Radical Beckmann Rearrangement and Its Application in the Formal Total Synthesis of Antimalarial Natural Product Isocryptolepine via C-H Activation

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1. General information:

All reagents and solvents were used as received from commercial sources. All experiments were carried out under argon atmosphere unless otherwise noted. Ketoximes/aldoximes were prepared as per the known procedure.[1] ^{18}O-enriched $NaN^{18}O_2$ was prepared according to the literature procedure.[2] Pre-coated plates (silica gel 60 PF254, 0.25 mm or 0.5 mm) were utilized for thin layer chromatography (TLC). Column chromatographic purifications were carried out on flash silica-gel (240–400 mesh) using petroleum ether and ethyl acetate as eluents. The ^{1}H, ^{13}C NMR spectra were recorded on 200/400/500 MHz, and 50/100/125 MHz NMR spectrometers, respectively in $CDCl_3$/DMSO-d_6. Chemical shifts were reported as δ values from standard peaks. Melting points were recorded are uncorrected. Mass spectra were taken on LC-MS (ESI) or GC-MS spectrometer. HRMS were scanned at NCL, Pune.

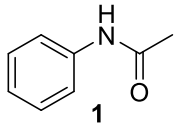
2. General experimental procedure for the radical Beckmann rearrangement:

All the reactions were performed on 50 mg of ketoxime/aldoxime.

The solution of ketoxime (1 equiv), ammonium persulfate (1.5 equiv) and DMSO (6 equiv) in 1,4-dioxane (2 mL) was heated at 100 ^{o}C in a Schlenk tube under argon atmosphere until completion of the reaction as indicated by thin layer chromatography. After completion, the reaction mixture was filtered through a cotton plug and 1,4-dioxane was evaporated under vacuum. The residue was dissolved in ethyl acetate (10 mL) and washed with warm water (4 mL) and brine (3 mL x 2). The organic layer was dried over anhydrous sodium sulfate and the crude product was purified by flash column chromatography using a gradient of ethyl acetate and petroleum ether to furnish corresponding amides in good to excellent yields.

3. Characterization Data of Beckmann rearrangement products:

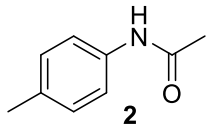
***N*-phenylacetamide:**[3]



1

Reaction time: 3 h; R_f = 0.3 (EtOAc:Pet. Ether, 2:3). White solid; 46.6 mg, 93%, mp 114-115 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (bs, 1H), 7.51 (d, J = 7.8 Hz, 2H), 7.30 (t, J = 7.3 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 137.8, 128.9, 124.3, 120.0, 24.4; GC-MS (M^+) 135.

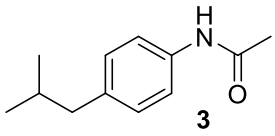
***N*-(p-tolyl)acetamide:**[3]



2

Reaction time: 1 h; R_f = 0.3 (EtOAc:Pet. Ether, 2:3). White solid; 46 mg, 92%, mp 151-153 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (bs, 1H), 7.38 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 2.31 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 135.3, 133.9, 129.4, 120.0, 24.5, 20.8; GC-MS (M^+) 149.

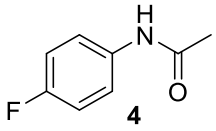
***N*-(4-isobutylphenyl)acetamide**:



3

Reaction time: 5 h; R_f = 0.3 (EtOAc:Pet. Ether, 2:3). White solid; 49 mg, 98%, mp 127-130 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (bs, 1H), 7.40 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 2.43 (d, J = 7.3 Hz, 2H), 2.16 (s, 3H), 1.83 (m, 1H), 0.89 (d, J = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 137.8, 135.5, 129.5, 119.8, 44.8, 30.2, 24.5, 22.3; HRMS-ESI (*m*/*z*) calcd $[C_{12}H_{17}ON+H]^{+}$: 192.1383, found 192.1380.

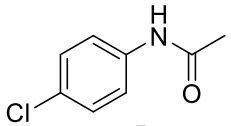
***N*-(4-fluorophenyl)acetamide:**[4]



4

Reaction time: 8 h; R_f = 0.4 (EtOAc:Pet. Ether, 2:3). White solid; 37.7 mg, 75%, mp 154-156 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (bs, 1H), 7.45 (dd, J_1 = 4.9 Hz, J_2 = 9.0 Hz, 2H), 7.00 (t, J = 8.6 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 160.6 and 158.1 (d, J = 243.5 Hz, 1C), 133.8, 121.83 and 121.76 (d, J = 7.7 Hz, 1C), 115.7 and 115.5 (d, J = 22.4 Hz, 1C), 24.3; GC-MS (M^{+}) 153.

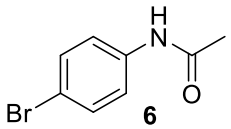
***N*-(4-chlorophenyl)acetamide:**[4]



5

Reaction time: 8 h; R_f = 0.4 (EtOAc:Pet. Ether, 2:3). White solid; 37.2 mg, 74%, mp 177-180 ^oC; ^1H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, J = 8.2 Hz, 2H), 7.29-7.27 (m, 3H), 2.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.3, 136.4, 129.3, 129.0, 121.1, 24.6; GC-MS (M^+) 169.

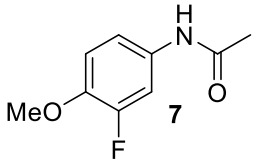
***N*-(4-bromophenyl)acetamide:**[5]



6

Reaction time: 8 h; R_f = 0.4 (EtOAc:Pet. Ether, 2:3). White solid; 41.1 mg, 82%, mp 165-168 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (s, 4H), 7.35 (bs, 1H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 136.9, 131.9, 121.3, 116.8, 24.6; GC-MS (M^+) 213.

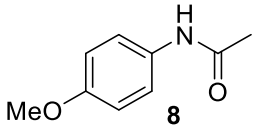
***N*-(3-fluoro-4-methoxyphenyl)acetamide:**



7

Reaction time: 4 h; R_f = 0.5 (EtOAc:Pet. Ether, 1:1). White solid; 39 mg, 78%, mp 165-168 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (bs, 1H), 7.41 (dd, *J* = 12.7, 2.2 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 6.89 (t, *J* = 9.0 Hz, 1H), 3.86 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 153.2 and 150.8 (d, *J* = 245.1 Hz, 1C), 144.4 and 144.3 (d, *J* = 10.8 Hz, 1C), 131.3 and 131.2 (d, *J* = 9.3 Hz, 1C), 115.72 and 115.69 (d, *J* = 3.1 Hz, 1C), 113.62 and 113.60 (d, *J* = 2.3 Hz, 1C), 109.4 and 109.2 (d, *J* = 23.1 Hz, 1C), 56.6, 24.3; HRMS-ESI (*m*/*z*) calcd $[C_9H_{10}O_2NF+H]^+$: 184.0768, found 184.0767.

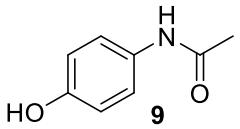
***N*-(4-methoxyphenyl)acetamide:**[4]



8

Reaction time: 2.5 h; R_f = 0.5 (EtOAc:Pet. Ether, 1:1). White solid; 48 mg, 96%, mp 130-133 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.8 Hz, 2H), 7.33 (bs, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.3, 156.4, 130.9, 121.9, 114.1, 55.5, 24.3; GC-MS (M^+) 165.

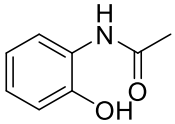
***N*-(4-hydroxyphenyl)acetamide:**[3]



9

Reaction time: 45 min.; R_f = 0.5 (EtOAc:Pet. Ether, 1:1). White solid; 33 mg, 66%, mp 166-168 ^{o}C; ^{1}H NMR (400 MHz, Acetone-d_6): δ 8.96 (bs, 1H), 8.21 (s, 1H), 7.43 (d, J = 9.0 Hz, 2H), 6.74 (d, J = 9.0 Hz, 2H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, Acetone-d_6): 168.2, 154.1, 132.7, 121.6, 115.8, 24.0; GC-MS (M^+) 165.

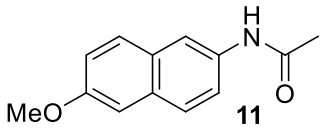
***N*-(2-hydroxyphenyl)acetamide:**[6]



10

Reaction time: 30 min.; R_f = 0.5 (EtOAc:Pet. Ether, 1:1). White solid; 32.3 mg, 65%, mp 206-209 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.74 (s, 1H), 9.30 (s, 1H), 7.67 (d, J = 7.6 Hz, 1H), 6.93 (t, J= 7.6 Hz, 1H), 6.85 (d, J= 7.1 Hz, 1H), 6.75 (t, J= 7.6 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.2, 148.1, 126.6, 124.8, 122.6, 119.2, 116.1, 23.8; HRMS-ESI (m/z) calcd $[C_8H_9O_2N+H]^+$: 152.0706, found 152.0704.

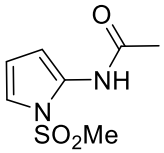
***N*-(6-methoxynaphthalen-2-yl)acetamide:**[7]



11

Reaction time: 20 min.; R_f = 0.5 (EtOAc:Pet. Ether, 2:3). White solid; 45 mg, 90%, mp 162-163 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.48 (bs, 1H), 7.44 (dd, J = 8.8, 2.0 Hz, 1H), 7.14 (dd, J = 8.8, 2.4 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1H), 3.91 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 157.1, 133.5, 131.7, 129.1, 127.4, 120.5, 119.2, 117.1, 105.6, 55.3, 24.6; GC-MS (M^+) 215.

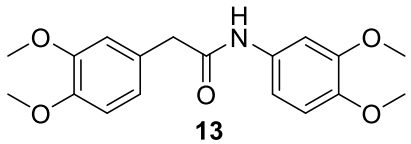
***N*-(1-(methylsulfonyl)-1H-pyrrol-2-yl)acetamide**:



12

Reaction time: 1.5 h; R_f = 0.3 (EtOAc:Pet. Ether, 1:1). Brown solid; 23.7 mg, 47 %, mp 125-127 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (bs, 1H), 6.87 (dd, J = 1.5 Hz, 1H), 6.53 (d, J = 1.2 Hz, 1H), 6.29 (t, J = 3.4 Hz, 3.7 Hz, 1H), 3.15 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.1, 127.3, 117.0, 112.3, 105.6, 42.2, 23.8; HRMS-ESI (*m*/*z*) calcd $[C_7H_{10}O_3N_2S+Na]^+$: 225.0304, found 225.0307.

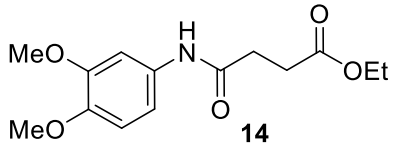
***N*,2-bis(3,4-dimethoxyphenyl)acetamide:**[8]



13

Reaction time: 3 h; R_f: 0.5 (EtOAc:Pet. Ether, 1:1); Silver white Solid; 32.5 mg, 65%; mp 140-142 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 1H), 7.11 (s, 1H), 6.90-8.86 (m, 2H), 6.84 (s, 1H), 6.76 (s, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.67 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 149.4, 139.3, 149.0, 148.6, 145.9, 131.2, 126.8, 121.8, 112.5, 111.7, 111.6, 111.2, 104.8, 56.1, 55.9, 44.3; GC-MS (M^+) 331.

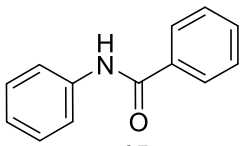
Ethyl 4-((3,4-dimethoxyphenyl)amino)-4-oxobutanoate:



14

Reaction time: 10 min; R_f: 0.5 (EtOAc:Pet. Ether, 1:1); Silver white Solid; 27 mg, 54%; mp 110-113 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.34 (s, 1H), 6.86 (dd, J = 7.8, 2.2 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.75 (t, J = 6.4 Hz, 2H), 2.64 (t, J = 6.4 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 169.6, 149.0, 145.7, 131.5, 111.6, 111.2, 104.8, 60.9, 56.1, 55.9, 32.0, 29.5, 14.1; HRMS-ESI (*m*/*z*) calcd $[C_{14}H_{19}O_5N+H]^+$: 282.1336, found 282.1328.

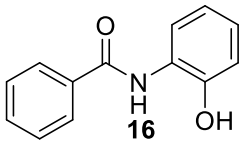
***N*-phenylbenzamide:**[9]



15

Reaction time: 9 h; R_f: 0.5 (EtOAc:Pet. Ether, 2:3); white Solid; 41.7 mg, 83%; mp 161-163 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (bs, 1H), 7.88 (d, J = 7.3 Hz, 2H), 7.66 (d, J = 7.6 Hz, 2H), 7.56 (t, J = 7.0 Hz, 1H), 7.49 (t, J = 7.0, 7.6 Hz, 2H), 7.38 (t, J = 7.02, 7.3 Hz, 2H), 7.17 (t, J = 7.0, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8. 137.9, 135.0, 131.8, 129.1, 128.8, 127.0, 124.6, 120.2; GC-MS (M^+) 197.

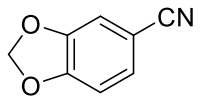
***N*-(2-hydroxyphenyl)benzamide**:[10]



16

Reaction Time: 05 h; R_f: 0.5 (EtOAc:Pet. Ether, 1:4); White Solid; 30 mg, 60%; mp 135-137 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.80 (s, 1H), 9.52(s, 1H), 7.96 (d, J = 7.6 Hz, 2H), 7.67 (d, J = 7.6 Hz, 1H), 7.61-7.50 (m, 3H), 7.10-6.80 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.5, 149.6, 134.5, 131.9, 128.7, 127.7, 126.0, 124.4, 119.3, 116.2; GC-MS (M^+) 213.

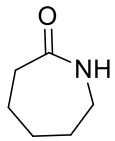
Benzo[d][1,3]dioxole-5-carbonitrile:[11]



24

Reaction time: 1 h; R_f = 0.5 (EtOAc:Pet. Ether, 1:5). White solid; 38 mg, 85%, mp 94-97 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (dd, J = 8.1 Hz, 1.5 Hz, 1H), 7.04 (d, J = 1.5 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 6.08 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 148.0, 128.2, 118.9, 111.4, 109.1, 104.9, 102.3; LC-MS (M+Na) 170.

Azepan-2-one:[12]

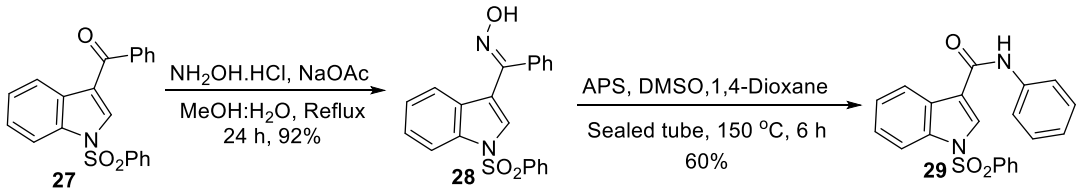


26

Reaction Time: 15 min. at 70 ^{o}C R_f: 0.5 (MeOH: DCM, 1:20); White Solid; 16 mg, 32%; mp 68-70 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.3 (bs, 1H), 3.25-3.15 (m, J = 2H), 2.50-2.45 (m, 2H), 1.80-1.60 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 42.9, 36.6, 30.6, 29.7, 23.2; LC-MS (M+H) 114.

4. Experimental procedures and data for Scheme 5 (Isocryptolepine Synthesis):

Synthesis of *N*-phenyl-1-(phenylsulfonyl)-1*H*-indole-3-carboxamide (29):



(*E*)-phenyl(1-(phenylsulfonyl)-1*H*-indol-3-yl)methanone oxime 28:

A two necked round bottom flask containing the solution of benzoyl compound **27** (1 g, 2.76 mmol, 1 equiv), $NH_2OH.HCl$ (4.8 g, 69.17 mmol, 25 equiv) and NaOAc (5 g, 60.9 mmol, 22 equiv) in MeOH:H_2O (50 mL:15 mL) was heated at 90 ^oC for 24 hours. After completion of the reaction, methanol was evaporated in vaccuo and the residue was extracted with ethyl acetate (20 mL). Organic layer was dried over sodium sulfate, concentrated and the crude product was purified by recrystallization in methanol to provide ketoxime **28** (959 mg, 92%) as a white solid.

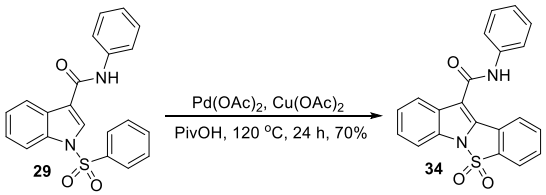
Reaction time: 24 h; R_f = 0.3 (EtOAc:Pet. Ether, 3:7). White solid; mp 186-187 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ 11.76 (s, 1H), 8.09 (s, 1H), 8.06 (d, J = 7.7 Hz, 2H), 8.00 (d, J = 8.3 Hz, 1H), 7.73 (t, J = 7.3 Hz, 1H), 7.63 (t, J = 7.8, 7.3 Hz, 2H), 7.42-7.34 (m, 6H), 7.16 (t, J = 7.8, 7.3 Hz,, 1H), 6.96 (t, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 148.5, 137.0, 136.4, 135.1, 134.0, 130.2, 129.3, 129.1, 128.7, 128.1, 127.3, 127.1, 125.2, 123.7, 121.9, 114.5, 113.4; HRMS-ESI (*m*/*z*) calcd $[C_{21}H_{16}O_3N_2S+H]^+$: 377.0954, found 377.0943.

***N*-Phenyl-1-(phenylsulfonyl)-1*H*-indole-3-carboxamide 29:**[13]

The reaction mixture containing ketoxime **28** (500 mg, 1.3 mmol, 1 equiv), APS (606 mg, 2.65 mmol, 2 equiv) and DMSO (0.56 mL, 7.96 mmol, 6 equiv) in 1,4-dioxane (10 mL) was heated at 150 ^{o}C for 6 hours in a glass tube sealed with Teflon cap. After completion of the reaction, 1,4-dioxane was evaporated under vacuum and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with brine (10 x 2 mL) and dried over sodium sulfate. Evaporation of ethyl acetate under vacuum followed by flash column chromatography of the residue with ethyl acetate: petroleum ether (3:7) gave (300 mg, 60%) of compound **29**.

Reaction time: 6 h; R_f = 0.5 (EtOAc:Pet. Ether, 3:7). White solid; mp 172-174 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (s, 1H), 8.12 (d, *J* = 7.6, 1H), 8.01 (d, *J* = 8.4, 1H), 7.94 (d, *J* = 7.6, 2H), 7.80 (bs, 1H), 7.65 (d, *J* = 8.0, 2H), 7.59 (t, *J* = 7.6, 1H), 7.48 (t, *J* = 7.6, 2H), 7.43-7.35 (m, 4H), 7.17 (t, *J* = 7.3, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.5, 137.62, 137.56, 135.0, 134.5, 129.6, 129.2, 127.8, 127.4, 127.0, 125.8, 124.63, 124.55, 121.7, 120.2, 118.0, 113.5; HRMS-ESI (*m*/*z*) calcd $[C_{21}H_{16}O_3N_2S+Na]^+$: 399.0774, found 399.0760.

***N*-phenylbenzo[4,5]isothiazolo[2,3-a]indole-11-carboxamide 5,5-dioxide (34):**

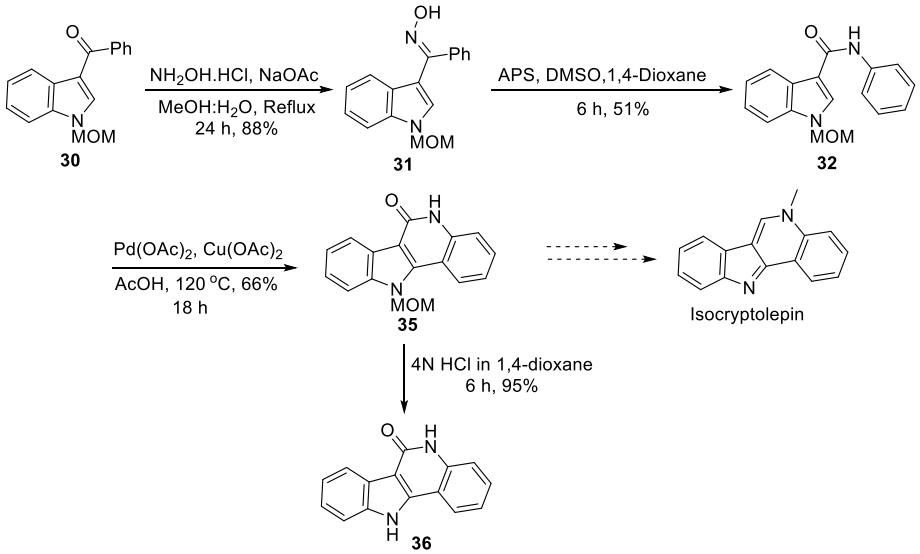


Amide **29** (200 mg, 0.53 mmol, 1 equiv), palladium acetate (23 mg, 0.1 mmol, 0.2 equiv) and copper acetate (96 mg, 0.53 mmol, 1 equiv) were taken in a schlenk tube equipped with a

magnetic stirring bar. It was kept under reduced pressure for some time, flushed with oxygen and kept under oxygen balloon pressure. After the addition of 1 mL of pivalic acid the reaction was heated at 120 ^{o}C for 24 h. It was then allowed to attain room temperature and ethyl acetate (15 mL) was added. The ethyl acetate layer was washed with aqueous saturated sodium bicarbonate (5 mL x 3), dried over sodium sulfate and concentrated under vacuum. Flash column chromatography using ethyl acetate: petroleum ether (3:7) yielded 140 mg of pure compound **34** (70%).

Reaction time: 24 h; R_f = 0.5 (EtOAc:Pet. Ether, 3:7). White solid; mp 202-207 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.71 (s, 1H), 8.31 (d, J = 7.8, 1H), 8.22 (d, J = 7.8, 1H), 7.94-790 (m, 2H), 7.81-7.76 (m, 4H), 7.55 (t, J = 7.8, 1H), 7.47-7.39 (m, 3H), 7.17 (t, J = 7.3, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 138.9, 137.5, 135.6, 132.4, 131.5, 131.1, 130.4, 129.1, 127.1, 125.8, 125.5, 124.5, 124.4, 123.4, 123.0, 120.4, 113.1, 111.5; HRMS-ESI (m/z) calcd $[C_{21}H_{14}O_3N_2S+Na]^+$: 397.0617, found 397.0606.

Formal Total synthesis of Isocryptolepine from MOM-protected indole:



(1-(methoxymethyl)-1*H*-indol-3-yl)(phenyl)methanone (30):

In a two necked round bottom flask containing the solution of (1*H*-indol-3-yl)(phenyl)methanone (200 mg, 0.90 mmol, 1 equiv) in DMF was added NaH (65 mg, 2.7 mmol, 3 equiv) at 0 ^{o}C and the reaction mixture was stirred for another 10 minutes. MOM chloride (0.1 mL, 1.35 mmol, 1.5 equiv) was added and the reaction mixture was stirred at rt for 6 h. After the completion of the reaction, ice was added followed by extraction with ethyl acetate (10 mL x 2). The organic layer was washed with brine (10 mL x 2) and dried over sodium sulfate. Concentration of organic layer under vacuum followed by column chromatography ethyl acetate: petroleum ether (3:7) yielded MOM protected ketone **30** in 216 mg.

Reaction time: 6 h; R_f = 0.4 (EtOAc:Pet. Ether, 3:7). White solid; 90%, mp 97-99 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45-8.42 (m, 1H), 7.85 (d, J = 7.3 Hz, 2H), 7.66 (s, 1H), 7.60-7.55 (m, 2H), 7.51 (t, J = 7.3 Hz, 2H), 7.41-7.36 (m, 2H), 5.50 (s, 2H), 3.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 140.6, 136.9, 136.7, 131.4, 128.7, 128.4, 127.5, 124.2, 123.2, 122.8, 166.7, 110.3, 78.1, 56.3; HRMS-ESI (*m*/*z*) calcd $[C_{17}H_{15}O_2N+Na]^+$: 288.0995, found 288.0988.

(*E*)-(1-(methoxymethyl)-1*H*-indol-3-yl)(phenyl)methanone oxime (31):

In a round bottom flask containing MOM ketone **30** (200 mg, 0.75 mmol, 1 equiv), hydroxylamine hydrochloride (1.3 g, 18.8 mol, 25 equiv) and sodium acetate (1.54 g, 18.8 mol, 25 equiv) was added 13 mL of methanol:water (10:3) and the resulting reaction mixture was heated at 90 ^{o}C for 24 h. After completion of the reaction as indicated by thin layer chromatography, methanol was evaporated followed by the addition of ethyl acetate (20 mL).

The organic layer was washed with cold water (10 mL x 2), dried over sodium sulfate and concentrated under vacuum. Flash column chromatography ethyl acetate: petroleum ether (3:7) afforded ketoxime **31** in 186 mg yield.

Reaction time: 24 h; R_f = 0.3 (EtOAc:Pet. Ether, 3:7). White solid; 88%, mp 155-157 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.39 (s, 1H), 8.07 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.46-7.39 (m, 5H), 7.16 (t, J = 7.3 Hz, 1H), 6.94 (t, J = 7.3 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 5.61(s, 2H), 3.21 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 150.3, 137.9, 135.7, 133.3, 128.8, 128.4, 128.2, 127.2, 122.0, 121.3, 120.3, 110.8, 107.0, 76.9, 55.6; HRMS-ESI (*m*/*z*) calcd $[C_{17}H_{16}O_2N_2+H]^+$: 281.1285, found 281.1281.

1-(methoxymethyl)-*N*-phenyl-1*H*-indole-3-carboxamide (32):

A Schlenk tube containing ketoxime **31** (100 mg, 0.35 mmol, 1 equiv) and ammonium peroxysulfate (122 mg, 0.53 mmol, 1.5 equiv) was kept under reduced pressure and flushed with Argon, followed by the addition of 1,4-dioxane (4 mL) and DMSO (0.15 mL, 2.14 mmol, 6 equiv). The reaction mixture was heated at 100 ^{o}C for 6 h. After completion of the reaction, 1,4-dioxane was evaporated and 10 mL ethyl acetate was added. The organic layer was washed with brine (5 mL X 2), dried over sodium sulfate and concentrated. Column chromatography ethyl acetate: petroleum ether (2:3) of the residue afforded 51 mg of **32**.

Reaction time: 6 h; R_f= 0.5 (EtOAc:Pet. Ether, 2:3). White solid; 51 mg, 51%, mp 78-82 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10-8.08 (m, 1H), 7.85 (s, 1H), 7.84 (bs, 1H), 7.68(d, J = 8.1 Hz, 2H), 7.55-7.55 (m, 1H), 7.40-734 (m, 4H), 7.14 (t, J = 7.3 Hz, 1H), 5.45 (s, 2H), 3.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 138.2, 136.7, 131.5, 129.1, 125.9, 124.1, 123.4, 122.4,

120.3, 120.1, 112.5, 111.0, 78.0, 56.2; HRMS-ESI (*m*/*z*) calcd $[C_{17}H_{16}O_2N_2+Na]^+$: 303.1104, found 303.1102.

11-(methoxymethyl)-5,11-dihydro-6*H*-indolo[3,2-c]quinolin-6-one (35):[14]

To a flame dried schlenk tube kept under oxygen balloon were added amide **32** (40 mg, 0.14 mmol, 1 eq), palladium acetate (6.5 mg, 0.02 mmol, 0.2 eq) and copper acetate (26 mg, 0.14 mmol, 1 eq). The schlenk tube was evacuated and charged with 1 mL of acetic acid under oxygen atmosphere. The reaction mixture was heated at 110 ^oC for 18 h. It was then allowed to come to the room temperature and ice water (5 mL) was added with stirring. The reaction mixture was extracted with ethyl acetate (10 mL X 2) and the combined organic layer was washed with aqueous saturated sodium bicarbonate (5 mL X 2). The organic layer was dried over sodium sulfate and purified by column chromatography with ethyl acetate:petroleum ether (1:1) to furnish tetracyclic amide **35** (26 mg, 66%).

