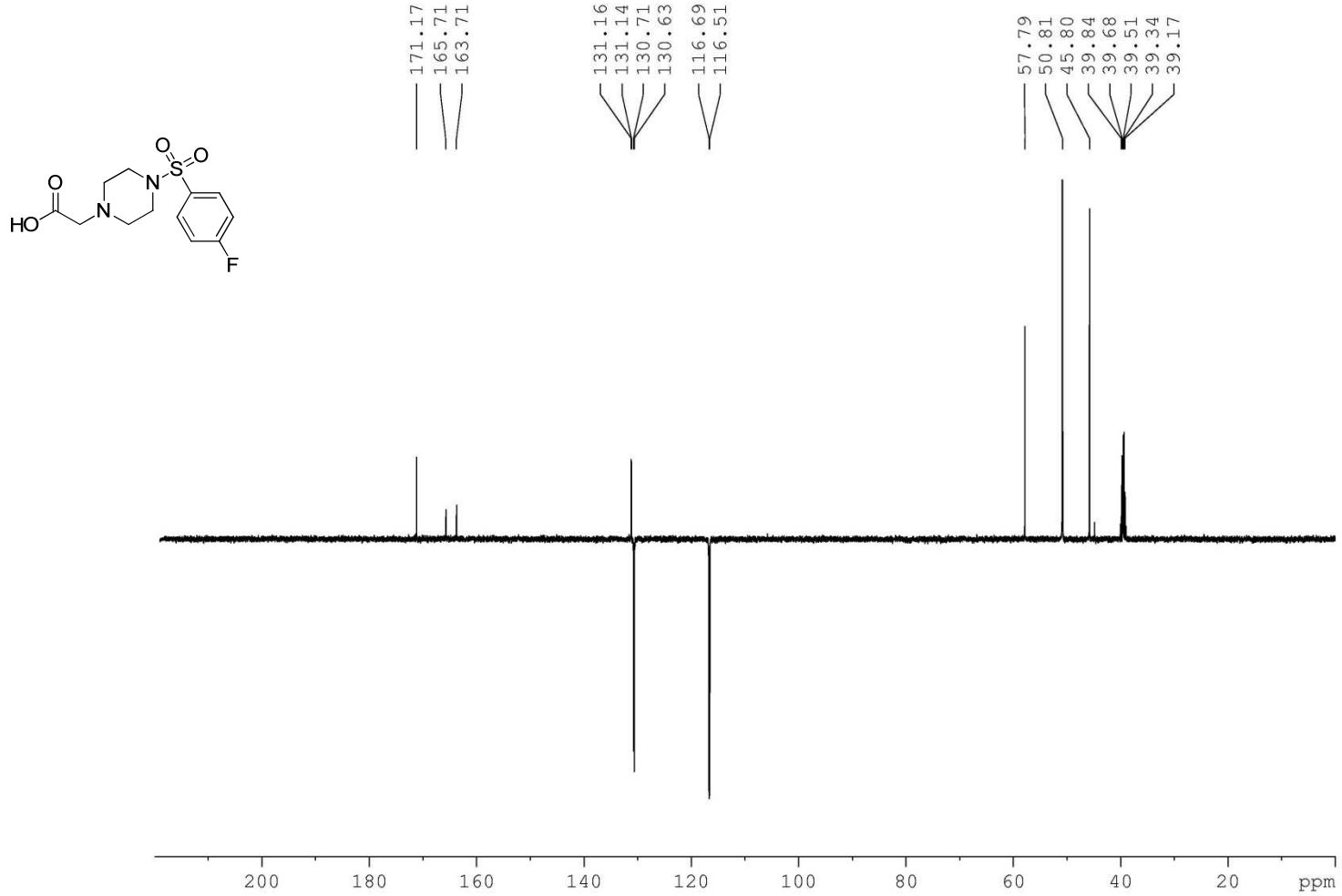
^{1}H NMR ($CDCl_3$, 400 MHz) of **1**.



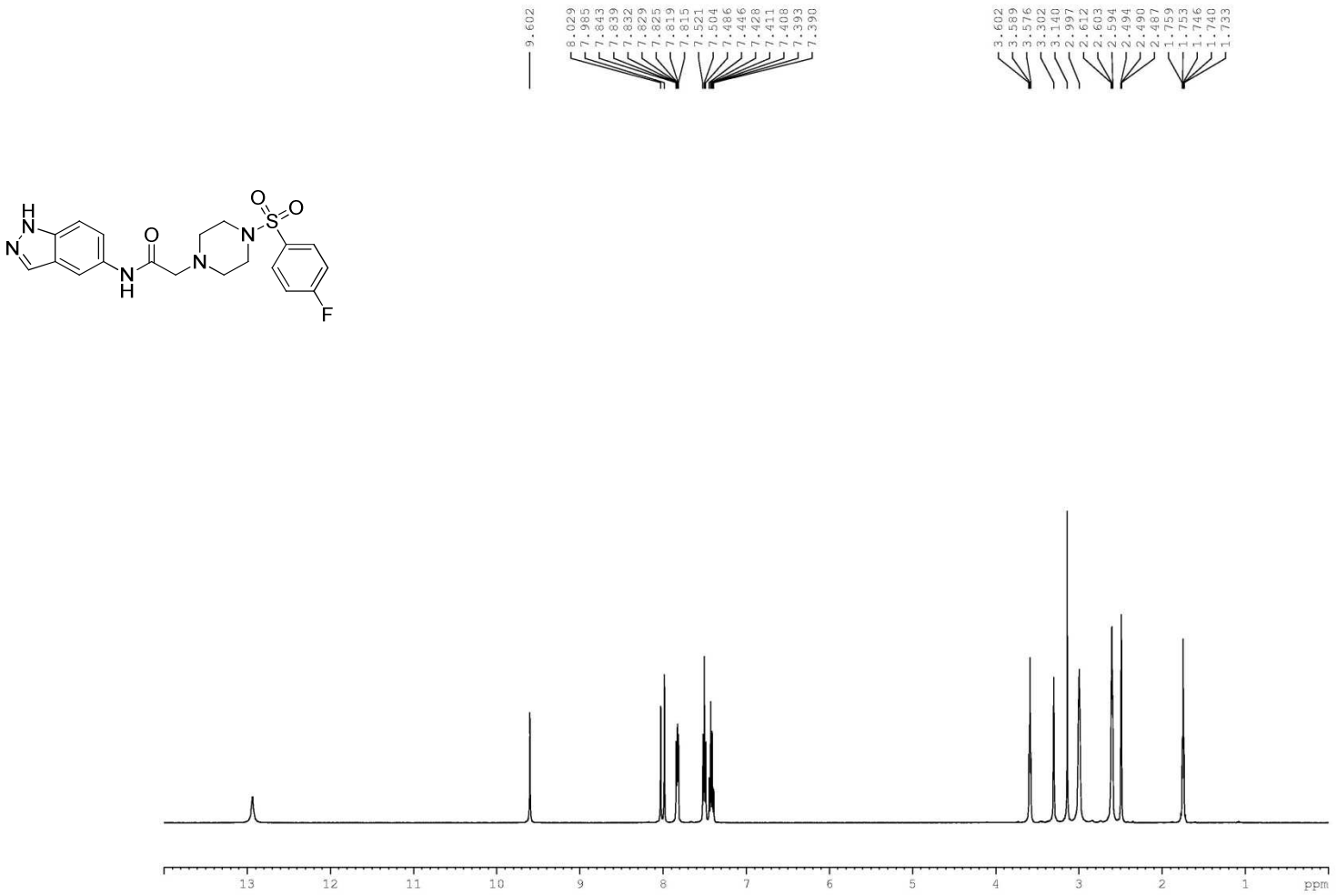
^{13}C NMR ($CDCl_3$, 101 MHz) of **1**.



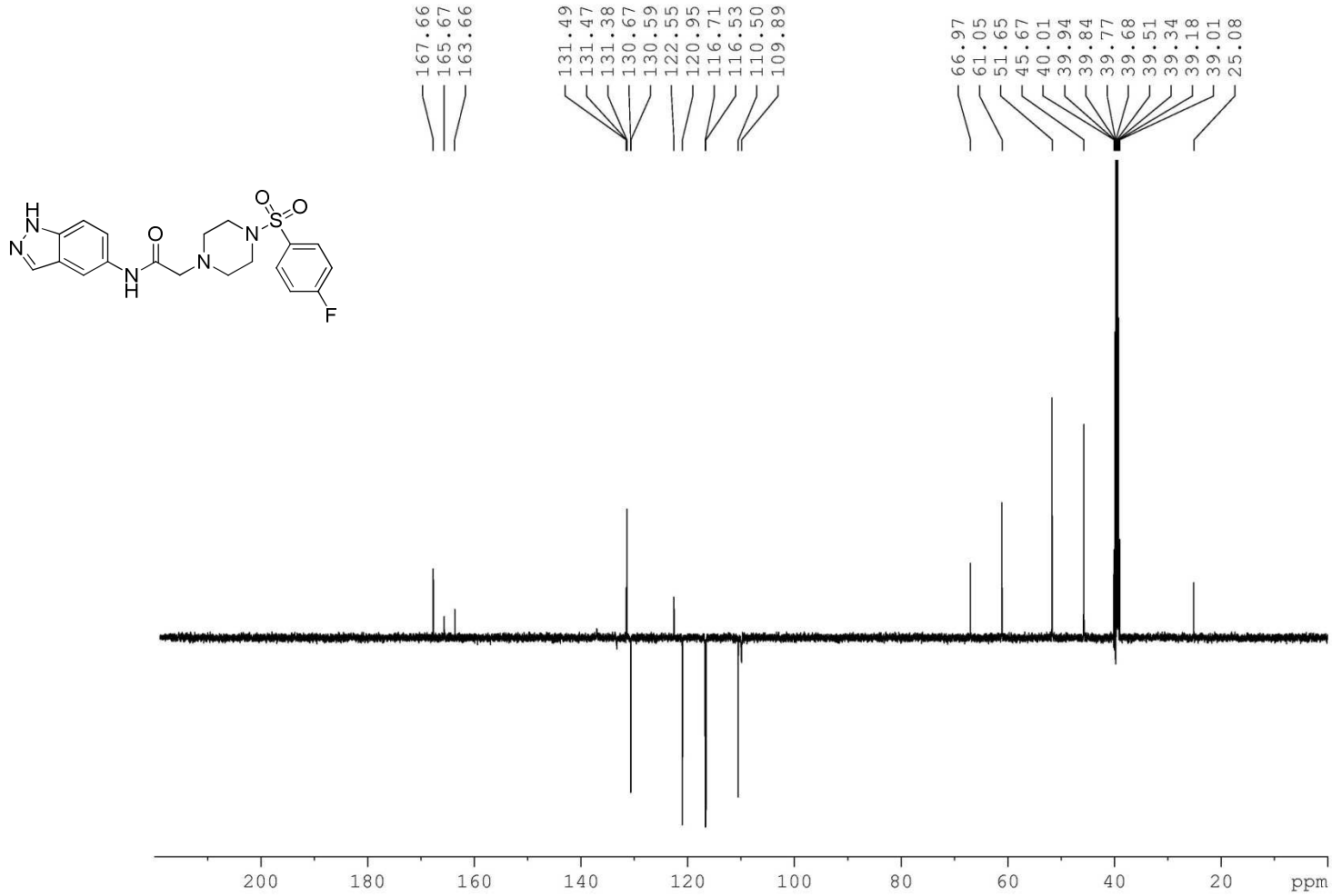
^{1}H NMR (DMSO-d_6, 500 MHz) of **9**.



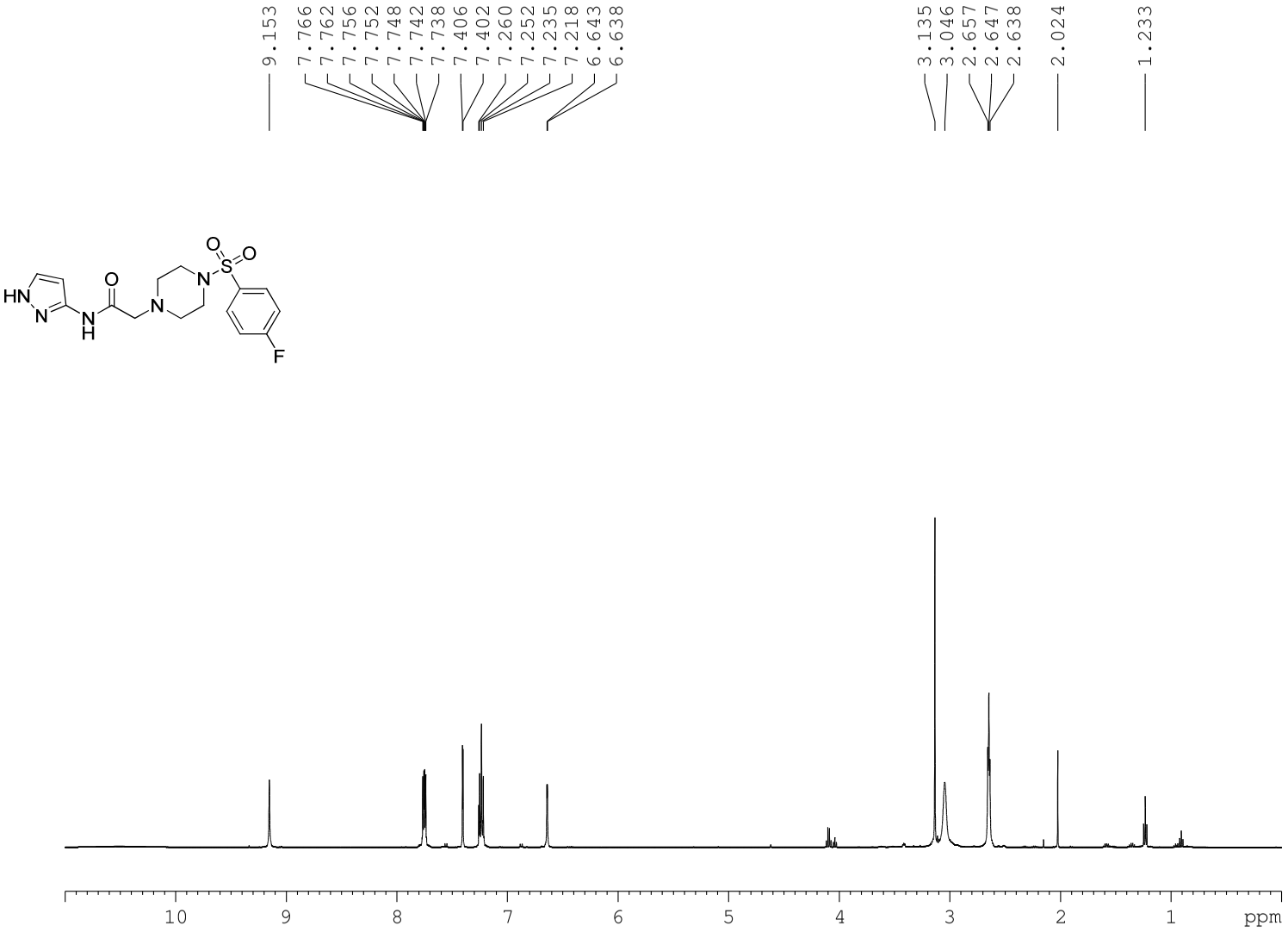
^{13}C NMR (DMSO-d_6, 126 MHz) of **9**.



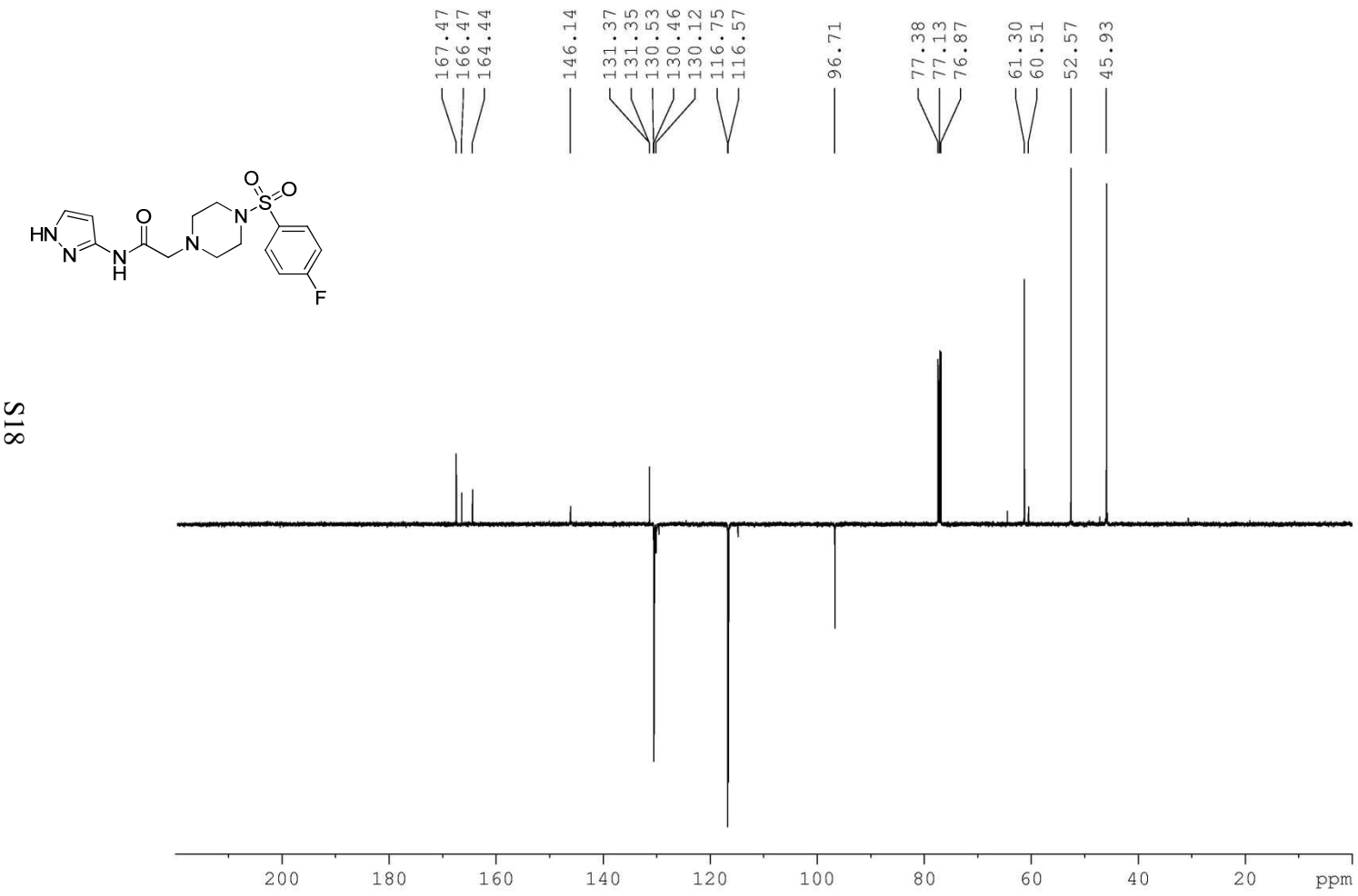
^{1}H NMR (DMSO-d_6, 500 MHz) of **11**.



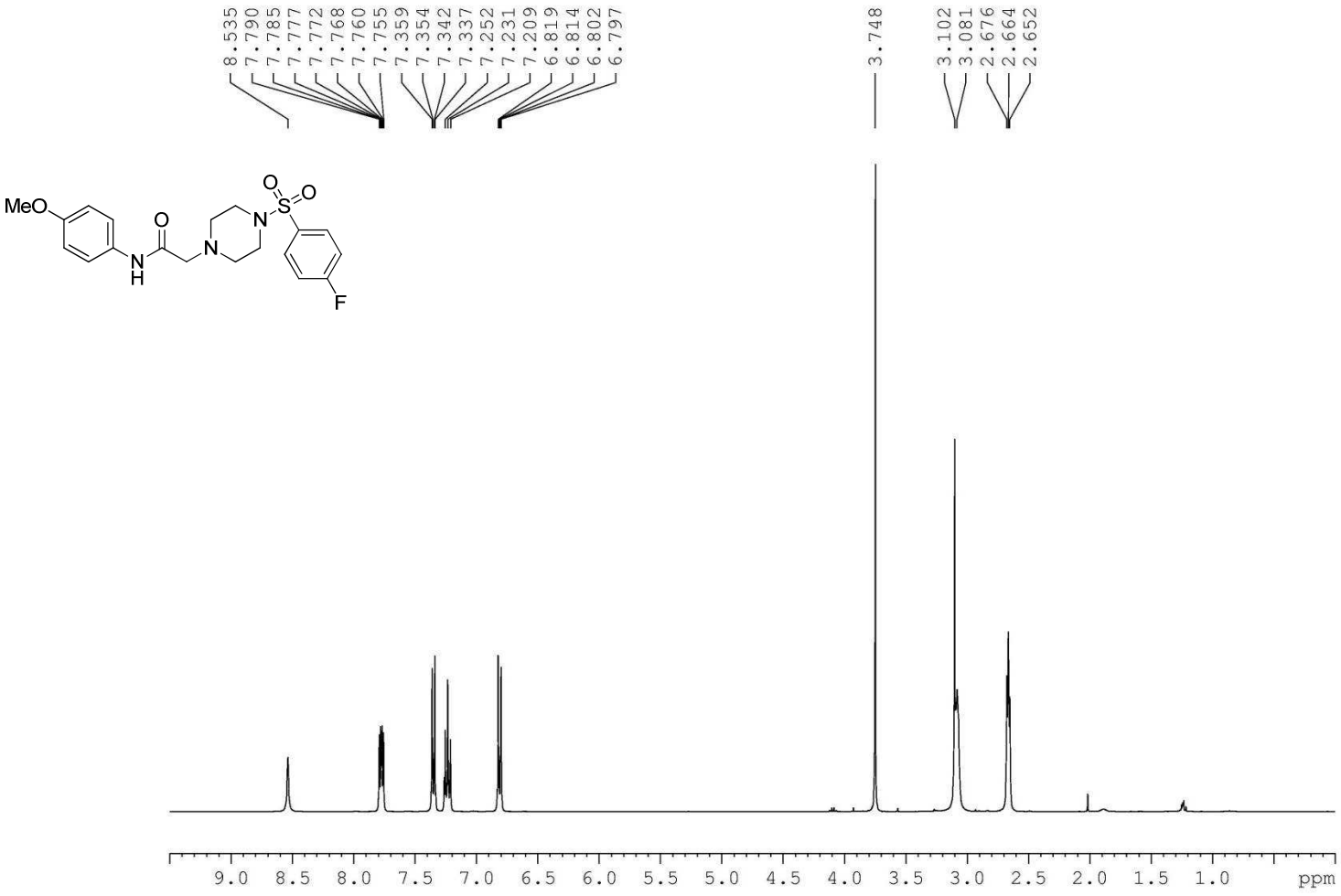
^{13}C NMR (DMSO-d_6, 126 MHz) of **11**.



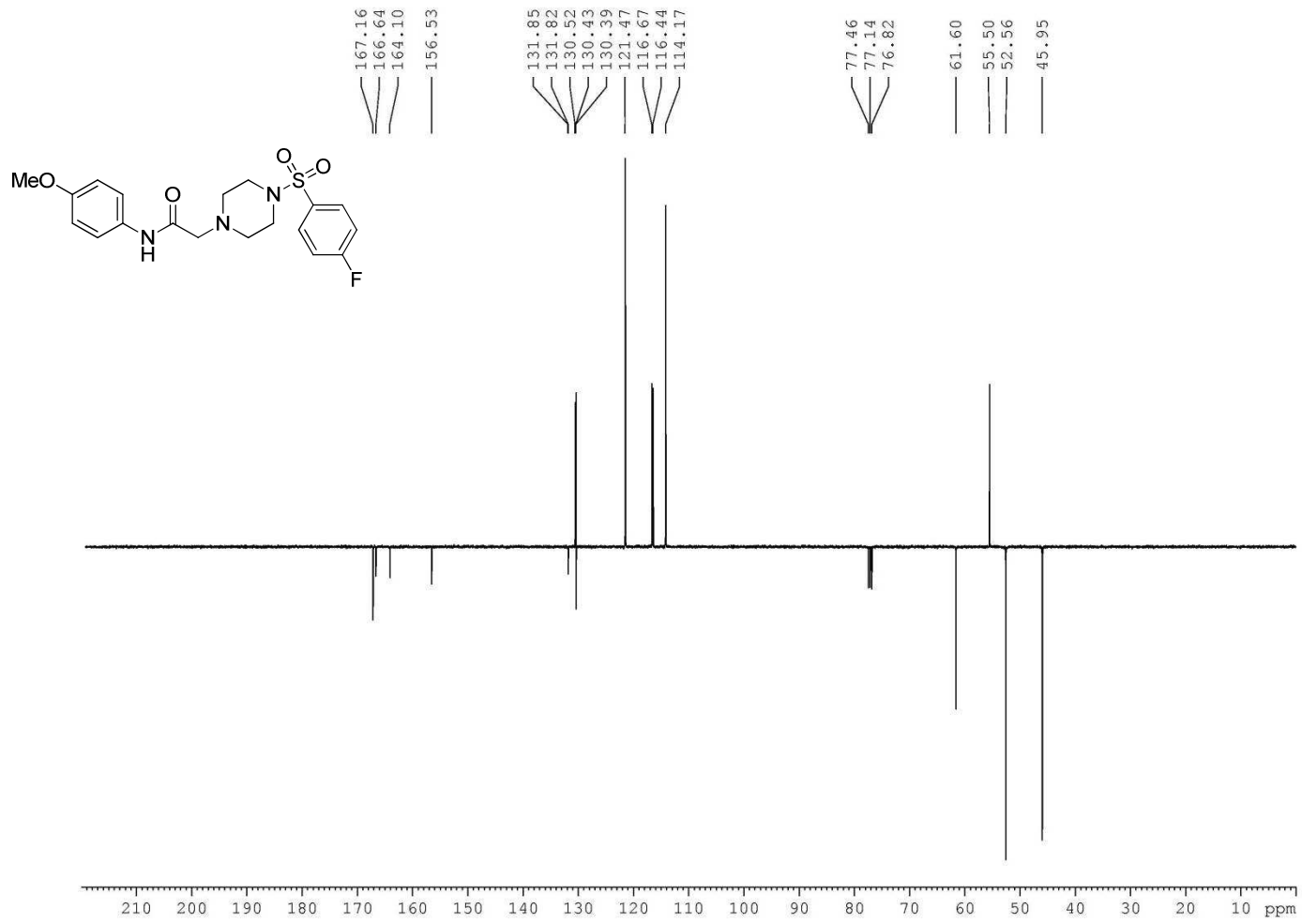
^{1}H NMR ($CDCl_3$, 500 MHz) of **12**.



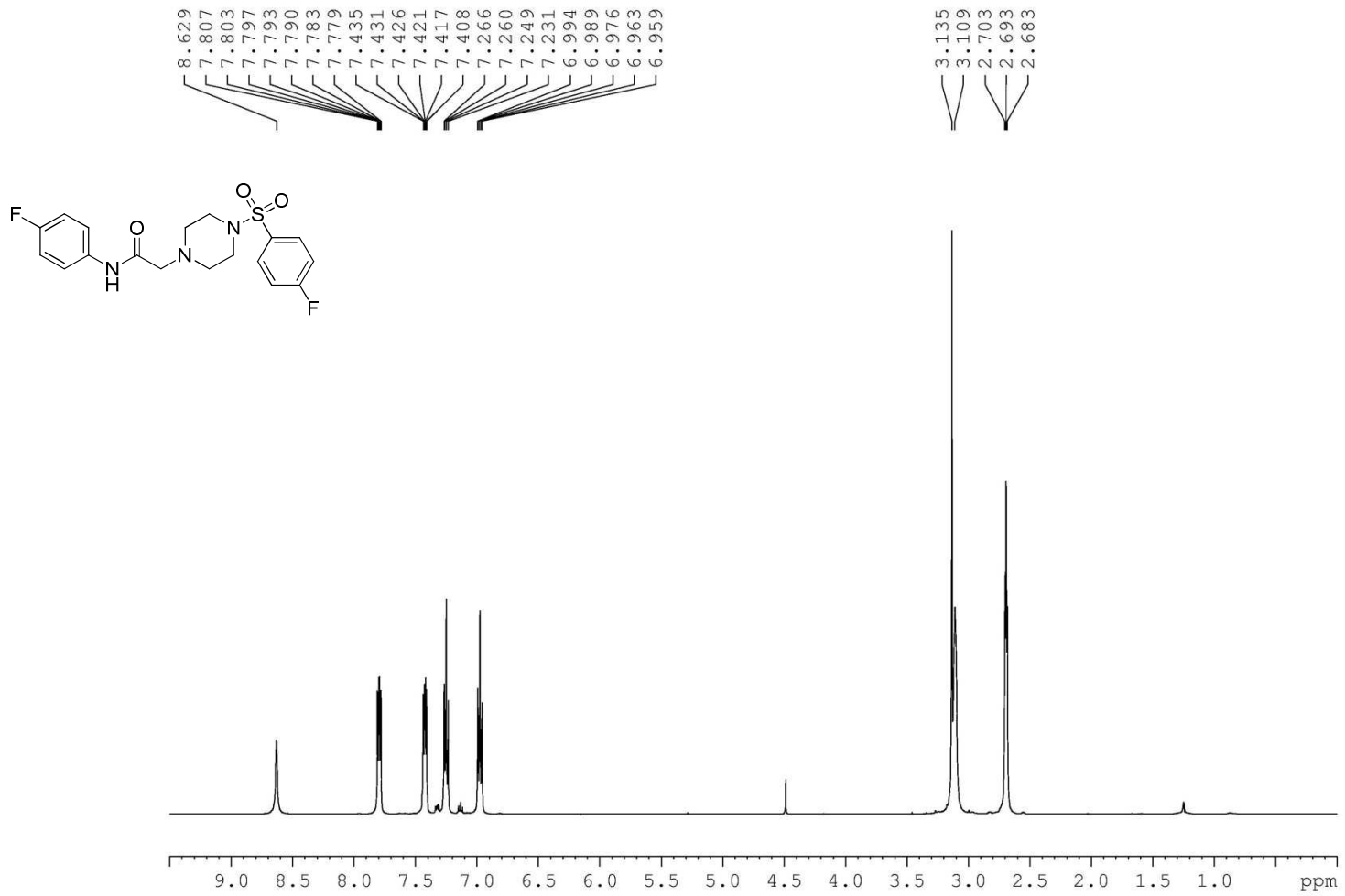
^{13}C NMR ($CDCl_3$, 126 MHz) of **12**.



