Electronic Supplementary Material (ESI) for RSC Medicinal Chemistry.

Supplementary Data

Design, Synthesis and Biological Evaluation of Combretastatin A-4 Sulfamate Derivatives as Potential Anti-Cancer Agents

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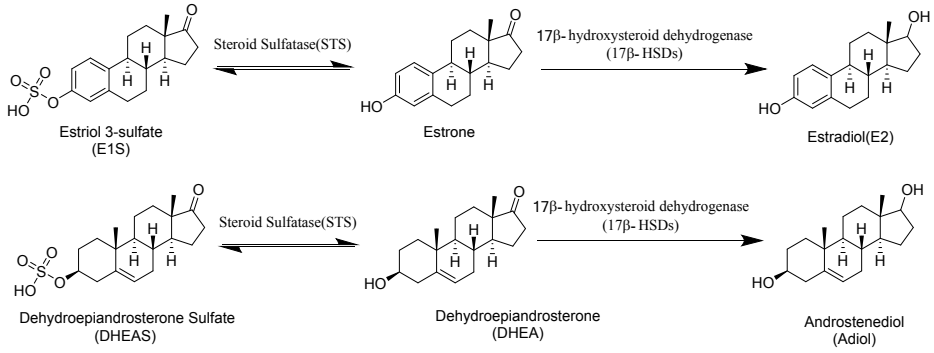
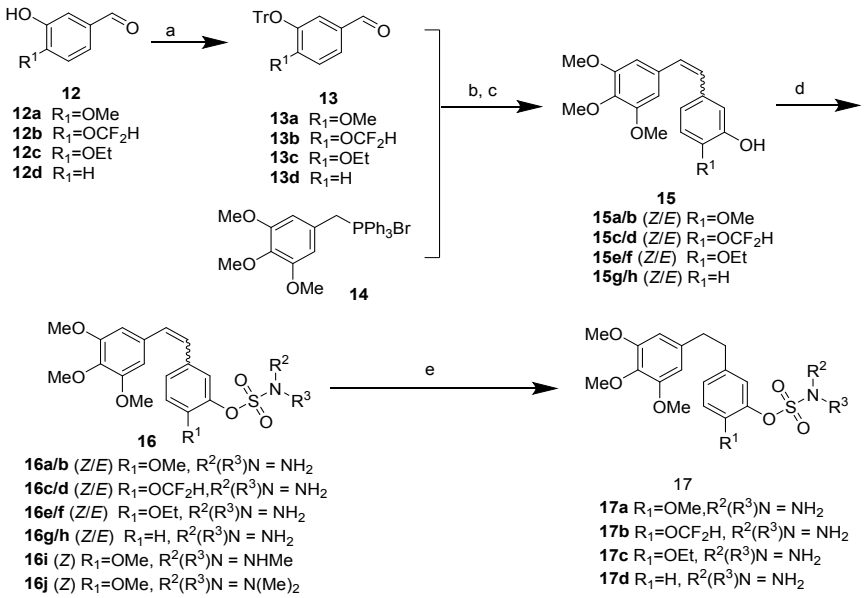


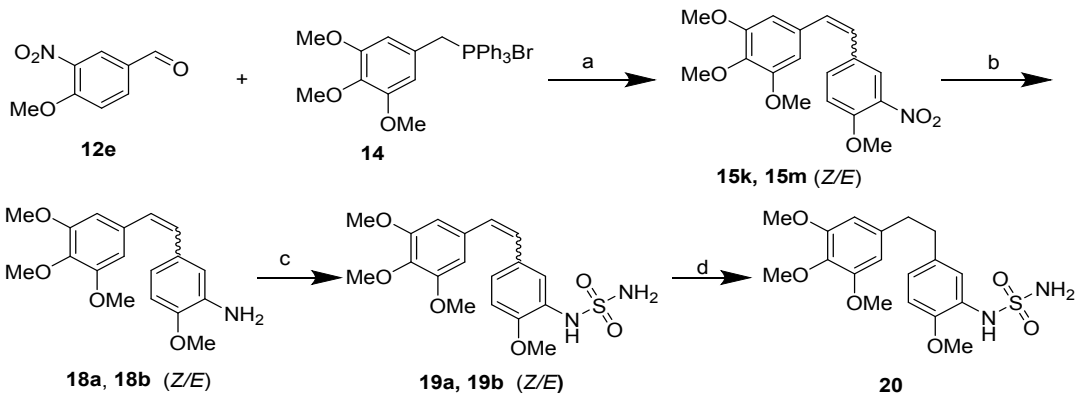
Scheme 1. The role of steroid sulfatase in hormone regulation.

Experimental Section

Chemistry (general information). All solvents, starting materials and reagents were purchased from Tansoole and used directly without further purification. The reaction was monitored by thin layer chromatography (TLC) using a 0.25 mm pre-coated silica gel plate, and visualized under UV light. The products were purified by flash column chromatography on silica gel, structure characterization and purity assessment were judged by NMR, HRMS and HPLC. Nuclear magnetic resonance (NMR) spectra were collected on a Bruker 500 MHz spectrometer and analysed by MestReNova using residual solvent proton and carbon peaks as reference. High resolution mass spectrometry (HRMS) was recorded on a Waters GCT Premier mass spectrometer. The chemical name was automatically generated using ChemBioDraw Ultra 14.0.



Scheme 2 . Synthetic Route of Combretastatin A-4 sulfamate Derivatives. Reagent and conditions: a) Ph_3CCl(TrCl), THF, Et_3N, rt, 2h; b) *n*-BuLi, THF, -78℃, 30mins, then added 13/THF solution, -78-RT, overnight; c) 37% HCl (aq.), toluene, rt, 2h; d) NaH, DMF, RSO_2Cl (R = NH_2, NHMe, $N(Me)_2$), 0℃ to RT, overnight; e) H_2 (1 atm), 10% Pd/C, EtOH, rt, 3h.



Scheme 3. Synthetic Route of Combretastatin Sulfamide Derivatives. Reagent and conditions: a) *n*-BuLi, THF, -78℃, 30mins, then added **12e**/THF solution, -78℃-rt, overnight; b) Zn, CH_3COOH, 2h, rt; c) NaH, DMF, NH_2SO_2Cl, 0℃-rt, overnight; d) H_2 (1 atm), 10% Pd/C, EtOH, rt, 3h.

General synthesis procedures for Compounds 13 *Representative example*: To a solution of the compound **12a** (5.00 g, 32.9 mmol) and trityl chloride (11.00 g, 39.5 mmol) in dry tetrahydrofuran (THF, 20 mL), triethylamine (0.5 mL) was added dropwise, the reaction was stirred for about 2 hours at room temperature until TLC indicated the reaction was completed. Water was added to quench the reaction, extracted with ethyl acetate,the combined organic phase was dried over anhydrous sodium sulfate,filtered and concentrated, the residue was recrystallized in a solvent mixture of ethyl acetate and petroleum ether (1/2, v/v) to give the desired compound 1**3a** (11.20 g).

4-methoxy-3-(trityloxy)benzaldehyde (**13a**): solid, mp 123-124 °C, yield 86%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.57 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.44-7.22 (m, 15H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.8, 158.0, 147.0, 146.3, 145.8, 143.8, 130.6, 129.1, 128.9, 128.0, 127.9, 127.6, 127.4, 127.2, 126.7, 124.6, 122.9, 114.2, 111.1, 110.3, 92.0, 55.7; HR-MS: m/z calcd. for $C_{27}H_{22}O_3$: 394.1569, found 394.1567(M^+).

4-(difluoromethoxy)-3-(trityloxy)benzaldehyde (**13b**): solid, 147-148°C, yield 85%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.92 (s, 1H), 7.54 (s, 1H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.29 (m, 15H), 6.64 (t, *J* = 72.5, 1H, OCF_2H); ^{19}F NMR (470 MHz, $CDCl_3$): δ -81.04 (s), -81.26 (s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.9, 143.4, 143.2, 128.8, 128.4, 128.0, 128.0, 127.8, 127.3, 121.4 (t, *J* = 194.0, OCF_2H), 82.1; HR-MS: m/z calcd. for $C_{27}H_{20}F_2O_3$: 430.1380, found: 430.1382(M^+).

4-ethoxy-3-(trityloxy)benzaldehyde (**13c**): solid, 141-142 °C, yield 88%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.60 (s, 1H), 7.51 (d, *J* = 6.7 Hz, 6H), 7.40 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.35-7.20 (m, 9H), 7.19 (s, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 3.84 (q, *J* = 6.9 Hz, 2H), 1.36 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9, 157.9, 146.0, 144.0, 129.4, 129.0, 127.6, 127.5, 127.0, 123.8, 111.8, 92.3, 64.2, 14.6; HR-MS: m/z calcd. for $C_{28}H_{24}O_3$: 408.1725, found: 408.1722(M^+).

3-(trityloxy)benzaldehyde (**13d**): solid, 104-145 °C, yield 90%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.74 (s, 1H), 7.36-7.27 (m, 15H), 7.24 (d, *J* = 7.1 Hz, 1H), 7.20 (s, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.98 (dd, *J* = 8.1, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.1, 157.1 , 147.0, 143.7, 137.0, 129.1, 129.0, 128.1, 128.0, 127.5, 127.4, 127.2, 123.0, 121.8, 91.3; HR-MS: m/z calcd for $C_{26}H_{20}O_2$, 364.1463, found: 364.1465(M^+).

General synthesis procedures for Compounds 15 *Representative example*: To a pre-cooled (-78 °C) suspension of compound **14** (13.28 g, 25.4 mmol) in dry THF (200 mL) under nitrogen protection, was slowly dropped *n*-butyl lithium cyclohexane solution (1.6 M), the reaction was stirred for 1 hour. Then a solution of compound **13a** (10.00 g, 35.4 mmol) in dry THF (20 mL) was added dropwise to the reaction. Warmed to room temperature and stirred overnight. The solution was poured into ice water, and extracted

with ethyl acetate. The combined organic phase was concentrated *in vacuum*, the residued was redissolved in toluene (80 mL), 37 % HCl (20 mL) was added dropwise, and the solution was stirred for 2h at room temperature until TLC indicated the reaction was completed. Washed with water, the organic phase was dried over anhydrous sodium sulfate, filtered, the filtrate was concentrated *in vacuum*, the residue was purified by flash column chromatography on silica gel (Ethyl acetate-petroleum ether, 3:1) to give the desired compounds **15a** (2.63 g, 33 %) and **15b** (2.38 g,).

(*Z*)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenol (**15a**): oil, yield 33%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90 (d, *J* = 1.5 Hz, 1H), 6.77 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.71 (d, *J* = 8.3 Hz, 1H), 6.51 (s, 2H), 6.44 (d, *J* = 12.0 Hz, 1H), 6.39 (d, *J* = 12.0 Hz, 1H), 5.59 (brs, 1H, OH), 3.82 (d, *J* = 2.4 Hz, 6H), 3.67 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.9, 147.0, 145.9, 145.3, 132.8, 130.7, 129.6, 129.1, 128.0, 127.3, 121.2, 115.2, 110.5, 106.2, 61.0, 56.0; HR-MS: m/z calcd. for $C_{18}H_{20}O_5$: 316.1311, found: 316.1315(M^+).

(*E*)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenol (**15b**): solid, mp 106-107 °C, yield 30%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, *J* = 1.7 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.92 (d, *J* = 16.0 Hz, 1H), 6.88 (d, *J* = 16.0 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.71 (s, 2H), 5.61 (brs, 1H, OH), 3.92 (s, 9H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.2, 147.2, 146.1, 145.6, 133.0, 131.0, 129.8, 129.4, 128.3, 127.6, 121.4, 115.4, 110.7, 106.5, 61.2, 56.3; HR-MS: m/z calcd. for $C_{18}H_{20}O_5$: 316.1311, found: 316.1310(M^+).

(*Z*)-2-(difluoromethoxy)-5-(3,4,5-trimethoxystyryl)phenol (**15c**): oil, yiled 35%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.99 (d, *J* = 8.3 Hz, 1H), 6.94 (d, *J* = 1.4 Hz, 1H), 6.78 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.58 (d, *J* = 12.0 Hz, 2H), 6.48 (d, *J* = 12.0 Hz, 2H), 6.40 (t, *J* = 74.0 Hz, 1H, OCF_2H), 6.09 (brs, 1H, OH), 3.80 (s, 3H), 3.64 (s, 6H); ^{19}F NMR (470 MHz, $CDCl_3$): δ -81.09 (s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.9, 147.6, 137.3, 137.0, 136.3, 132.2, 130.7, 128.7, 121.3, 120.5, 118.2, 117.3, 116.1 (t, *J* = 260.0 Hz, OCF_2H), 106.2, 60.9, 55.9; HR-MS: m/z calcd. for $C_{18}H_{18}F_2O_5$: 352.1122, found: 352.1125(M^+).

(*E*)-2-(difluoromethoxy)-5-(3,4,5-trimethoxystyryl)phenol (**15d**): solid, mp 121-122 °C, yield 37%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (s, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 16.0 Hz, 1H), 6.90 (d, *J* = 16.0 Hz, 1H), 6.72 (s, 2H), 6.54 (t, *J* = 74.0 Hz, 1H, OCF_2H), 5.72 (brs, 1H, OH), 3.91(s, 6H), 3.87 (s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$): δ -80.27 (s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.5, 147.8, 136.4, 132.9, 129.5, 127.0, 120.3, 119.2, 118.5, 114.3 (t, *J* = 260.0 Hz, OCF_2H), 103.9, 61.1, 56.3; HR-MS: m/z calcd. for $C_{18}H_{18}F_2O_5$: 352.1122, found: 352.1126(M^+).

(*Z*)-2-ethoxy-5-(3,4,5-trimethoxystyryl)phenol (**15e**): oil, yield 38%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.93 (d, *J* = 1.1 Hz, 1H), 6.78 (dd, *J* = 8.5, 0.9 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.53 (s, 2H), 6.47 (d, *J* = 12.0 Hz, 1H), 6.41 (d, *J* = 12.0 Hz, 1H), 5.58 (brs, 1H, OH), 4.09 (q, *J* = 7.0 Hz, 2H), 3.84 (s, 3H), 3.70 (s, 6H), 1.43 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.2, 152.9, 151.4, 146.3, 130.5, 129.7, 129.0, 124.7, 121.2, 115.1, 114.1, 111.4, 111.0, 106.1, 64.9, 56.0; HR-MS m/z ESI-HRMS: m/z calcd. for $C_{19}H_{22}O_5$: 330.1467, found: 330.1471(M^+).

(*E*)-2-ethoxy-5-(3,4,5-trimethoxystyryl)phenol (**15f**): solid, mp 117-118 °C, yield 40%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (d, *J* = 1.1 Hz, 1H), 6.78 (d, *J* = 9.0 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.53 (s, 2H), 6.46 (d, *J* = 16.0 Hz, 1H), 6.41 (d, *J* = 16.0 Hz, 1H), 5.59 (brs, 1H, OH), 4.12 (q, *J* = 7.0 Hz, 2H), 3.84 (s, 3H), 3.70 (s, 6H), 1.26 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.2, 152.9 , 151.4, 146.3, 130.5, 129.6, 129.0, 124.7, 121.2, 115.1, 114.1, 111.4, 111.0, 106.2, 65.0, 56.0; HR-MS: m/z calcd. for $C_{19}H_{22}O_5$, 330.1467, found: 330.1470(M^+).

(*Z*)-3-(3,4,5-trimethoxystyryl)phenol (**15g**): oil, yield 36%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.02 (t, *J* = 8.0 Hz, 1H), 6.84 (brs, 1H, OH), 6.75 (d, *J* = 7.4 Hz, 2H), 6.66-6.43 (m, 3H), 6.42 (s, 1H), 6.37 (d, *J* = 12.0 Hz, 1H), 3.74 (s, 3H), 3.55 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.1, 152.6, 138.8, 132.6, 130.2, 130.0, 129.8, 129.4, 120.9, 115.6, 114.3, 106.3, 60.8, 55.8; HR-MS: m/z calcd for $C_{17}H_{18}O_4$: 286.1205, found: 286.1206(M^+).

(*E*)-3-(3,4,5-trimethoxystyryl)phenol (**15h**): solid, mp 91-93 °C, yield 38%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (t, *J* = 7.8 Hz, 1H), 7.07-7.00 (m, 2H), 6.96 (d, *J* = 16.0 Hz, 1H), 6.92 (d, *J* = 16.0 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.71 (s, 2H), 3.89 (d, *J* = 3.5 Hz, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.4, 153.3, 138.8, 137.6, 133.3, 129.8, 128.7, 128.1, 118.9, 114.9, 113.1, 103.7, 61.0, 56.1; HR-MS: m/z calcd for $C_{17}H_{18}O_4$: 286.1205, found: 286.1206(M^+).

General synthesis procedures for Compounds 16a-16j, 19a and 19j *Representative example*: To a ice-bath cooled solution of **15a** (1.00 g, 3.2 mmol) in dry N, N-dimethylformamide (DMF, 8 mL) was added sodiun hydride (0.15 g, 6.3 mmol), after stirred at 0 °C for 1 hour, a solution of amino-type sulfonyl chloride (0.82 g, 6.3 mmol) in DMF (5 mL) was added dropwise, then the reaction was warmed to room temperature and stirred overnight. The reaction was quenched with water, extracted with ethyl acetate, the combined organic layer was washed with brine and water, dried over anhydrous sodium sulfate, filtered, concentrated *in vacuum*, the residue was purified by flash column chromatography on silica gel (elute with ethyl acetate/petroleum ether, 3:1, v/v) to obtain the desired compound **16a** (0.77 g) .

(*Z*)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl sulfamate (**16a**): solid, mp 116-117 °C, yield 62%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (s, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 6.48 (d, *J* = 12.1 Hz, 1H), 6.43 (d, *J* = 12.1 Hz, 3H), 5.29 (s, 2H), 3.82 (d, *J* = 13.8 Hz, 6H), 3.68 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.1, 150.8, 138.9, 137.4, 132.5, 130.6, 130.3, 128.8, 128.3, 124.3, 112.8, 106.2, 61.0, 56.3, 56.1; HR-MS: m/z calcd. for $C_{18}H_{21}NO_7S$: 395.1039, found:395.1040(M^+).

(*E*)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl sulfamate (**16b**): solid, mp 169-171 °C,yield 60%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.95 (s, 2H), 7.54 (s, 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.19 (d, *J* = 16.0 Hz, 1H), 7.17 (s, 1H), 7.14 (d, *J* = 16.0 Hz, 1H), 6.91 (s, 2H), 3.83 (s, 9H), 3.67 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 153.1, 151.2, 139.2, 137.3, 132.8, 130.1, 127.4, 126.7, 125.4, 120.7, 113.6, 103.8, 60.1, 56.0, 55.9; HR-MS: m/z calcd. for $C_{18}H_{21}NO_7S$: 395.1039, found: 395.1041(M^+).

(*Z*)-2-(difluoromethoxy)-5-(3,4,5-trimethoxystyryl)phenyl sulfamate (**16c**): solid, mp 161-163 °C, yield 63%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.50 (s, 2H), 7.05 (d, *J* = 8.2 Hz, 1H), 7.01 (t, *J* = 75 Hz, OCF_2H, 1H), 6.92 (s, 1H), 6.72 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.54 (s, 2H), 6.52 (d, *J* = 12.0 Hz, 1H), 6.49 (d, *J* = 12.0 Hz, 1H), 3.64 (s, 3H), 3.58 (s, 6H); ^{19}F NMR (470 MHz, DMSO-d_6) δ -81.38 (s); ^{13}C NMR (125 MHz, DMSO-d_6): δ 152.6, 148.6, 137.5, 136.9, 135.5, 131.7, 130.1, 128.7, 121.7, 119.9, 116.9, 116.6 (t, *J* = 262.5 Hz, OCF_2H), 106.2, 60.1, 55.5; HR-MS: m/z calcd for $C_{18}H_{19}F_2NO_7S$: 431.0850, found: 431.0849(M^+).

(*E*)-2-(difluoromethoxy)-5-(3,4,5-trimethoxystyryl)phenyl sulfamate (**16d**): solid, mp 146-148 °C, yield 65%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.27 (s, 2H), 7.68 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 16.0 Hz, 1H), 7.18 (d, *J* = 16.0 Hz, 1H), 7.09 (t, *J* = 75 Hz, OCF_2H, 1H), 6.95 (s, 2H), 3.84 (s, 6H), 3.68 (s, 3H); ^{19}F NMR (470 MHz, DMSO-d_6): δ -81.33 (s); ^{13}C NMR (125 MHz, DMSO-d_6): δ 153.2, 142.2, 141.2, 137.6, 135.6, 132.4, 129.9, 125.9, 125.1, 121.3, 120.9, 116.5 (t, *J* = 262.5 Hz, OCF_2H), 104.1, 60.1, 56.0; HR-MS: m/z calcd. for $C_{18}H_{19}F_2NO_7S$: 431.0850, found: 431.0848(M^+).

(*Z*)-2-ethoxy-5-(3,4,5-trimethoxystyryl)phenyl sulfamate (**16e**): solid, mp 153-155 °C, yield 66%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (s, 1H), 7.14 (d, *J* = 8.6 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.49 (d, *J* = 12.0 Hz, 1H), 6.44 (d, *J* = 12.0 Hz, 3H), 5.15 (s, 2H), 4.10 (q, *J* = 6.9 Hz, 2H), 3.82 (s, 3H), 3.69 (s, 6H), 1.43 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.1, 150.0, 139.2, 137.5, 132.5, 130.7, 130.3, 128.8, 128.3, 124.5, 113.8, 106.2, 65.0, 61.1, 56.2, 14.8; HR-MS: m/z calcd. for $C_{19}H_{23}NO_7S$: 409.1195, found: 409.1193(M^+).

(*E*)-2-ethoxy-5-(3,4,5-trimethoxystyryl)phenyl sulfamate (**16f**): solid, mp 172-174 °C, yield 70%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (s, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 6.63 (d, *J* = 16.0 Hz,

1H), 6.58 (d, *J* = 16.0 Hz, 3H), 5.18 (s, 2H), 4.21 (q, *J* = 6.9 Hz, 2H), 3.93 (s, 3H), 3.71 (s, 6H), 1.48 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.4, 150.3, 139.4, 137.8, 132.8, 130.9, 130.6, 129.1, 128.6, 124.8, 114.1, 106.5, 65.3, 61.3, 56.4, 15.1; HR-MS: m/z calcd for $C_{19}H_{23}NO_7S$, 409.1195, found: 409.1194(M^+).

(*Z*)-3-(3,4,5-trimethoxystyryl)phenyl sulfamate (**16g**): solid, mp 108-110 °C, yield 68%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (s, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.15 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.55 (d, *J* = 12.0 Hz, 1H), 6.52 (d, *J* = 12.0 Hz, 1H), 6.40 (s, 2H), 5.36 (s, 2H), 3.77 (s, 3H), 3.63 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.9, 150.1, 139.4, 137.3, 132.3, 131.6, 130.7, 129.7, 128.7, 128.5, 127.8, 122.8, 122.3, 120.9, 106.4, 61.0, 56.1; HR-MS: m/z calcd. for $C_{17}H_{19}NO_6S$: 365.0933, found: 365.0936(M^+).

(*E*)-3-(3,4,5-trimethoxystyryl)phenyl sulfamate (**16h**): solid, mp 136-138 °C, yield 67%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (s, 1H), 7.40 (s, 1H), 7.36 (s, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 16.0 Hz, 1H), 6.91 (d, *J* = 16.0 Hz, 1H), 6.69 (s, 2H), 5.28 (s, 2H), 3.87 (s, 6H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.5, 150.7, 139.6, 138.4, 132.6, 130.5, 130.2, 126.7, 125.4, 121.0, 119.7, 104.0, 61.1, 56.23; HR-MS: m/z calcd. for $C_{17}H_{19}NO_6S$: 365.0933, found: 365.0936(M^+).

(*Z*)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl methylsulfamate (**16i**): solid, mp 120-122 °C, yield 62%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (s, 2H), 6.87 (d, *J* = 9.0 Hz, 1H), 6.51 (d, *J* = 12.0 Hz, 1H), 6.47 (d, *J* = 12.0 Hz, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.71 (s, 6H), 2.82 (d, *J* = 5.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.9, 145.9, 145.3, 137.2, 132.9, 130.7, 129.7, 129.1, 121.3, 115.2, 110.5, 106.2, 61.0, 56.1, 56.1; HR-MS: m/z calcd for $C_{19}H_{23}NO_7S$: 409.1195, found: 409.1196(M^+).

(*Z*)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl dimethylsulfamate (**16j**): solid, mp 103-105 °C, yield 61%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (s, 1H), 7.10 (s, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.42 (d, *J* = 12.0 Hz, 1H), 6.44 (s, 1H), 6.46 (d, *J* = 12.0 Hz, 1H), 6.47 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.67 (s, 3H), 3.64(s, 3H), 2.88 (s, 3H), 2.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.1, 150.8, 139.0, 137.4, 132.5, 130.4, 130.1, 128.4, 124.0, 112.5, 105.9, 60.9, 56.1, 55.9, 38.6; HR-MS: m/z calcd. for $C_{20}H_{25}NO_7S$, 423.1354, found: 423.1352(M^+).

(*Z*)-3,4,5-trimethoxy-4'-methoxy-3'-amino sulfamate stibene (**19a**): solid, mp 143-145 °C, yield 64%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, *J* = 1.7 Hz, 1H), 7.01 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.95 (s, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.49 (d, *J* = 4.2 Hz, 4H), 4.75 (s, 2H), 3.82 (d, *J* = 2.4 Hz, 6H), 3.71 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.1, 148.2, 137.5, 133.1, 130.4, 129.6, 129.5, 126.5, 125.5, 119.9, 110.4, 106.6, 61.1, 56.3, 56.0; HR-MS: m/z calcd for $C_{18}H_{22}N_2O_6S$: 394.1199, found: 394.1197(M^+).

(*E*)-3,4,5-trimethoxy-4'-methoxy-3'-amino sulfamate stibene (**19b**): solid, mp 159-161 °C, yield 69%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.02 (s, 1H), 6.94 (s, 2H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.71 (s, 2H), 4.87 (s, 2H), 3.89 (d, *J* = 11.0 Hz, 9H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.5, 148.9, 133.2, 131.1, 127.9, 127.2, 126.9, 123.5, 117.9, 111.0, 103.6, 61.1, 56.3, 56.1; HR-MS: m/z calcd. for $C_{18}H_{22}N_2O_6S$: 394.1199, found: 394.1195(M^+).

General synthesis procedures for Compounds 17a-17d and 20 *Representative example*: To a solution compound **16a** (0.50 g, 1.3 mmol) in absolute ethanol (10 mL), 10% Pd/C (0.12 g) was added, the reaction flask was vacuumed and recharged with hydrogen for three times, then stirred at room temperature for 3 hours until TLC indicated the hydrogenation reaction was completed. Filtered and concentrated to get the desired compound **17a** (0.38 g).

2-methoxy-5-(3,4,5-trimethoxyphenethyl)phenyl sulfamate (**17a**): solid, mp 131-132 °C, yield 76%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (s, 1H), 7.02 (d, *J* = 10.0 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.33 (s, 2H), 5.28 (s, 2H), 3.83 (s, 3H), 3.80 (s, 9H), 2.82 (dd, *J* = 8.0, 3.8 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ

153.1, 149.8, 138.9, 137.2, 136.3, 135.0, 128.0, 124.1, 113.1, 105.7, 60.9, 56.4, 56.2, 38.1, 36.9; HR-MS: m/z calcd for $C_{18}H_{23}NO_7S$: 397.1195, found: 397.1196(M^+)..

2-(difluoromethoxy)-5-(3,4,5-trimethoxyphenethyl)phenyl sulfamate (**17b**): solid, mp 142-144 °C, yield 73%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.17 (s, 2H), 7.38 (d, *J* = 7.0 Hz, 1H), 7.22 (s, 2H), 7.15 (t, *J* = 75 Hz, 1H), 6.55 (s, 2H), 3.74 (s, 3H), 3.61 (s, 6H), 2.94-2.87 (m, 2H), 2.84-2.78 (m, 2H); ^{19}F NMR (470 MHz, DMSO-d_6) δ -81.36 (s); ^{13}C NMR (125 MHz, DMSO-d_6): δ 152.7, 142.9, 141.6, 139.0, 136.9, 135.8, 126.0, 123.7, 120.7, 118.6, 116.5, 114.5, 105.7, 60.0, 55.8, 37.2, 36.5; HR-MS: m/z calcd. for $C_{18}H_{21}F_2NO_7S$: 433.1007, found: 433.1004(M^+).

2-ethoxy-5-(3,4,5-trimethoxyphenethyl)phenyl sulfamate (**17c**): solid, mp 122-124 °C, yield 75%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.87 (s, 2H), 7.29 (d, *J* = 7.2Hz, 1H), 7.10 (dd, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.54 (s, 2H), 4.04 (q, *J* = 6.9 Hz, 2H), 3.74 (s, 6H), 3.61 (s, 3H), 2.80 (d, *J* = 5.7 Hz, 4H), 1.32 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 152.7, 149.1, 147.8, 139.0, 137.2, 135.7, 133.9, 127.8, 127.6, 127.0, 126. 7, 123.21, 114.3, 105.7, 64.2, 60.0, 55.8, 37.5, 36.2, 14.6; HR-MS: m/z calcd. for $C_{19}H_{25}NO_7S$: 411.1352, found: 411.1352(M^+)..

3-(3,4,5-trimethoxyphenethyl)phenyl sulfamate (**17d**): solid, mp 118-120 °C, yield 78%; ^{1}H NMR (500MHz, $CDCl_3$): δ 7.29 (s, 1H), 7.11 (s, 2H), 7.06 (s, 1H), 6.30 (s, 2H), 5.42 (s, 2H), 3.77 (d, *J* = 3.6 Hz, 9H), 2.87 (d, *J* = 8.0 Hz, 2H), 2.83 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.0, 150.2, 143.9, 137.2, 136.0, 129.7, 127.4, 122.2, 119.7, 105.6, 60.9, 56.1, 37.9, 37.6; HR-MS: m/z calcd. for $C_{17}H_{21}NO_6S$: 367.1090, found: 367.1091(M^+)..

3,4,5-trimethoxy-4'-methoxy-3'-amino sulfamate diphenylethane (**20**): solid, mp 124-126 °C, yield 80%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.03 (s, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.36 (s, 2H), 5.02 (s, 2H), 3.79 (d, *J* = 6.9 Hz, 12H), 2.82 (d, *J* = 3.4 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.1, 147.8, 137.4, 136.2, 134.7, 132.1, 132.1, 126.5, 124.8, 120.6, 110.8, 105.7, 60.9, 56.2, 56.0, 38.3, 37.2; HR-MS: m/z calcd. for $C_{18}H_{24}N_2O_6S$: 396.1355, found: 396.1353(M^+).

Synthesis of Compounds 18a, 18b Under nitrogen pretection, to a pre-cooled suspension of compound **12e** (28.29 g, 55.2 mmol) in dry THF (300 mL) , n-butyl lithium cyclohexane solution (1.6 M) was added dropwise, after stirred at -78 °C for 1 hour, a solution of compound **14** (10.00 g, 55.2 mmol) in dry THF (30 mL) was added ,then the reaction was warmed to room temperature and stirred overnight. The solution was poured into ice water, extracted with ethyl acetate, the combined organic phase was concentrated *in vacuum*, the residue was redissolved in acetic acid (20 mL), zinc powder (16.82 g, 255.2 mmol) was added portionwise, the reaction was stirred for 2 hours at room temperature. TLC indicated the reaction completed. The solution was diluted with ethyl acetate, the solid was filtered, the filtrate was washed with brine and saturated sodium bicarbonate solution and water, then dried over anhydrous sodium sulfate. Filtered and concentrated *in vacuum* to remove the solvent, the residue was purified by flash column chromatography on silica gel (eluted with ethyl acetate-petroleum ether, 3:1, v/v) to afford compounds **18a** (2.17 g) and **18b** (1.92 g).

(*Z*)-2-methoxy-5-(3, 4, 5-trimethoxystyryl) aniline (**18a**): oil,yield 30%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.67 (s, 1H), 6.65 (s, 2H), 6.54 (s, 2H),6.43 (d, *J* = 12.0 Hz, 1H), 6.35 (d, *J* = 12.0 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.68 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.5, 147.5, 137.7, 136.4, 133.7, 130.5, 128.4, 126.4, 117.8, 112.3, 110.5, 103.4, 61.0, 56.2, 55.7; HR-MS: m/z calcd. for $C_{18}H_{21}NO_4$, 315.1471, found: 315.1470(M^+).

(*E*)-2-methoxy-5-(3, 4, 5-trimethoxystyryl) aniline (**18b**): solid, mp 116-117 °C, yield 26%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.88 (s, 1H), 6.86 (d, *J* = 4.7 Hz, 1H), 6.80 (d, *J* = 16.0 Hz, 1H), 6.73 (d, *J* = 16.0 Hz, 1H), 6.70 (s, 2H), 3.90 (s, 6H), 3.86 (d, *J* = 3.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.4,

147.4, 137.6, 136.4, 133.6, 130.4, 128.3, 126.4, 117.8, 112.3, 110.5, 103.4, 61.0, 56.1, 55.6; HR-MS: m/z calcd. for $C_{18}H_{21}NO_4$, 315.1471, found: 315.1472(M^+).

Biological activity assay

In vitro antiproliferation activity test. The experiment was performed in Nanjing OGPharmaceutical Co., Ltd.. Cancer cell lines were obtained from the American type Culture Collection (ATCT, Rockville, USA) and were cultured according to the supplier's instructions. Human lung cancer cell A549, human gastric cancer cell MGC-803, human breast cancer cell MCF-7 and human hepatoma cell HepG2 were cultured in RPMI 1640 medium containing 10 % fetal bovine serum, human colon cancer cell HCT-116, human cervical cancer cells HeLa and human gastric cancer cells MKN45 were maintained in Dulbecco's minimal essential medium (DMEM) containing 10 % fetal bovine serum and maintained at 37 °C and 5 % CO_2 incubators (SANYO, MCO-15AC). The cell proliferation inhibition test was performed using the EnoGeneCell Counting Kit-8 (CCK-8) Cell Viability Assay Kit, and the experiment was performed using a viable cell ratio of 90% or more. Cells were digested and counted to prepare a cell suspension at a concentration of 1×10^5 cells/mL. A 100 μL cell suspension was added to each well in a 96-well plate (1×10^4 cells per well) for 24 hours at 37 °C and 5 % CO_2 incubators, 100 μL of the corresponding drug-containing medium was added to each well while the negative control group, the vehicle control group and the positive control group were set up with 5 wells in each group. The 96-well plate was placed at 37 °C and CO_2 incubator for 72 hours, afterwards 10 μL of CCK-8 solution was added to each well. And the plates were incubated in the incubator for 4 hours, the OD values were determined at 450 nm with a spectrophotometric plate reader(Thermo scientific, MUTISKAN MK3). Each sample was test for three time at ten different concentration. The inhibitory rate was determined as follows: inhibitory% = $(OD_{sample}-OD_{blank})/(OD_{control}-OD_{blank})\times100\%$, and the IC50 value (inhibitory concentration for 50% of cells) was determined using the GraphPad Prism software.

In vitro sulfatase activity test. The steroid sulfatase was purchased from Sigma-Aldrich. The test compounds were weighted and dissolved in dimethylsulfoxide, then diluted with Tri-HCl buffer (0.1M, pH = 7.4) at 2, 5, 10, 20, 50, 100, 200, 500, 1000, 2000, 5000 and 10000 times. Steriod sulfatase and potassium *p*-nitrophenyl sulfate were directly dissolved in Tris-HCl buffer. To a 96-well plate was incubated with 40 μL of the test sample, 50 μL of aryl sulfatase and 50 μL of potassium *p*-nitrophenyl sulfate for 5 minutes, the OD values were determined by a microplate reader at 405 nm. The blank control (no sulfatase) and standard control (no sample) were also test in same procedure by adding Tris-HCl buffer to make up the volume. Each sample was test for three time at ten different concentration. The inhibitory rate was determined as follows: inhibitory% = $\{1-(OD_{sample}-OD_{blank})/(OD_{control}-OD_{blank})\}\times100\%$, and the IC50 value was determined using the GraphPad Prism software.

In vitro tubulin polymerization assay. Pig brain microtubule protein was isolated by three cycles of temperature-dependent assembly/disassembly in 100 mM PIPES (pH 6.5), 1 mM MgSO4, 2 mM EGTA, 1 mM GTP and 1 mM 2-mercaptoethanol. In the first cycle of polymerization, glycerol and phenylmethylsulfonyl fluoride were added to 4 M and 0.2 mM, respectively. Homogeneous tubulin was prepared from microtubule protein by phosphocellulose (P11) chromatography. The purified proteins were stored in aliquots at -70 °C.

Tubulin（4.8 mg/ml） protein was mixed with different concentrations of compound in PEM buffer (100 mM PIPES, 1 mM $MgCl_2$, and 1 mM EGTA) containing 1 mM GTP and 5 % glycerol. Microtubule polymerization was monitored at 37 °C by light scattering at 340 nm using a SPECTRA MAX 190 (Molecular Device) spectrophotometer. The plateau absorbance values were used for calculations. Each sample was test for three time at ten different concentration. The inhibitory rate was determined as follows: inhibitory% = $\{1-(OD_{sample}-OD_{blank})/(OD_{control}-OD_{blank})\}\times100\%$, and the IC50 value (inhibitory concentration for 50% of cells) was determined using the GraphPad Prism software.

Molecular Docking

The crystal structure of tubulin-Combretastatin A4 complex (PDB: 5LYJ) and arylsulfatse-EMATE complex (PDB:1P49) were retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) protein data bank. Compound **16a** were constructed using the sketcher module in Sybyl and their minimum energy conformations were calculated using the minimize module of Sybyl. The force field was Tripos with an 8 Å cutoff for non-bonded interactions, and the atomic point charges were also calculated with Gasteiger-Huckel. Minimizations were achieved using the steepest descent method for the first 100 steps, followed by the Broyden-Fletcher-Goldfarb-Shanno (BFGS) method until the root-mean-square (RMS) of the gradient became < 0.005 kcal/(mol·Å). The Surflex-Dock module implemented in the Sybyl program was used for the docking studies. The colchicine binding-site of tubulin and EMATE binding-site of steriod sulfatase were used for the docking simulation, the original ligand (CA-4 and EMATE) in the crystal structure was used as control. Compound **16a** were docked into the binding site by an empirical scoring function and a patented search engine in Surflex-Dock, applied with the automatic docking. Other parameters were established by default in the software

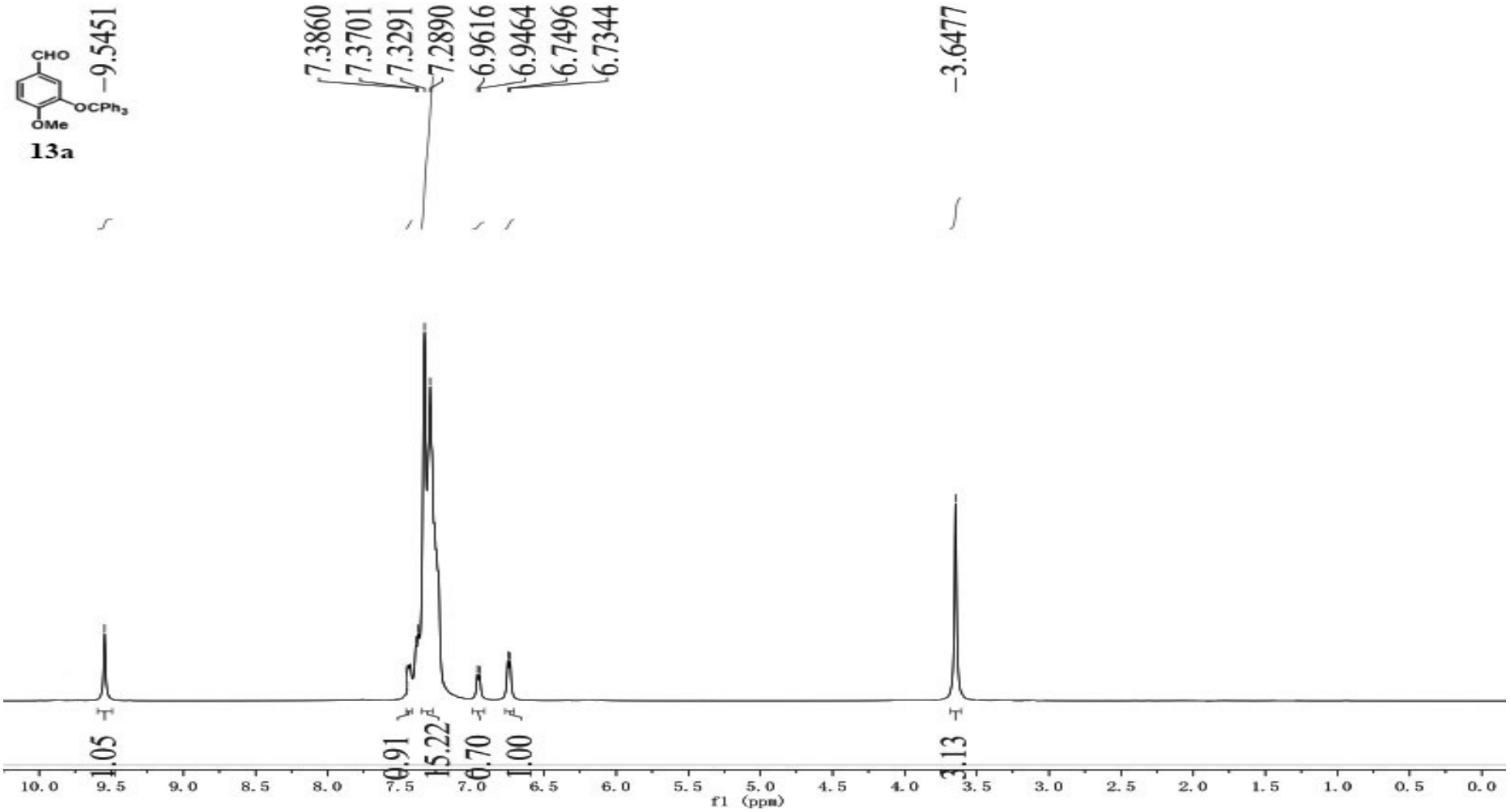
Structure activity relationship discussion on arylsulfatase and tubulin polymeriztion inhibition

From the inhibitory activity results of **16a, 16b** and **17a** on arylsulfatase and tubulin, we can infer that the cis-isomer is better than trans-isomer and saturated bond linked analogues. The electronic effects of R group was studied by comparing the activity of compound **16a, 16c, 16e** and **16g** on both targets. The potency of **16c** with difluoromethoxy group increased slightly relating to the electronic withdrawing effect of difluomethyl group, which indicate an electronic withdrawing group on this position is favorable for arylsulfatase inhibition while unfavorable for tubulin inhibition at the same time. The steric effects of R group was studied by the comparison of compound **16a, 16e** and **16g**. Compound **16a** showed comparable potency on steroid sulfatase (IC_{50} = 6.16 μM) with EMATE (IC_{50} = 5.01 μM) and similar potency on cel with combretastatin A-4. **16g** (R = H), removing the methoxyl group of **16a**, showed the increasing inhibitory activity for sulfatase about ten times (IC_{50} = 0.47 μM), however the potency of **16g** on cell dropped rapidly as it lost the potency on tubulin inhibition (IC_{50} > 100 μM). On the contrary, when the methoxyl of **16a** was replaced with a little bulky ethoxyl group to give **16e** (R = OEt), the potency on tubulin increased (IC_{50} = 3.10 μM), although its potency on steroid sulfatase dramatically decreased (IC_{50} = 90.19 μM), the cell level activity is close with that of EMATE. These results indicate the steric effect at R position is favorable for tubulin inhibition but unfavorable for arylsulfatase inhibition. The substitution effect of the amino group of sulfamide was studied from **16i** and **16j**, the monomethylated and dimethylated 16a. By comparing with 16a, their potency on steroid sufatase inhibition were lost. however, their potency on tubulin polymerzation were different, monomethyl substitution (**16i**, IC_{50} = 1.80 uM) showed improved the potency with about 3 times, while dimethyl substition (**16j**, IC_{50} = 12.50 uM) illlustrated the decreased potency about 2 times. This result indicates that the amino group of **16a** probably has critical hydrogen bond interaction with the binding site of both targets, in other words, the steric hindrance factors caused by substitution on amino group can also affect activity. The lost contribution to cytotoxicity of **16i** on sulfatase inhibition was probably compensatrated by its improved potency on tubulin. In addition, **19a** showed no activity on arylsulfatase, which implies that a hydrogen bond donor probably exists in the binding site. This is consistent with the fact that sulfatase only specific hydrolysis of sulphate instead of sulfamide. From the structure-activity-relationship ananlysis of **16**(**c-j**) on arylsulfatase and tubulin inhibtion and their contribution to anti-tumor activity, we can conclude that tubulin inhibition plays a dominant role over arylsulfatase inhibition in this kind dual inhibitor.

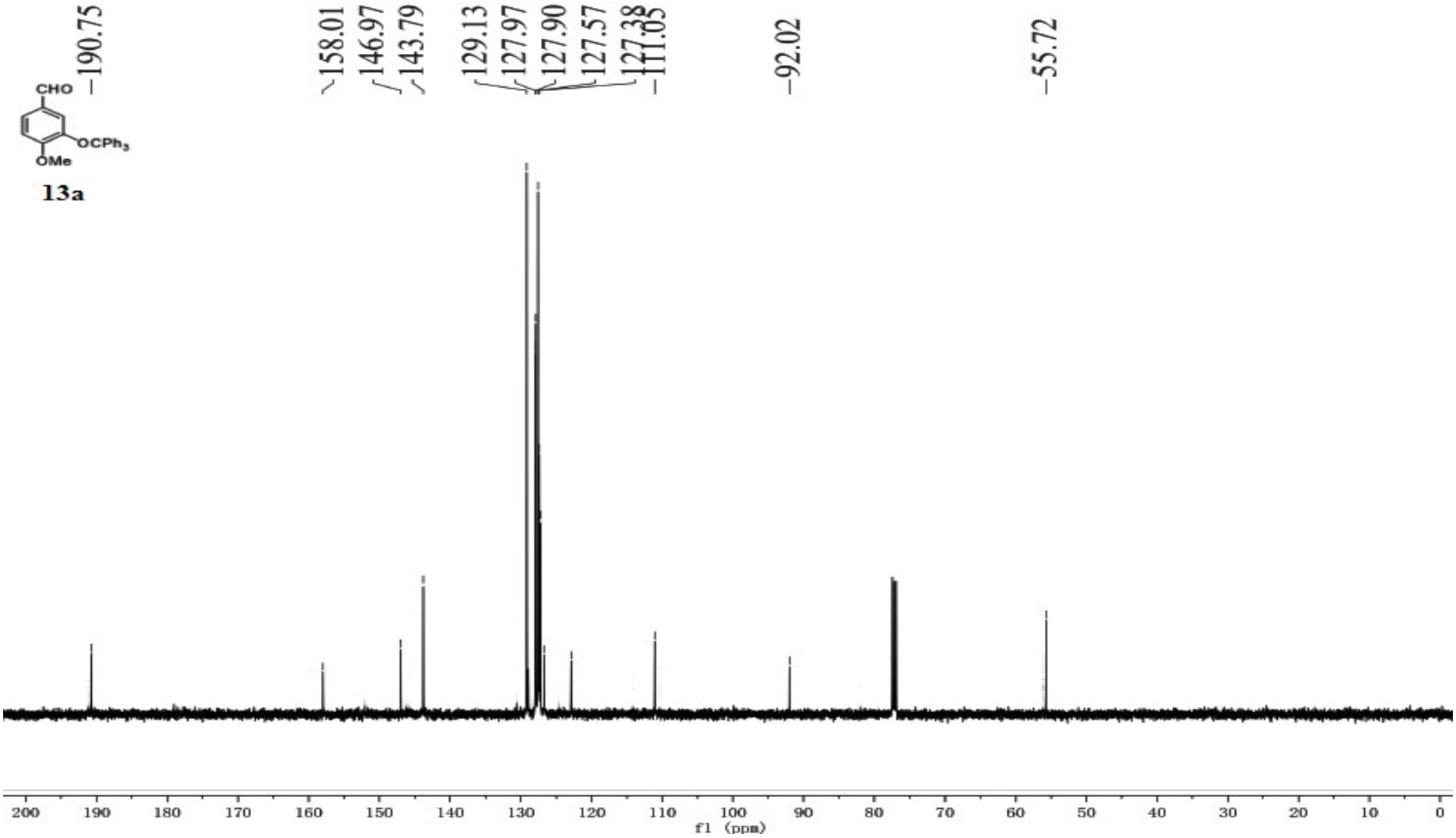
HPLC condition and the purity data of compounds 16a-16j, 17a-17d, 19a, 19b, 20.