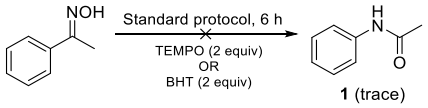
Reaction time: 18 h; R_f = 0.3 (EtOAc:Pet. Ether, 2:3). White solid; 26 mg, 66%, mp 272-274 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 11.70 (bs, 1H), 8.67 (d, *J* = 7.3 Hz, 1H), 8.40 (d, *J* = 8.3 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.58 (t, *J* = 7.3 Hz, 7.5 Hz, 1H), 7.51 (t, *J* = 7.3 Hz, 7.1 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 7.1 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 5.95 (s, 2H), 3.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 141.4, 140.1, 138.2, 129.2, 125.0, 124.3, 123.6, 122.5, 122.46, 117.2, 112.8, 109.0, 75.3, 56.3; HRMS-ESI (*m*/*z*) calcd $[C_{17}H_{15}O_2N_2+H]^+$: 279.1128, found 279.1126.

5,11-dihydro-6*H*-indolo[3,2-c]quinolin-6-one (36):[14]

In a round bottom flask, the solution of MOM-protected amide **35** (20 mg, 0.07 mmol, 1 eq) and 4N HCl in 1,4-dioxane (1 mL) was refluxed for 6 h. After completion of the reaction as indicated by thin layered chromatography, solvent was evaporated under vacuum and ethyl acetate (10 mL) was added. The ethyl acetate layer was washed with aqueous saturated sodium bicarbonate (5 mL X 2), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography using ethyl acetate:petroleum ether (1:1) afforded 16 mg of **36**.

Reaction time: 16 h; R_f = 0.4 (EtOAc:Pet. Ether, 1:1). White solid; 16 mg, 95%, mp 337-339 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.57 (s, 1H), 11.43 (s, 1H), 8.20 (d, J = 7.8 Hz, 2H), 7.62 (d, J = 8.3 Hz, 1H), 7.53-7.44 (m, 2H), 7.37 (t, J = 8.1 Hz, 1H), 7.31-7.24 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.1, 140.9, 138.2, 137.9, 129.4, 124.6, 124.2, 122.3, 121.7, 121.2, 120.9, 116.2, 112.2, 111.9, 106.6.

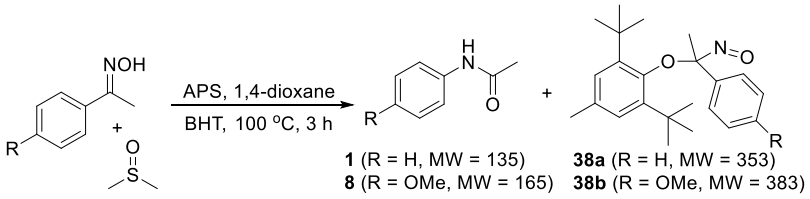
5. Radical trapping experiment:



In a round bottom flask equipped with a stirring bar and water condenser, the solution of acetophenone oxime (50 mg, 1 equiv, 0.37 mmol), ammonium persulfate (168 mg, 2 equiv, 0.74 mmol), TEMPO (115 mg, 2 equiv, 0.74 mmol) and DMSO (157 µL, 6 equiv, 2.46 mmol) in 1,4-dioxane (2 mL) was heated at 100 ^{o}C for 6 h. The reaction was followed by TLC, however only a trace amount of amide **1** was observed.

The same reaction was performed in the presence of BHT (326 mg, 4 equiv, 1.47 mmol) as a radical scavenger. In this case also only a trace amount of product **1** was seen on TLC.

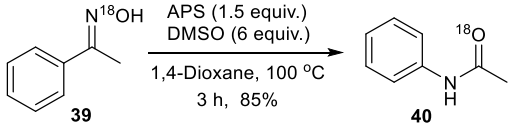
Trapping of intermediates with BHT following the above mentioned procedure:



The trapped intermediates **38a-b** were detected by LC-MS and HRMS.

6. ^{18}O Labeling Experiment:

^{18}O-enriched acetophenone oxime to ^{18}O-enriched acetanilide (40):



^{18}O-Labelled $NH_2{}^{18}OH$ was prepared starting from $H_2{}^{18}O$ and ammonia following the reported procedure.[39] It was used for the preparation of previously known ^{18}O-labelled acetophenone oxime **39**.[39b] Treatment of the oxime **39** under our standard protocol (General procedure, page 1) furnished ^{18}O-labelled acetanilide (**40**) in 85% yield. Spectral and analytical data was in agreement with the above reported compound **1**. More than 50% of acetanilide (**40**) had incorporated the heavy oxygen atom (approximate calculation from Mass spectrum). HRMS-ESI (*m*/*z*) calcd $[C_8H_9{}^{18}ON+H]^+$: 138.0799, found 138.0797.

7. References:

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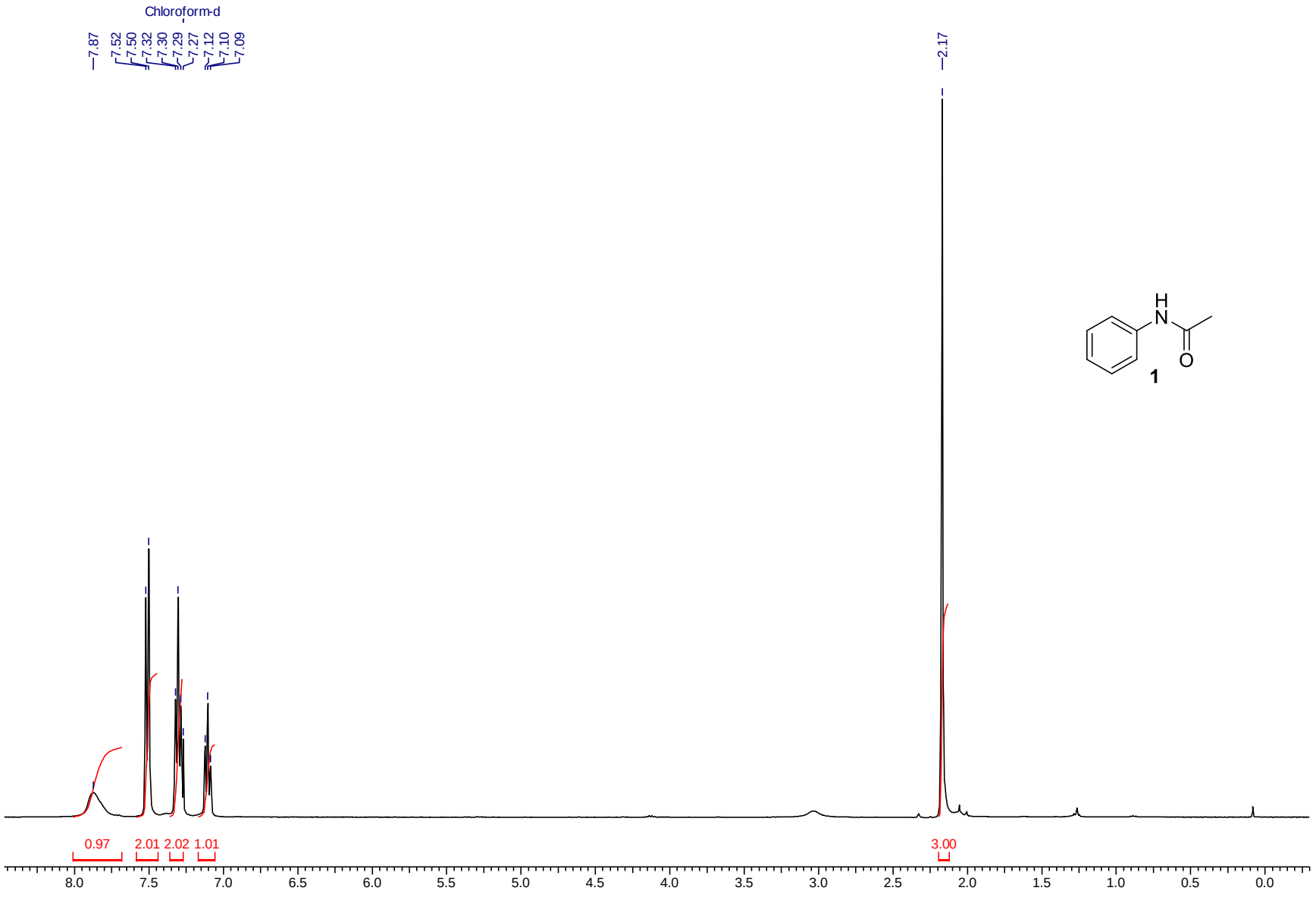
^{1}H NMR, 400MHz



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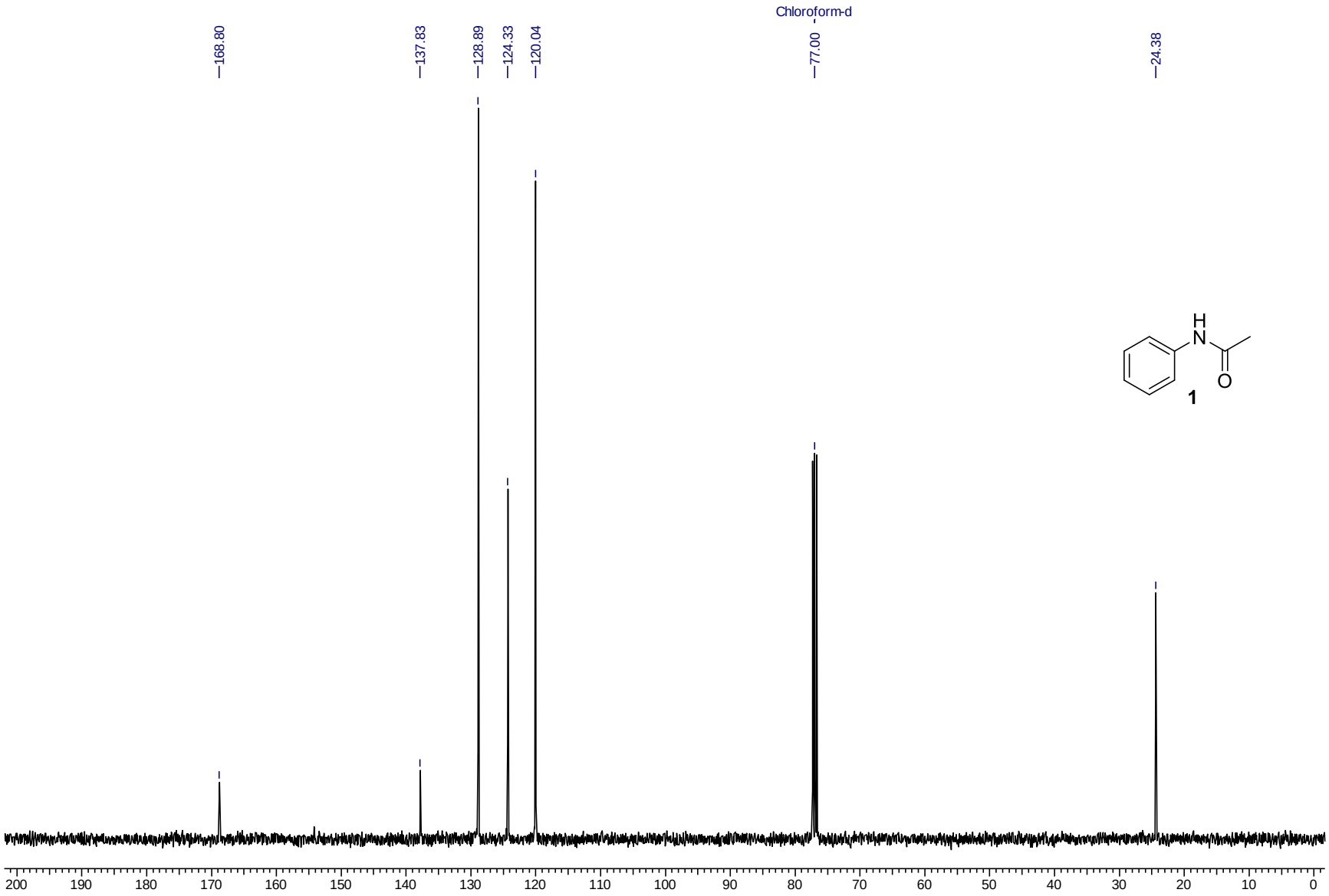
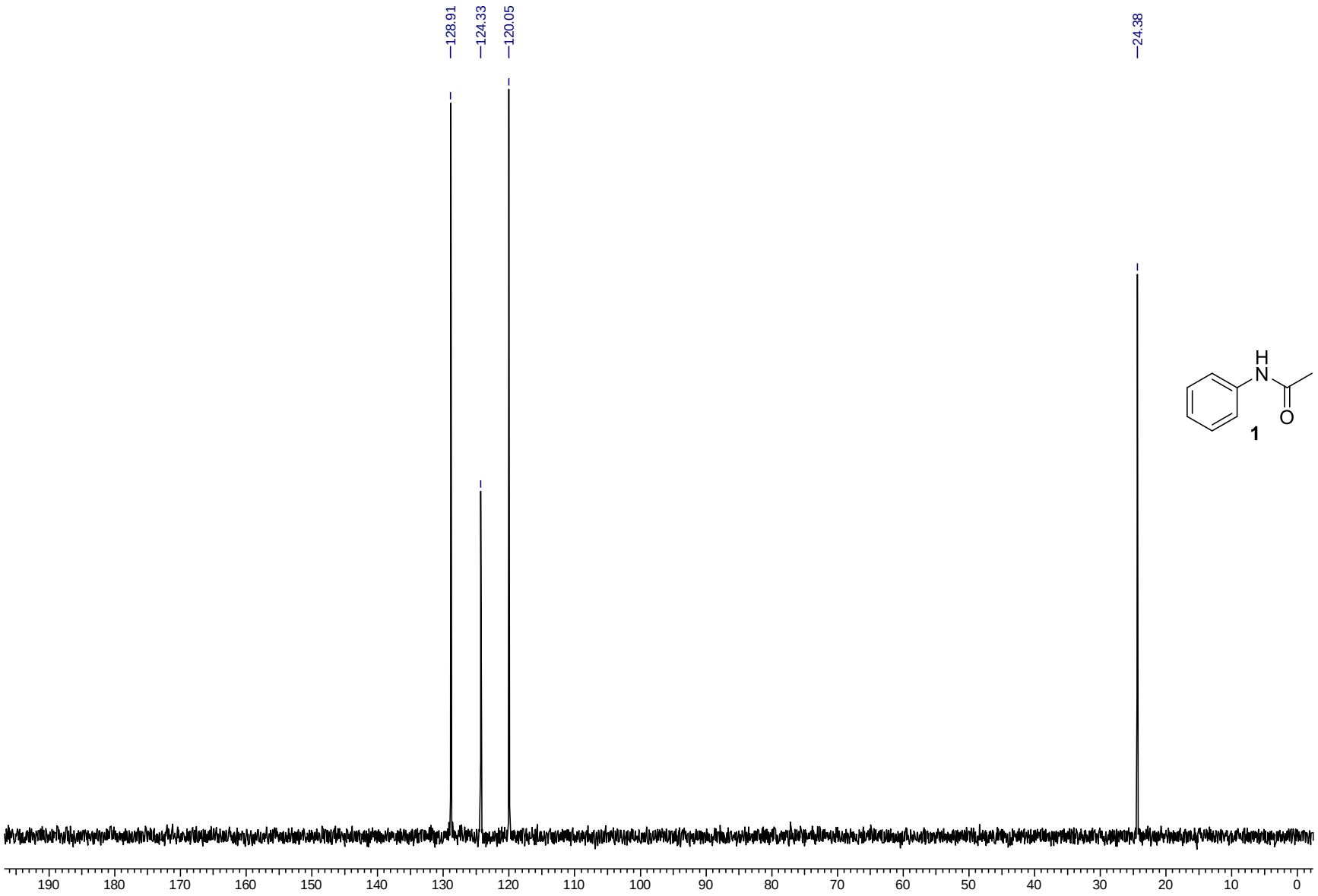


DEPT NMR, 100MHz



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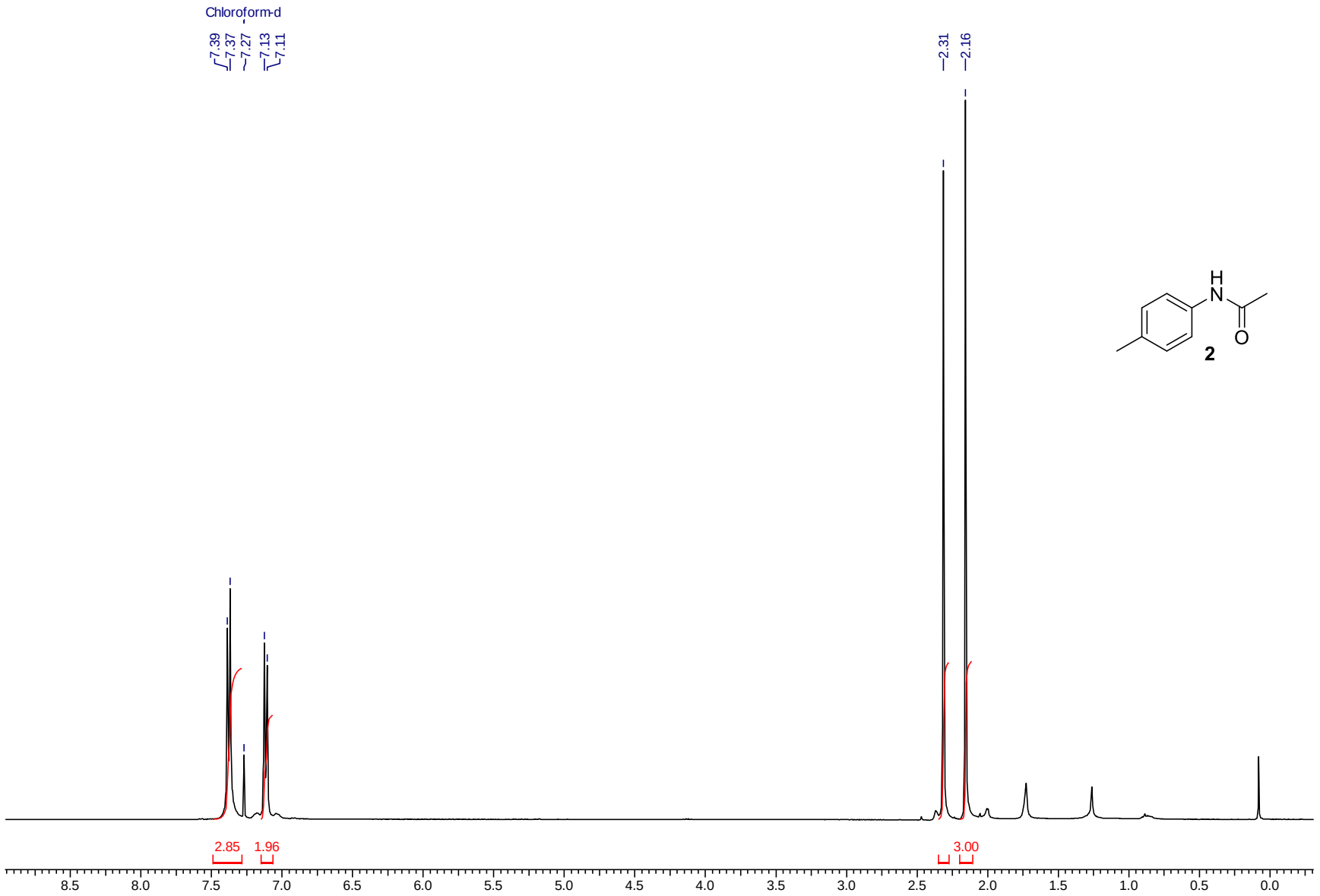

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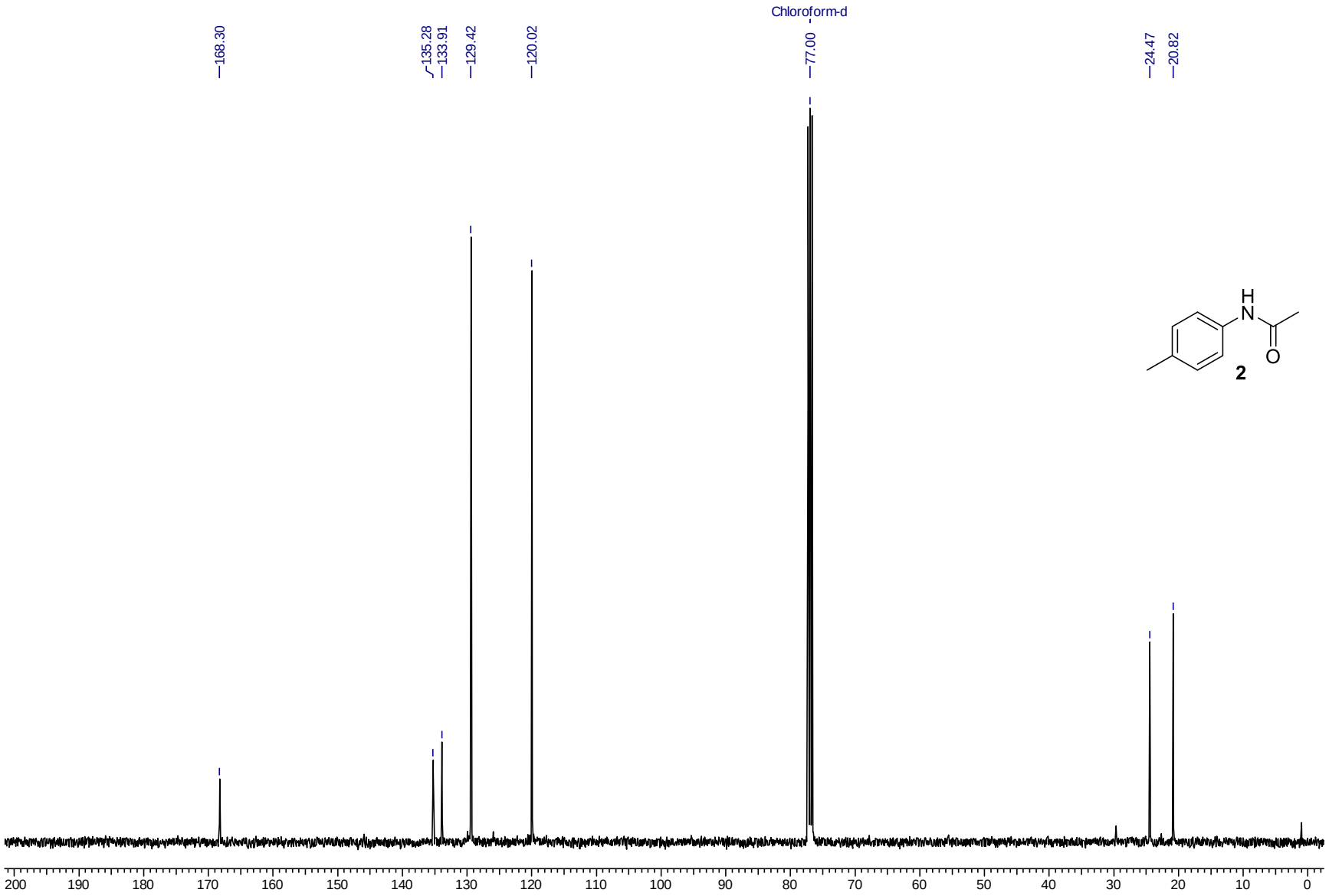

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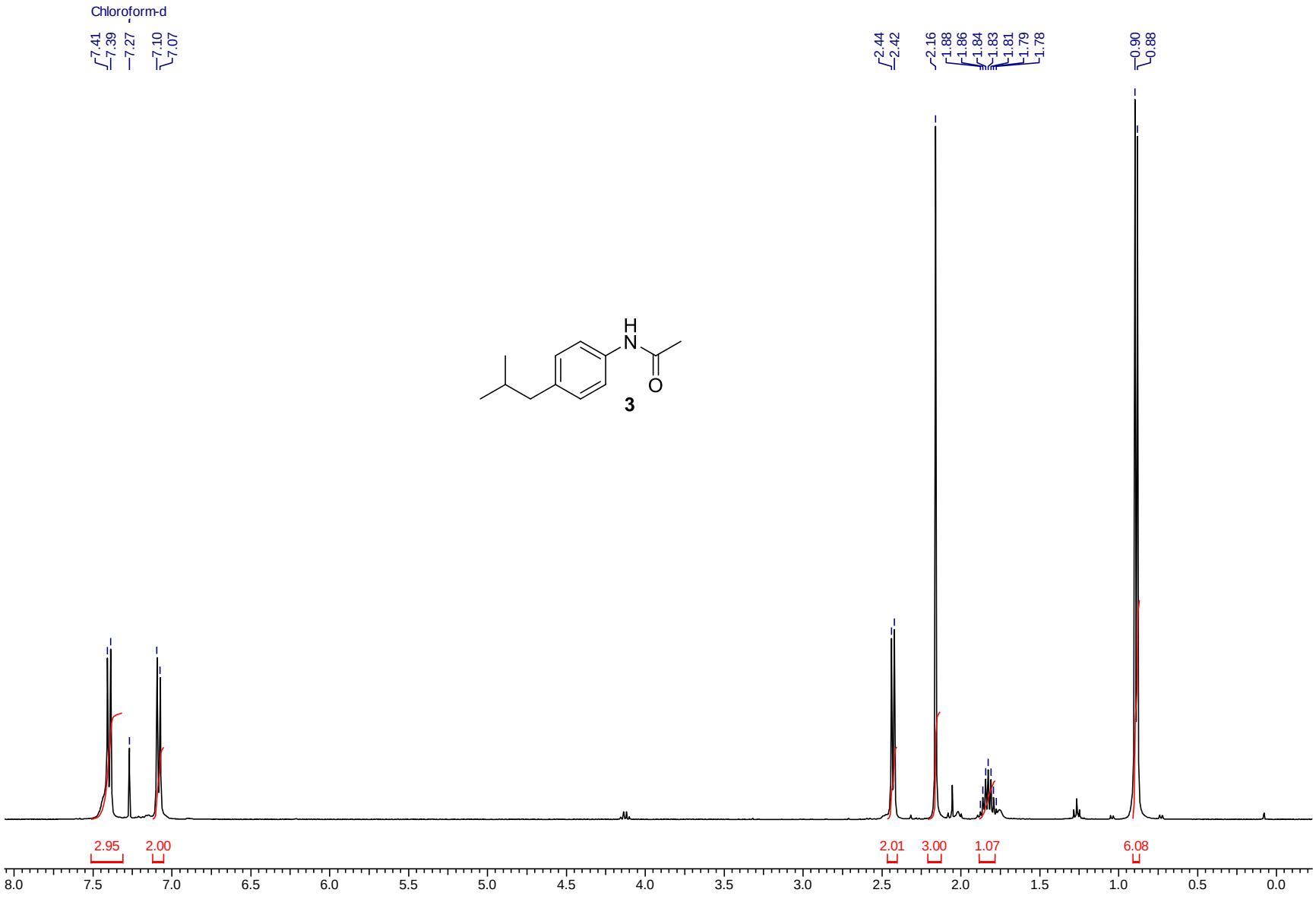