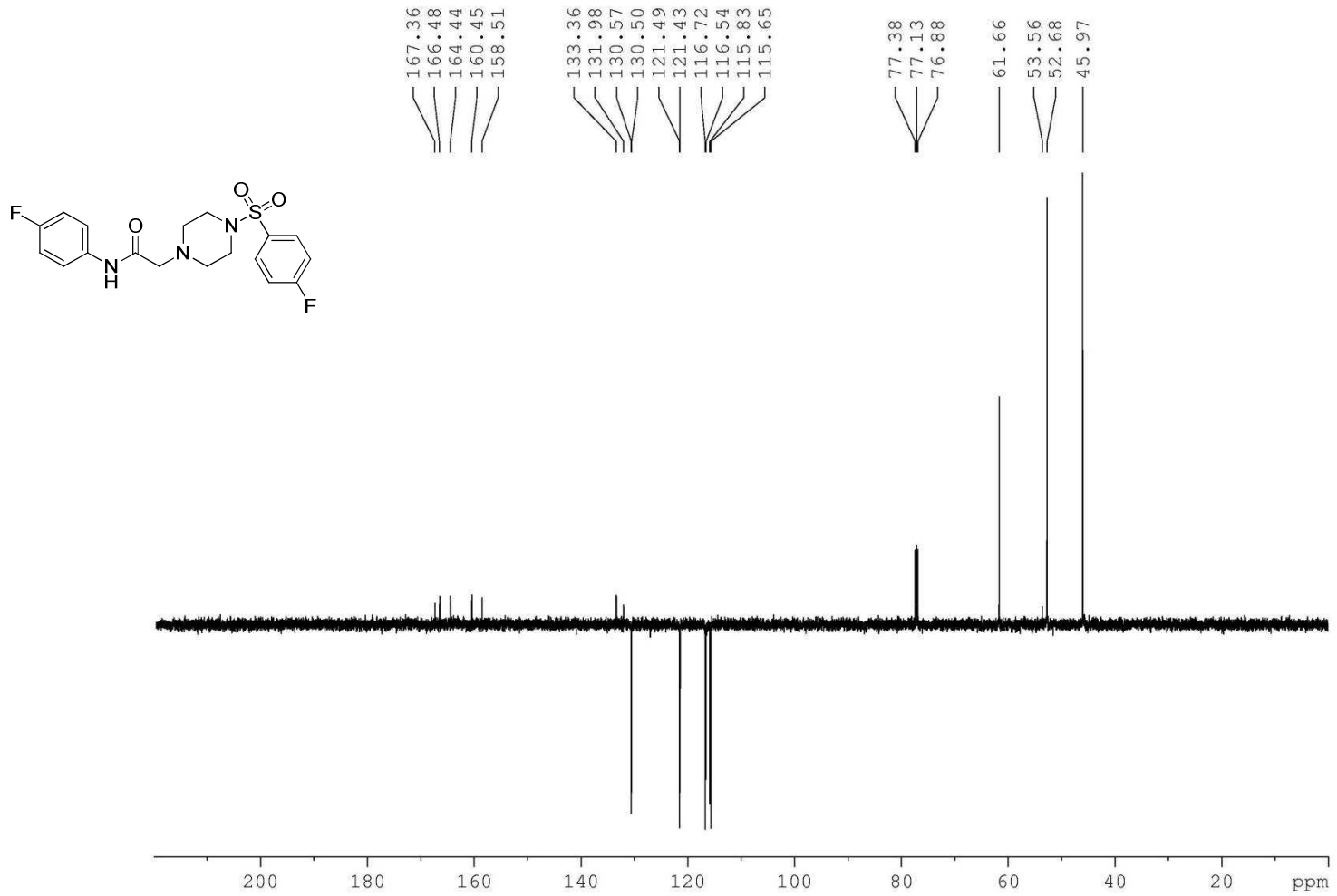
^{1}H NMR ($CDCl_3$, 400 MHz) of **13**.



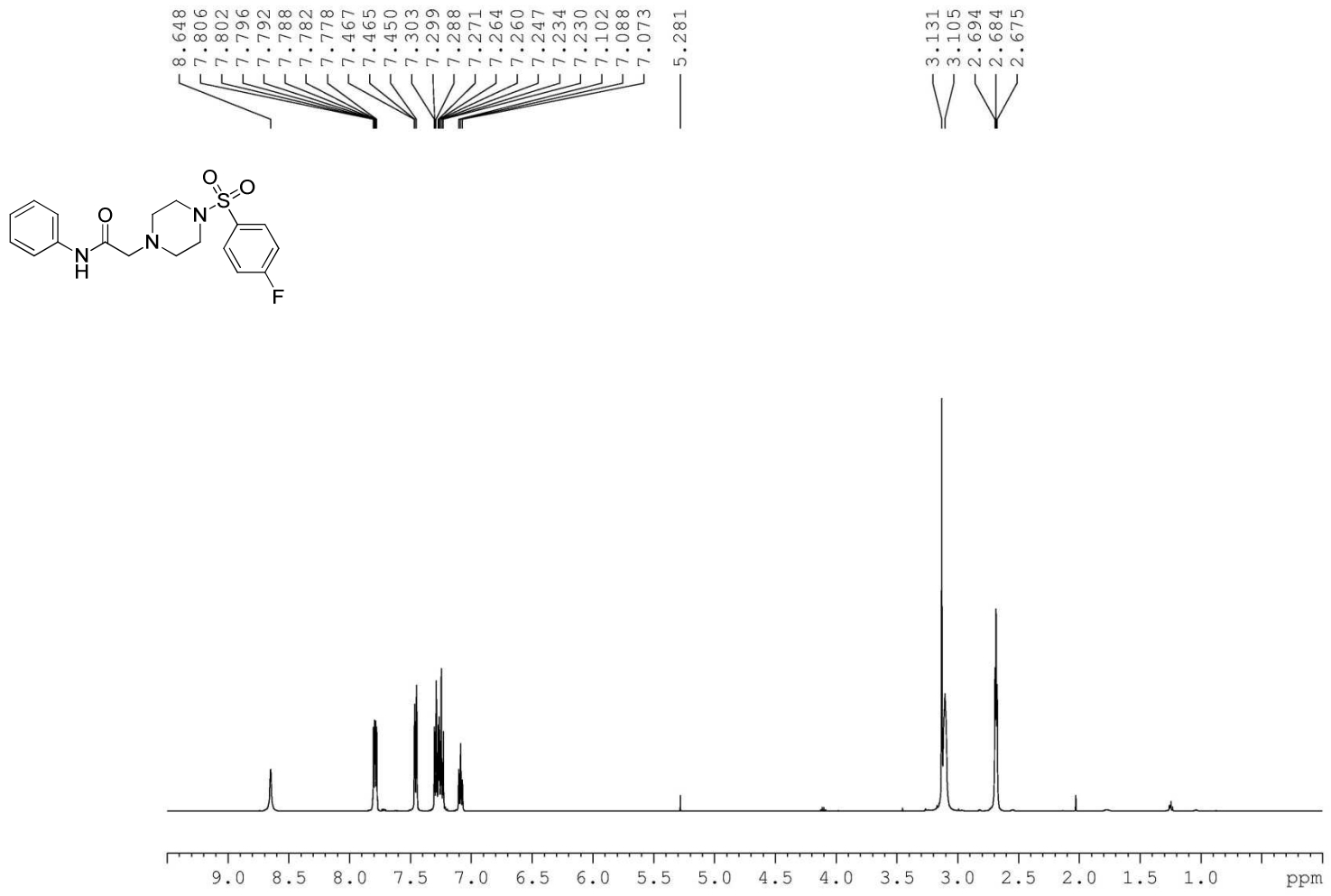
^{13}C NMR ($CDCl_3$, 101 MHz) of **13**.



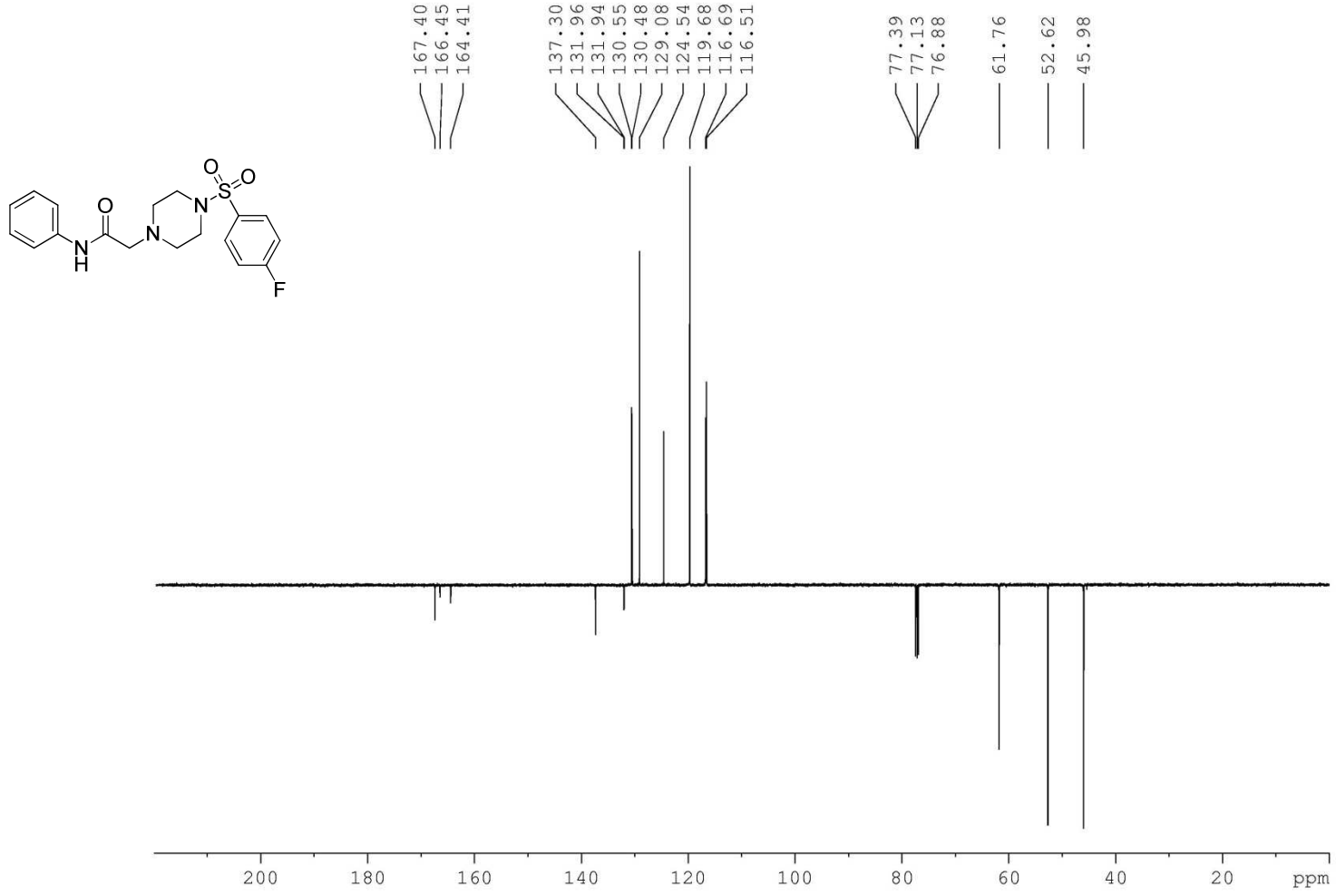
^{1}H NMR ($CDCl_3$, 500 MHz) of **14**.



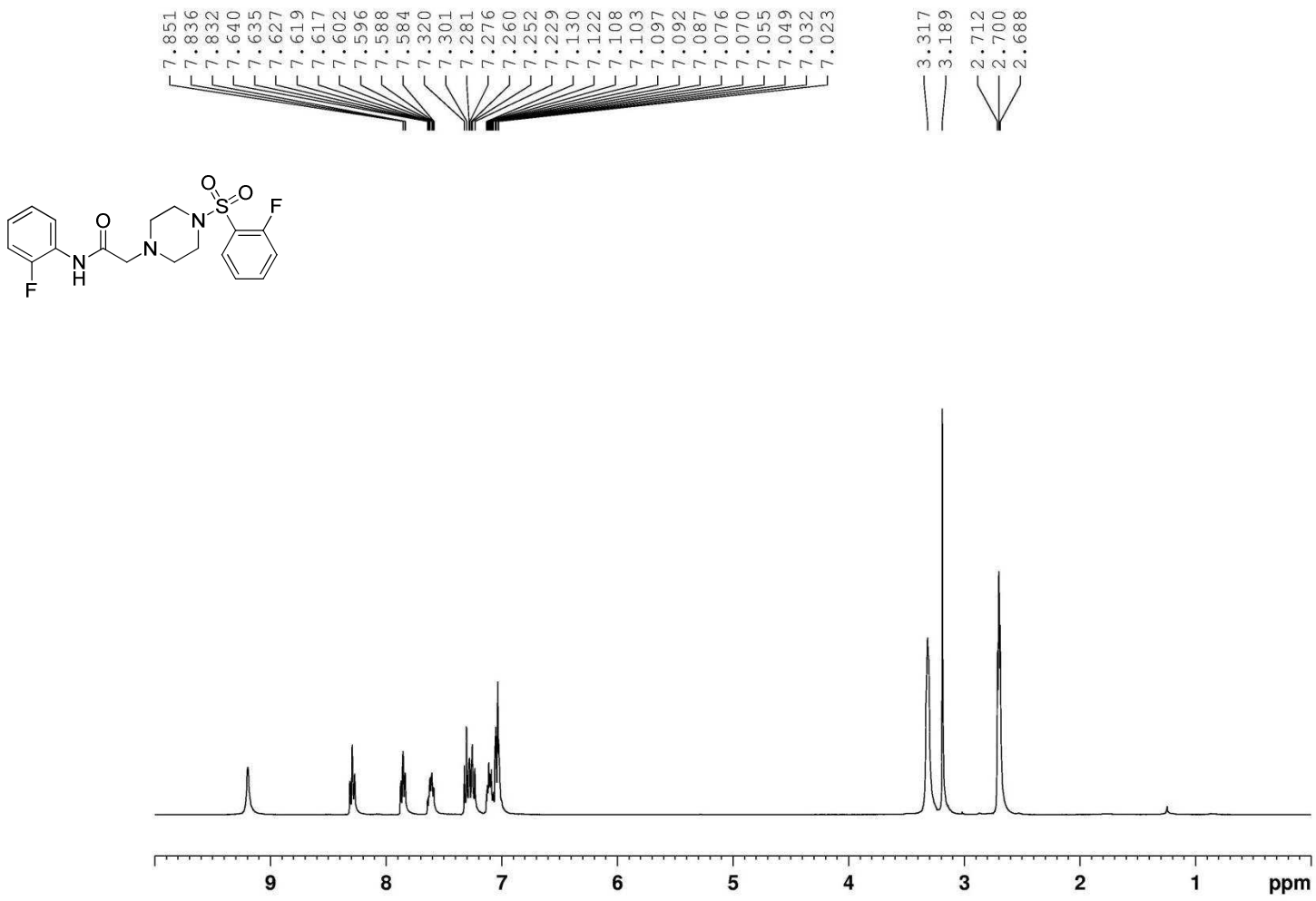
^{13}C NMR ($CDCl_3$, 126 MHz) of **14**.



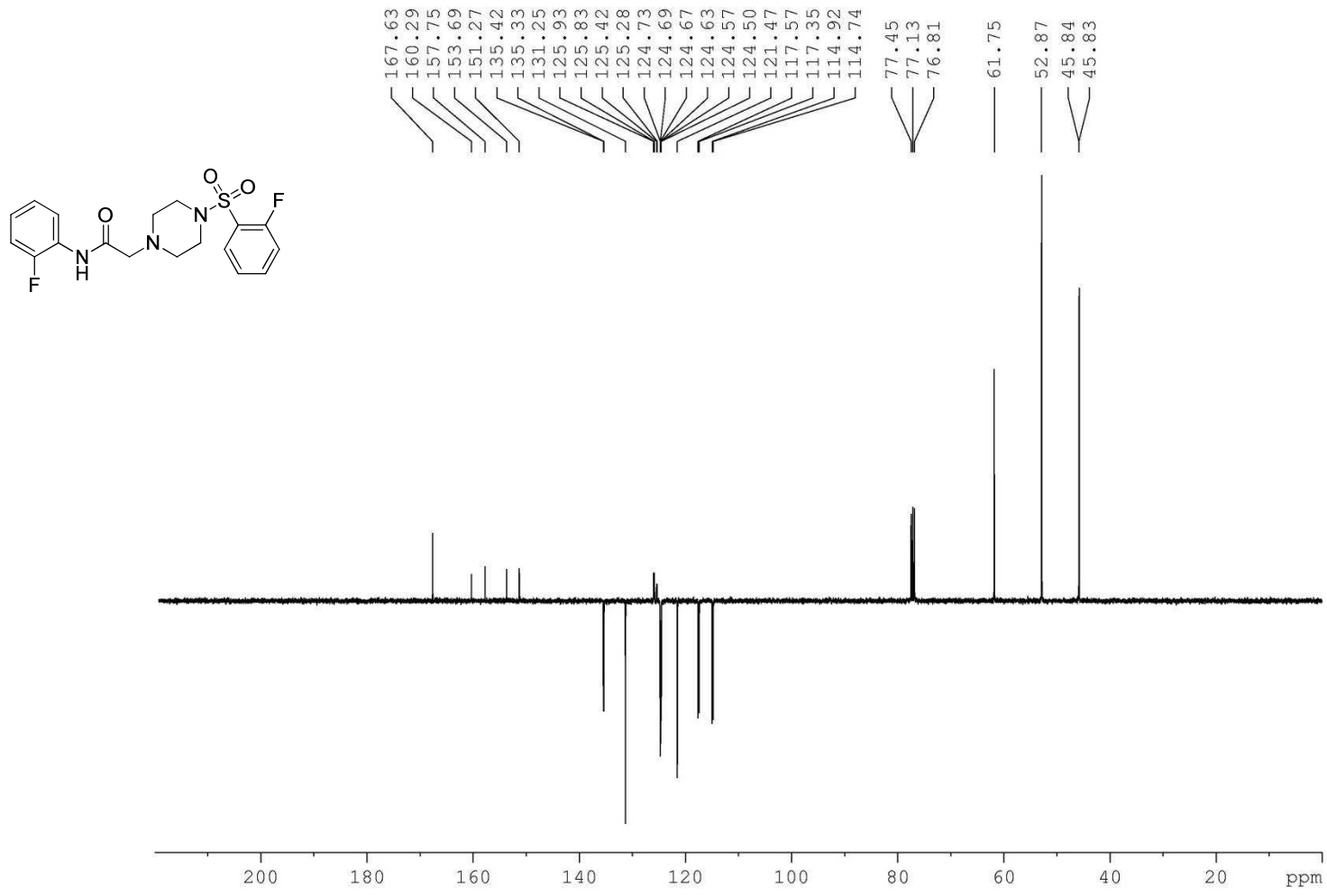
^{1}H NMR ($CDCl_3$, 500 MHz) of **15**.



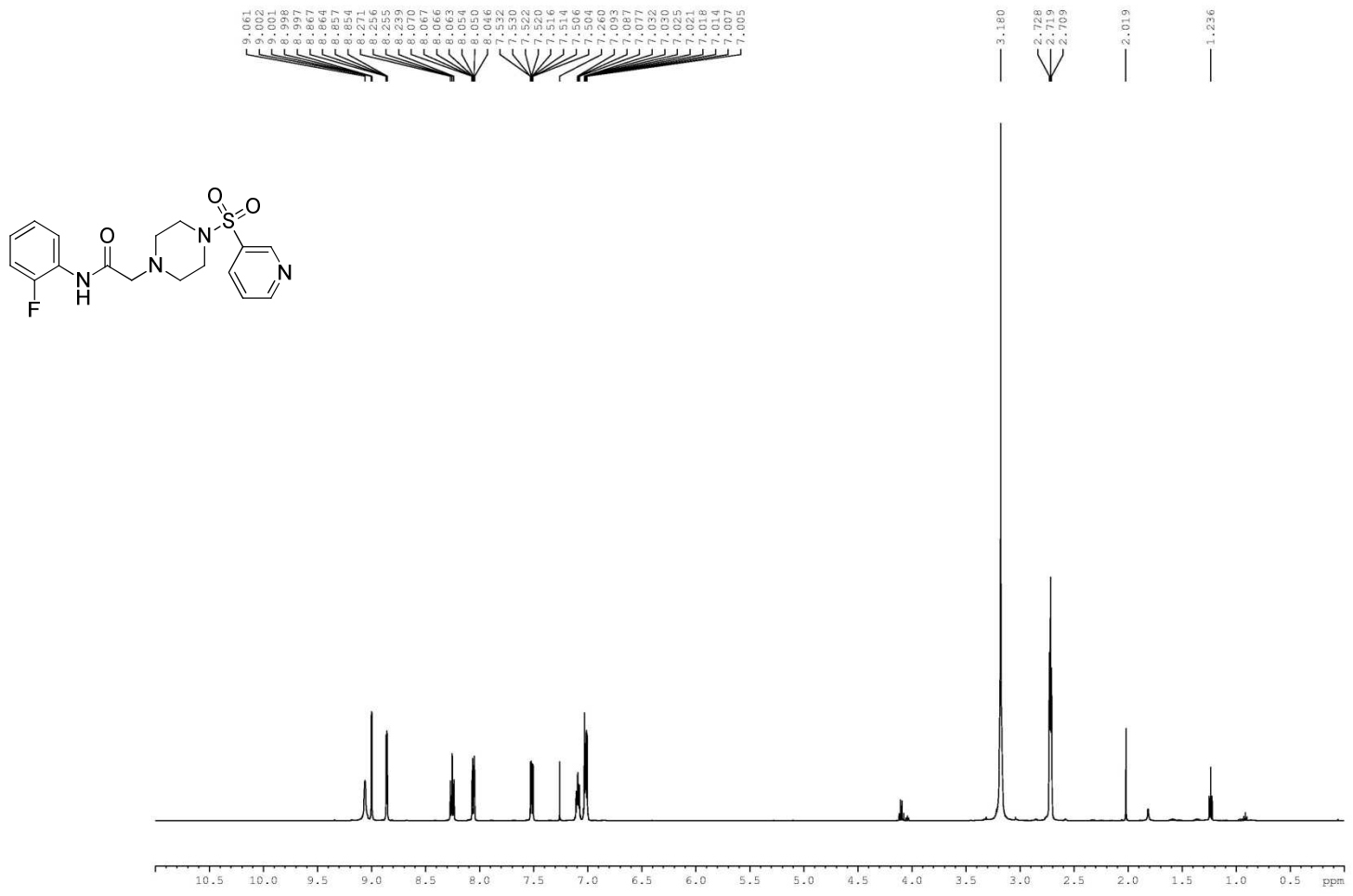
^{13}C NMR ($CDCl_3$, 126 MHz) of **15**.



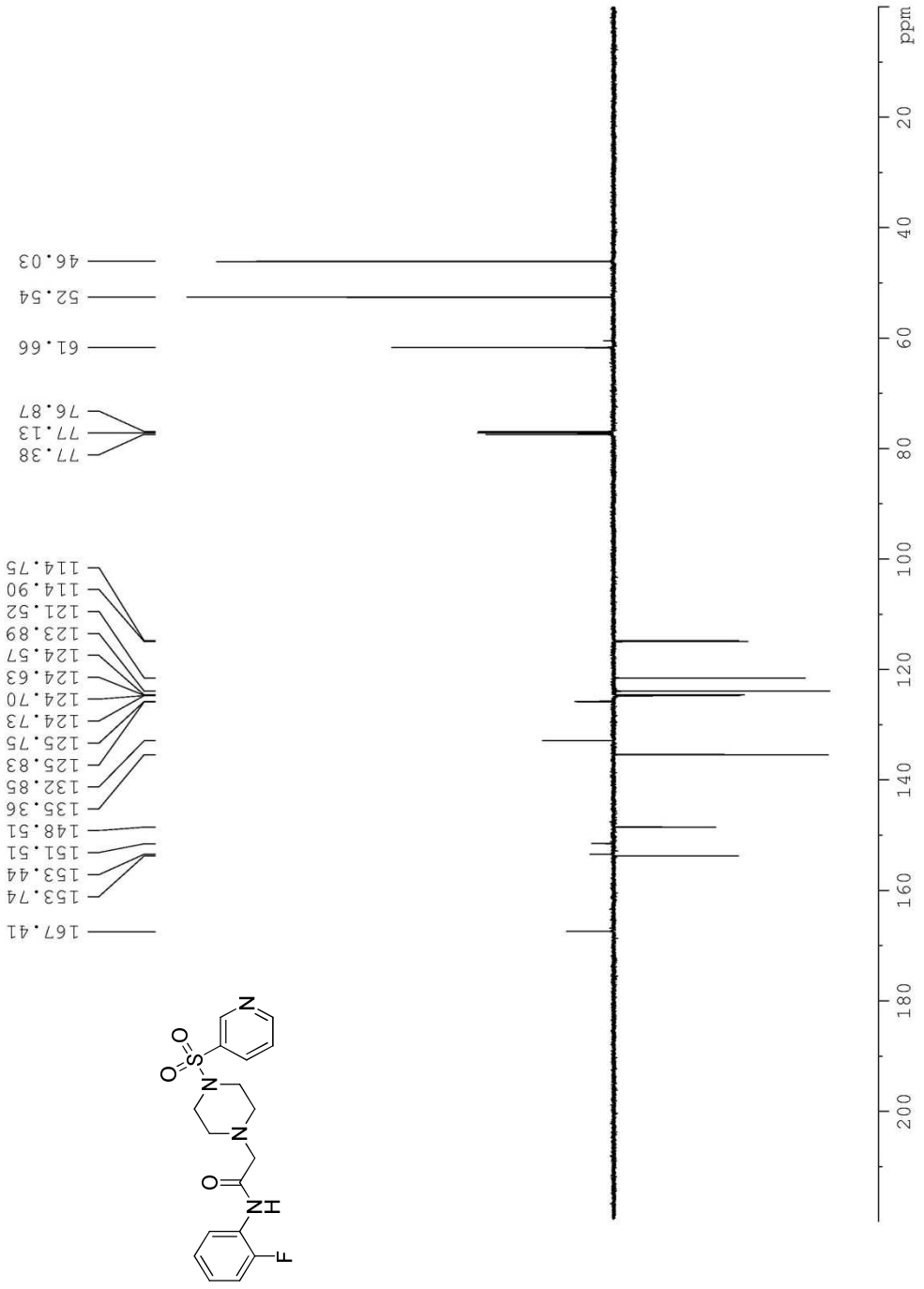
^{1}H NMR ($CDCl_3$, 400 MHz) of **16**.



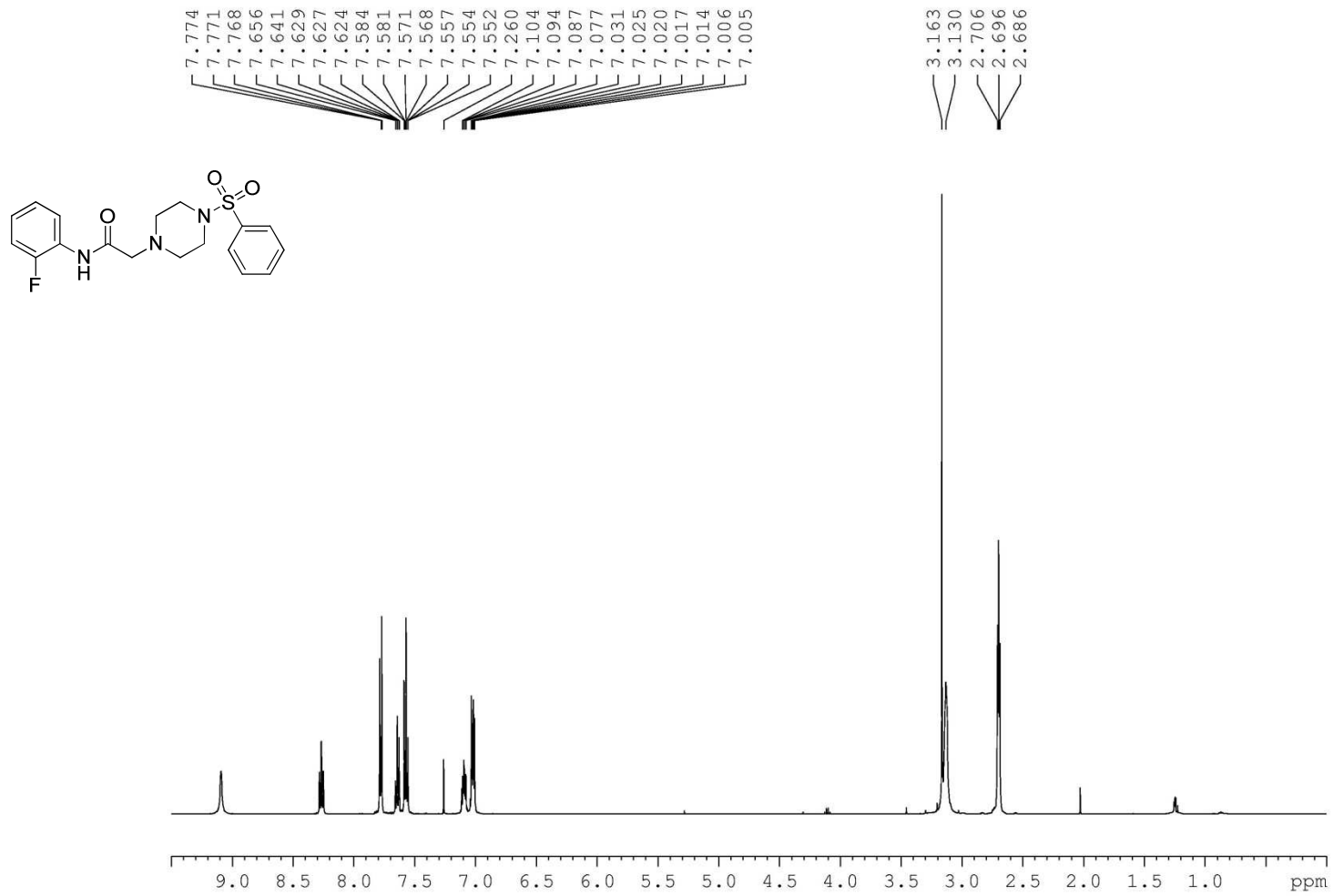
^{13}C NMR ($CDCl_3$, 100 MHz) of **16**.