Equipment	Shimadzu LC-15C with double pump, UV detector			
Column	Shimadzu Wondasil C18-WR (150×4.6 mm, 5 μm particle size)			
Condition	CH_3CN(0.1% CF_3COOH) : H_2O(0.1 % CF_3COOH) = 20 : 80 (v/v) as eluent, flow rate: 1.0 mL/min, detection wavelength: 276 nm. The purity was determined by area normalization.			
Results	Compd. No.	Retention time (min)	Relative purity (%)	Spectra (page)
	16a	11.68	98.70	S42
	16b	9.161	99.88	S46
	16c	9.916	95.66	S51
	16d	9.543	98.49	S56
	16e	9.446	98.23	S60
	16f	9.522	99.82	S64
	16g	9.193	96.00	S68
	16h	9.184	99.58	S72
	16i	9.524	97.23	S76
	16j	10.29	95.77	S80
	17a	9.054	99.30	S84
	17b	9.202	96.76	S88
	17c	9.451	98.13	S92
	17d	9.060	93.79	S96
	19a	9.215	95.45	S104
	19b	8.791	96.84	S108
	20	8.703	95.16	S112

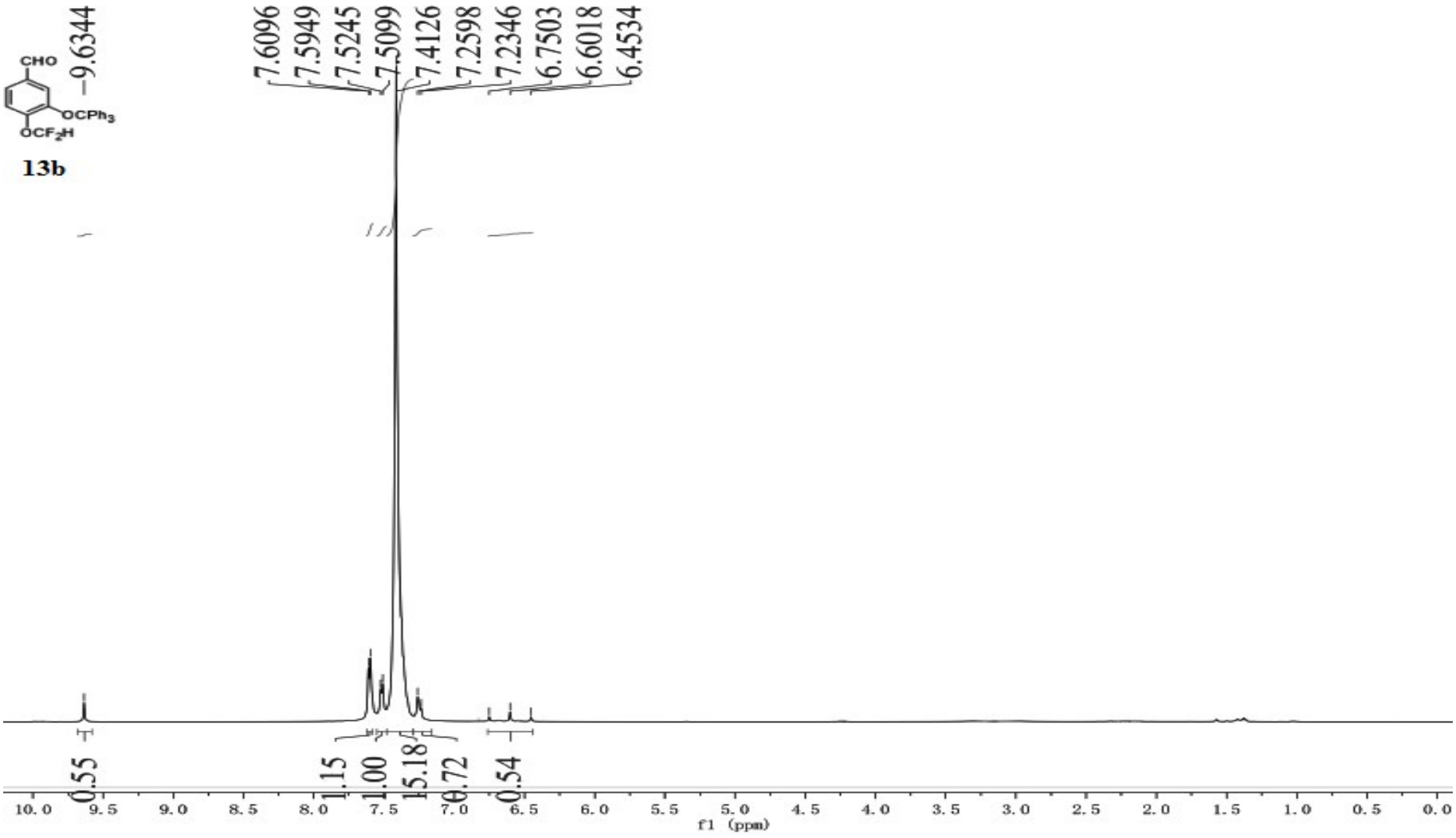
Compound 13a. **^{1}H NMR** $CDCl_3$, 500 MHz



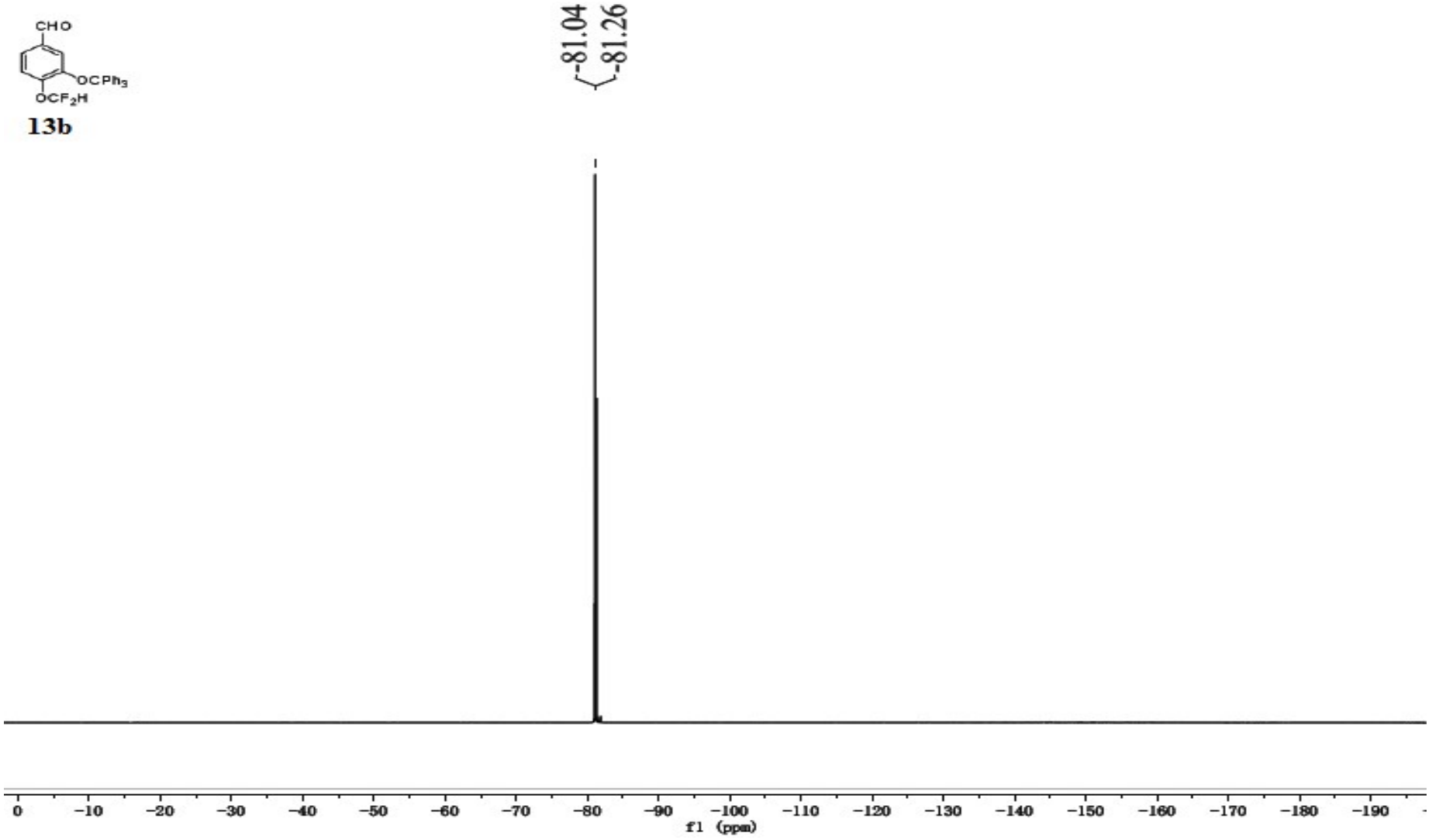
Compound 13a. ^{13}C NMR, $CDCl_3$, 125 MHz



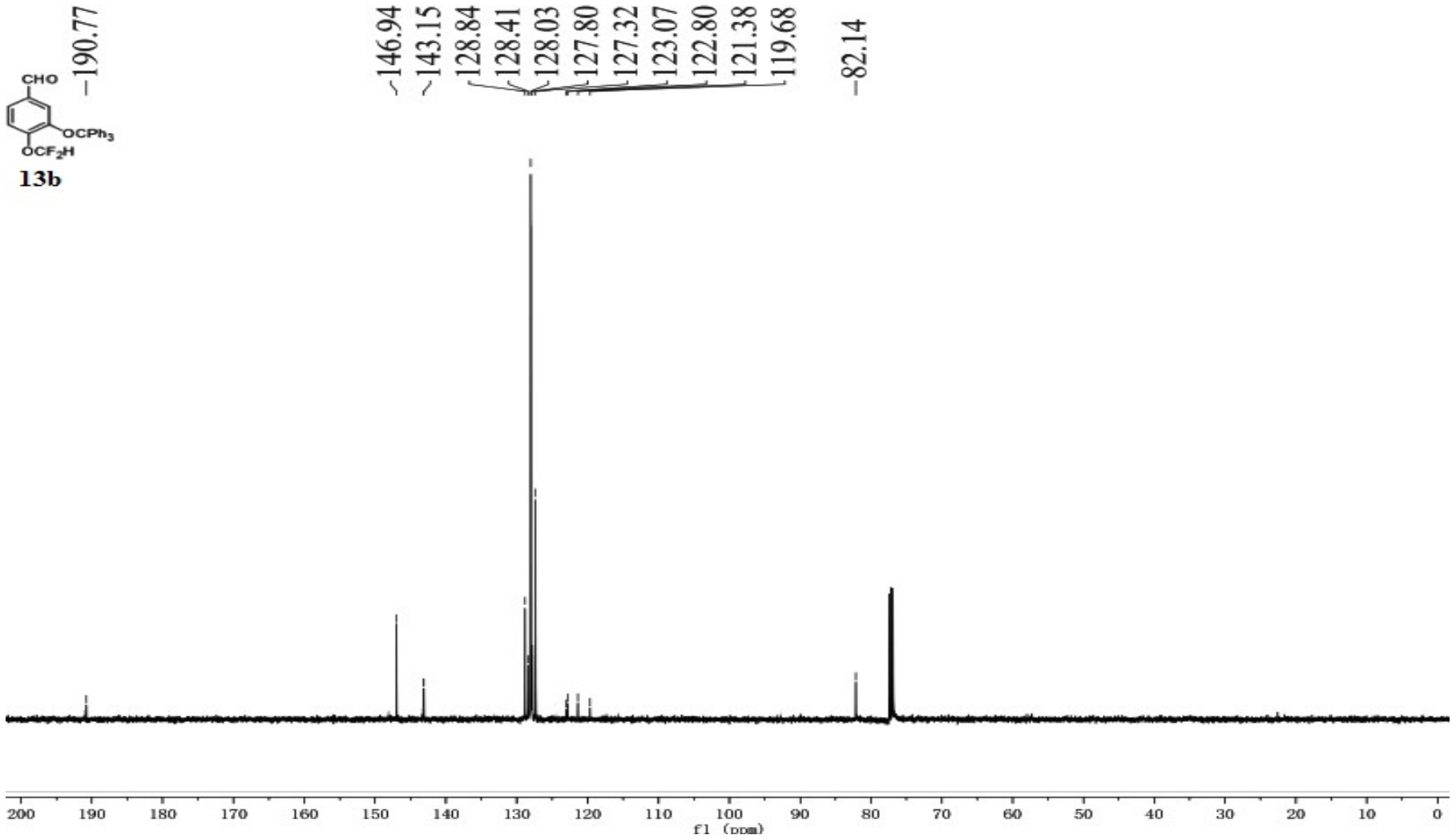
Compound 13b. ^{1}H NMR, $CDCl_3$, 500 MHz



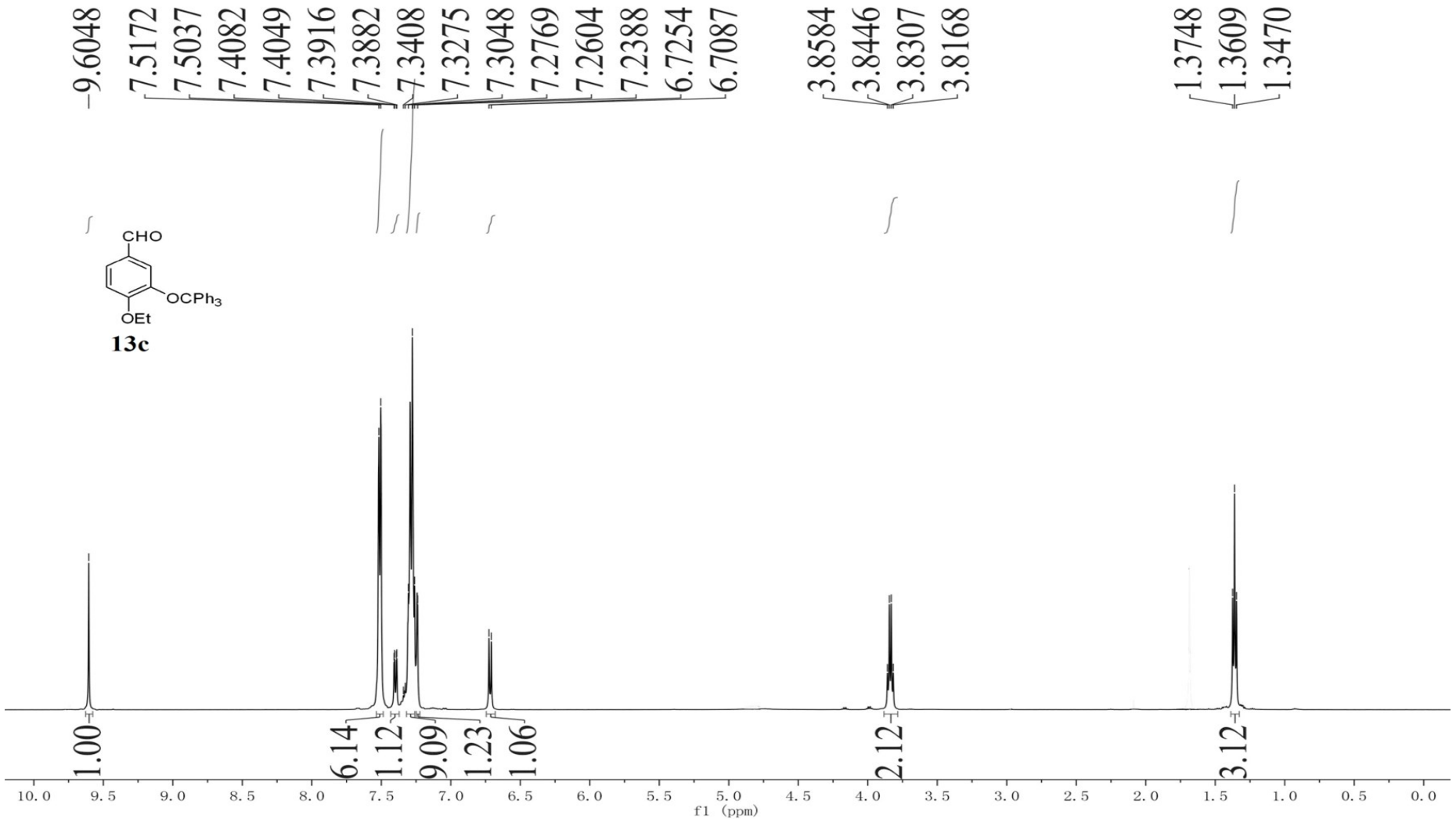
Compound 13b. ^{19}F NMR, $CDCl_3$, 145MHz



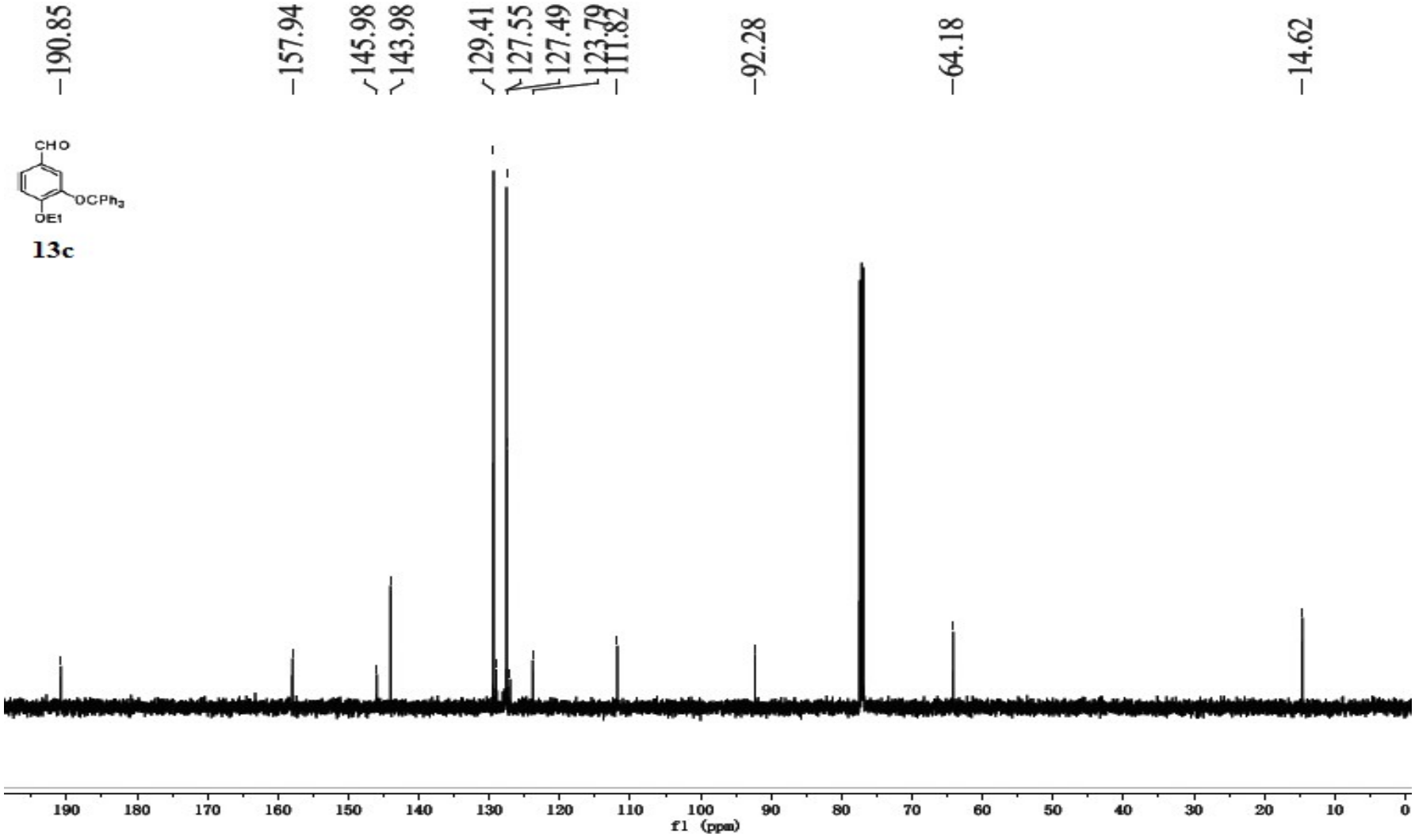
Compound 13b. ^{13}C NMR, $CDCl_3$, 125 MHz



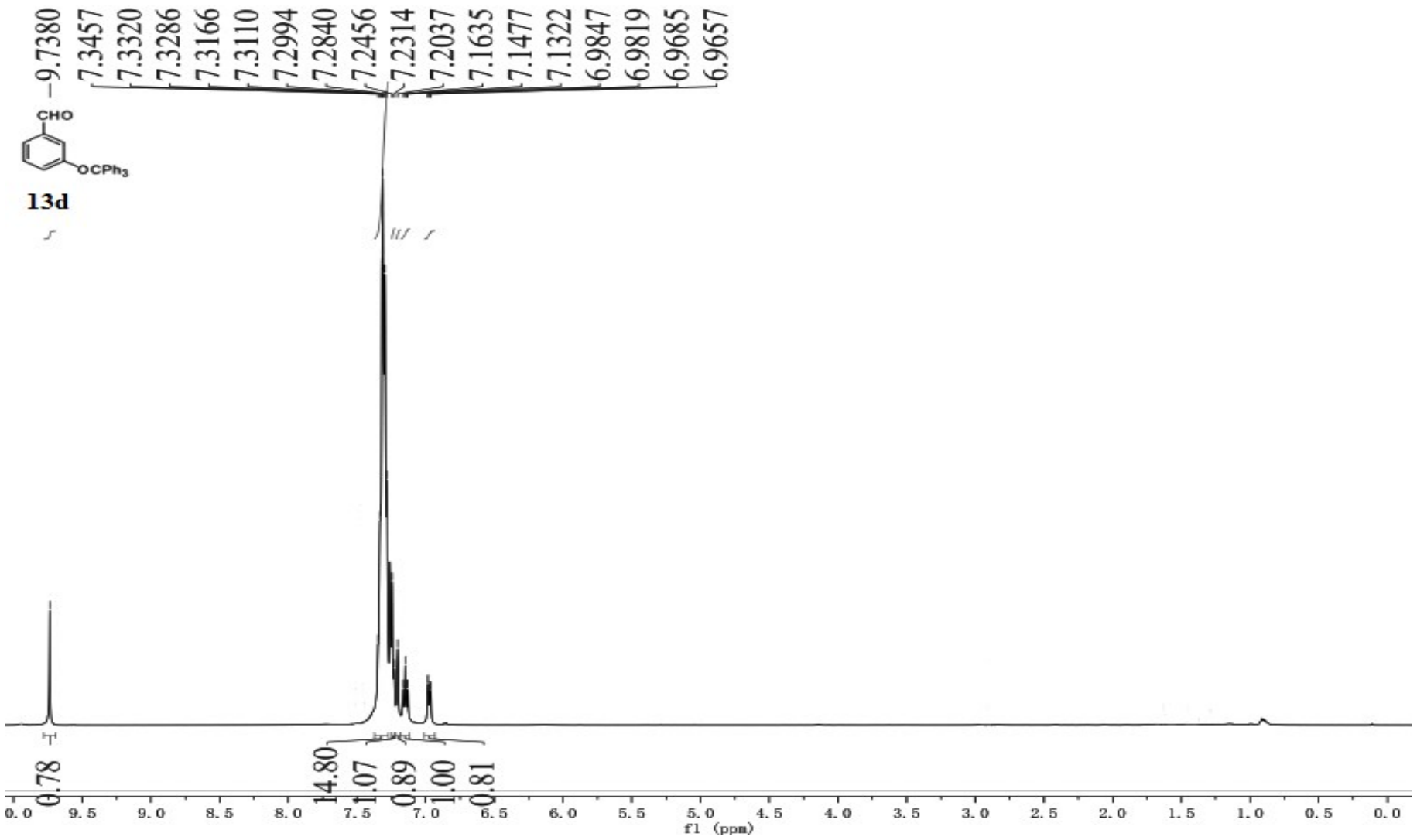
Compound 13c. ^{1}H NMR, $CDCl_3$, 500 MHz



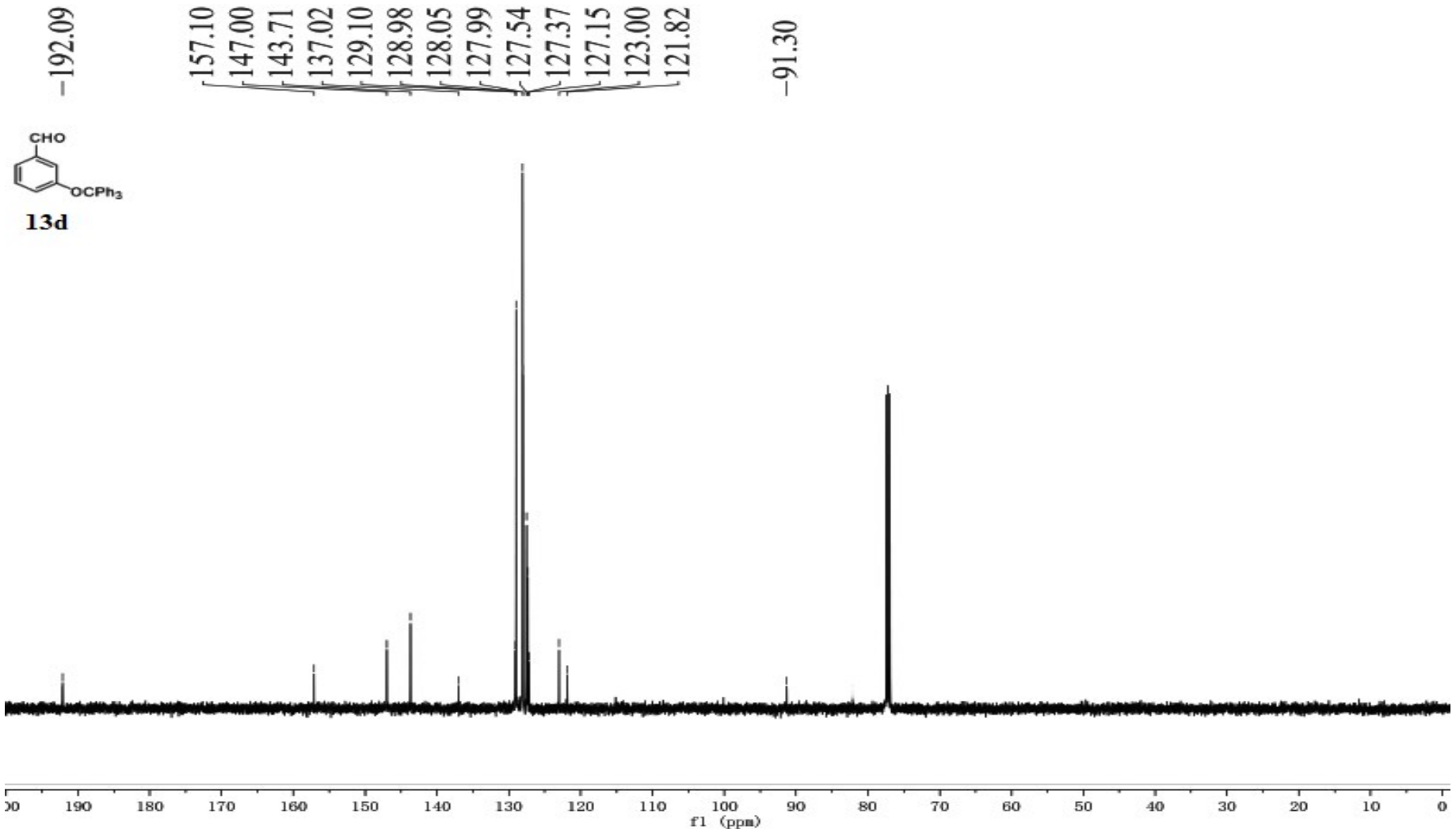
Compound 13c. ^{13}C NMR, $CDCl_3$, 125 MHz


190.85
157.94
145.98
143.98
129.41
127.55
127.49
123.79
111.82
92.28
64.18
14.62
CHO
OCPh3
OEt
13c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

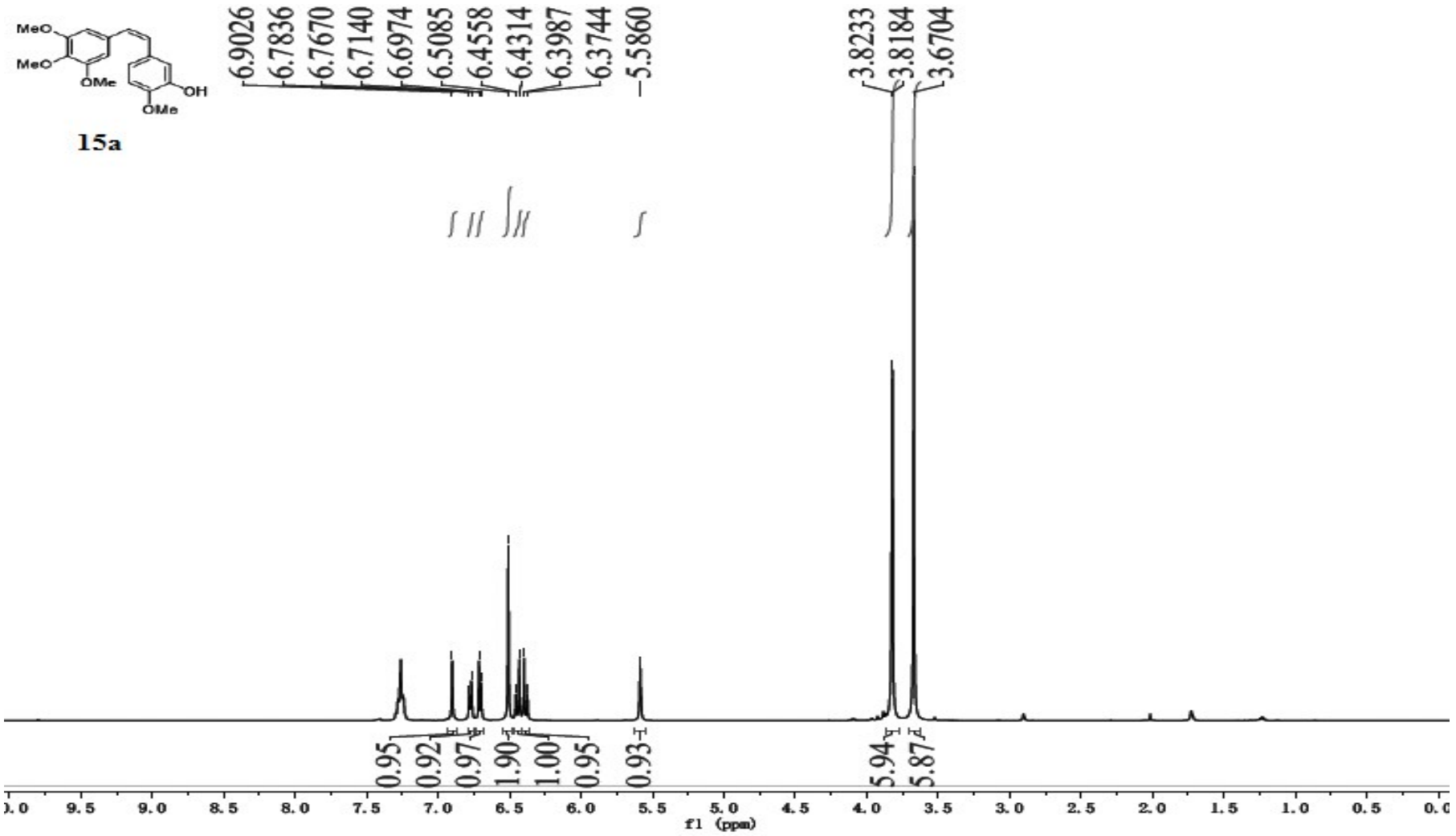
Compound 13d. ^{1}H NMR, $CDCl_3$, 500 MHz



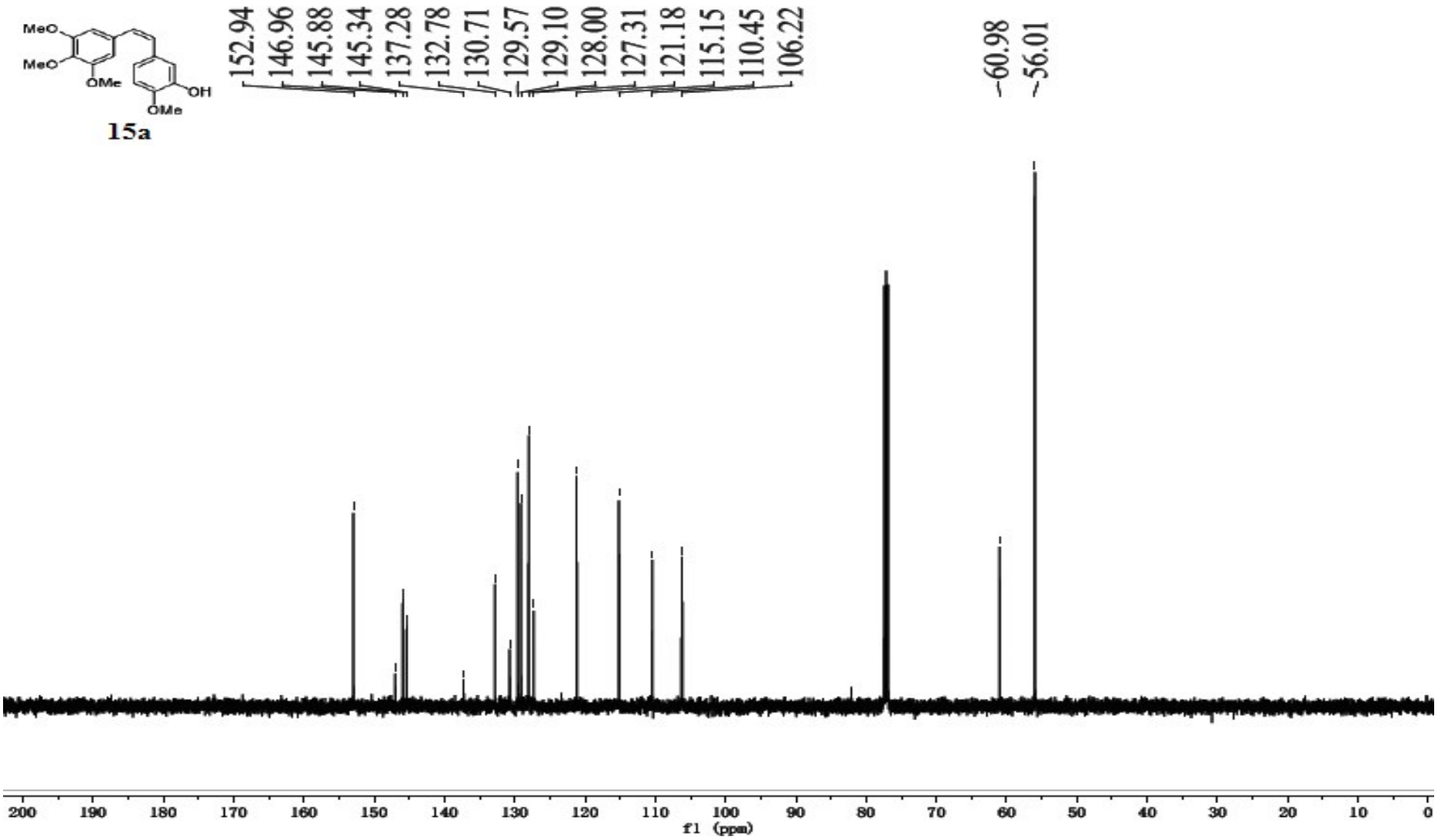
Compound 13d. ^{13}C NMR, $CDCl_3$, 125 MHz



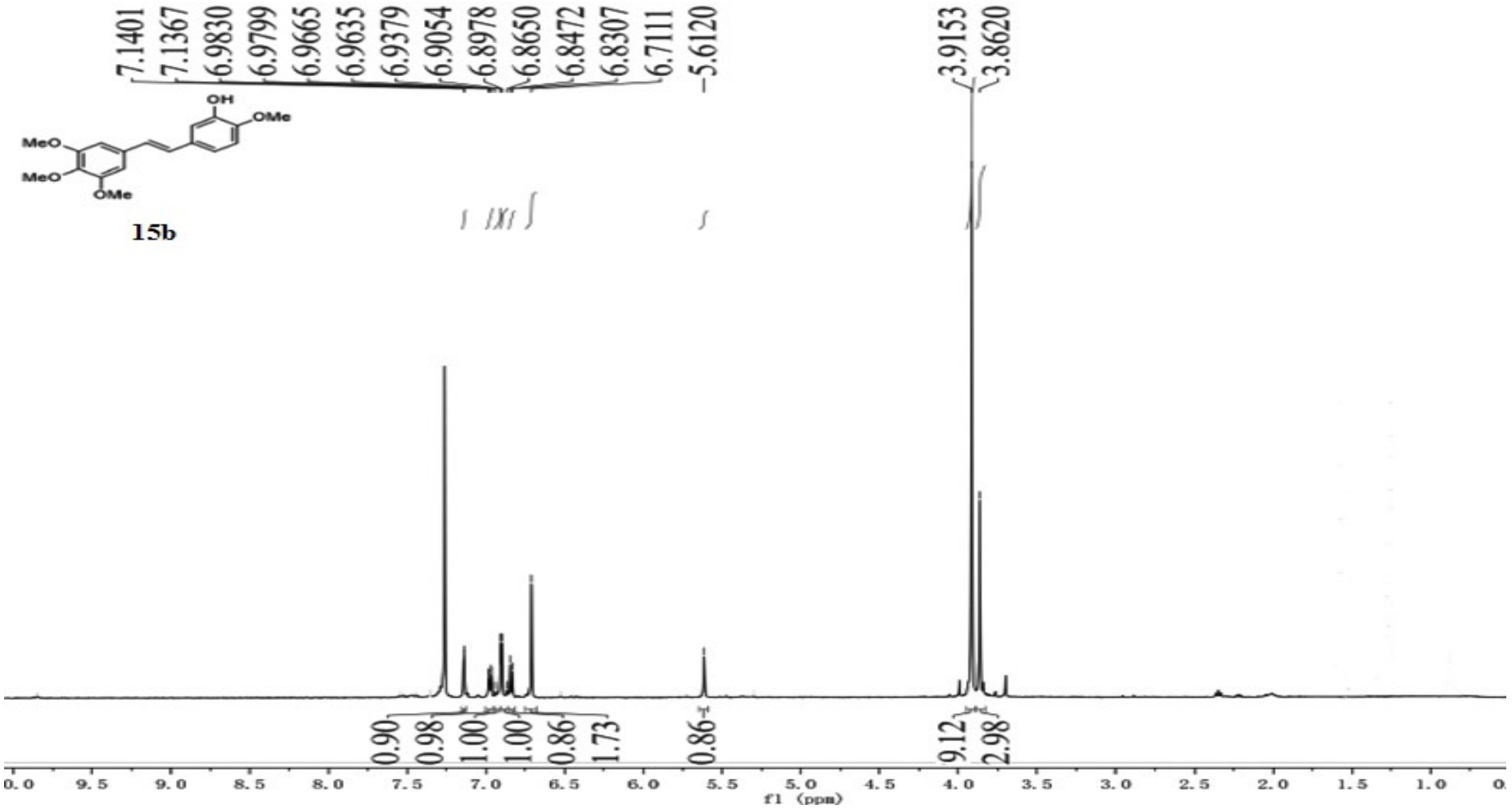
Compound 15a. ^{1}H NMR, $CDCl_3$, 500 MHz



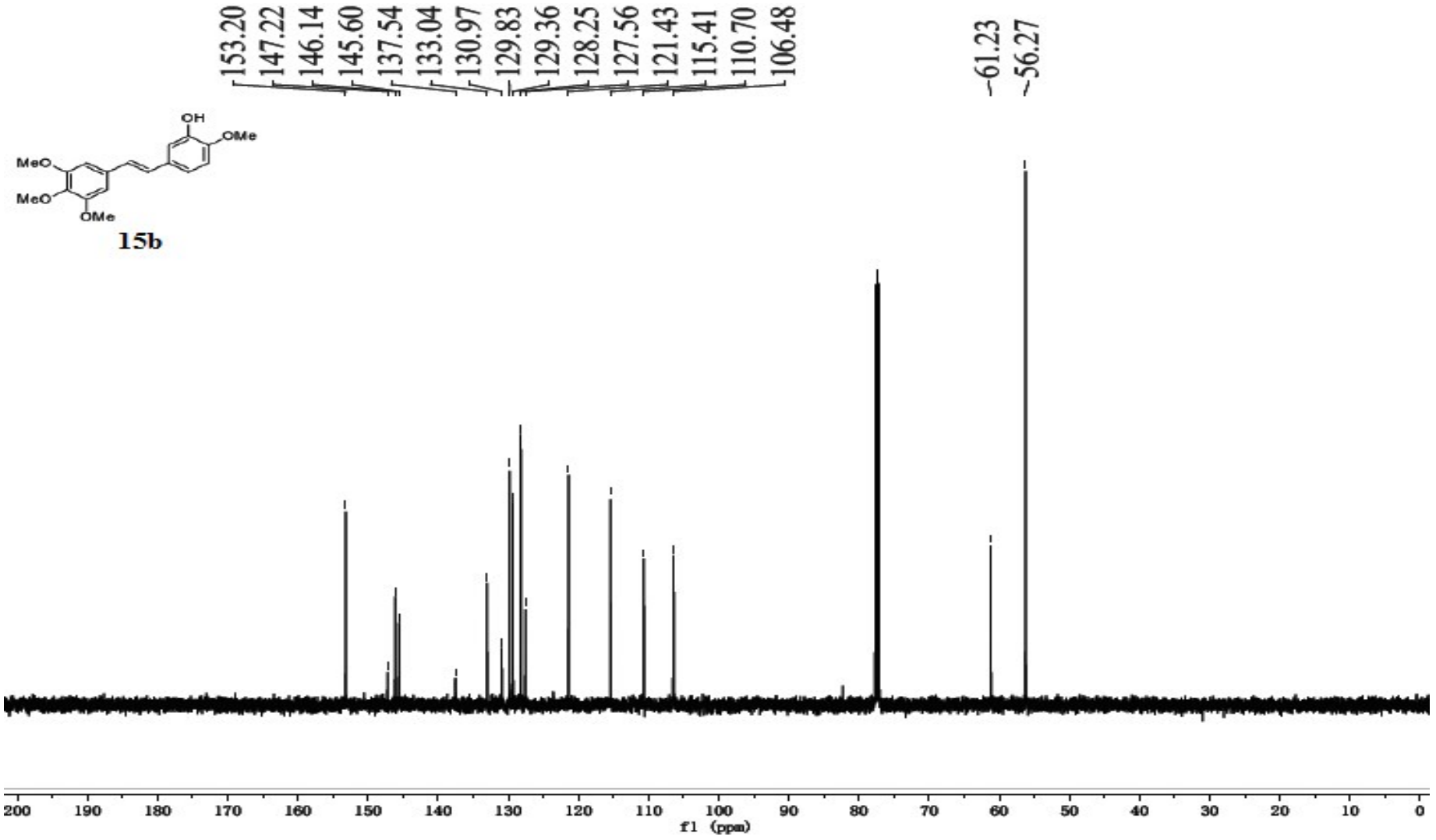
Compound 15a. ^{13}C NMR, $CDCl_3$, 125 MHz



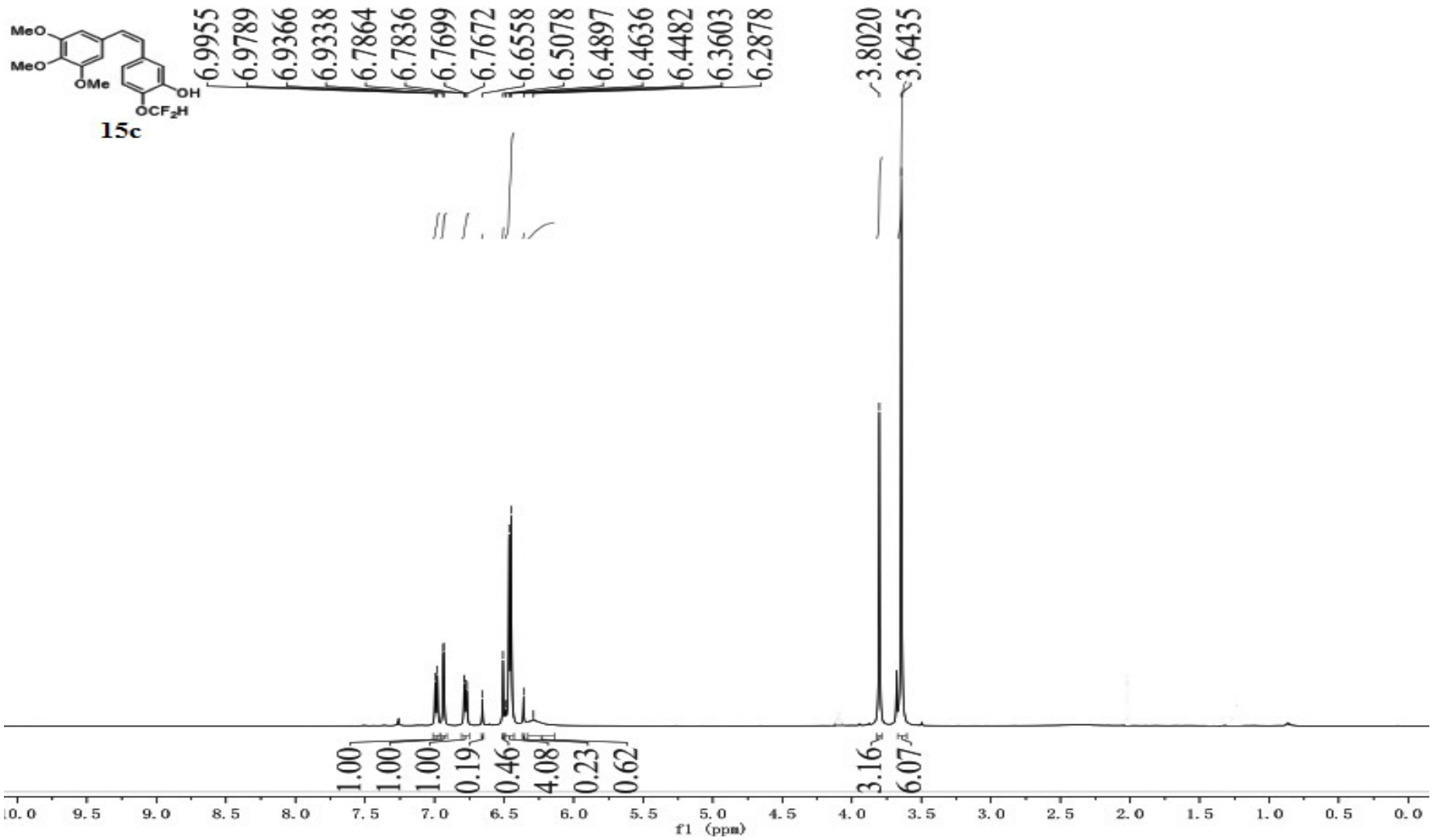
Compound 15b. ^{1}H NMR, $CDCl_3$, 500 MHz



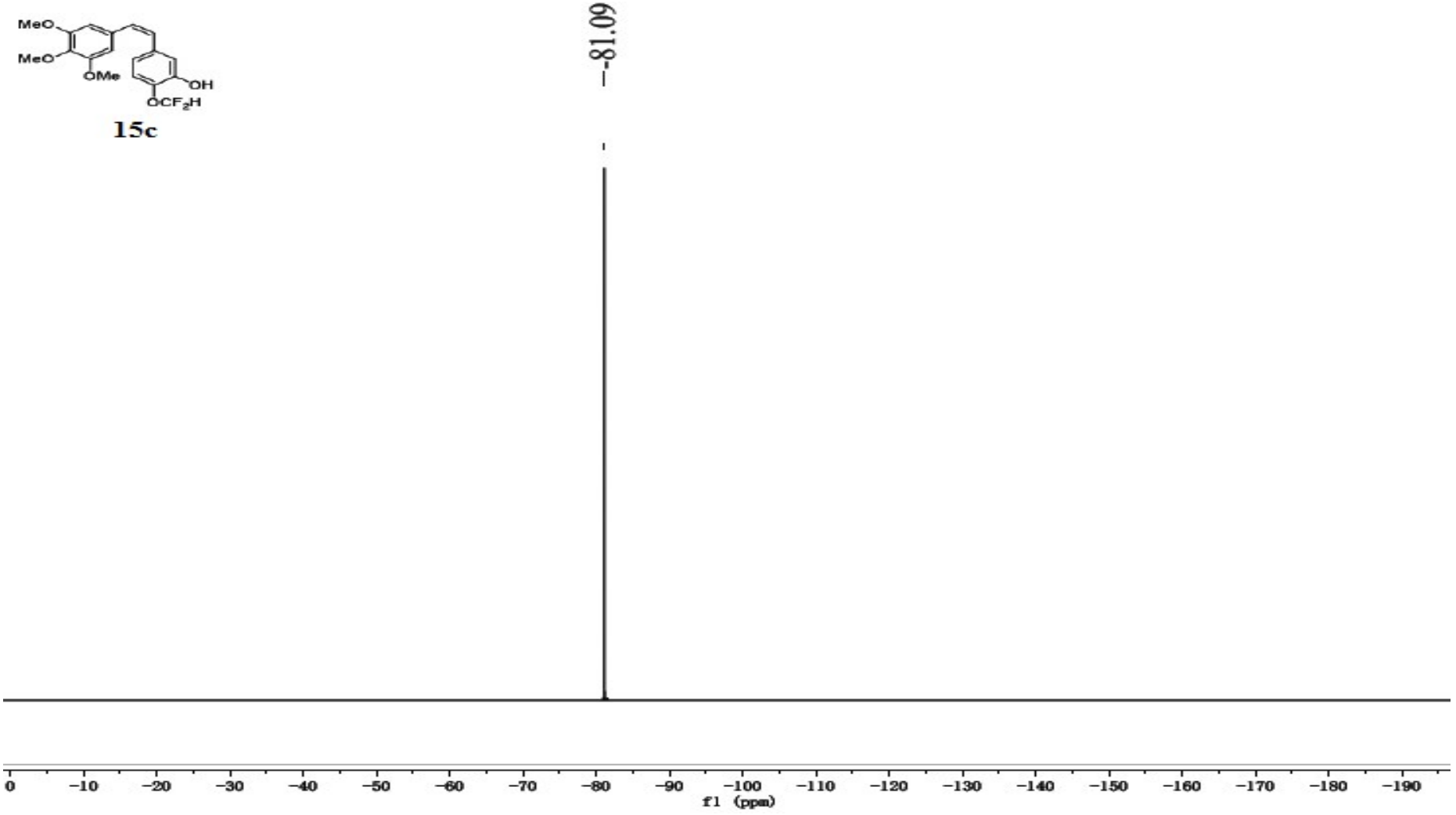
Compound 15b. ^{13}C NMR, $CDCl_3$, 125 MHz


153.20
147.22
146.14
145.60
137.54
133.04
130.97
129.83
129.36
128.25
127.56
121.43
115.41
110.70
106.48
61.23
56.27
OH
OMe
MeO
MeO
OMe
15b
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

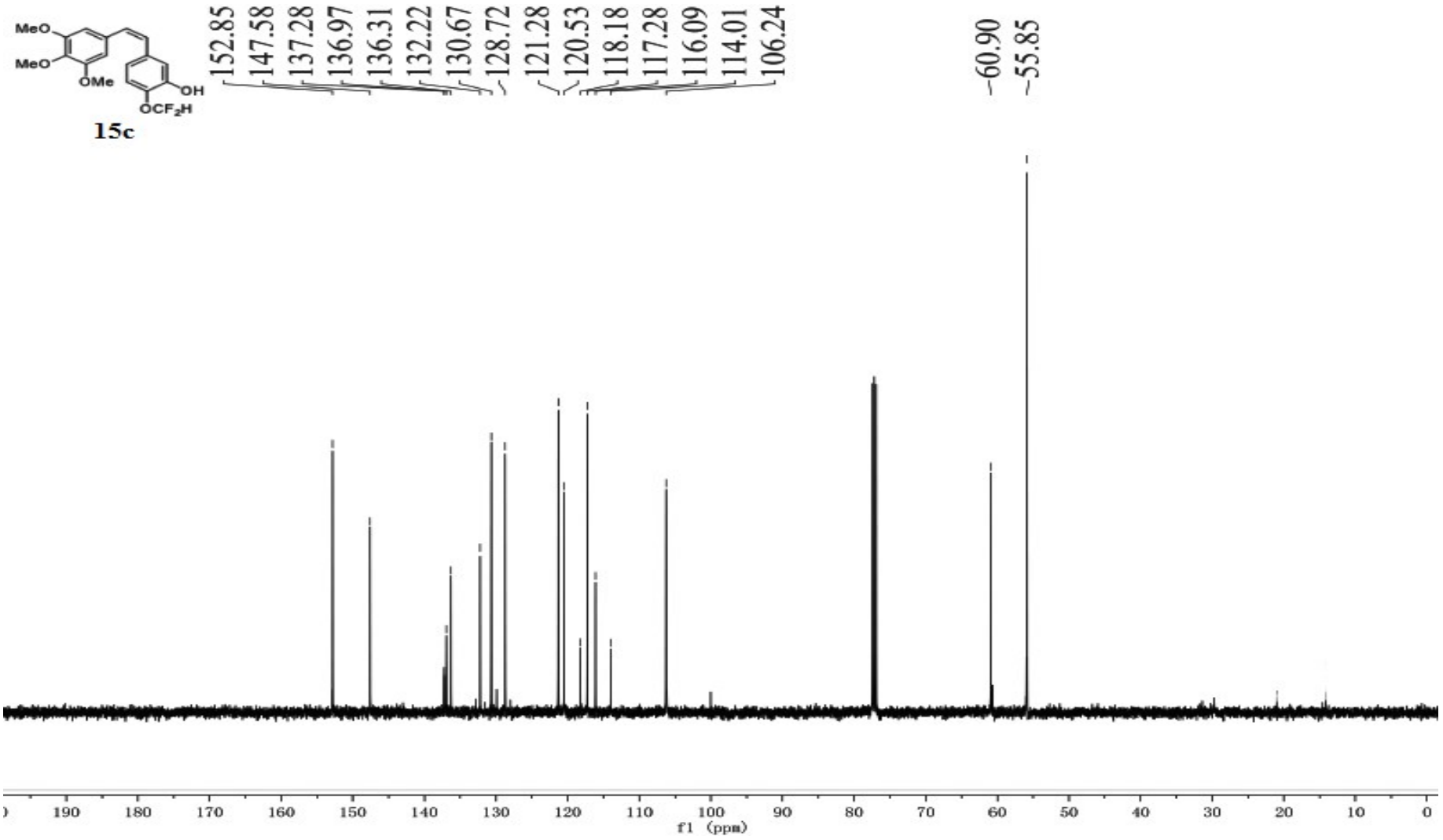
Compound 15c. ^{1}H NMR, $CDCl_3$, 500 MHz



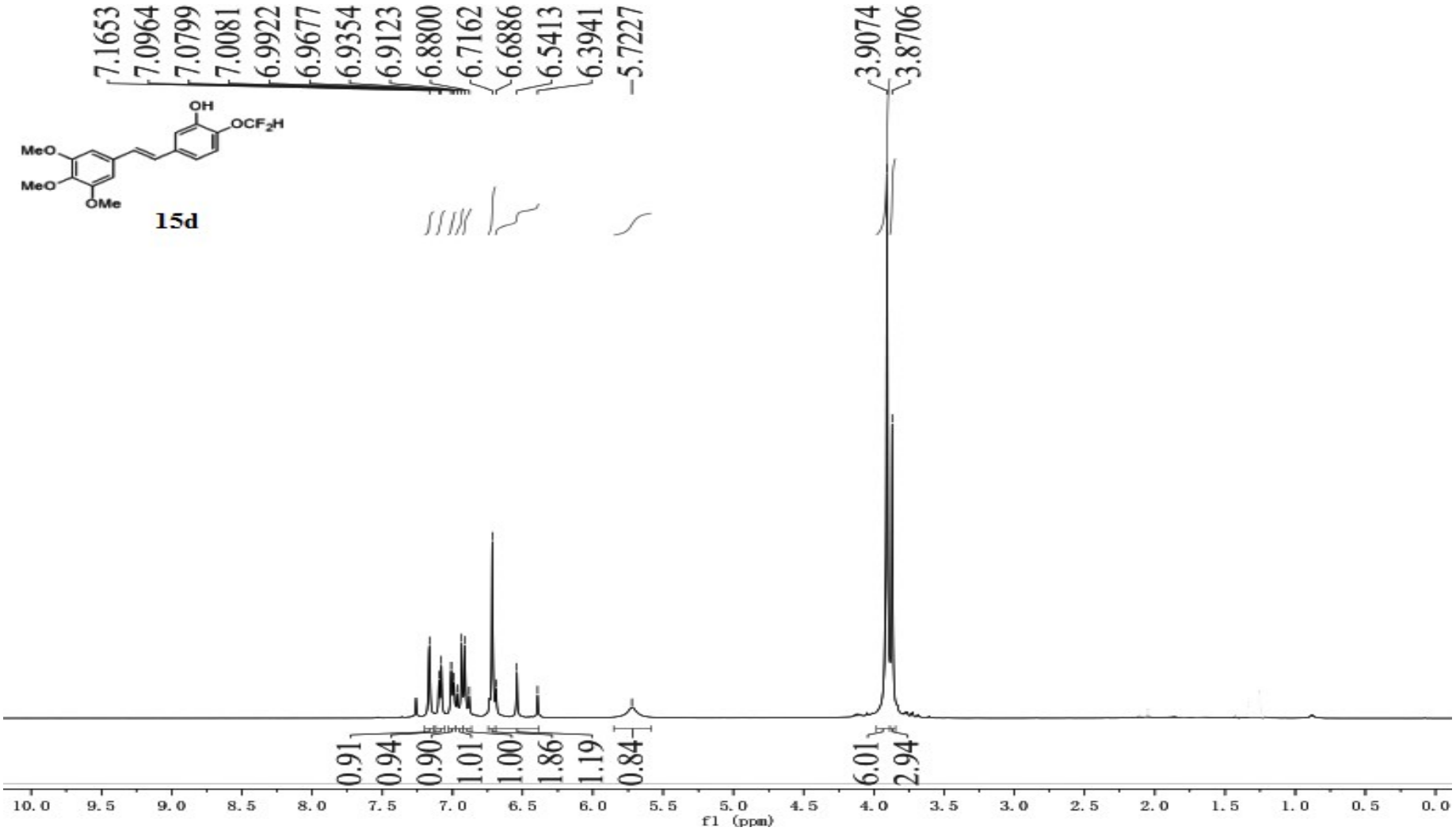
Compound 15c. ^{19}F NMR, $CDCl_3$, 145 MHz