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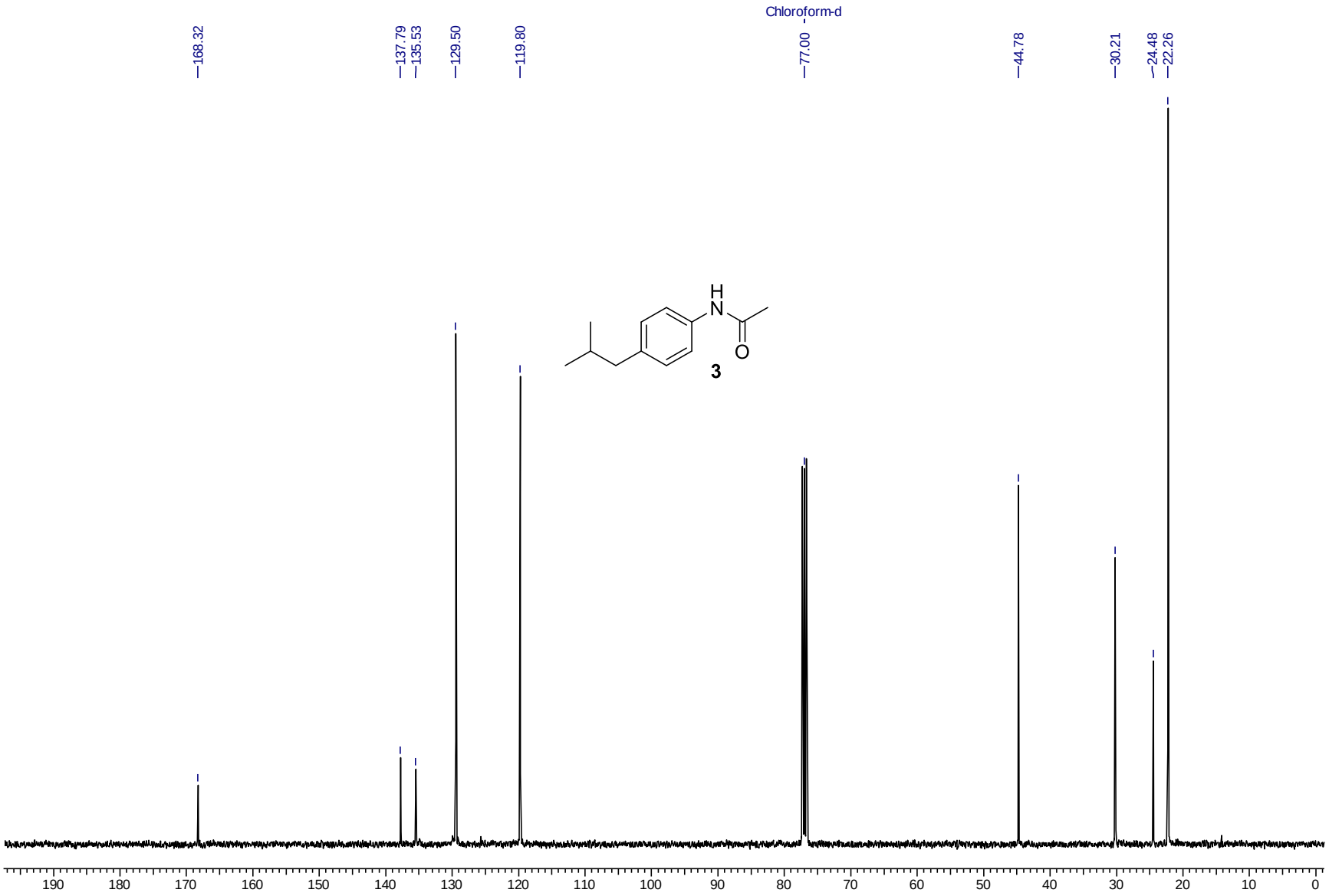

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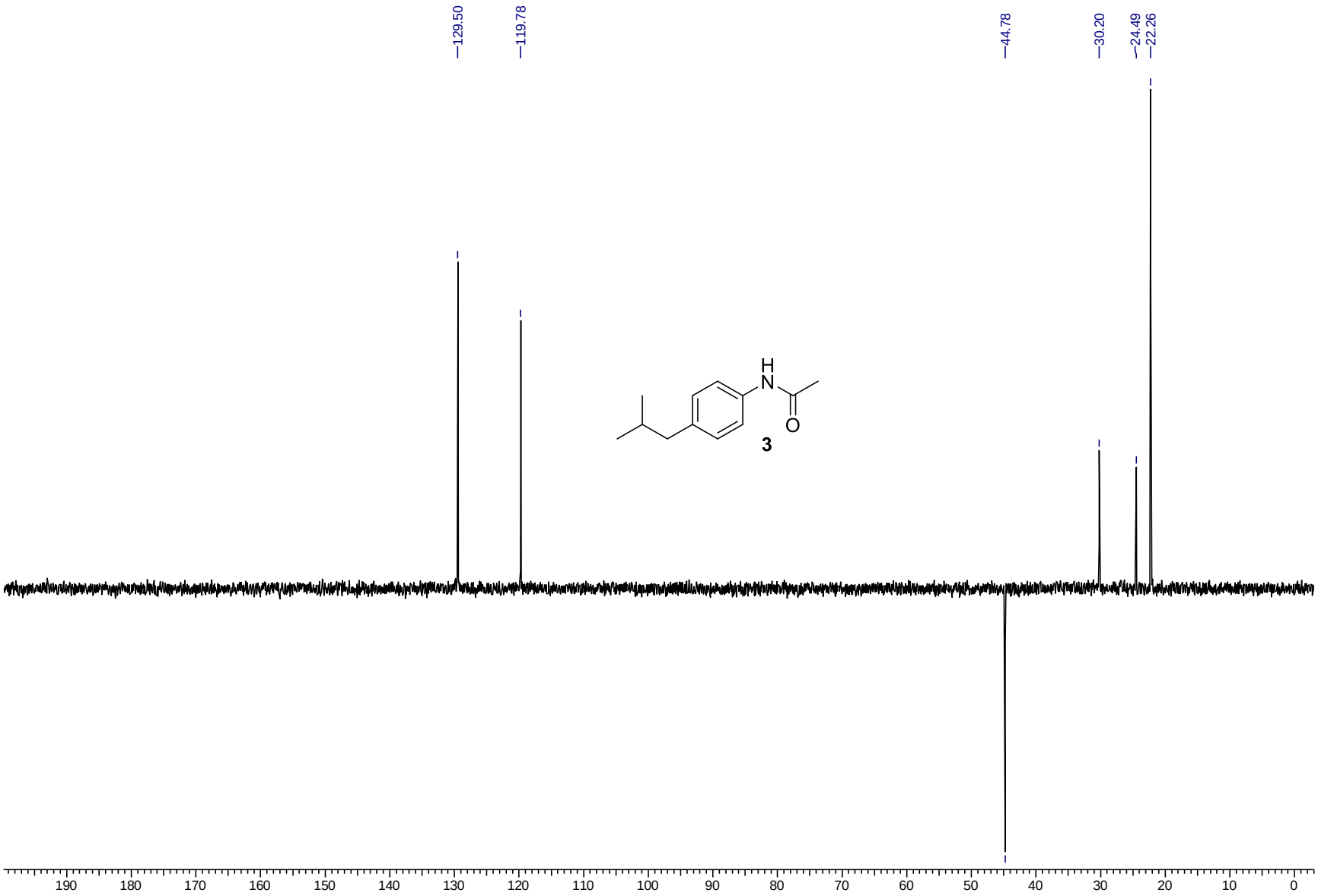

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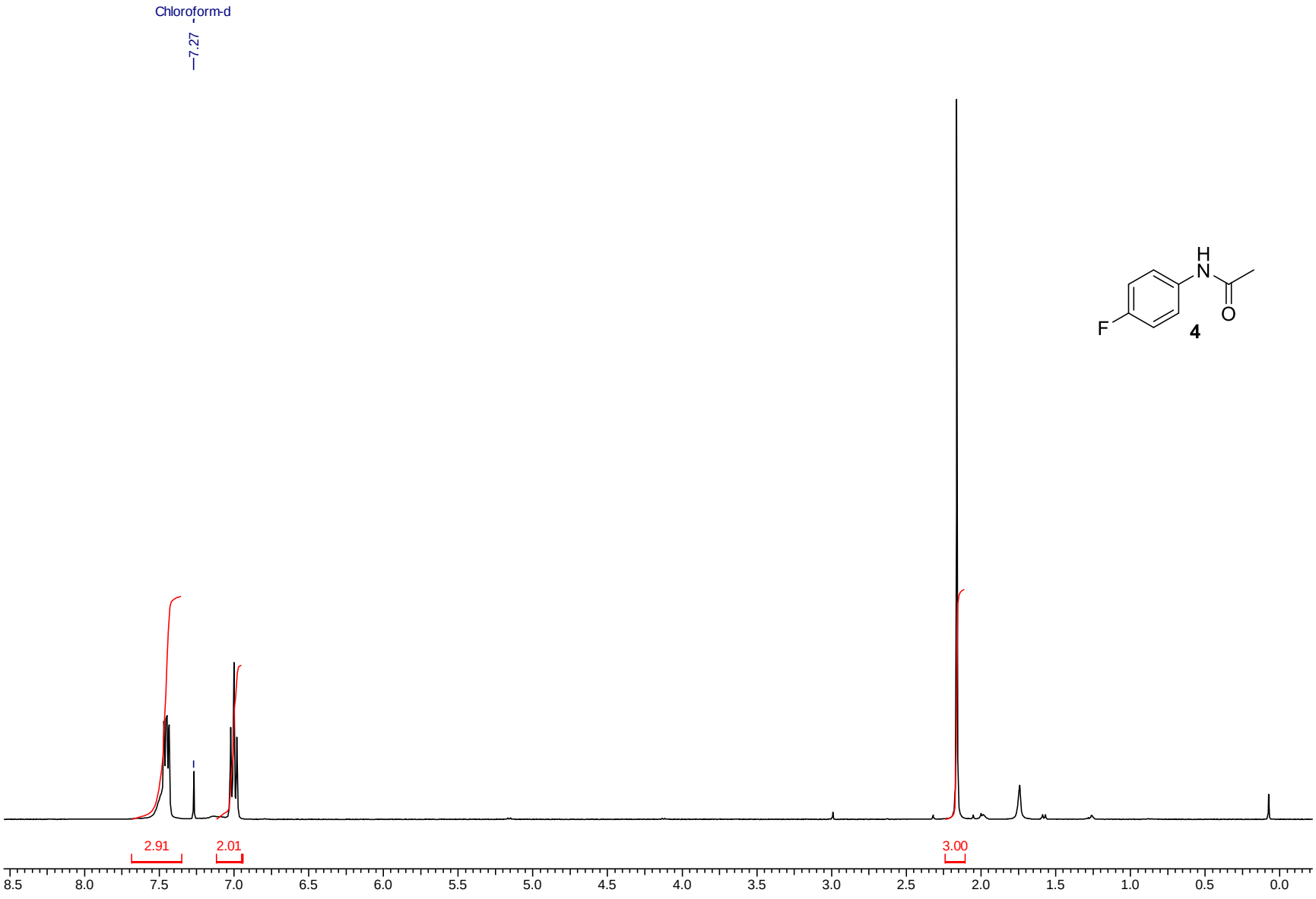

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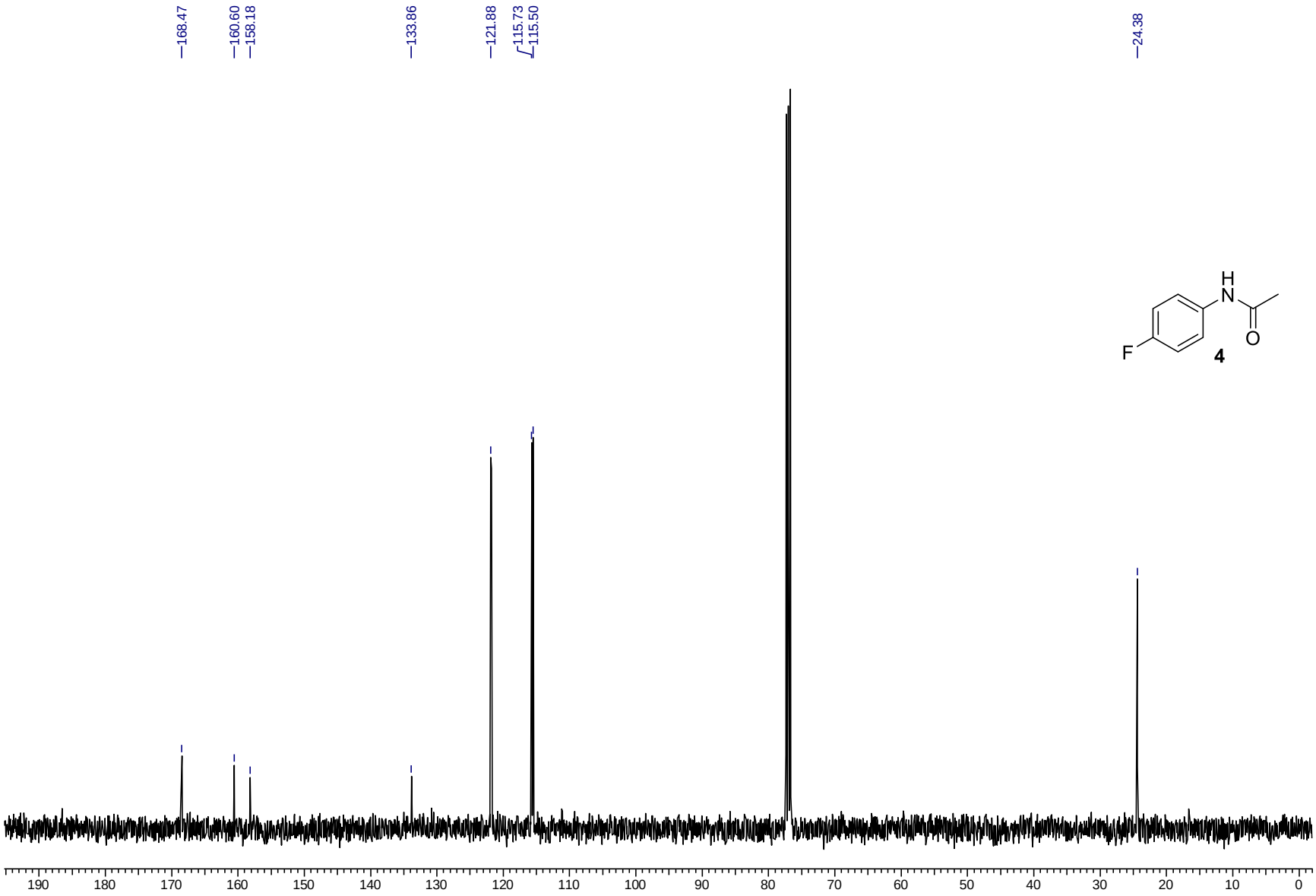
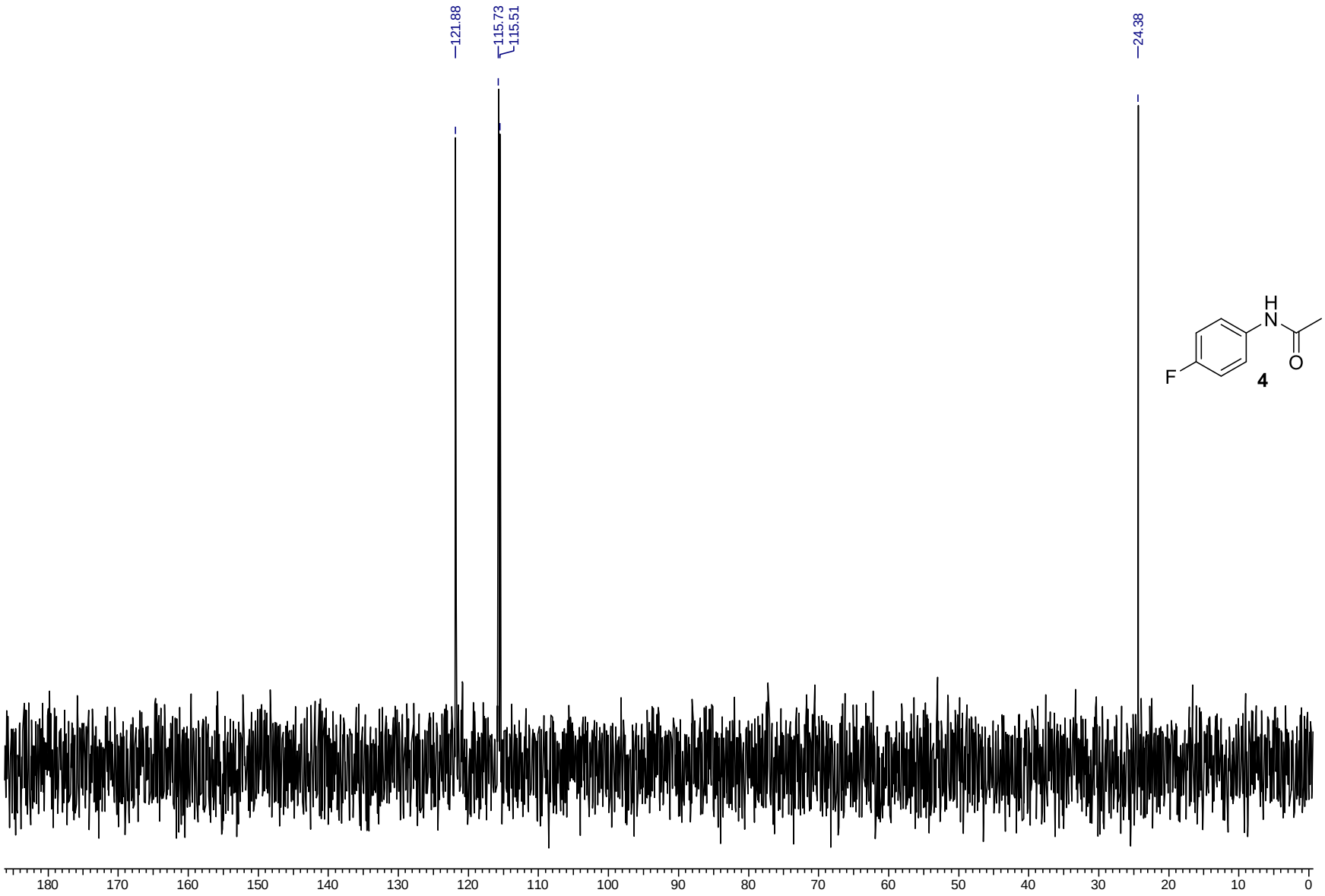


DEPT NMR, 100MHz



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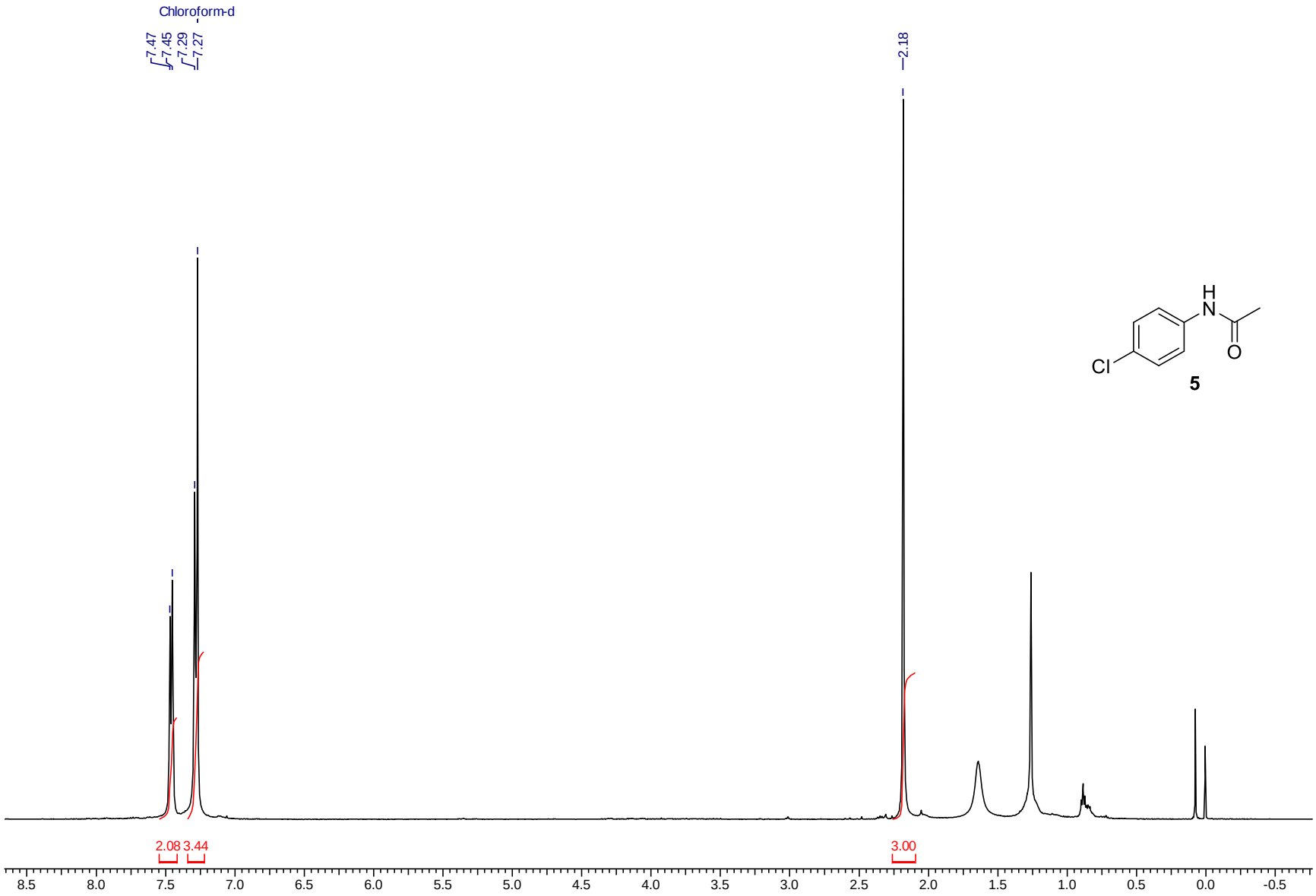

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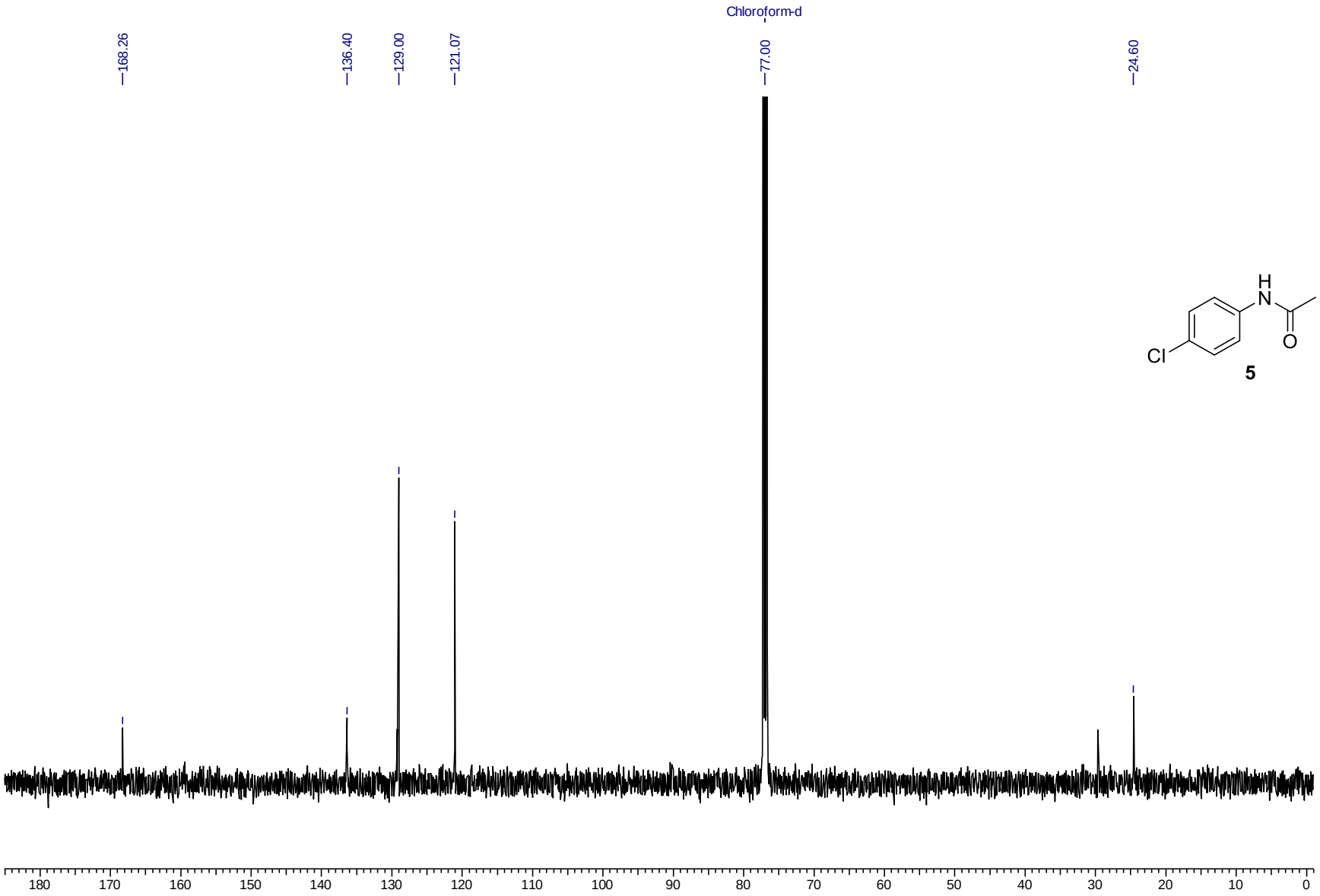

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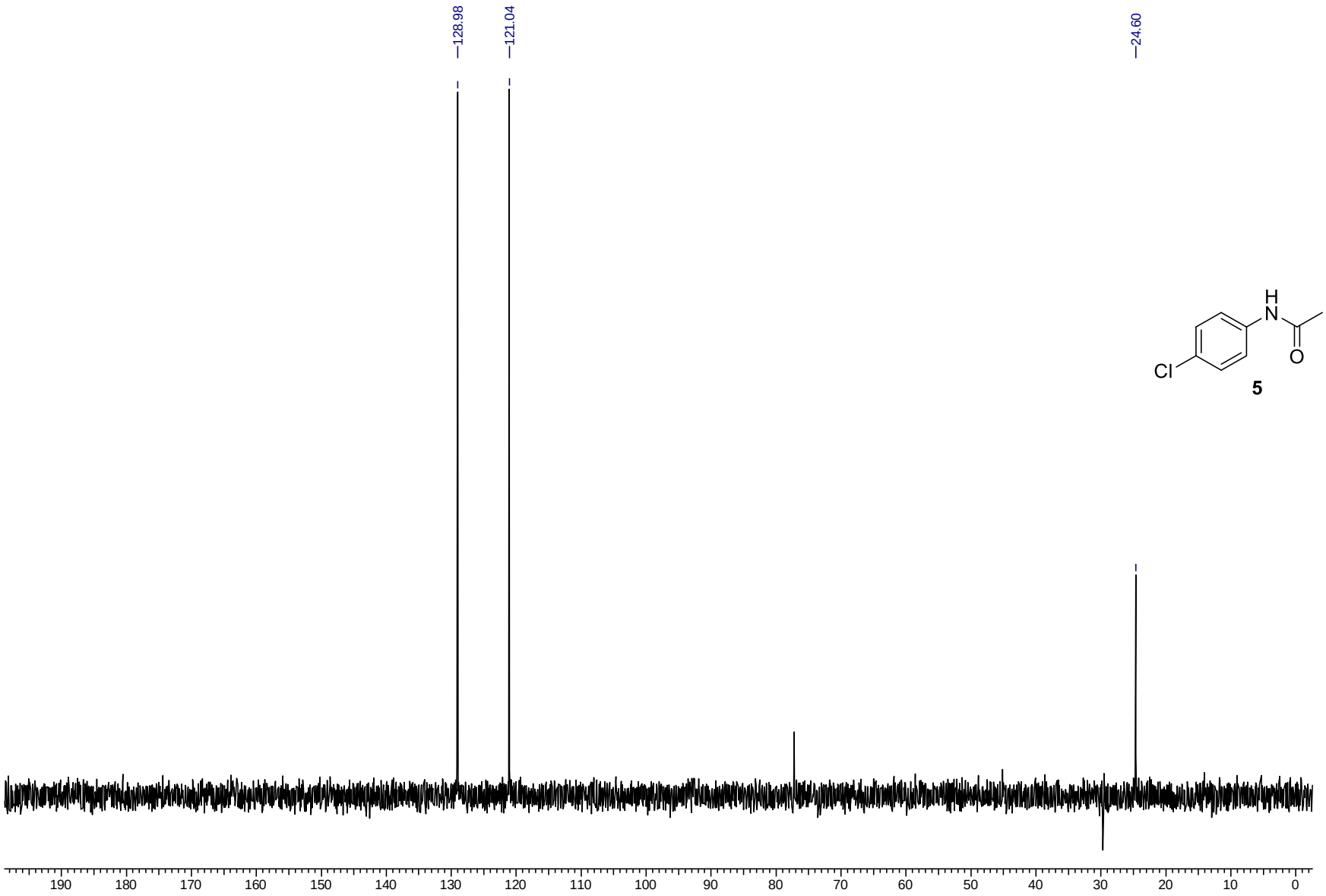
DEPT NMR, 125MHz