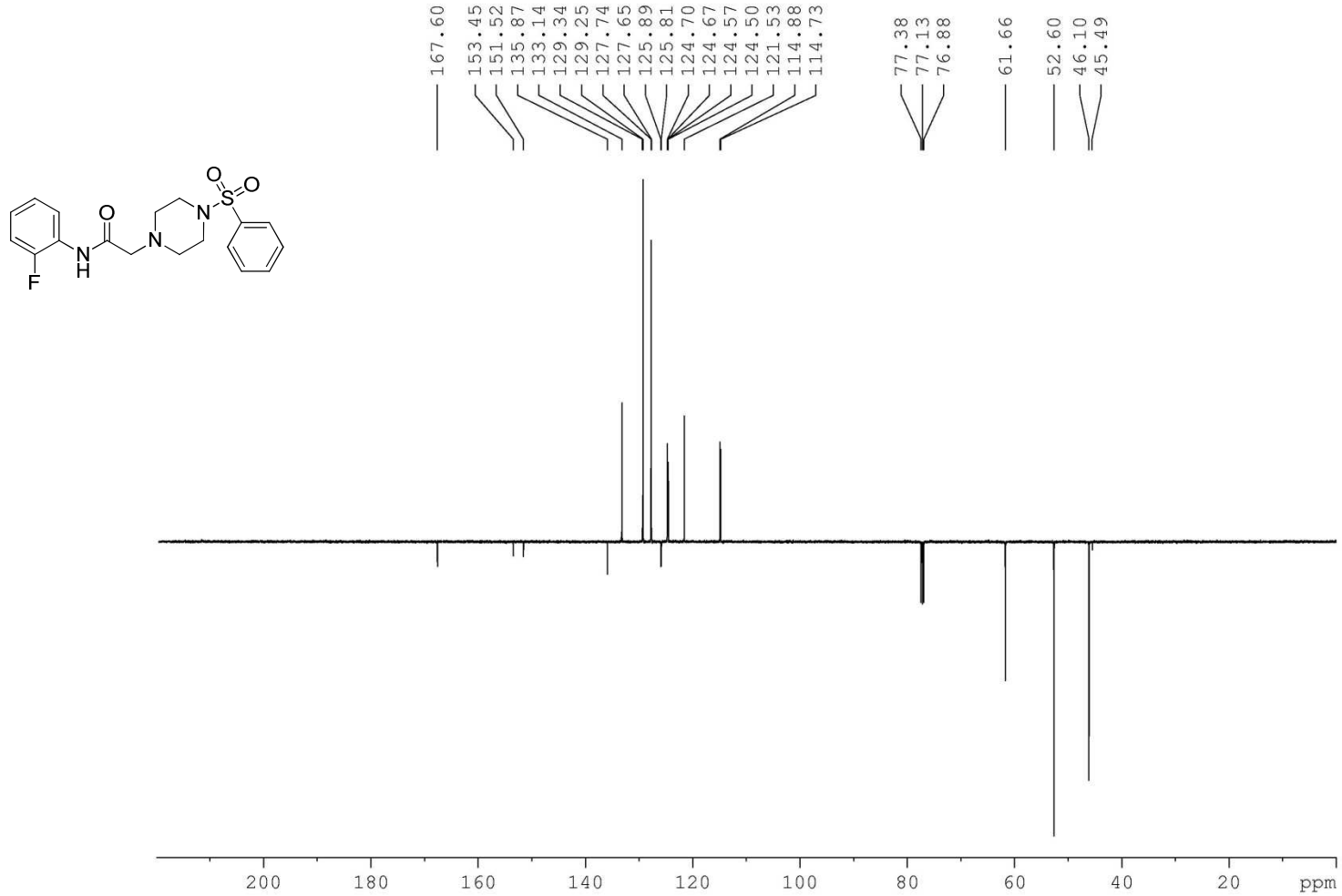
^{1}H NMR ($CDCl_3$, 500 MHz) of **17**.



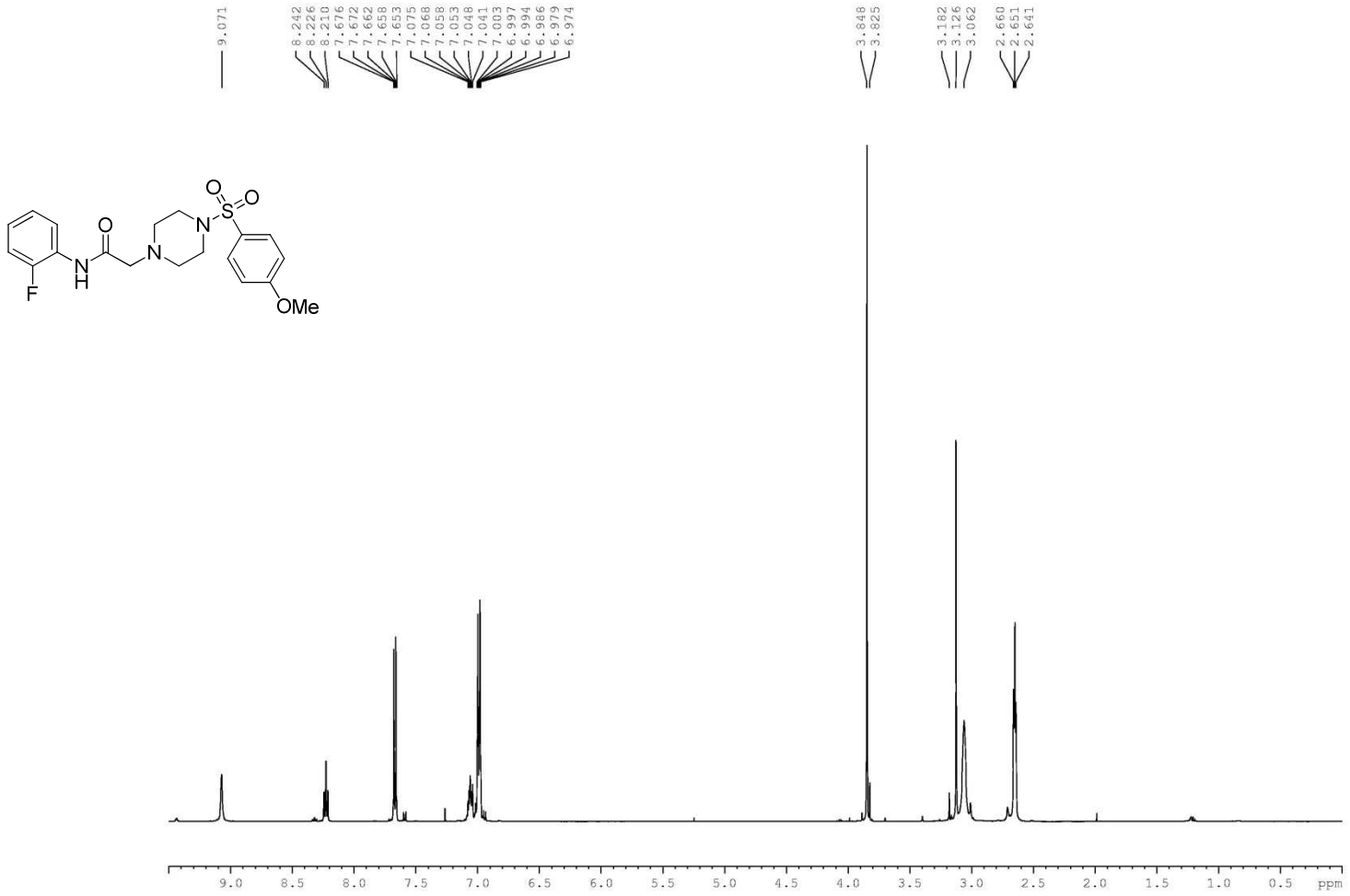
^{13}C NMR ($CDCl_3$, 126 MHz) of **17**.



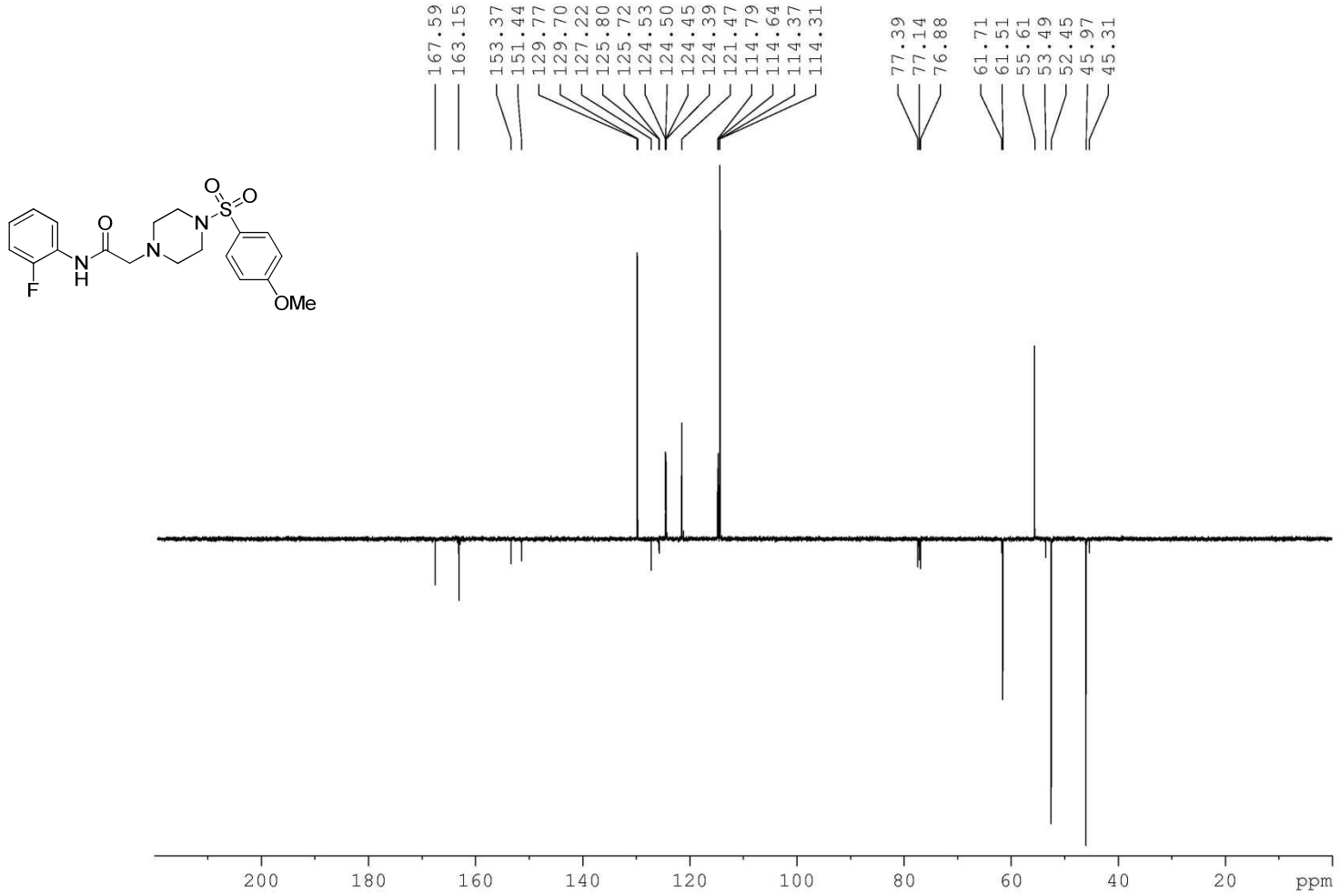
^{1}H NMR ($CDCl_3$, 500 MHz) of **18**.



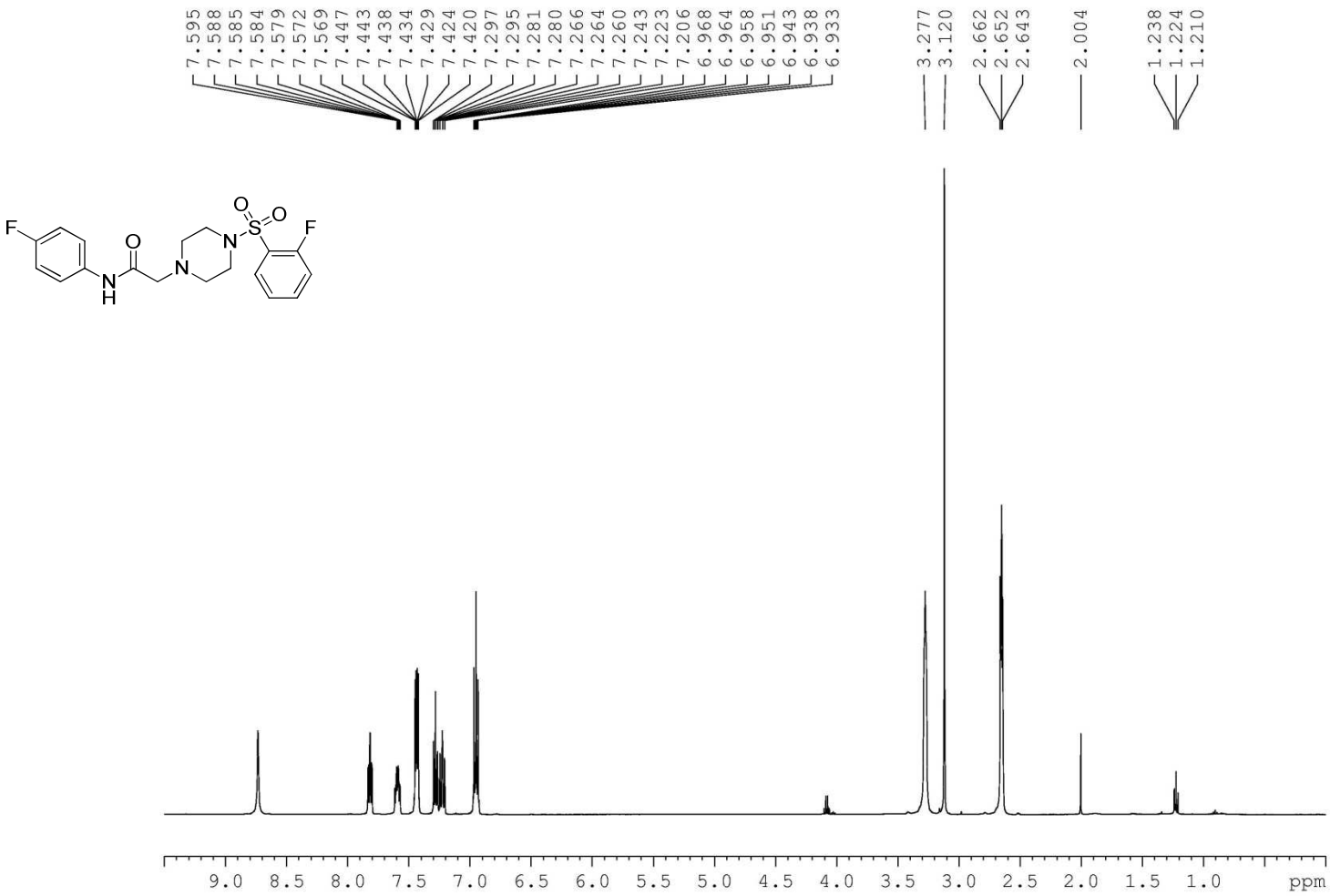
^{13}C NMR ($CDCl_3$, 126 MHz) of **18**.



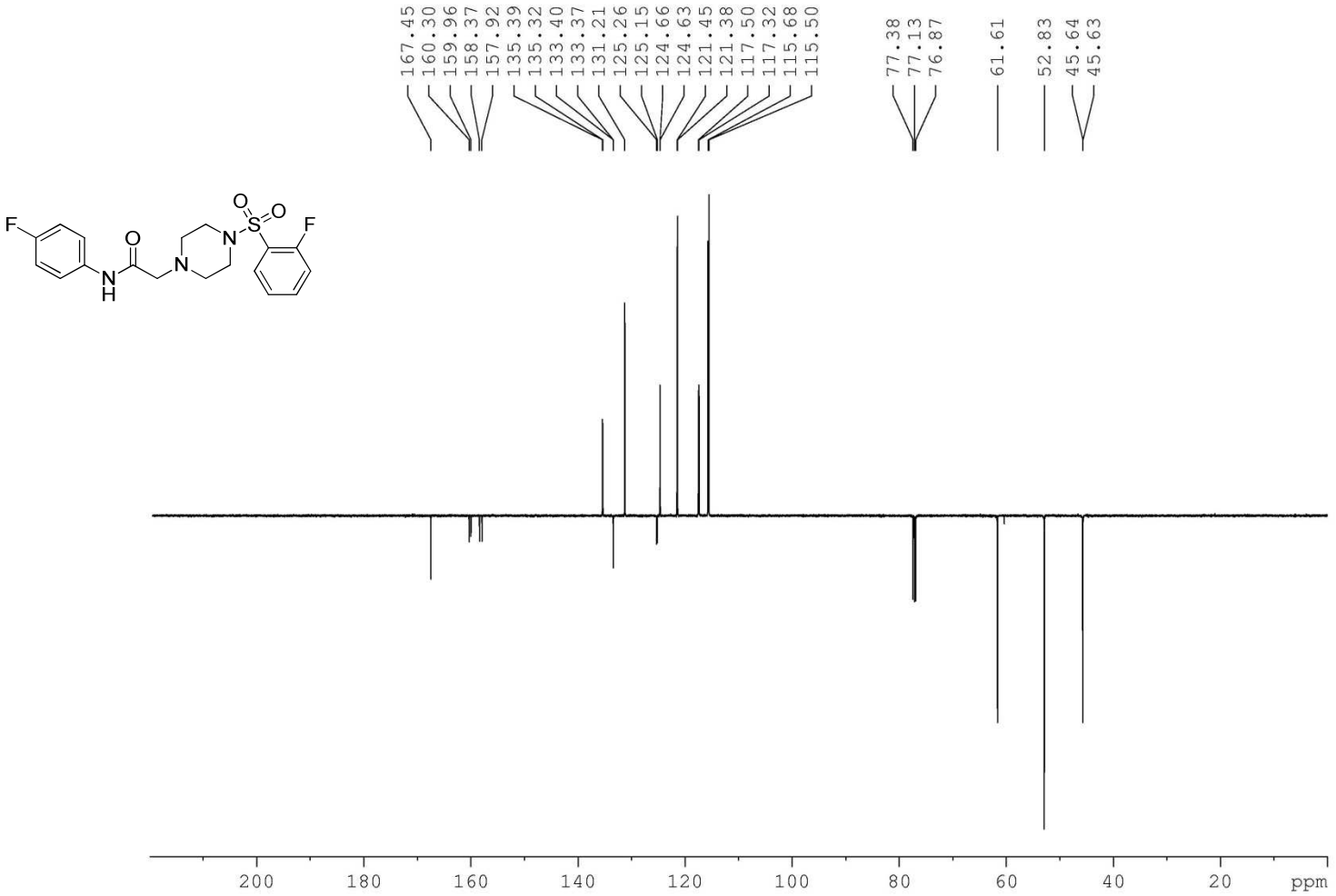
^{1}H NMR ($CDCl_3$, 500 MHz) of **19**.



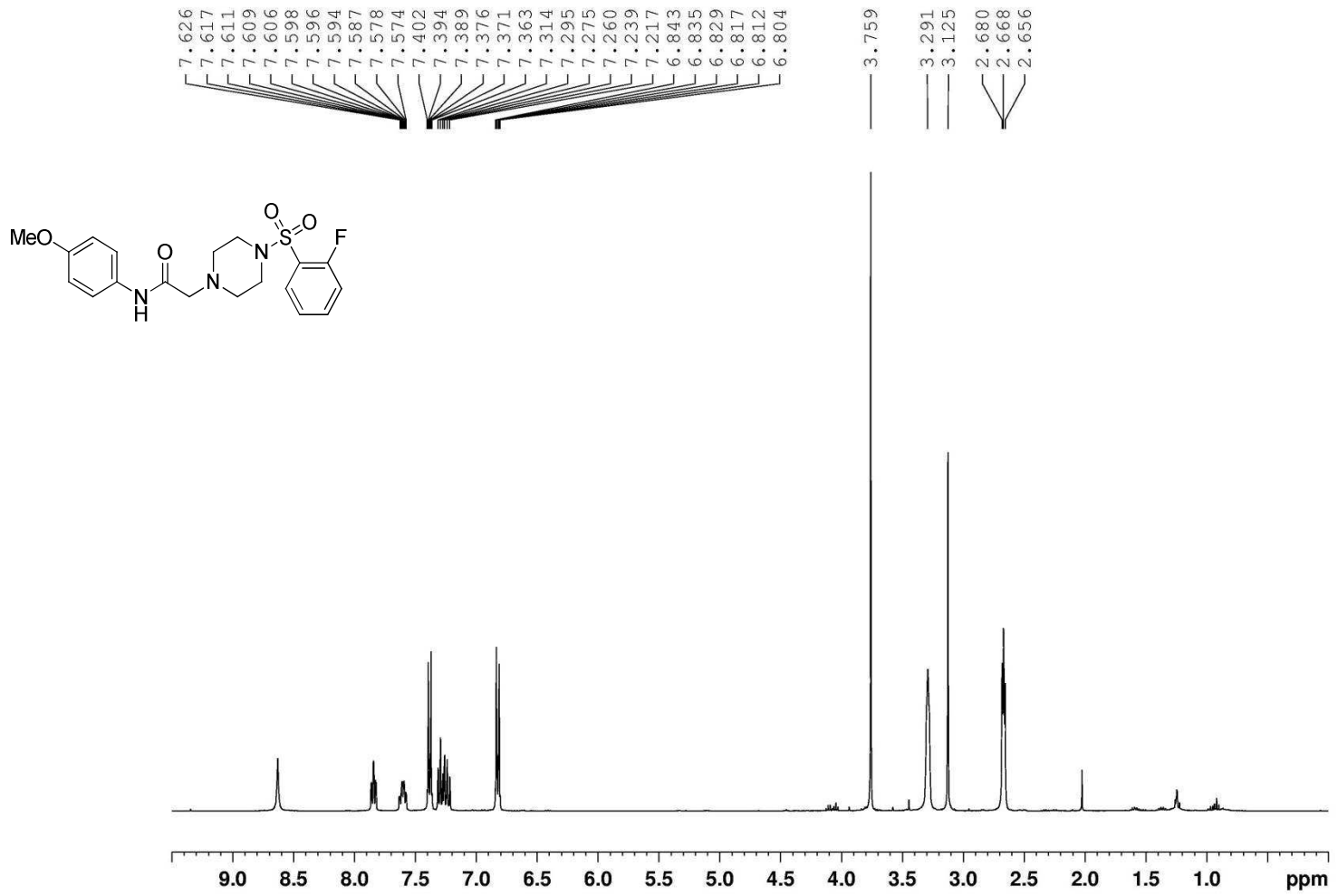
^{13}C NMR ($CDCl_3$, 126 MHz) of **19**.



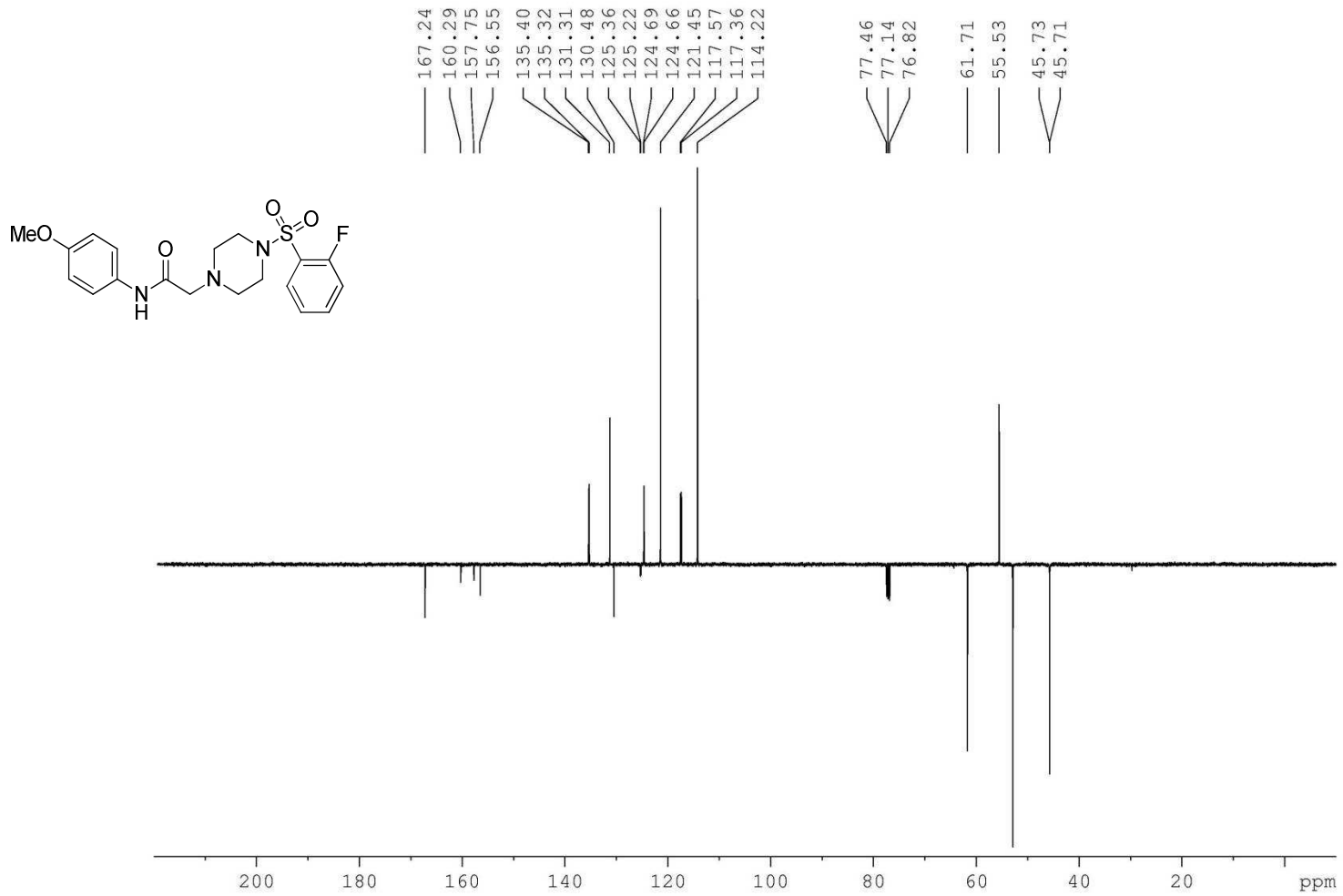
^{1}H NMR ($CDCl_3$, 500 MHz) of **20**.



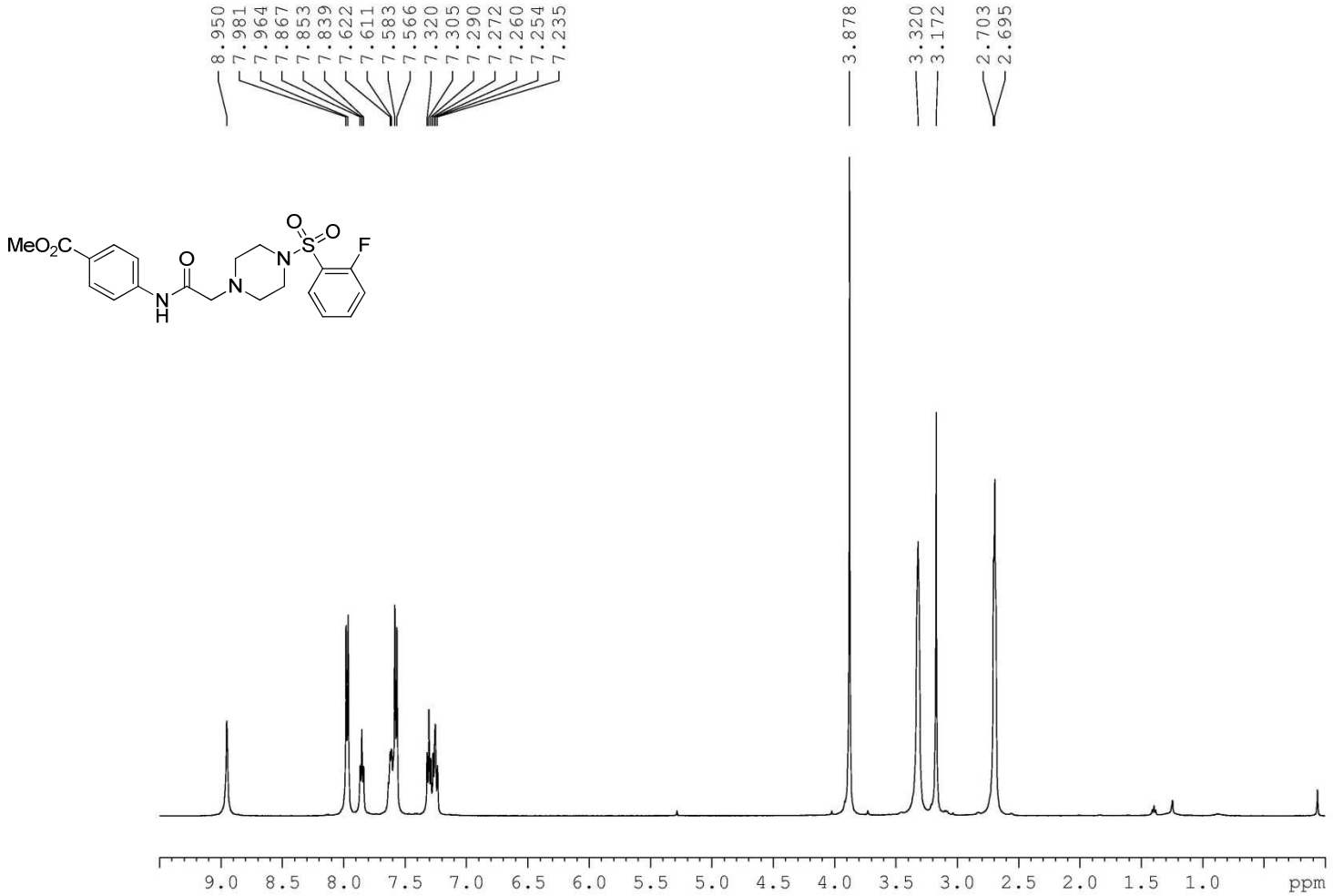
^{13}C NMR ($CDCl_3$, 126 MHz) of **20**.