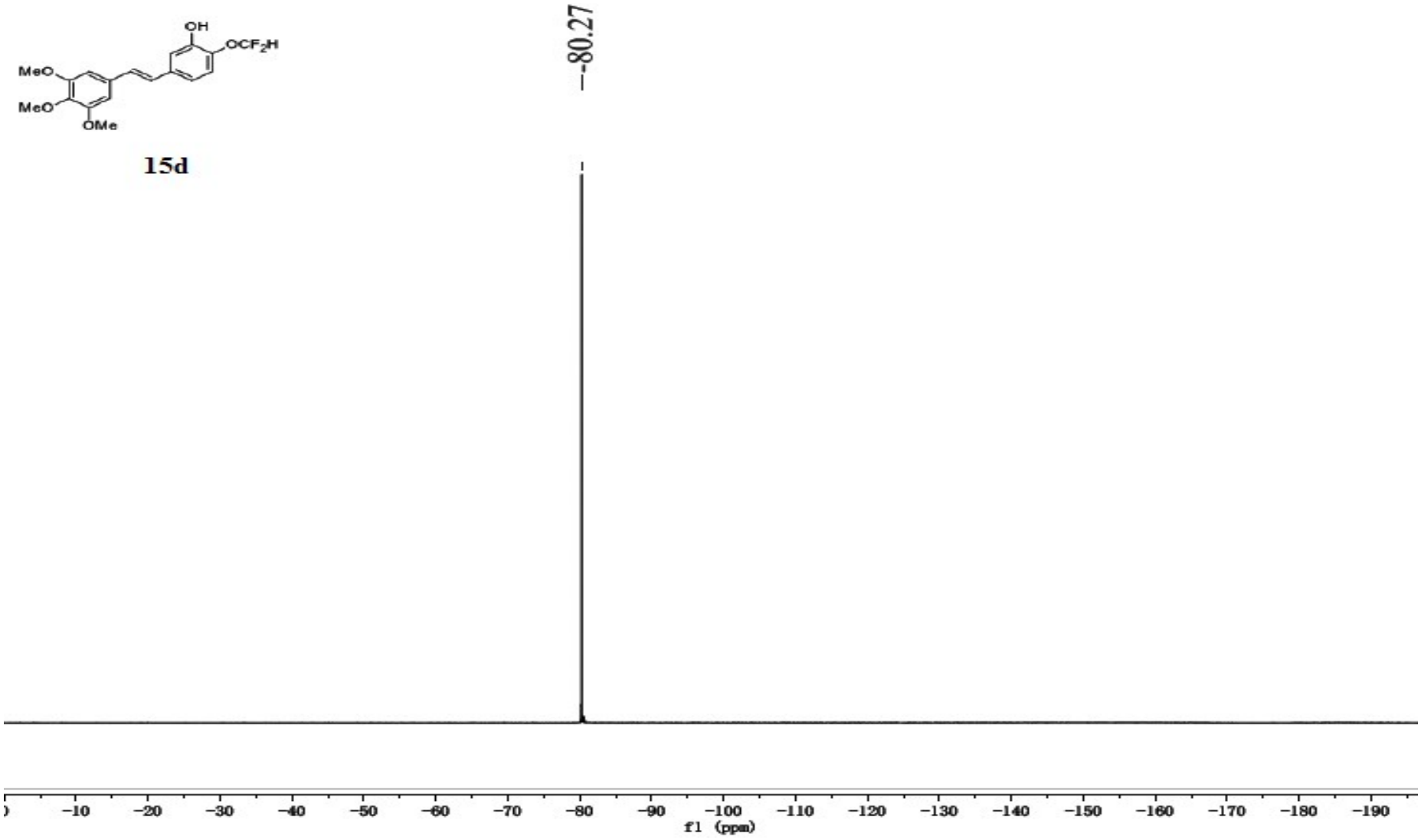
Compound 15c. ^{13}C NMR, $CDCl_3$, 125 MHz



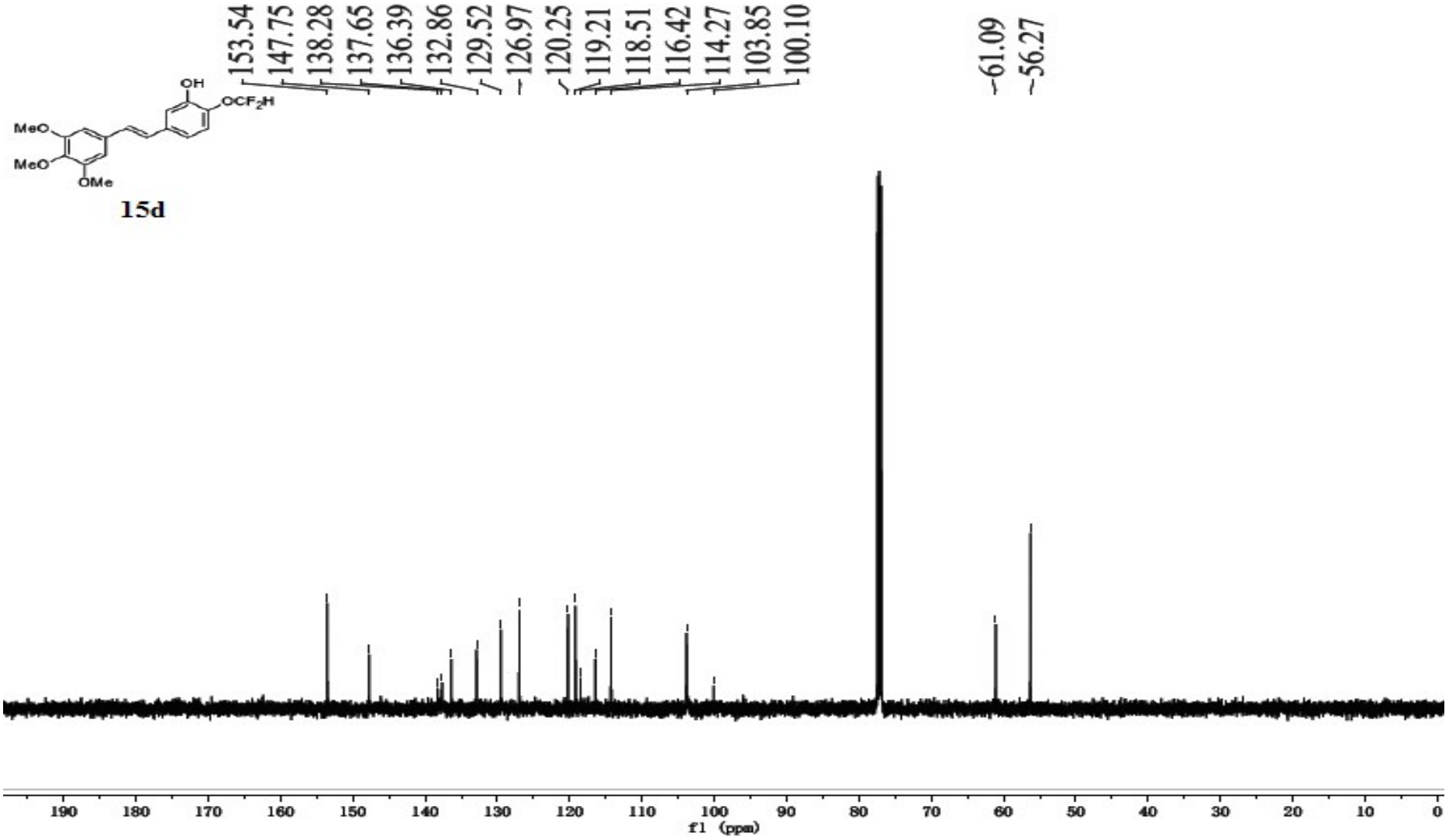
Compound 15d. ^{1}H NMR, $CDCl_3$, 500 MHz



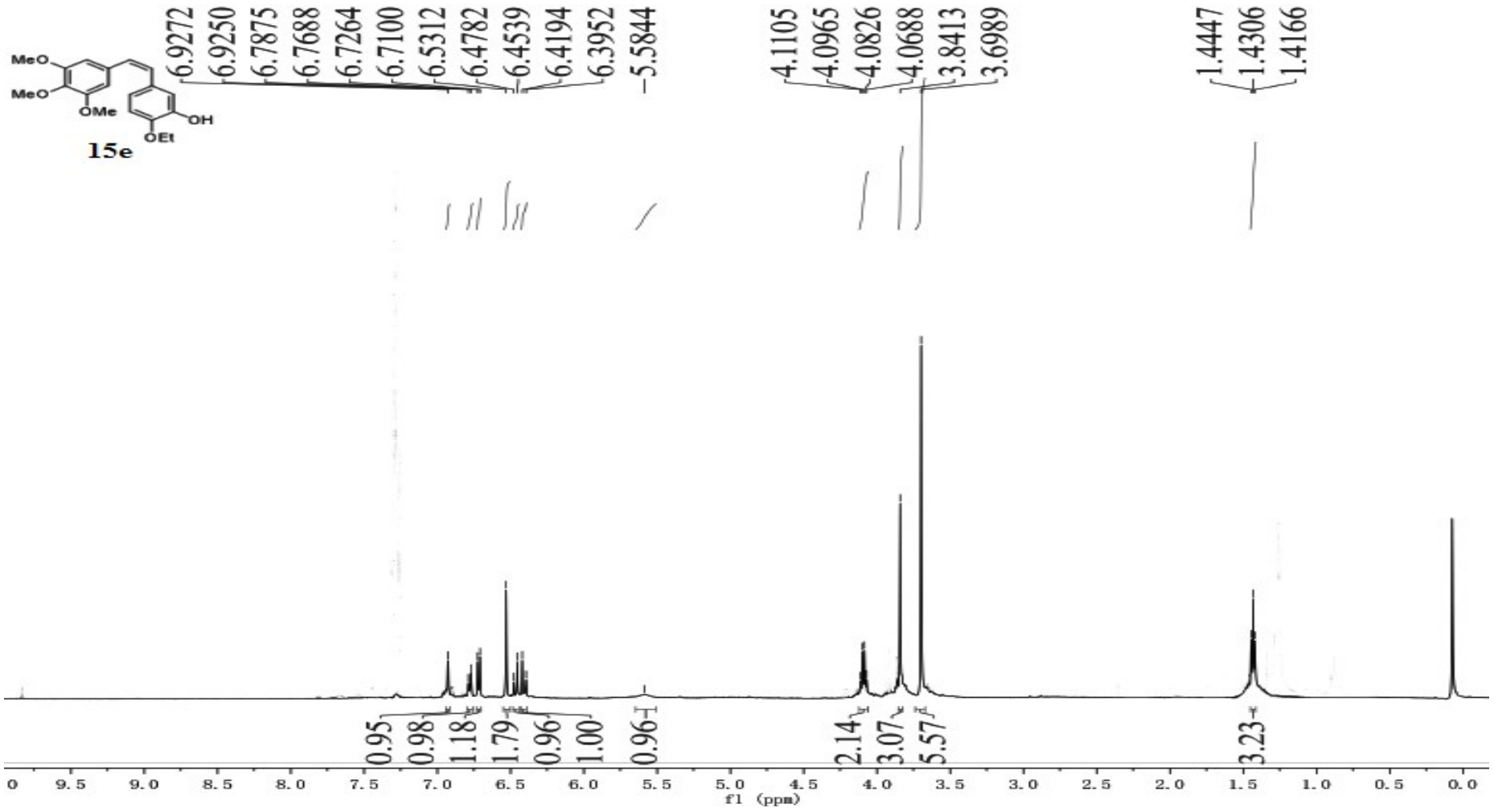
Compound 15d. ^{19}F NMR, $CDCl_3$, 145 MHz



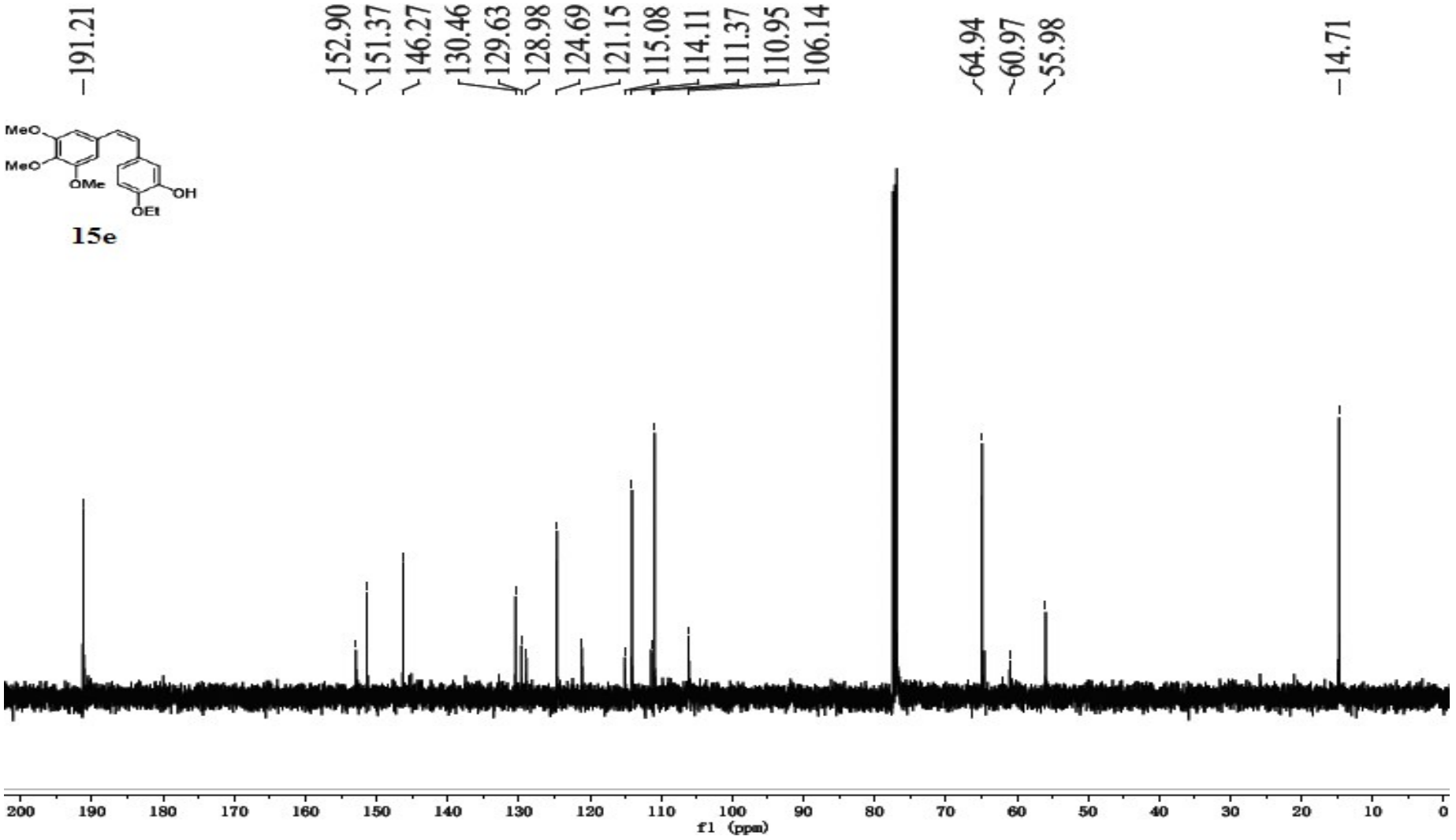
Compound 15d. ^{13}C NMR, $CDCl_3$, 125 MHz


153.54
147.75
138.28
137.65
136.39
132.86
129.52
126.97
120.25
119.21
118.51
116.42
114.27
103.85
100.10
61.09
56.27
OH
OCF2H
MeO
MeO
OMe
15d
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

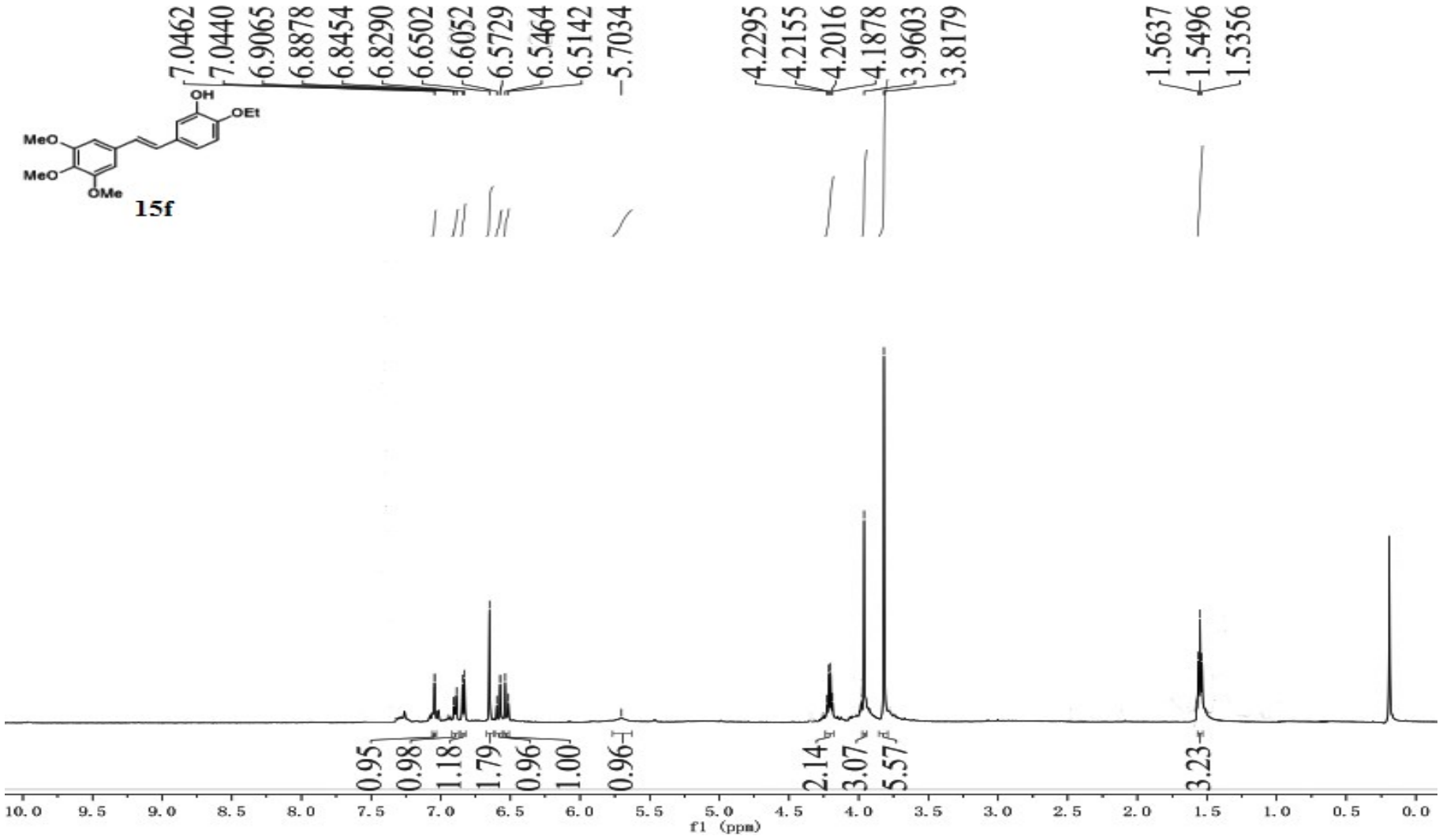
Compound 15e. ^{1}H NMR, $CDCl_3$, 500 MHz



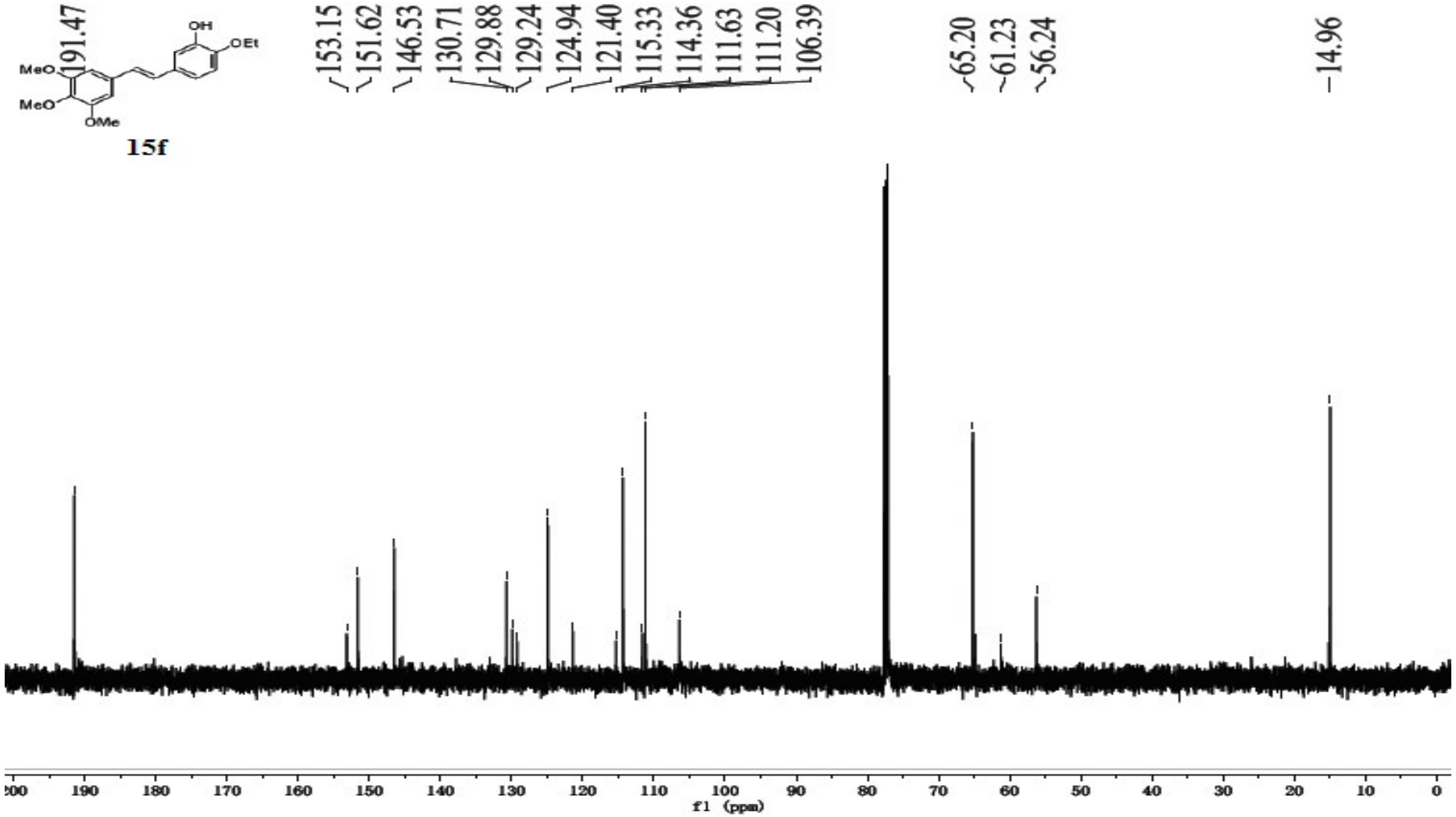
Compound 15e. ^{13}C NMR, $CDCl_3$, 125 MHz



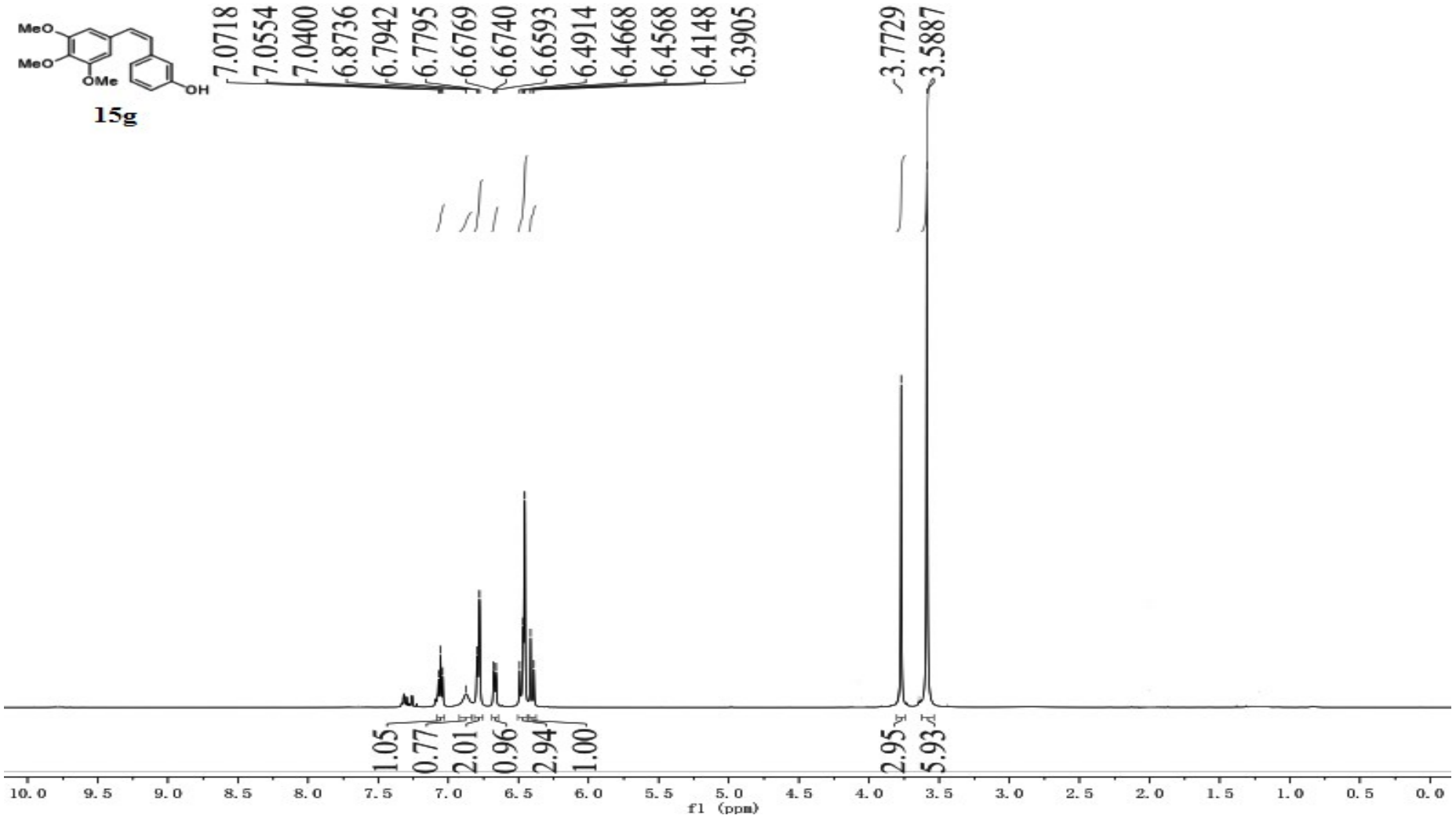
Compound 15f. ^{1}H NMR, $CDCl_3$, 500 MHz



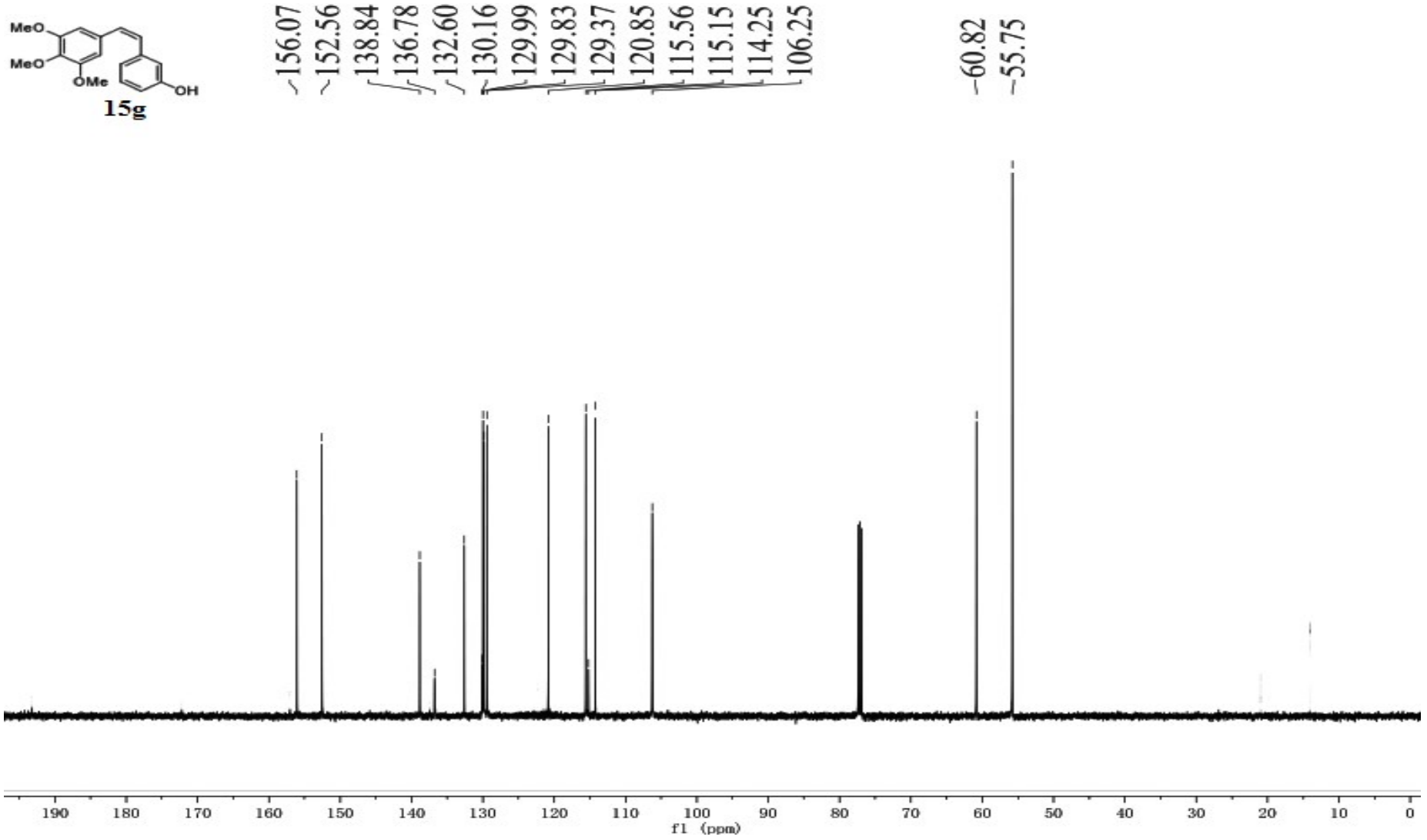
Compound 15f. ^{13}C NMR, $CDCl_3$, 125 MHz



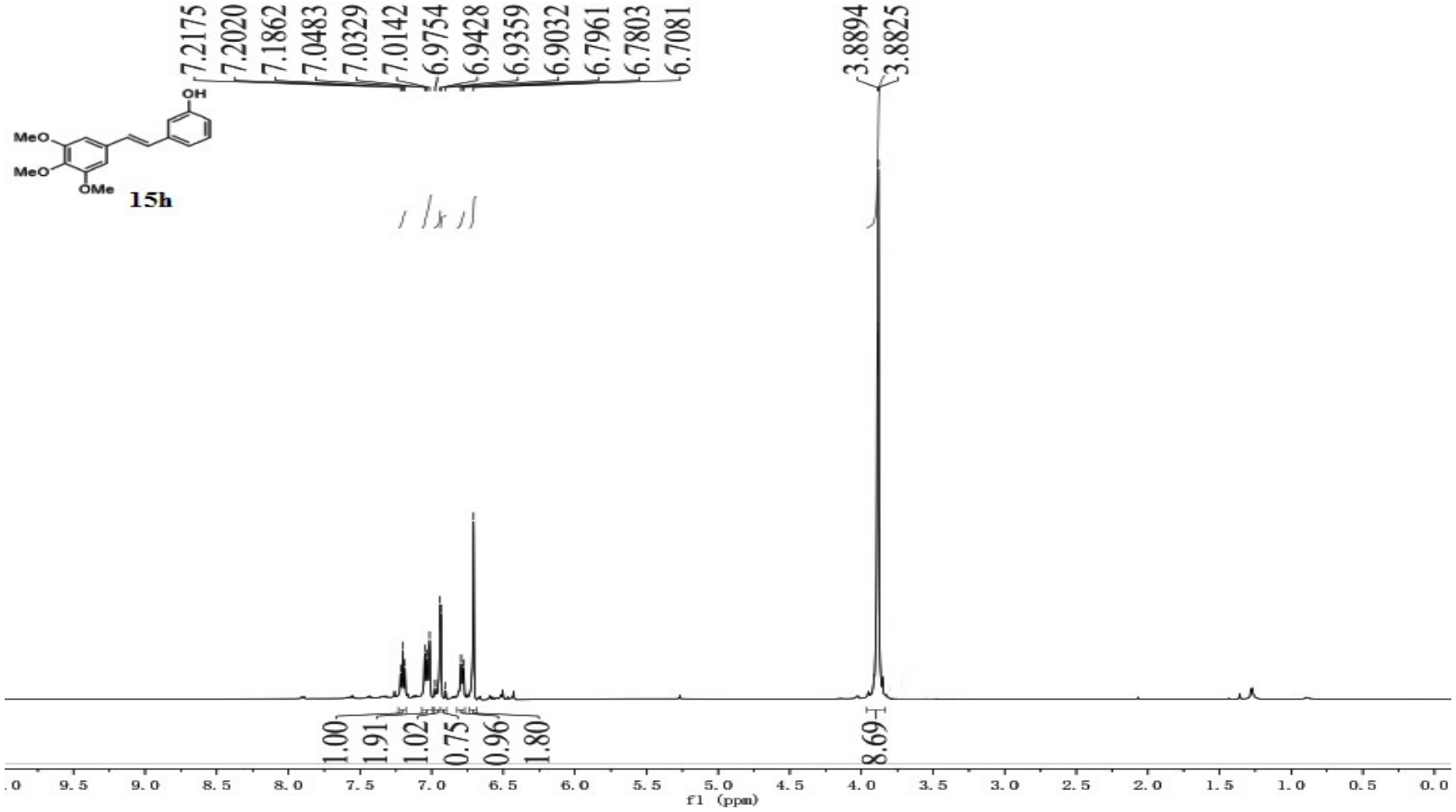
Compound 15g. ^{1}H NMR, $CDCl_3$, 500 MHz



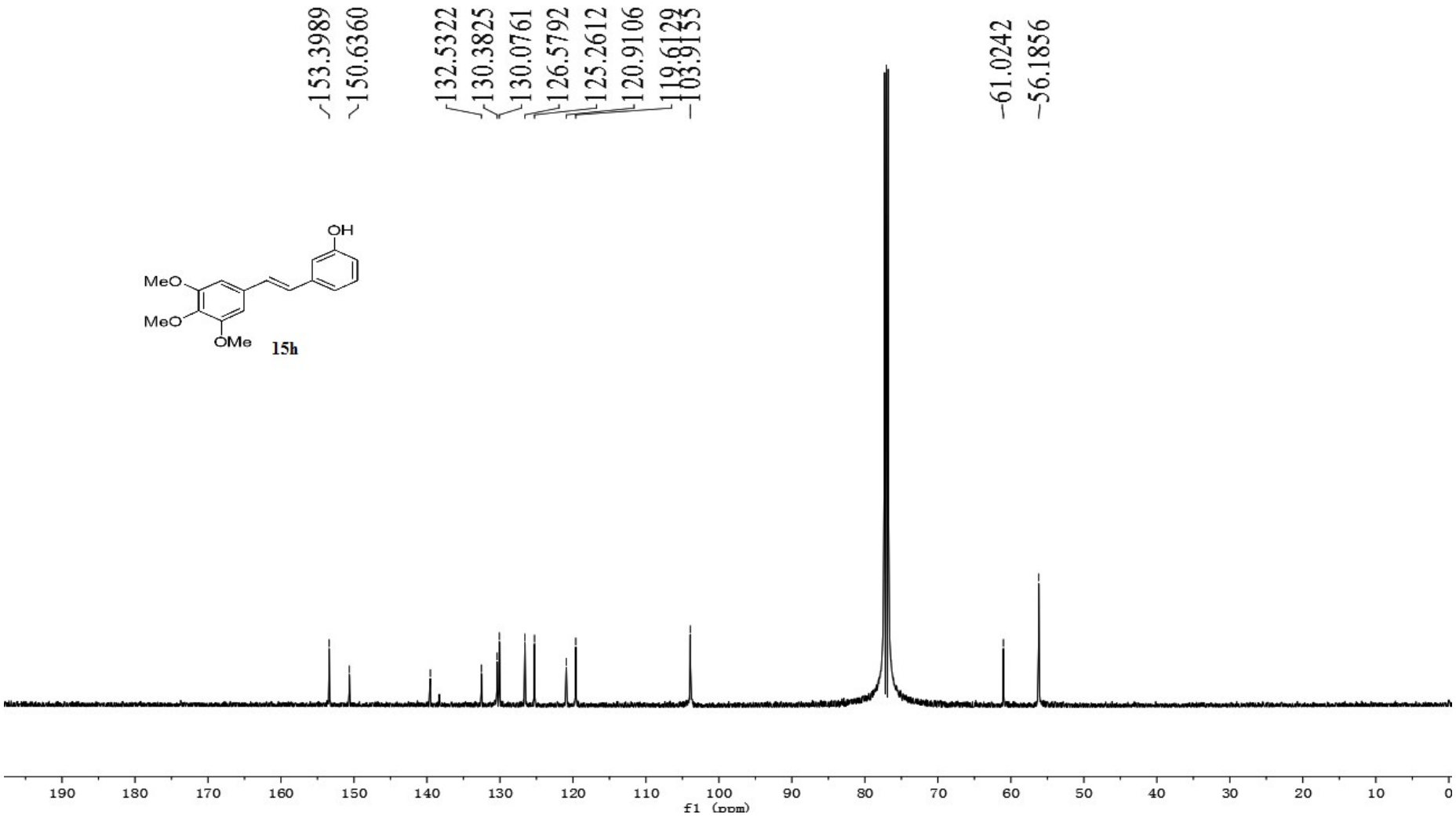
Compound 15g. ^{13}C NMR, $CDCl_3$, 125 MHz



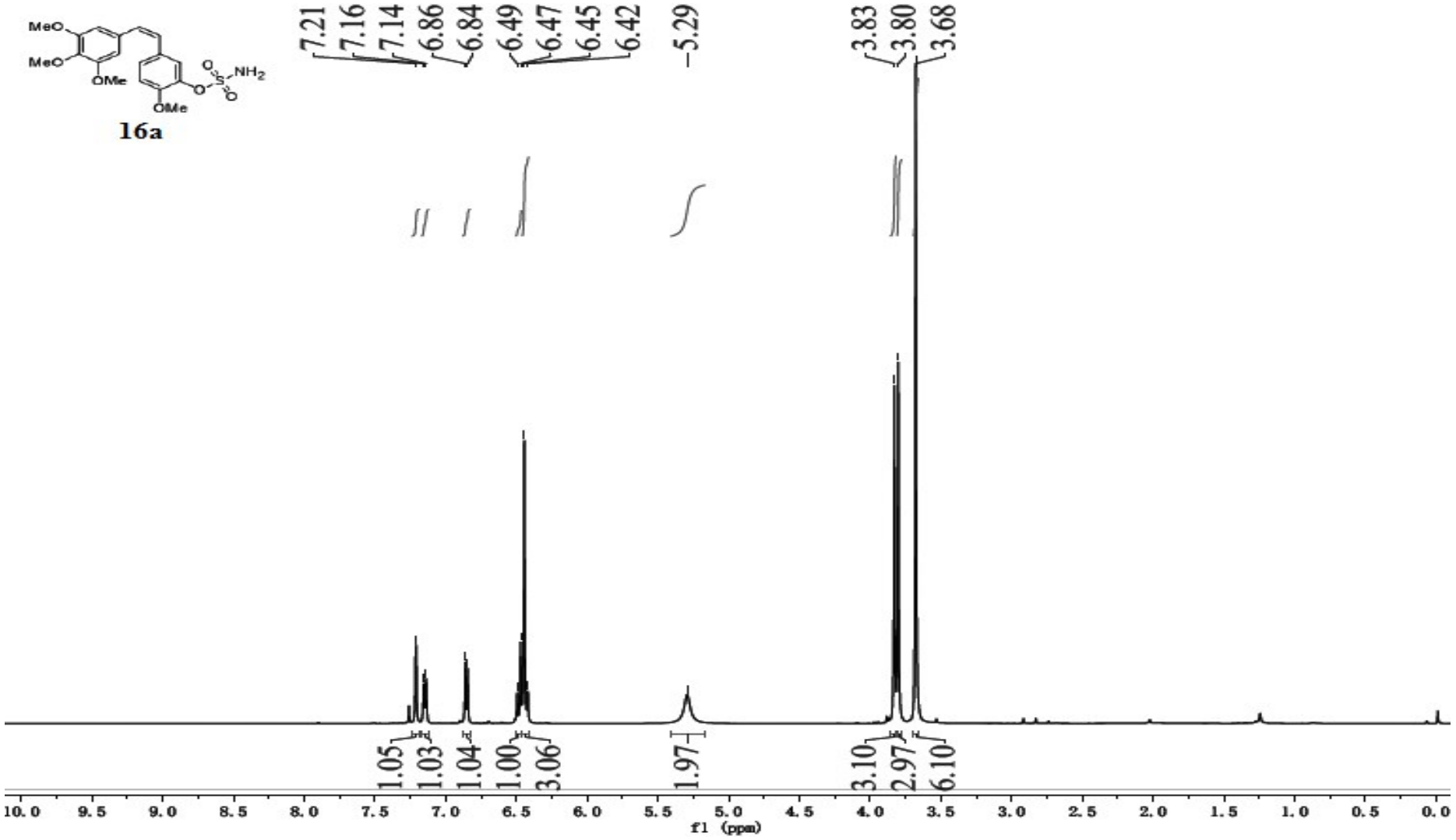
Compound 15h. ^{1}H NMR, $CDCl_3$, 500 MHz



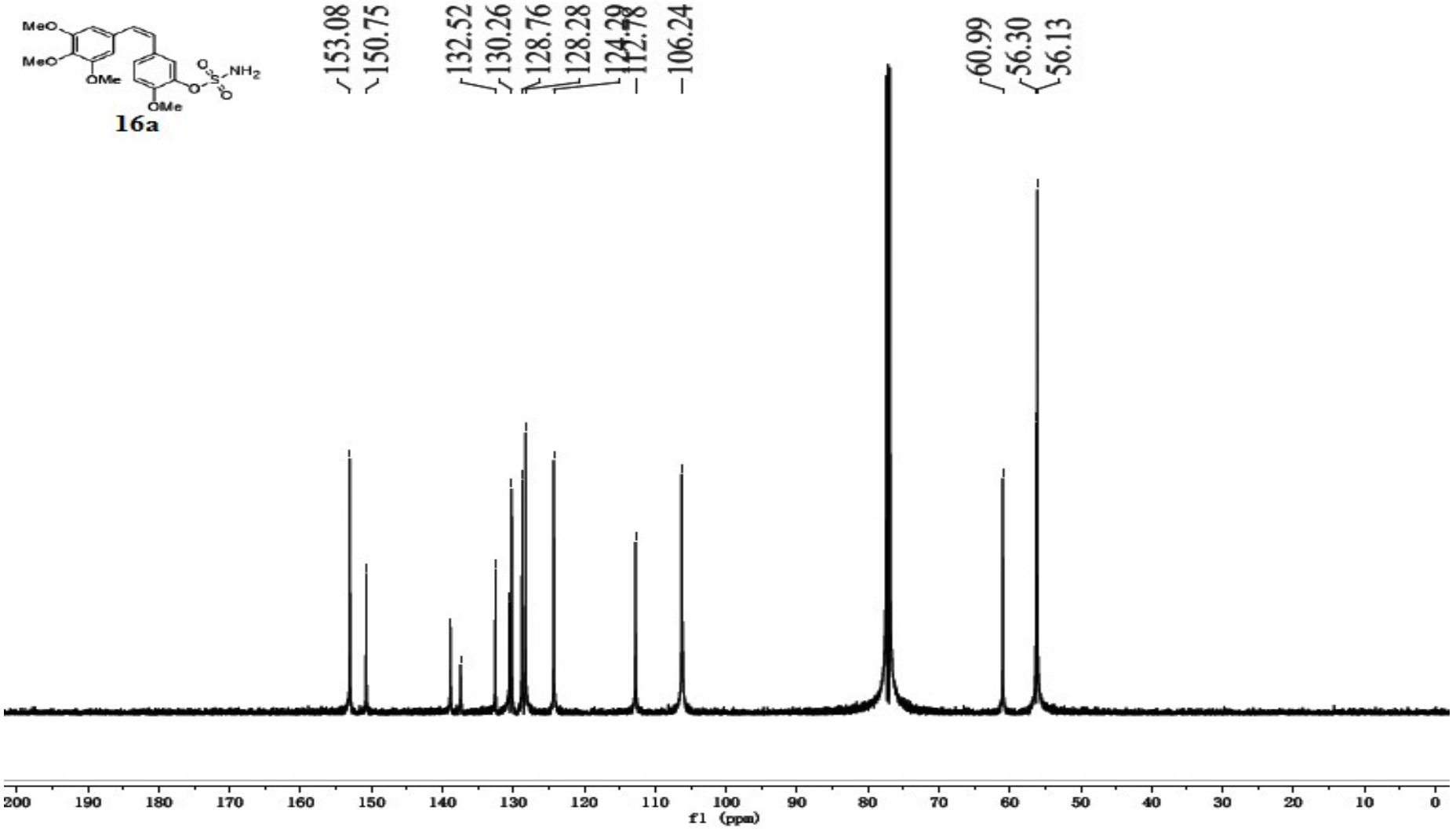
Compound 15h. ^{13}C NMR, $CDCl_3$, 125 MHz



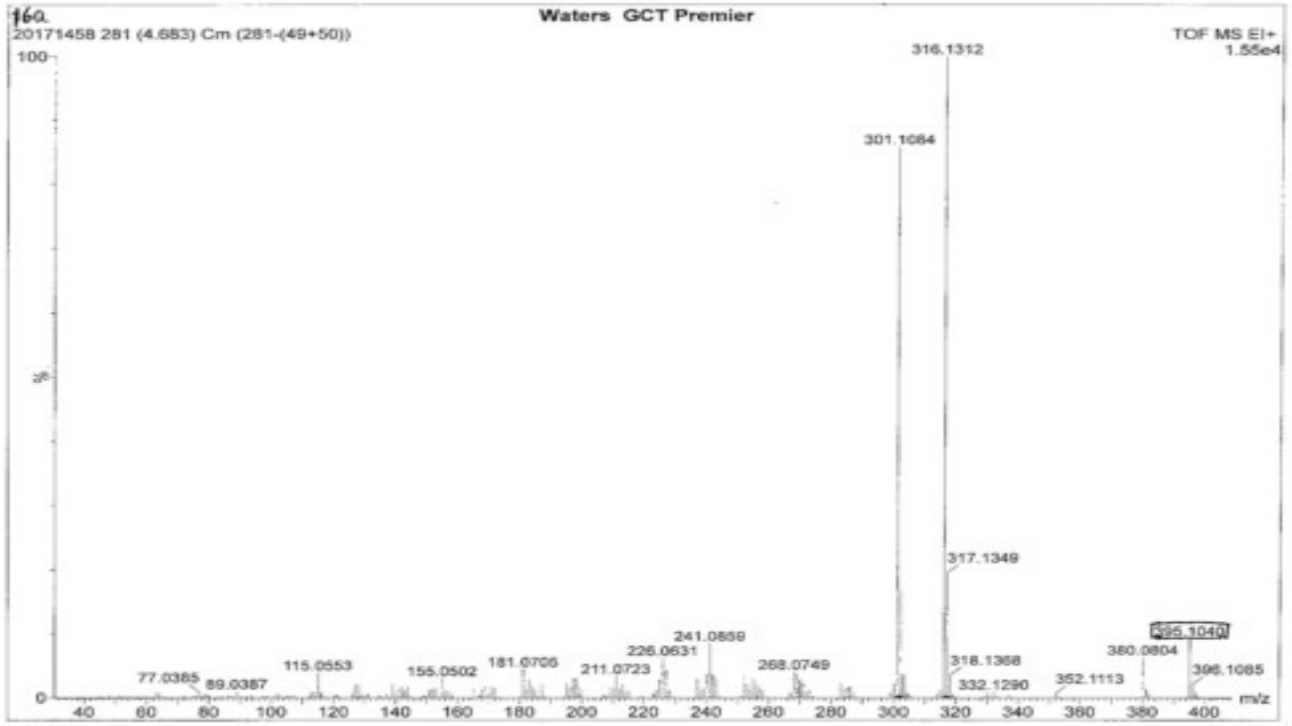
Compound 16a. ^{1}H NMR, $CDCl_3$, 500 MHz



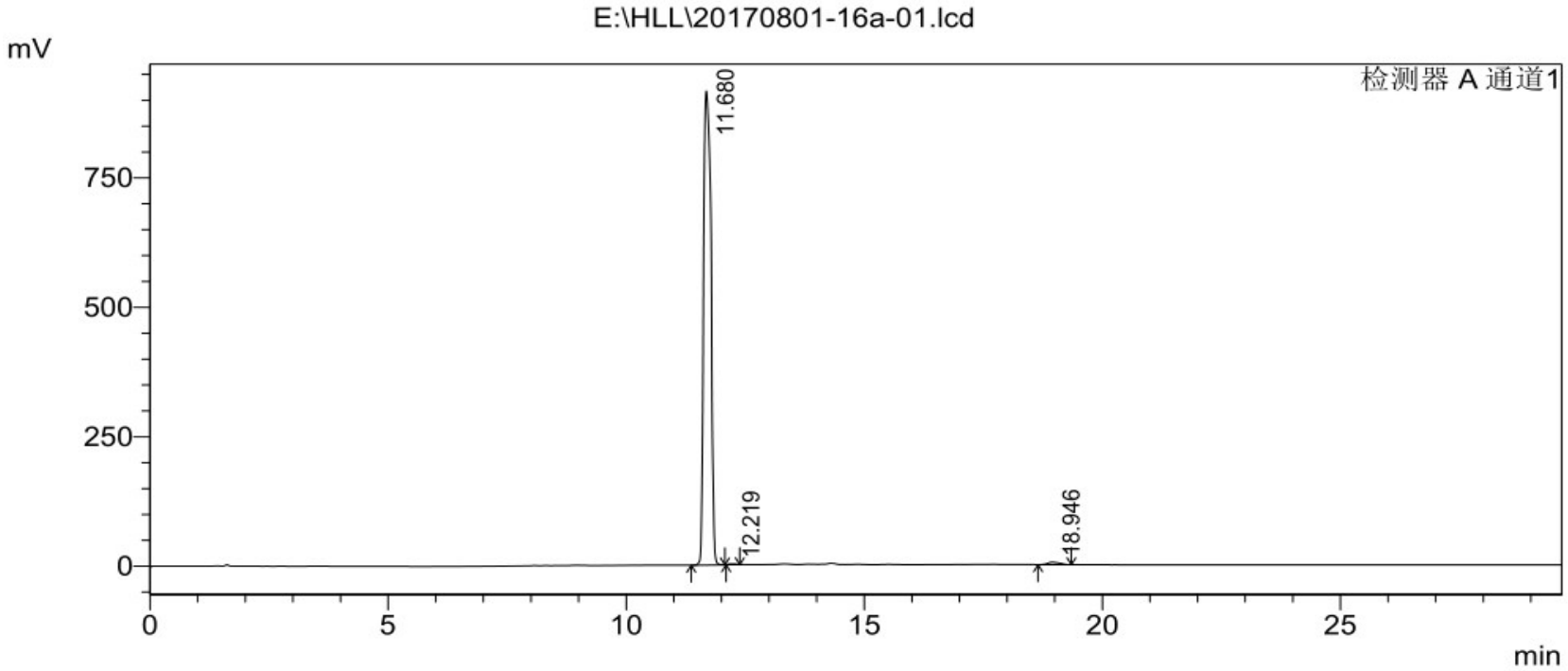
Compound 16a. ^{13}C NMR, $CDCl_3$, 125 MHz