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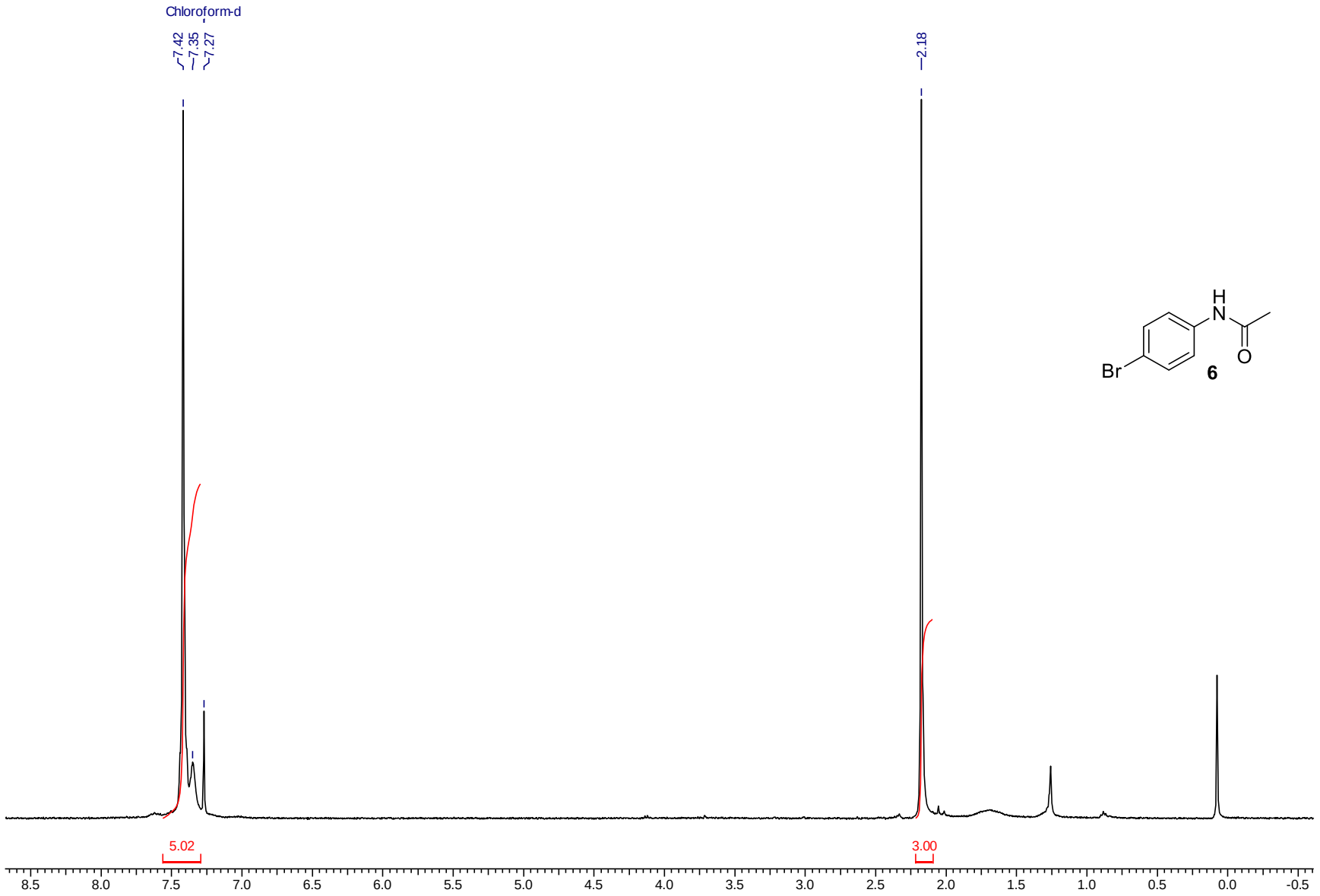

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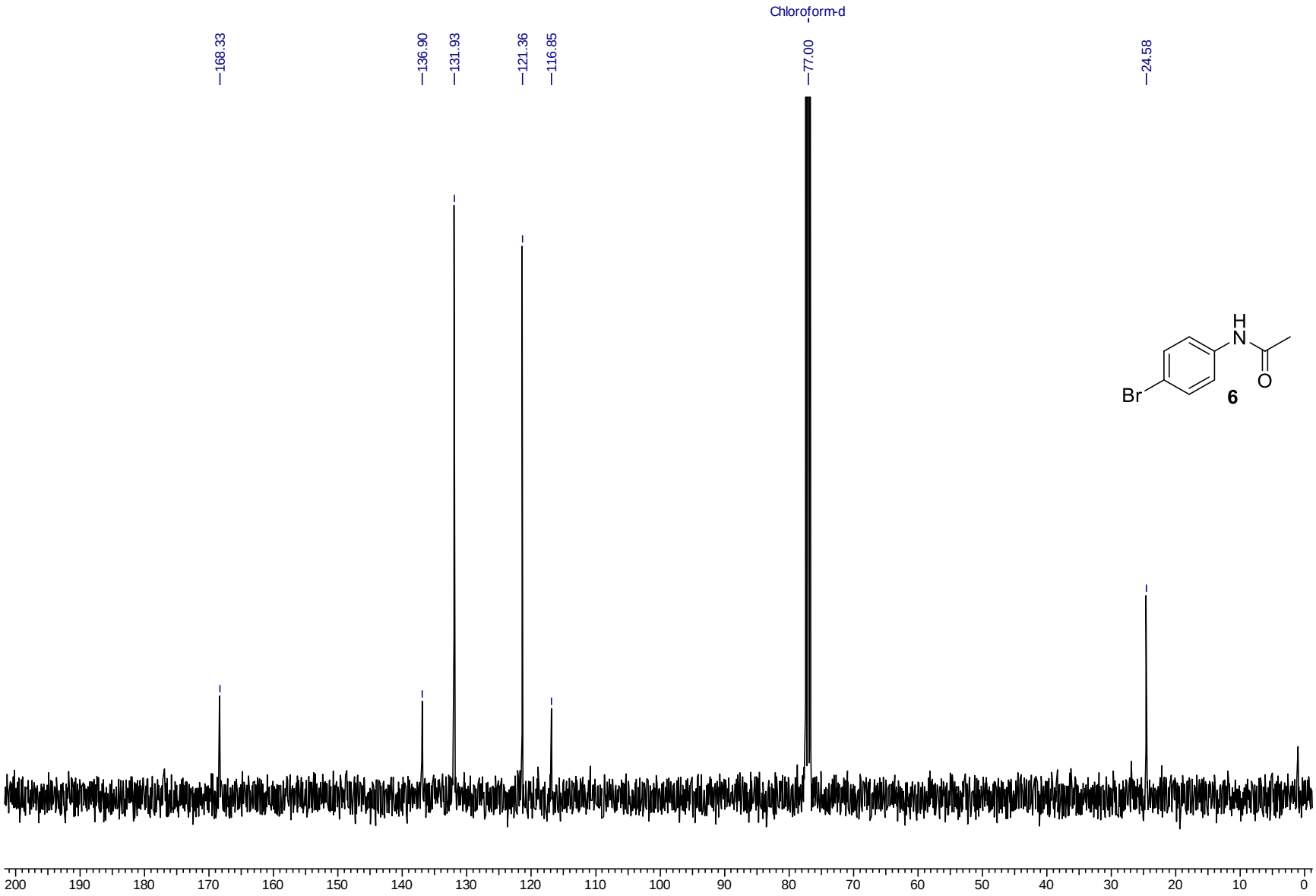

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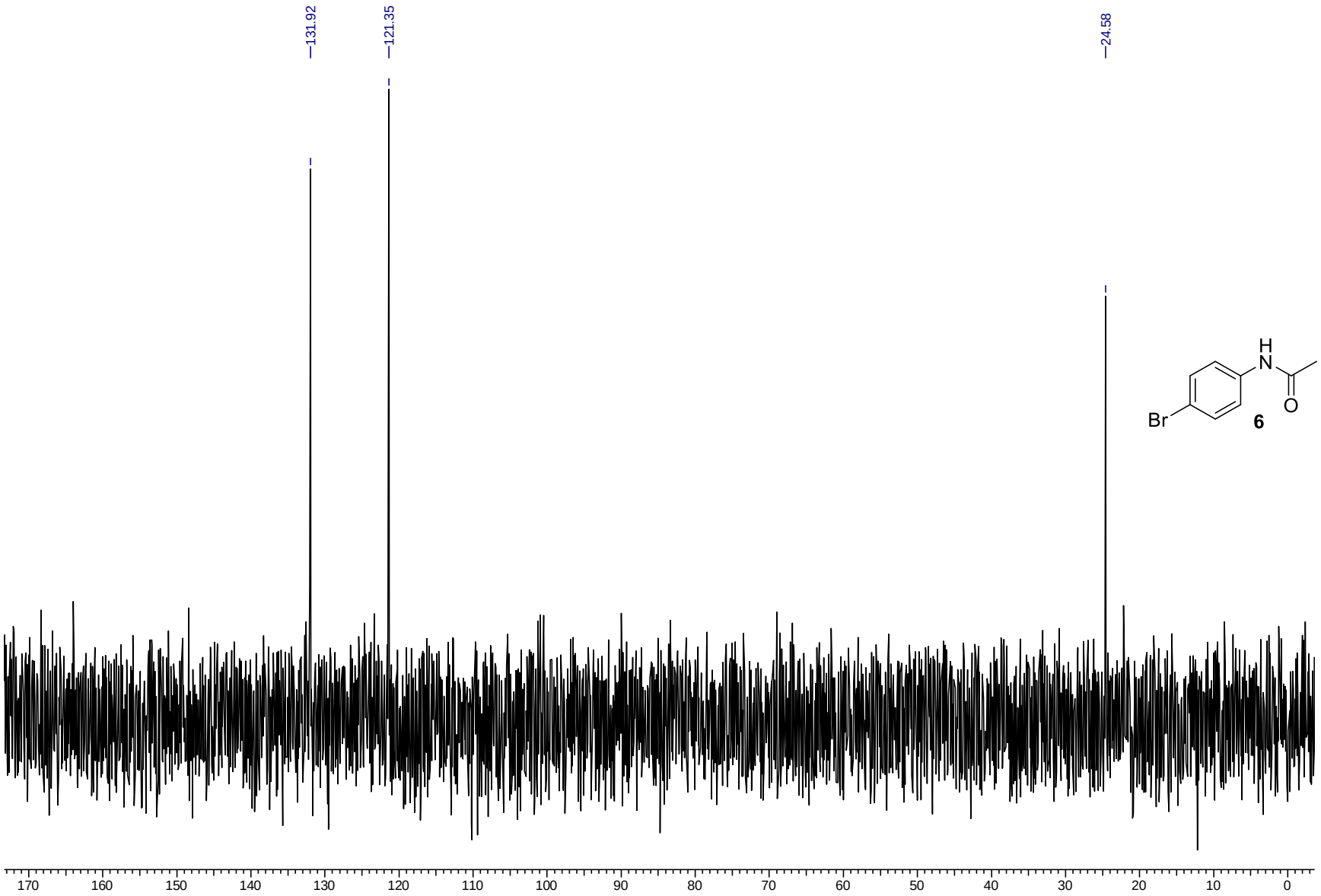

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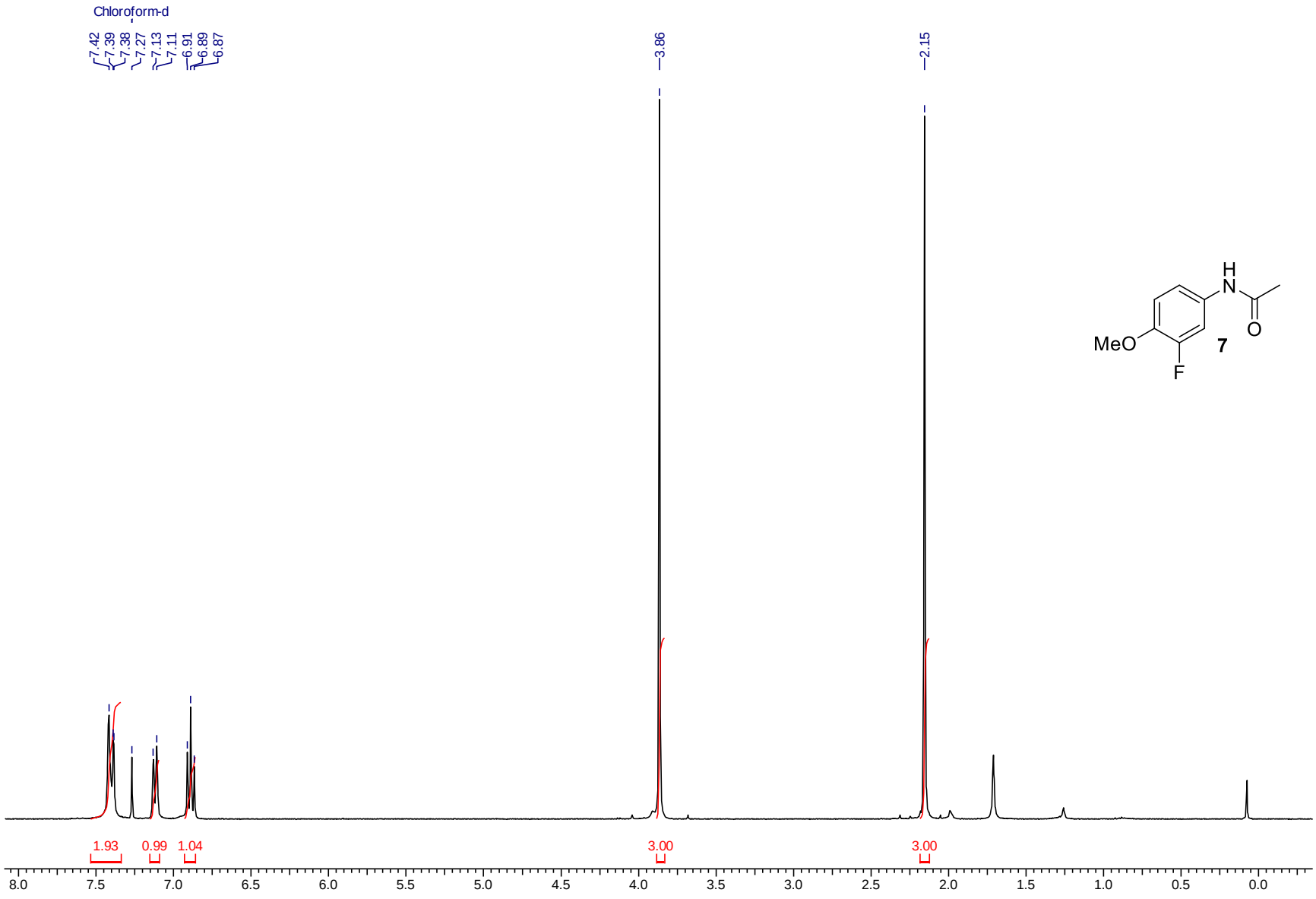
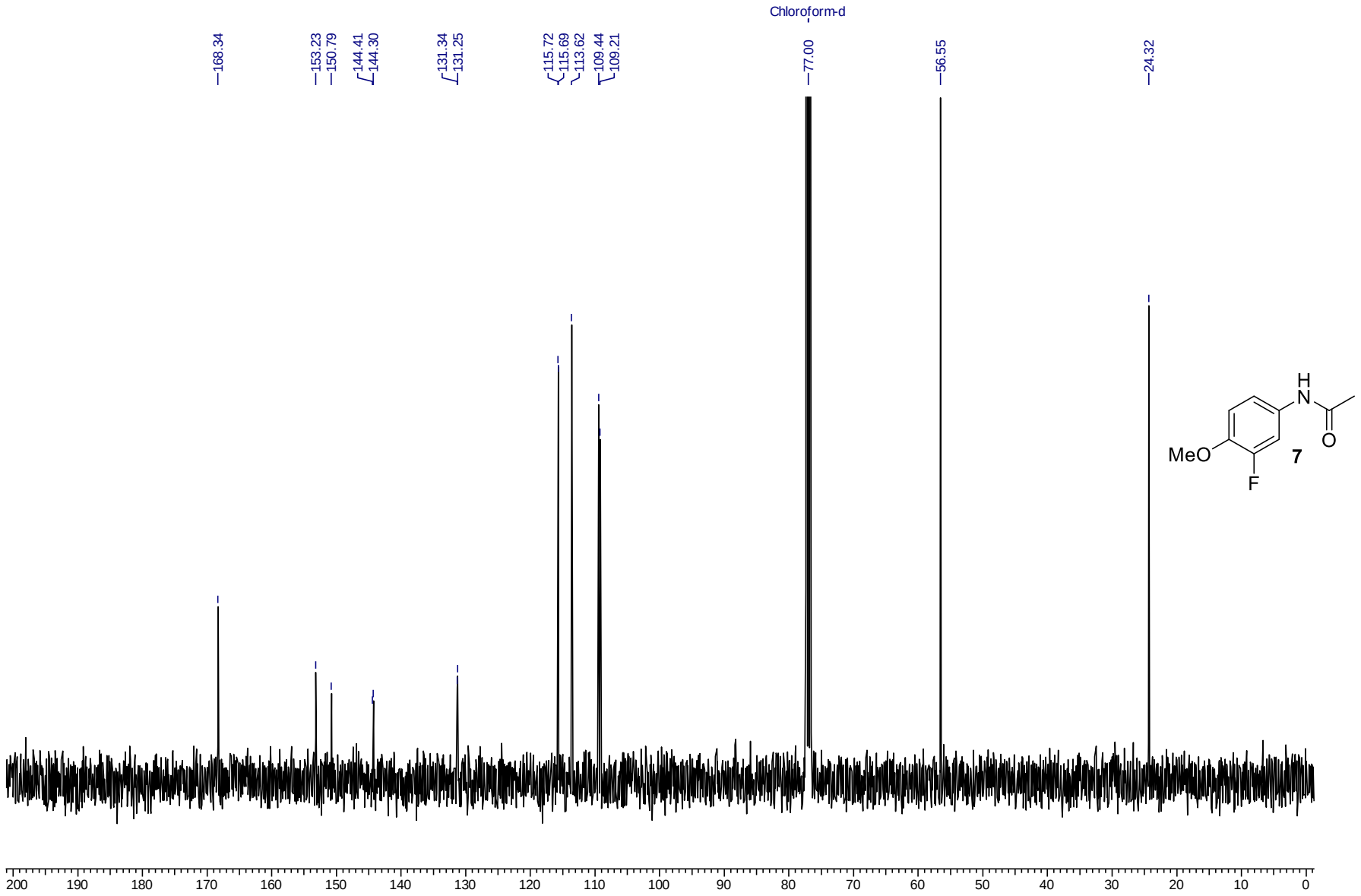