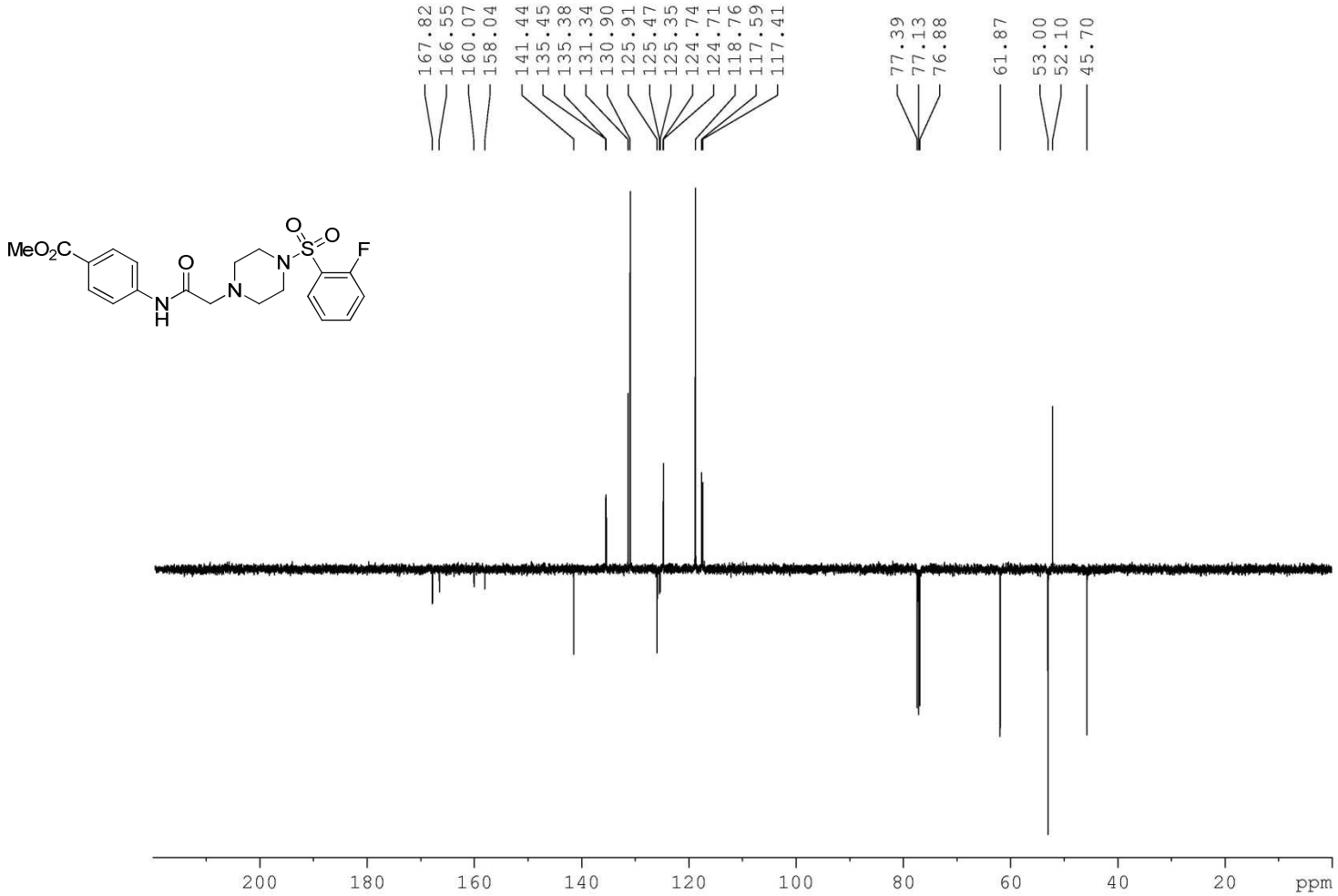
^{1}H NMR ($CDCl_3$, 500 MHz) of **21**.



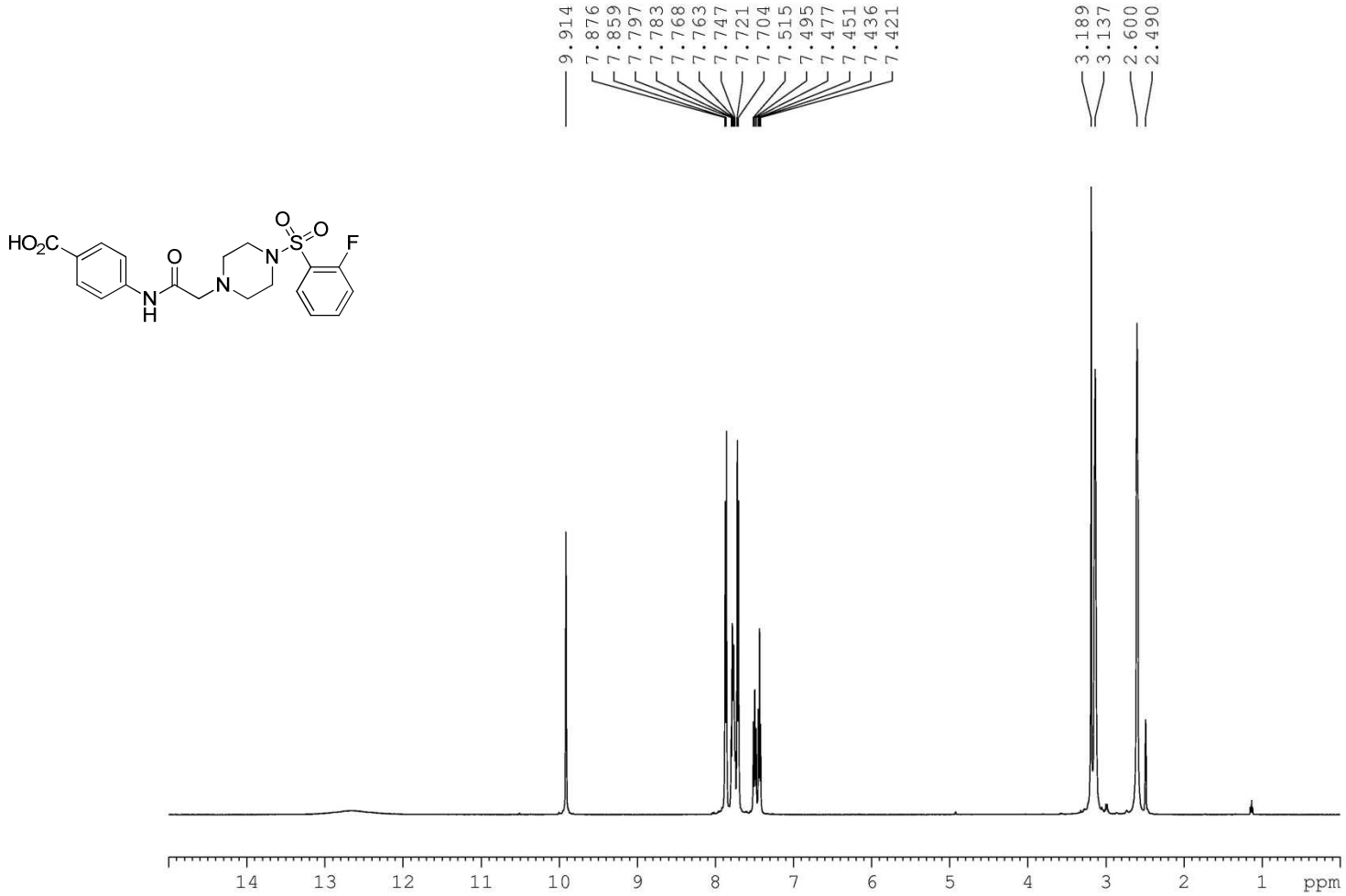
^{13}C NMR ($CDCl_3$, 126 MHz) of **21**.



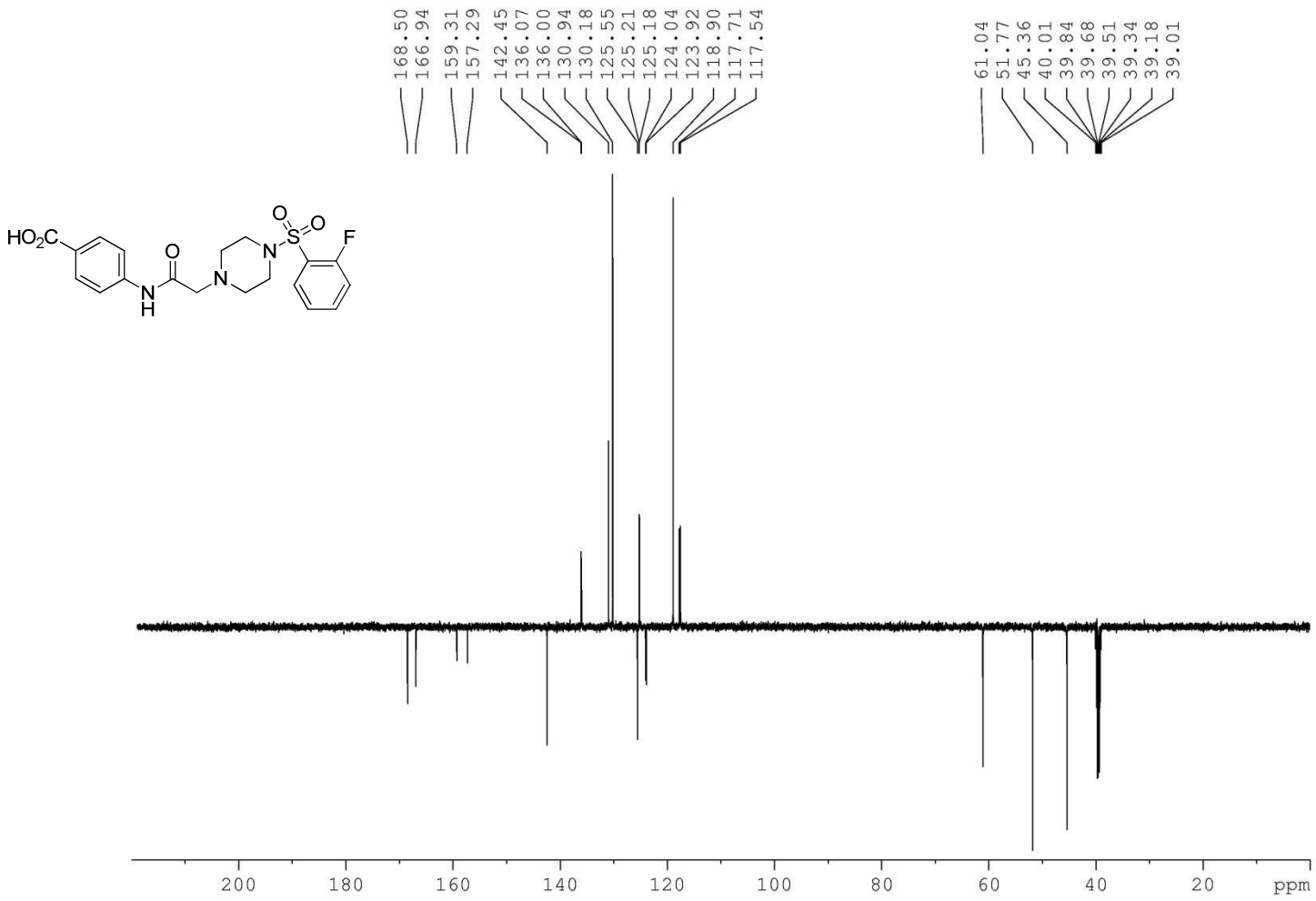
^{1}H NMR ($CDCl_3$, 500 MHz) of **22**.



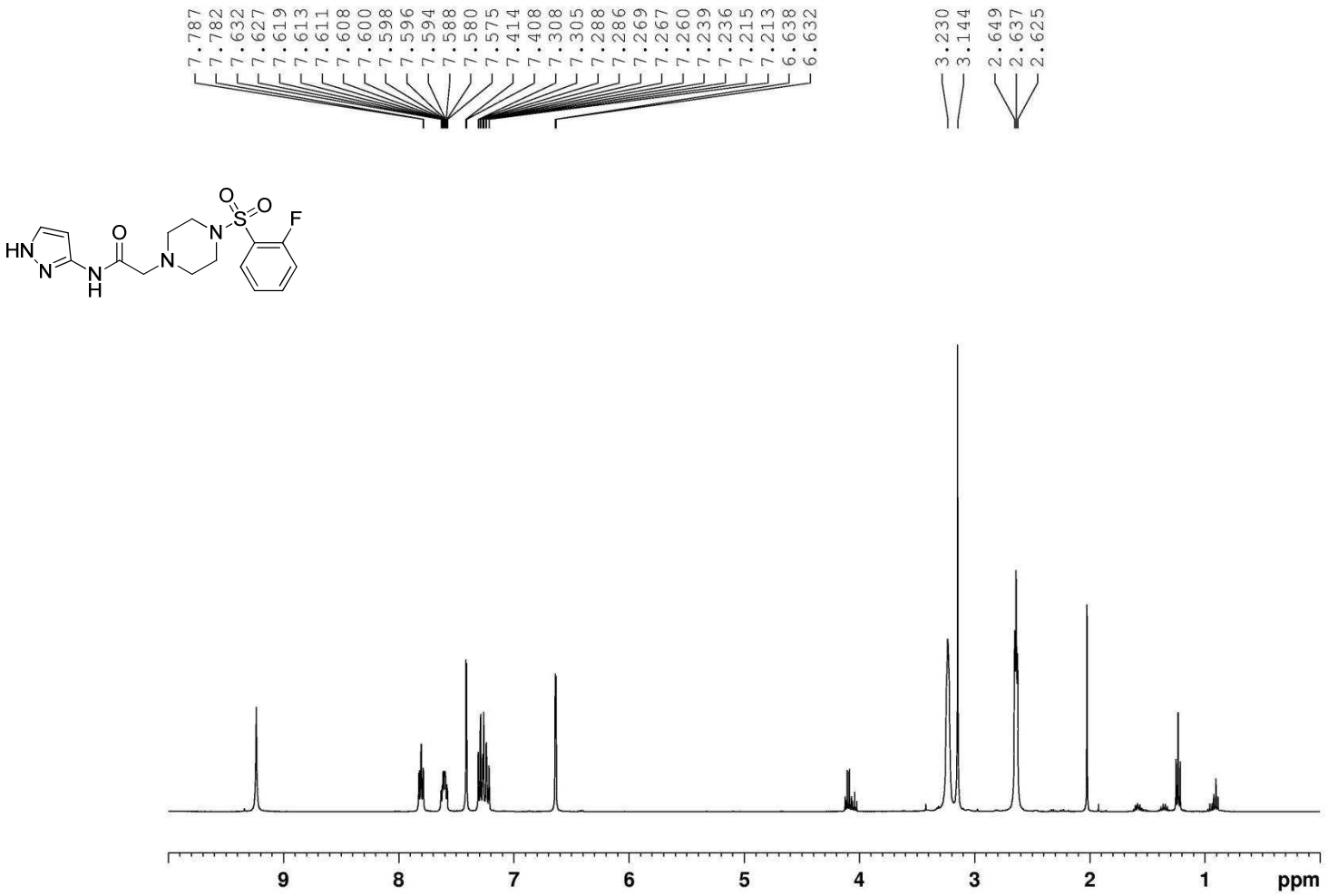
^{13}C NMR ($CDCl_3$, 126 MHz) of **22**.



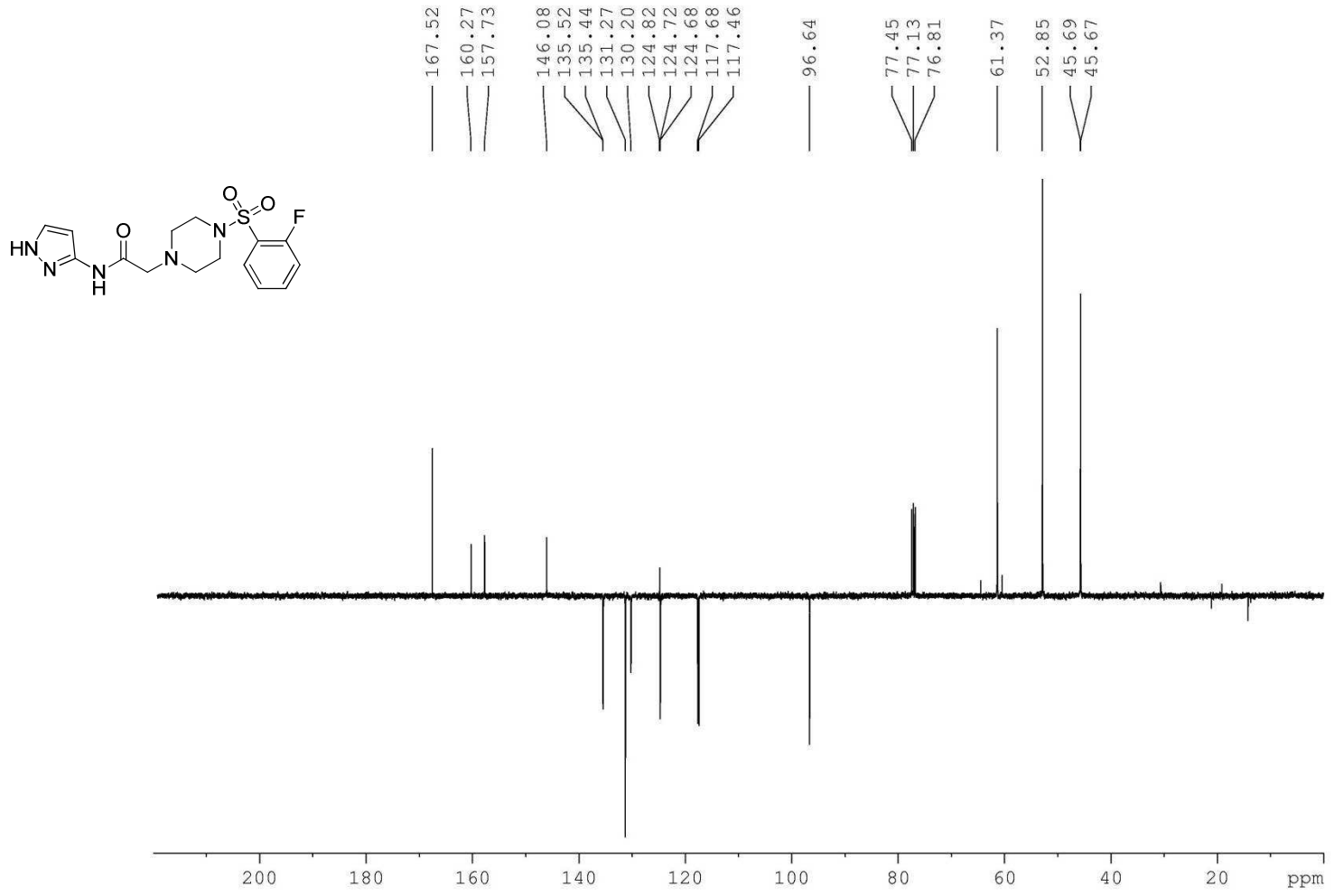
^{1}H NMR (DMSO-d_6, 500 MHz) of **23**.



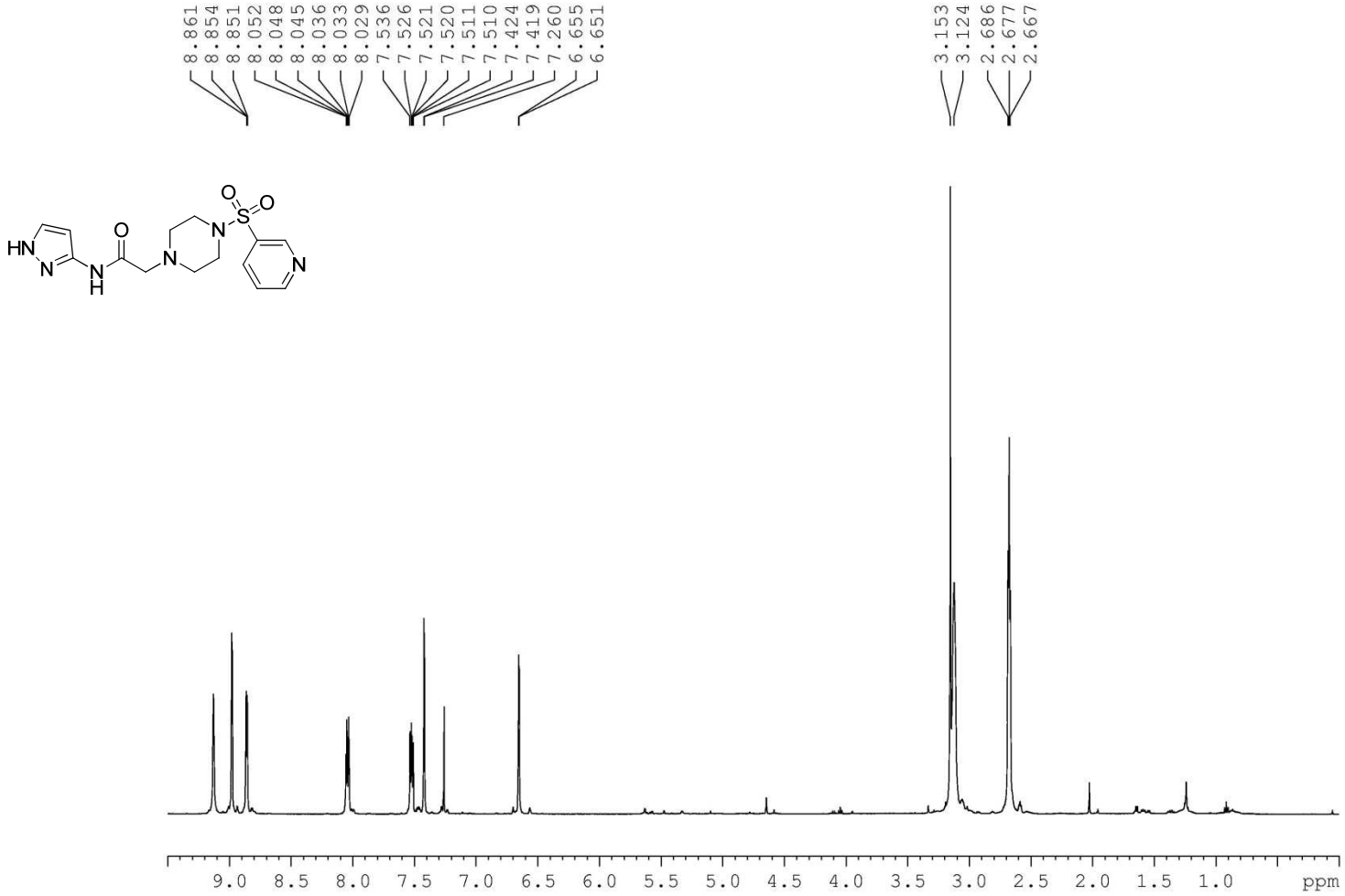
^{13}C NMR (DMSO-d_6, 126 MHz) of **23**.



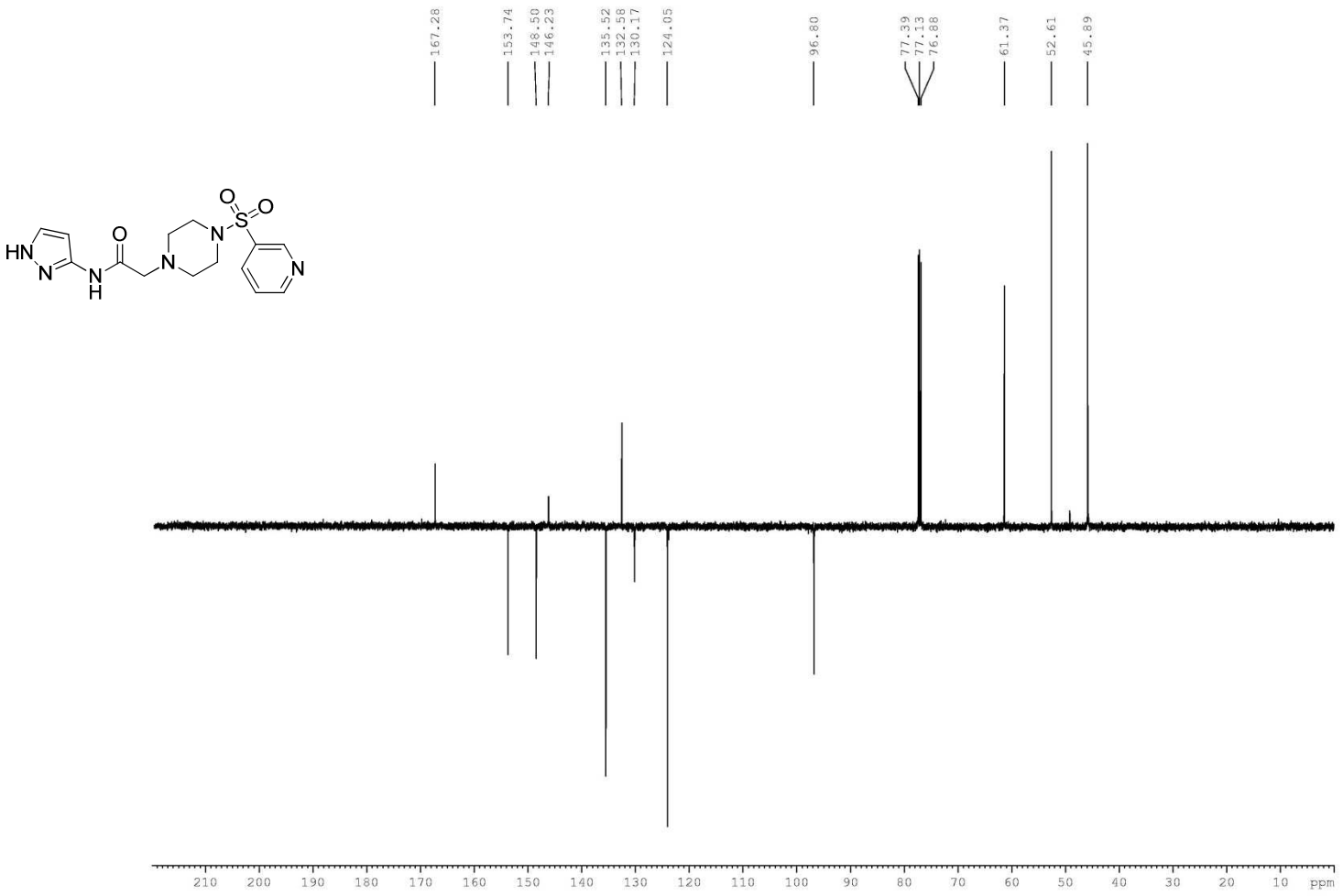
^{1}H NMR ($CDCl_3$, 400 MHz) of **24**.



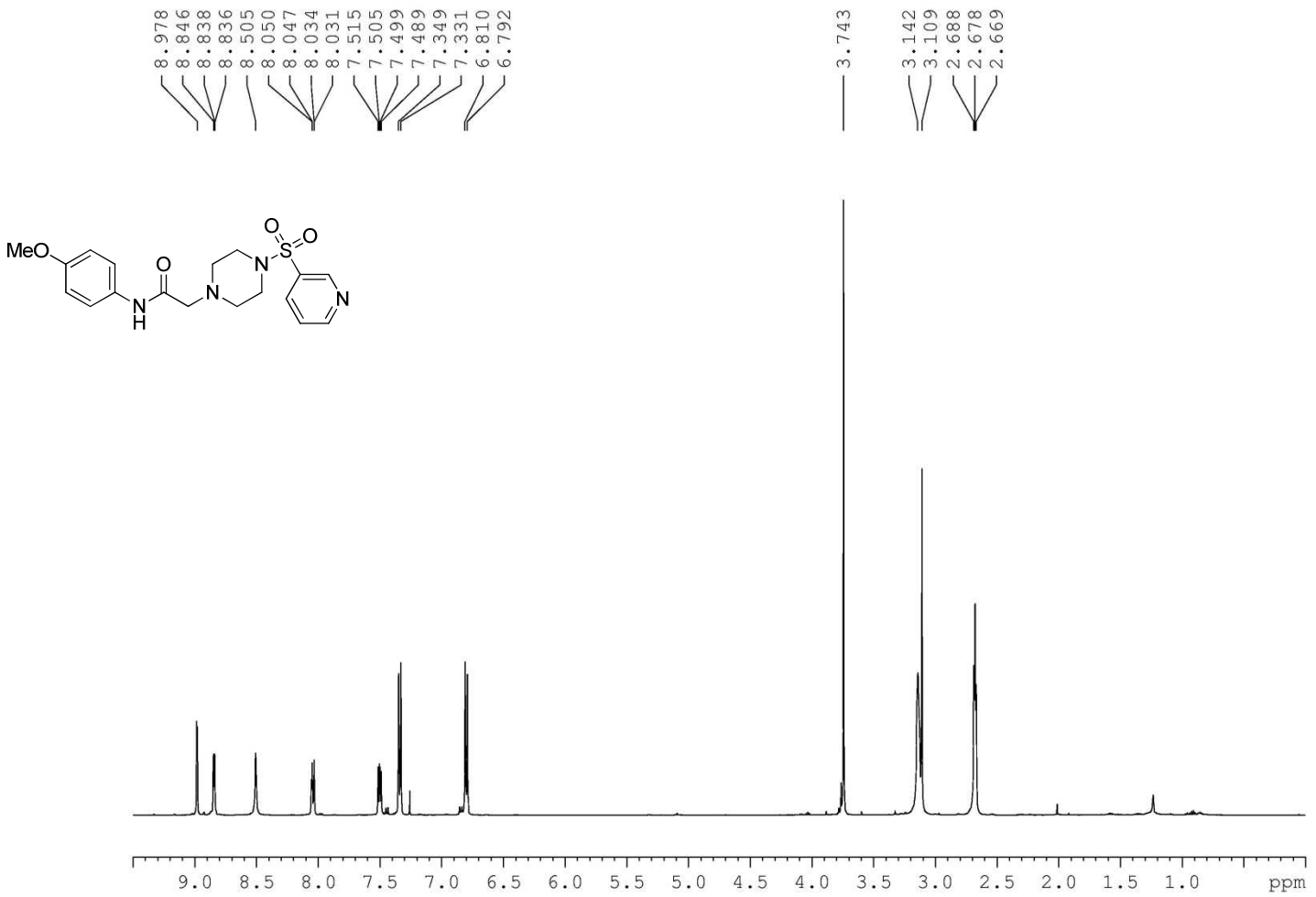
^{13}C NMR ($CDCl_3$, 101 MHz) of **24**.