MeO
MeO
OMe
OMe
O
S
O
O
NH2
16a
153.08
150.75
132.52
130.26
128.76
128.28
124.29
112.78
106.24
60.99
56.30
56.13
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Compound 16a. HRMS


160
Waters GCT Premier
20171458 281 (4.683) Cm (281-(49+50))
TOF MS EI+
1.55e4
100
%
0
316.1312
301.1084
317.1349
241.0859
226.0631
211.0723
181.0705
155.0502
115.0553
77.0385
89.0387
268.0749
318.1368
332.1290
352.1113
380.0804
396.1040
396.1085
m/z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400

HPLC Spectrum of compound 16a



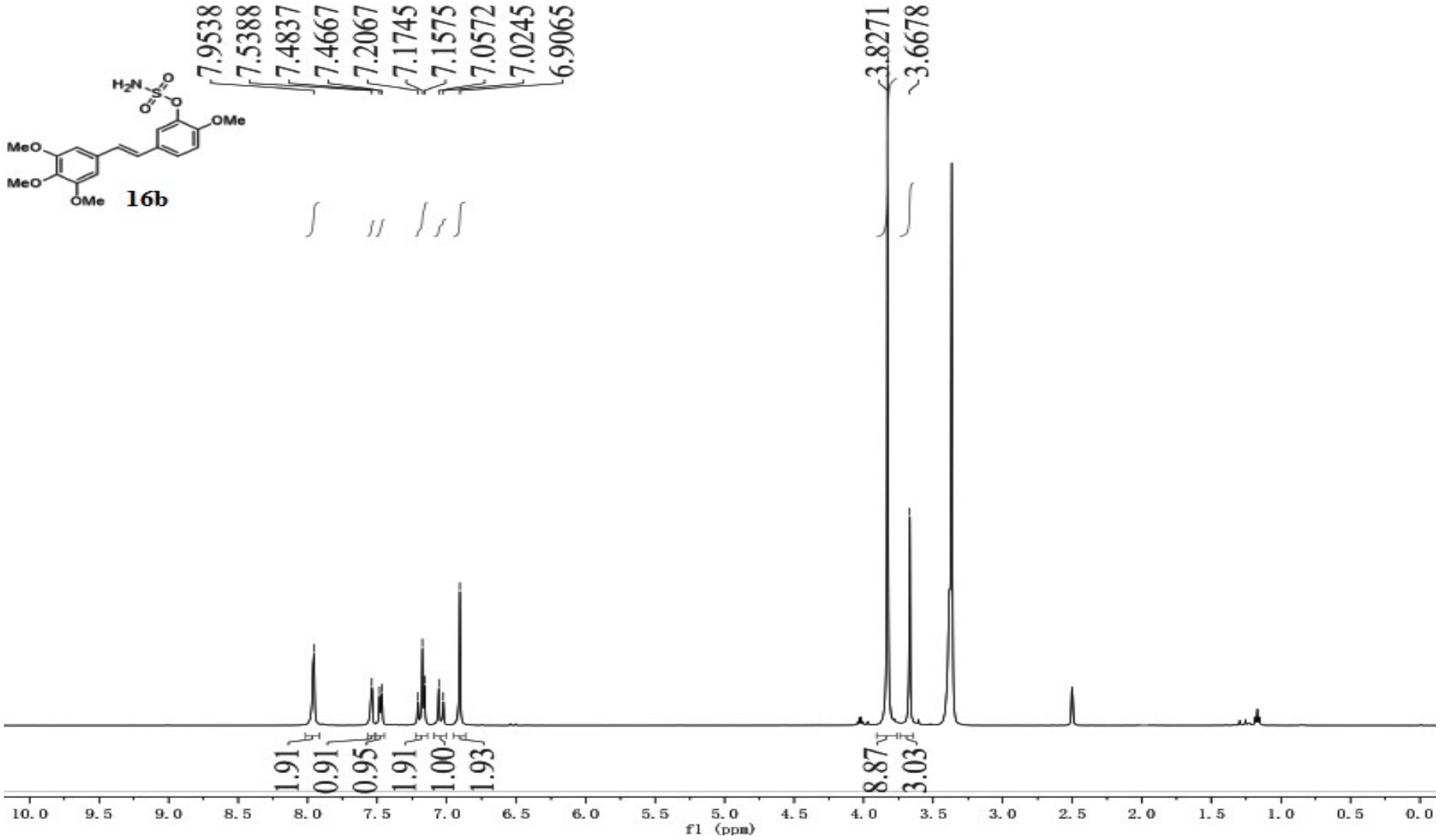
1 检测器 A 通道1/220nm

峰表

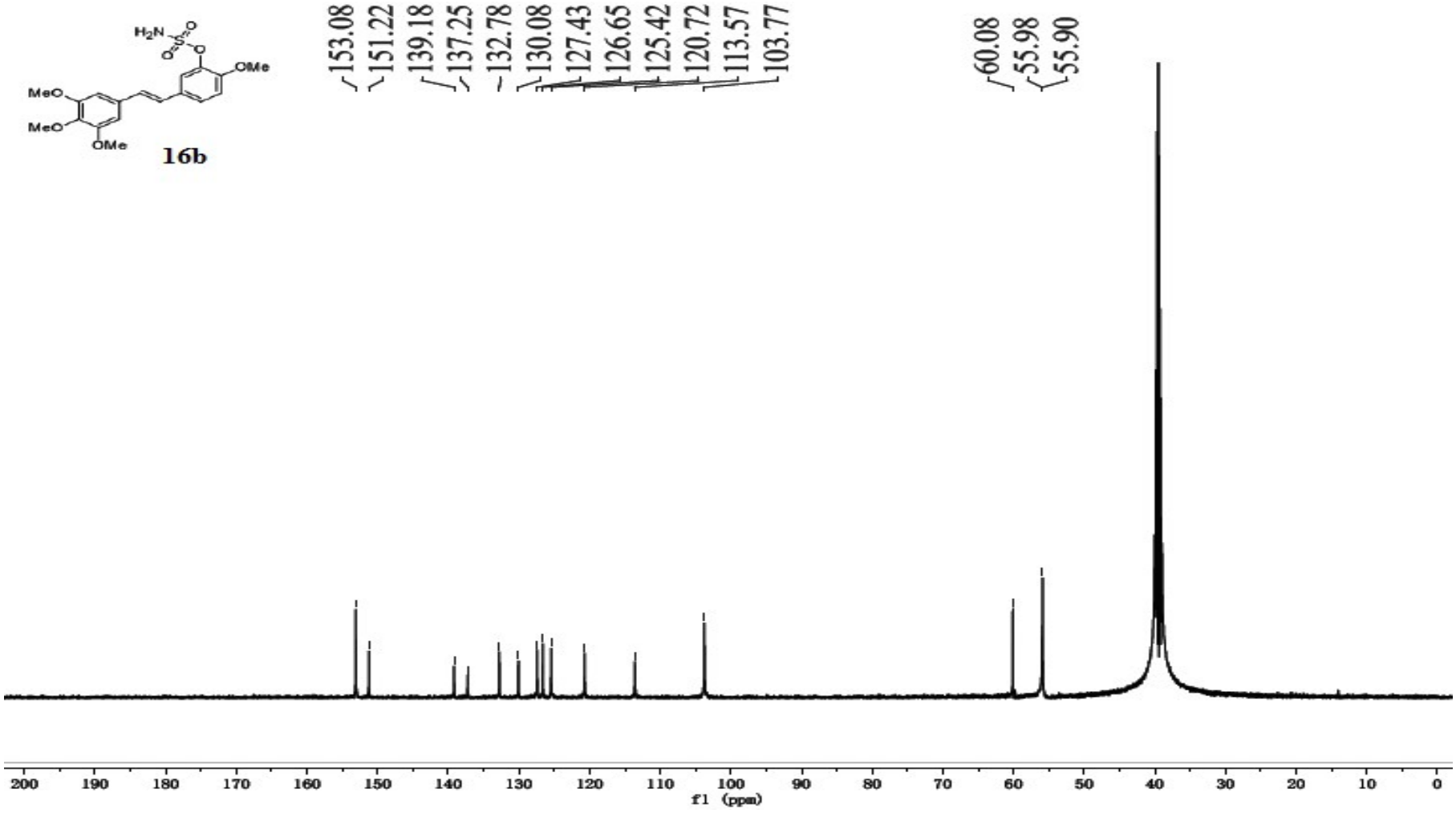
检测器 A Ch1 220nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	11.680	9829679	915884	98.972	99.307
2	12.219	17965	1645	0.181	0.178
3	18.946	84123	4746	0.847	0.515
总计		9931766	922274	100.000	100.000

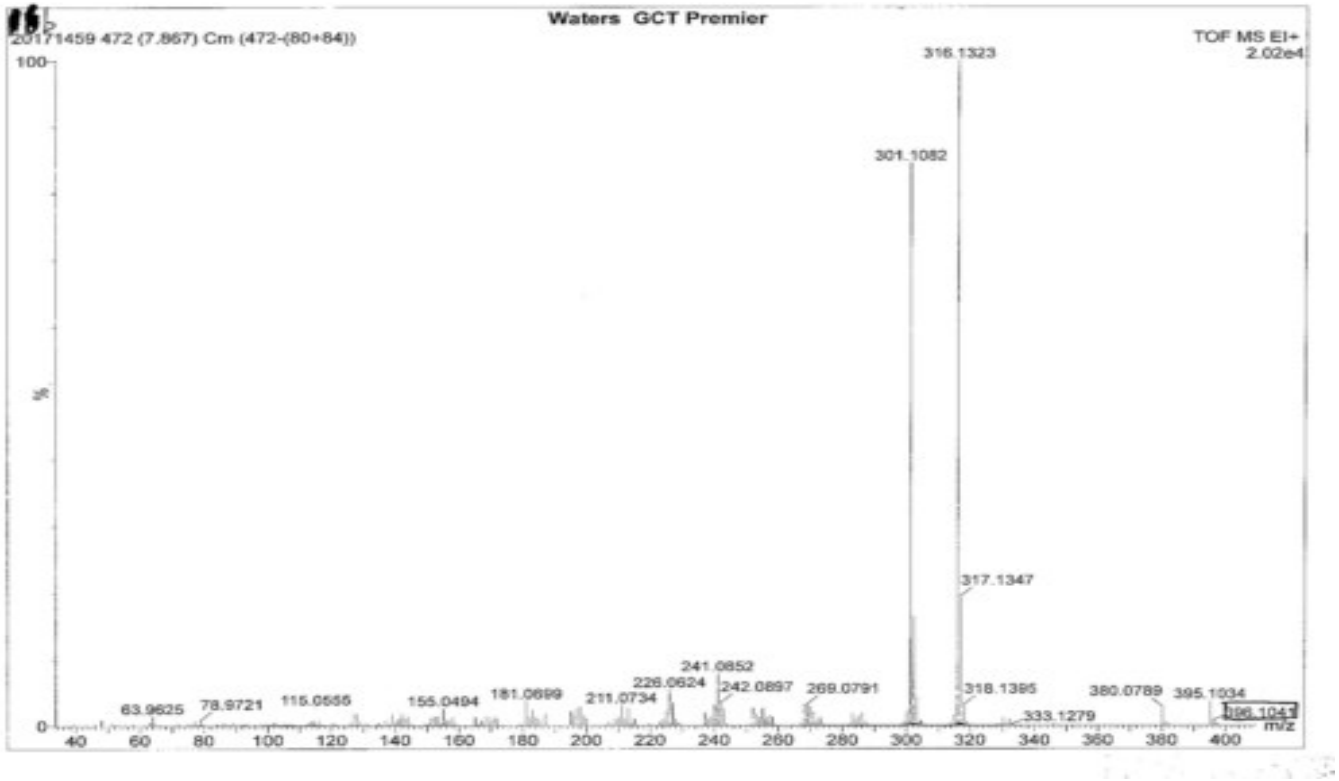
Compound 16b. [1]H NMR, DMSO, 500 MHz



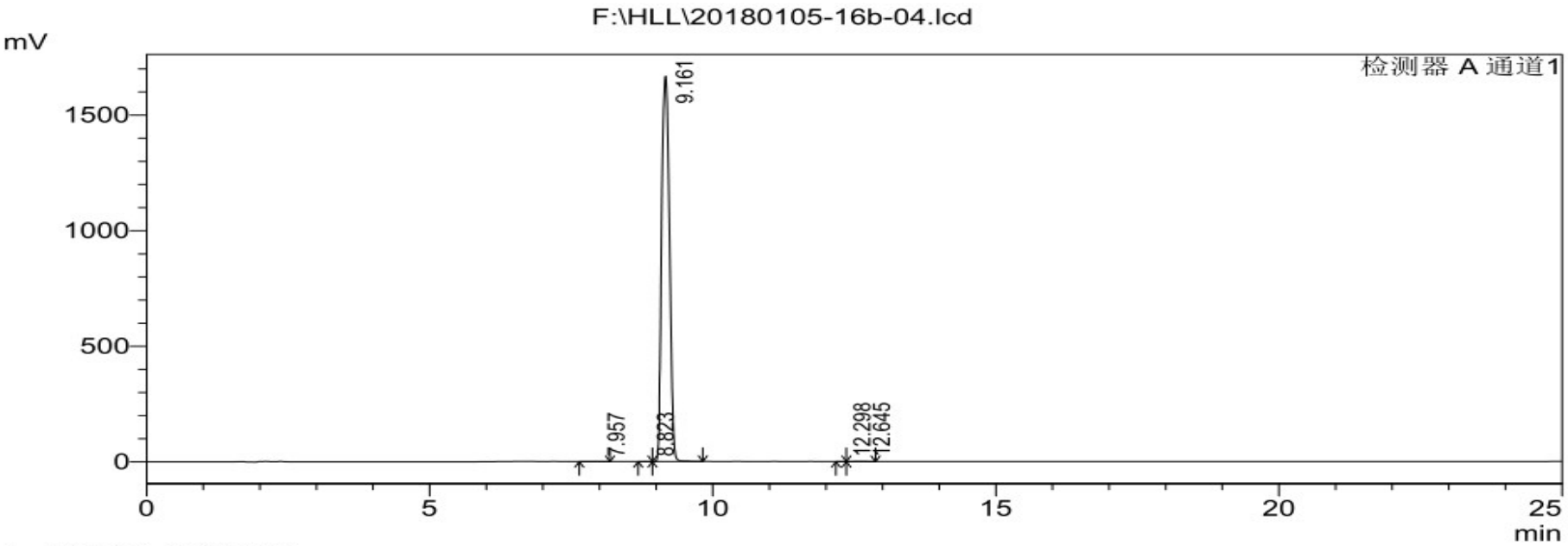
Compound 16b. ^{13}C NMR, DMSO, 125 MHz



HR-MS Spectrum of Compound 16b


Waters GCT Premier
20171459 472 (7.867) Cm (472-(80+84))
TOF MS EI+
2.02e4
316.1323
301.1082
317.1347
241.0852
226.0624
242.0897
269.0791
211.0734
181.0699
155.0494
115.0555
78.9721
63.9625
318.1385
380.0789
395.1034
333.1279
396.1041
100
%
0
m/z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400

HPLC Spectrum of Compound 16b



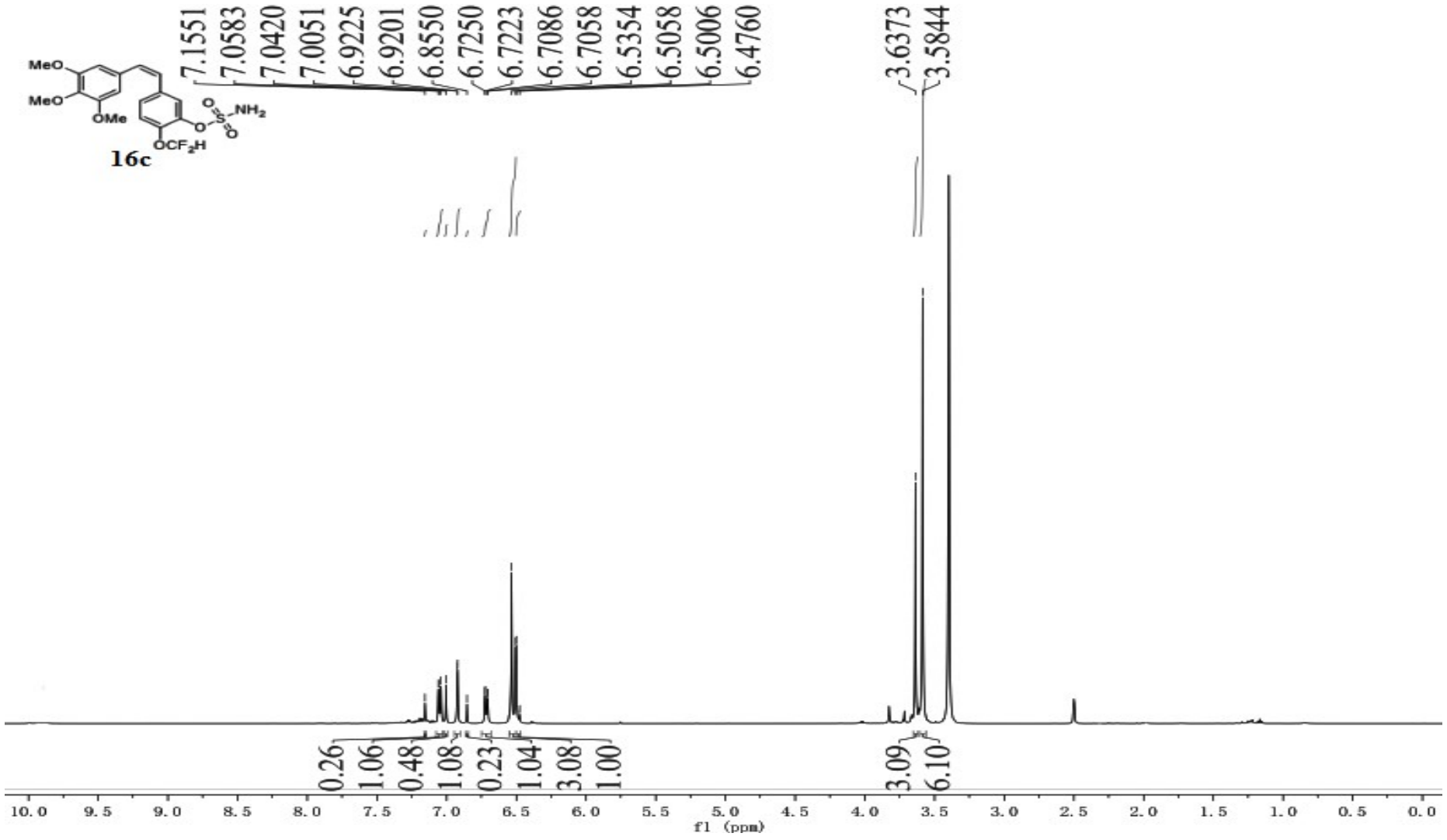
1 检测器 A 通道1/276nm

峰表

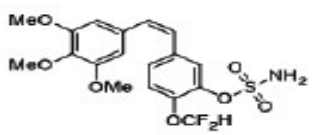
检测器 A Ch1 276nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	7.957	4050	347	0.025	0.021
2	8.823	2179	264	0.014	0.016
3	9.161	16077698	1668058	99.883	99.908
4	12.298	644	95	0.004	0.006
5	12.645	11966	826	0.074	0.049
总计		16096536	1669588	100.000	100.000

Compound 16c. ^{1}H NMR, DMSO, 500 MHz



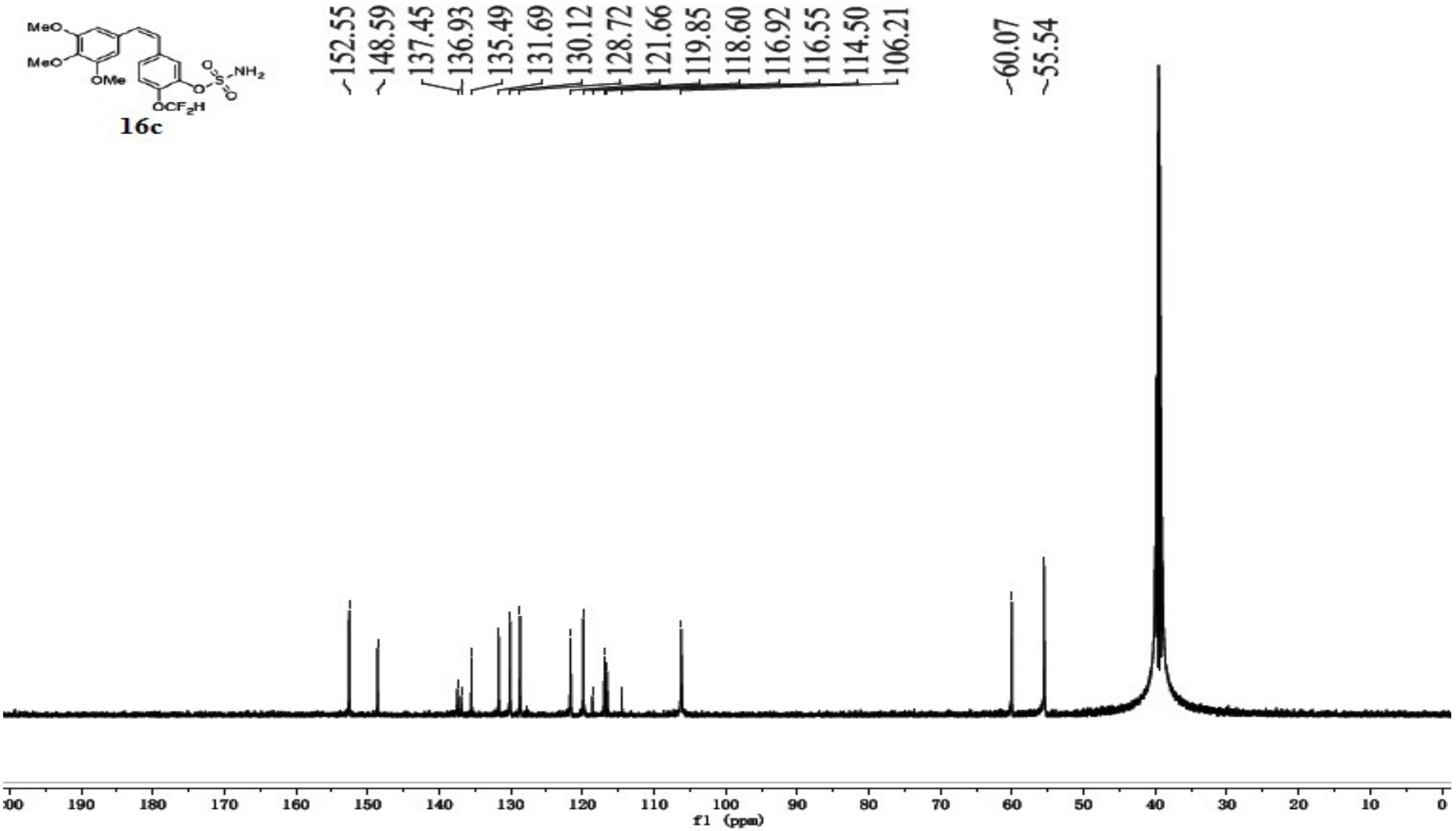
Compound 16c. ^{19}F NMR, DMSO, 145 MHz


MeO
MeO
OMe
OCF2H
O
S
NH2
O

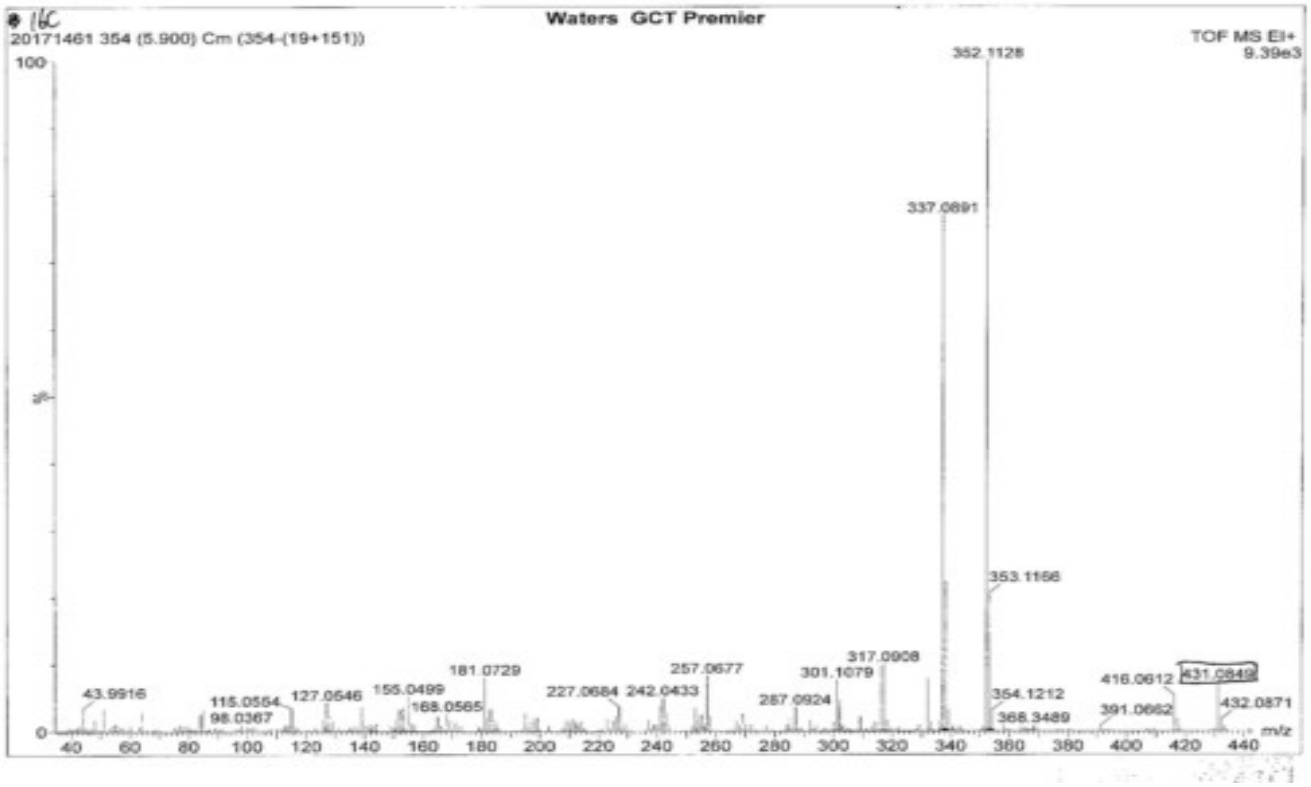
16c

-81.38
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-20
f1 (ppm)

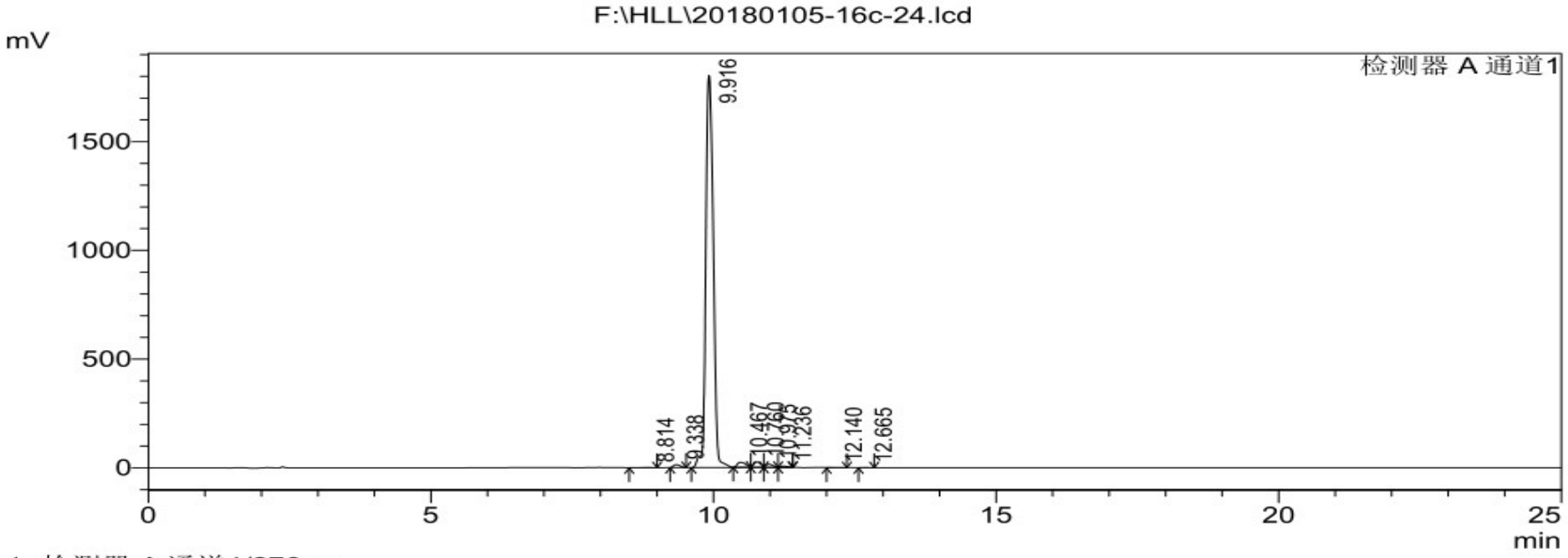
Compound 16c. ^{13}C NMR, DMSO, 125 MHz



HR-MS Spectrum of Compound 16c.


16
Waters GCT Premier
20171461 354 (5.900) Cm (354-(19+151))
TOF MS EI+
9.39e3
100
%
0
352.1128
337.0891
353.1156
317.0908
301.1079
257.0677
181.0729
227.0684
242.0433
287.0924
155.0499
168.0565
127.0546
115.0554
98.0367
43.9916
354.1212
368.3489
416.0612
431.0849
391.0662
432.0871
m/z
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440

HPLC Spectrum of compound 16c



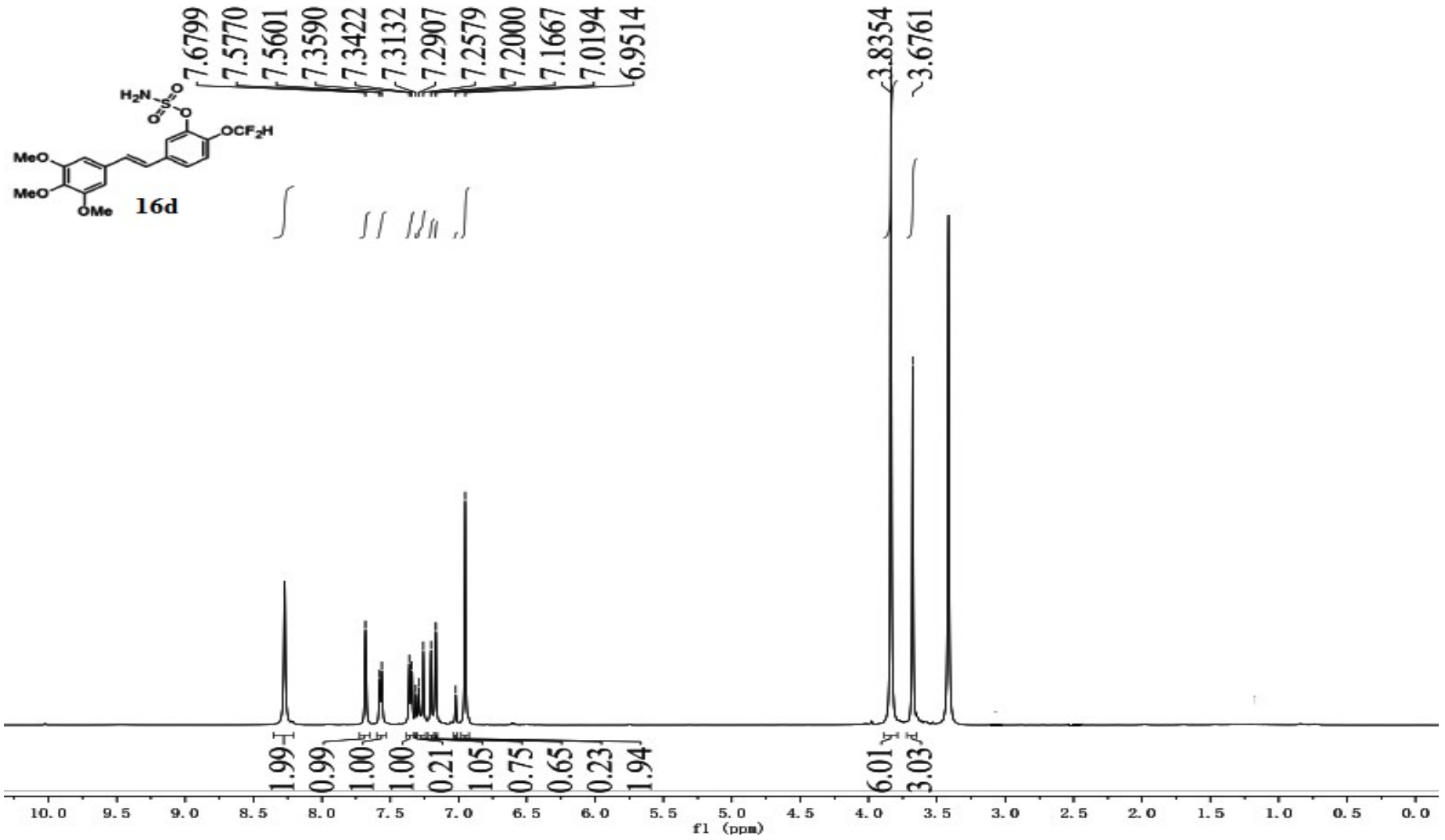
1 检测器 A 通道1/276nm

峰表

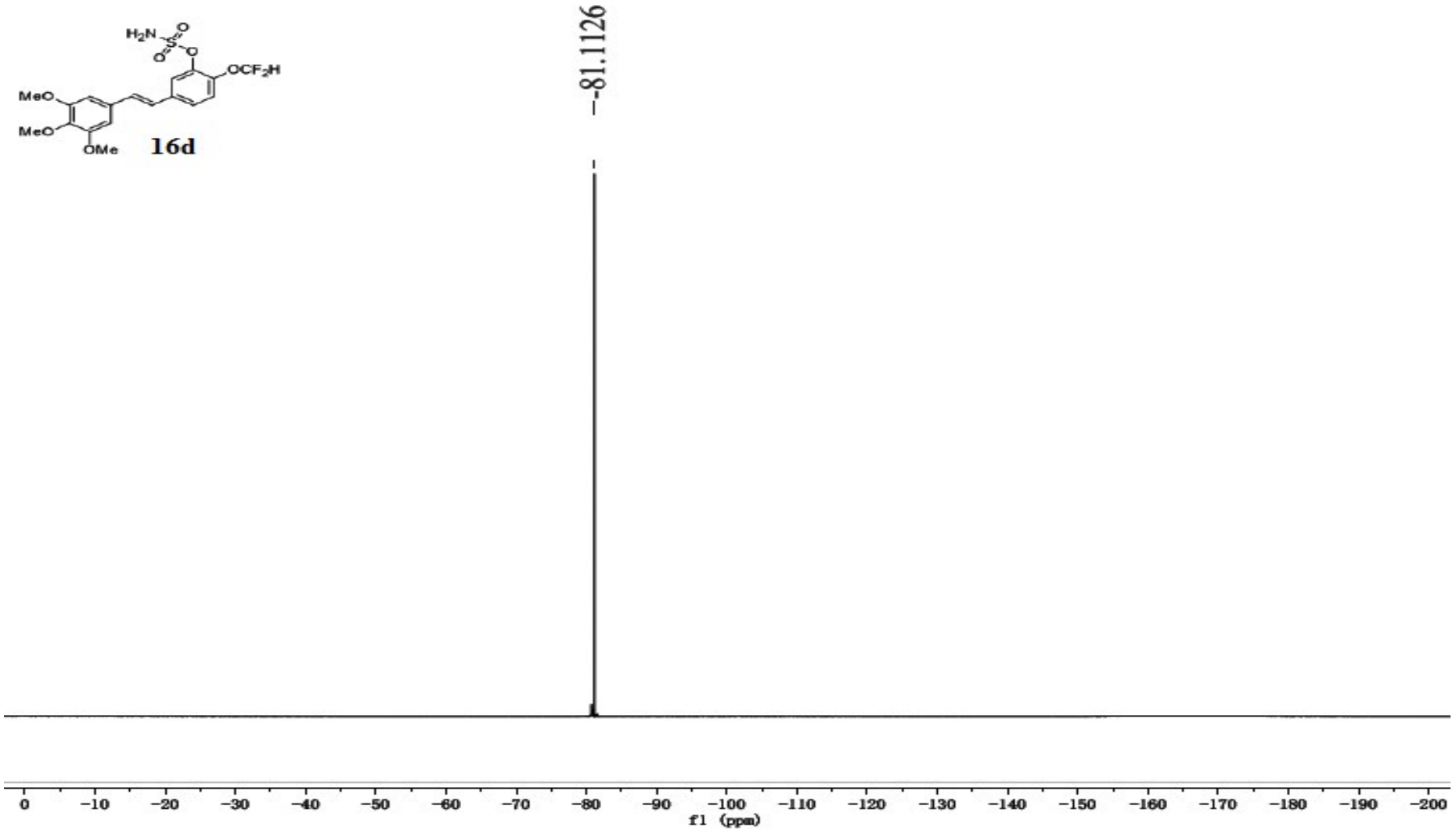
检测器 A Ch1 276nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	8.814	8860	867	0.051	0.046
2	9.338	107015	13160	0.618	0.698
3	9.916	16561461	1803048	95.662	95.578
4	10.467	235658	22578	1.361	1.197
5	10.760	213206	24809	1.232	1.315
6	10.975	124078	14238	0.717	0.755
7	11.236	44303	5525	0.256	0.293
8	12.140	13396	1689	0.077	0.090
9	12.665	4414	545	0.025	0.029
总计		17312392	1886459	100.000	100.000

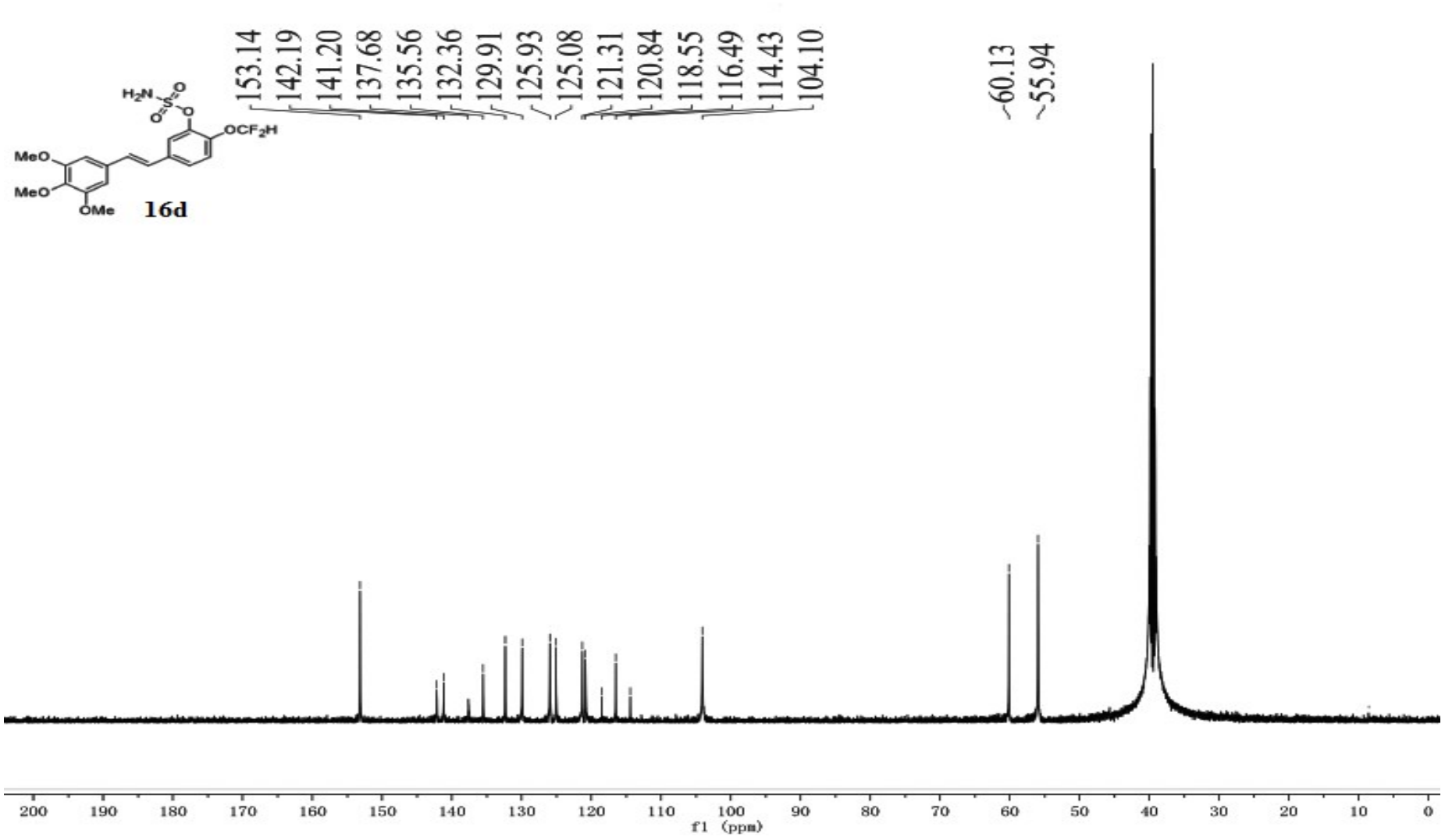
Compound 16d. ^{1}H NMR, DMSO, 500 MHz



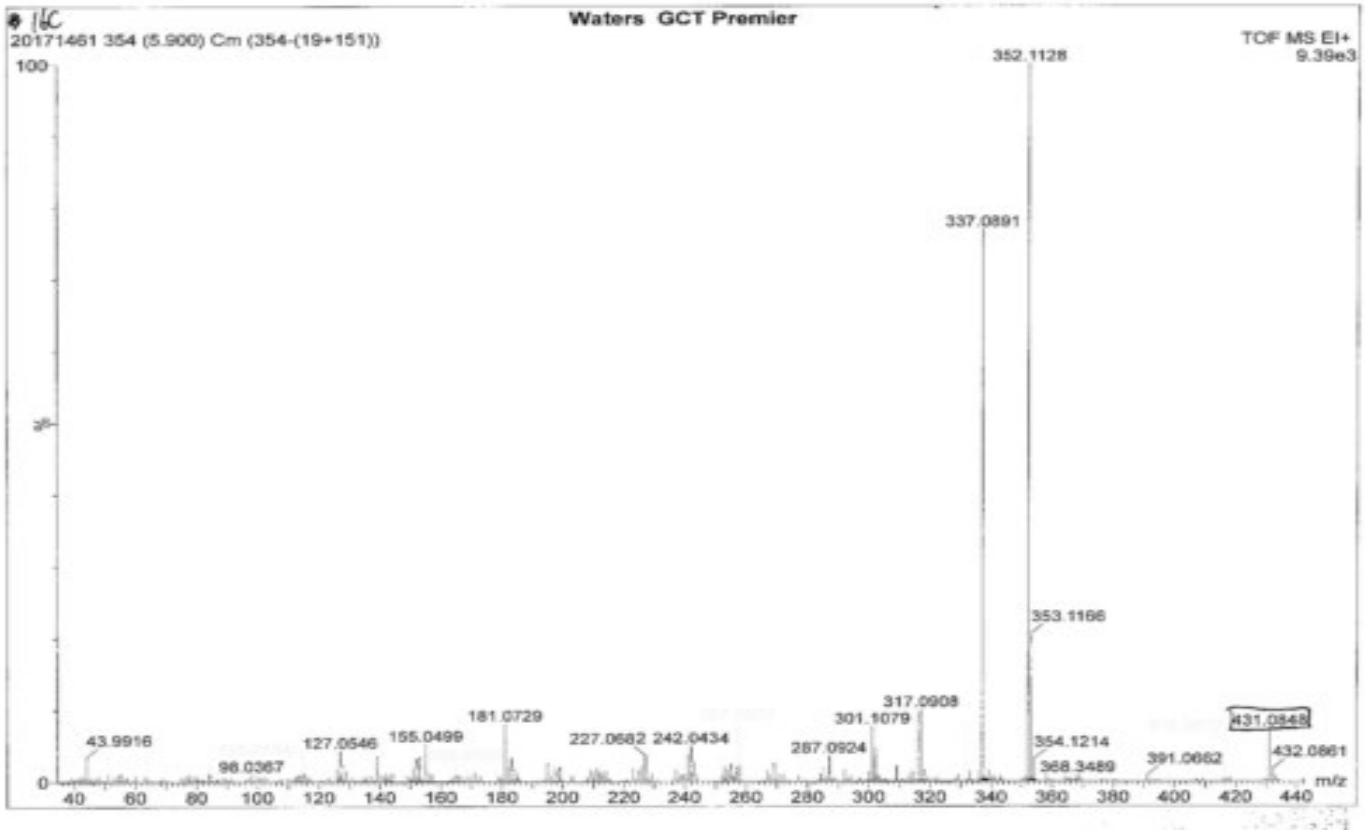
Compound 16d. ^{19}F NMR, DMSO, 145 MHz


H2N
O
O
O
OCF2H
MeO
MeO
OMe
16d
-81.1126
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

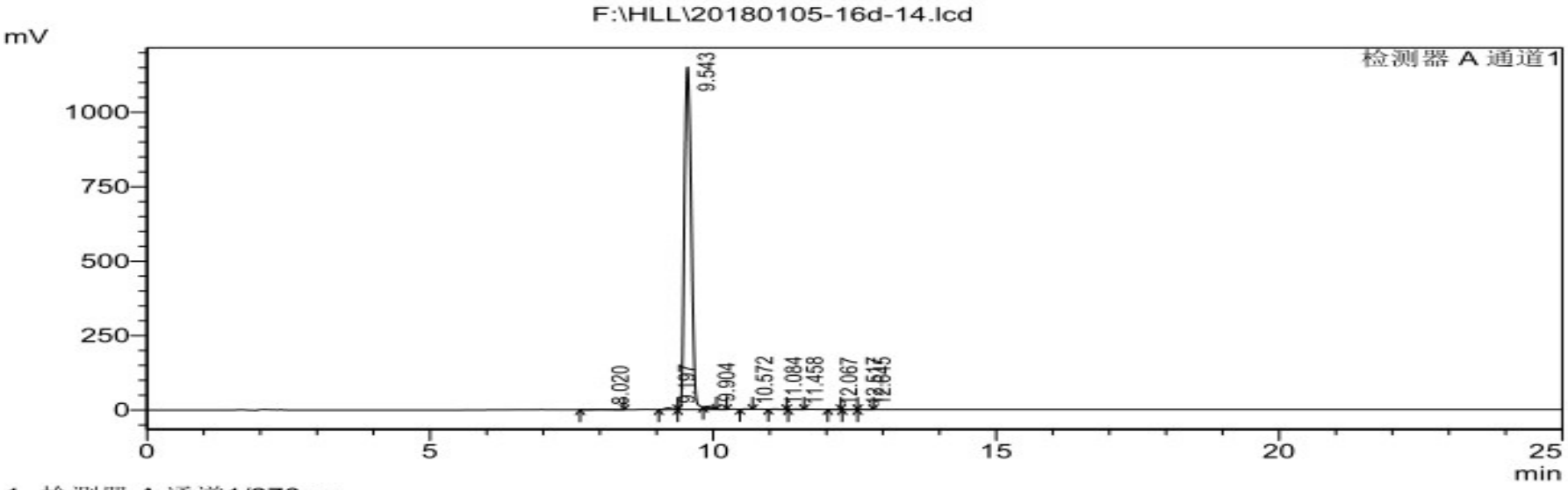
Compound 16d. ^{13}C NMR, DMSO, 125 MHz



HR-MS Spectrum of Compound 16d.