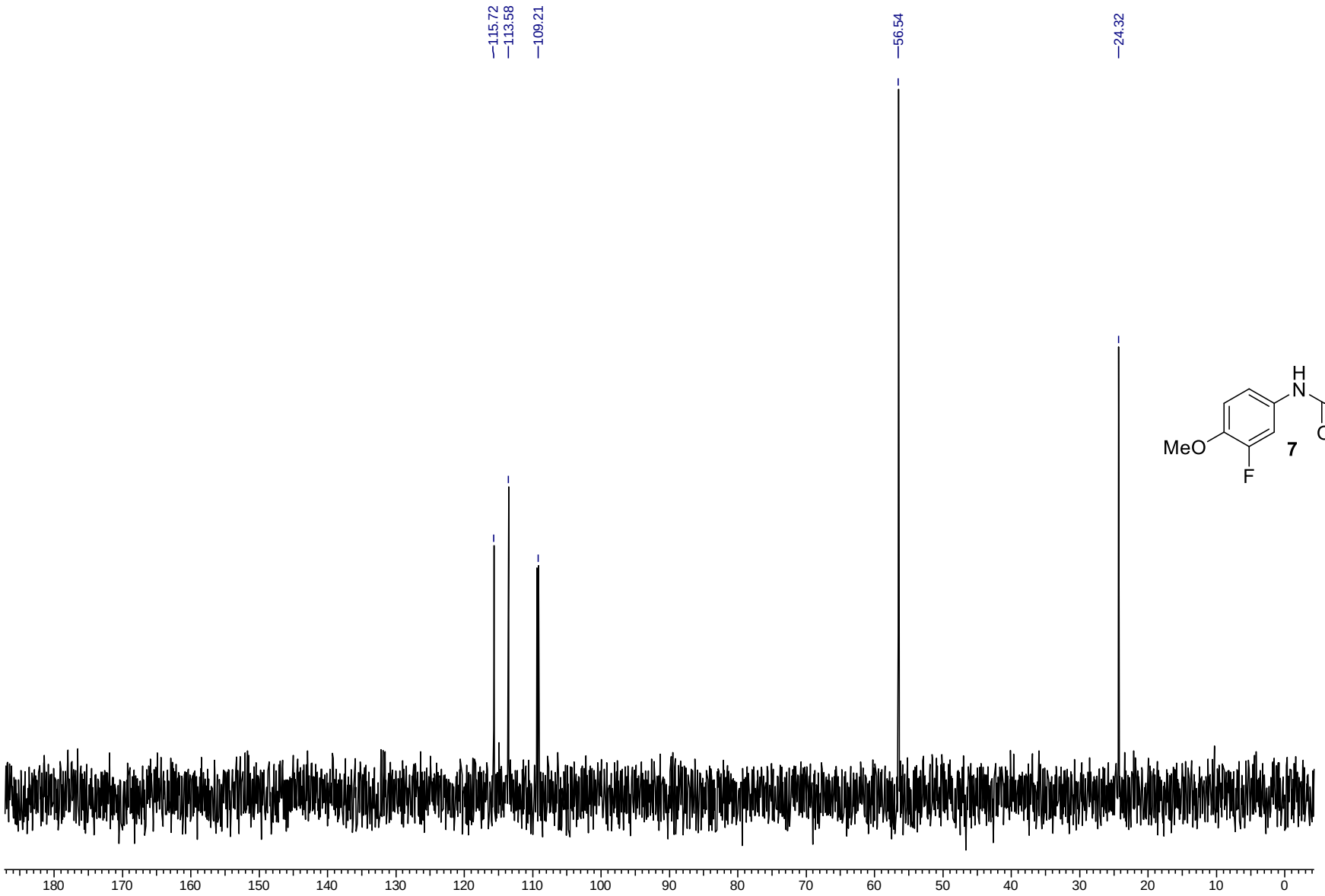
7

^{13}C NMR, 100MHz



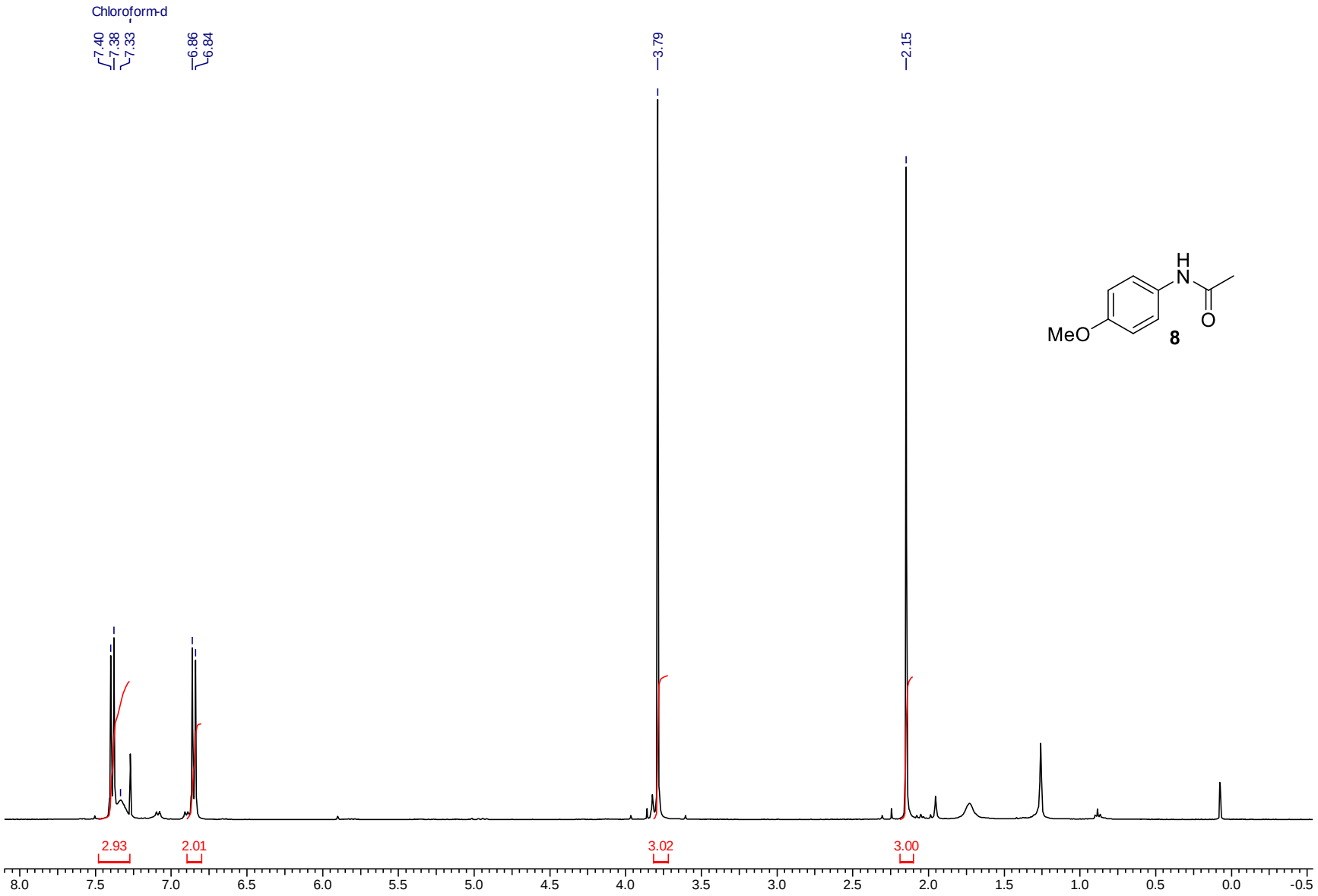
7

DEPT NMR, 100MHz



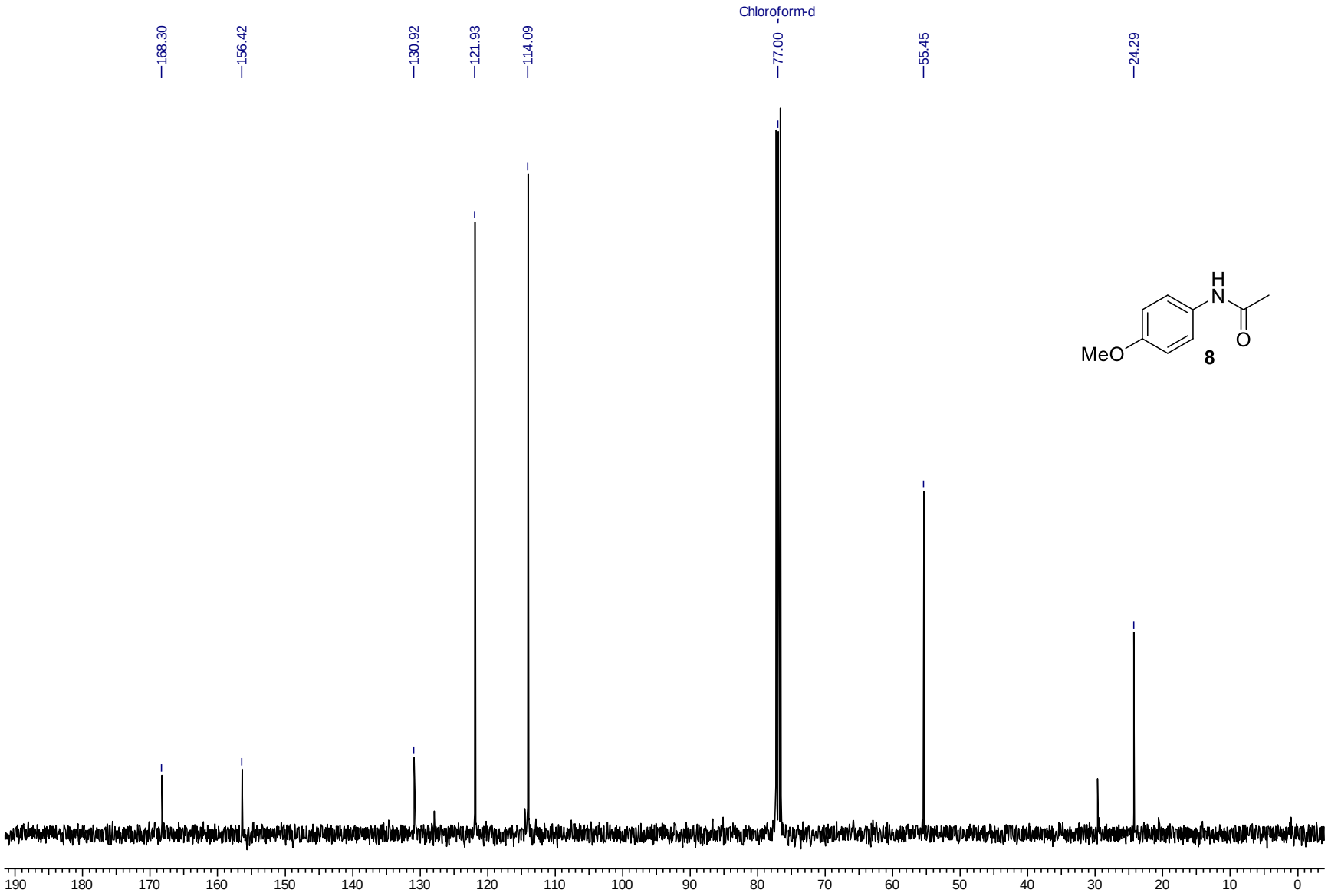
7

^{1}H NMR, 400MHz



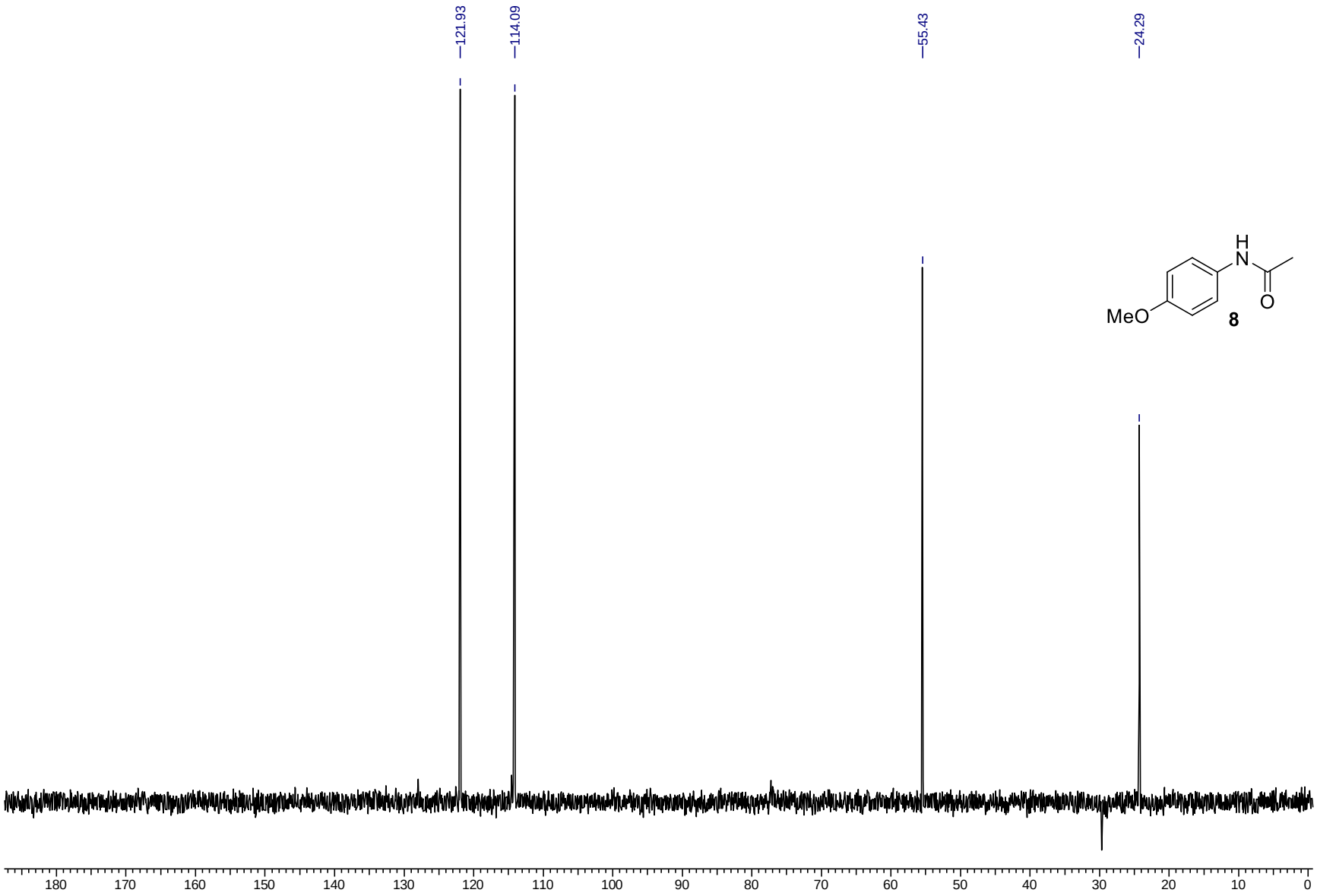
8

^{13}C NMR, 100MHz

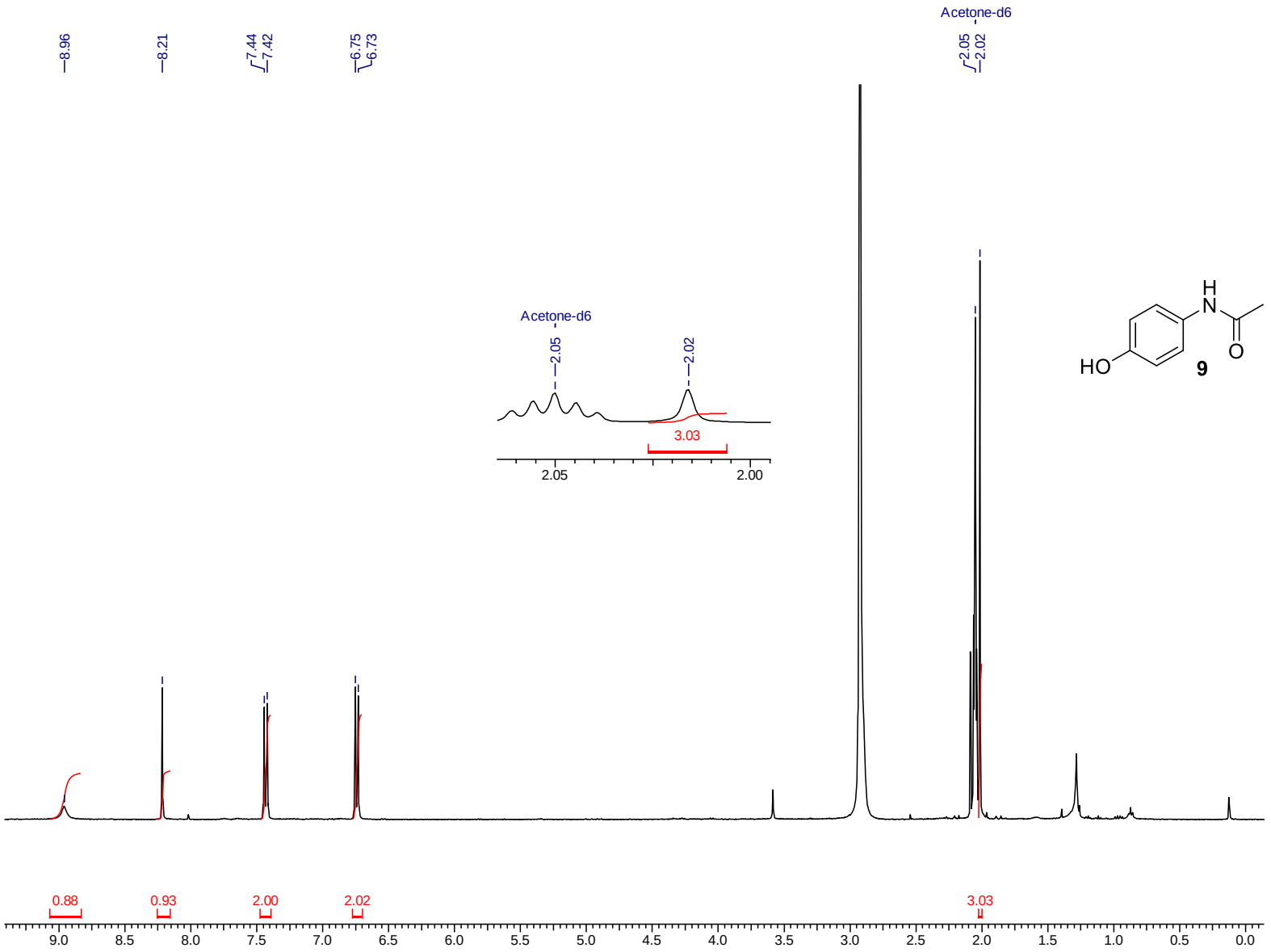


8

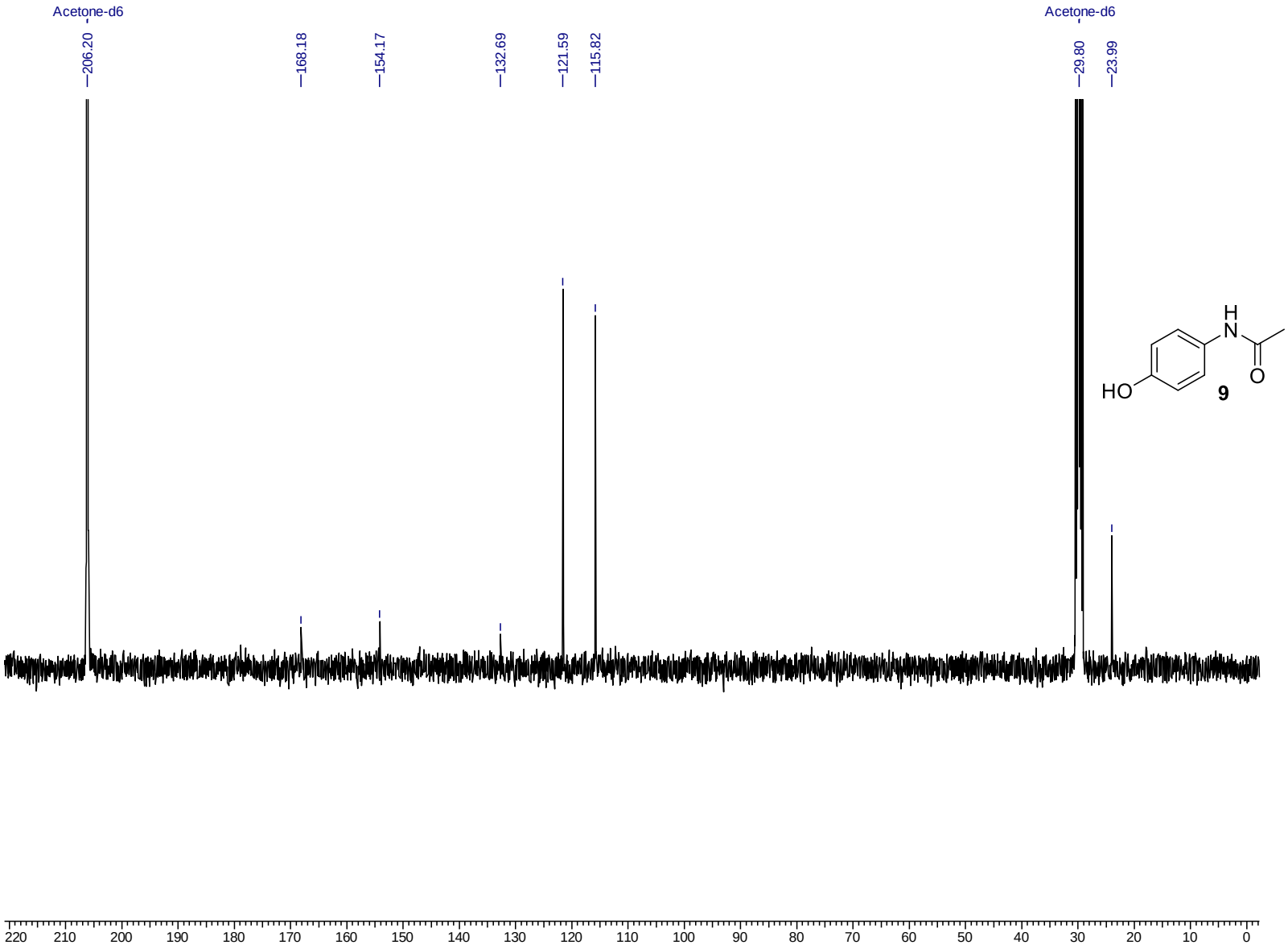
DEPT NMR, 100MHz



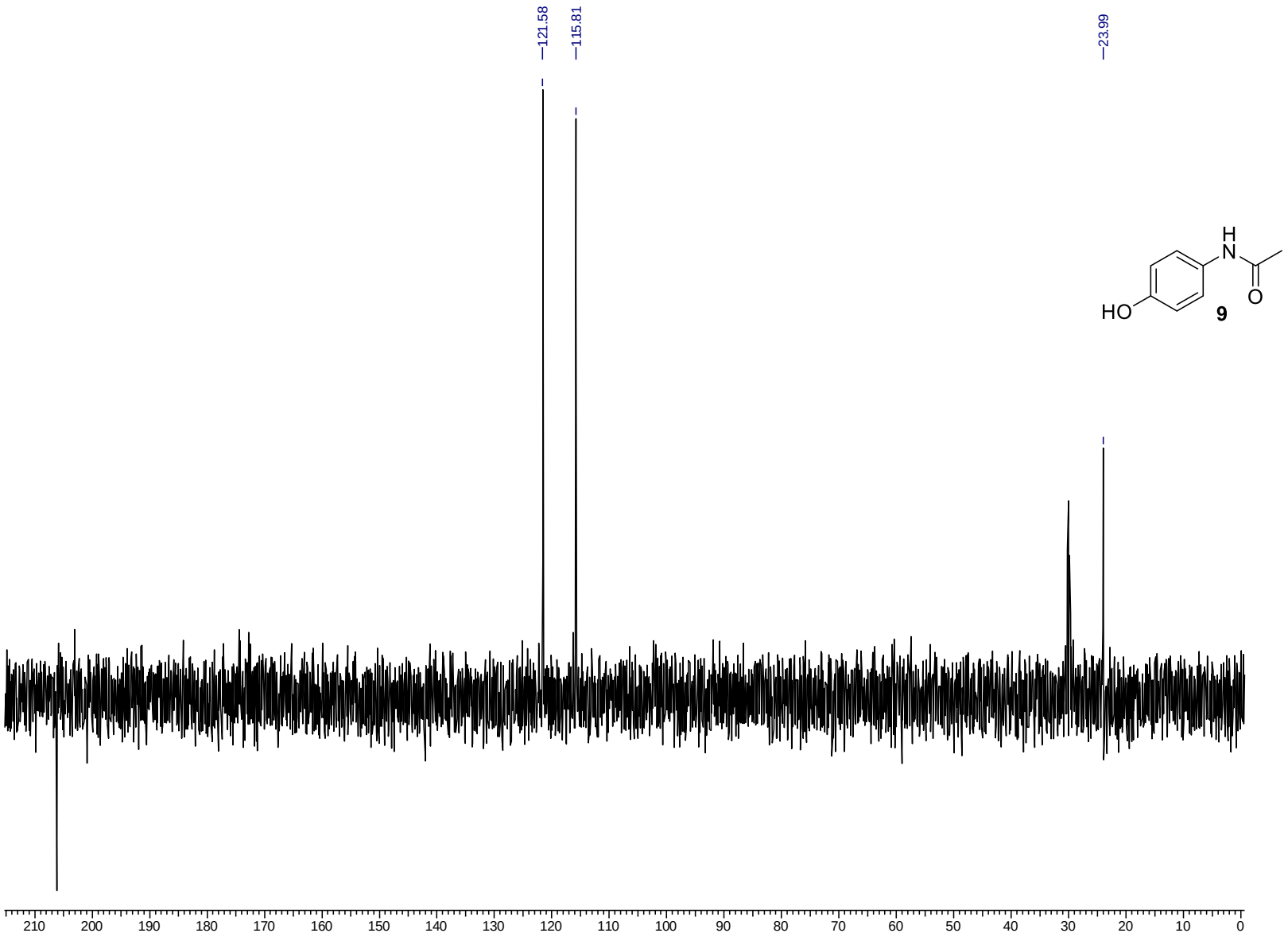
^{1}H NMR, 400MHz



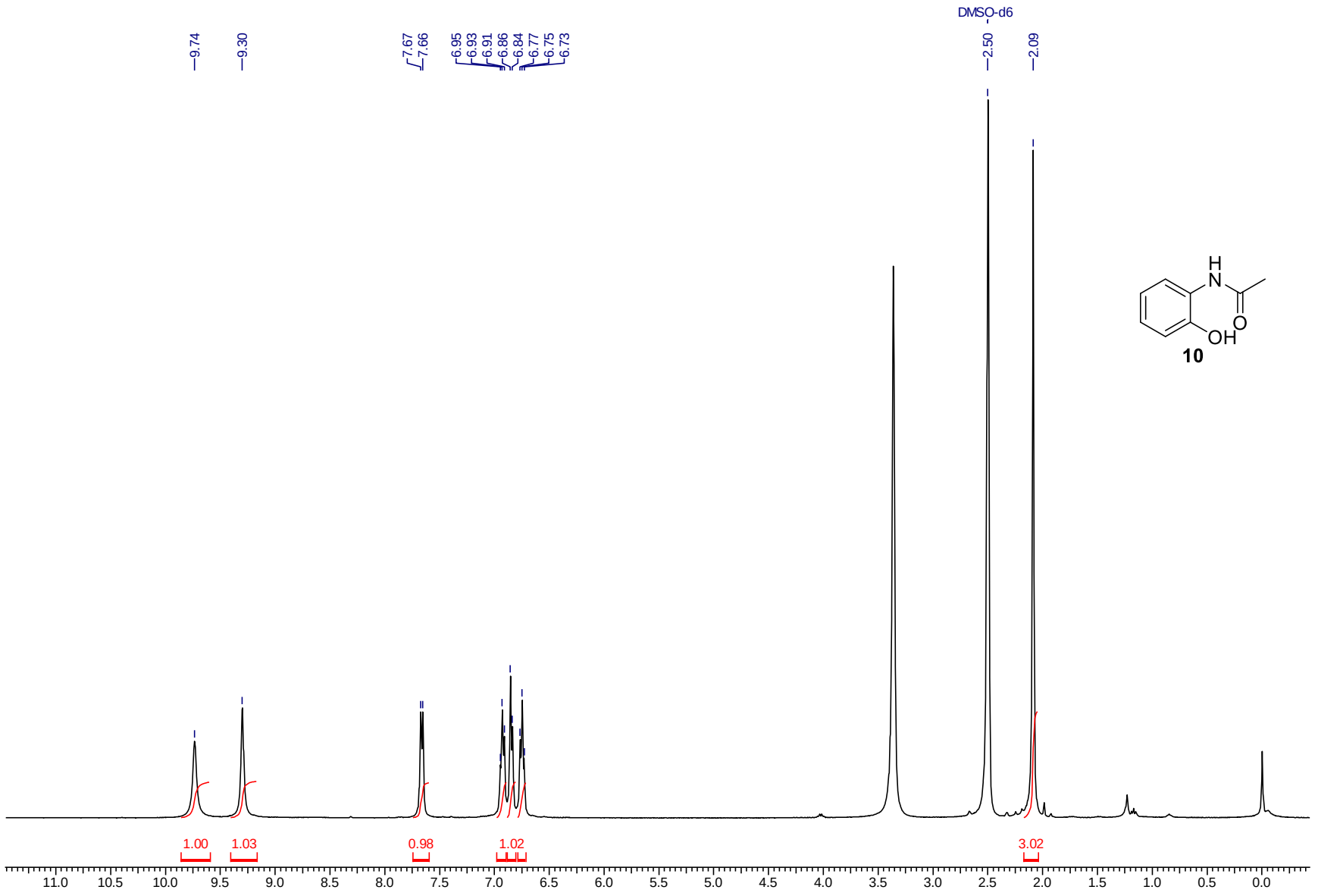
^{13}C NMR, 100MHz



DEPT NMR, 100MHz