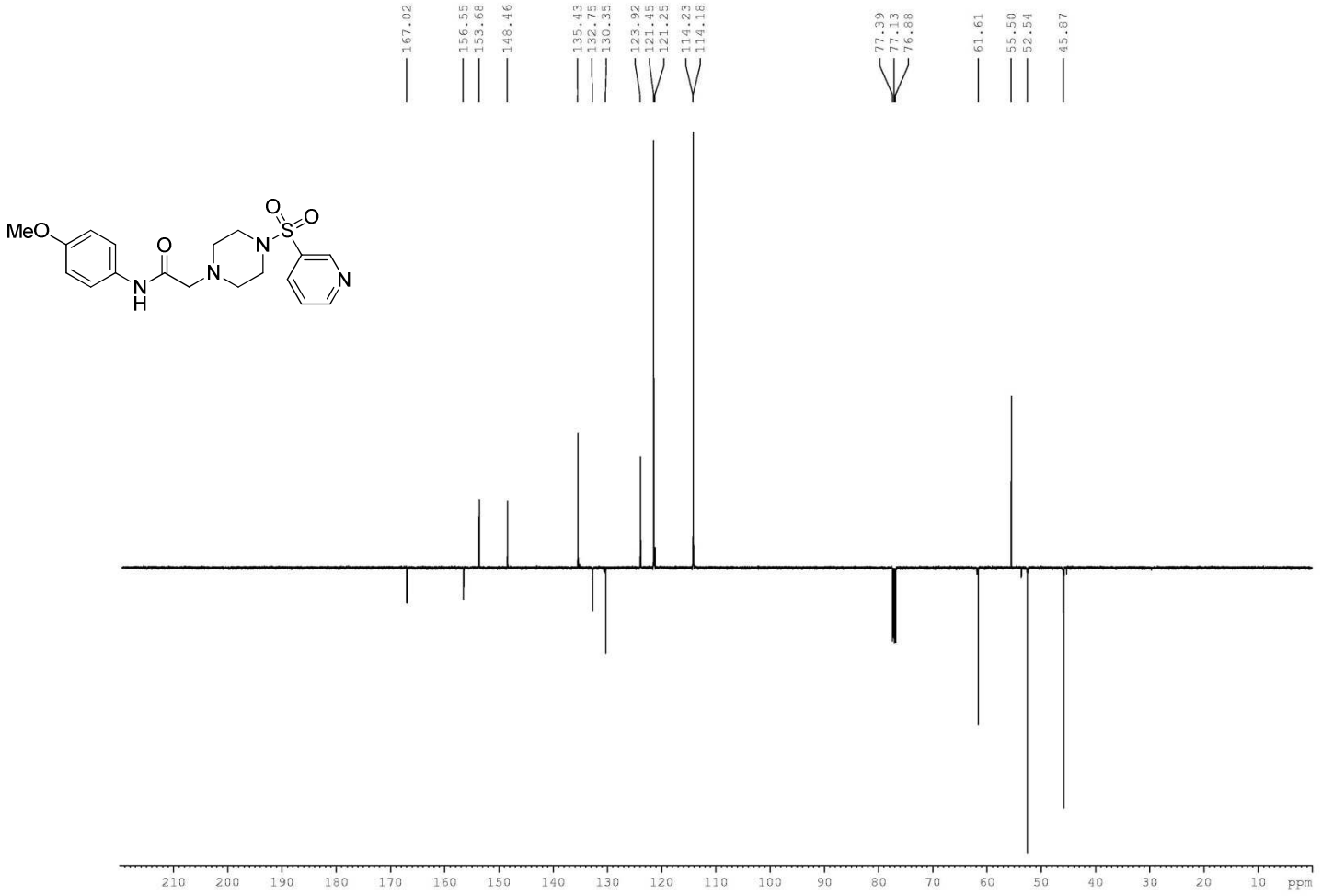
^{1}H NMR ($CDCl_3$, 500 MHz) of **25**.



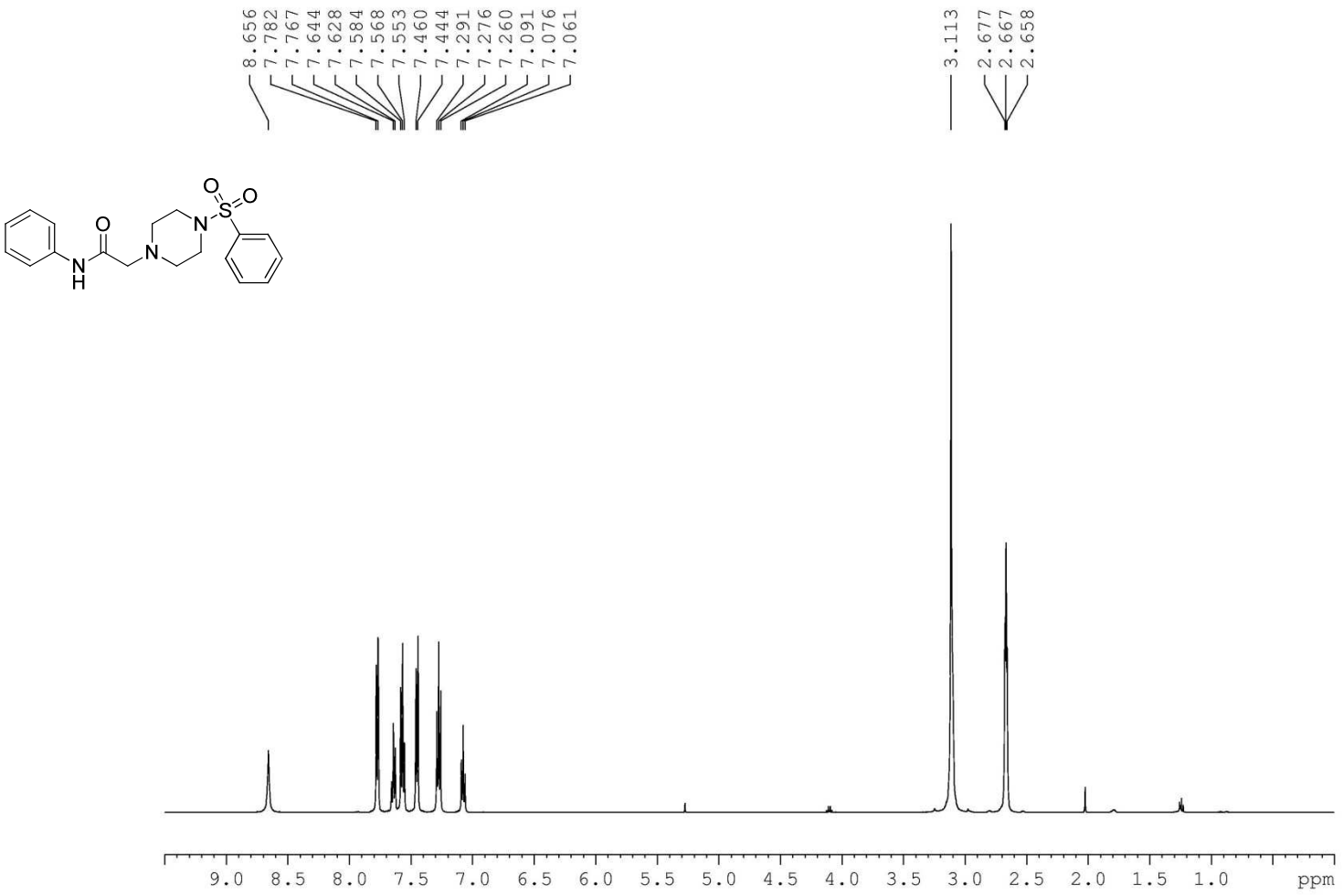
^{13}C NMR ($CDCl_3$, 126 MHz) of **25**.



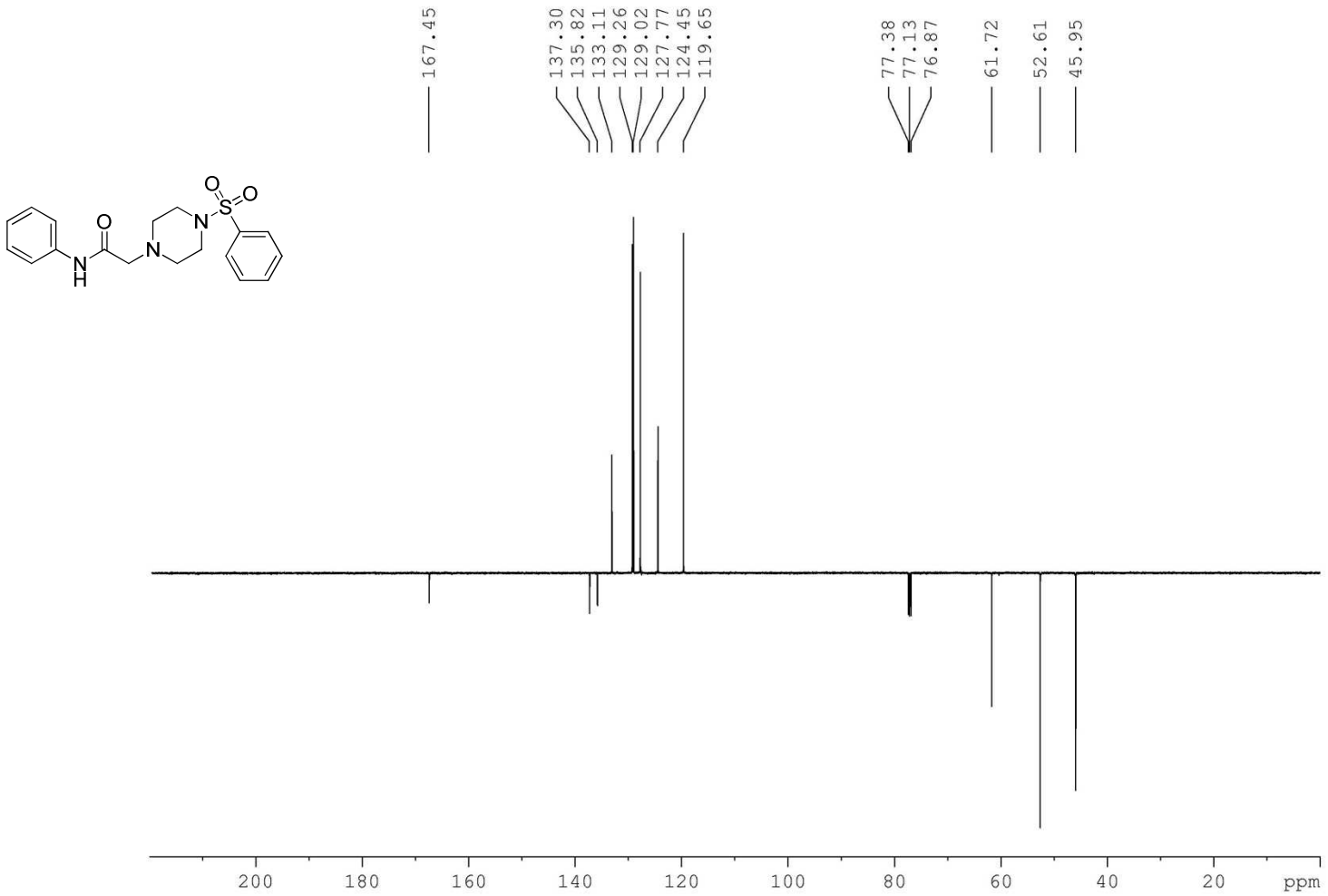
^{1}H NMR ($CDCl_3$, 500 MHz) of **26**.



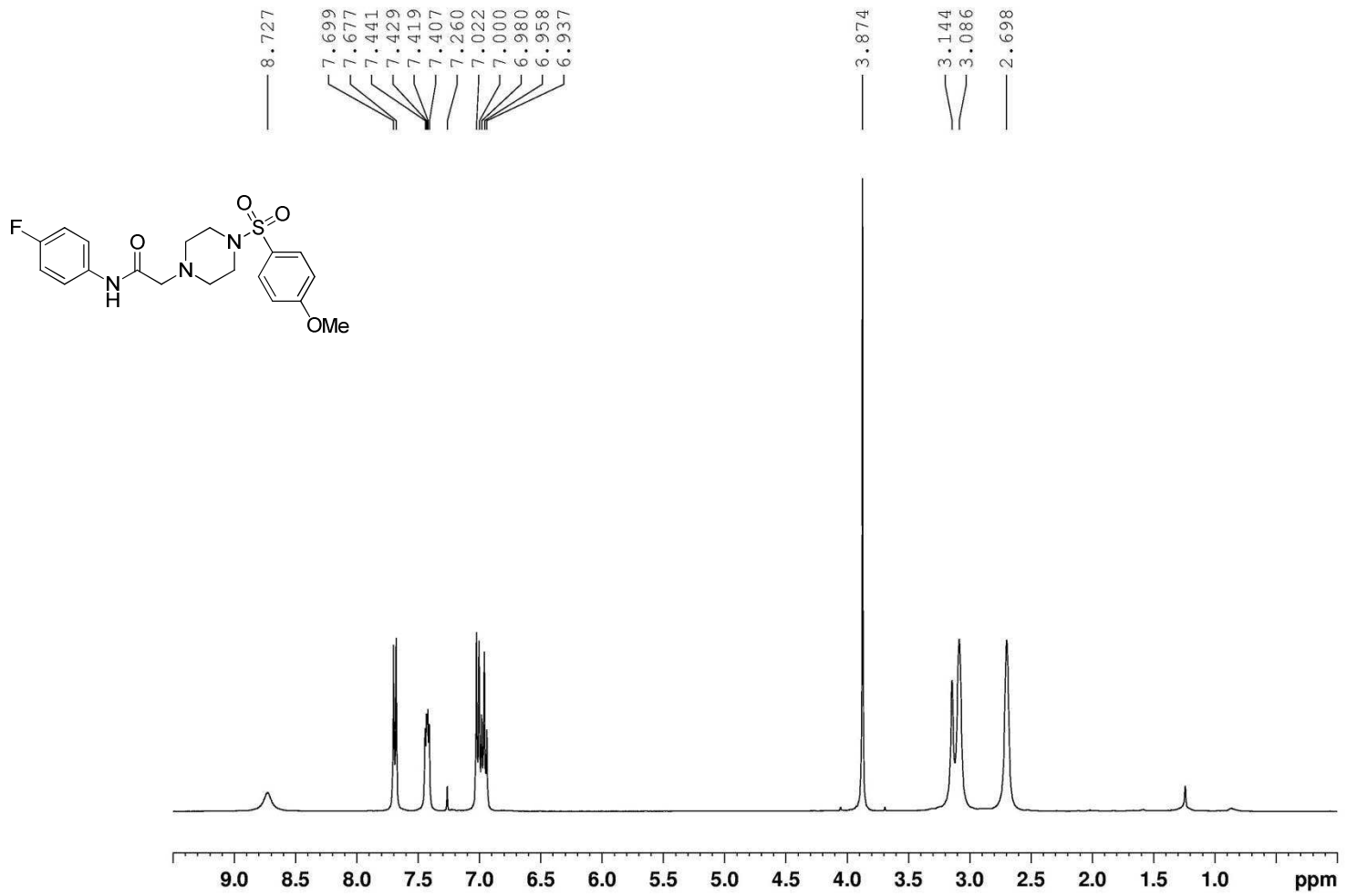
^{13}C NMR ($CDCl_3$, 126 MHz) of **26**.



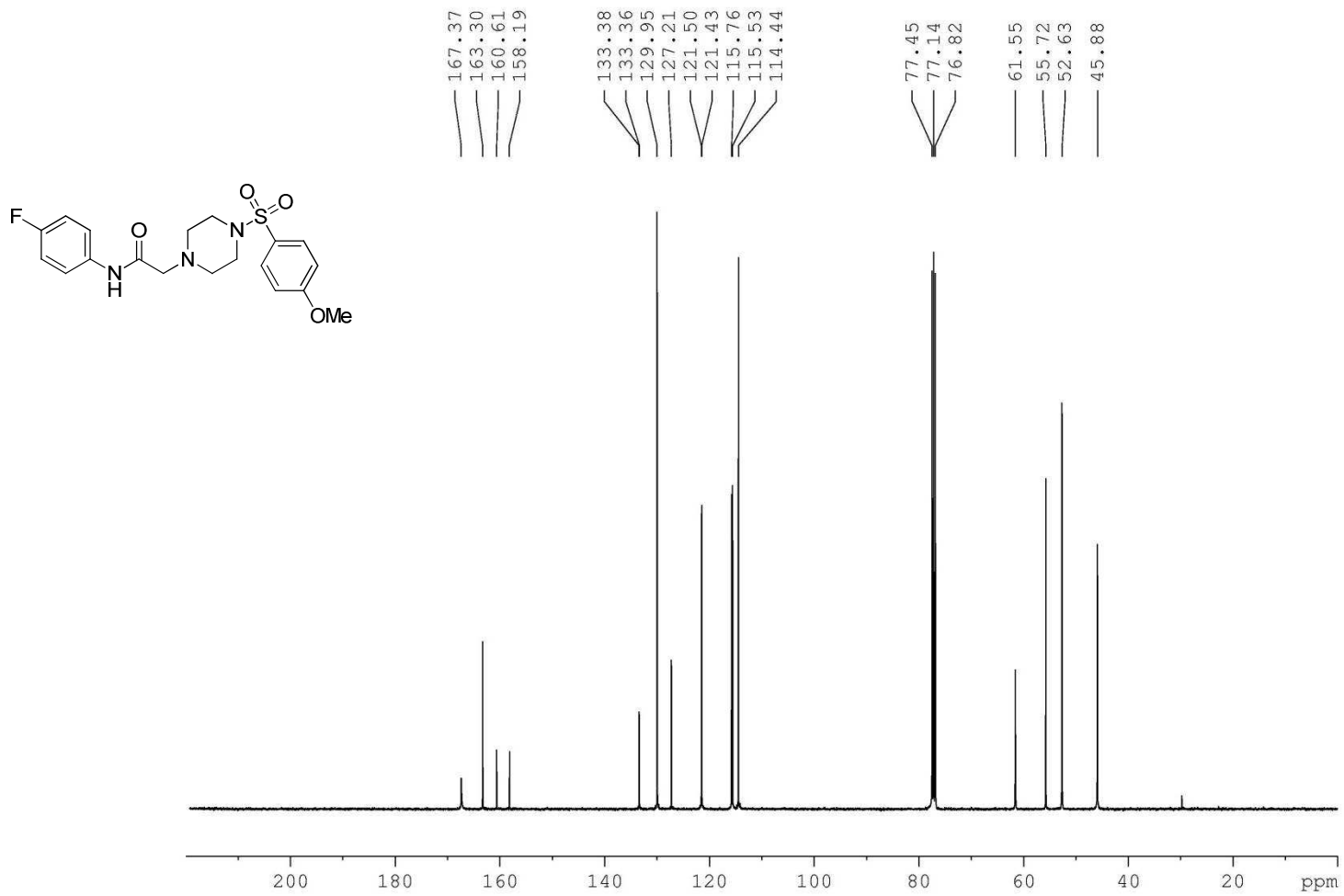
^{1}H NMR ($CDCl_3$, 500 MHz) of **27**.



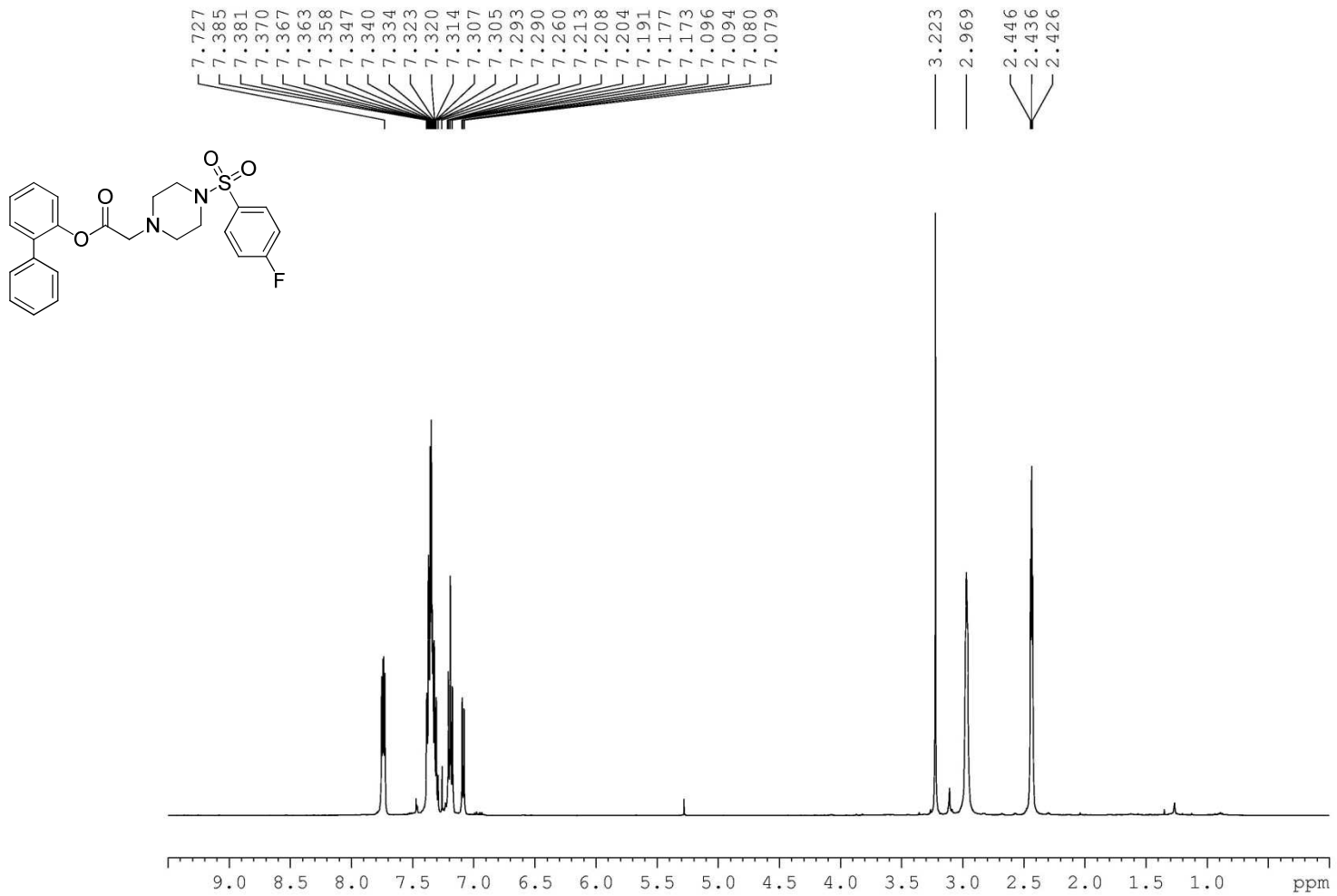
^{13}C NMR ($CDCl_3$, 126 MHz) of **27**.



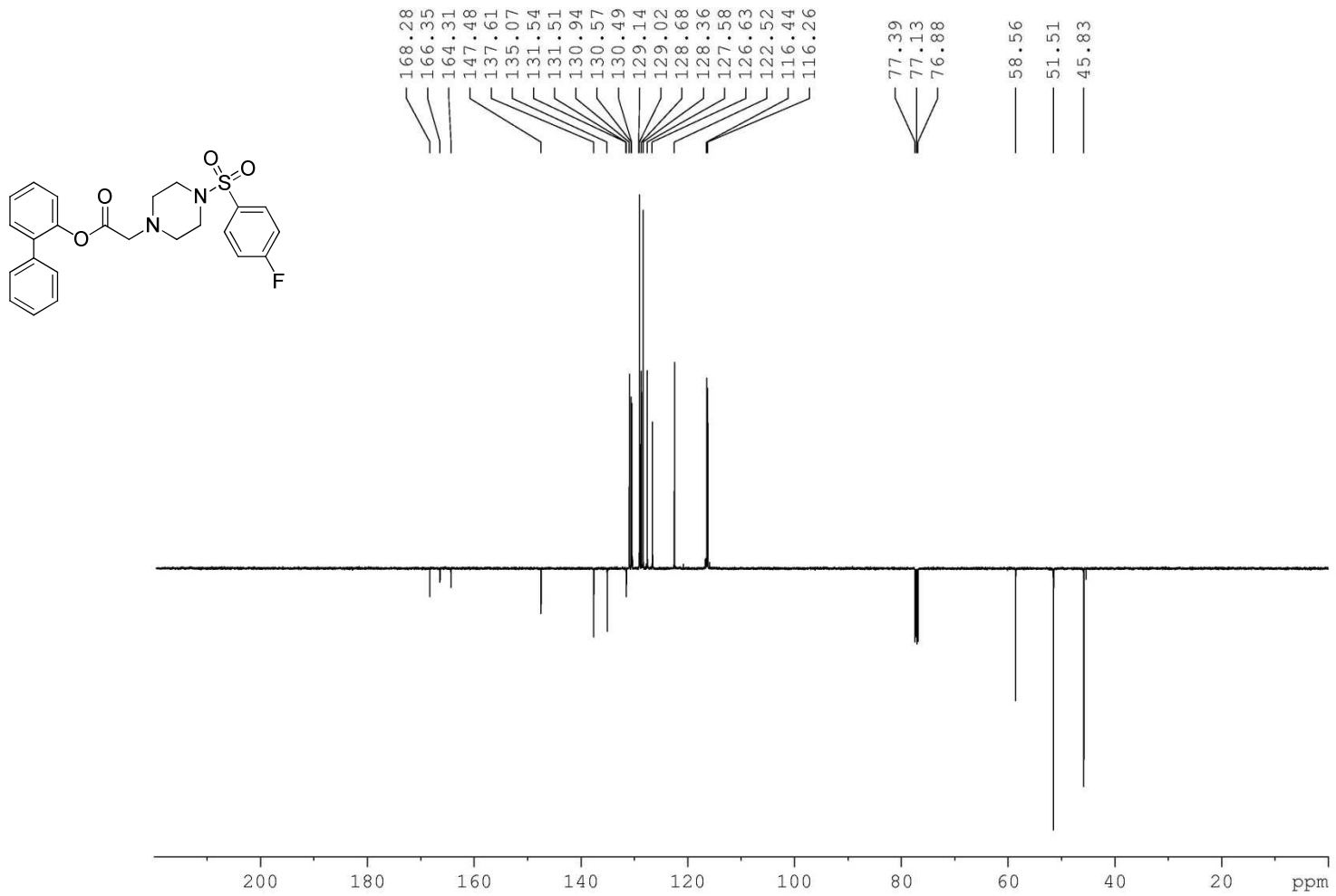
^{1}H NMR ($CDCl_3$, 500 MHz) of **28**.