HPLC Spectrum of Compound 16d



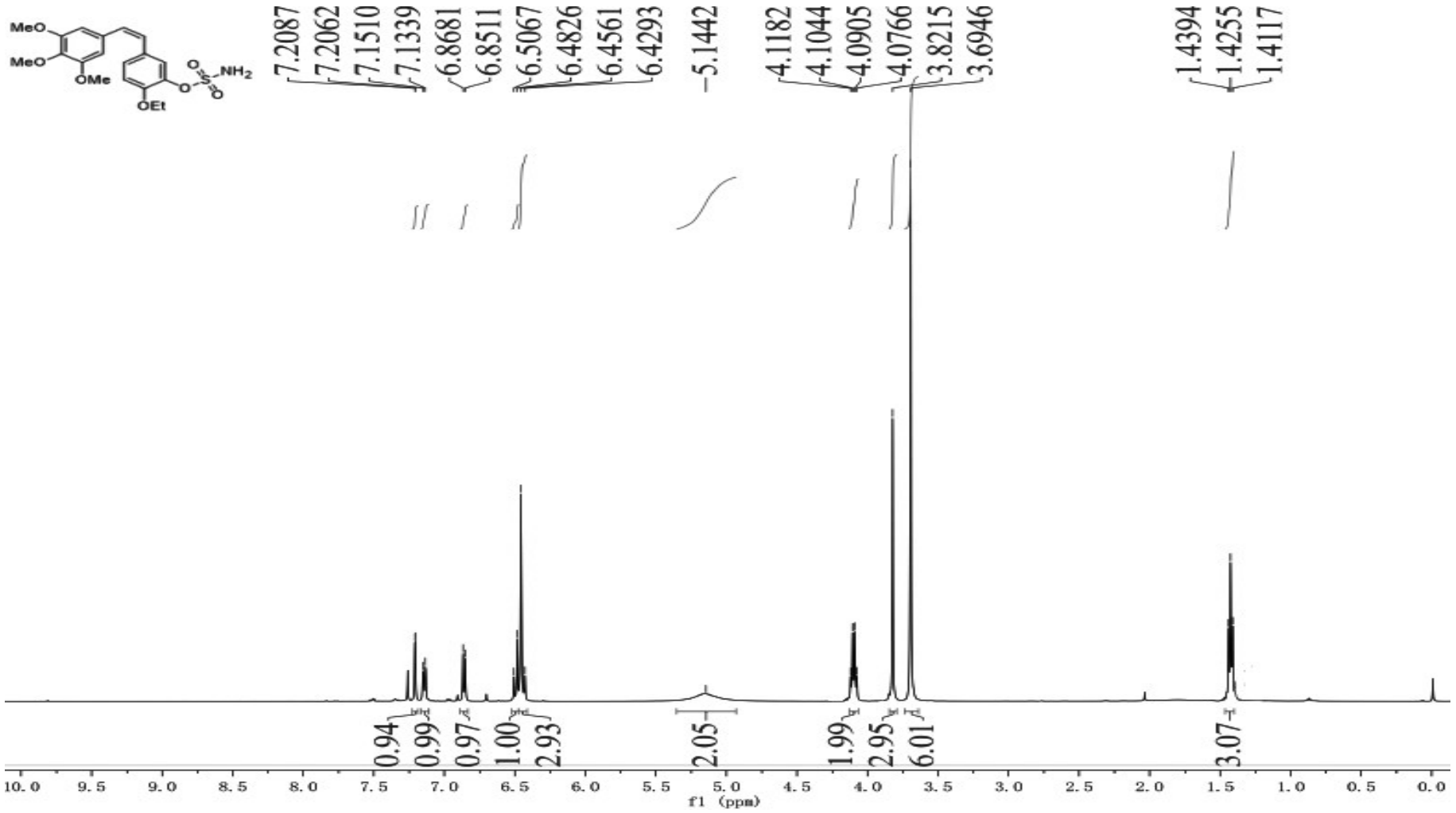
1 检测器 A 通道1/276nm

峰表

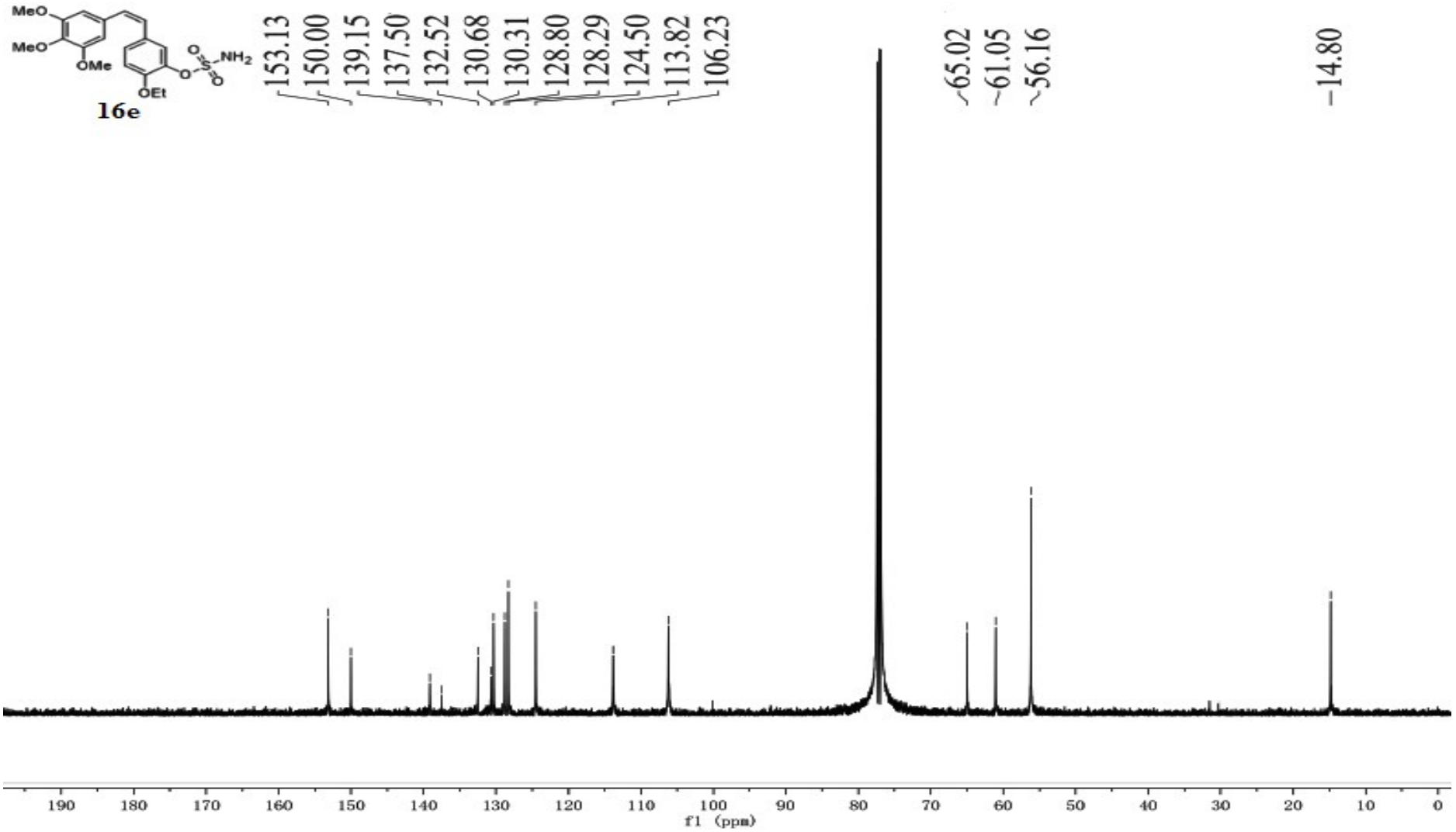
检测器 A Ch1 276nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	8.020	15843	1021	0.161	0.087
2	9.197	56374	5447	0.572	0.467
3	9.543	9704265	1150511	98.488	98.603
4	9.904	40013	5433	0.406	0.466
5	10.572	9751	1341	0.099	0.115
6	11.084	9877	1100	0.100	0.094
7	11.458	8797	1023	0.089	0.088
8	12.067	159	20	0.002	0.002
9	12.517	2680	314	0.027	0.027
10	12.645	5453	603	0.055	0.052
总计		9853213	1166813	100.000	100.000

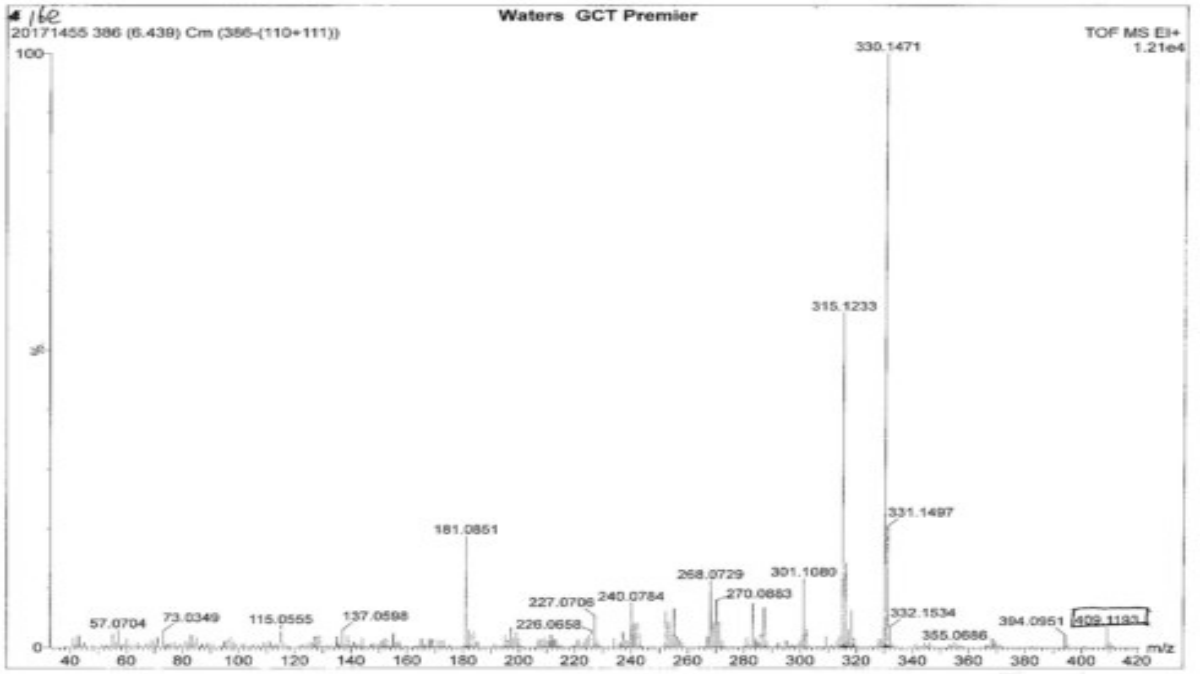
Compound 16e. ^{1}H NMR, $CDCl_3$, 500 MHz



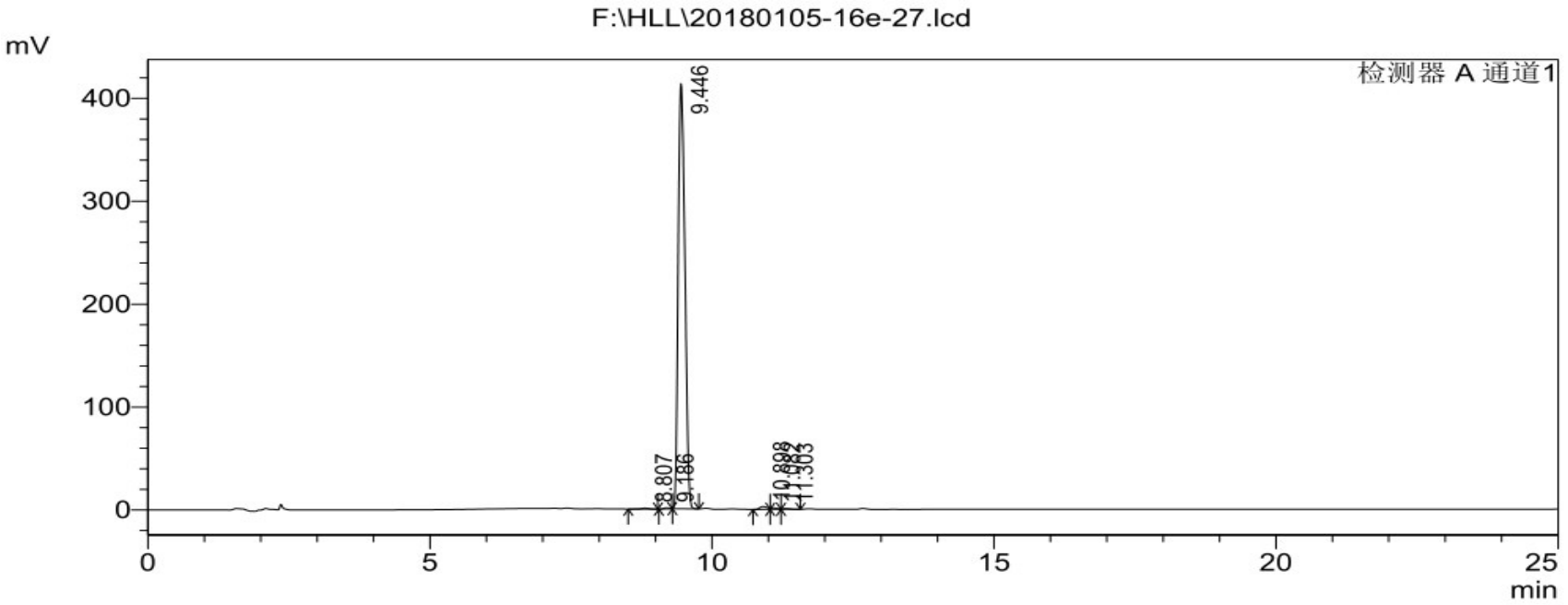
Compound 16e. ^{13}C NMR, $CDCl_3$, 125 MHz


MeO
MeO
OMe
OEt
O
S
O
NH2
16e
153.13
150.00
139.15
137.50
132.52
130.68
130.31
128.80
128.29
124.50
113.82
106.23
65.02
61.05
56.16
14.80
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

HR-MS Spectrum of Compound 16e


4 16e
Waters GCT Premier
20171455 386 (6.439) Cm (386-(110+111))
TOF MS EI+
1.21e4
100
%
0
330.1471
315.1233
331.1497
181.0851
268.0729
301.1080
270.0883
240.0784
227.0706
226.0658
332.1534
394.0951
409.1193
355.0686
57.0704
73.0349
115.0555
137.0598
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420
m/z

HPLC Spectrum of Compound 16e



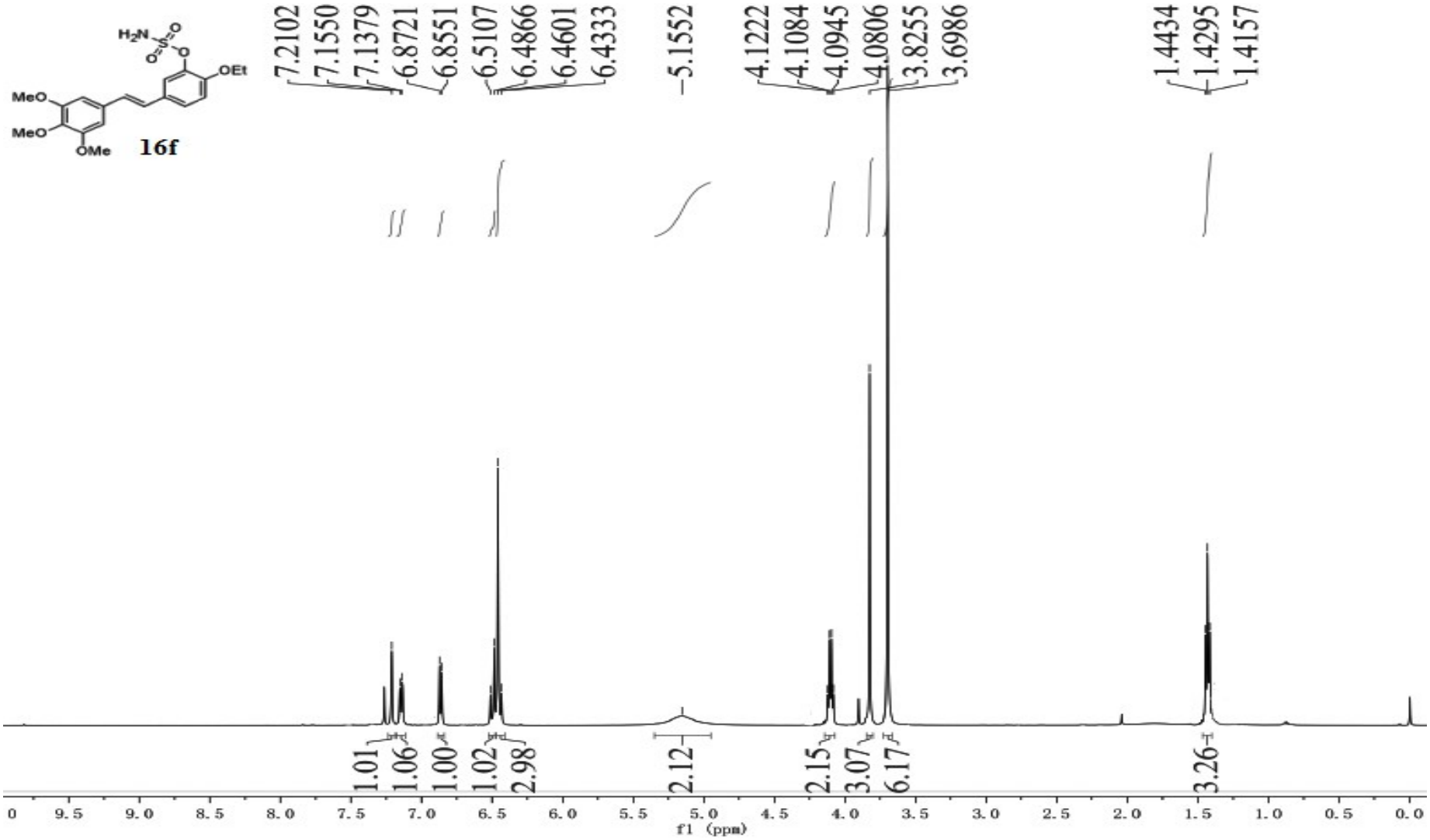
1 检测器 A 通道1/276nm

峰表

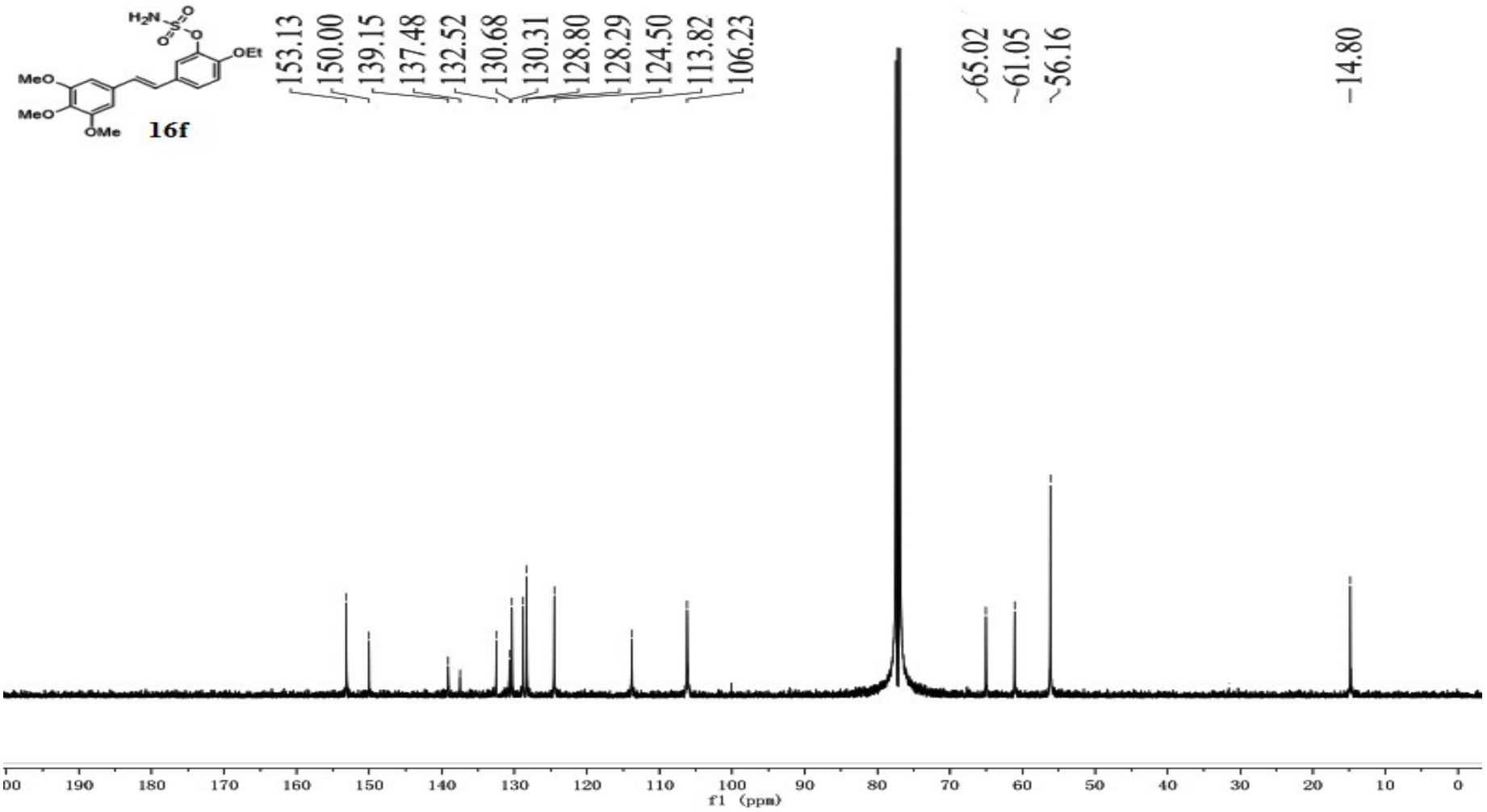
检测器 A Ch1 276nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	8.807	10538	990	0.302	0.236
2	9.186	6848	988	0.196	0.235
3	9.446	3425827	413356	98.226	98.363
4	10.898	26072	2694	0.748	0.641
5	11.082	11249	1390	0.323	0.331
6	11.303	7167	815	0.206	0.194
总计		3487701	420233	100.000	100.000

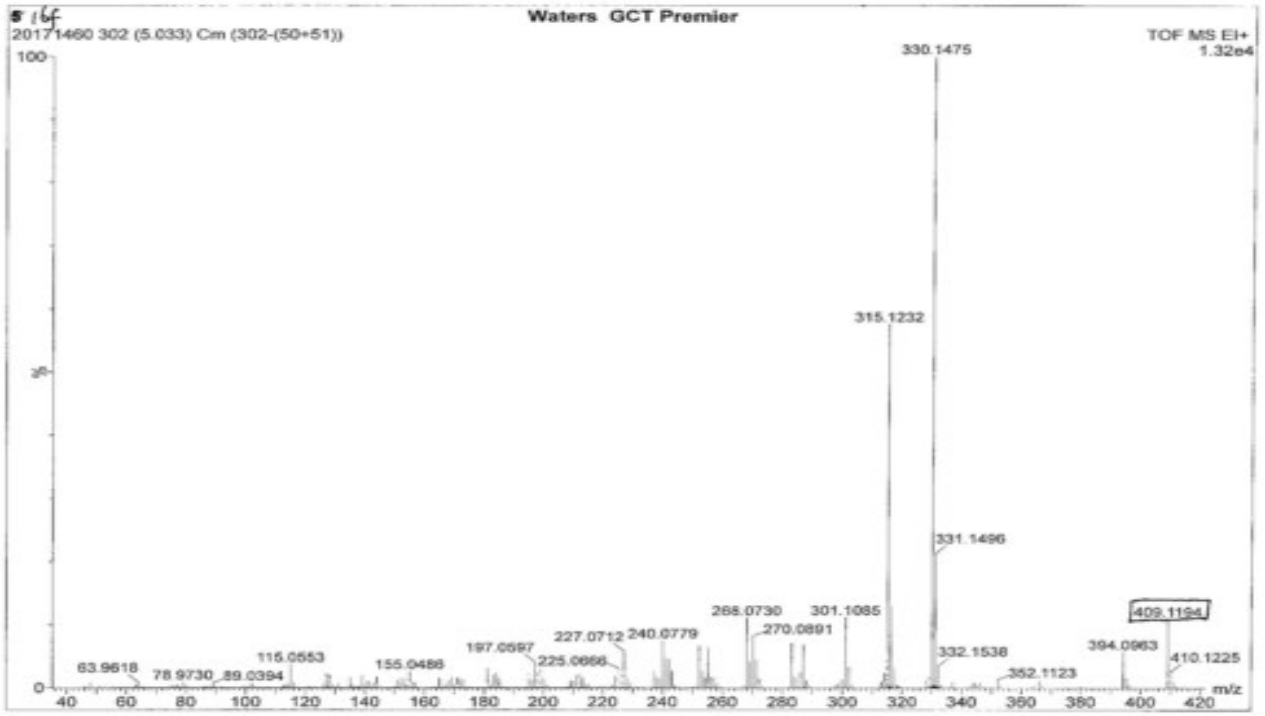
Compound 16f. ^{1}H NMR, $CDCl_3$, 500 MHz



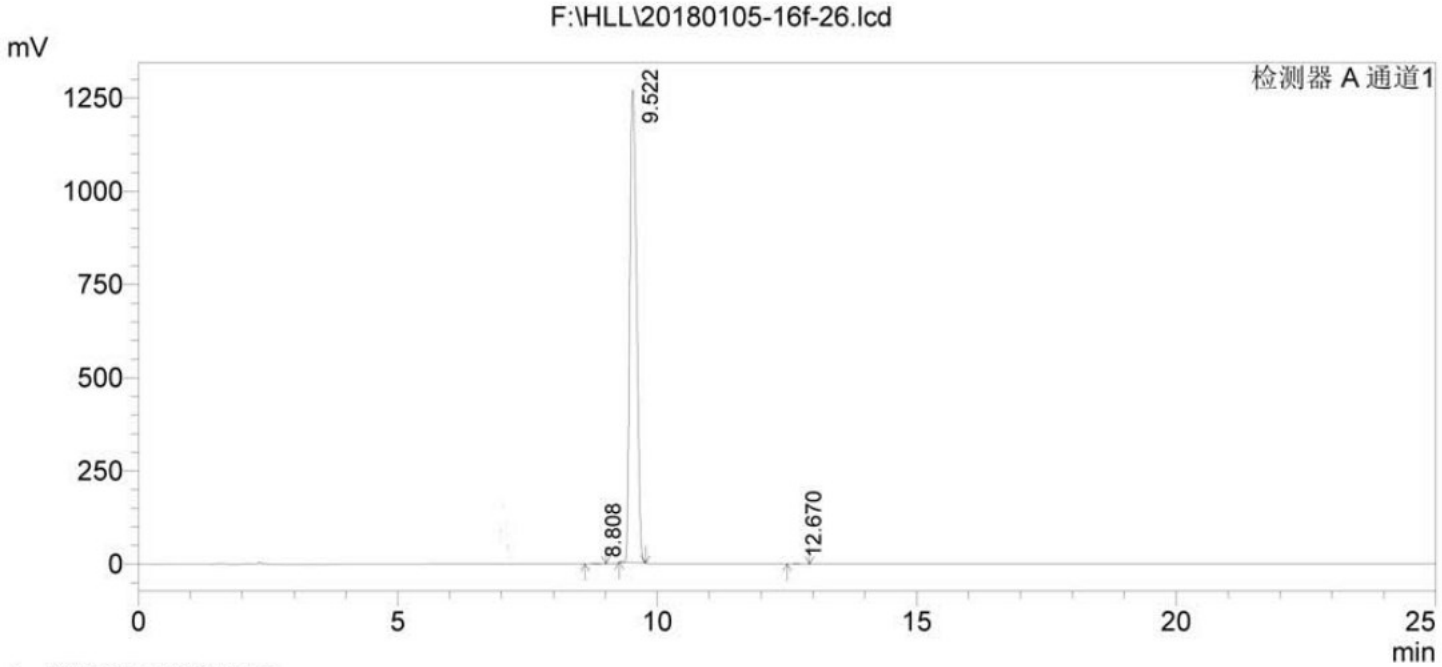
Compound 16f. ^{13}C NMR, $CDCl_3$, 125 MHz


16f
153.13
150.00
139.15
137.48
132.52
130.68
130.31
128.80
128.29
124.50
113.82
106.23
65.02
61.05
56.16
14.80
f1 (ppm)

HR-MS Spectrum of Compound 16f.


S 16f
Waters GCT Premier
20171460 302 (5.033) Cm (302-(50+51))
TOF MS EI+
1.32e4
100
%
0
330.1475
315.1232
331.1496
409.1194
268.0730
301.1085
270.0891
227.0712
240.0779
197.0597
225.0666
115.0553
155.0486
63.9618
78.9730
89.0394
332.1538
352.1123
394.0963
410.1225
m/z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420

HPLC Spectrum of Compound 16f

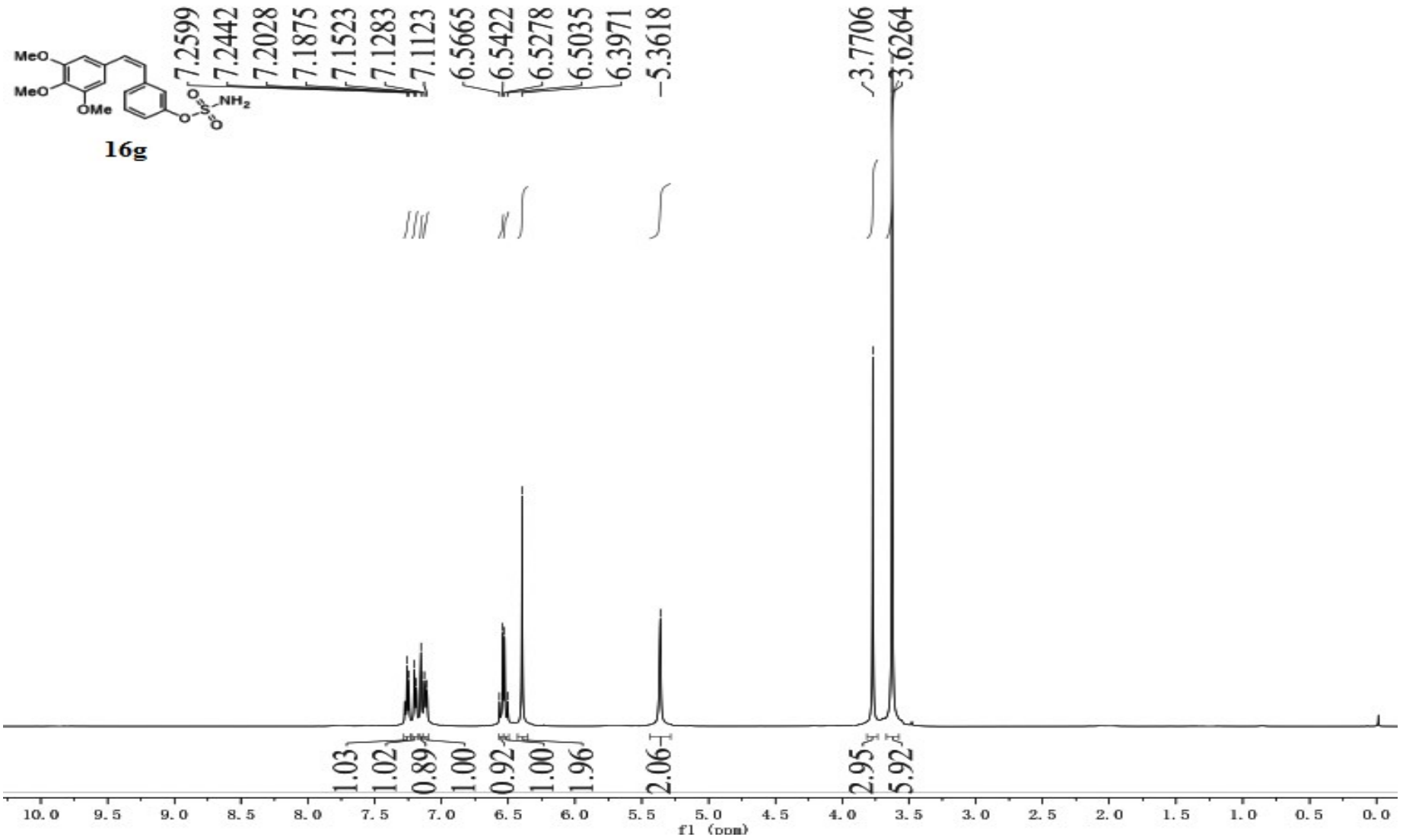


峰表

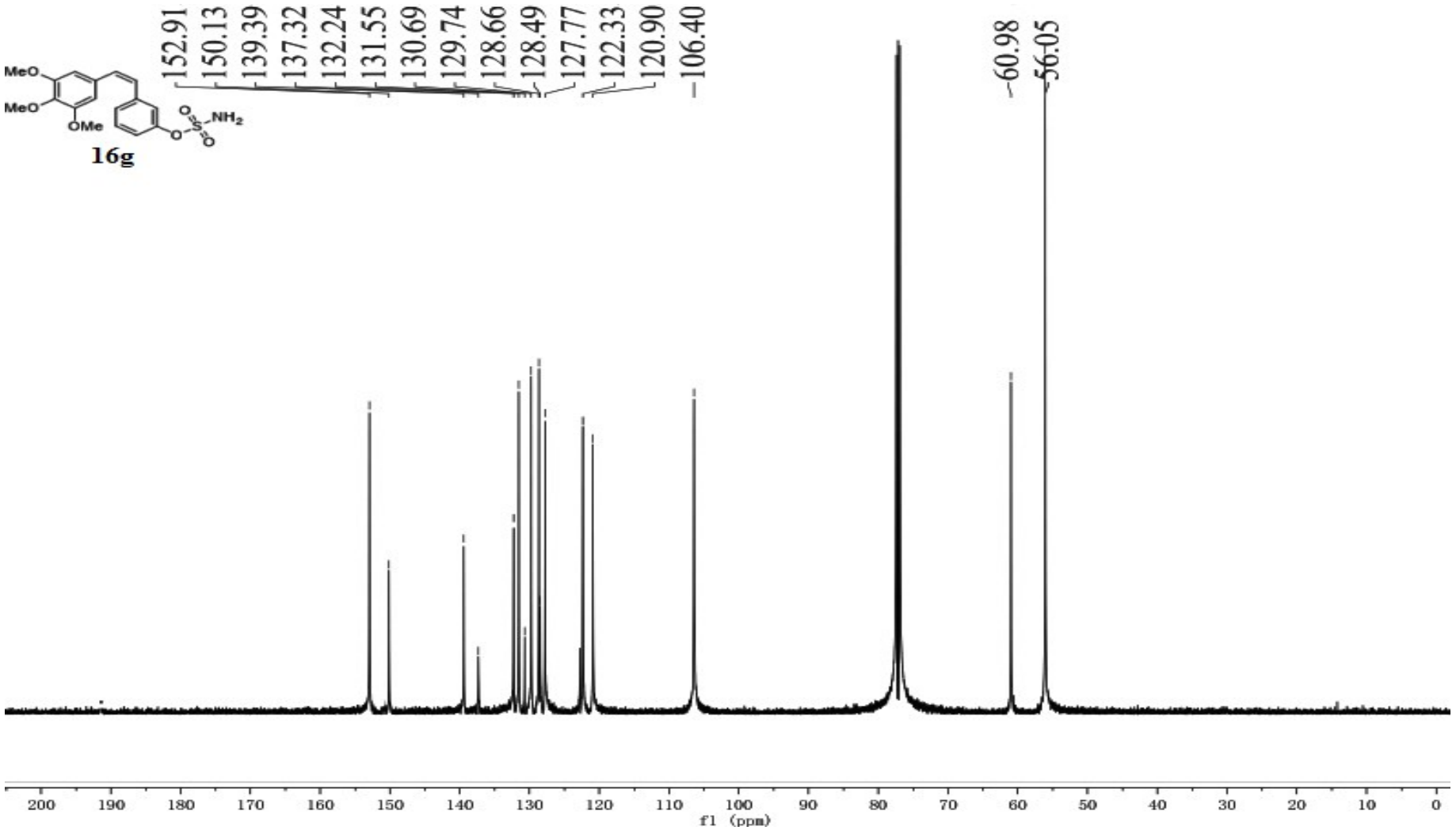
检测器 A Ch1 276nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	8.808	10675	1159	0.093	0.091
2	9.522	11497680	1269609	99.823	99.816
3	12.670	9737	1175	0.085	0.092
总计		11518092	1271943	100.000	100.000

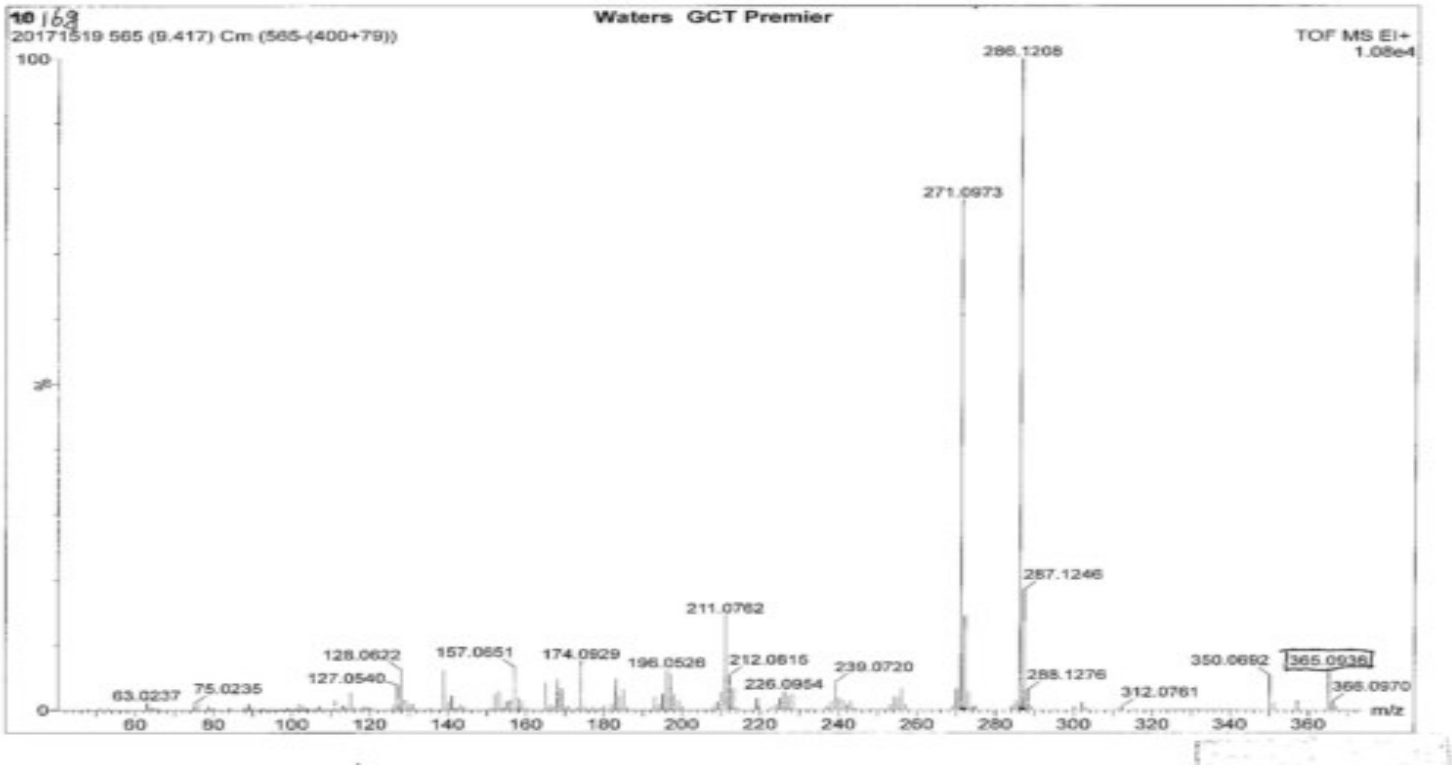
Compound 16g. ^{1}H NMR, $CDCl_3$, 500 MHz



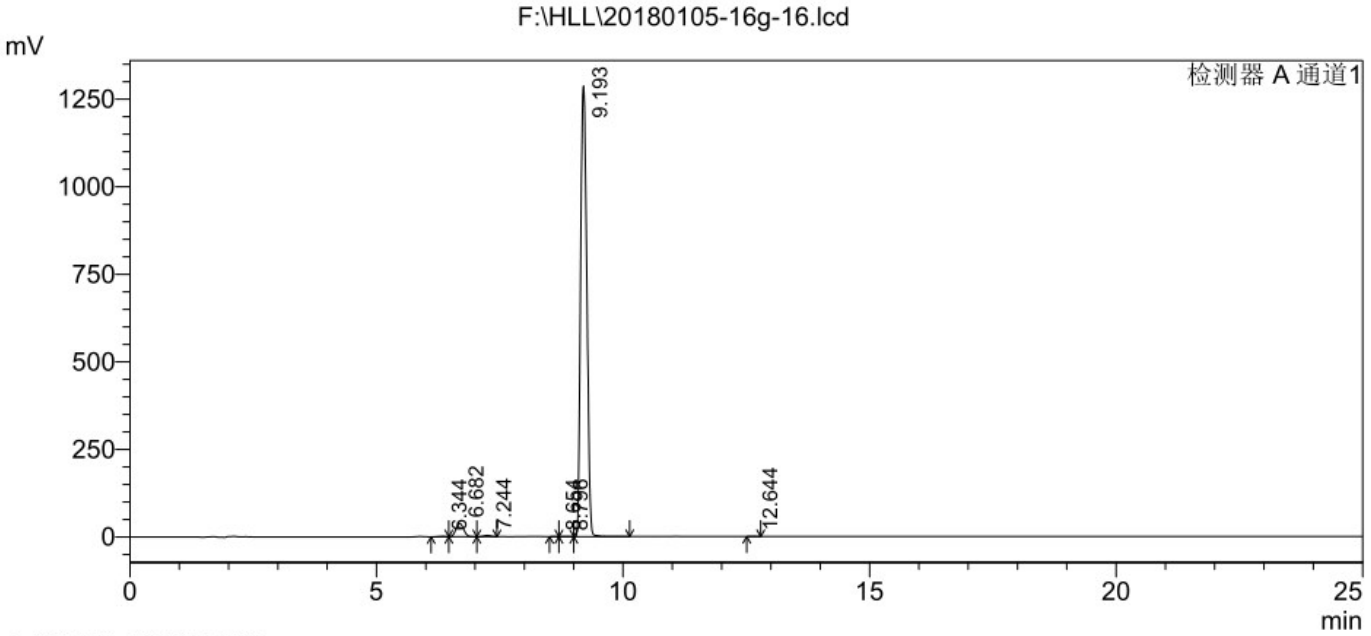
Compound 16g. ^{13}C NMR, $CDCl_3$, 125 MHz


MeO
MeO
OMe
O
S
O
NH2
16g
152.91
150.13
139.39
137.32
132.24
131.55
130.69
129.74
128.66
128.49
127.77
122.33
120.90
106.40
60.98
56.05
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

HR-MS Spectrum of Compound 16g


Waters GCT Premier
20171519 565 (9.417) Cm (565-(400+79))
TOF MS EI+
1.08e4
100
%
0
286.1208
271.0973
287.1246
211.0762
128.0622
157.0651
174.0929
196.0526
212.0615
239.0720
127.0540
226.0954
288.1276
350.0692
365.0936
366.0970
312.0761
63.0237
75.0235
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
m/z

HPLC Spectrum of Compound 16g



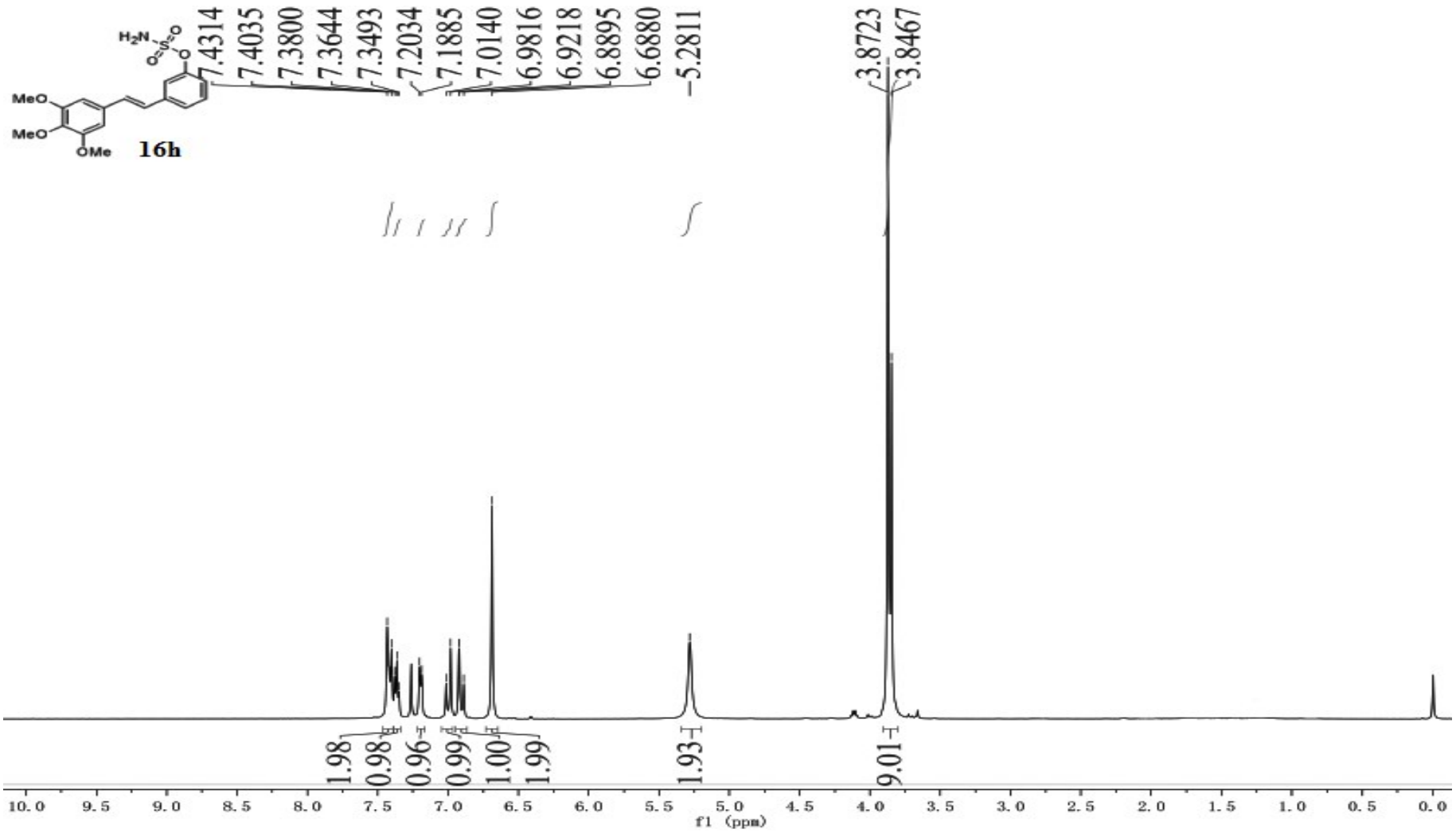
1 检测器 A 通道1/276nm

峰表

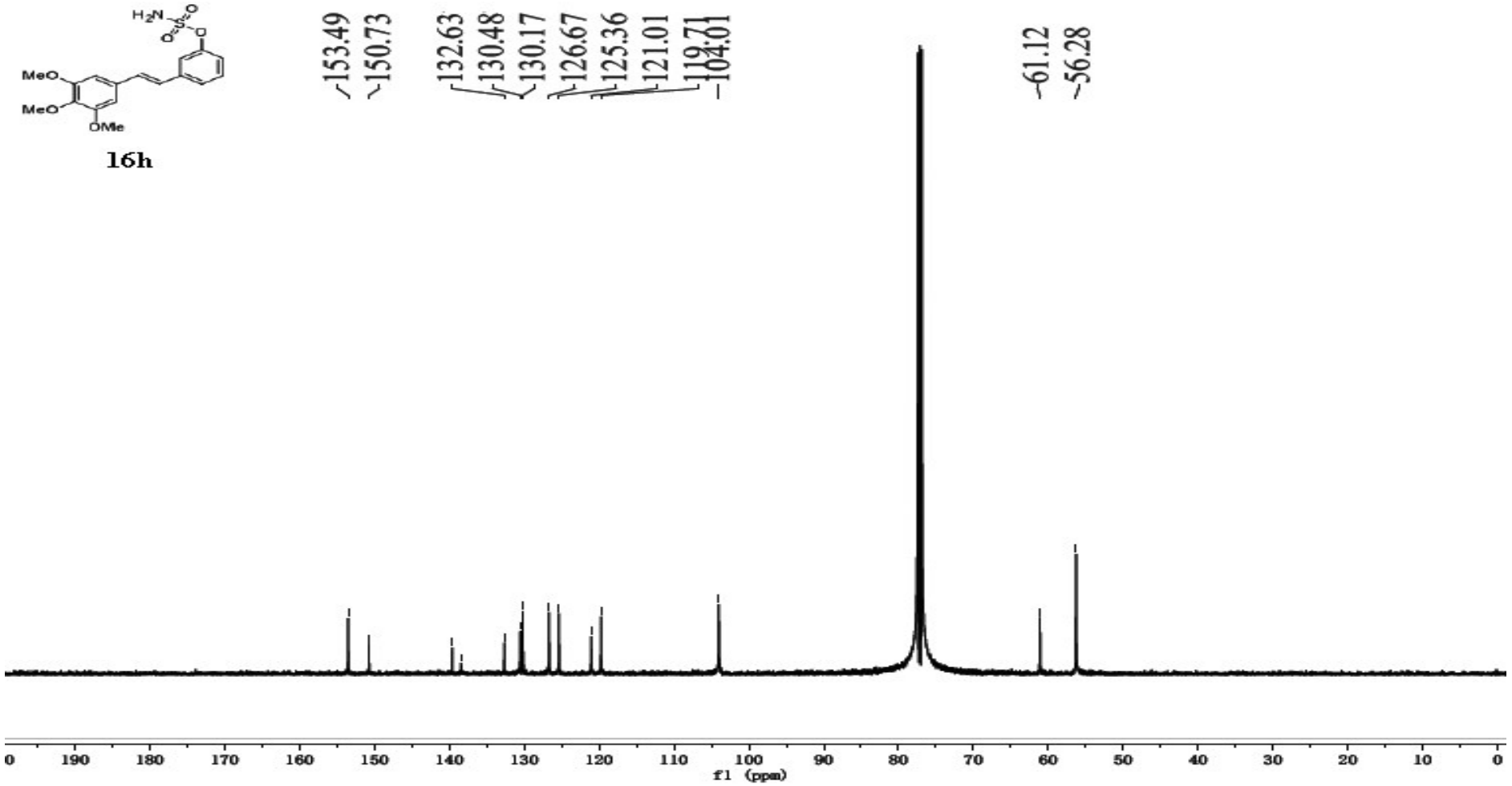
检测器 A Ch1 276nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	6.344	12526	1068	0.107	0.080
2	6.682	414643	38084	3.538	2.862
3	7.244	32215	3347	0.275	0.252
4	8.654	2151	297	0.018	0.022
5	8.796	4645	441	0.040	0.033
6	9.193	11249758	1287105	95.999	96.726
7	12.644	2689	334	0.023	0.025
总计		11718626	1330675	100.000	100.000

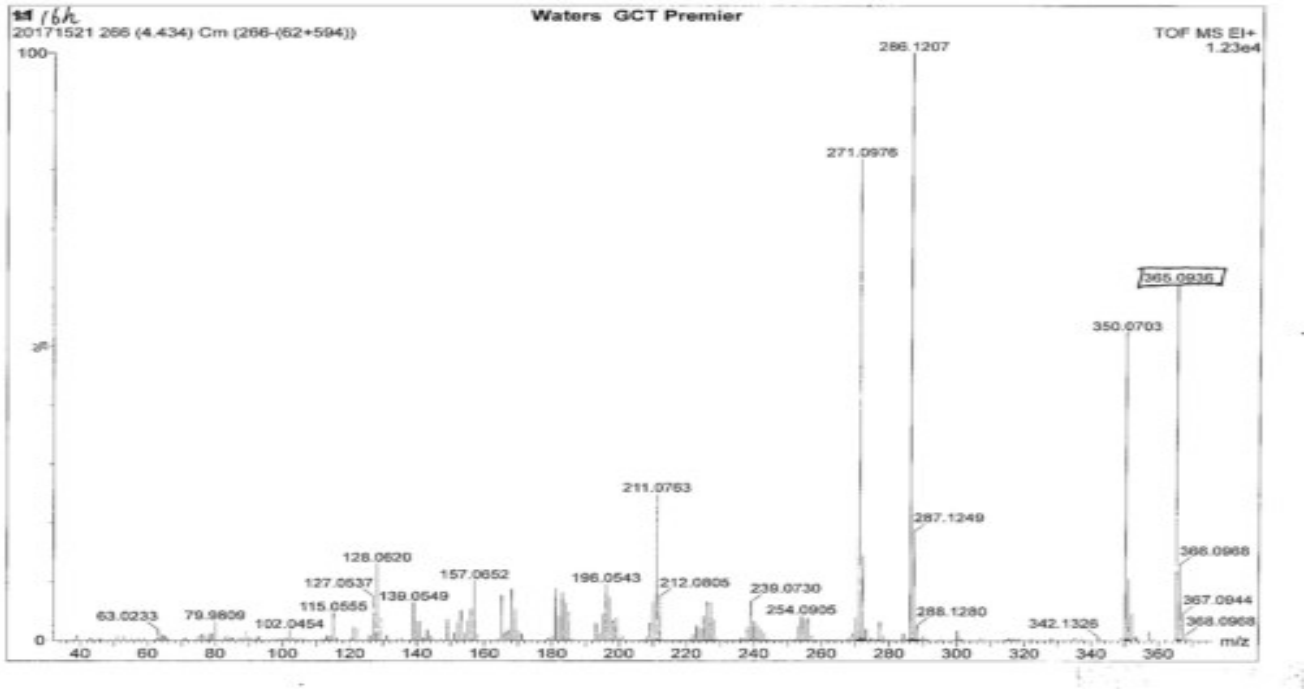
Compound 16h. ^{1}H NMR, $CDCl_3$, 500 MHz



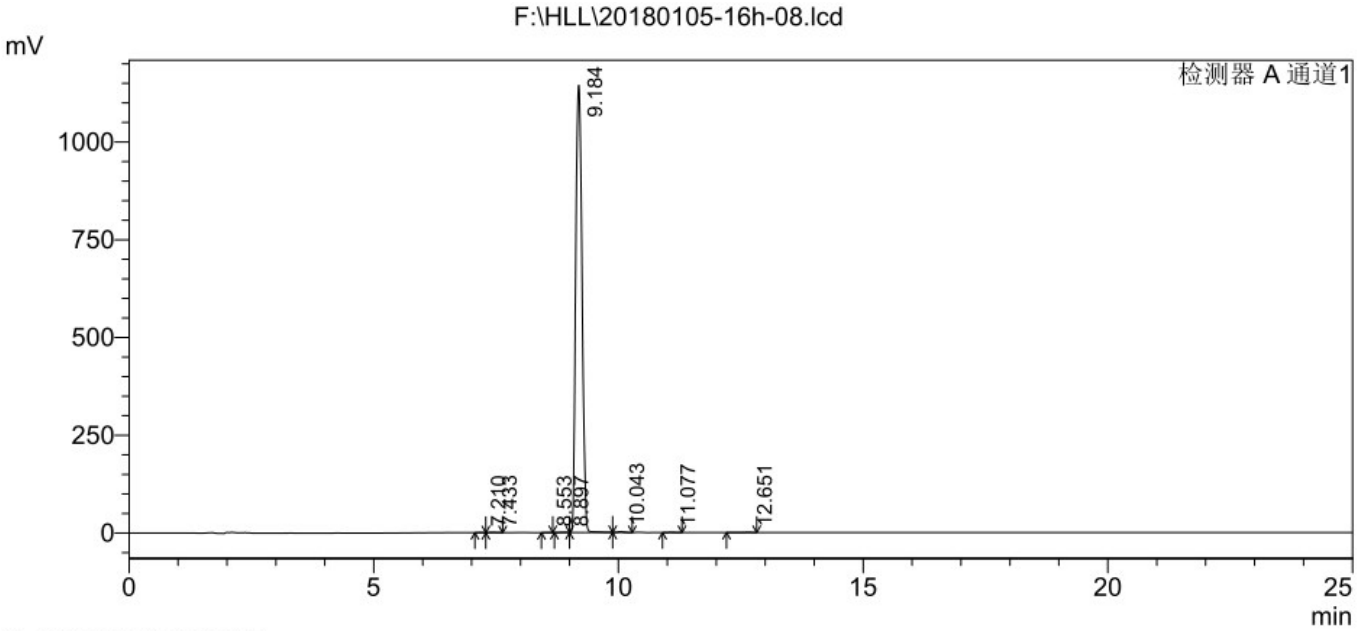
Compound 16h. ^{13}C NMR, $CDCl_3$, 125 MHz