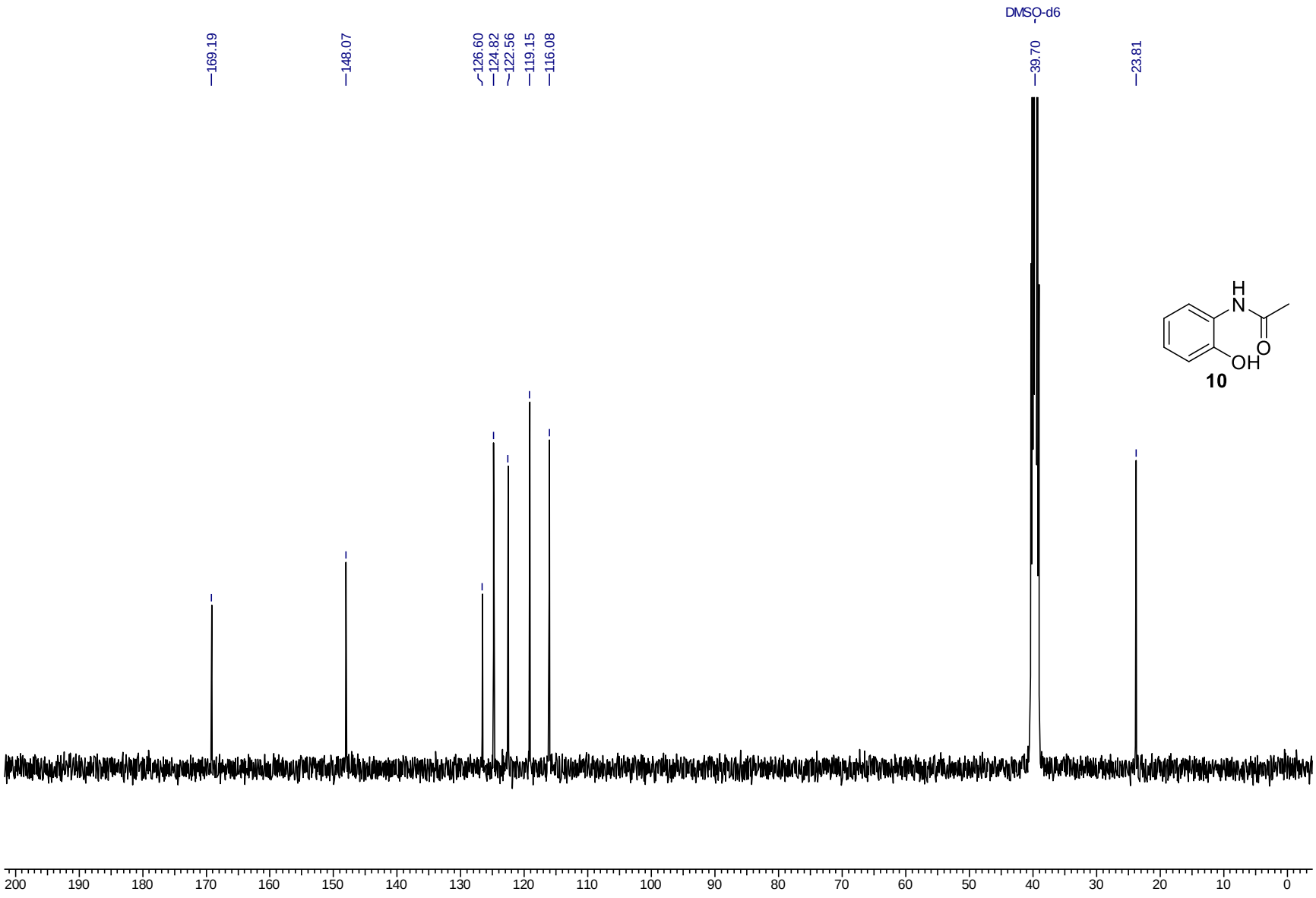


^{1}H NMR, 400MHz

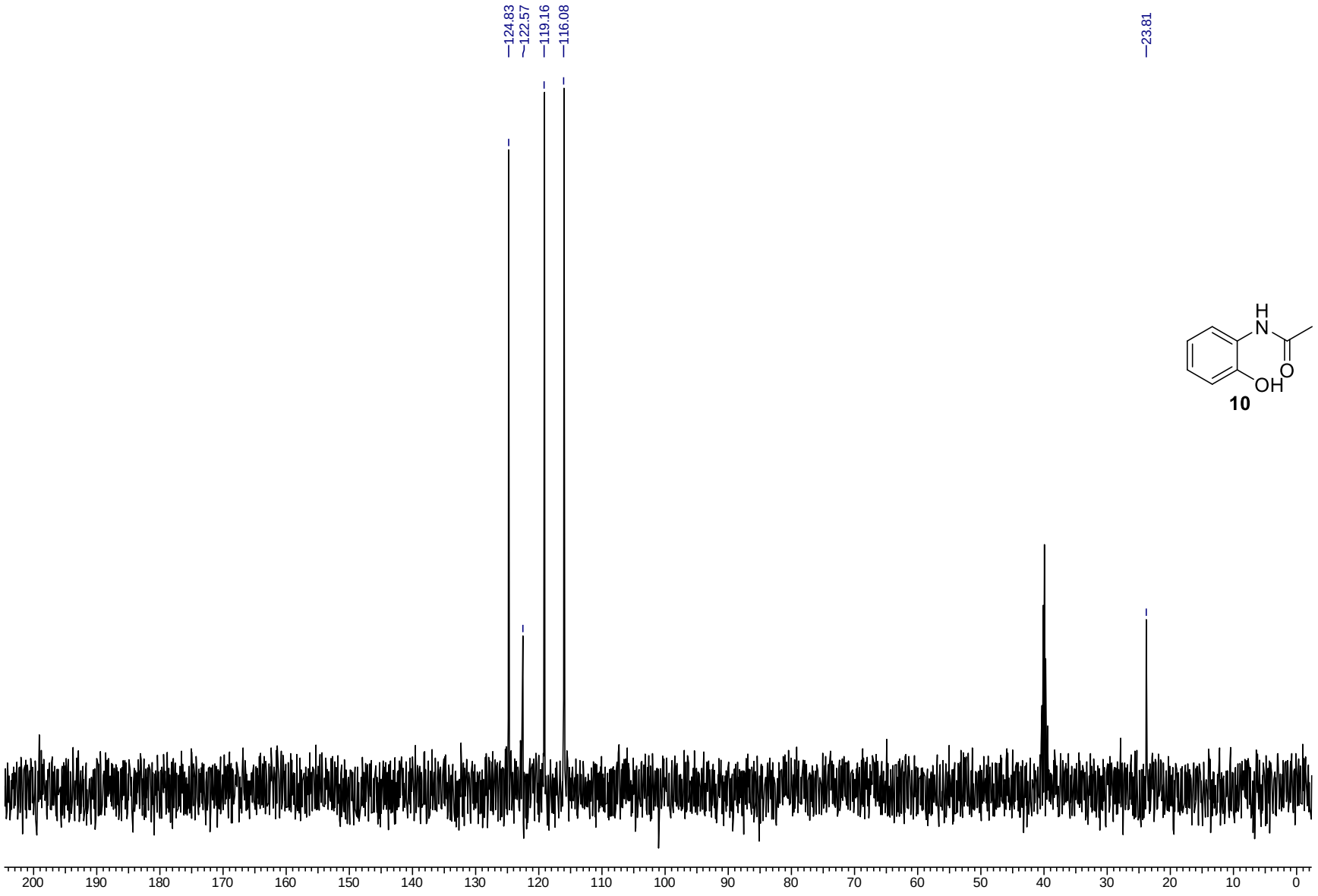


10

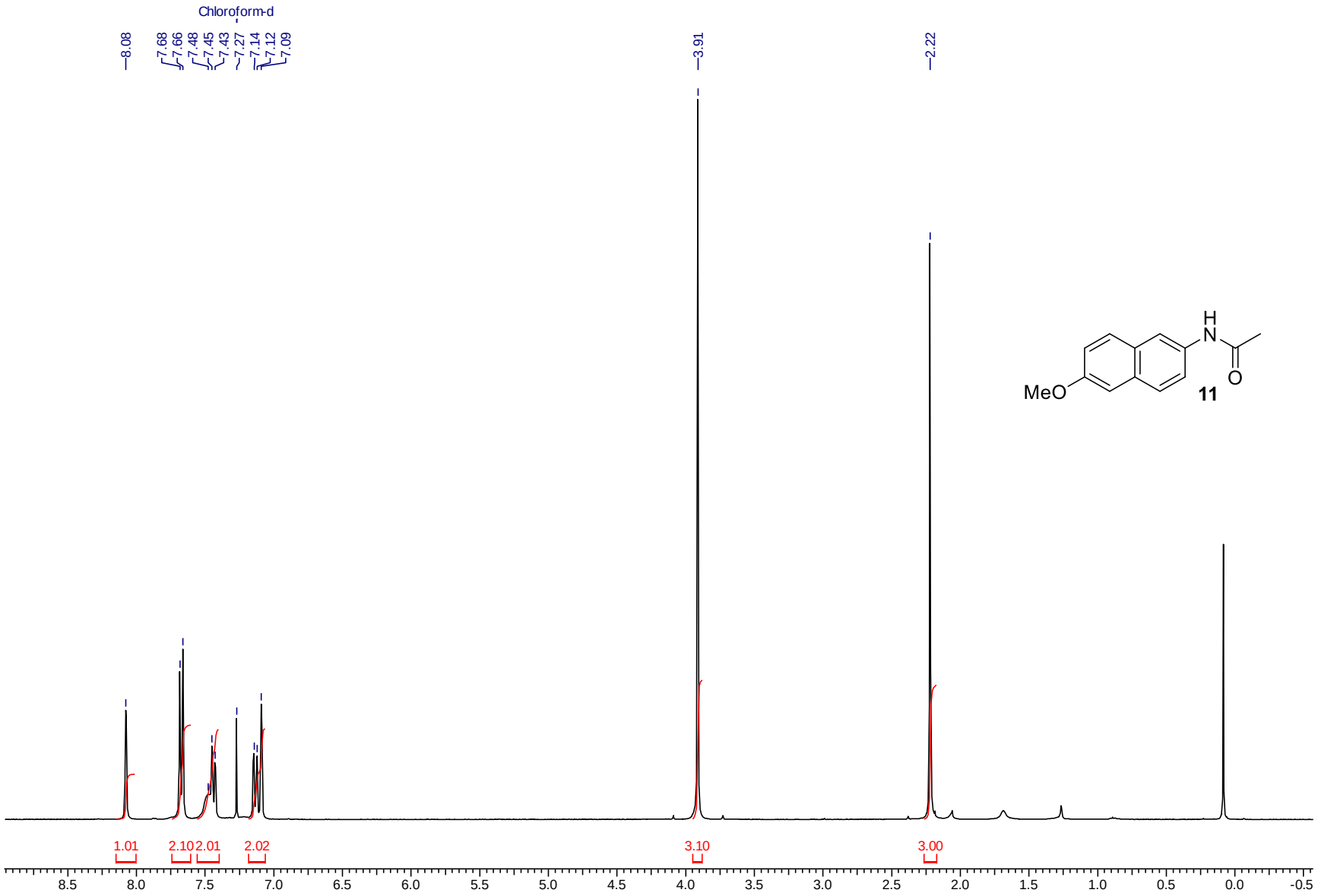
^{13}C NMR, 100MHz



DEPT NMR, 100MHz

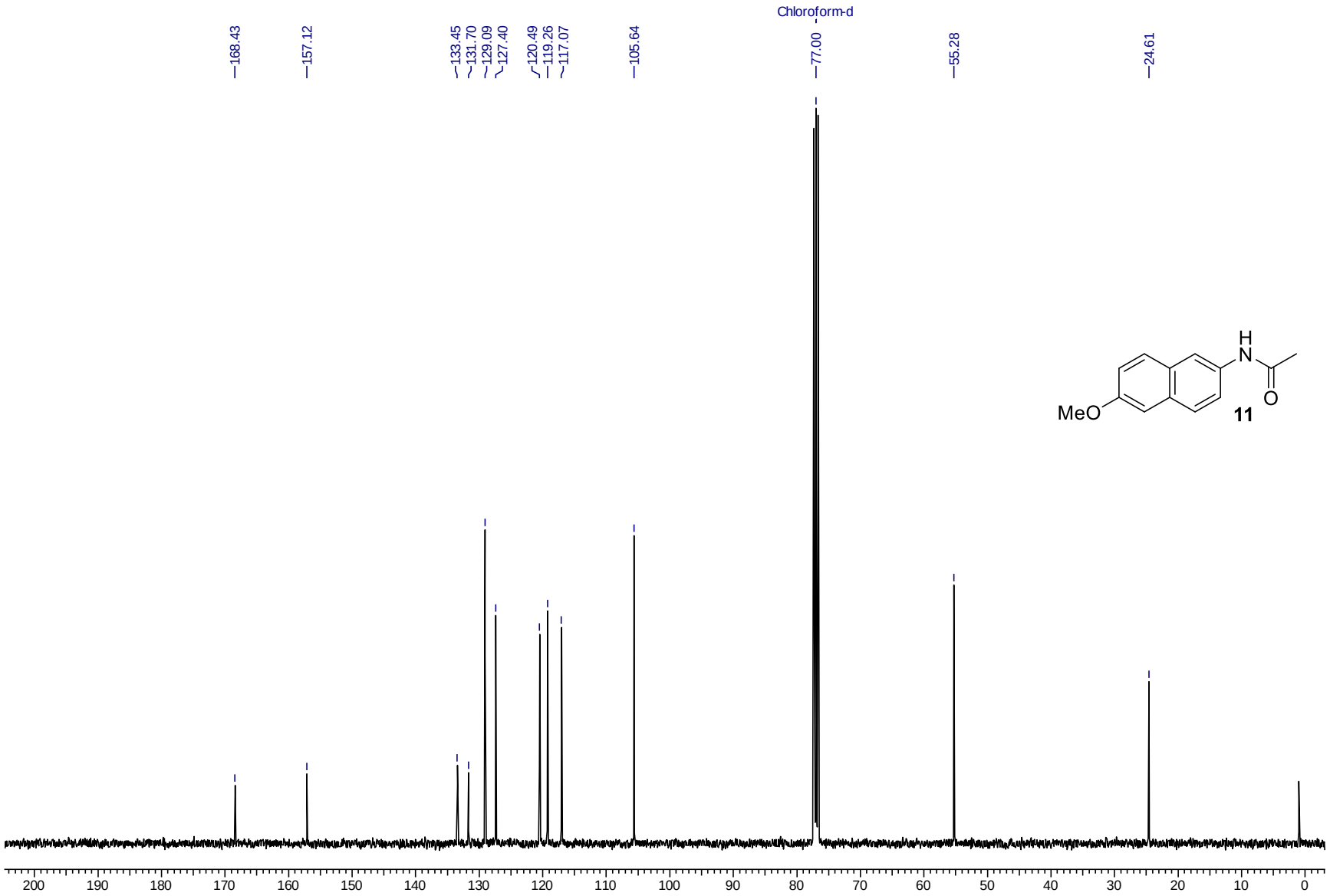


^{1}H NMR, 400MHz

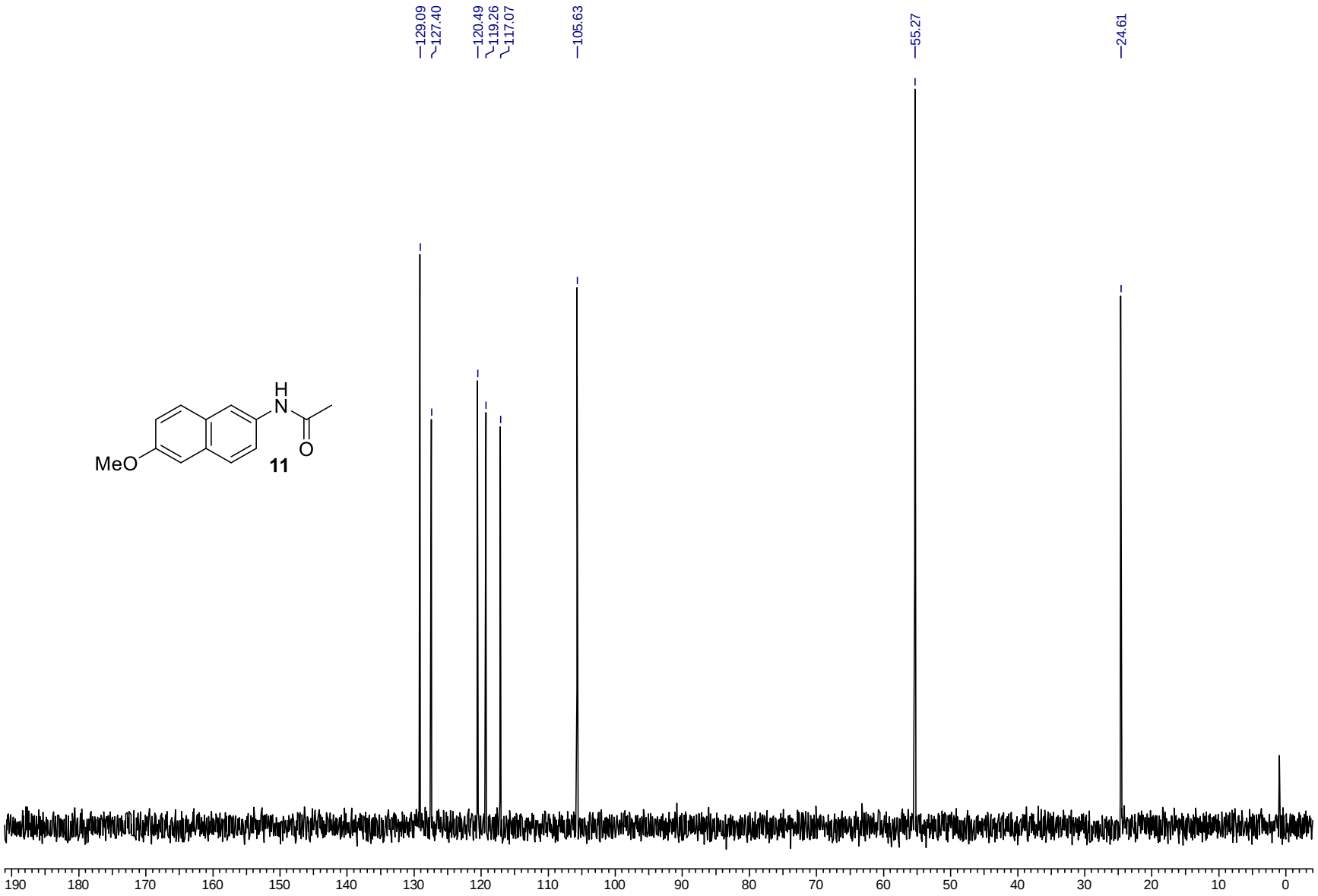


11

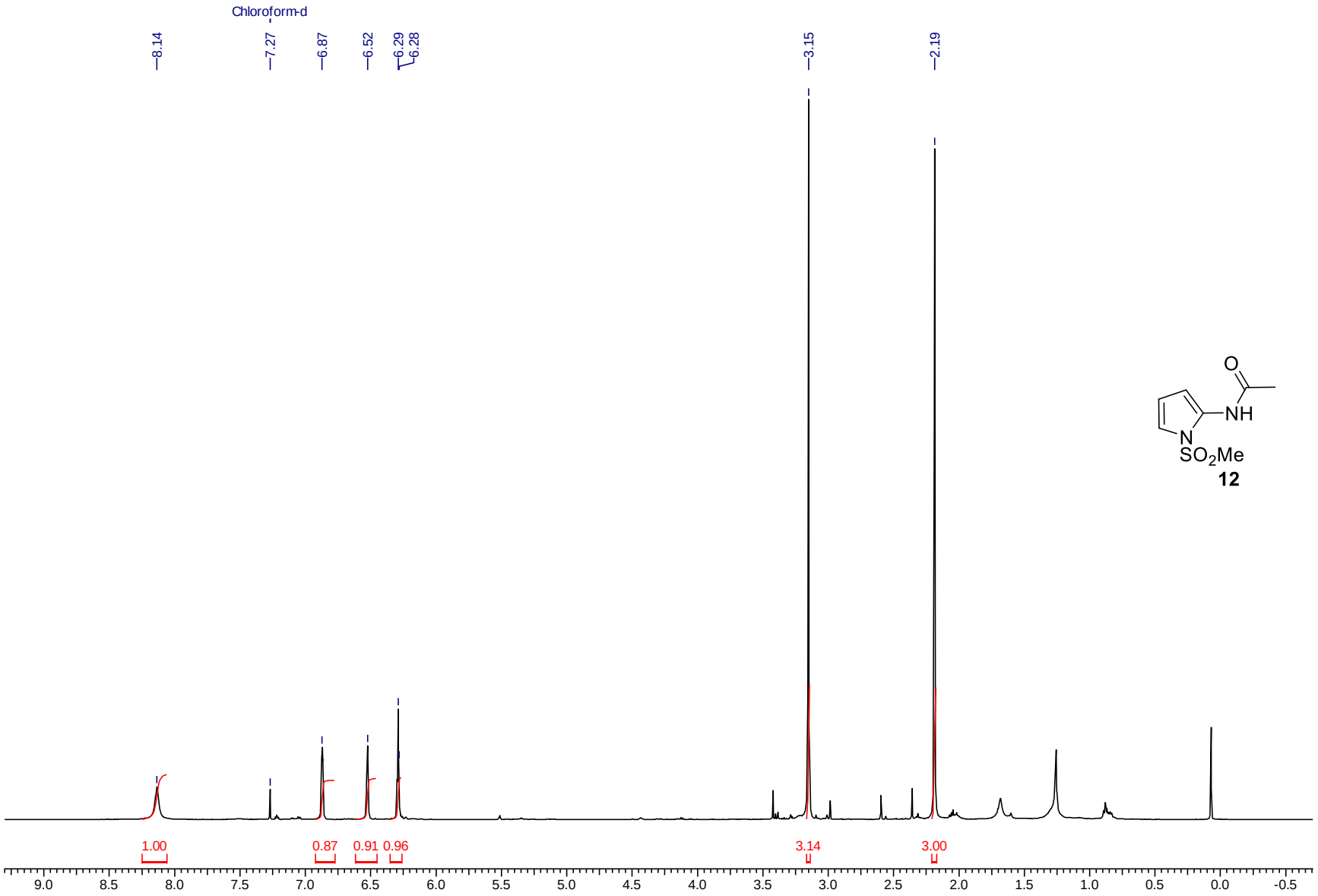
^{13}C NMR, 100MHz



DEPT NMR, 100MHz

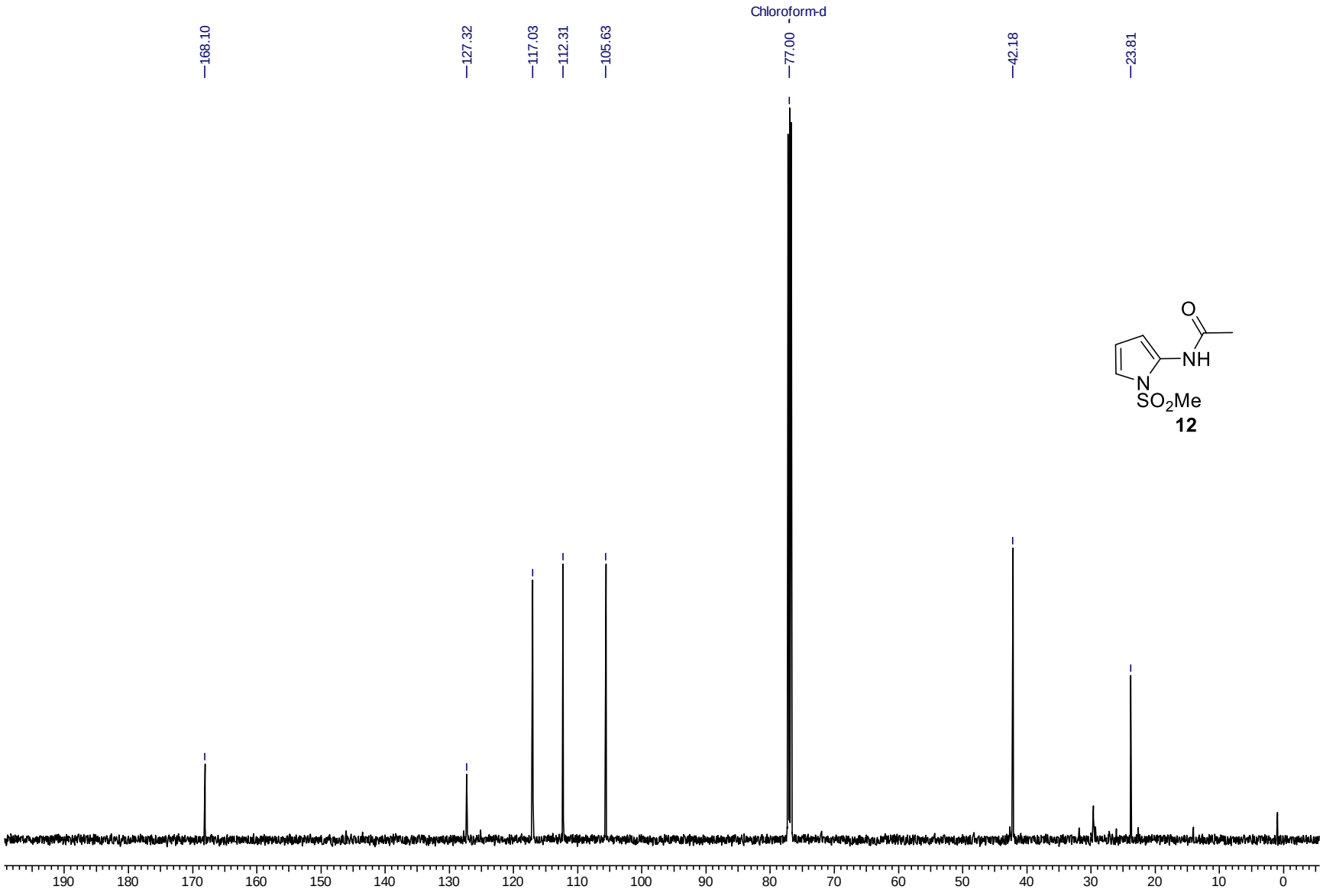


^{1}H NMR, 500MHz

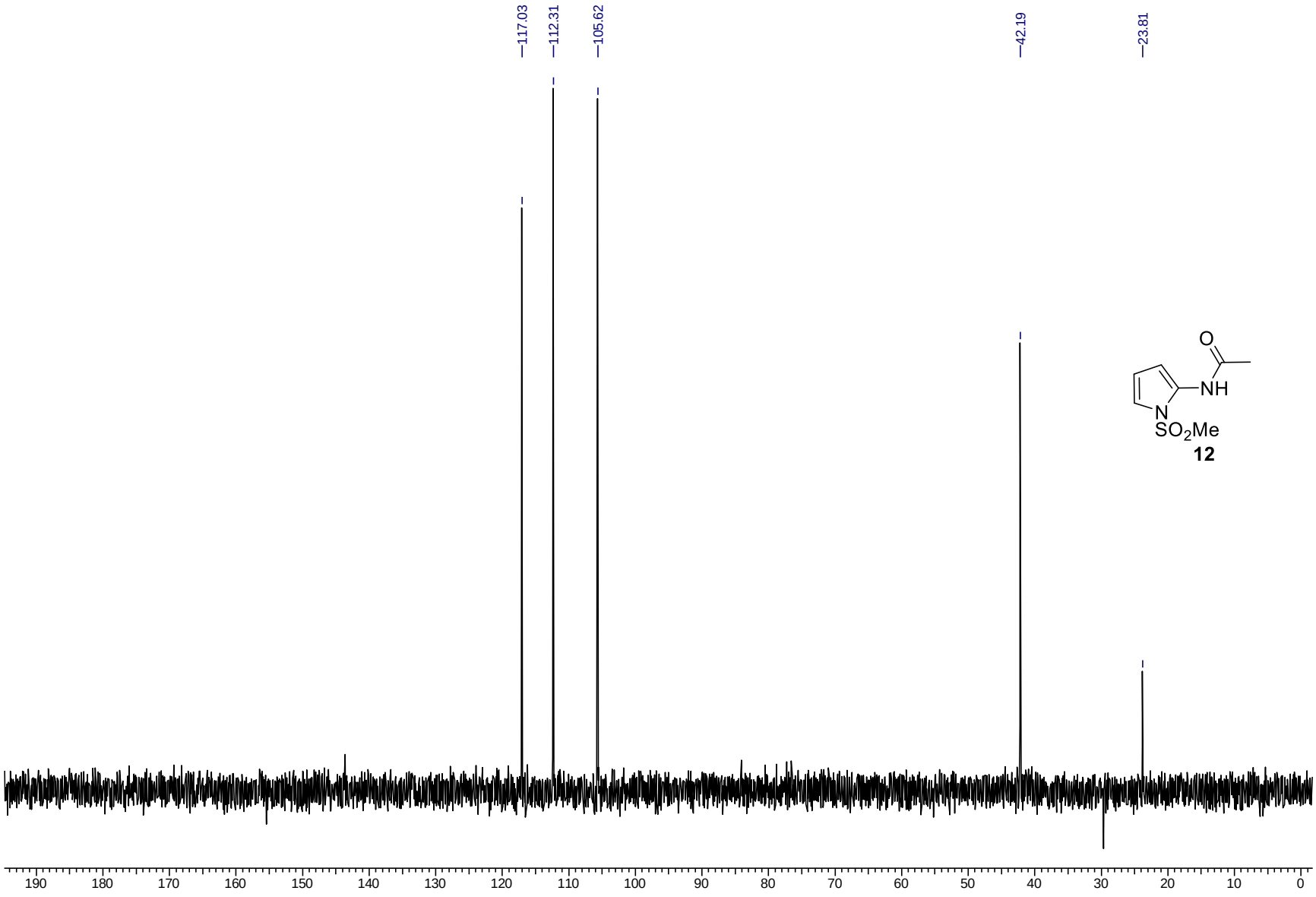


12

^{13}C NMR, 125MHz