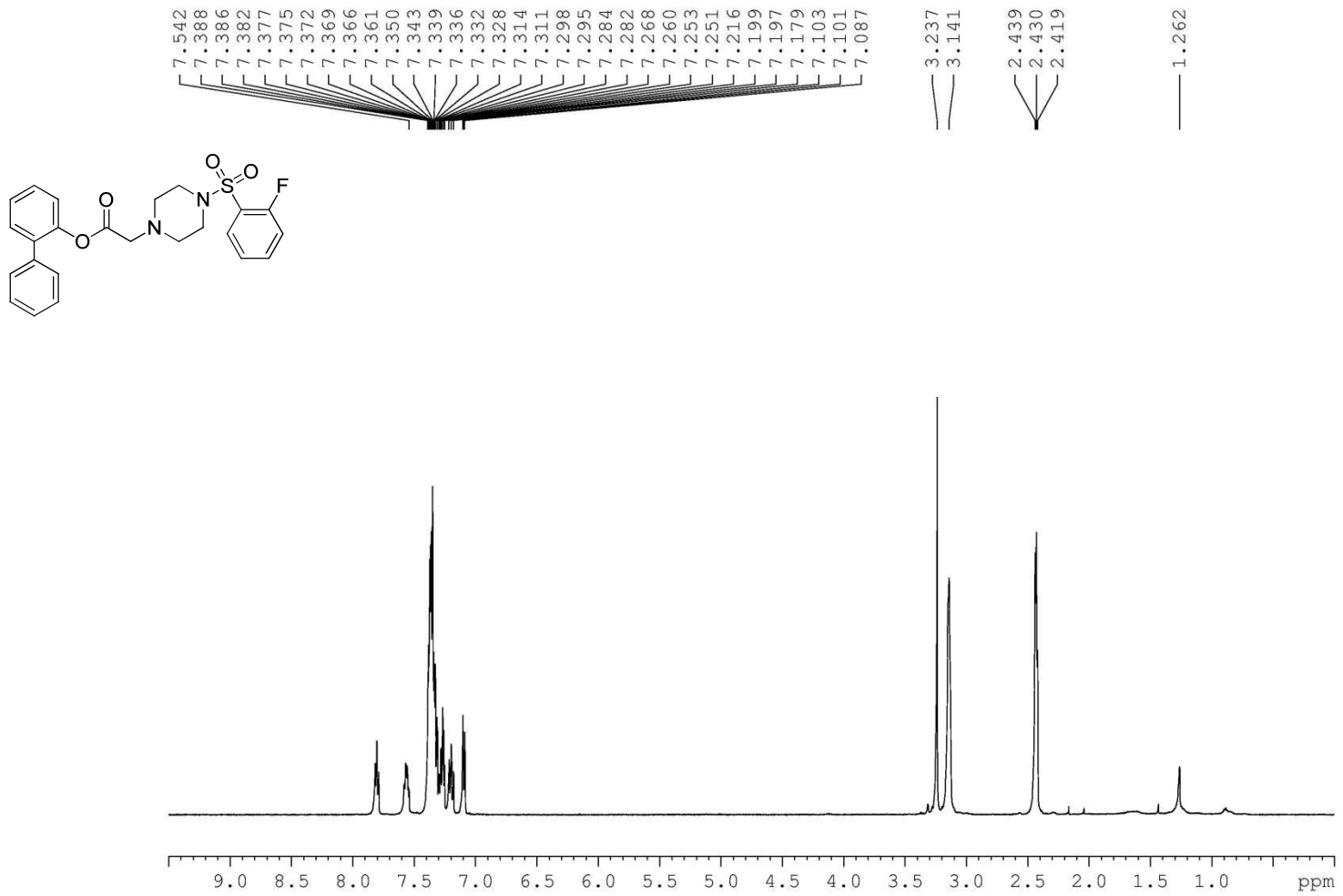
^{13}C NMR ($CDCl_3$, 101 MHz) of **28**.



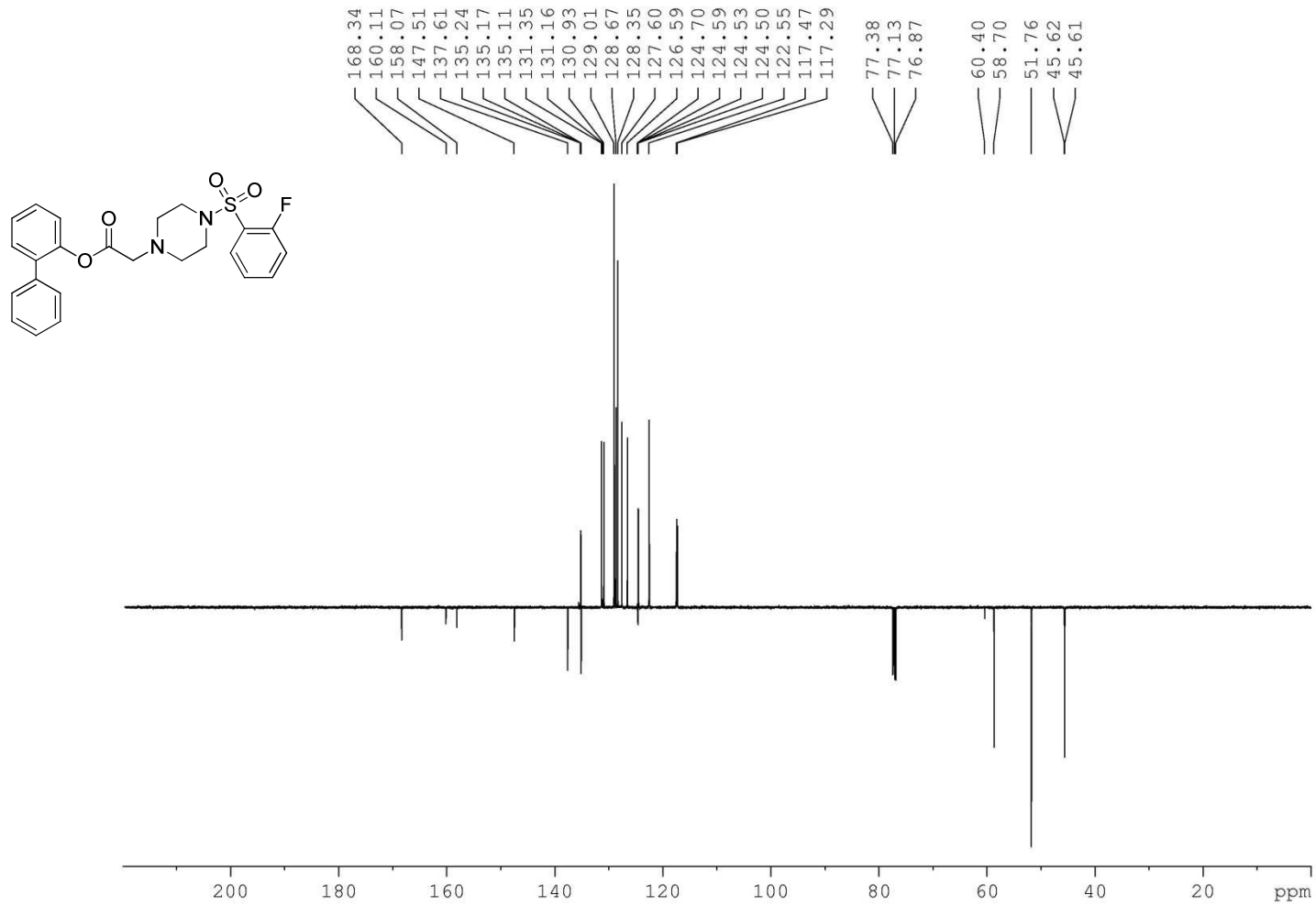
^{1}H NMR ($CDCl_3$, 500 MHz) of **29**.



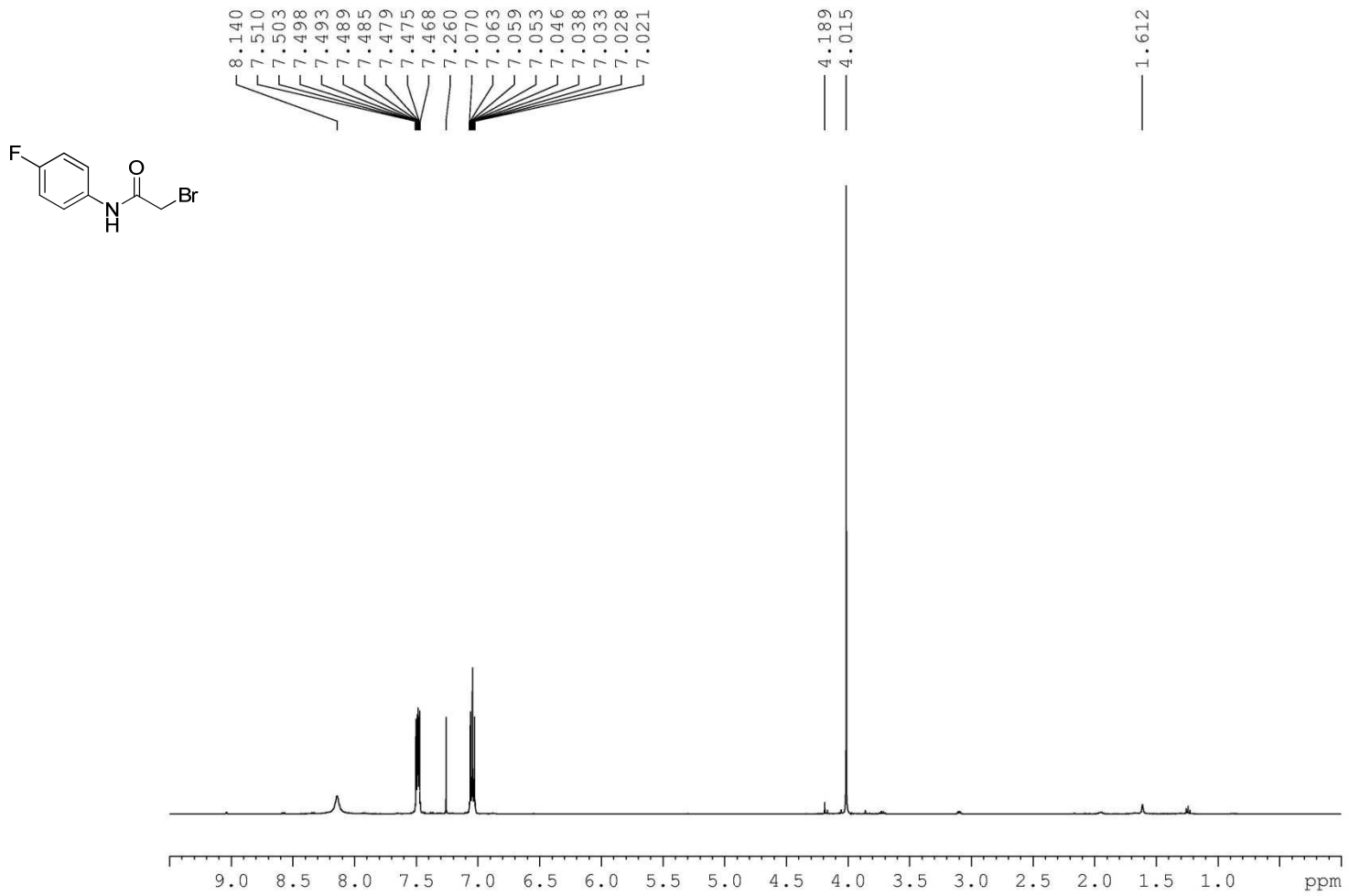
^{13}C NMR ($CDCl_3$, 126 MHz) of **29**.



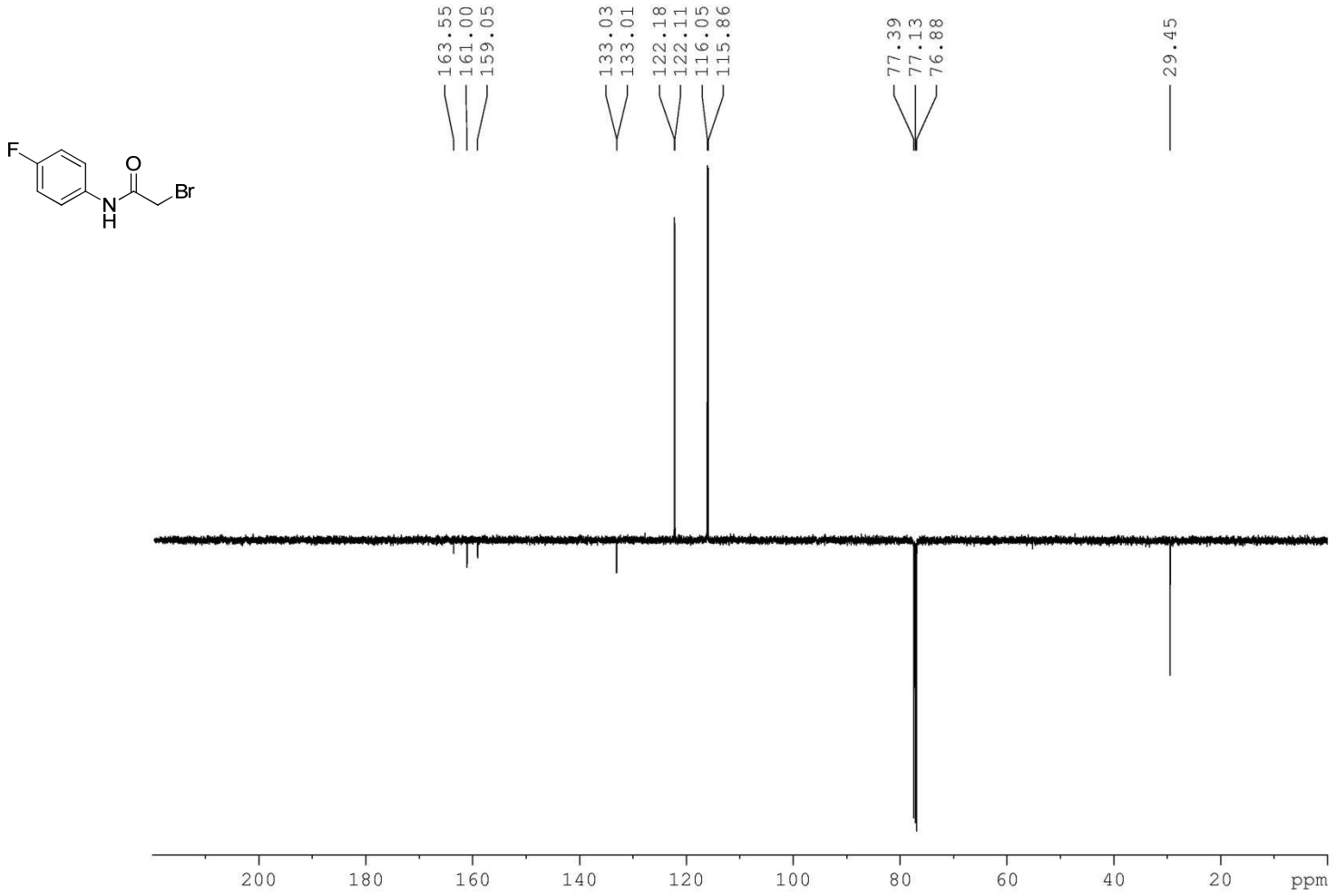
^{1}H NMR ($CDCl_3$, 500 MHz) of **30**.



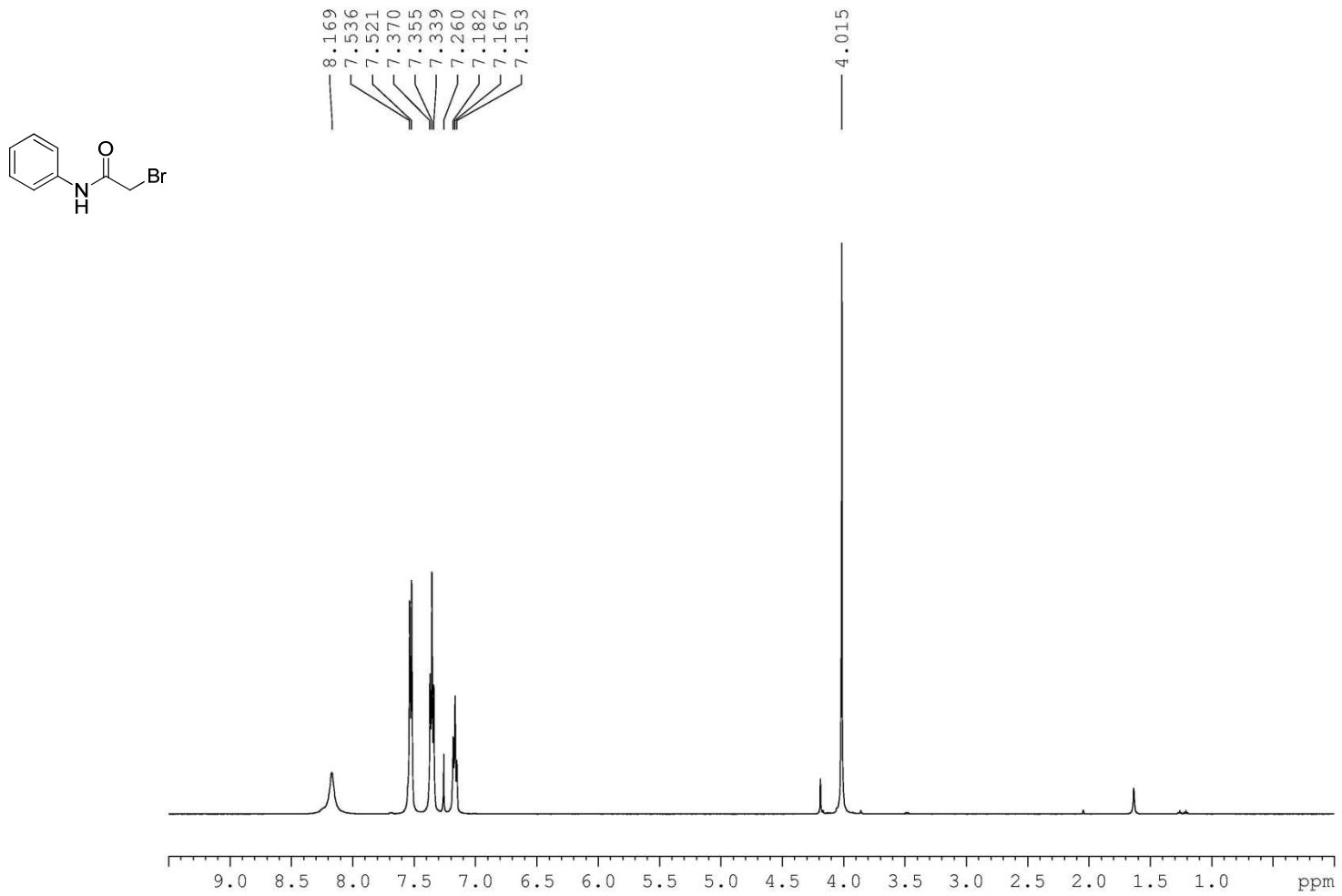
^{13}C NMR ($CDCl_3$, 126 MHz) of **30**.



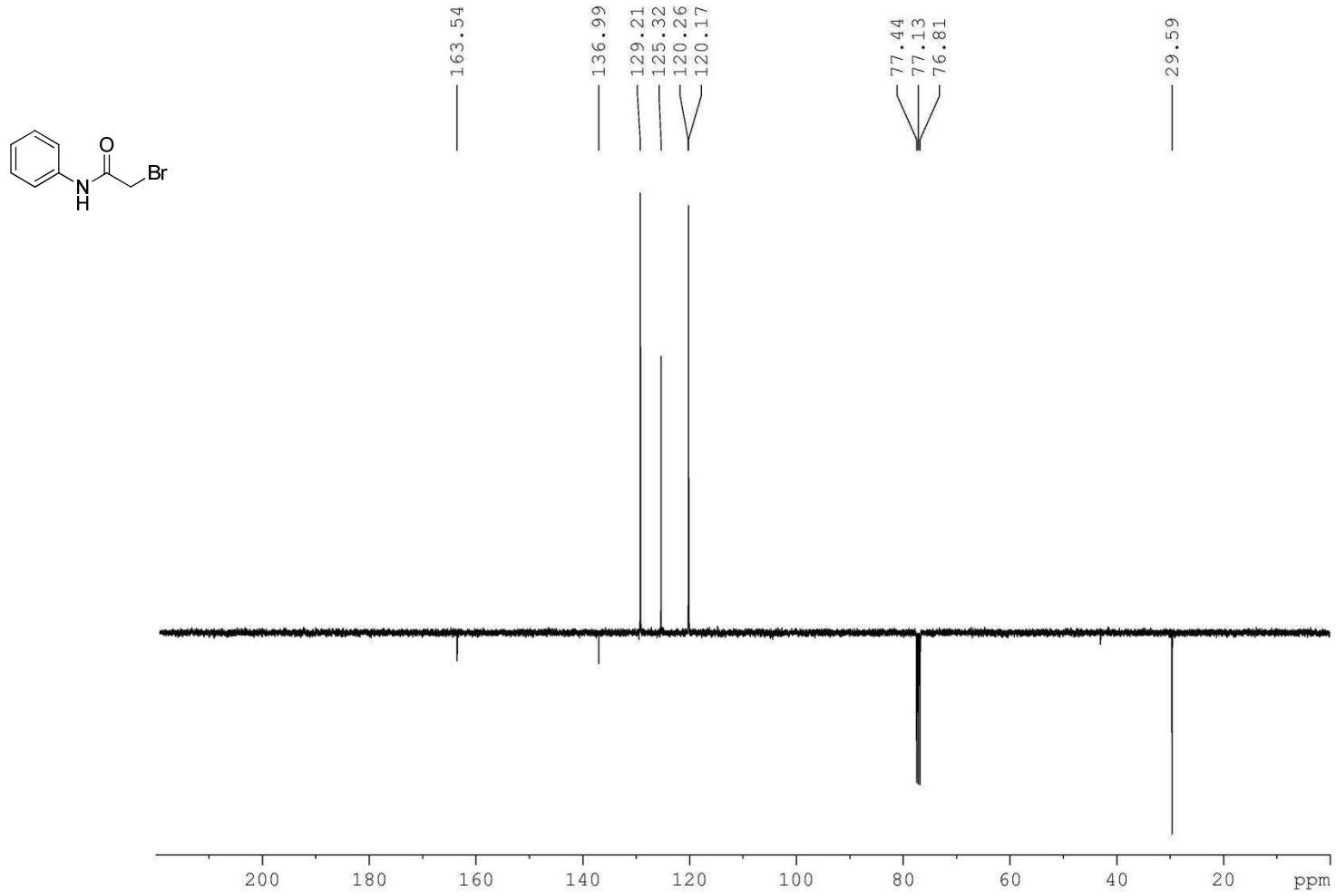
^{1}H NMR ($CDCl_3$, 500 MHz) of **S1**.



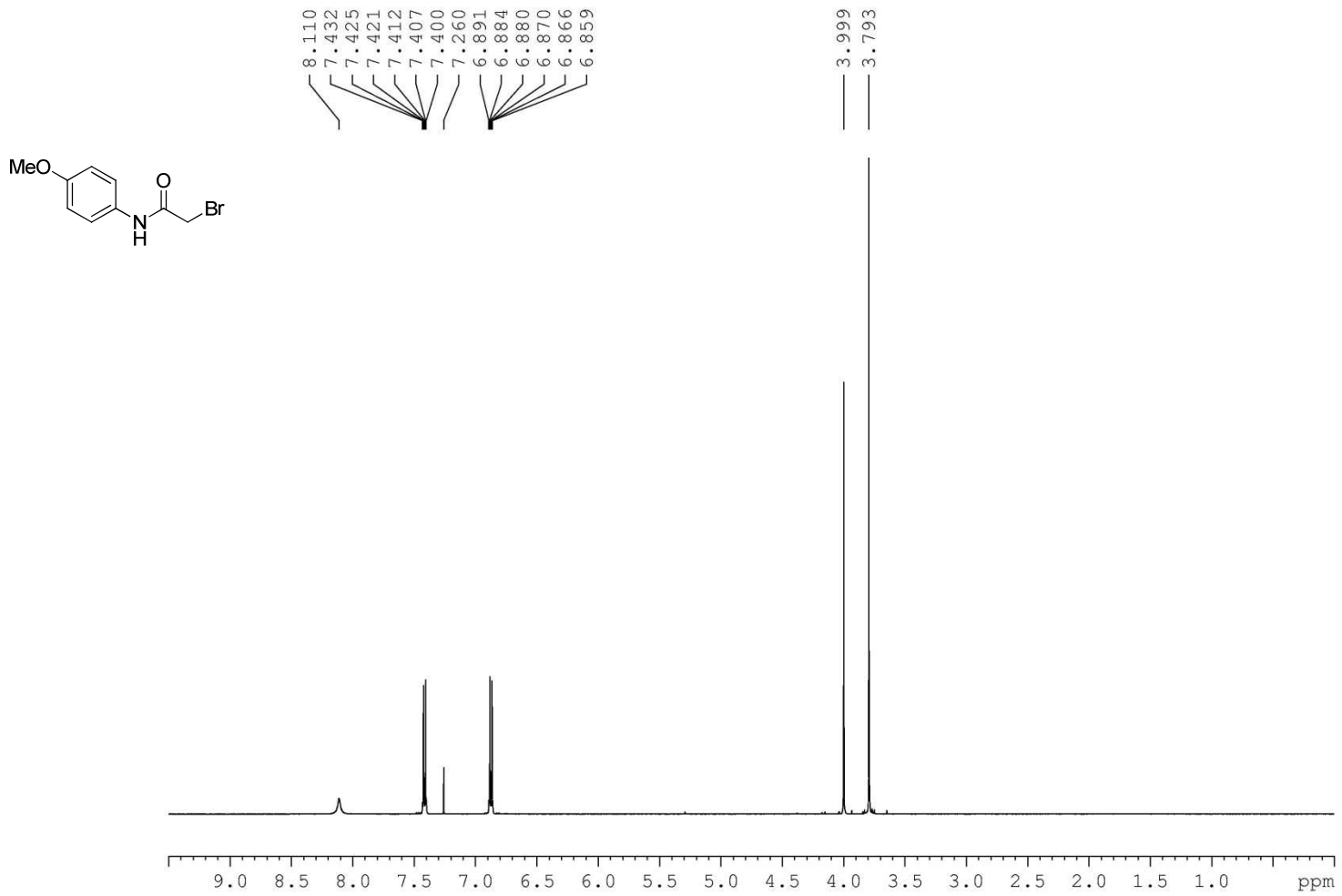
^{13}C NMR ($CDCl_3$, 126 MHz) of **S1**.



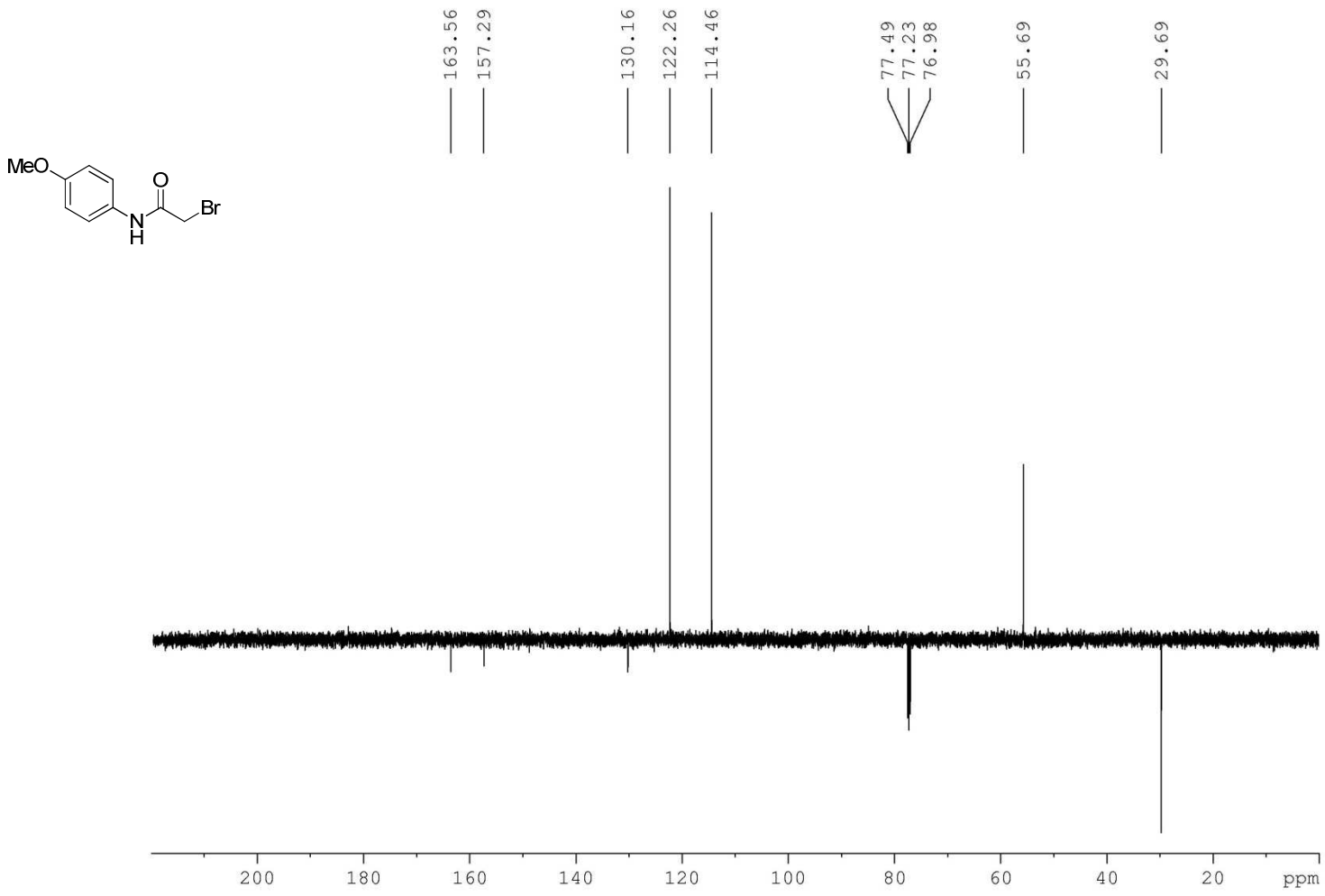
^{1}H NMR ($CDCl_3$, 400 MHz) of **S2**.