HR-MS Spectrum of Compound 16h


11 16h
Waters GCT Premier
20171521 266 (4.434) Cm (266-(62+594))
TOF MS EI+
1.23e4
100
%
0
286.1207
271.0976
365.0936
350.0703
211.0763
287.1249
368.0968
128.0620
157.0652
127.0537
196.0543
212.0805
239.0730
139.0549
115.0555
254.0905
63.0233
79.9809
102.0454
288.1280
342.1325
367.0944
368.0968
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360
m/z

HPLC Spectrum of Compound 16h



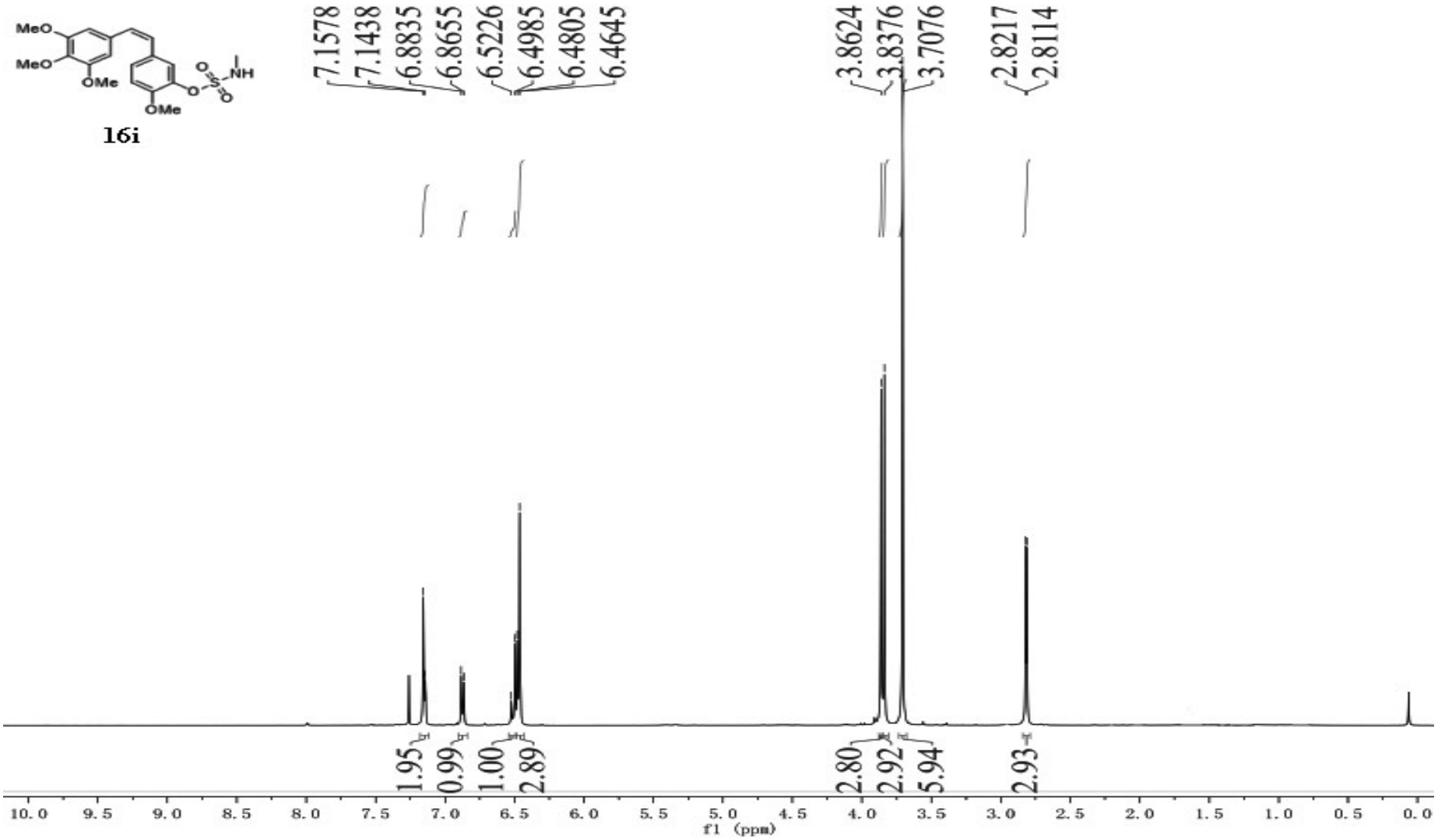
1 检测器 A 通道1/276nm

峰表

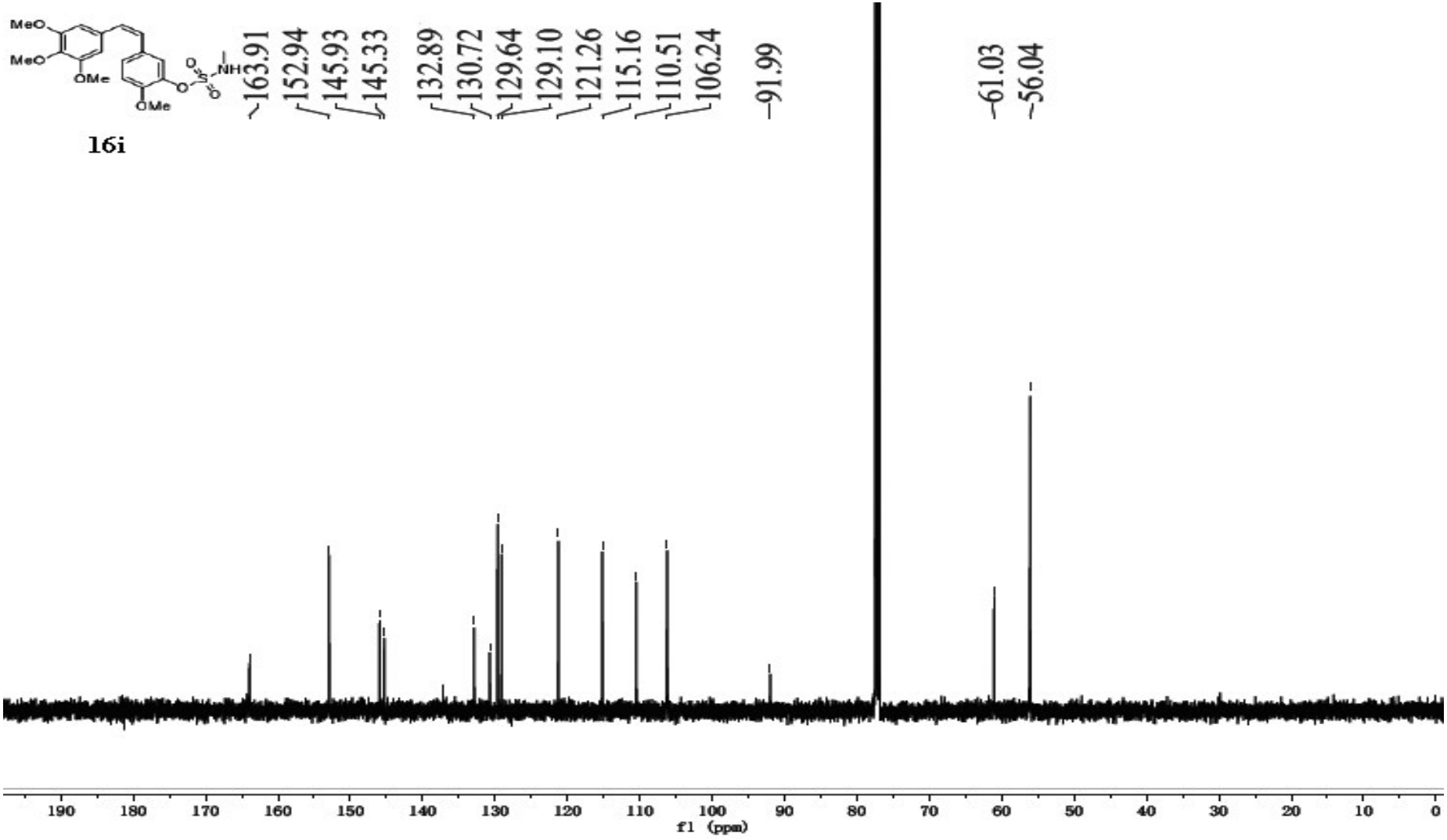
检测器 A Ch1 276nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	7.210	2191	272	0.021	0.024
2	7.433	8018	813	0.078	0.071
3	8.553	541	67	0.005	0.006
4	8.897	4617	427	0.045	0.037
5	9.184	10221479	1143653	99.580	99.591
6	10.043	16395	1949	0.160	0.170
7	11.077	5398	600	0.053	0.052
8	12.651	5914	574	0.058	0.050
总计		10264552	1148355	100.000	100.000

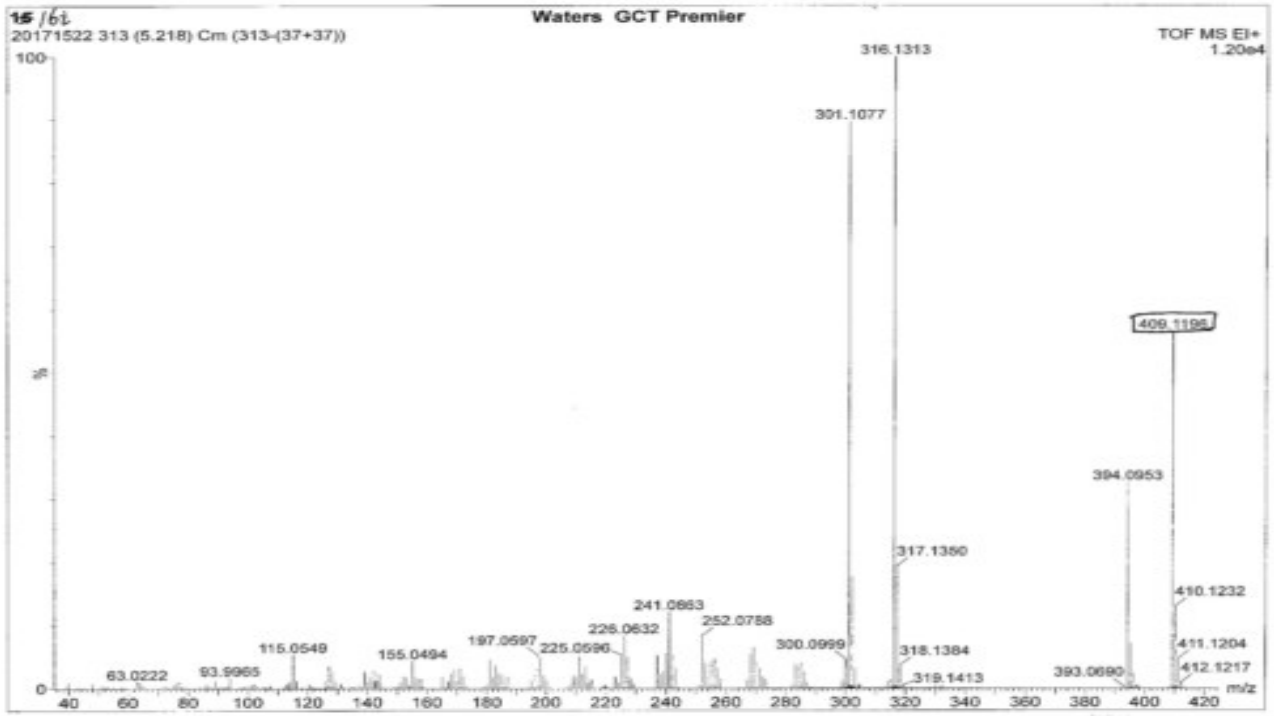
Compound 16i. ^{1}H NMR, $CDCl_3$, 500 MHz



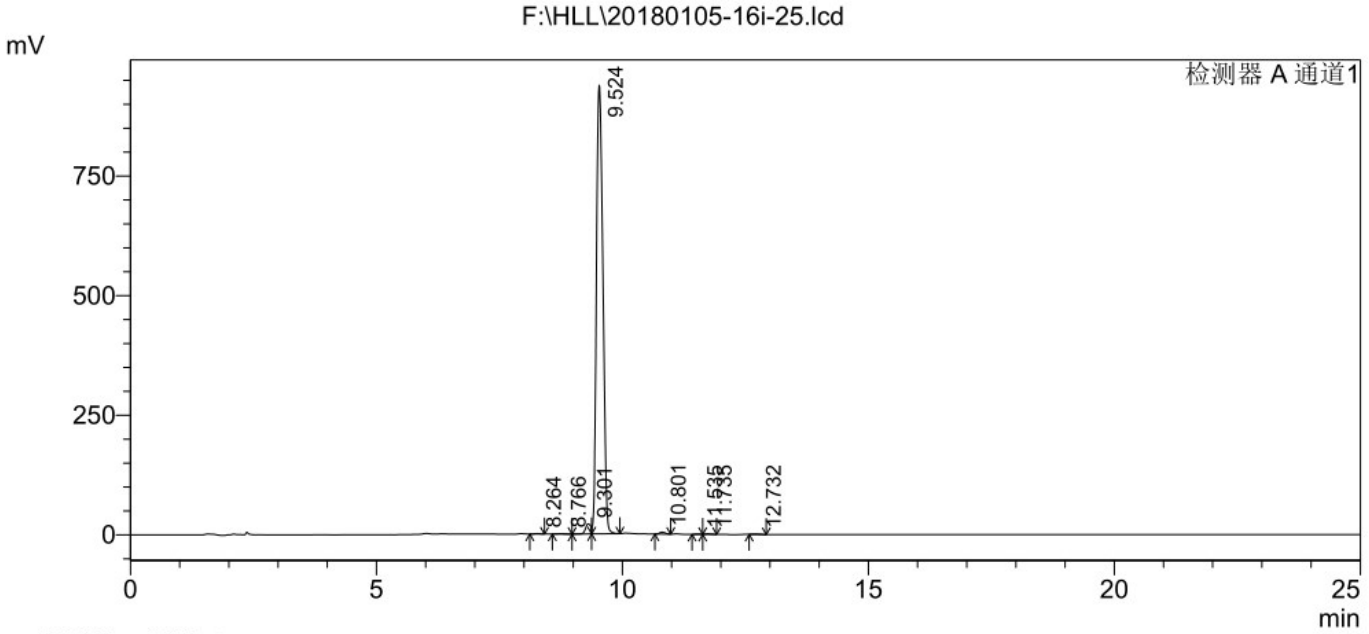
Compound 16i. ^{13}C NMR, $CDCl_3$, 125 MHz



HR-MS Spectrum of Compound 16i


15 /61
Waters GCT Premier
20171522 313 (5.218) Cm (313-(37+37))
TOF MS EI+
1.20e4
100
%
0
316.1313
301.1077
409.1196
394.0953
317.1350
410.1232
241.0663
252.0788
226.0632
411.1204
412.1217
115.0549
155.0494
197.0597
225.0596
300.0999
318.1384
319.1413
393.0690
63.0222
93.9965
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420
m/z

HPLC Spectrum of Compound 16i



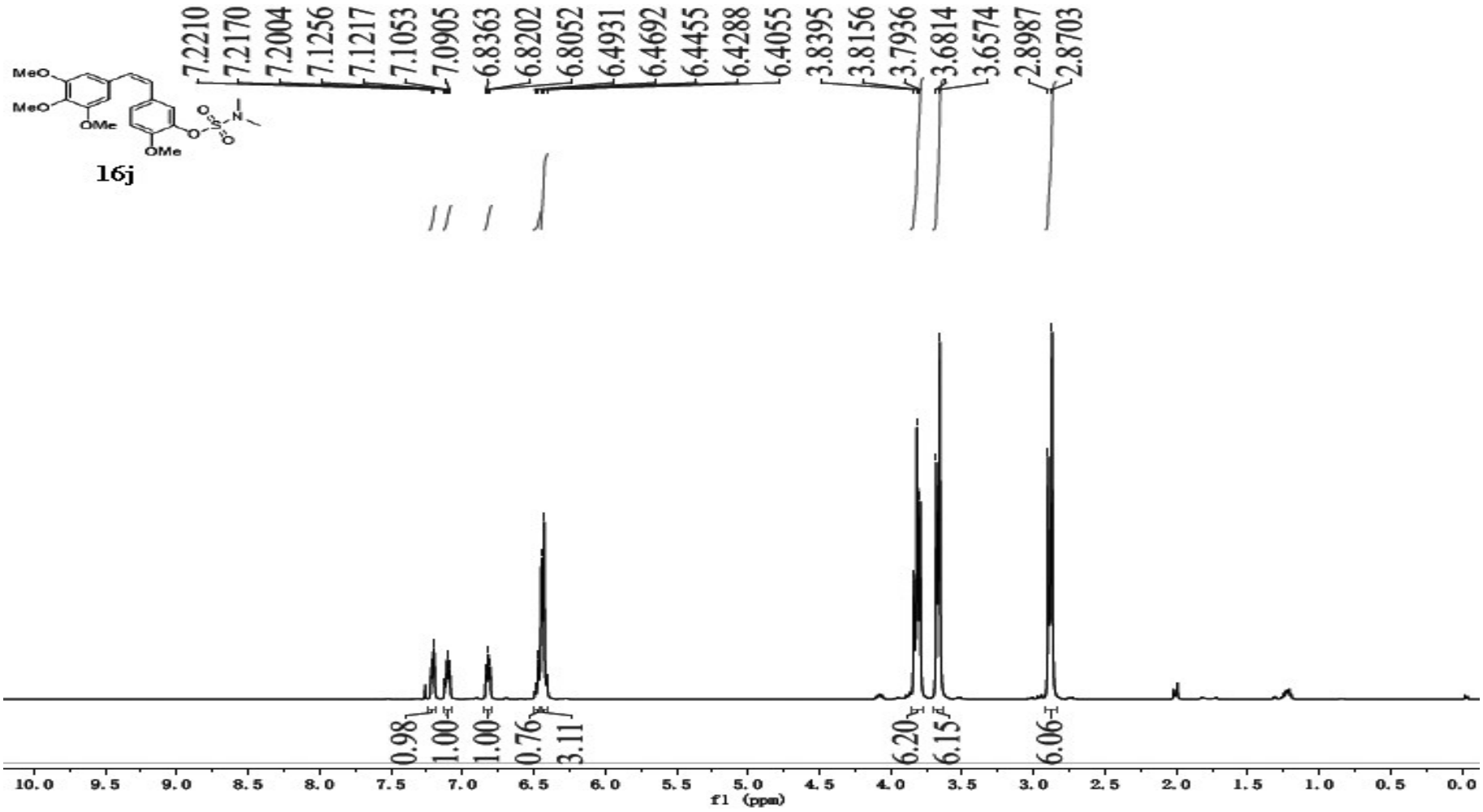
1 检测器 A 通道1/276nm

峰表

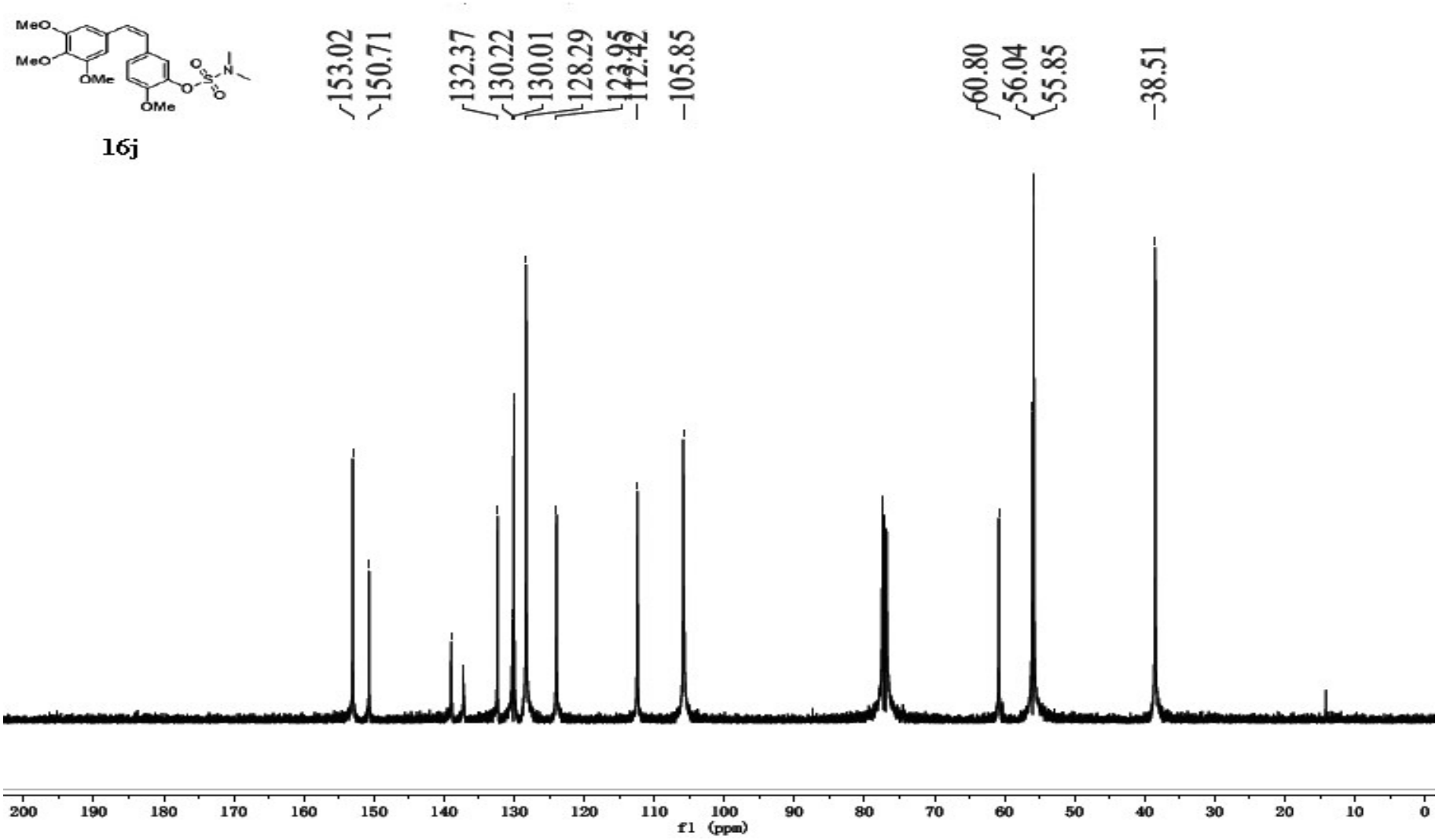
检测器 A Ch1 276nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	8.264	8322	1039	0.094	0.107
2	8.766	9019	748	0.102	0.077
3	9.301	163247	21183	1.850	2.187
4	9.524	8578025	938128	97.230	96.859
5	10.801	35031	4162	0.397	0.430
6	11.535	6253	789	0.071	0.081
7	11.735	10326	1158	0.117	0.120
8	12.732	12142	1341	0.138	0.138
总计		8822365	968548	100.000	100.000

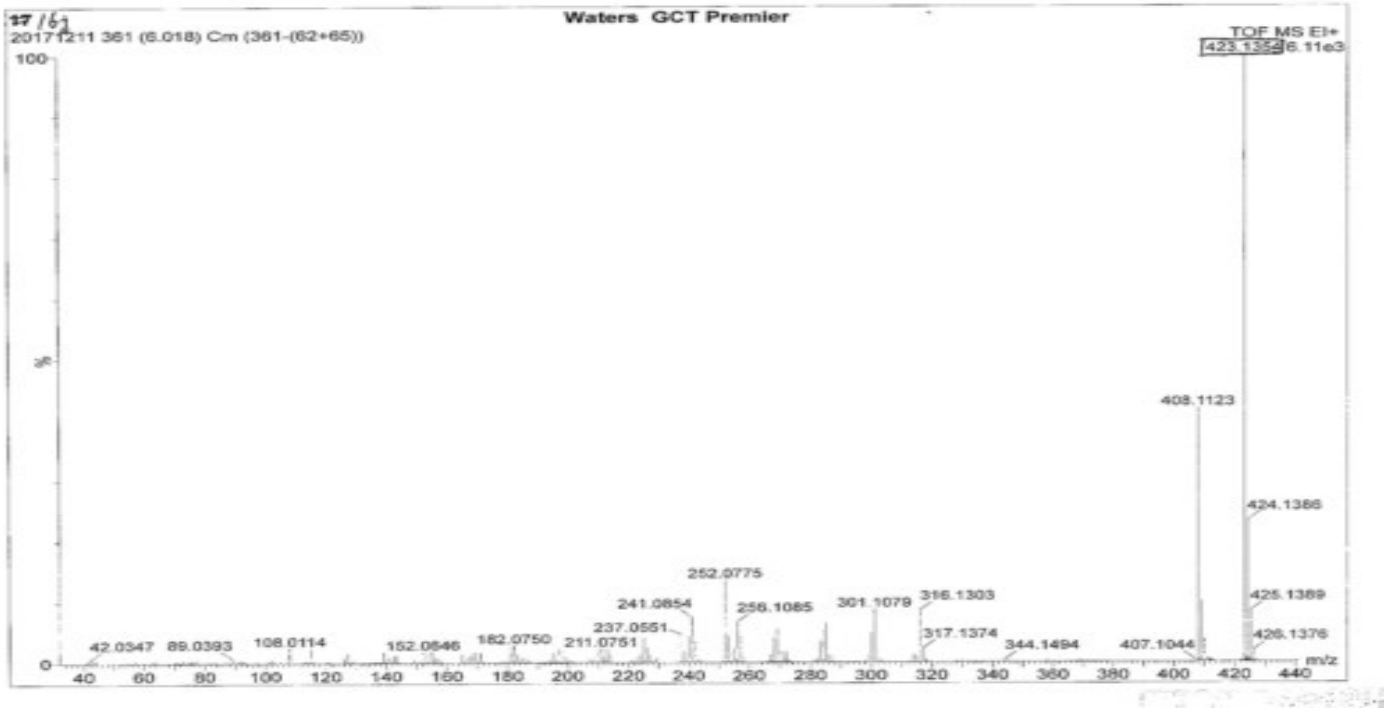
Compound 16j. ^{1}H NMR, $CDCl_3$, 500 MHz



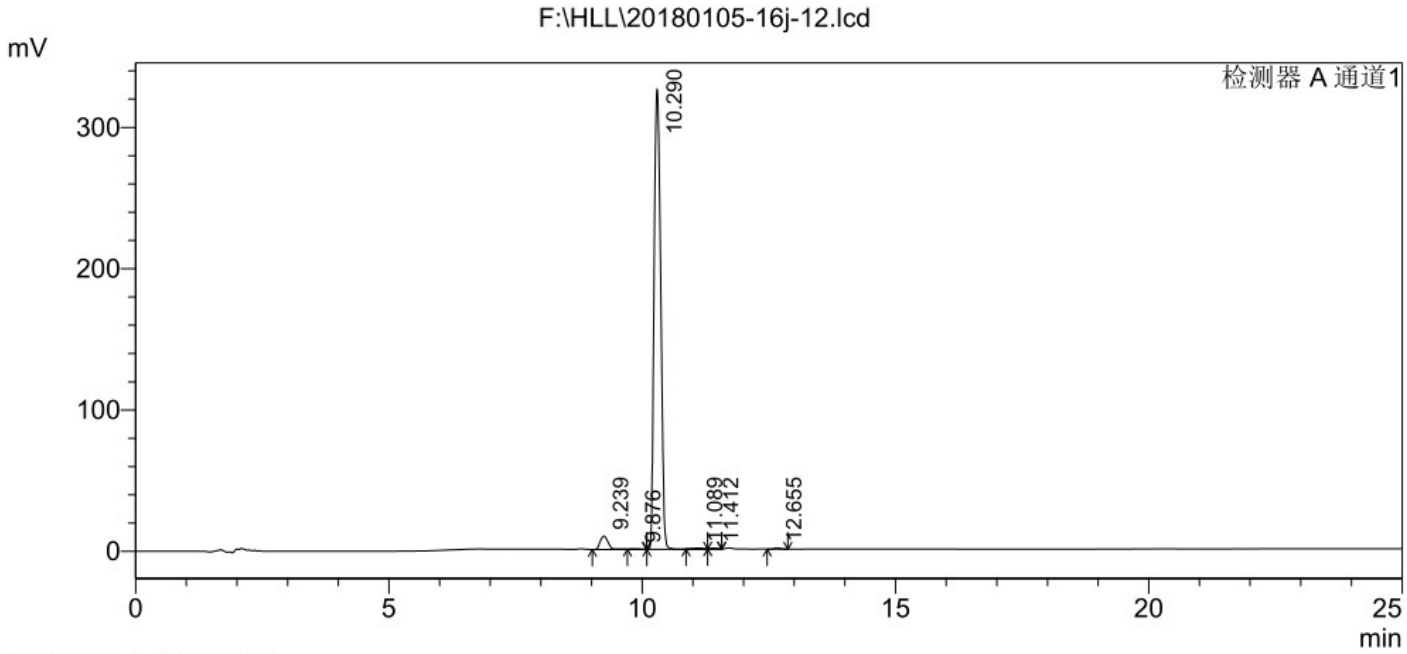
Compound 16j. ^{13}C NMR, $CDCl_3$, 125 MHz



HR-MS Spectrum of Compound 16j


17 /61
Waters GCT Premier
20171211 361 (6.018) Cm (361-(62+65))
TOF MS EI+
423.1354 6.11e3
100
%
0
408.1123
424.1386
252.0775
241.0854
256.1085
301.1079
316.1303
425.1389
237.0551
317.1374
426.1376
42.0347
89.0393
108.0114
152.0646
182.0750
211.0751
344.1494
407.1044
m/z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440

HPLC Spectrum of Compound 16j



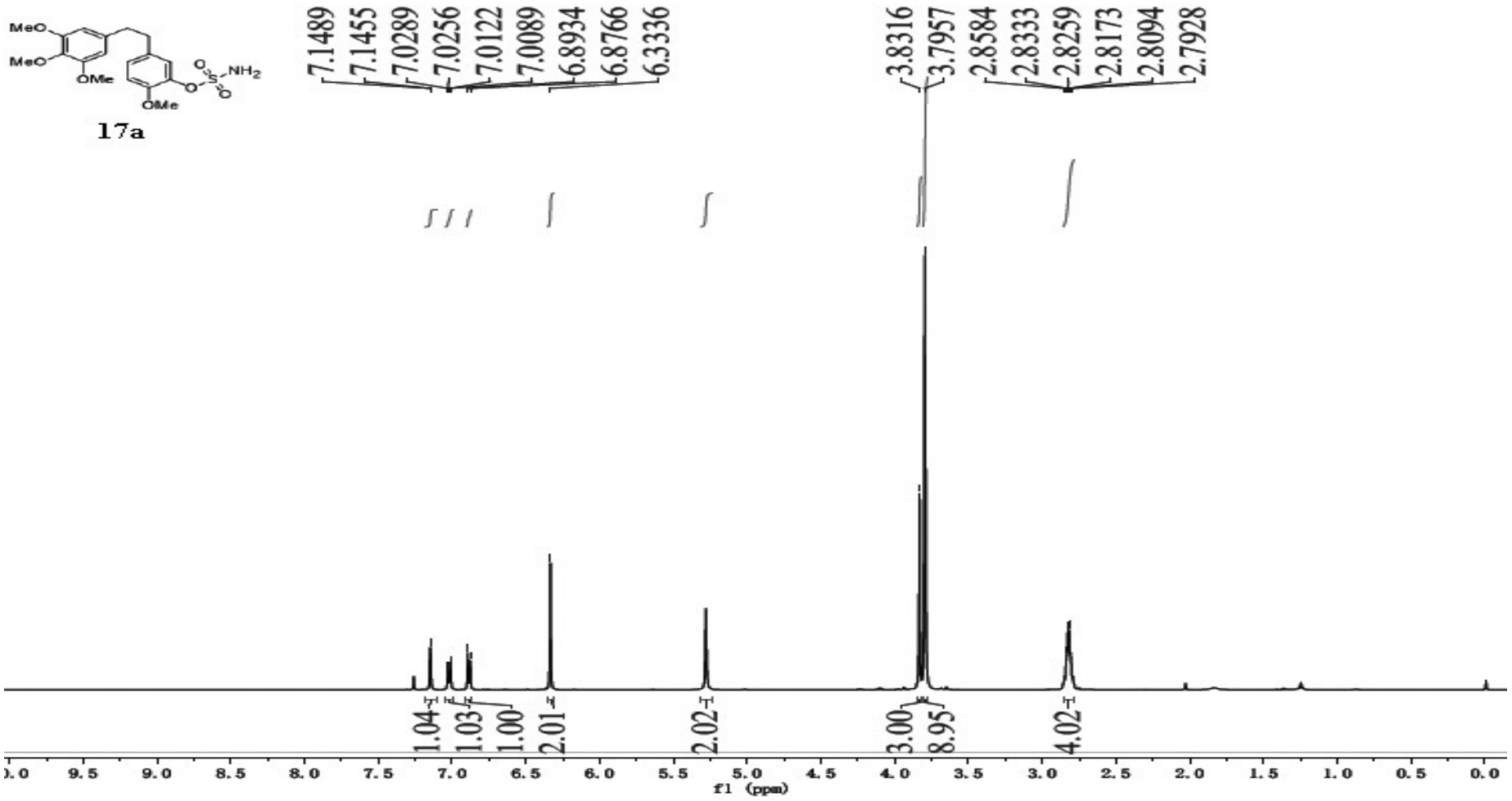
1 检测器 A 通道1/276nm

峰表

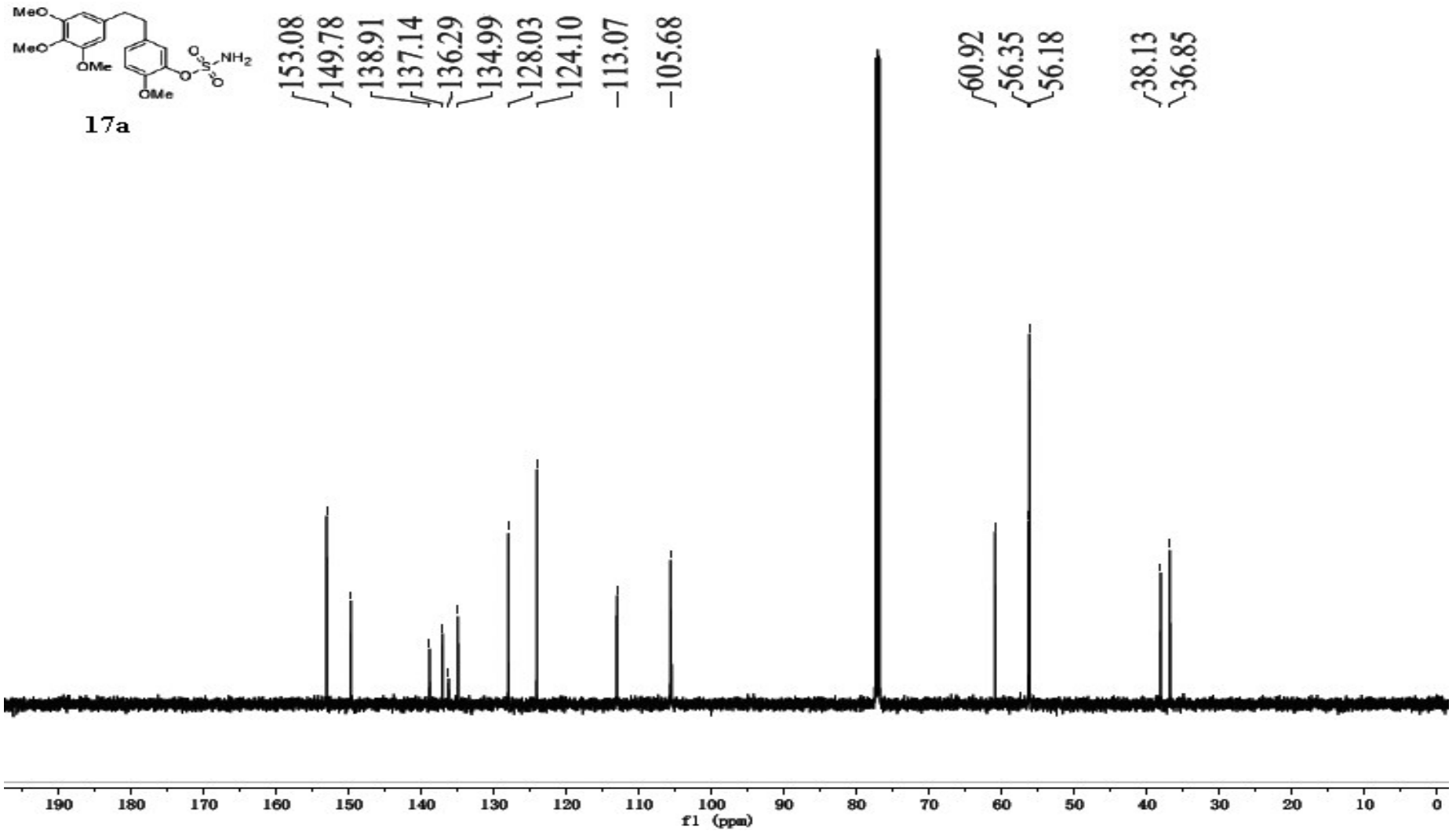
检测器 A Ch1 276nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	9.239	106616	9525	3.474	2.819
2	9.876	2591	244	0.084	0.072
3	10.290	2939479	325931	95.771	96.478
4	11.089	8162	695	0.266	0.206
5	11.412	4872	583	0.159	0.173
6	12.655	7568	850	0.247	0.252
总计		3069289	337829	100.000	100.000

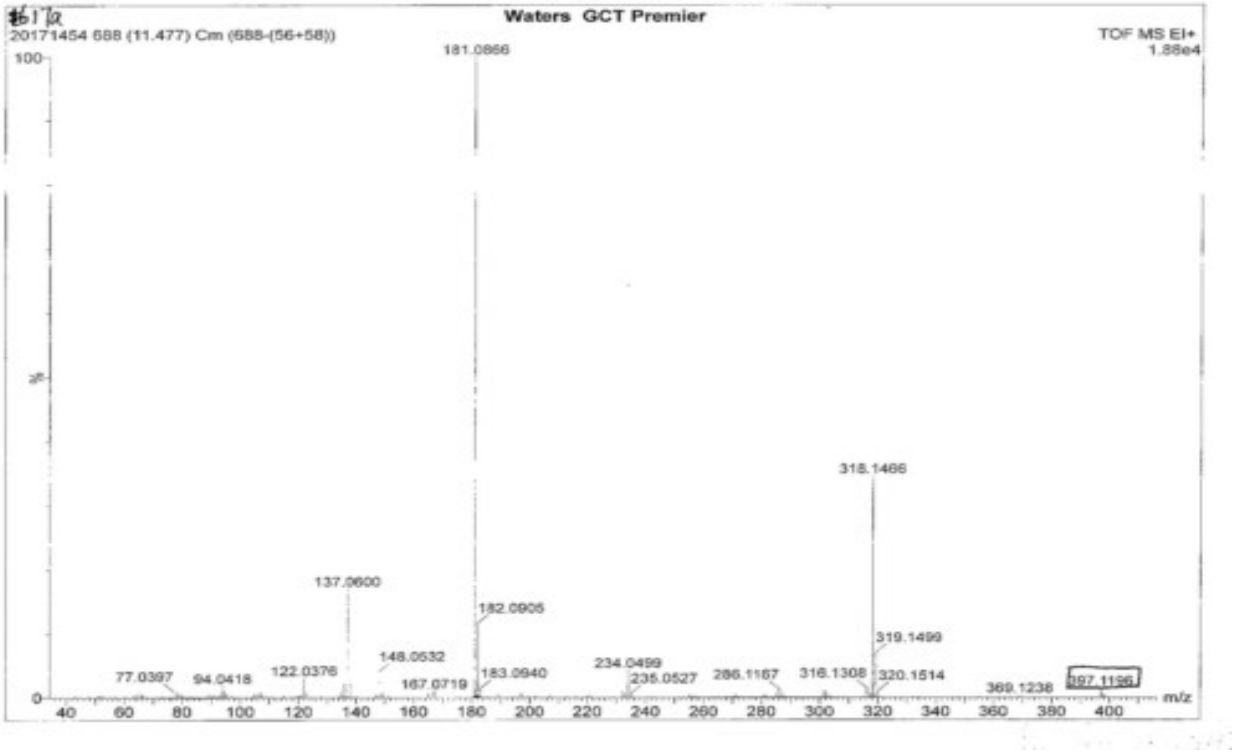
Compound 17a. ^{1}H NMR, $CDCl_3$, 500 MHz



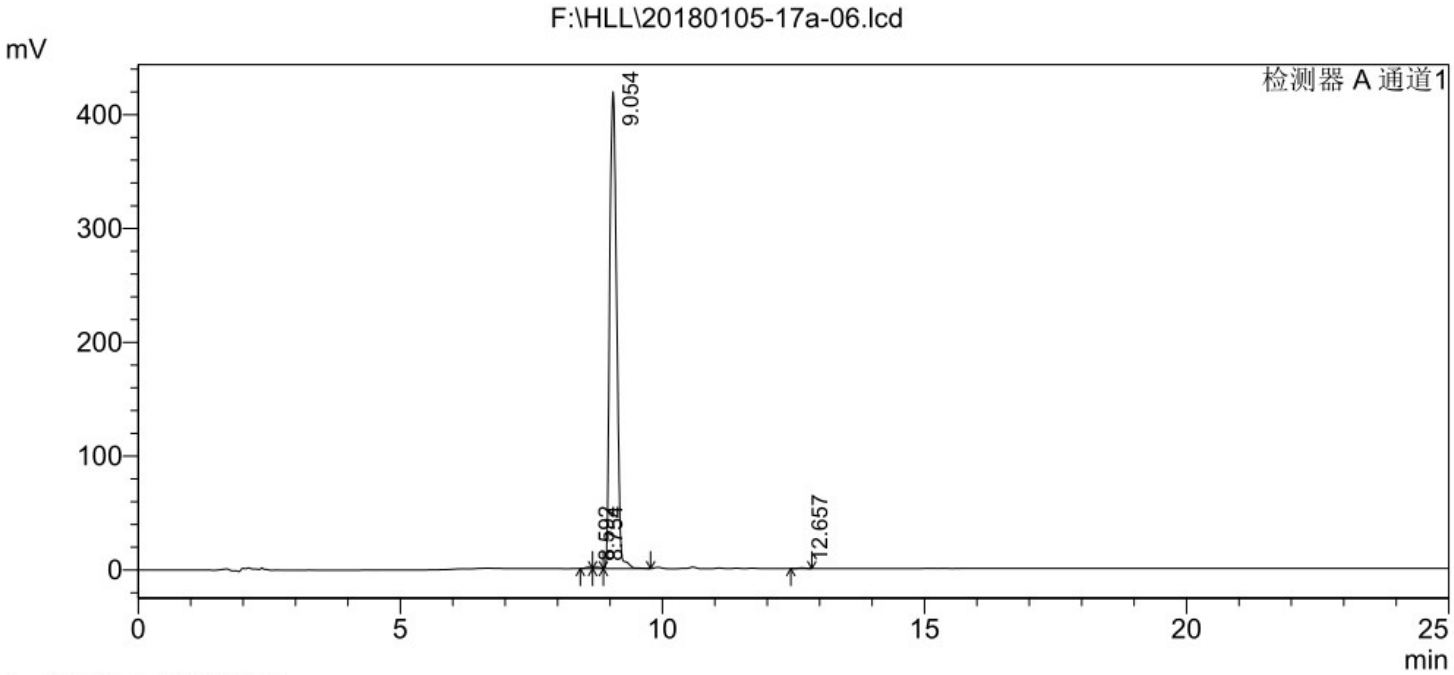
Compound 17a. ^{13}C NMR, $CDCl_3$, 125 MHz


MeO
MeO
OMe
OMe
O
S
O
NH2
17a
153.08
149.78
138.91
137.14
136.29
134.99
128.03
124.10
113.07
105.68
60.92
56.35
56.18
38.13
36.85
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

HR-MS Spectrum of Compound 17a


Waters GCT Premier
20171454 688 (11.477) Cm (688-(56+58))
TOF MS EI+
1.88e4
181.0866
318.1486
137.0600
182.0905
319.1499
148.0532
234.0499
77.0397
94.0418
122.0376
183.0940
235.0527
286.1167
316.1308
320.1514
167.0719
369.1238
397.1136
m/z

HPLC Spectrum of Compound 17a



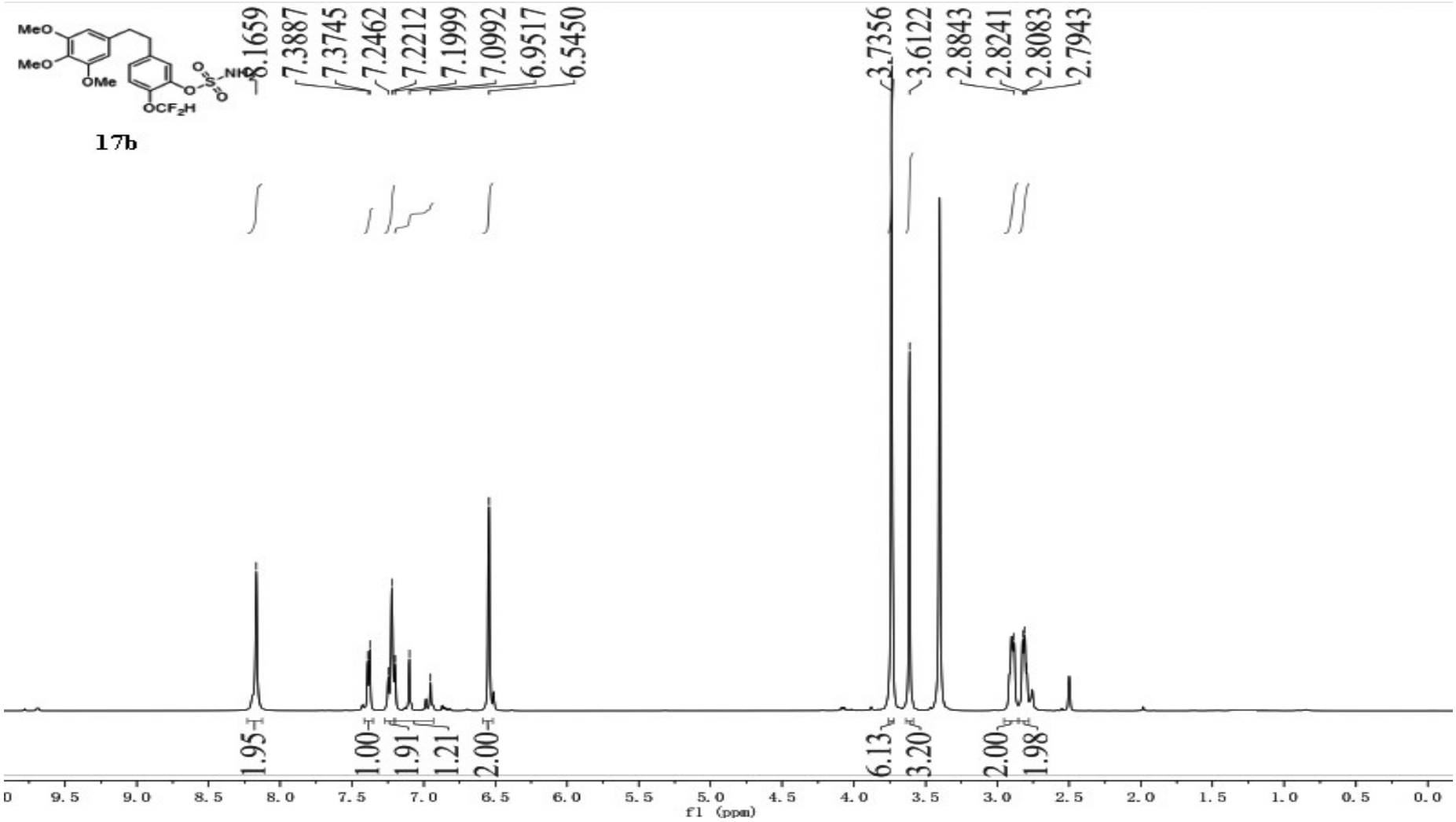
1 检测器 A 通道1/276nm

峰表

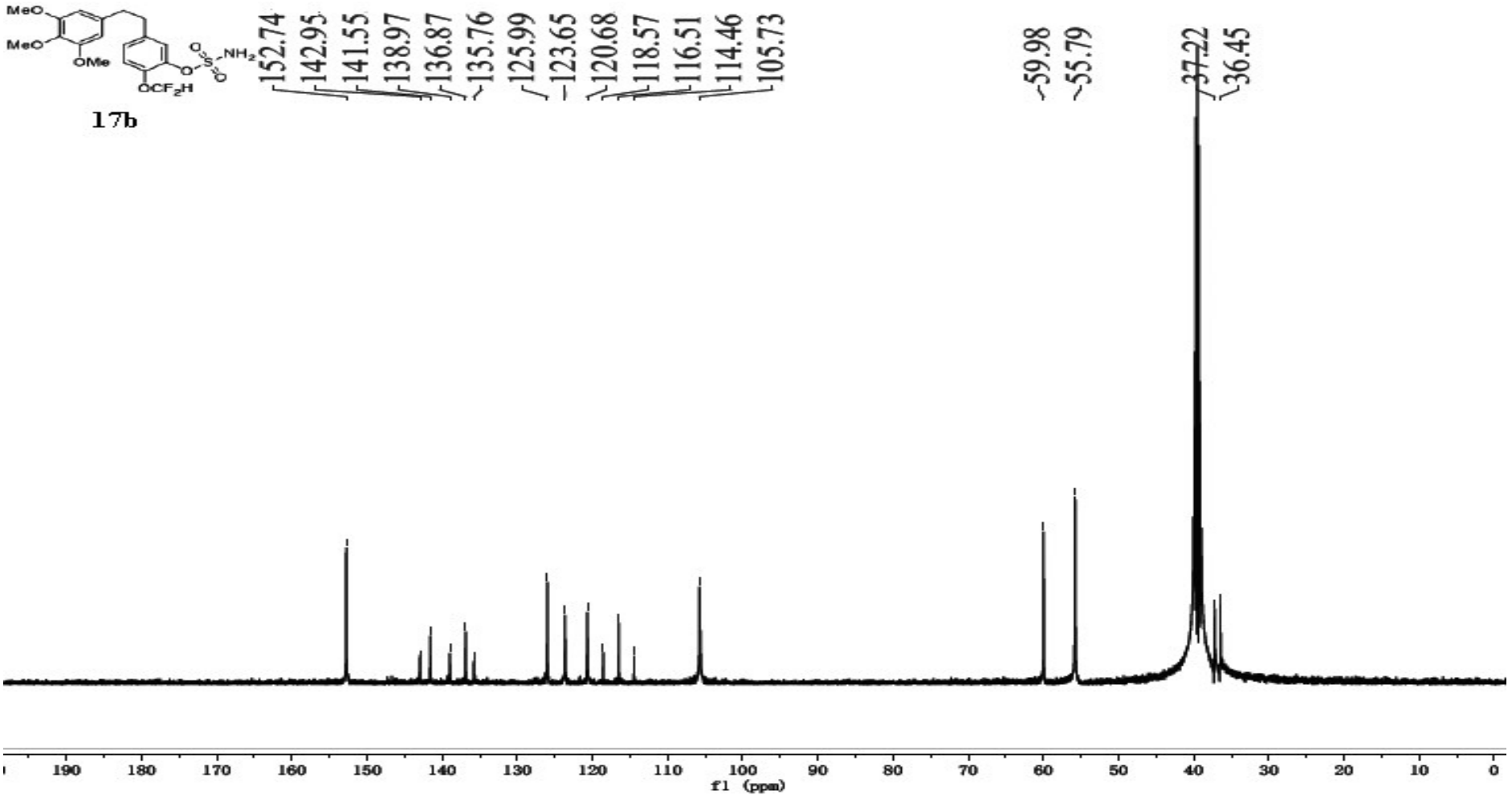
检测器 A Ch1 276nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	8.592	10131	1168	0.260	0.277
2	8.754	10999	1158	0.283	0.274
3	9.054	3862292	419207	99.301	99.301
4	12.657	6054	627	0.156	0.148
总计		3889476	422160	100.000	100.000