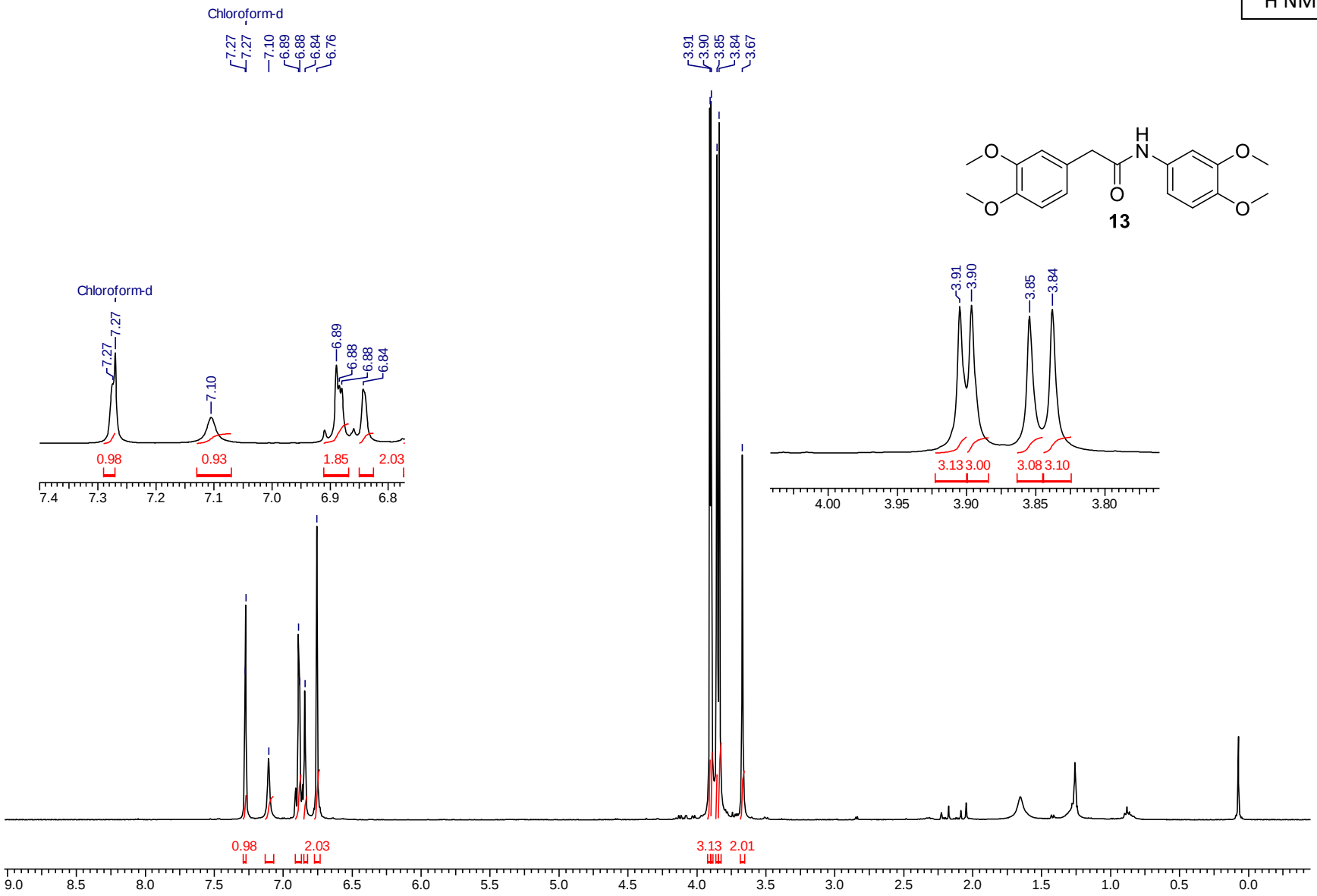


DEPT NMR, 125MHz

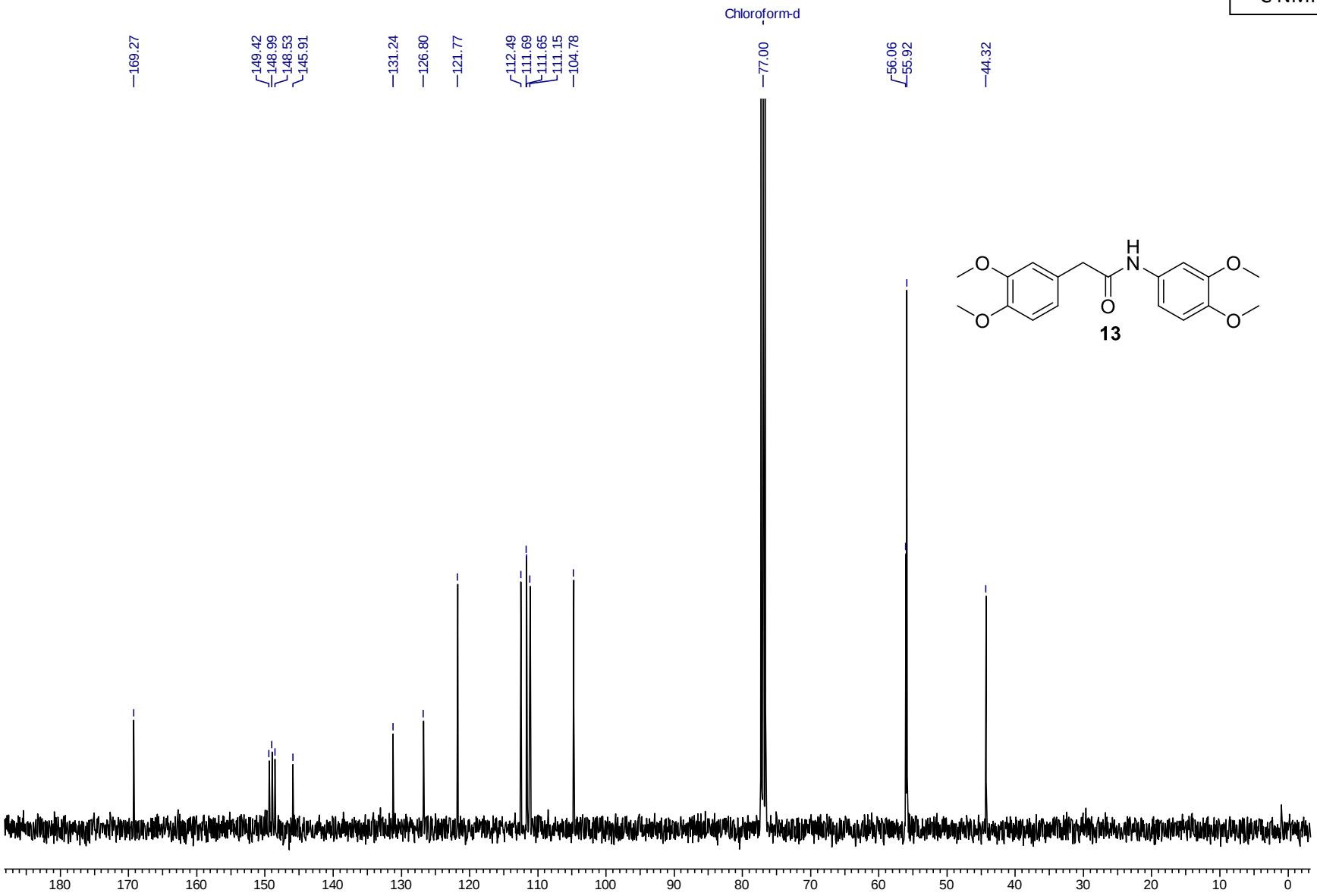


12

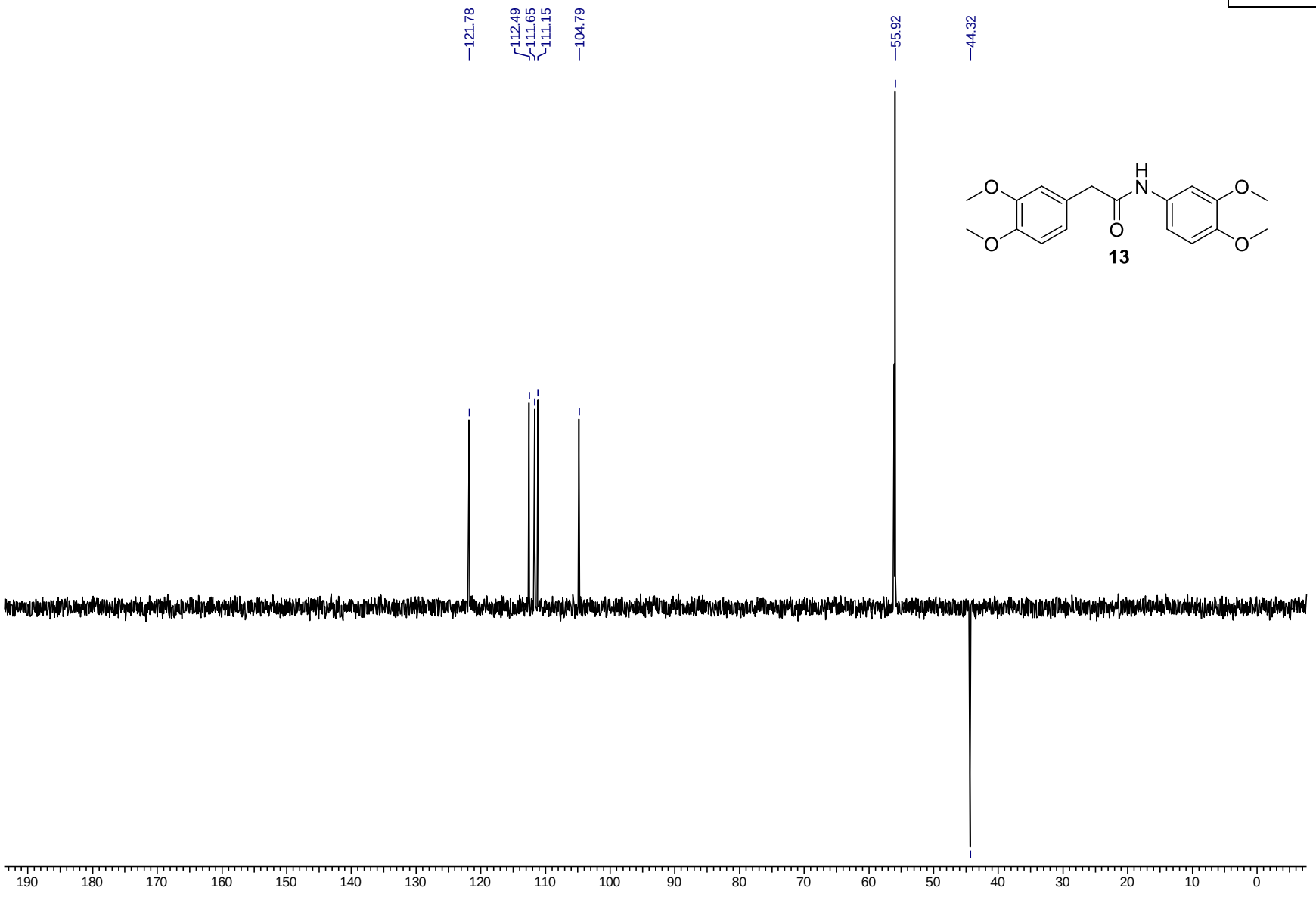
^{1}H NMR, 400MHz



^{13}C NMR, 100MHz

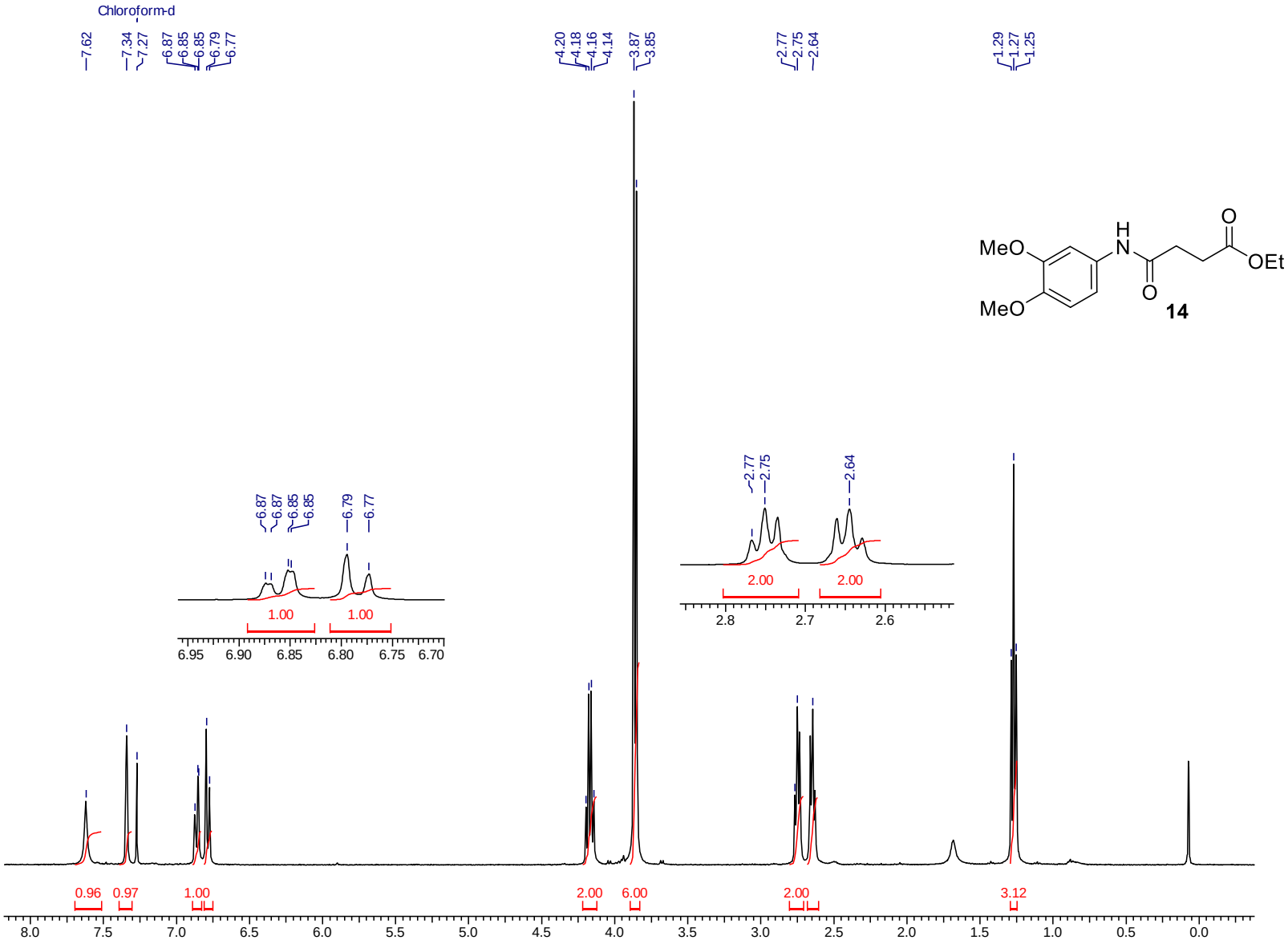


DEPT NMR, 100MHz

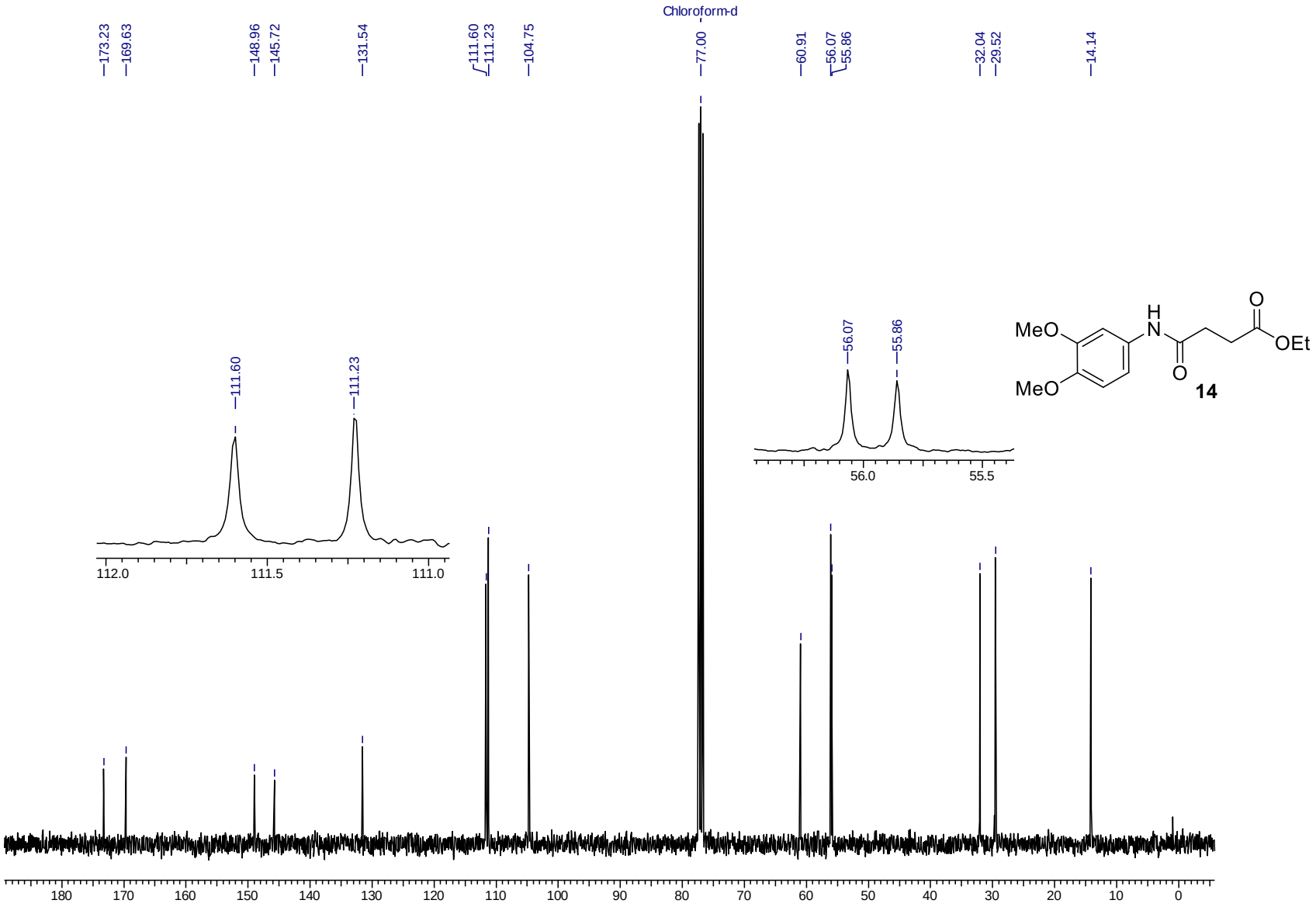


13

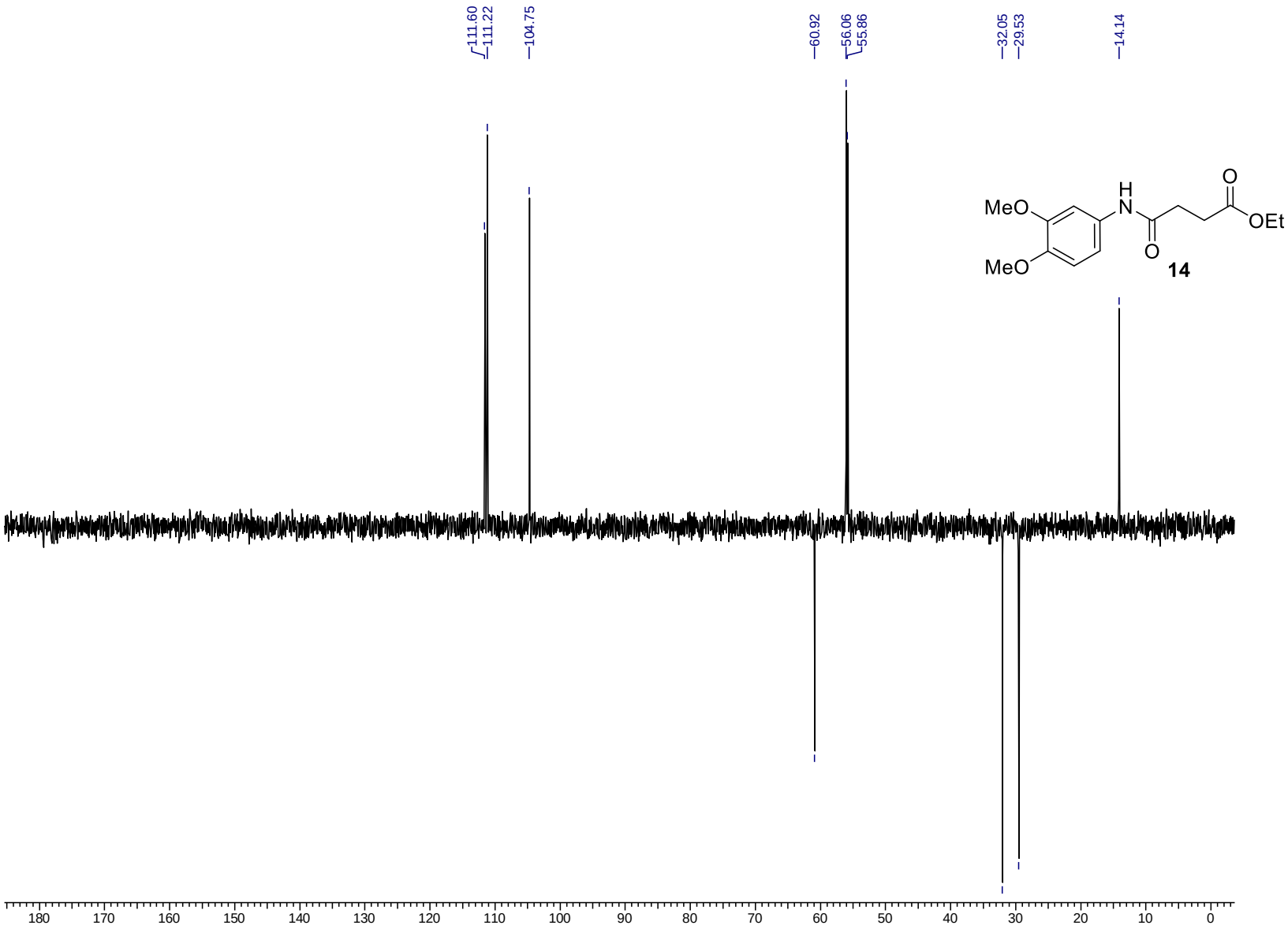
^{1}H NMR, 400MHz



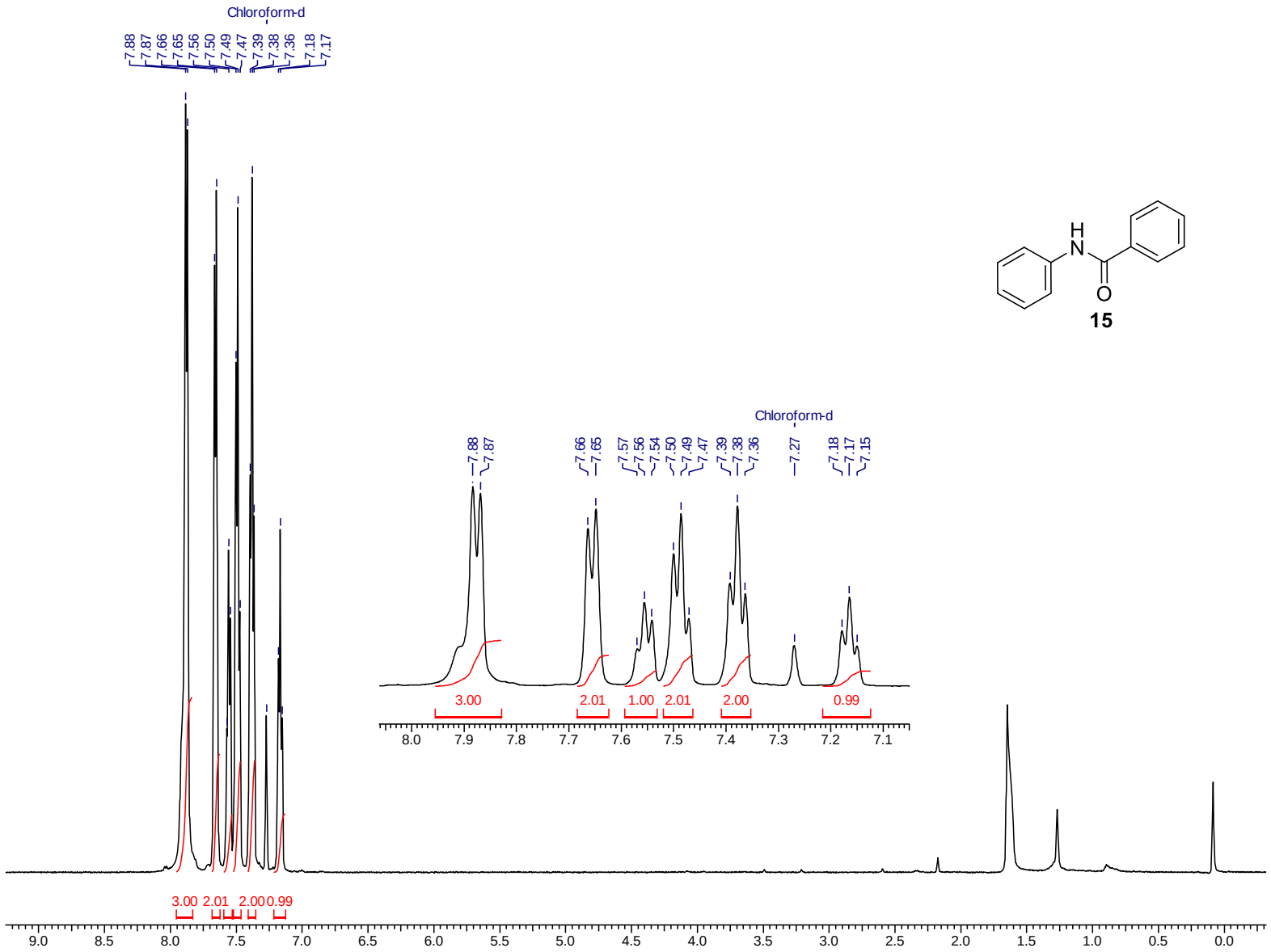
^{13}C NMR, 100MHz



DEPT NMR, 100MHz

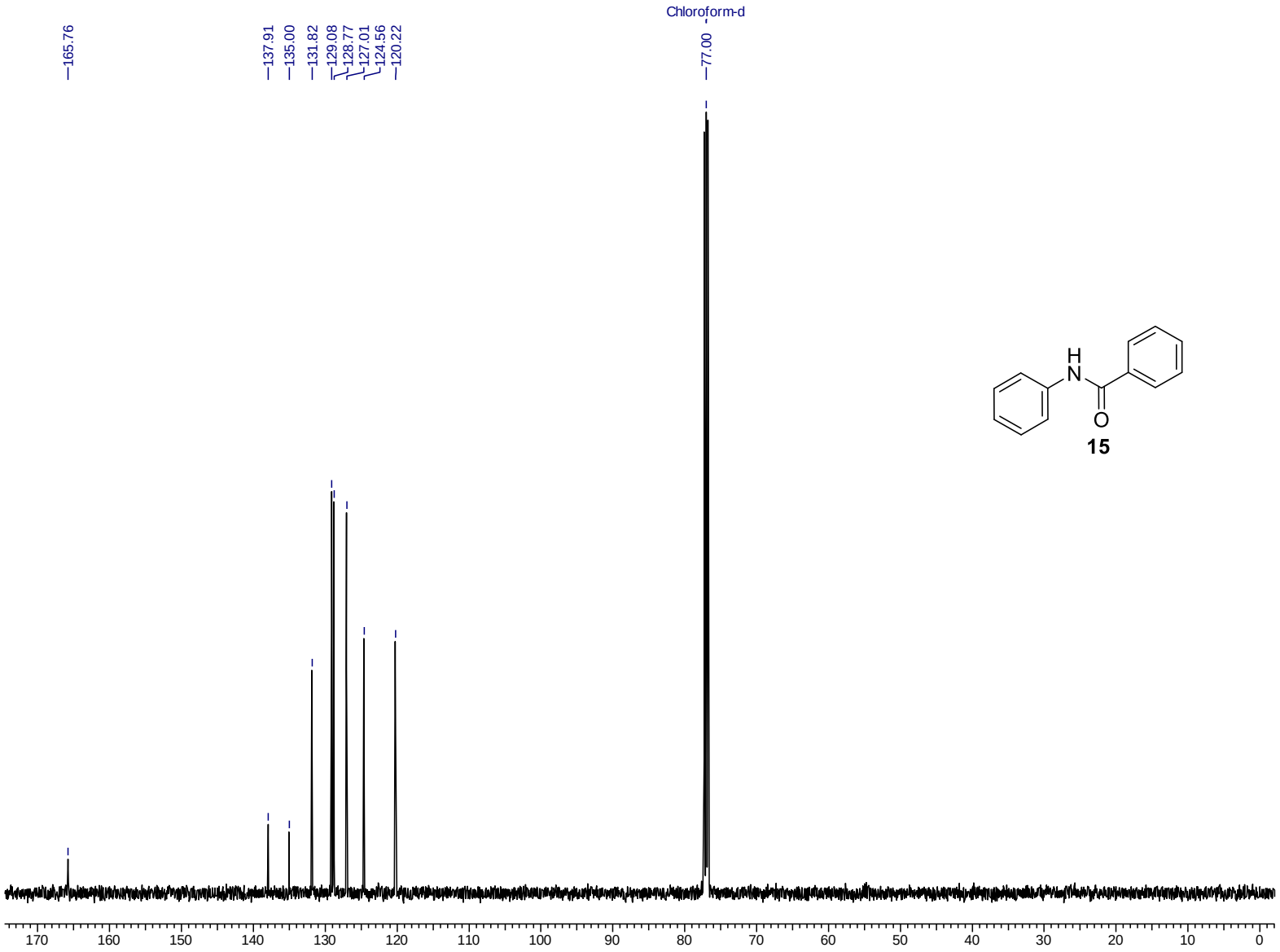


^{1}H NMR, 500MHz