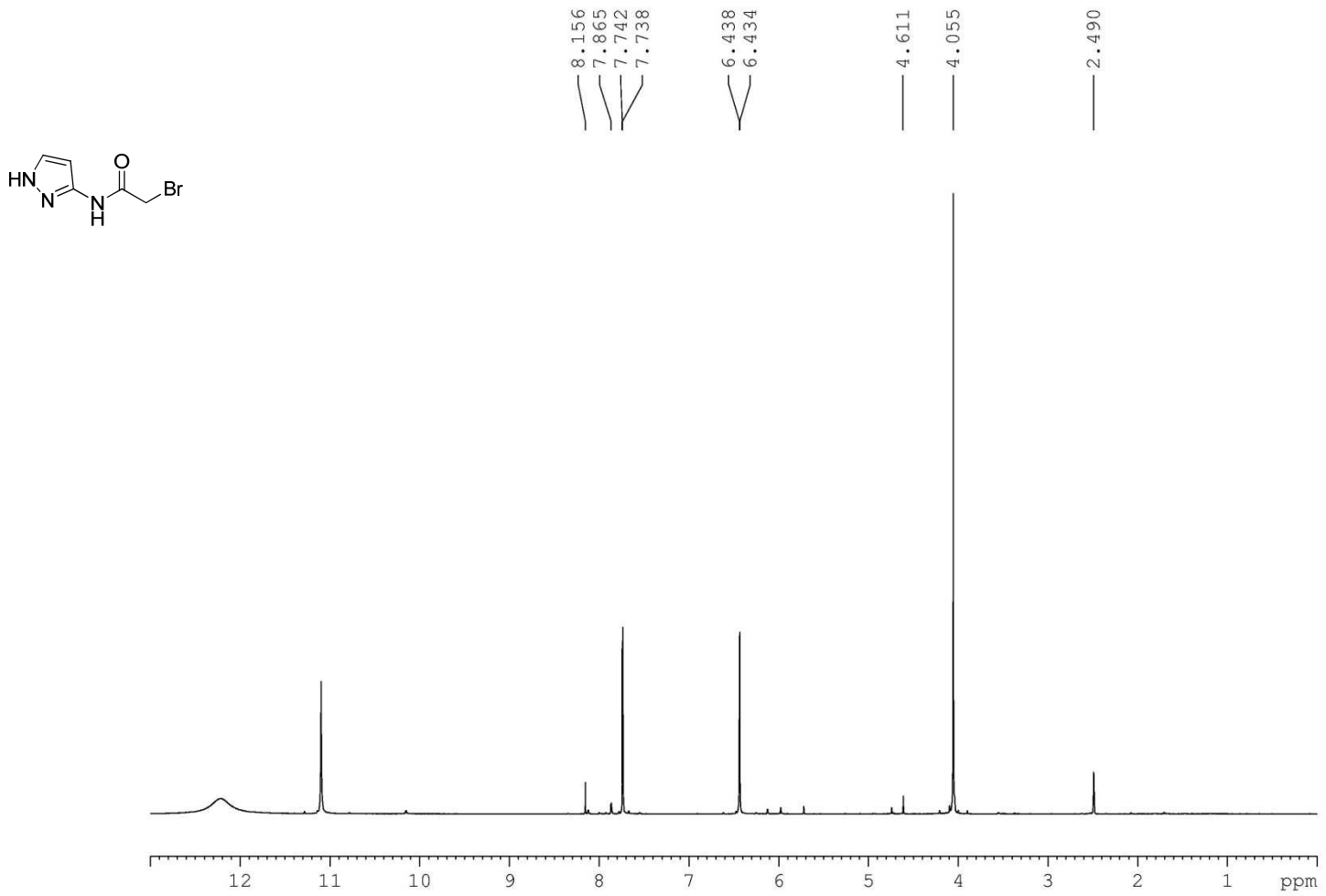
^{13}C NMR ($CDCl_3$, 101 MHz) of **S2**.



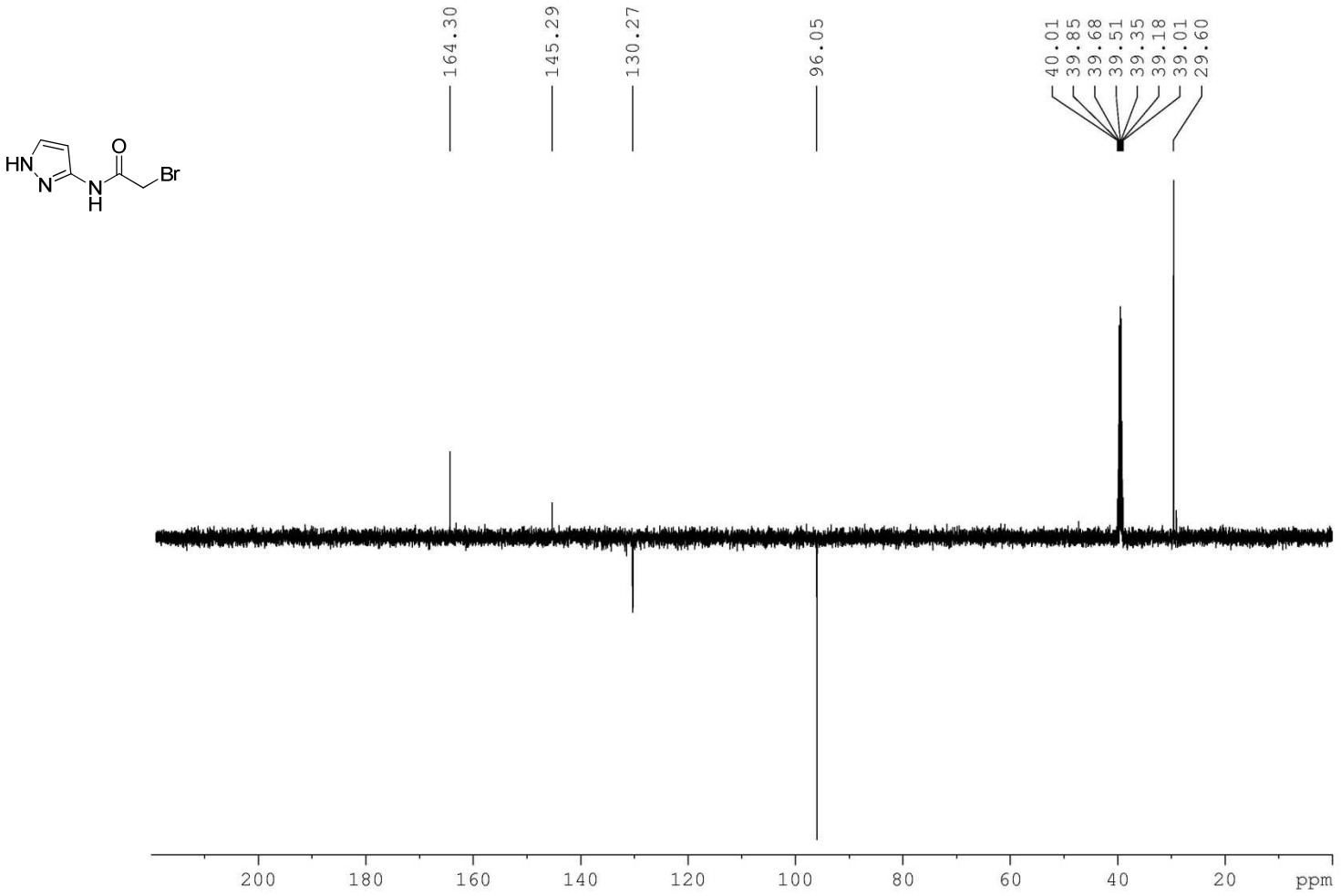
^{1}H NMR ($CDCl_3$, 500 MHz) of **S3**.



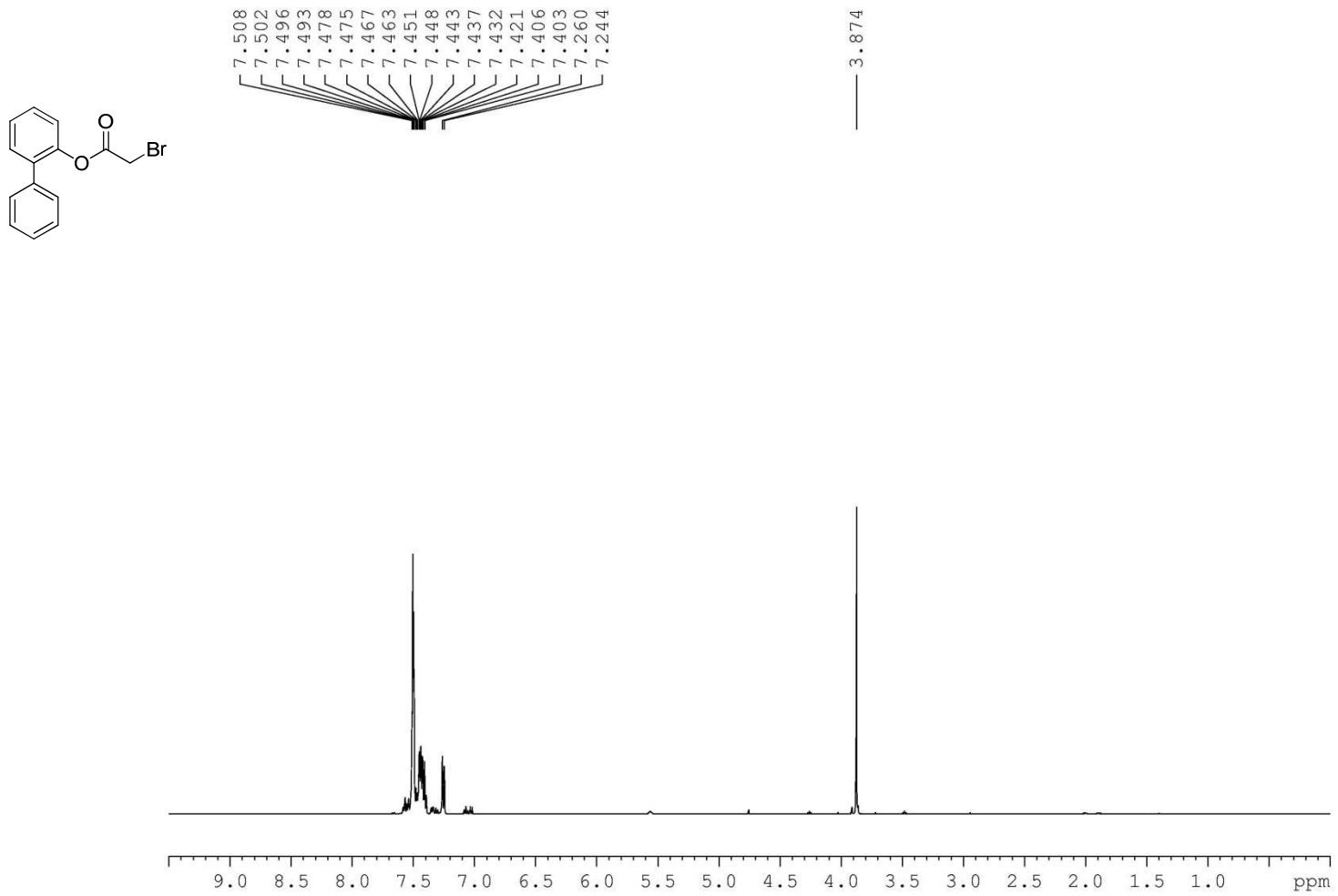
^{13}C NMR ($CDCl_3$, 126 MHz) of **S3**.



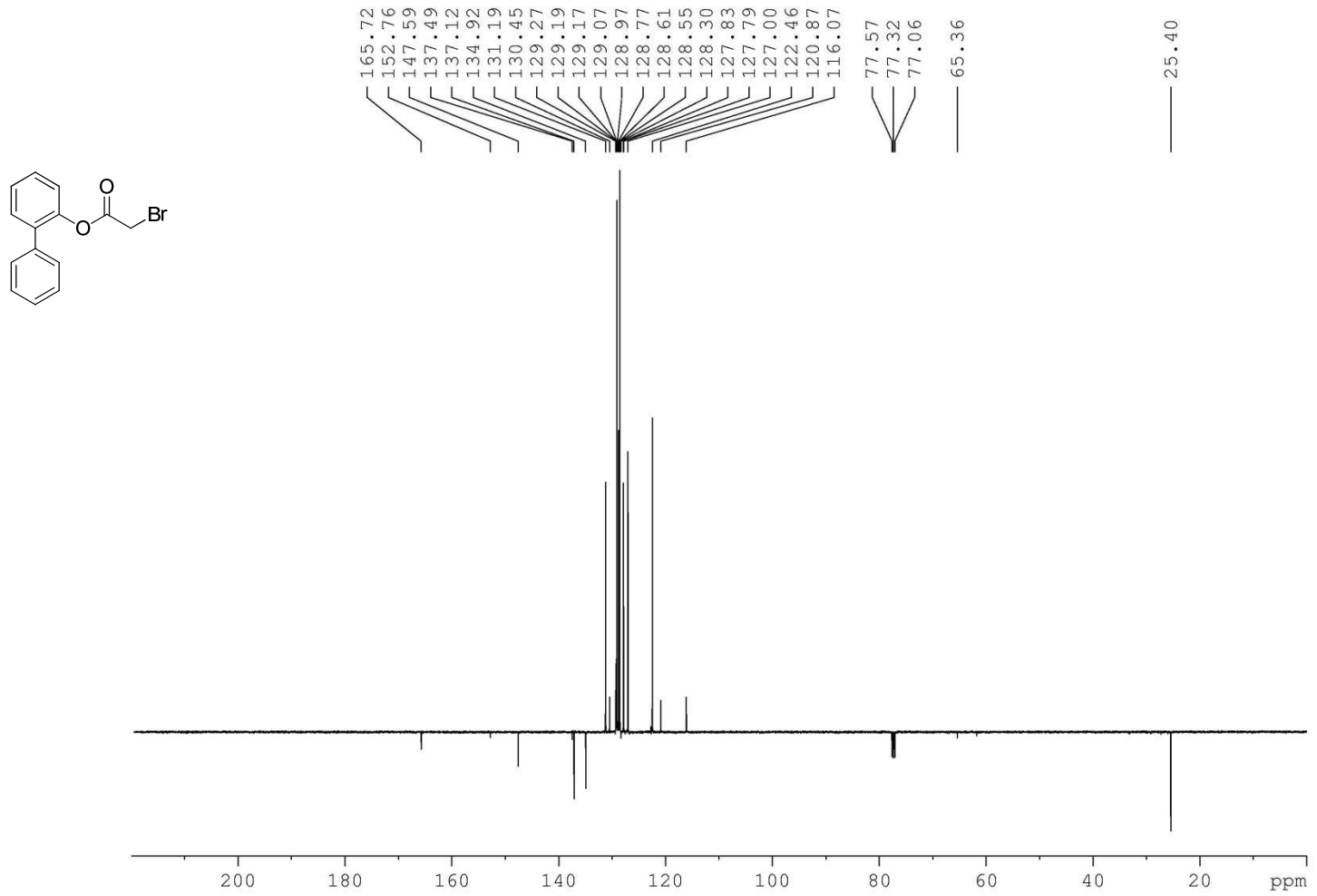
^{1}H NMR (DMSO-d_6, 500 MHz) of **S4**.



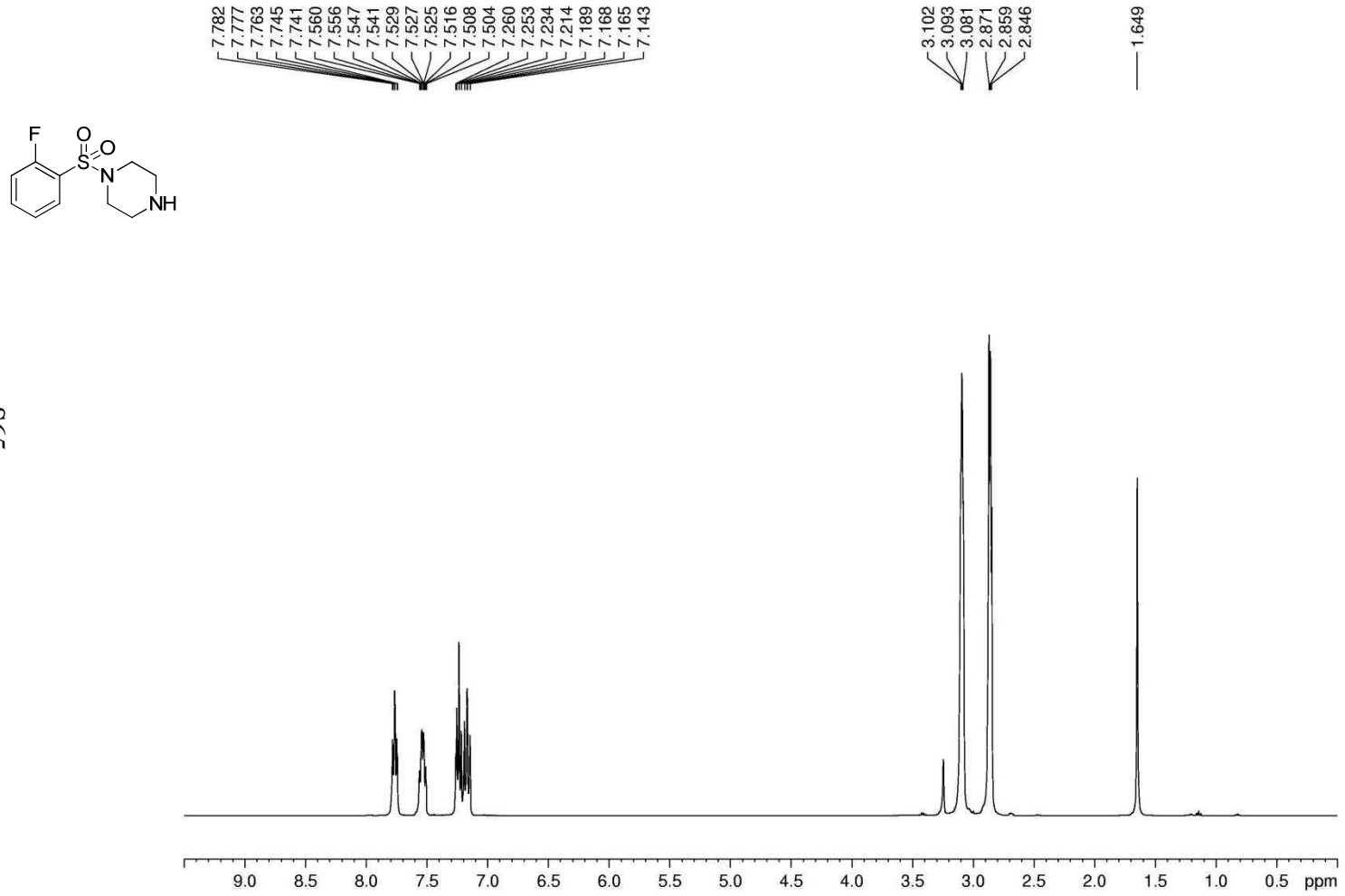
^{13}C NMR (DMSO-d_6, 126 MHz) of **S4**.



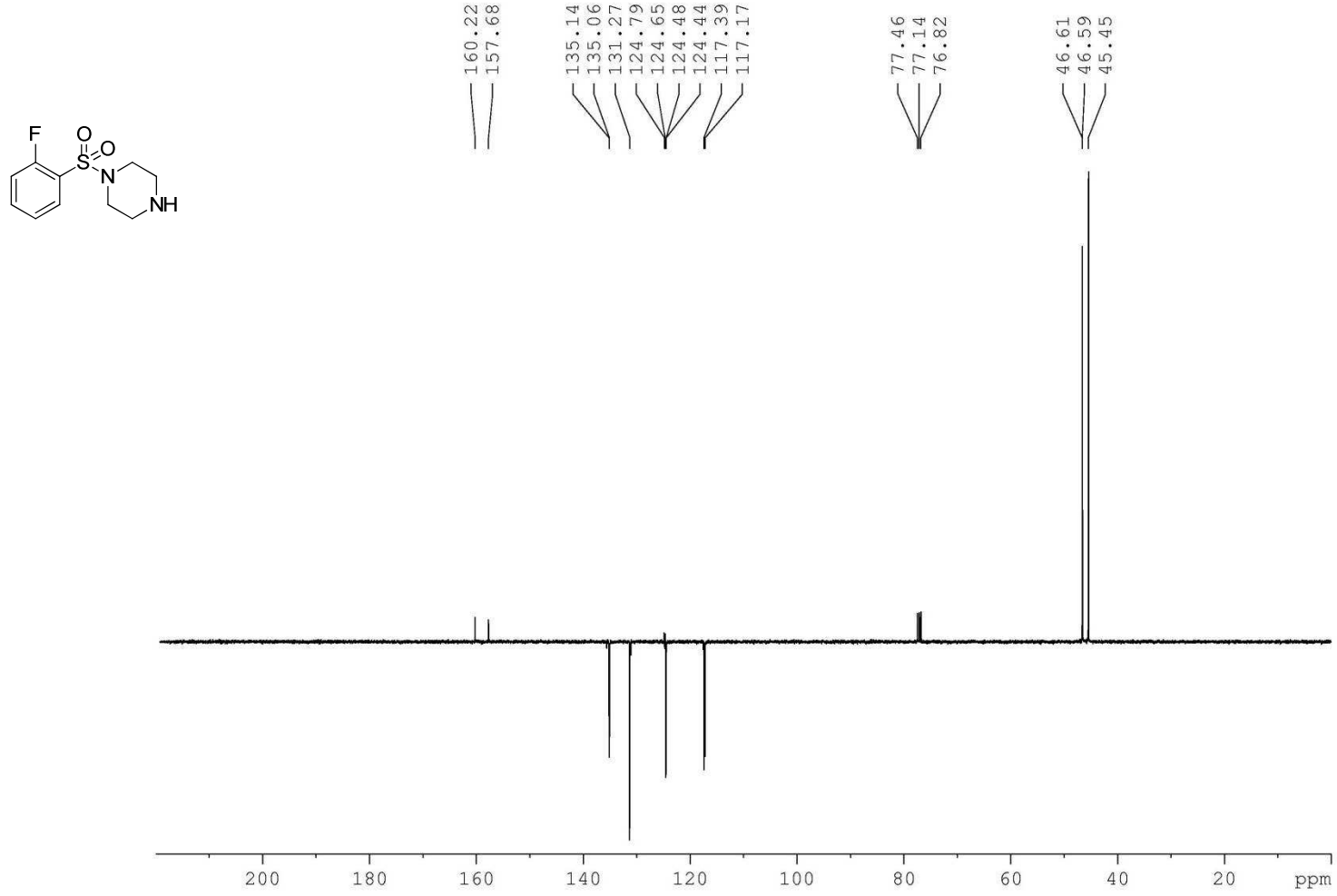
^{1}H NMR ($CDCl_3$, 400 MHz) of **S5**.



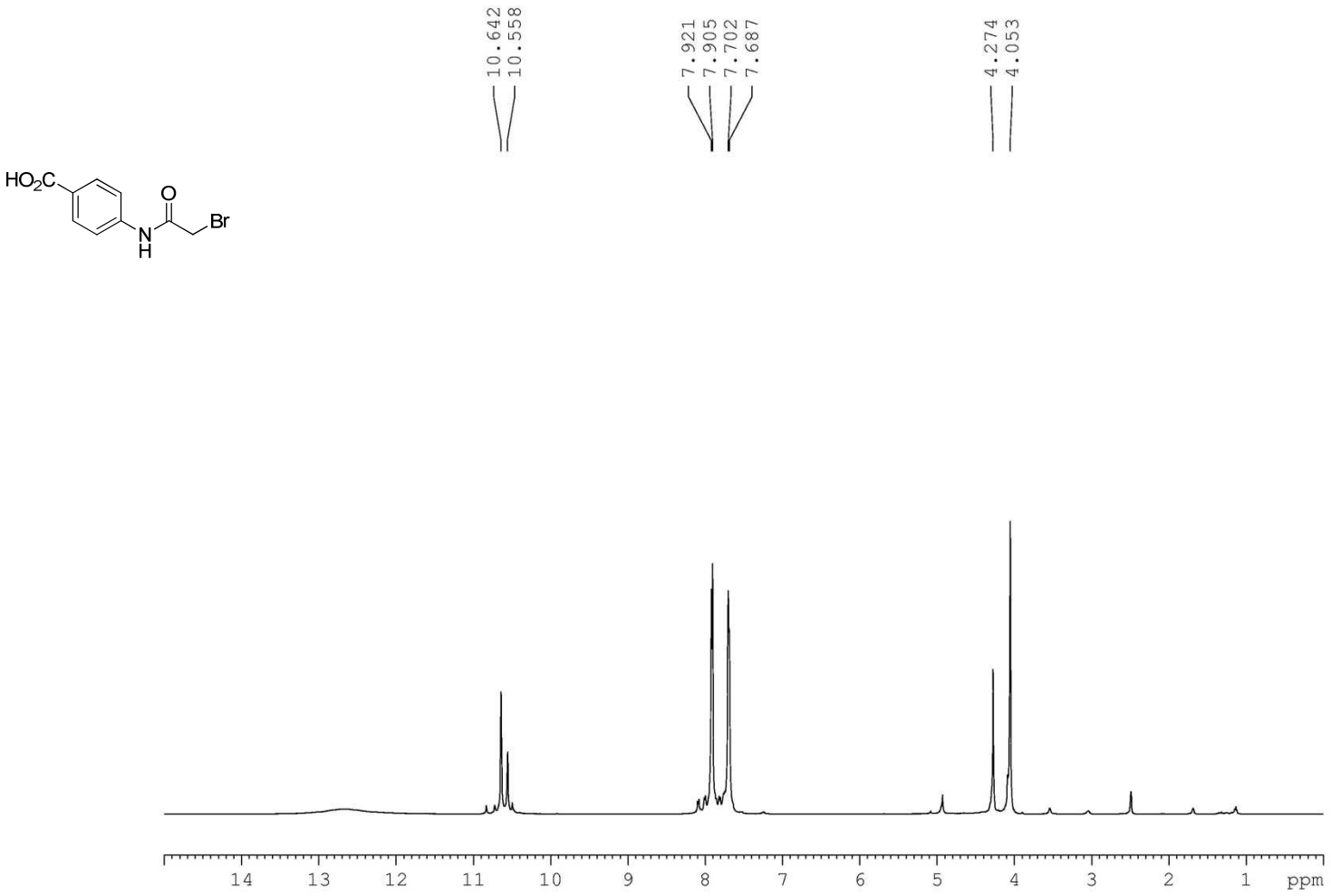
^{13}C NMR ($CDCl_3$, 126 MHz) of **S5**.



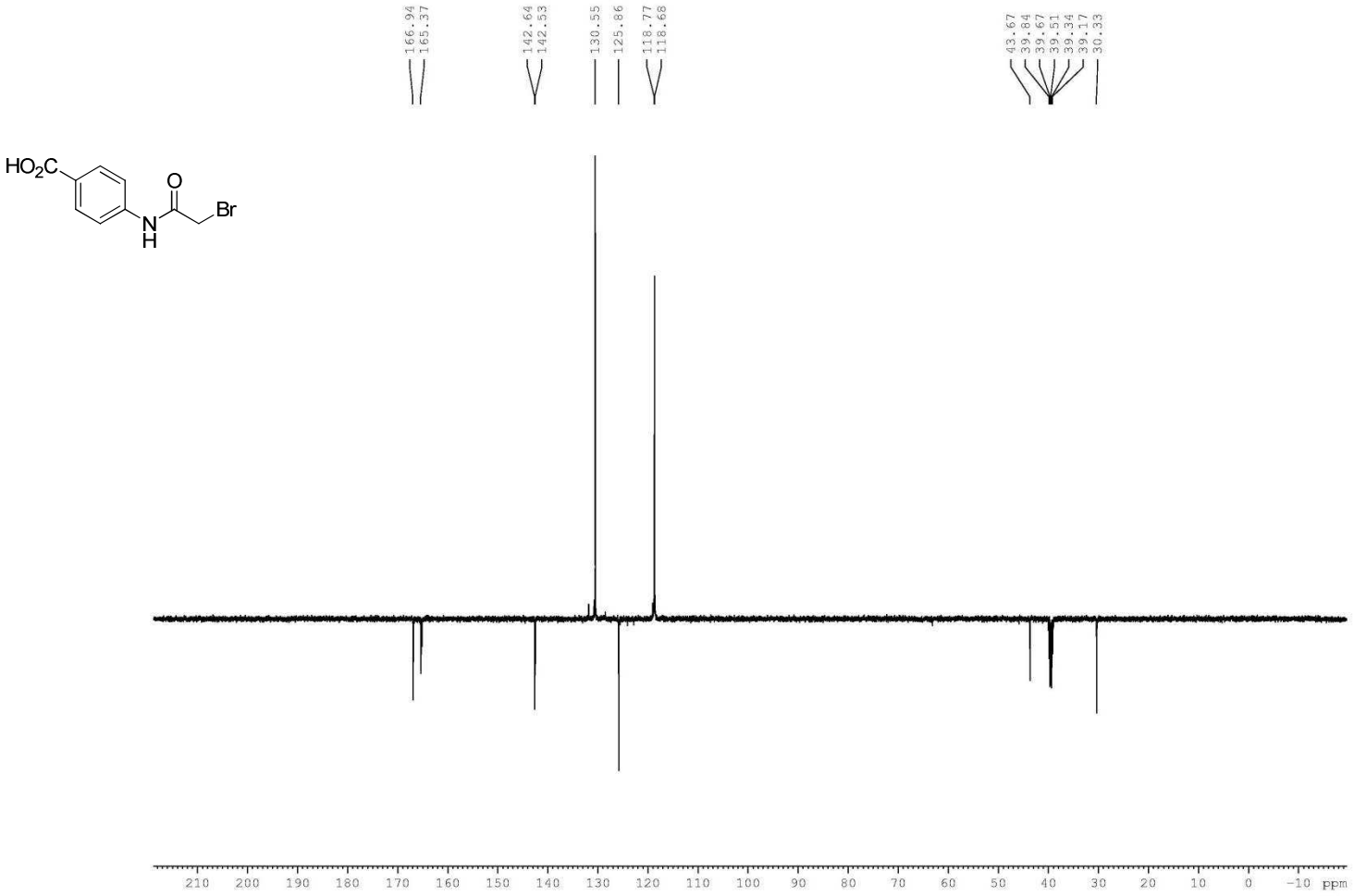
^{1}H NMR ($CDCl_3$, 400 MHz) of **S6**.