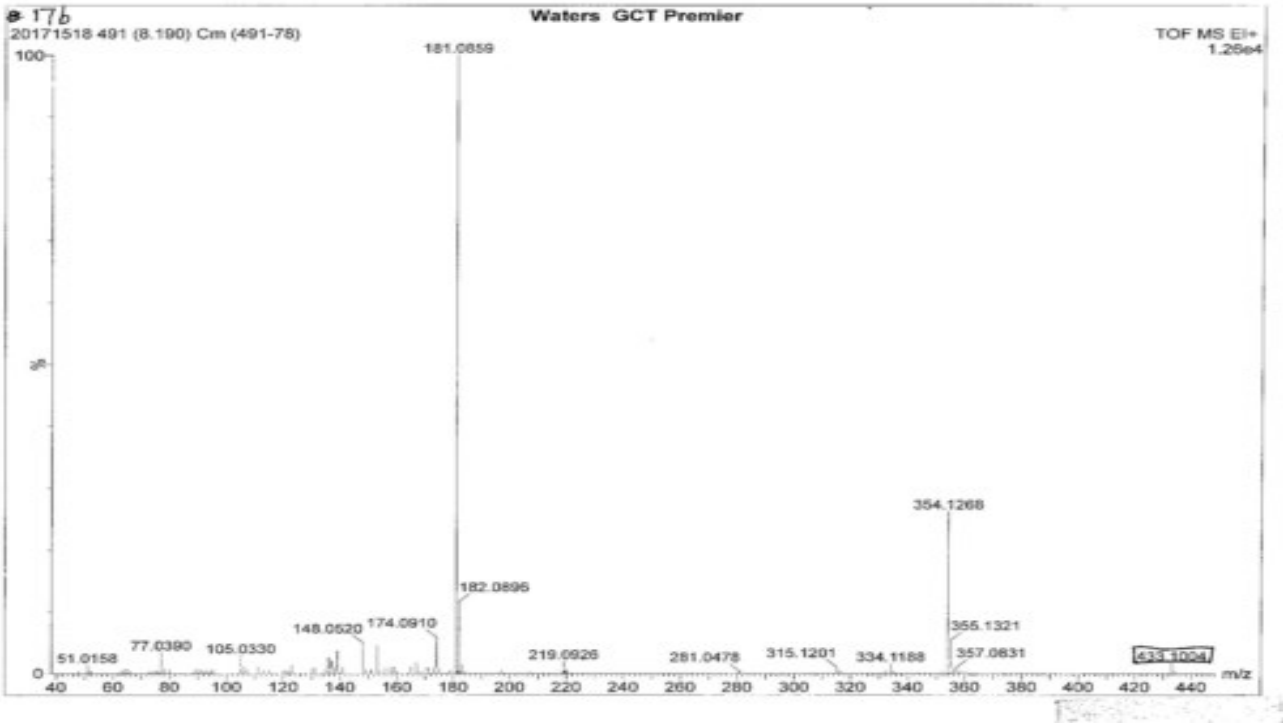
Compound 17b. ^{1}H NMR, DMSO, 500 MHz



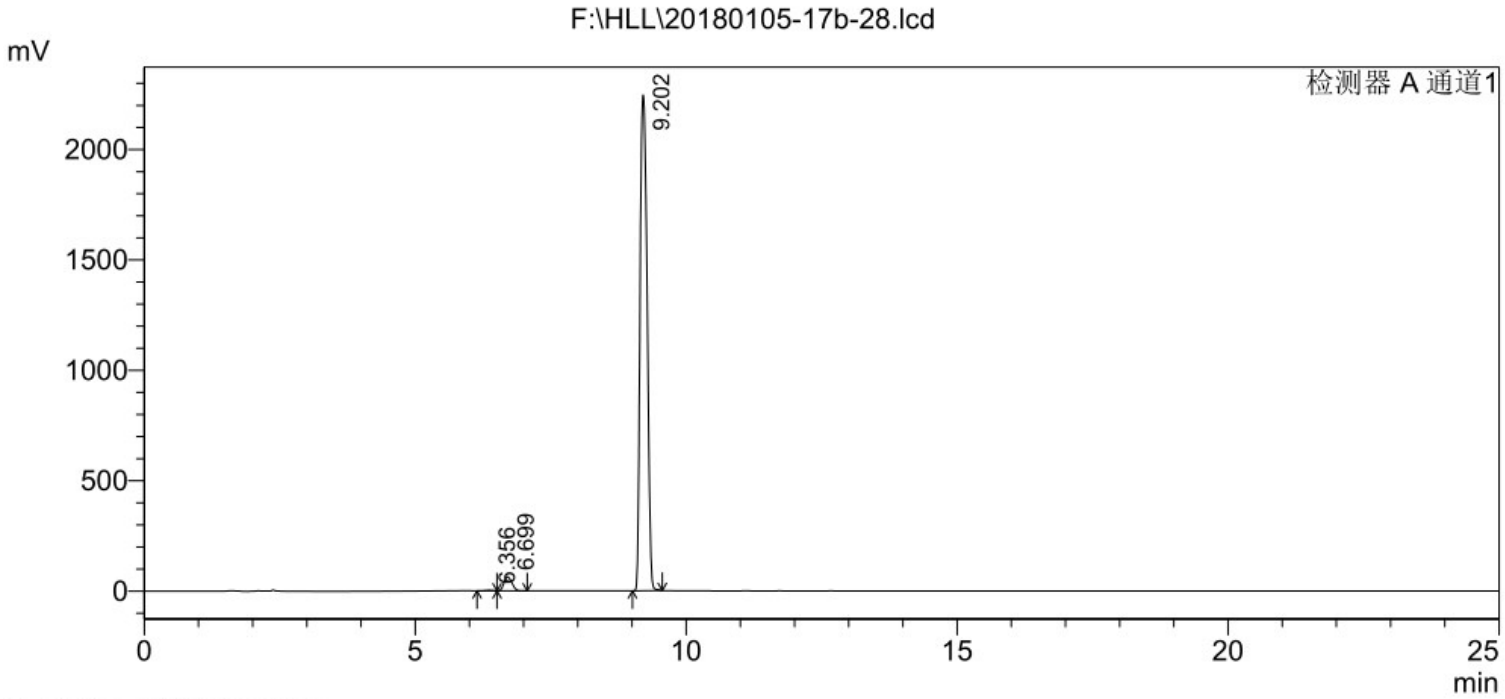
Compound 17b. ^{13}C NMR, DMSO, 125 MHz


MeO
MeO
OMe
OCF2H
NH2
17b
152.74
142.95
141.55
138.97
136.87
135.76
125.99
123.65
120.68
118.57
116.51
114.46
105.73
59.98
55.79
37.22
36.45
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

HR-MS Spectrum of Compound 17b


17b
Waters GCT Premier
20171518 491 (8.190) Cm (491-78)
TOF MS EI+
1.25e4
100
%
0
181.0859
354.1268
182.0896
355.1321
148.0520
174.0910
77.0390
105.0330
51.0158
219.0926
281.0478
315.1201
334.1188
357.0831
433.1004
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440
m/z

HPLC Spectrum of Compound 17b



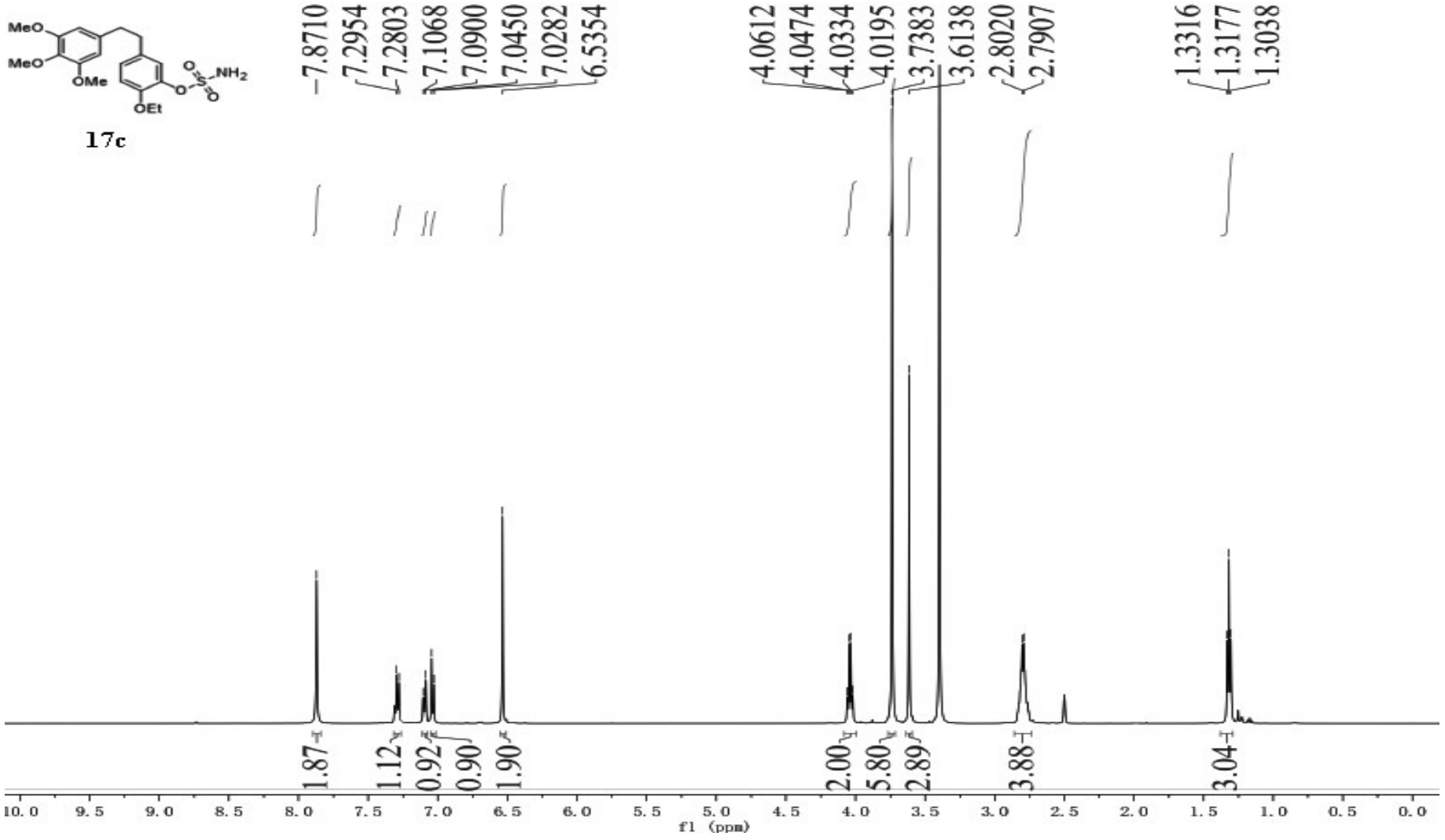
1 检测器 A 通道1/276nm

峰表

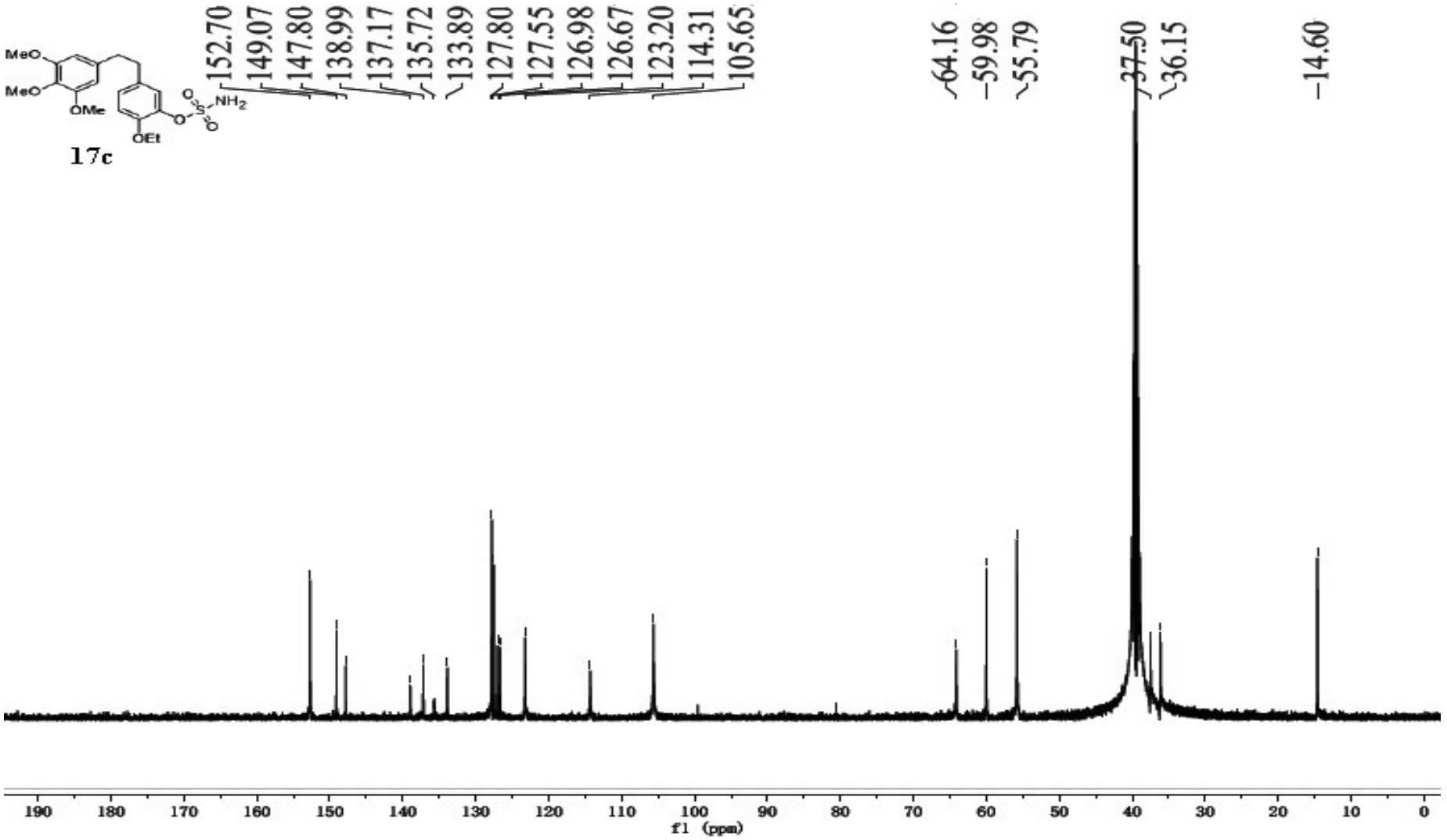
检测器 A Ch1 276nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	6.356	28395	2610	0.135	0.113
2	6.699	652399	64095	3.105	2.772
3	9.202	20328934	2245772	96.760	97.115
总计		21009728	2312477	100.000	100.000

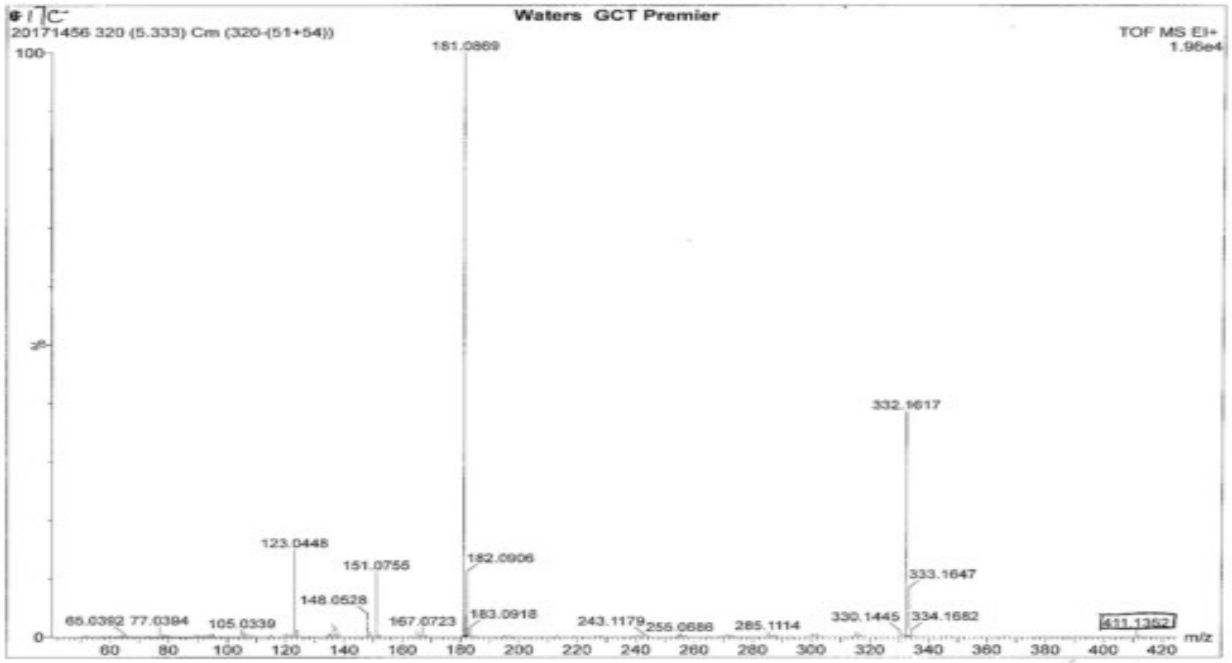
Compound 17c. ^{1}H NMR, DMSO, 500 MHz



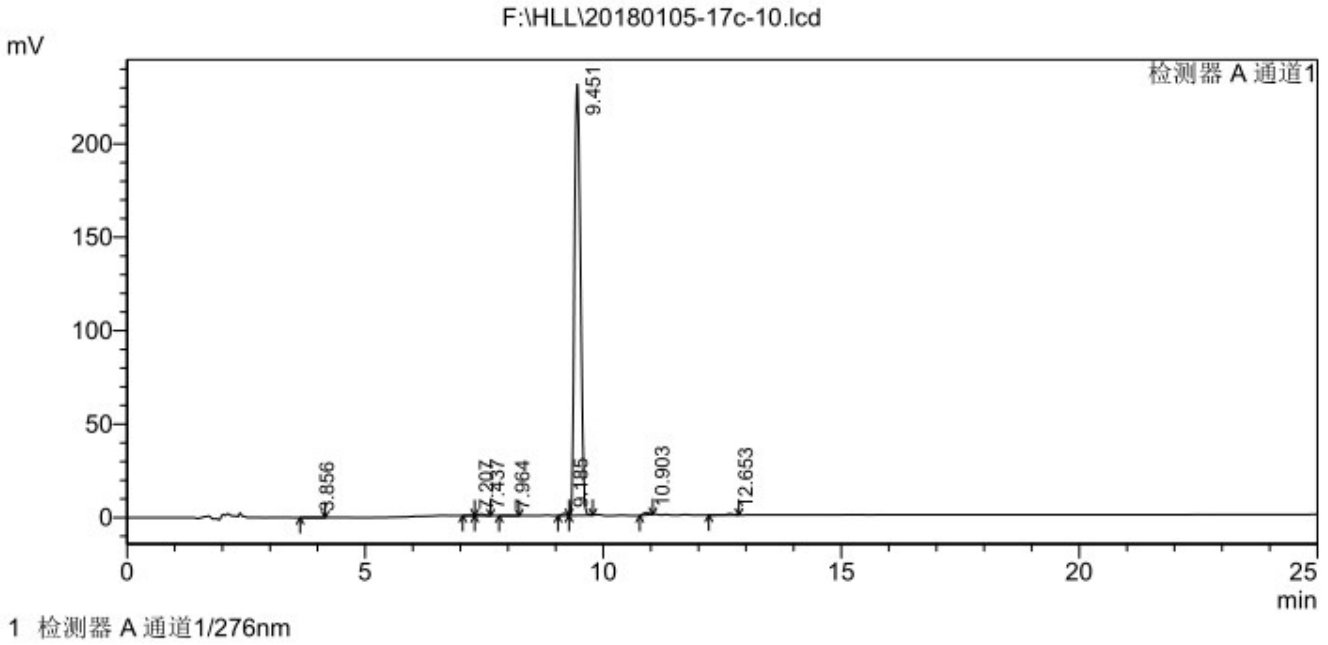
Compound 17c. ^{13}C NMR, DMSO, 125 MHz


MeO
MeO
OMe
OEt
O
S
O
O
NH2
17c
152.70
149.07
147.80
138.99
137.17
135.72
133.89
127.80
127.55
126.98
126.67
123.20
114.31
105.65
64.16
59.98
55.79
37.50
36.15
14.60
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

HR-MS Spectrum of Compound 17c


Waters GCT Premier
20171456 320 (5.333) Cm (320-(51+54))
TOF MS EI+
1.96e4
100
%
0
181.0869
332.1617
123.0448
151.0755
182.0906
333.1647
148.0528
183.0918
65.0392 77.0384
105.0339
167.0723
243.1179
255.0686
285.1114
330.1445
334.1682
411.1352
60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420
m/z

HPLC Spectrum of Compound 17c

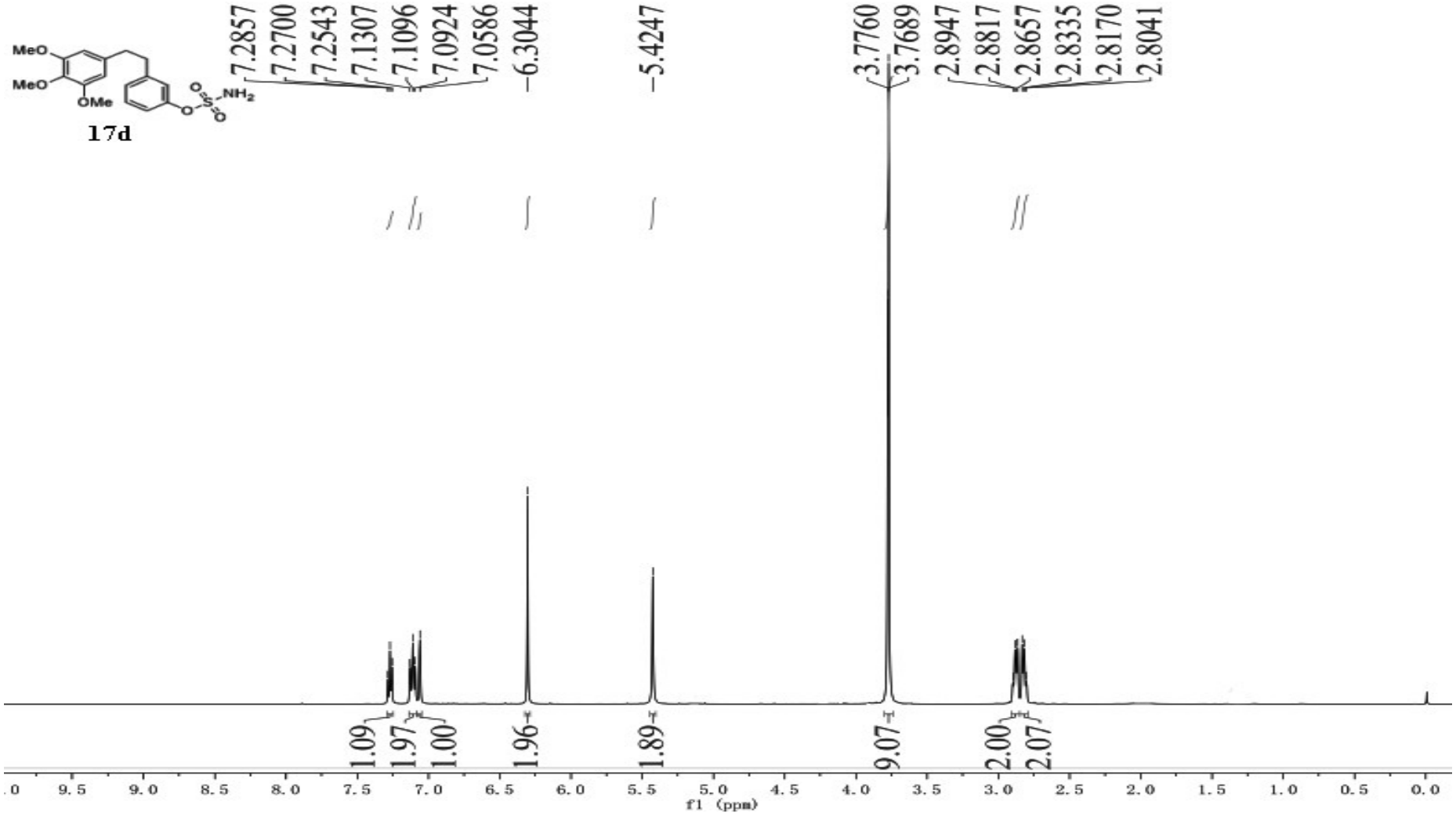


峰表

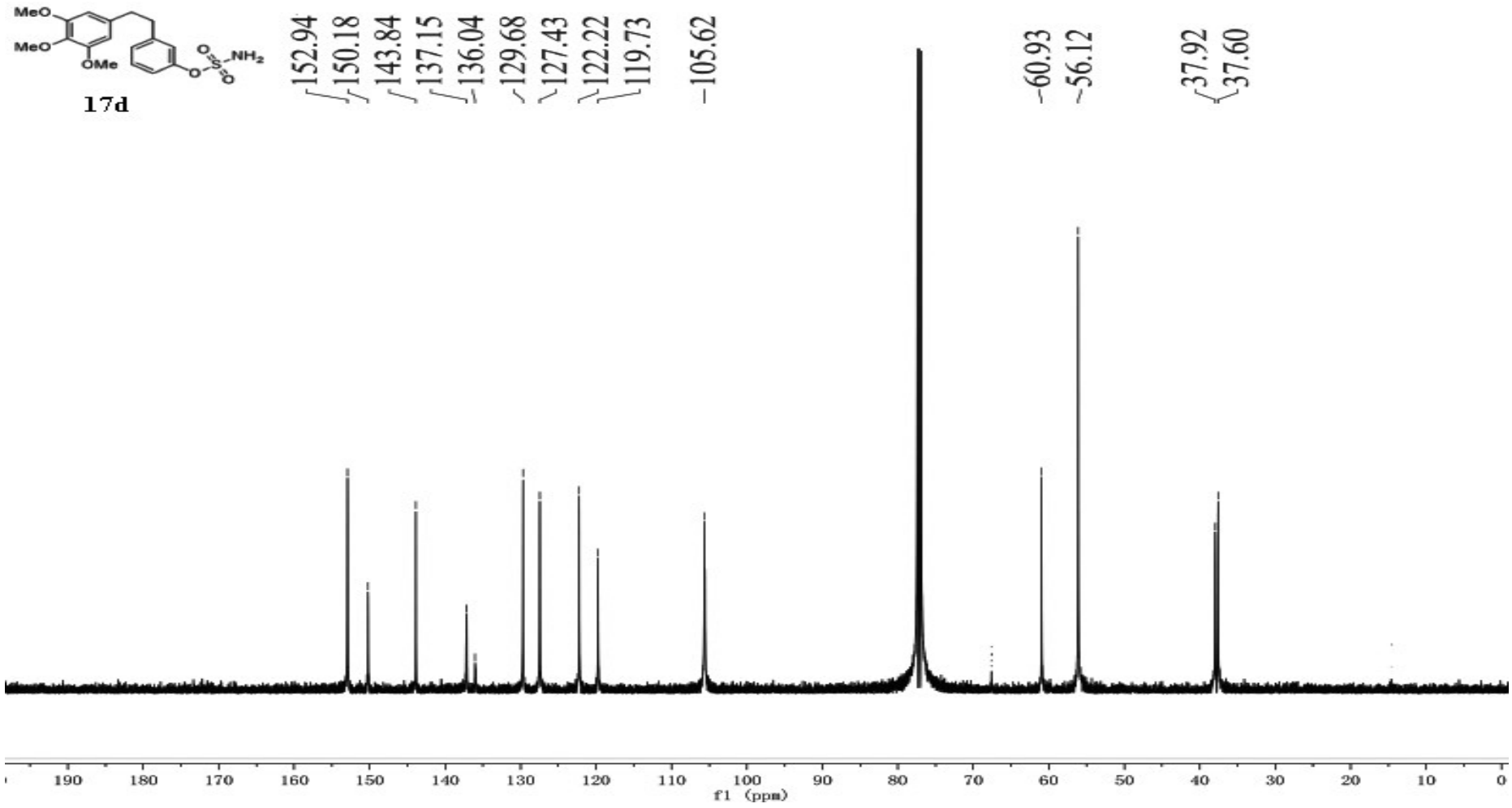
检测器 A Ch1 276nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	3.856	1930	140	0.093	0.060
2	7.207	1435	161	0.069	0.069
3	7.437	7933	843	0.383	0.358
4	7.964	1820	163	0.088	0.069
5	9.185	8642	1067	0.417	0.454
6	9.451	2032398	230837	98.134	98.196
7	10.903	10280	1205	0.496	0.512
8	12.653	6603	662	0.319	0.282
总计		2071042	235078	100.000	100.000

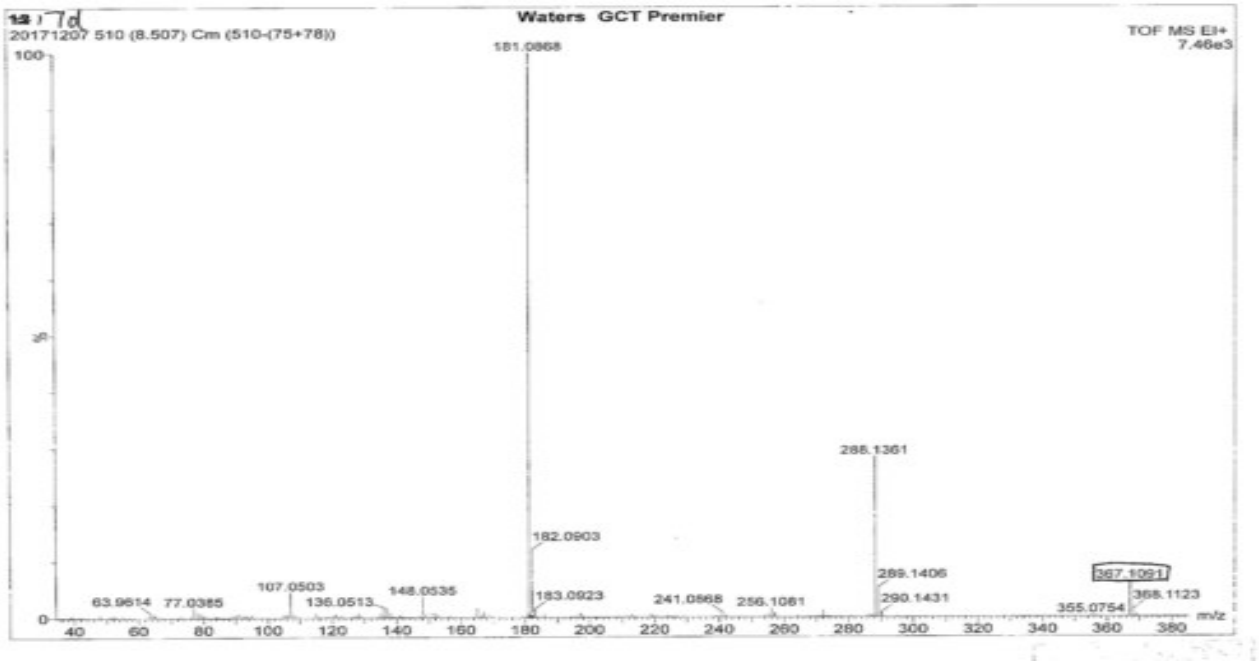
Compound 17d. ^{1}H NMR, $CDCl_3$, 500 MHz



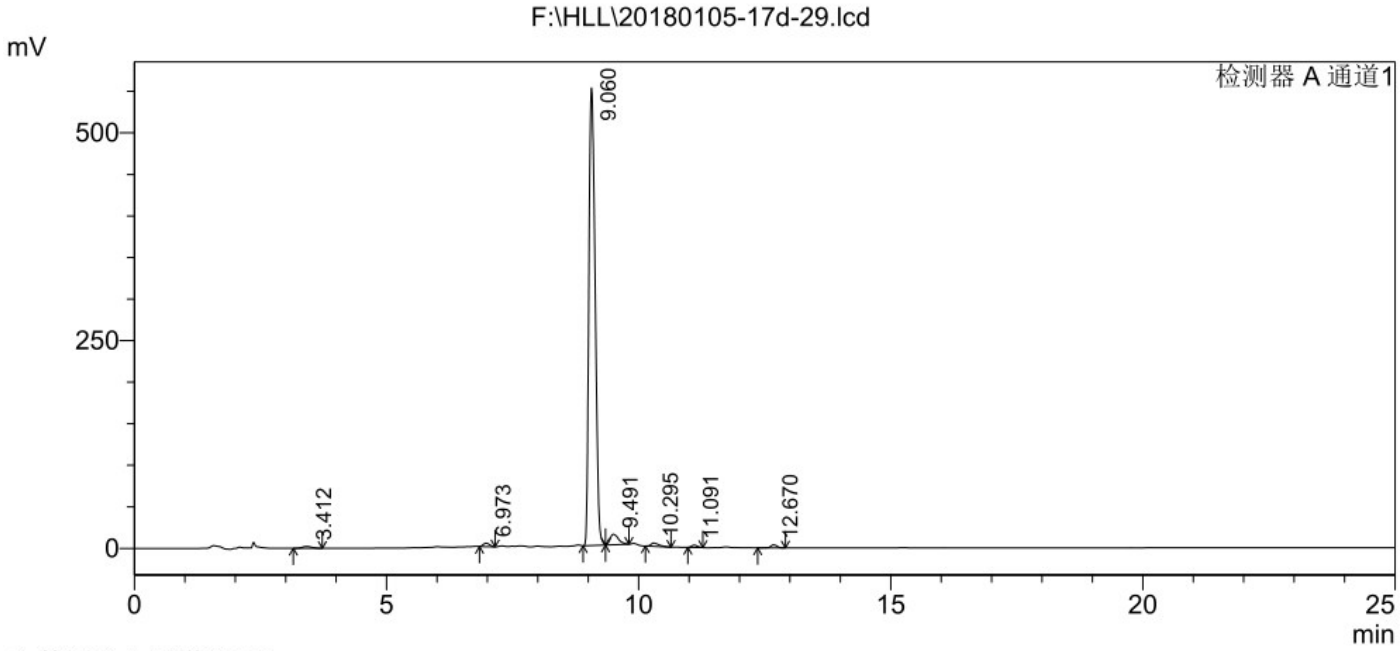
Compound 17d. ^{13}C NMR, $CDCl_3$, 125 MHz


MeO
MeO
OMe
O
S
O
NH2
17d
152.94
150.18
143.84
137.15
136.04
129.68
127.43
122.22
119.73
105.62
60.93
56.12
37.92
37.60
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

HR-MS Spectrum of Compound 17d


Waters GCT Premier
20171207 510 (8.507) Cm (510-(75+78))
TOF MS EI+
7.46e3
181.0868
288.1361
182.0903
289.1406
290.1431
367.1091
368.1123
183.0923
241.0868
256.1081
355.0754
63.9614
77.0385
107.0503
136.0513
148.0535
100
%
0
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
m/z

HPLC Spectrum of Compound 17d



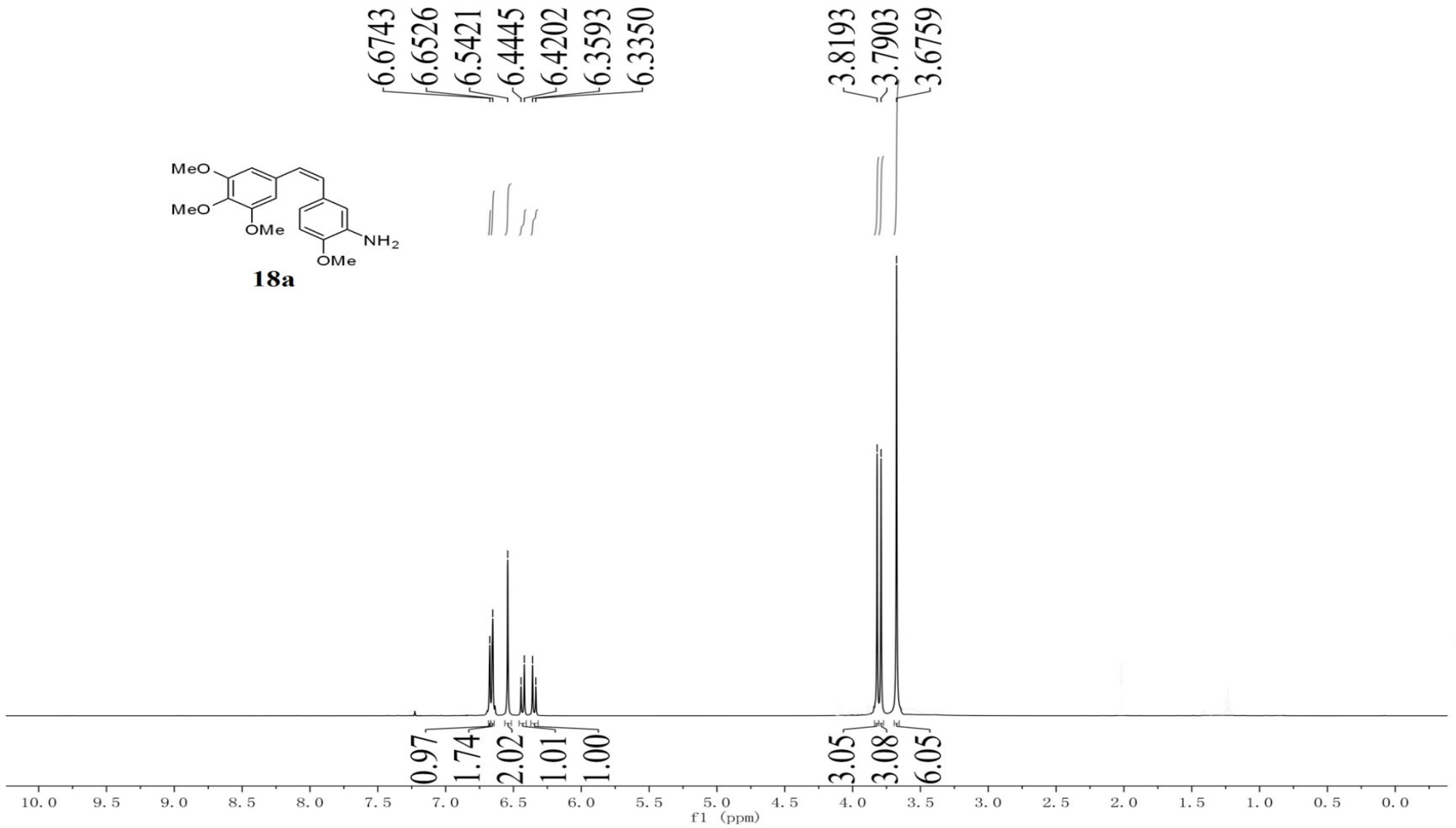
1 检测器 A 通道1/276nm

峰表

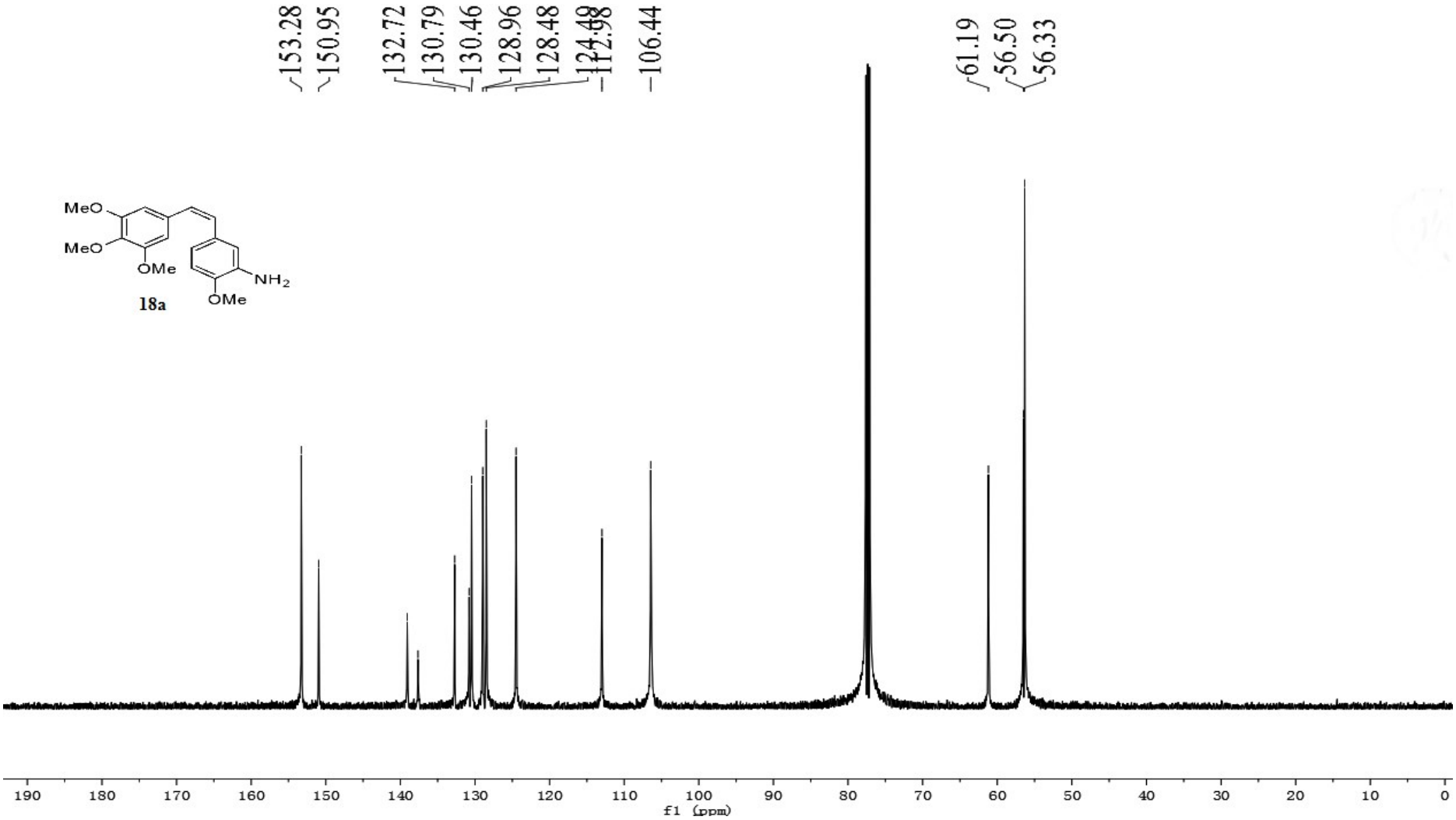
检测器 A Ch1 276nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	3.412	29600	2268	0.587	0.391
2	6.973	35950	4149	0.713	0.715
3	9.060	4728066	550993	93.794	94.945
4	9.491	148428	12651	2.944	2.180
5	10.295	45359	4046	0.900	0.697
6	11.091	21860	2653	0.434	0.457
7	12.670	31662	3567	0.628	0.615
总计		5040925	580326	100.000	100.000

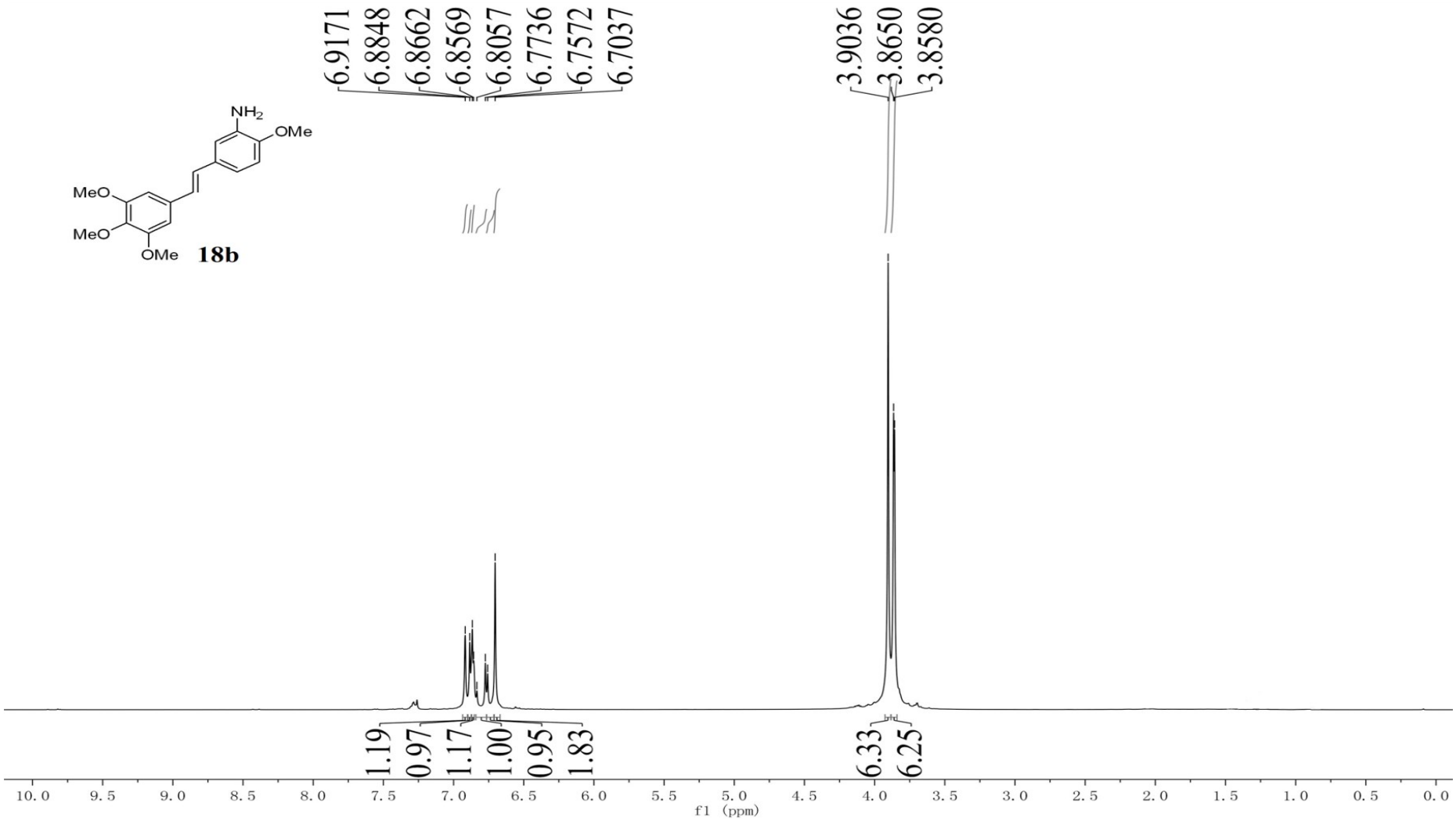
Compound 18a. ^{1}H NMR, $CDCl_3$, 500 MHz


6.6743
6.6526
6.5421
6.4445
6.4202
6.3593
6.3350
3.8193
3.7903
3.6759
MeO
MeO
OMe
NH2
OMe
18a
0.97
1.74
2.02
1.01
1.00
3.05
3.08
6.05
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

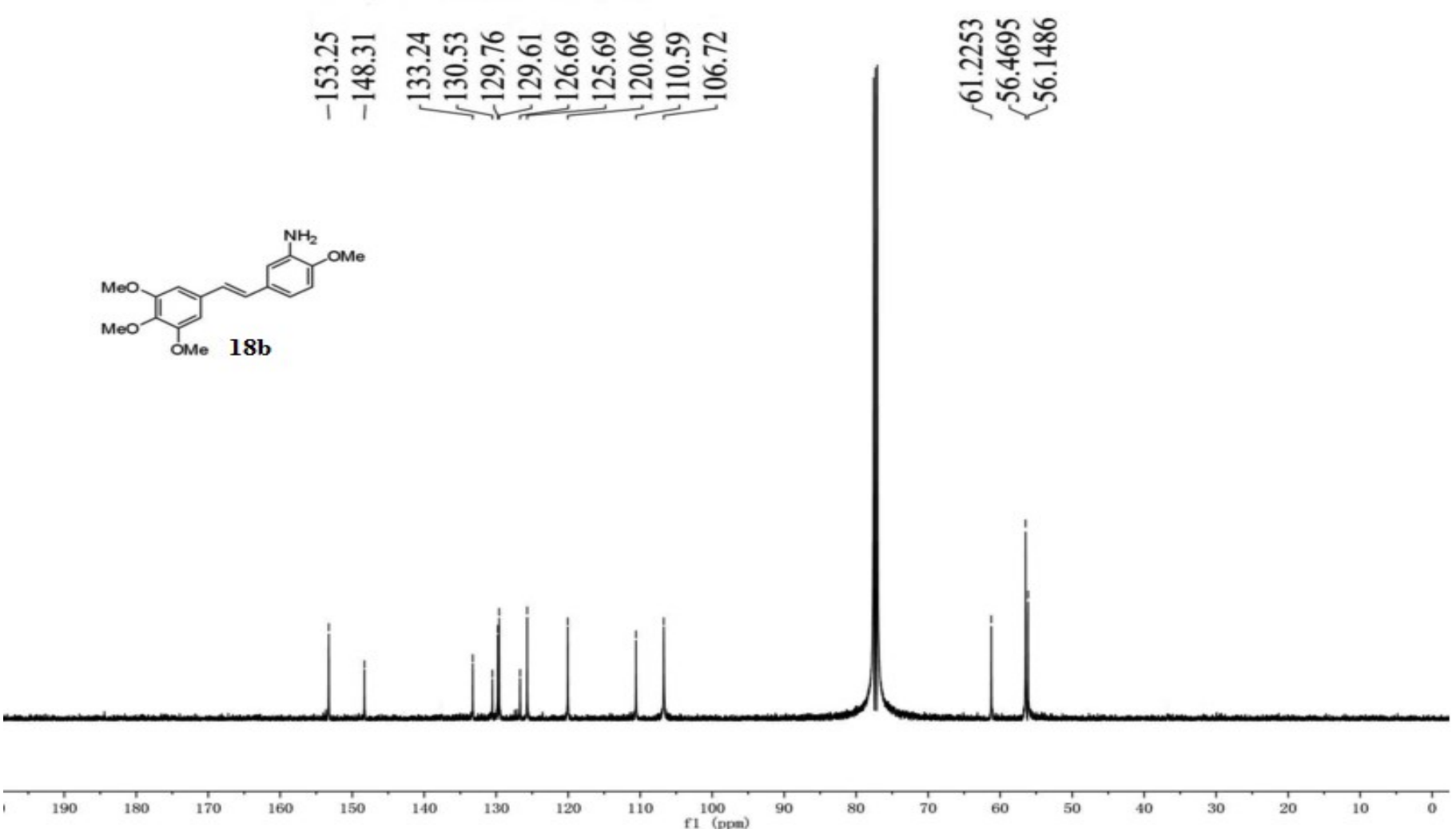
Compound 18a. ^{13}C NMR, $CDCl_3$, 125 MHz



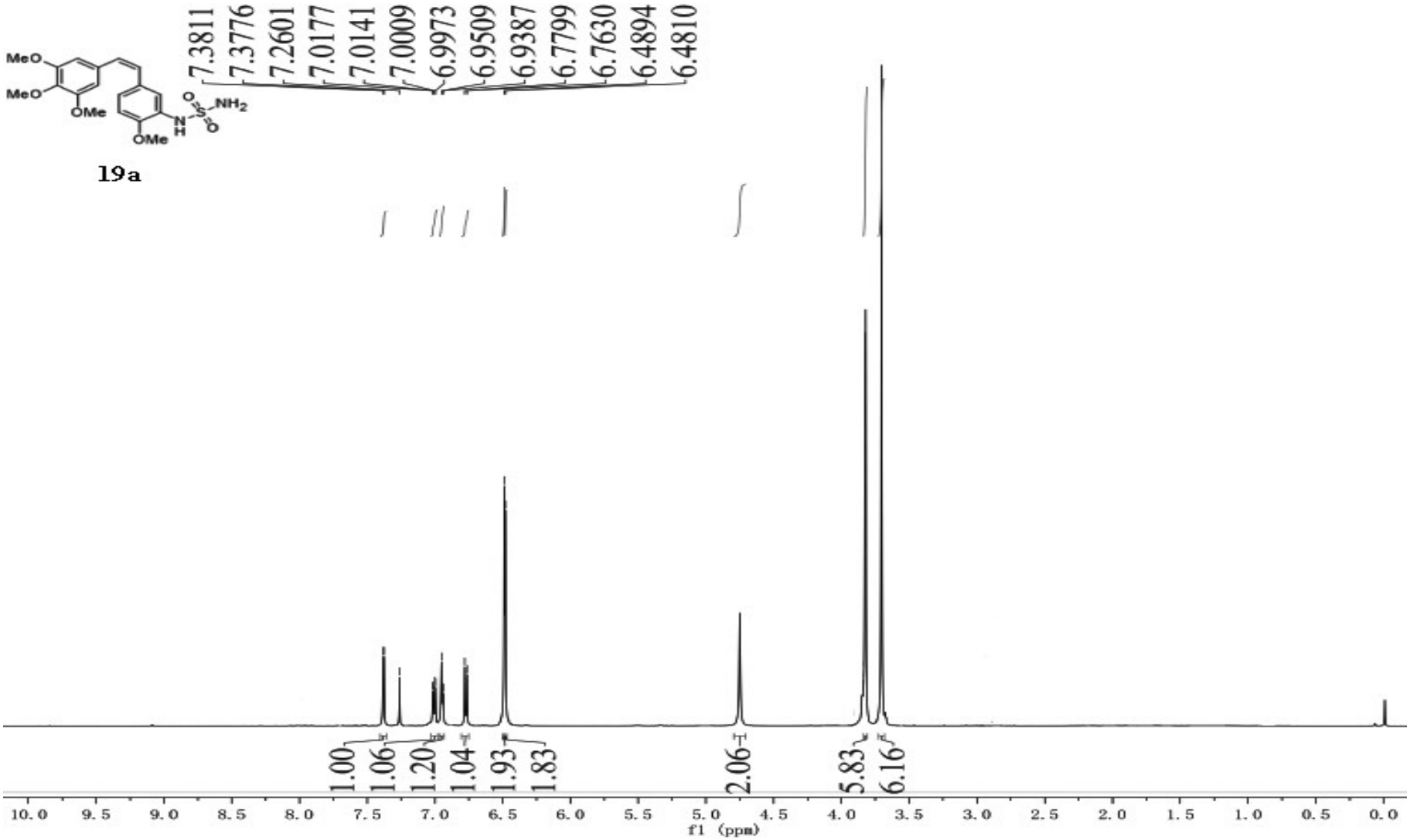
Compound 18b. ^{1}H NMR, $CDCl_3$, 500 MHz