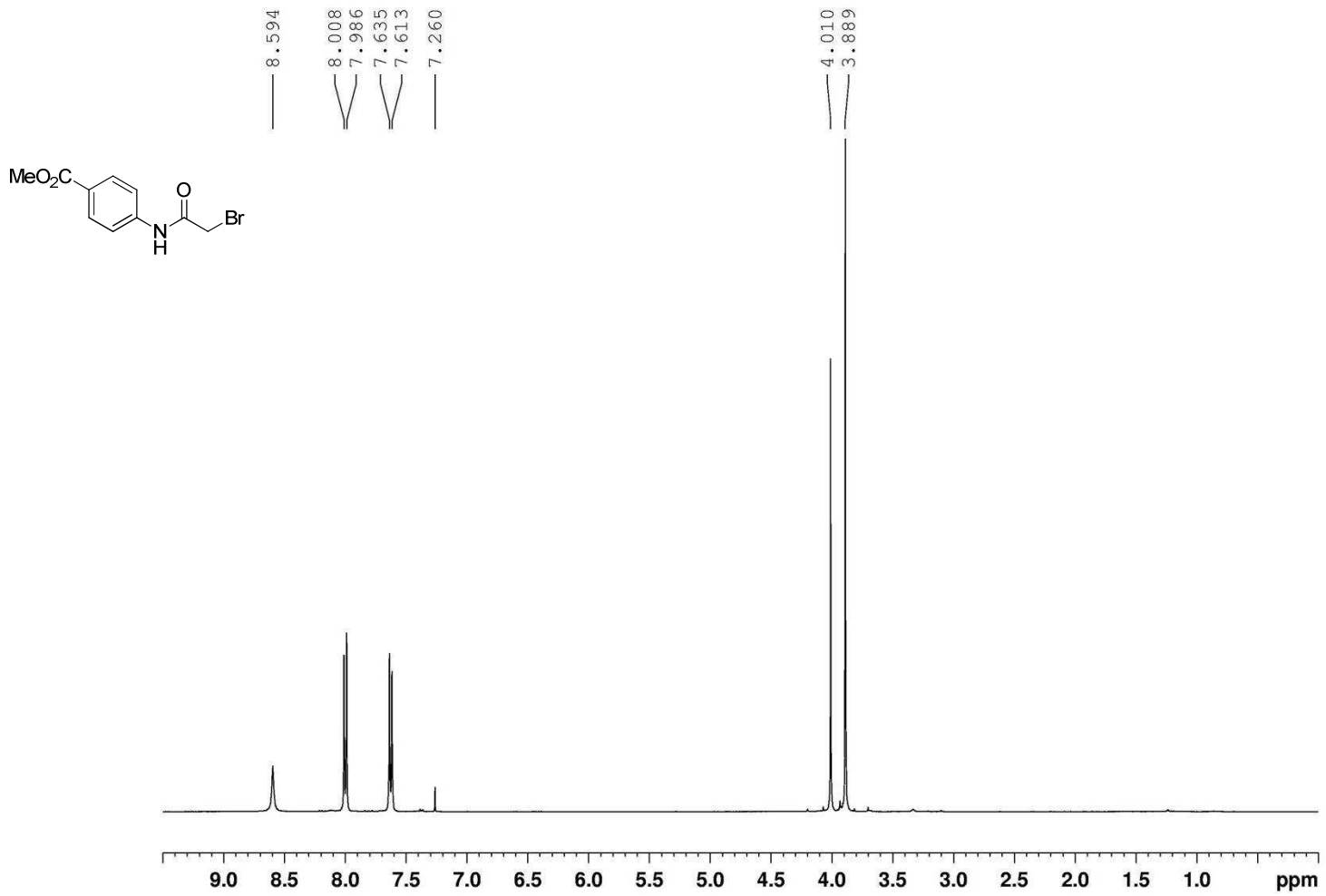
^{13}C NMR ($CDCl_3$, 100 MHz) of **S6**.



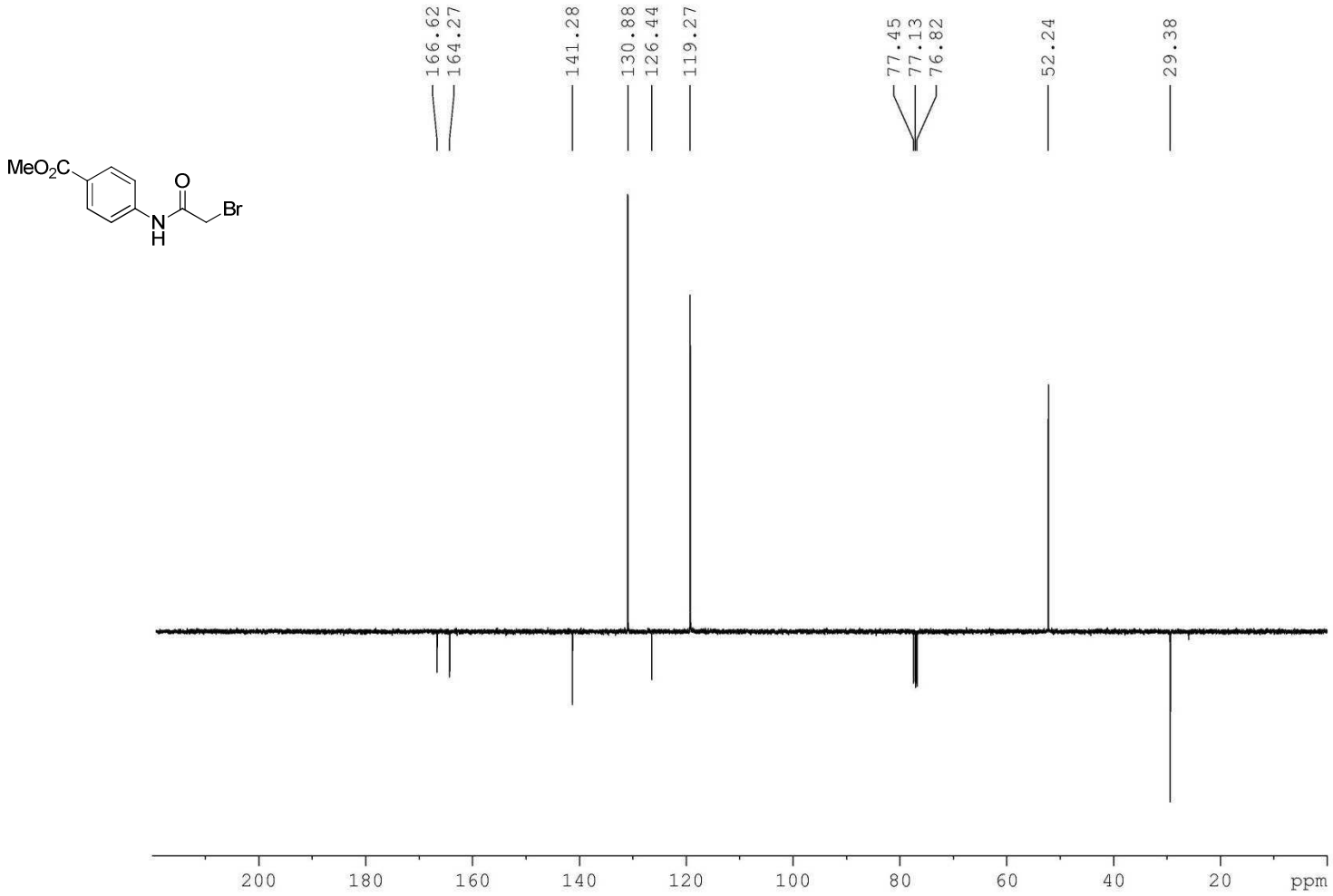
^{1}H NMR (DMSO-d_6, 400 MHz) of **S7**.



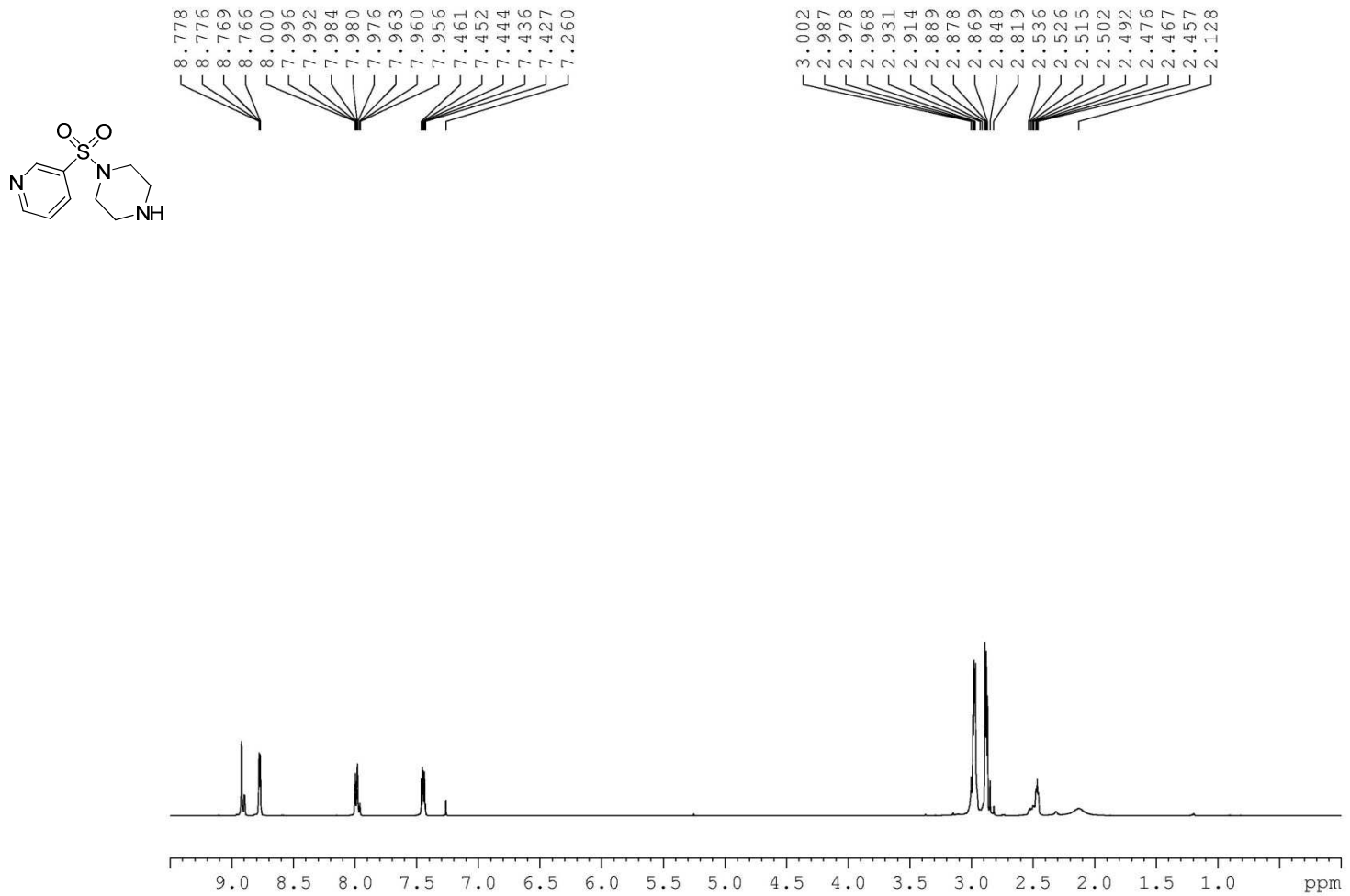
^{13}C NMR (DMSO-d_6, 126 MHz) of **S7**.



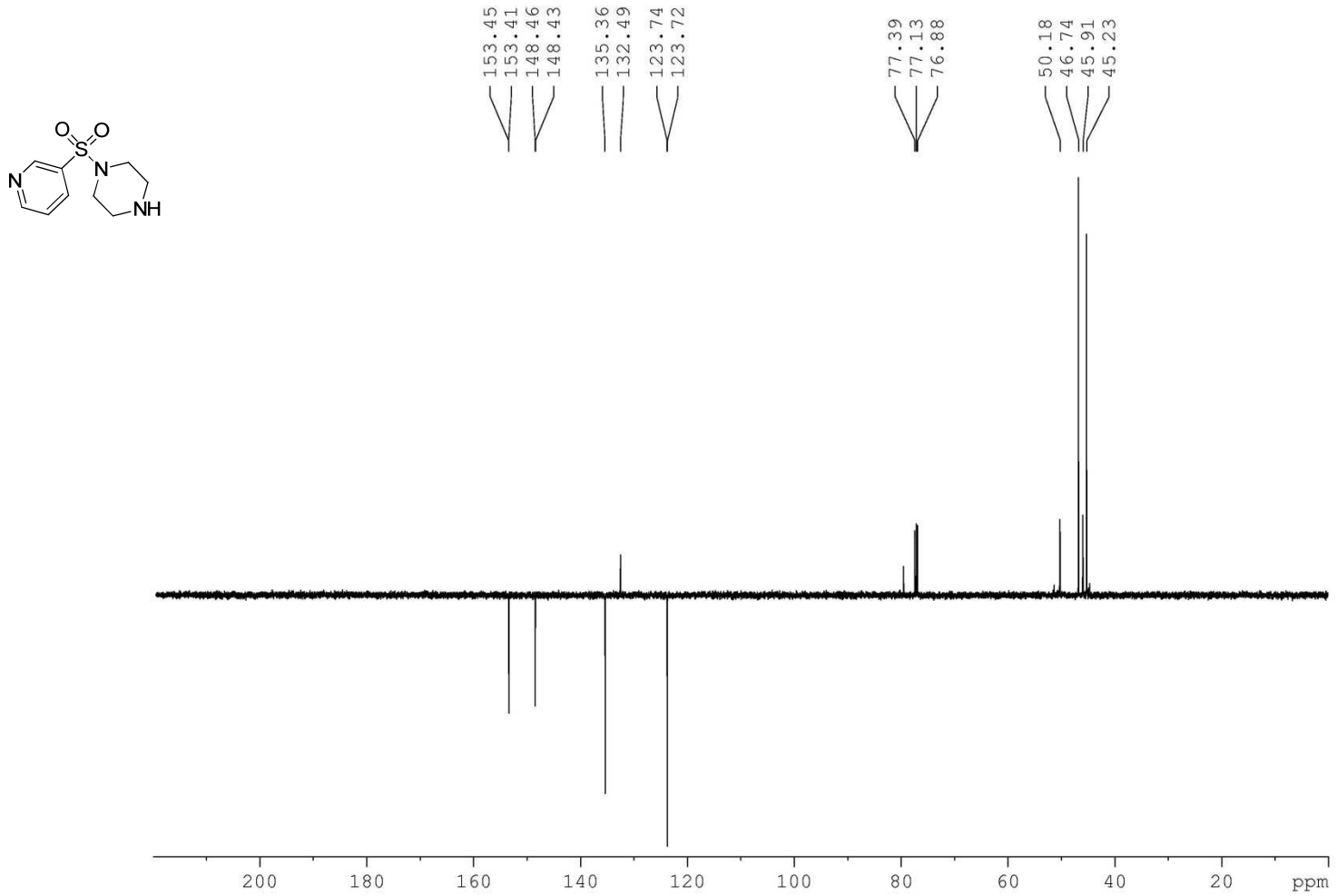
^{1}H NMR ($CDCl_3$, 400 MHz) of **S8**.



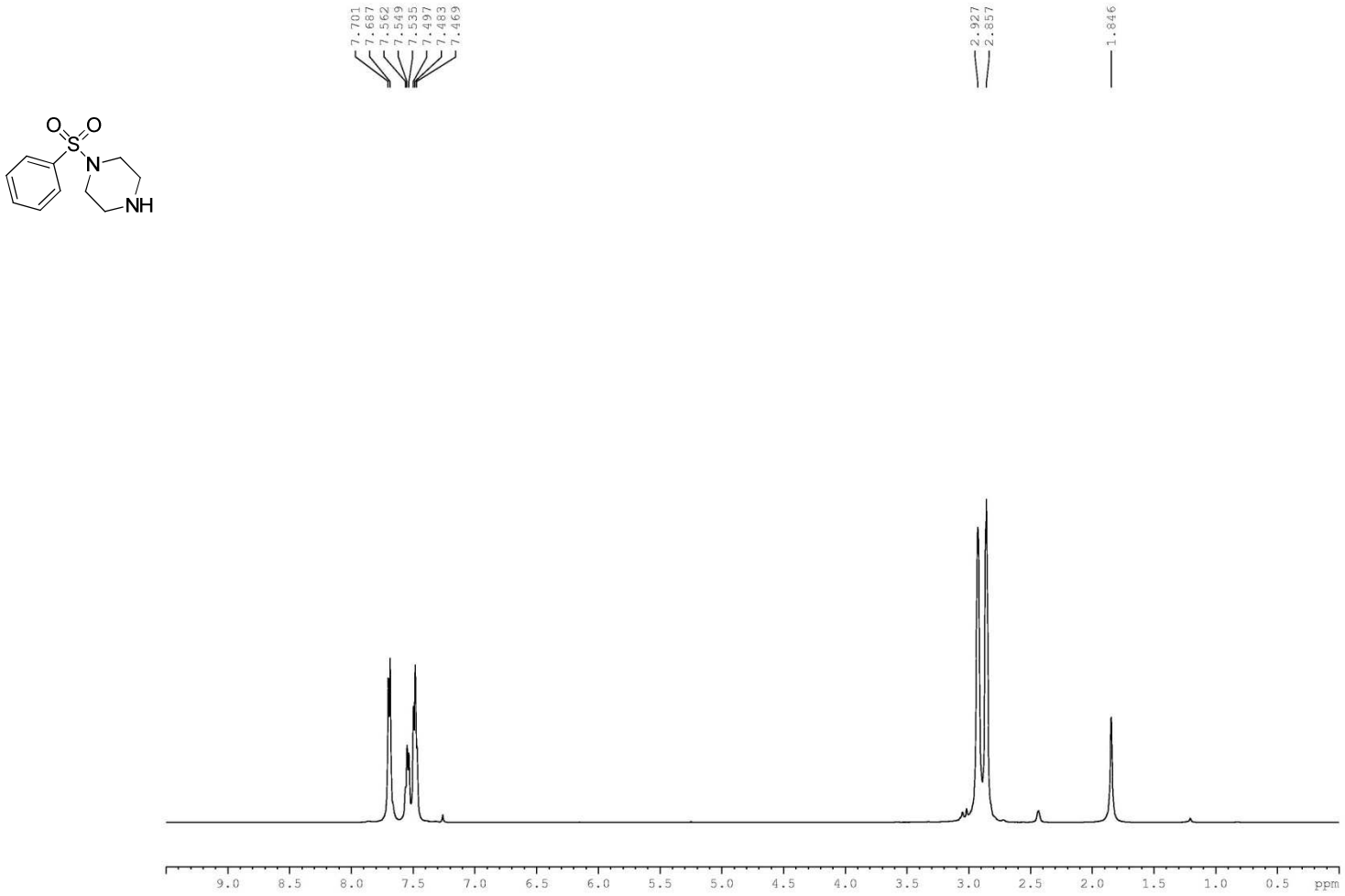
^{13}C NMR ($CDCl_3$,100MHz) of **S8**.



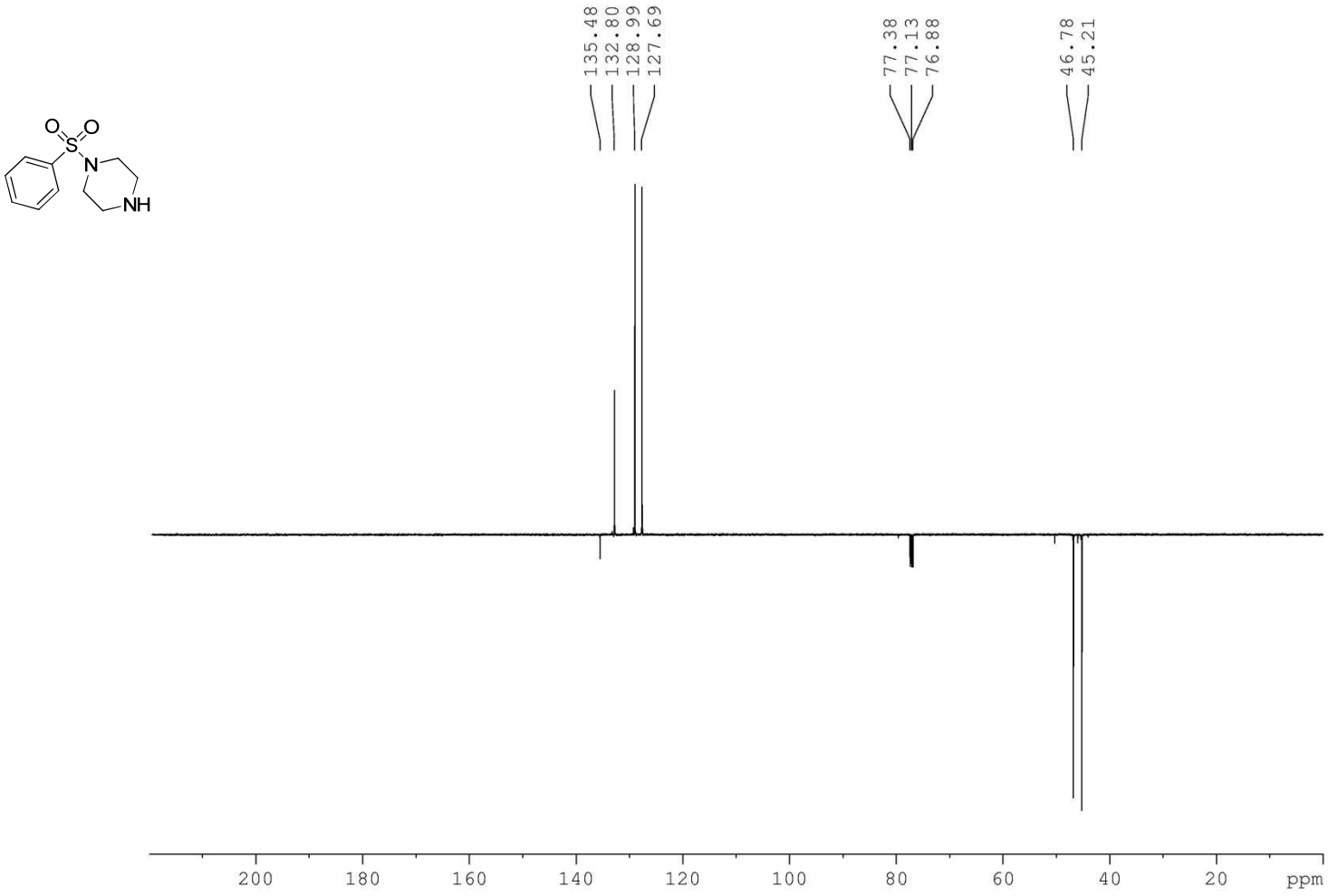
^{1}H NMR ($CDCl_3$, 500 MHz) of **S9**.



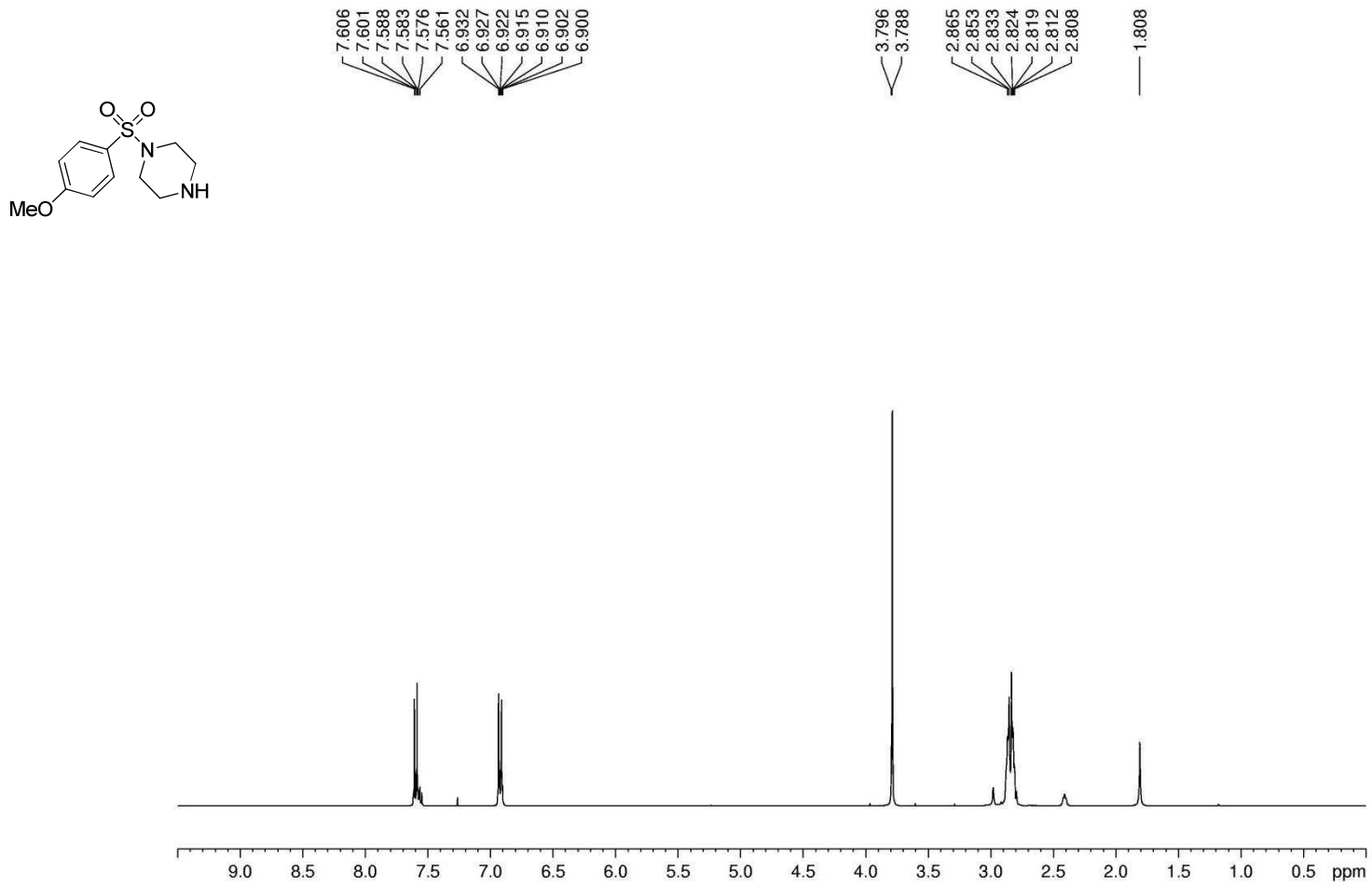
^{13}C NMR ($CDCl_3$, 126 MHz)of **S9**.



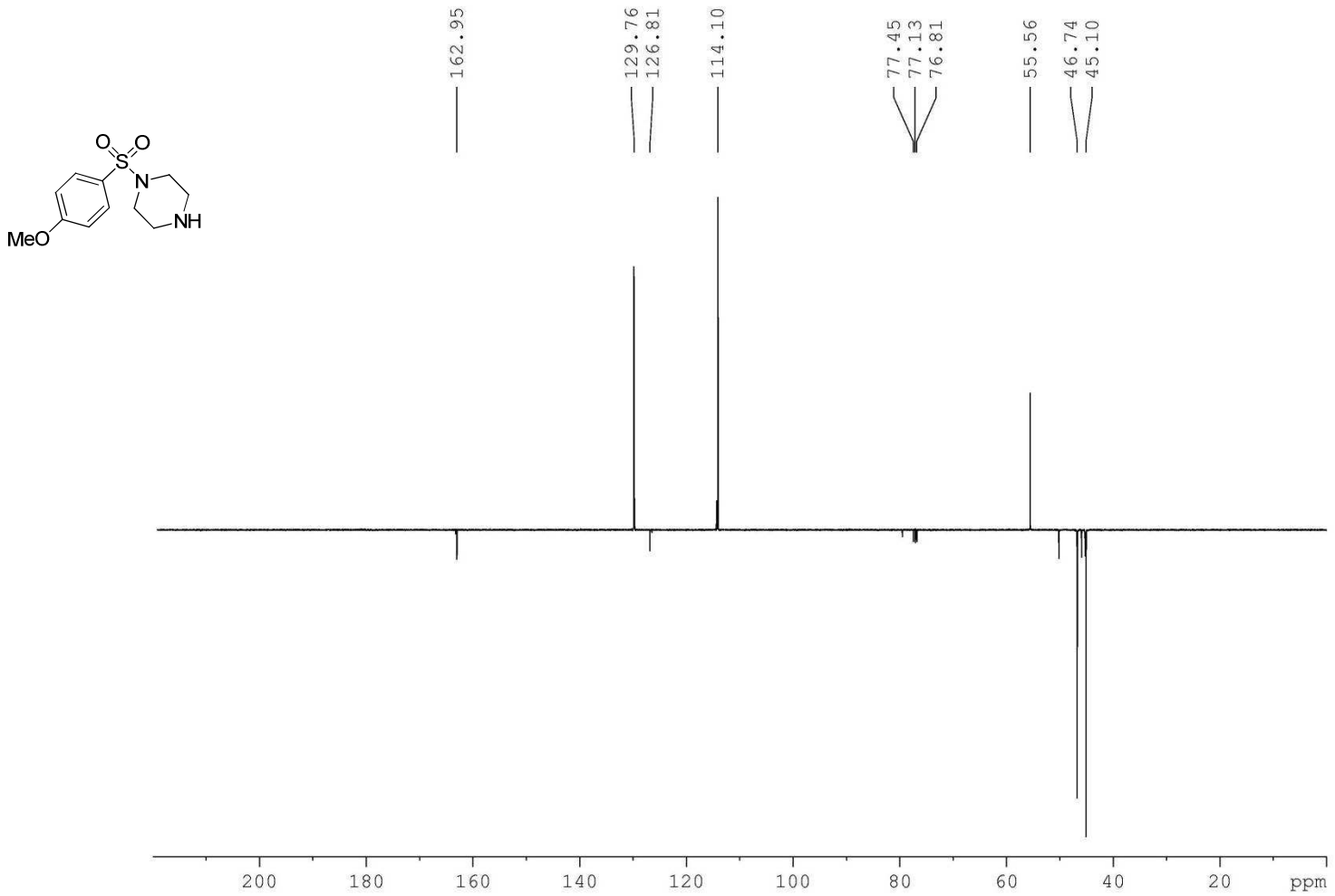
^{1}H NMR ($CDCl_3$, 400 MHz) of **S10**.



^{13}C NMR ($CDCl_3$, 126 MHz) of **S10**.



^{1}H NMR ($CDCl_3$, 500 MHz) of **S11**.



^{13}C NMR ($CDCl_3$, 126 MHz) of **S11**.