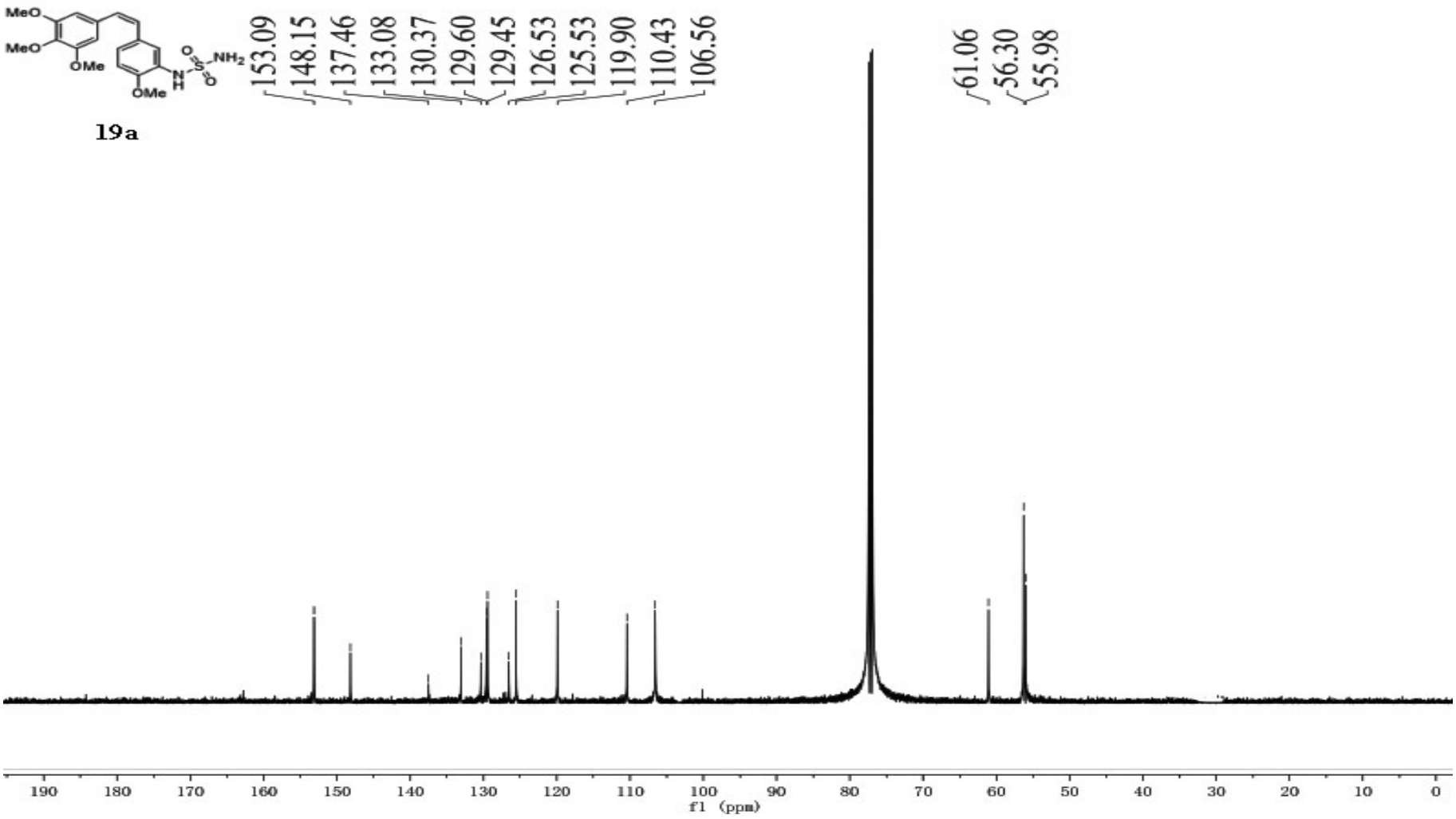
Compound 18b. ^{13}C NMR, $CDCl_3$, 125 MHz



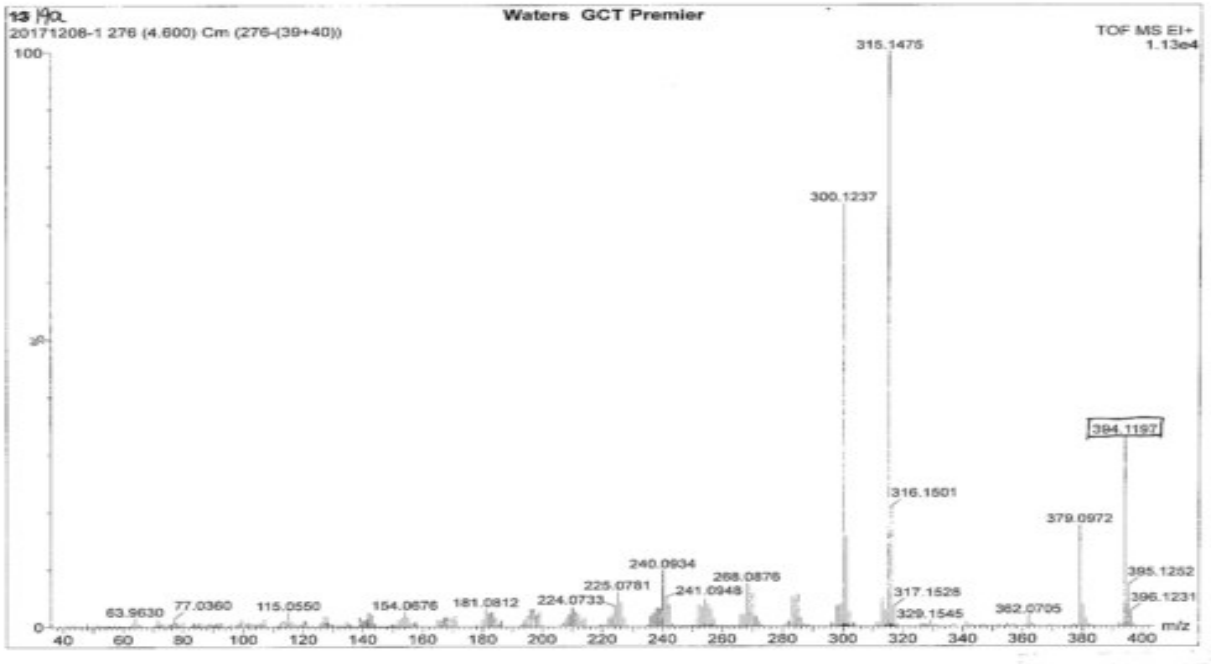
Compound 19a. ^{1}H NMR, $CDCl_3$, 500 MHz



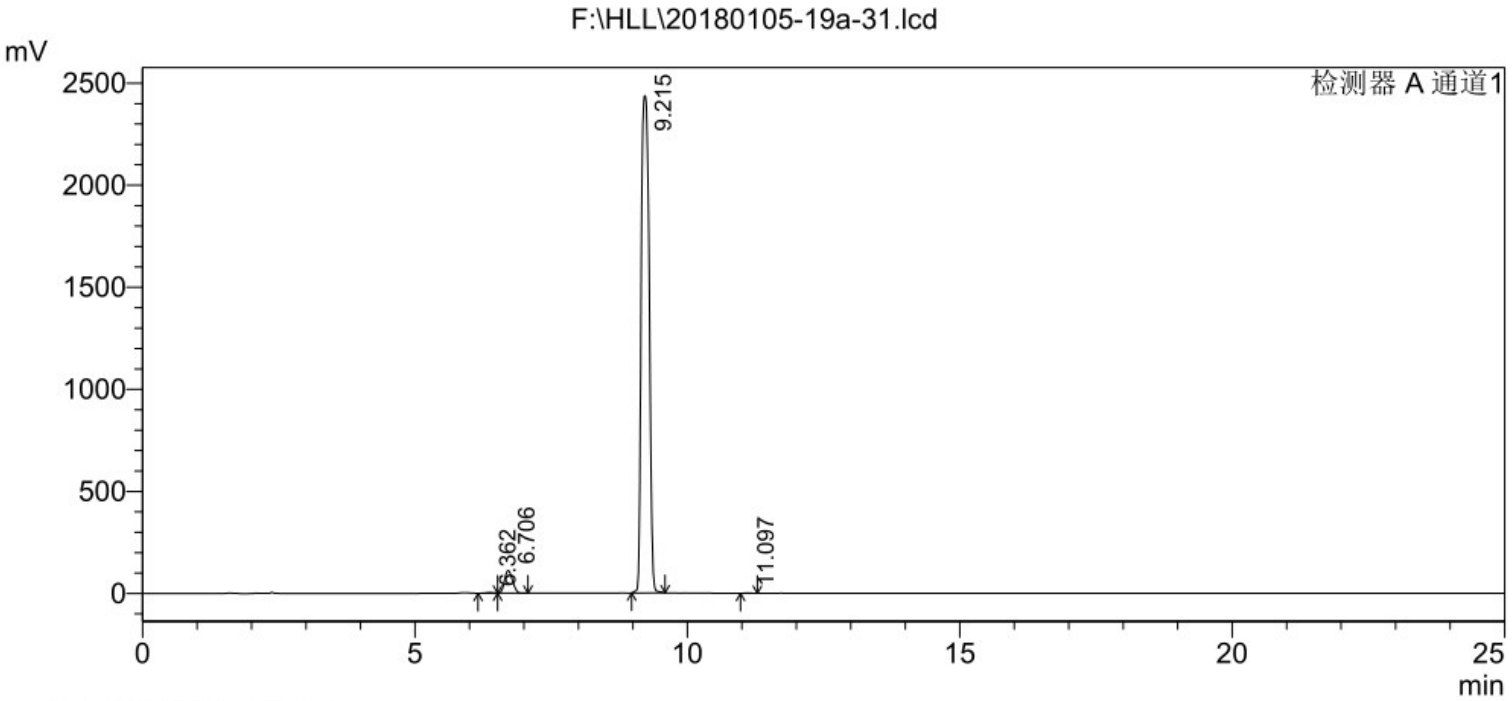
Compound 19a. ^{13}C NMR, $CDCl_3$, 125 MHz



HR-MS Spectrum of Compound 19a


Waters GCT Premier
20171208-1 276 (4.600) Cm (276-(39+40))
TOF MS EI+
1.13e4
100
%
0
315.1475
300.1237
394.1197
316.1501
379.0972
240.0934
268.0876
225.0781
241.0948
224.0733
181.0812
154.0676
115.0550
77.0360
63.9630
317.1528
329.1545
382.0705
395.1252
396.1231
m/z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400

HPLC Spectrum of Compound 19a



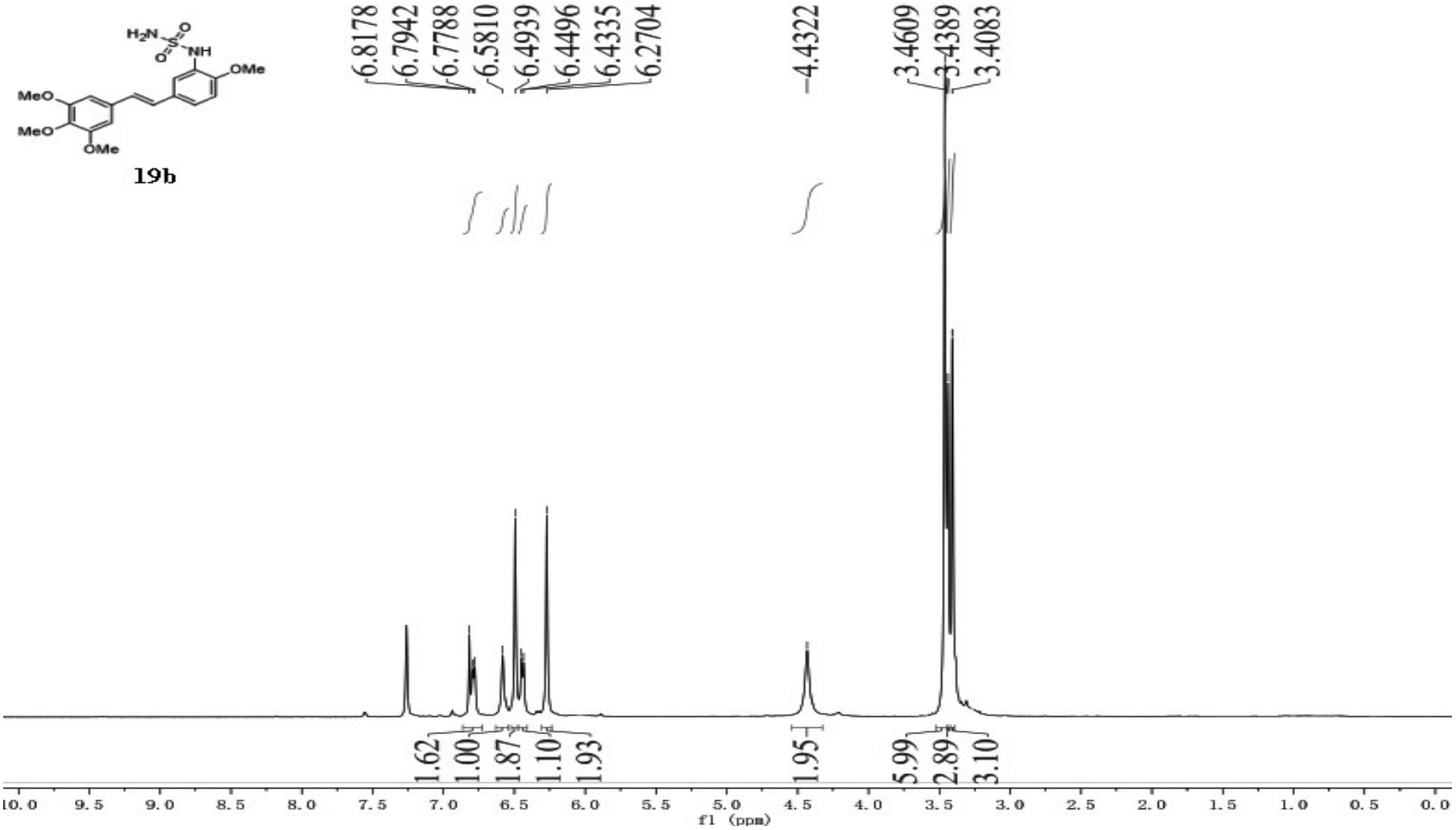
1 检测器 A 通道1/276nm

峰表

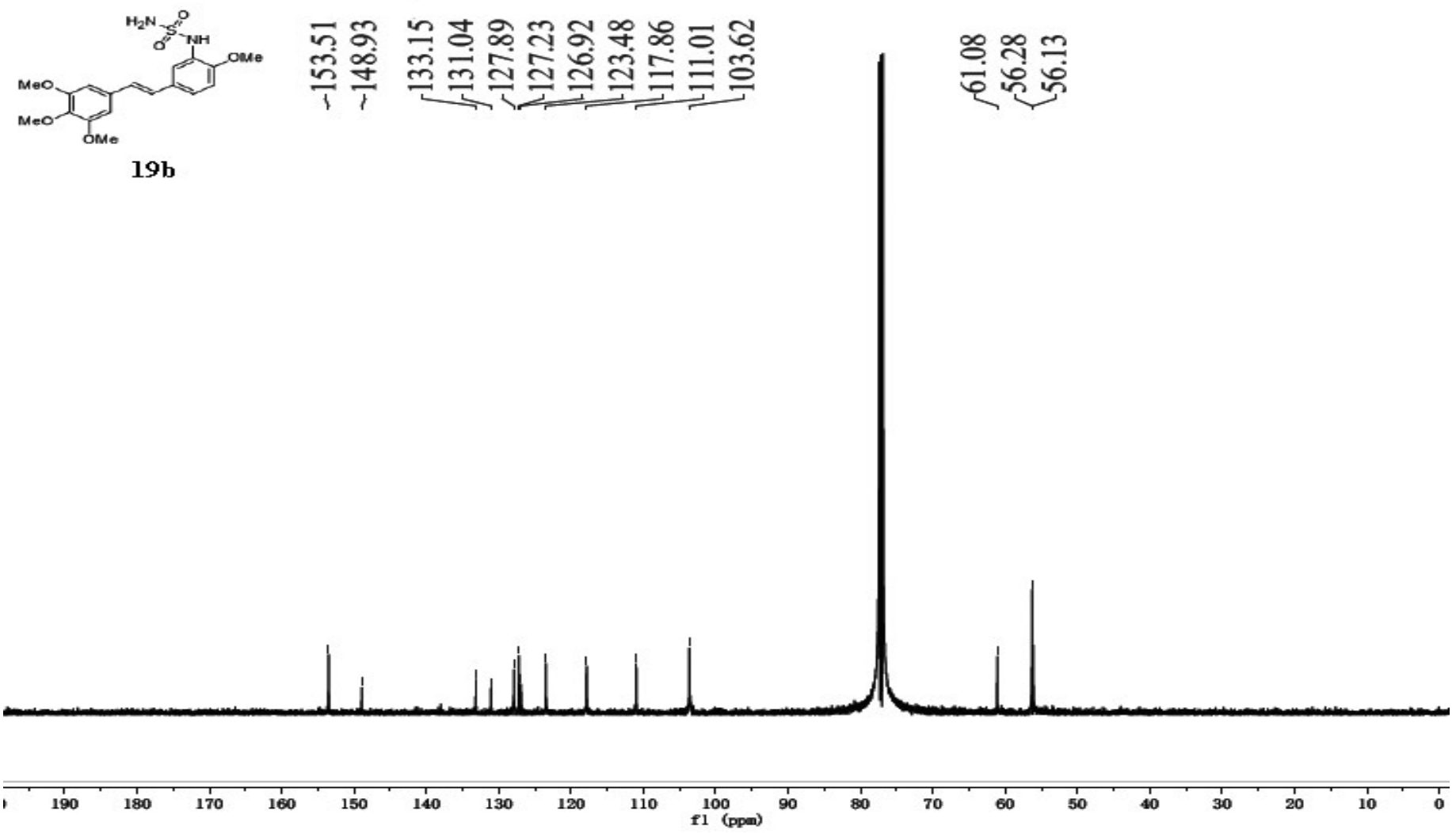
检测器 A Ch1 276nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	6.362	35707	3313	0.138	0.130
2	6.706	1128465	111793	4.371	4.377
3	9.215	24643151	2437373	95.447	95.437
4	11.097	11438	1416	0.044	0.055
总计		25818762	2553896	100.000	100.000

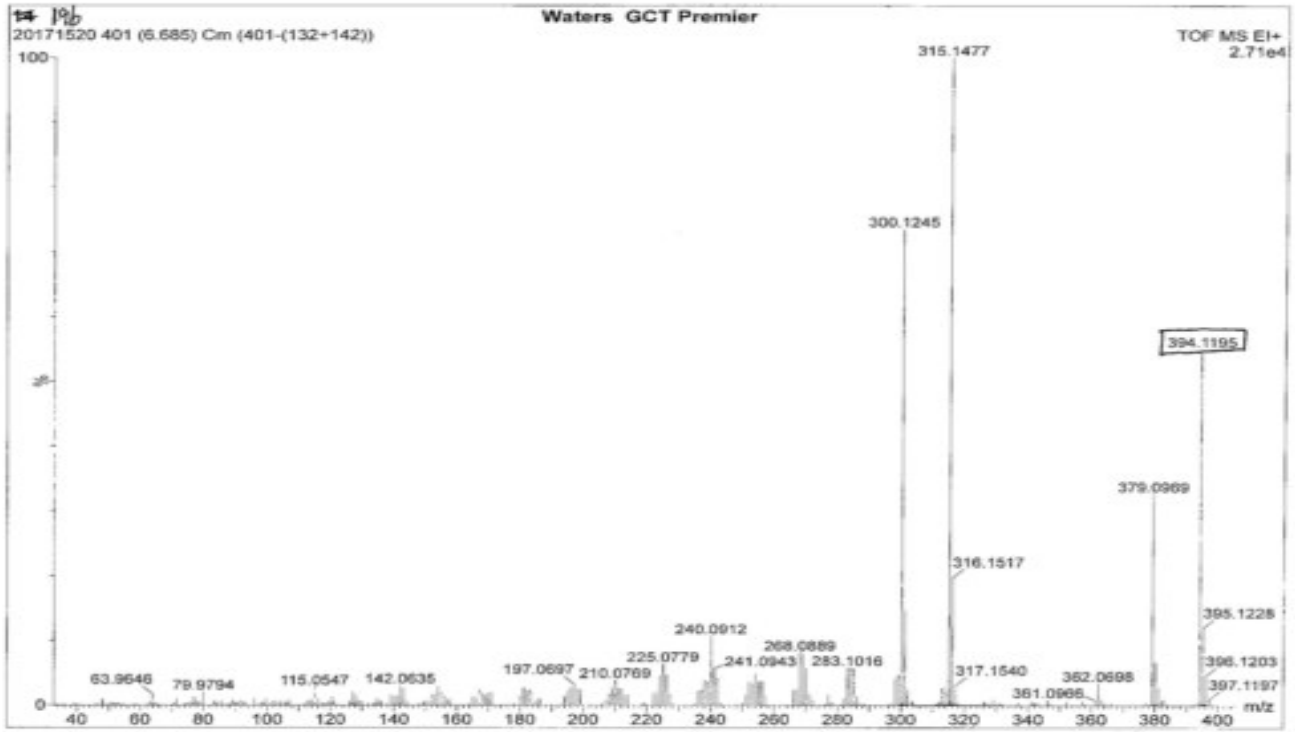
Compound 19b. ^{1}H NMR, $CDCl_3$, 500 MHz



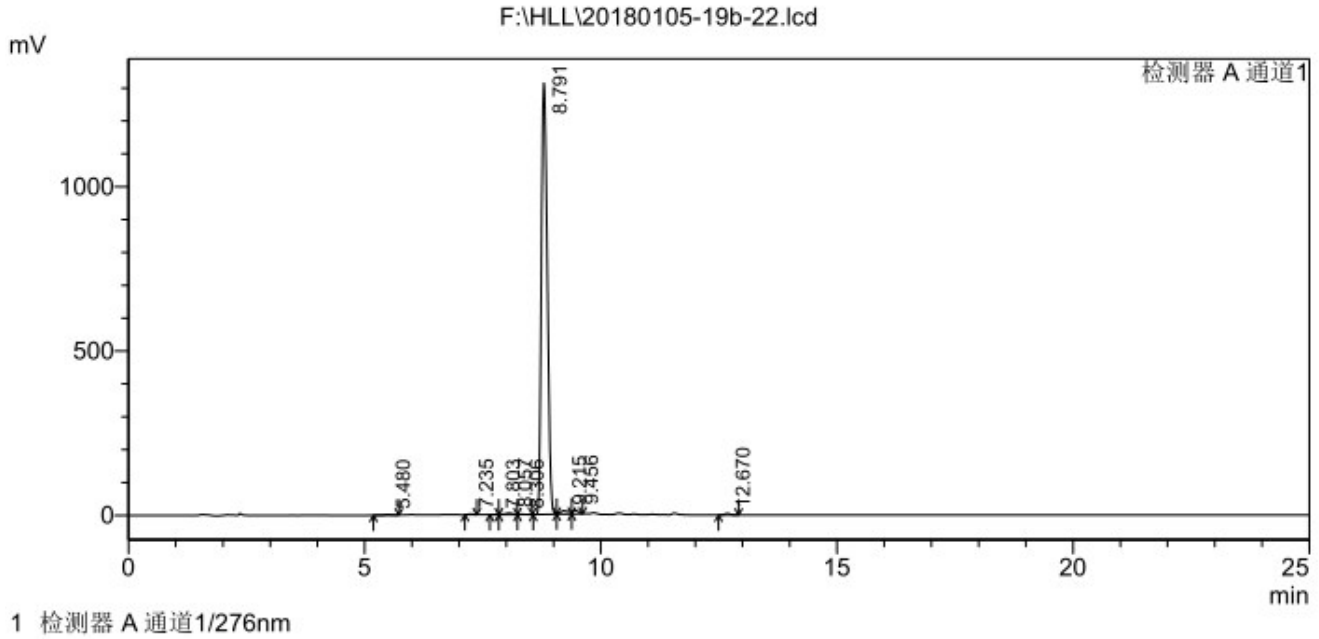
Compound 19b. ^{13}C NMR, $CDCl_3$, 125 MHz


19b
153.51
148.93
133.15
131.04
127.89
127.23
126.92
123.48
117.86
111.01
103.62
61.08
56.28
56.13
f1 (ppm)

HR-MS Spectrum of Compound 19b


Waters GCT Premier
20171520 401 (6.685) Cm (401-(132+142))
TOF MS EI+
2.71e4
100
%
0
315.1477
300.1245
394.1195
379.0969
316.1517
395.1228
396.1203
397.1197
240.0912
268.0889
225.0779
241.0943
283.1016
197.0697
210.0769
317.1540
362.0698
361.0966
63.9646
79.9794
115.0547
142.0635
m/z
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400

HPLC Spectrum of Compound 19b



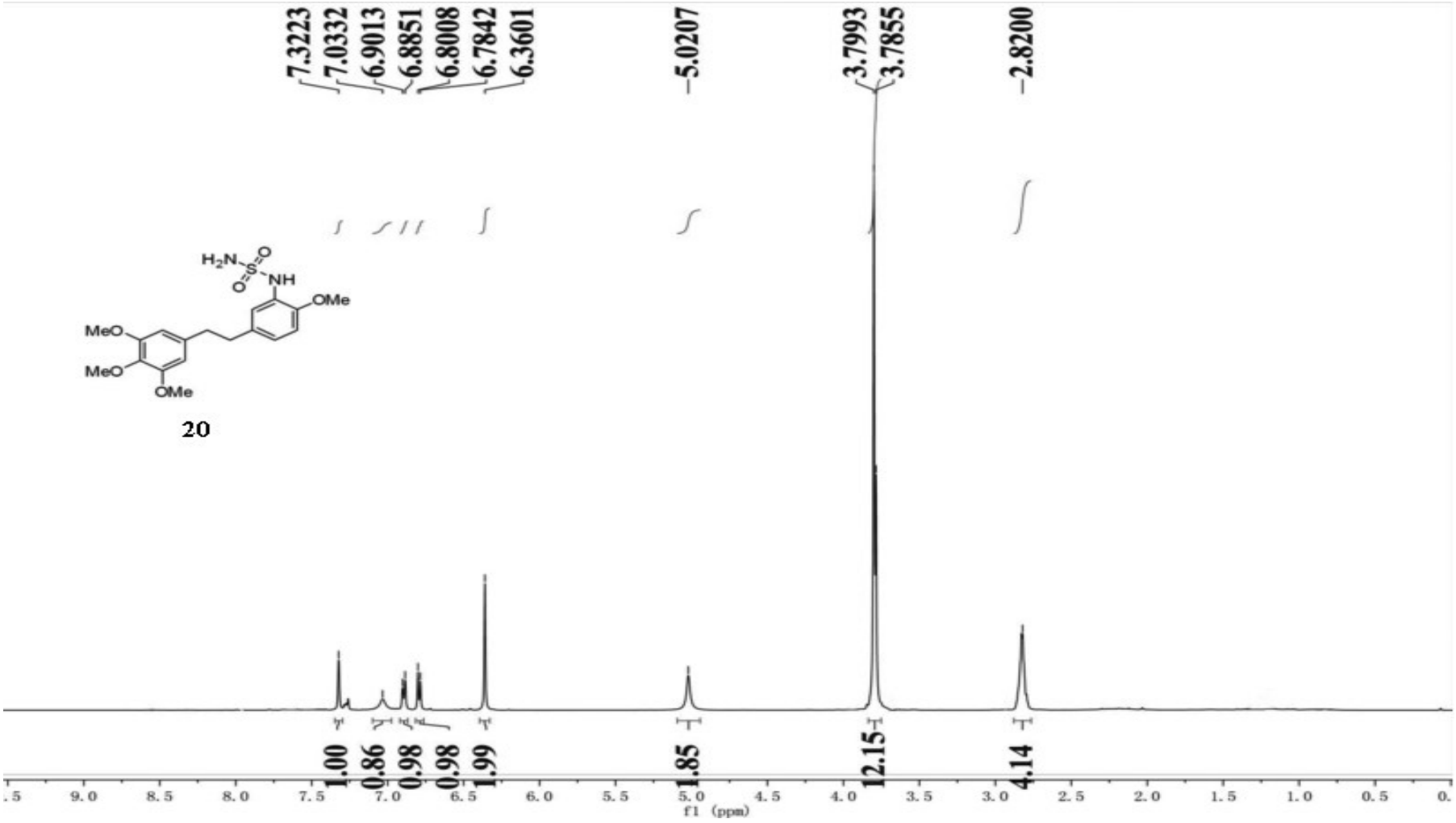
1 检测器 A 通道1/276nm

峰表

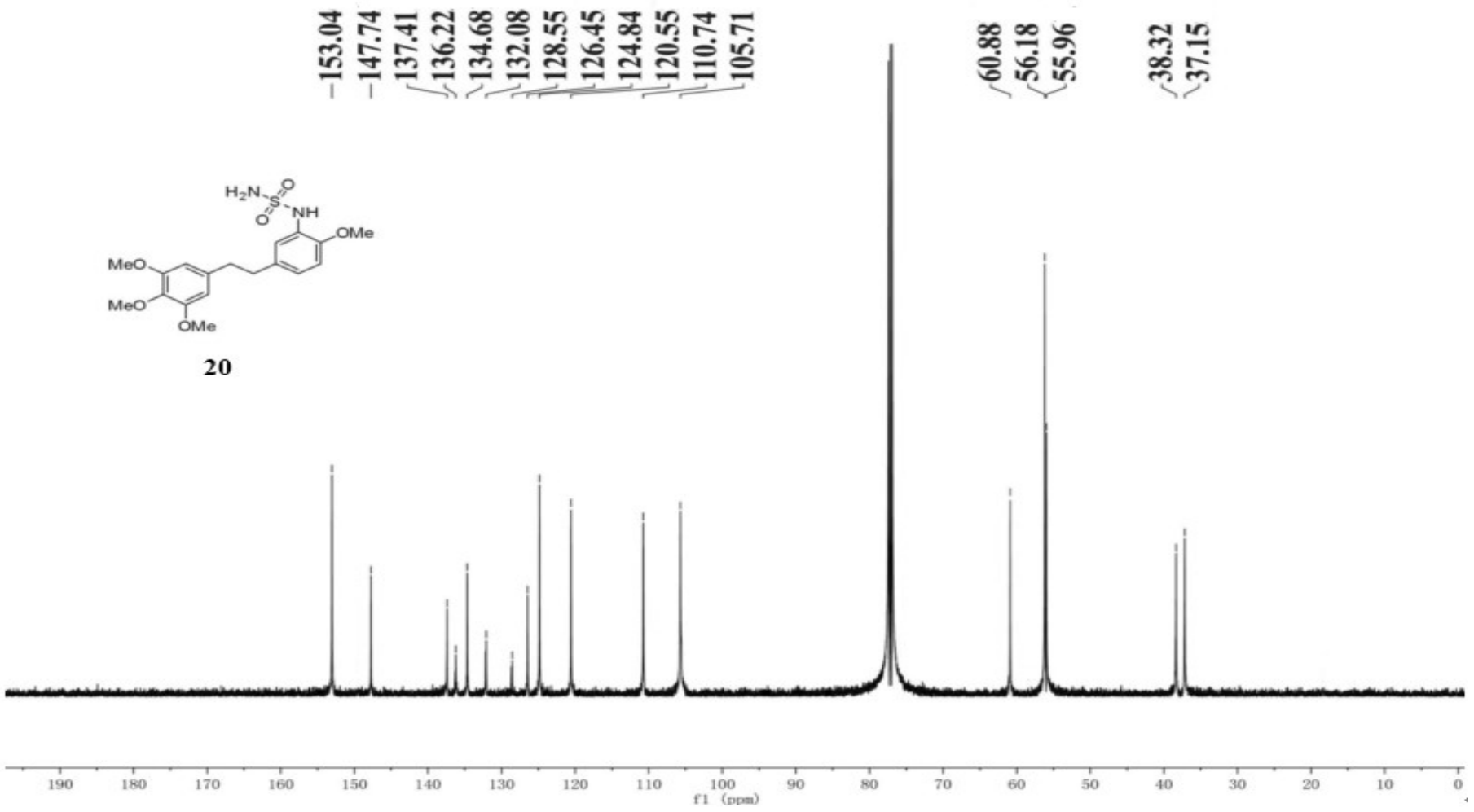
检测器 A Ch1 276nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	5.480	16005	1114	0.135	0.083
2	7.235	16719	2121	0.141	0.157
3	7.803	9204	1523	0.077	0.113
4	8.057	61842	4631	0.520	0.343
5	8.306	13515	1366	0.114	0.101
6	8.791	11506218	1312769	96.838	97.293
7	9.215	131130	10057	1.104	0.745
8	9.456	85787	10902	0.722	0.808
9	12.670	41554	4810	0.350	0.356
总计		11881973	1349293	100.000	100.000

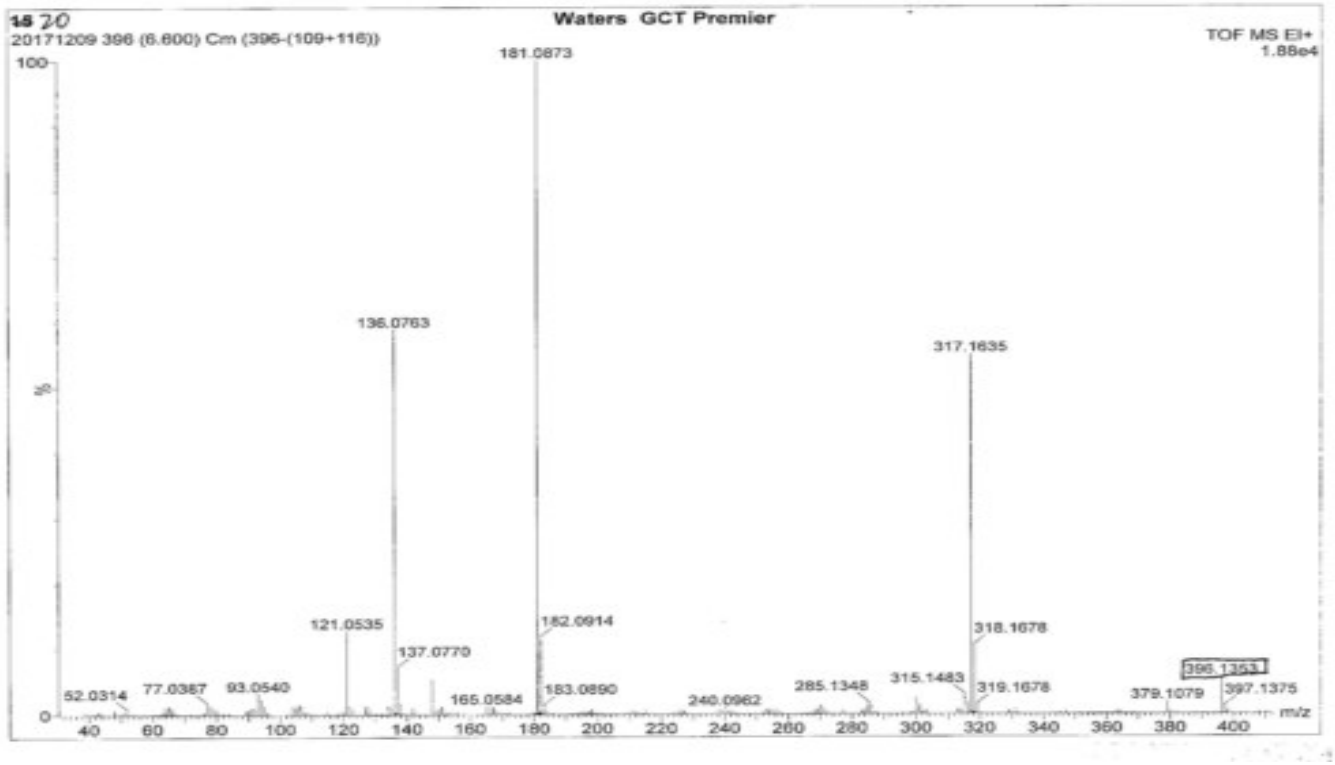
Compound 20. ^{1}H NMR, $CDCl_3$, 500 MHz



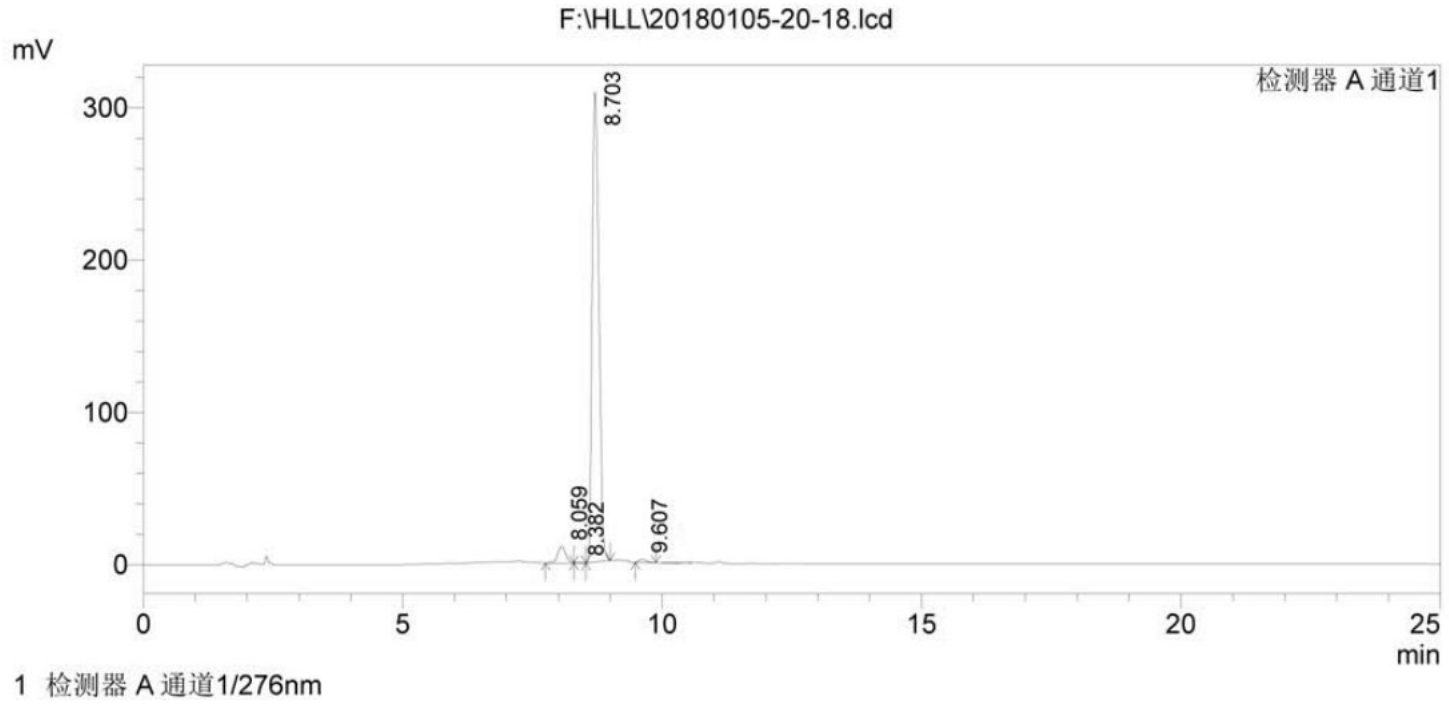
Compound 20. ^{13}C NMR, $CDCl_3$, 125 MHz



HR-MS Spectrum of Compound 20


18 20
Waters GCT Premier
20171209 396 (6.600) Cm (396-(109+116))
TOF MS EI+
1.88e4
100
%
0
181.0873
136.0763
317.1635
121.0535
182.0914
137.0770
318.1678
396.1353
397.1375
52.0314
77.0387
93.0540
165.0584
183.0890
240.0962
285.1348
315.1483
319.1678
379.1079
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400
m/z

HPLC Spectrum of Compound 20



峰表

检测器 A Ch1 276nm

峰#	保留时间	面积	高度	面积 %	高度 %
1	8.059	116890	10901	3.980	3.381
2	8.382	4646	528	0.158	0.164
3	8.703	2794785	308899	95.164	95.807
4	9.607	20484	2090	0.697	0.648
总计		2936806	322418	100.000	100.000

The antiproliferation effect of 16a,16i and CA-4 on six tumor cells

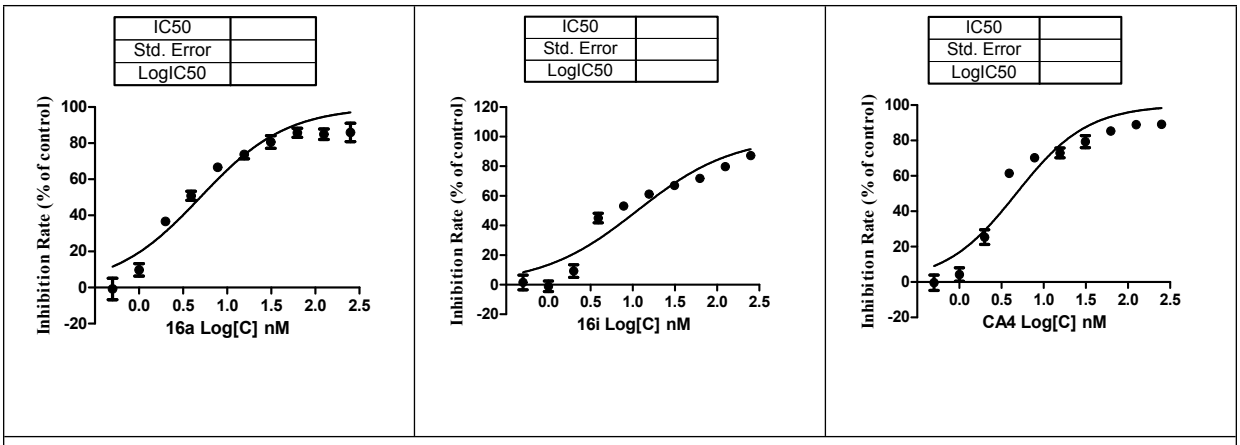


Figure 1：Antiproliferation inhibition 16a、16i and CA4 on HCT-116 cell，Mean ± SD，n=5。

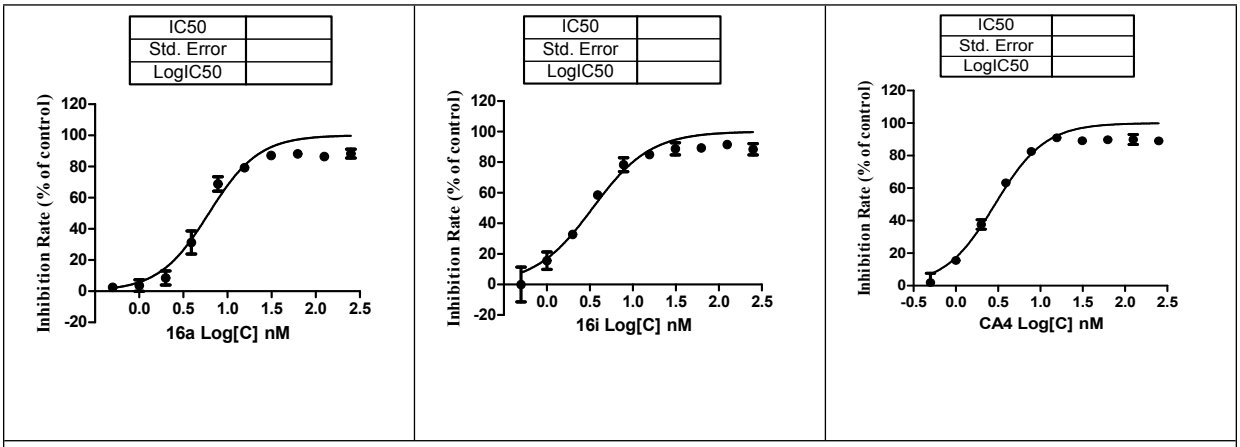


Figure 2：Antiproliferation inhibition 16a、16i and CA4 on Hela cell，Mean ± SD，n=5。

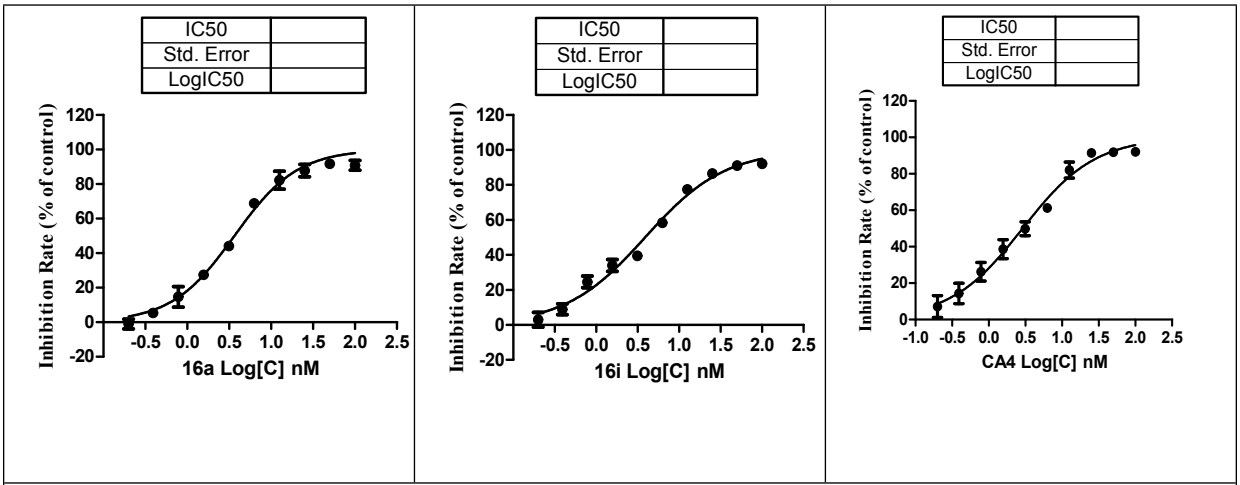


Figure 3：Antiproliferation inhibition 16a、16i and CA4 on HeGp2 cell，Mean ± SD，n=5。

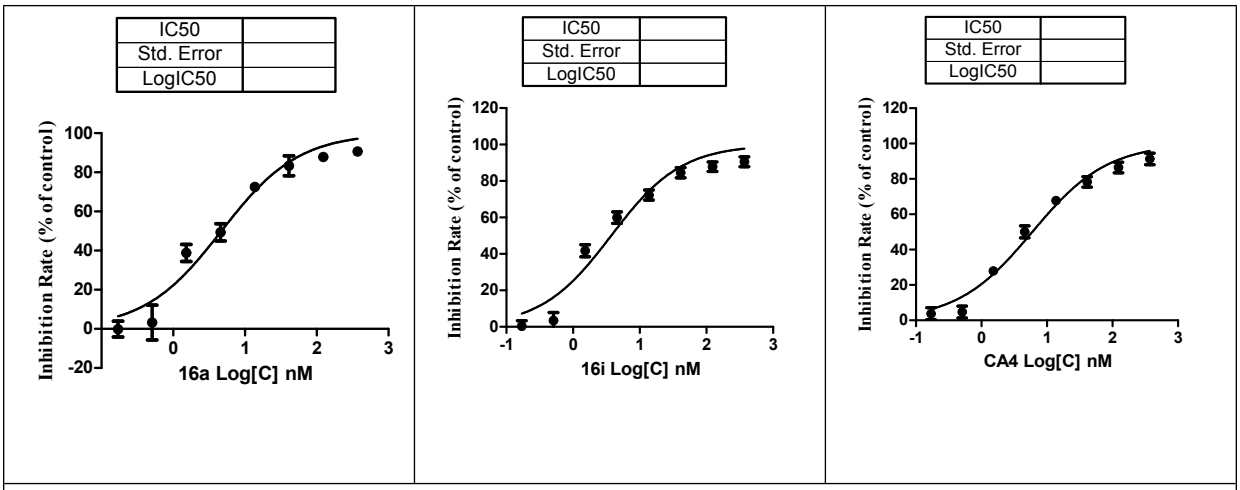


Figure 4：Antiproliferation inhibition 16a、16i and CA4 on MGC-803 cell，Mean ± SD，n=5。

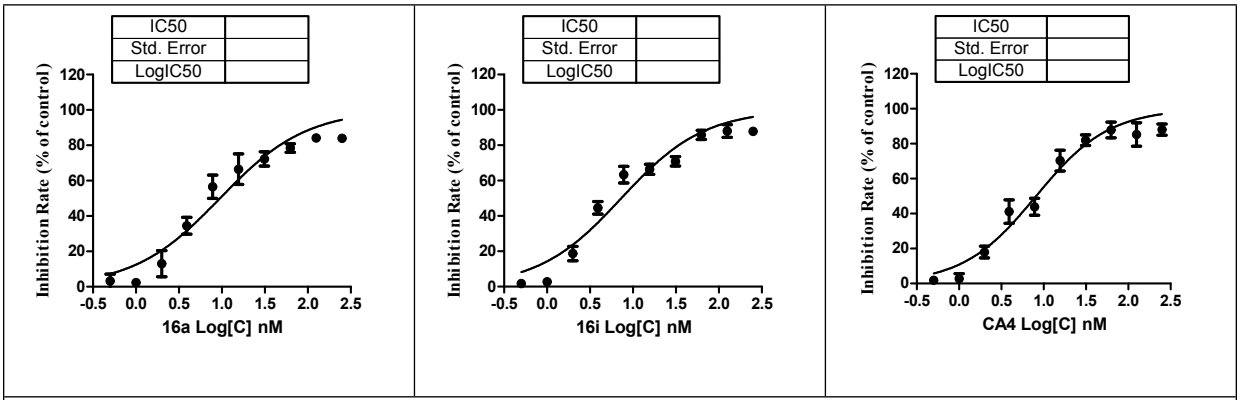


Figure 5：Antiproliferation inhibition 16a、16i and CA4 on MKN45 cell，Mean ± SD，n=5。

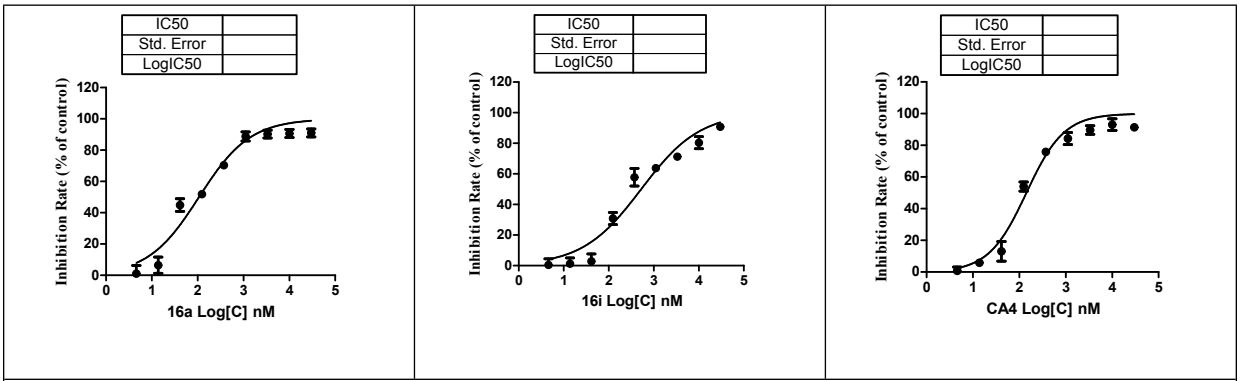


Figure 6：Antiproliferation inhibition 16a、16i and CA4 on MCF-7 cell，Mean ± SD，n=5。