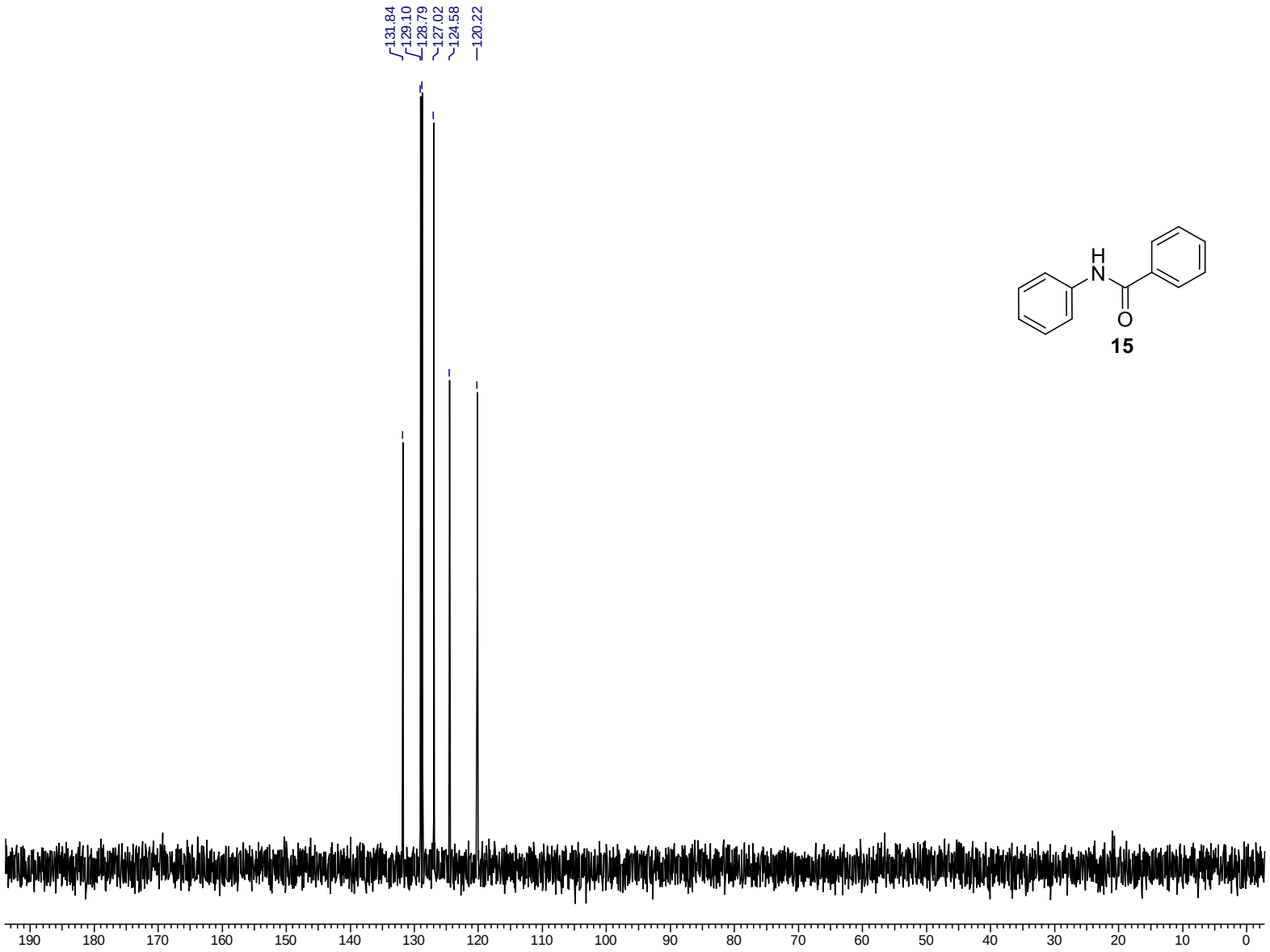
15

^{13}C NMR, 125MHz



15

DEPT NMR, 125MHz



15

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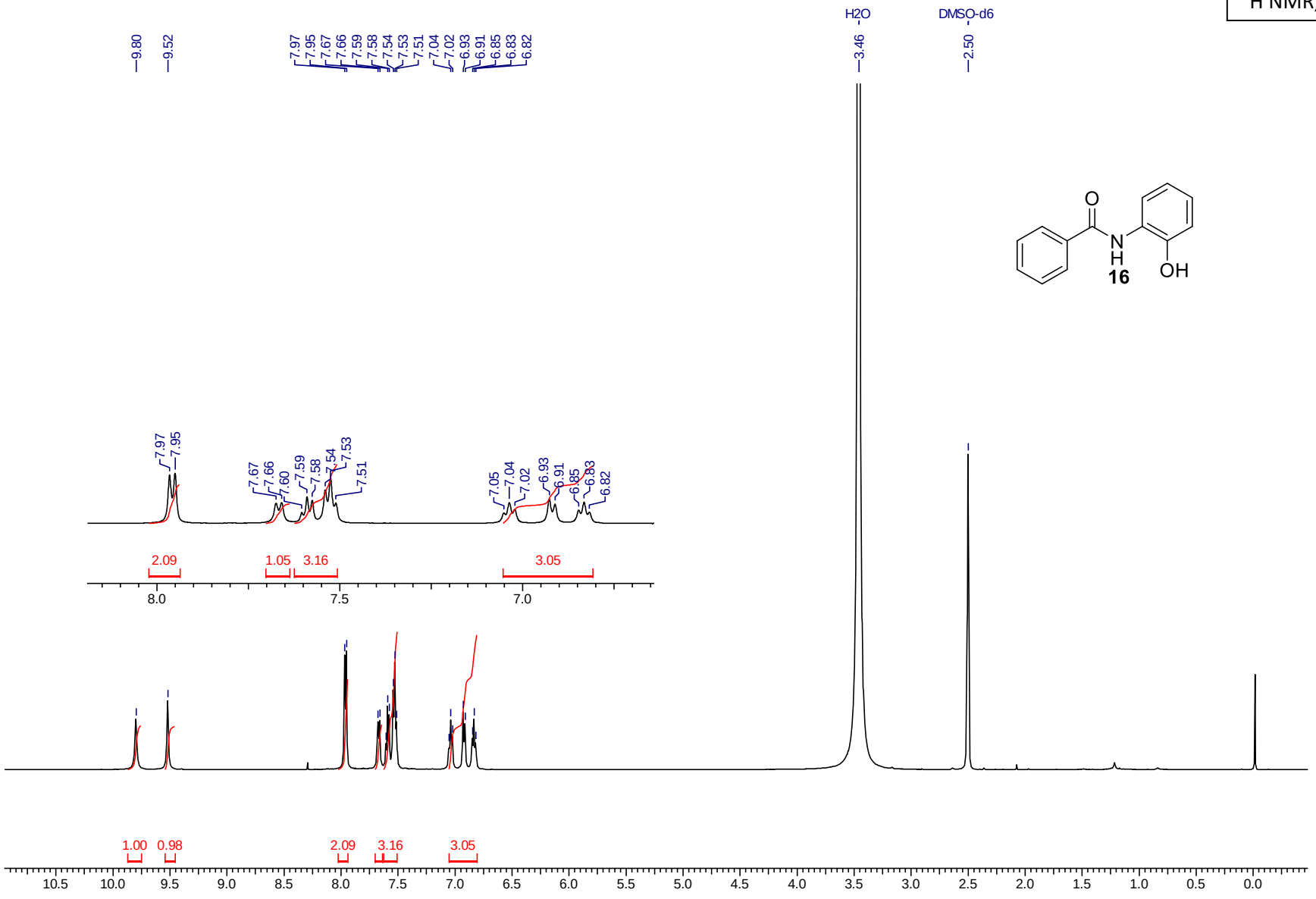
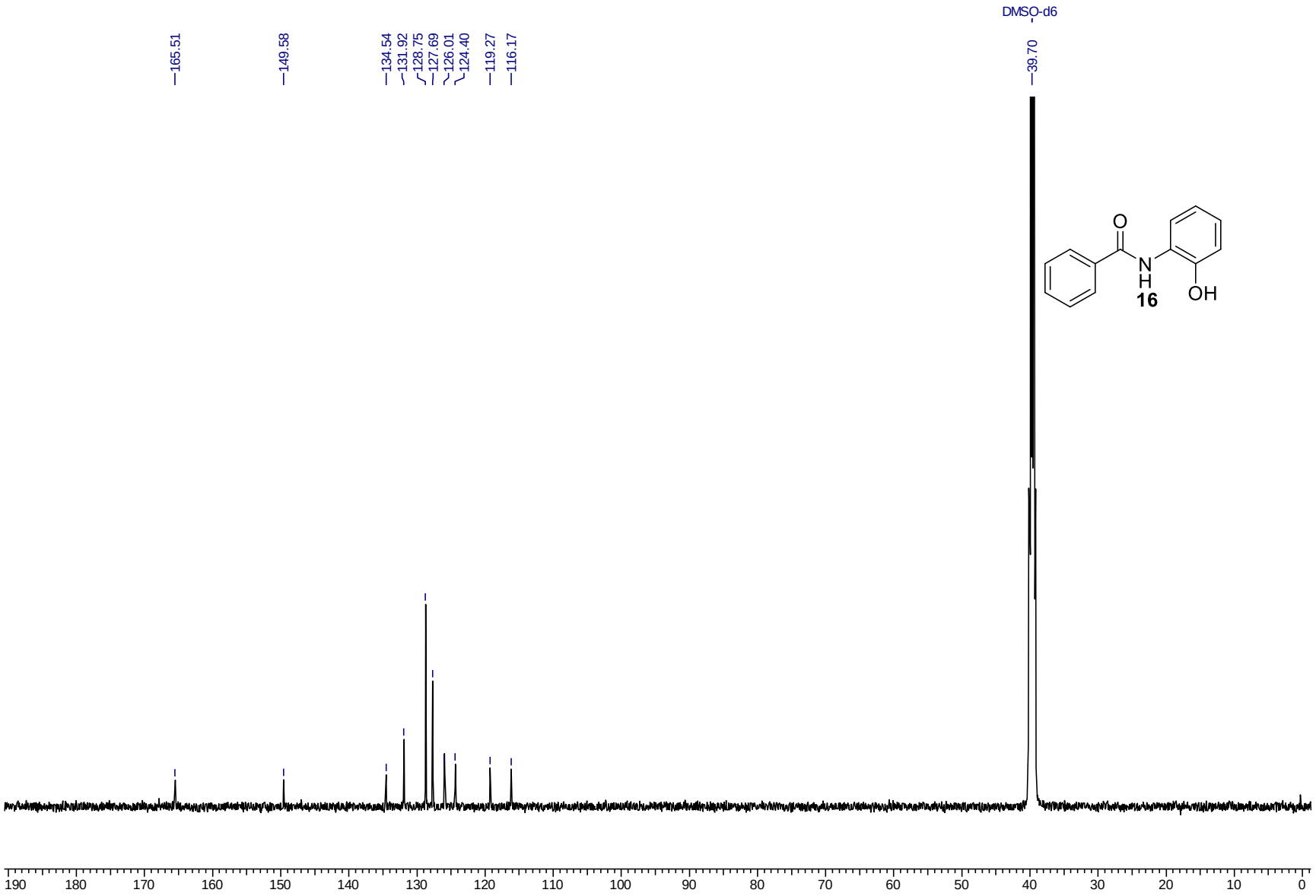
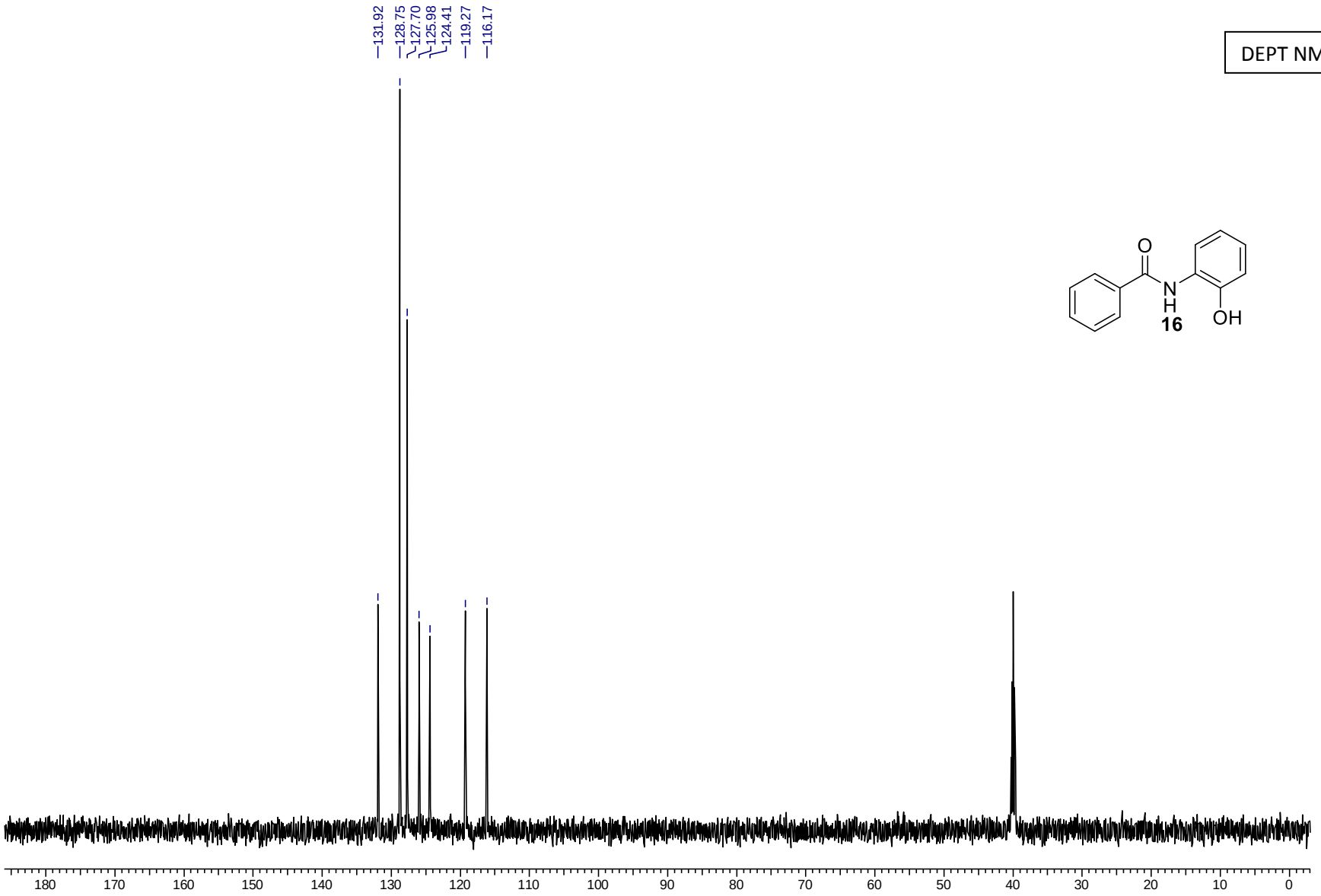


^{13}C NMR, 125MHz

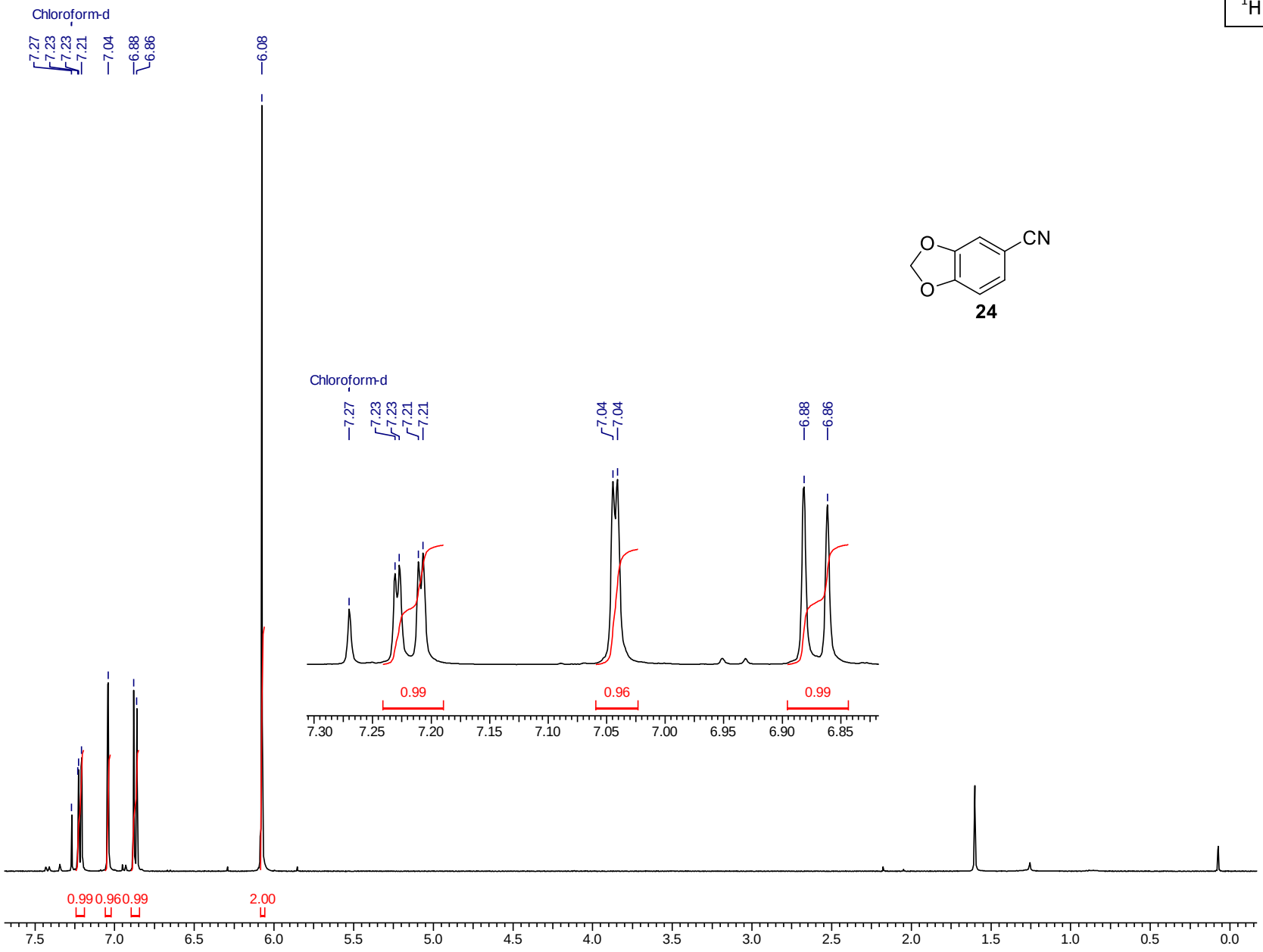


DEPT NMR, 125MHz



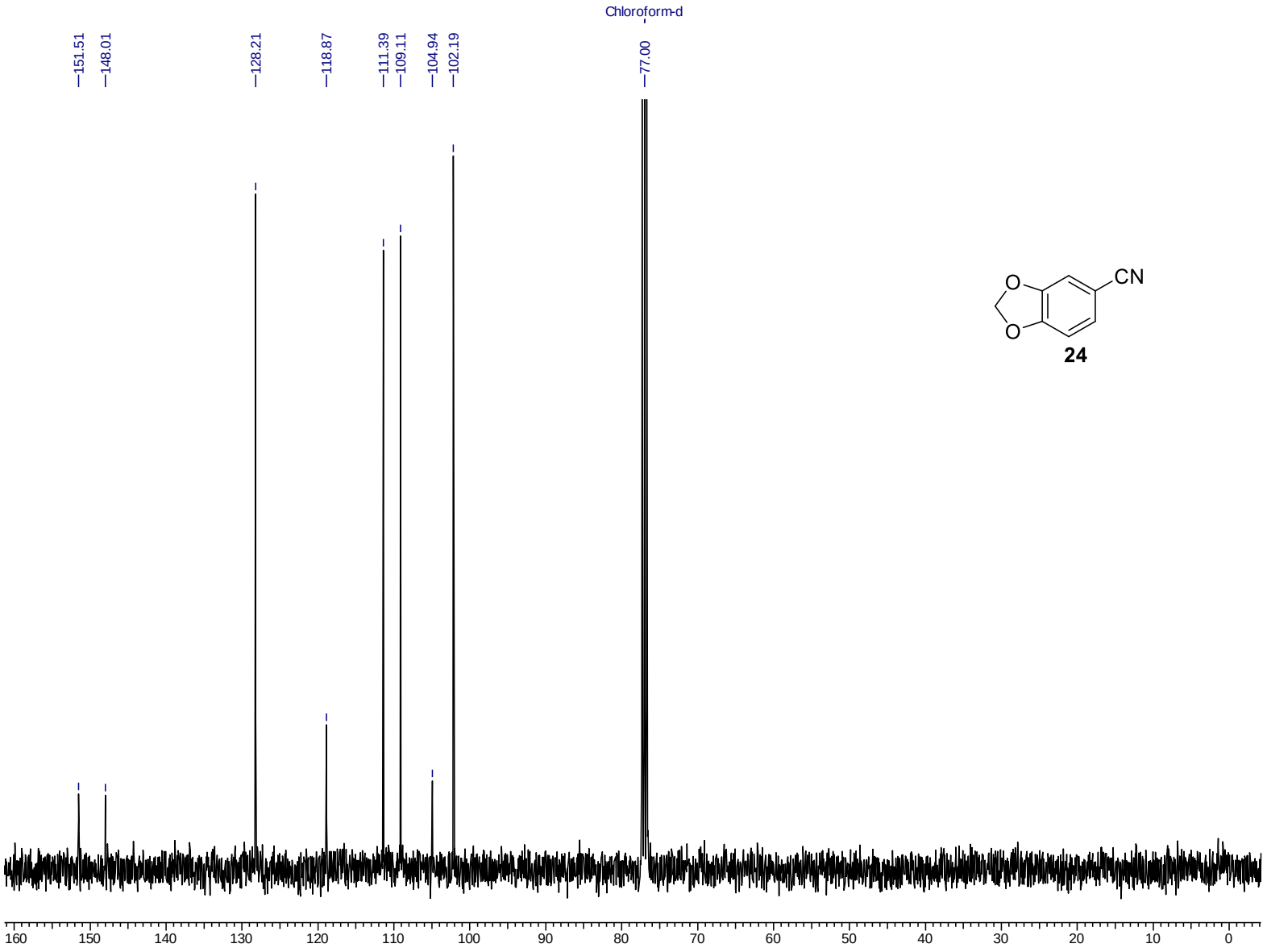
16

^{1}H NMR, 400MHz



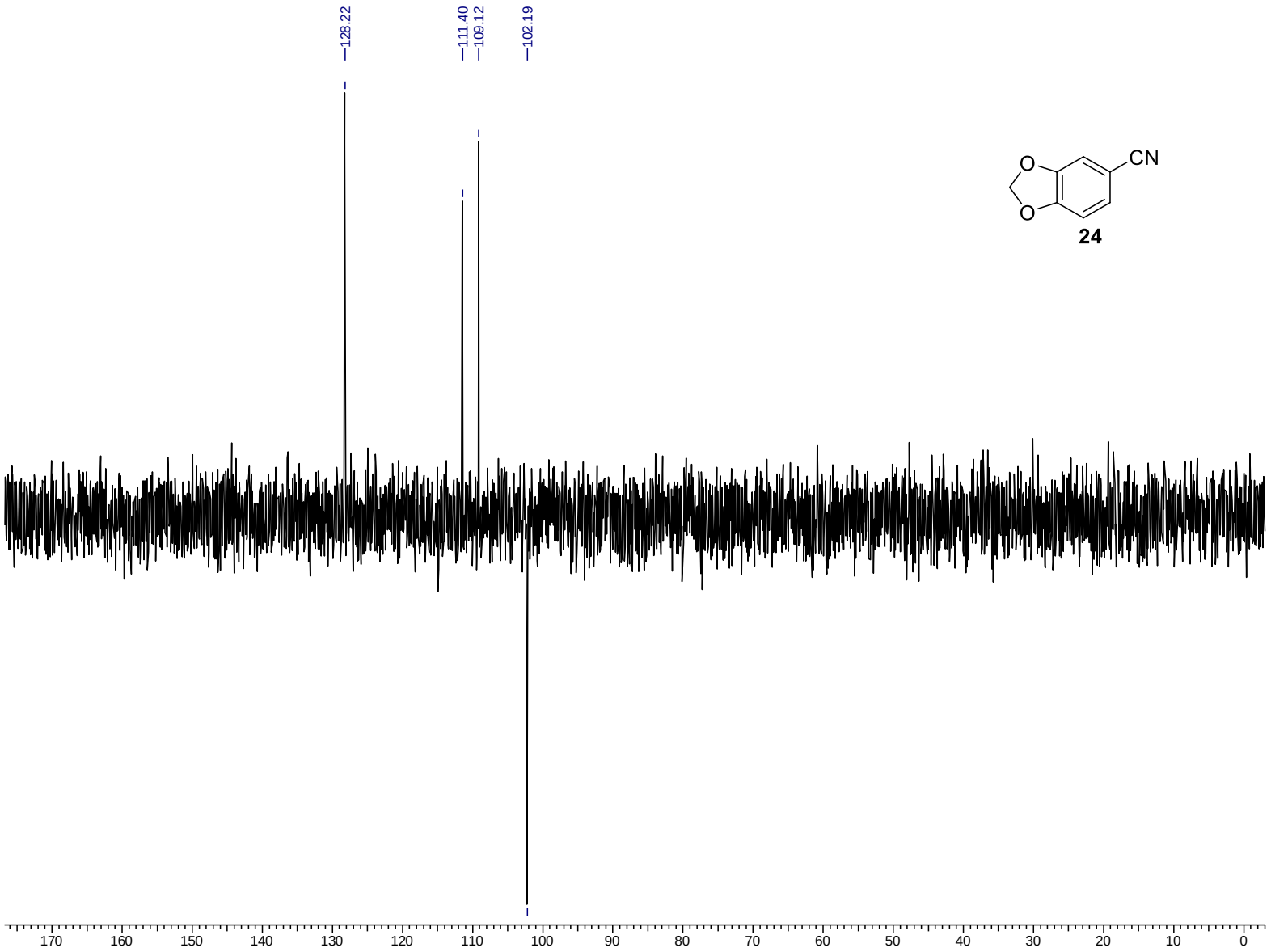
24

^{13}C NMR, 100MHz

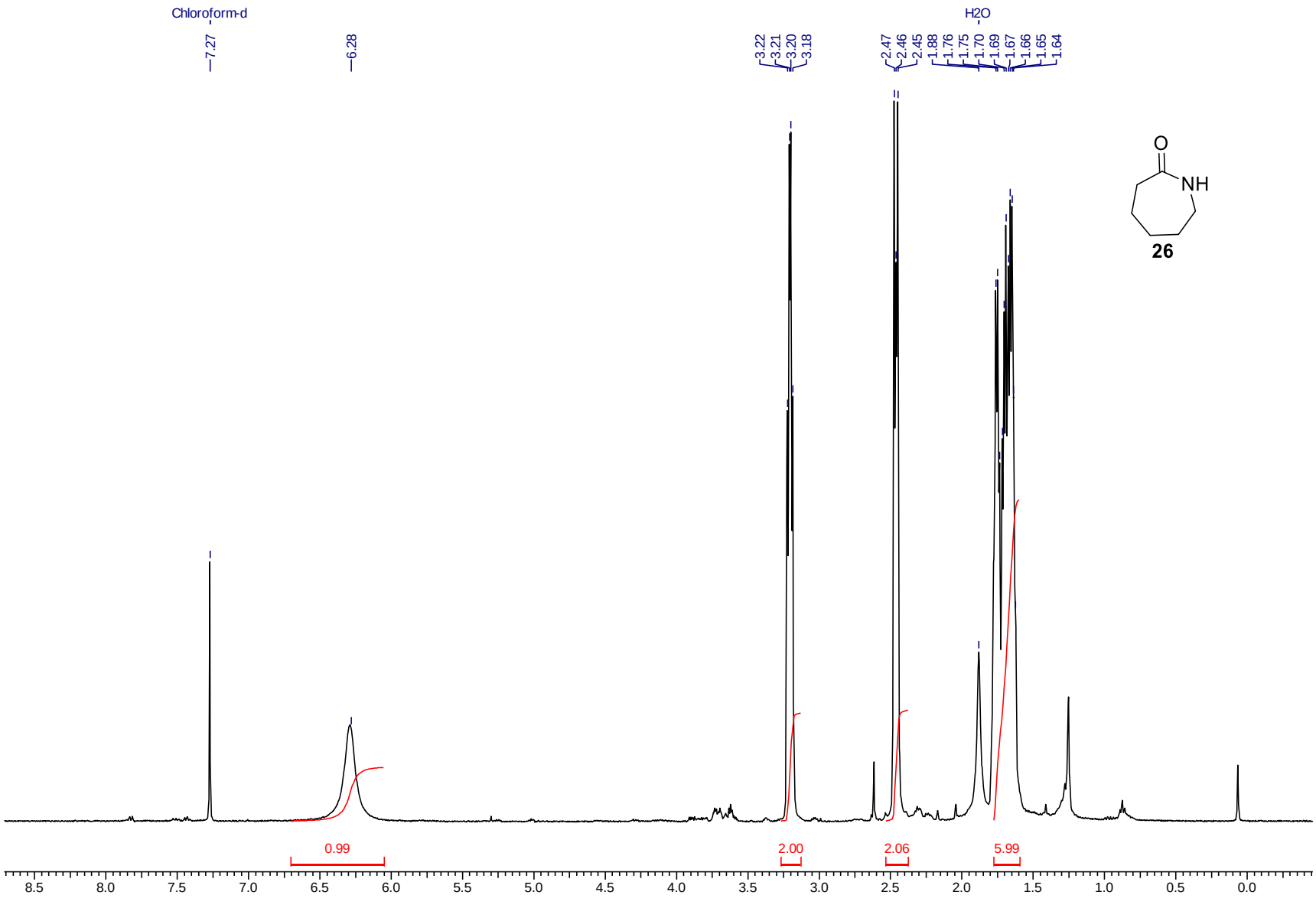


24

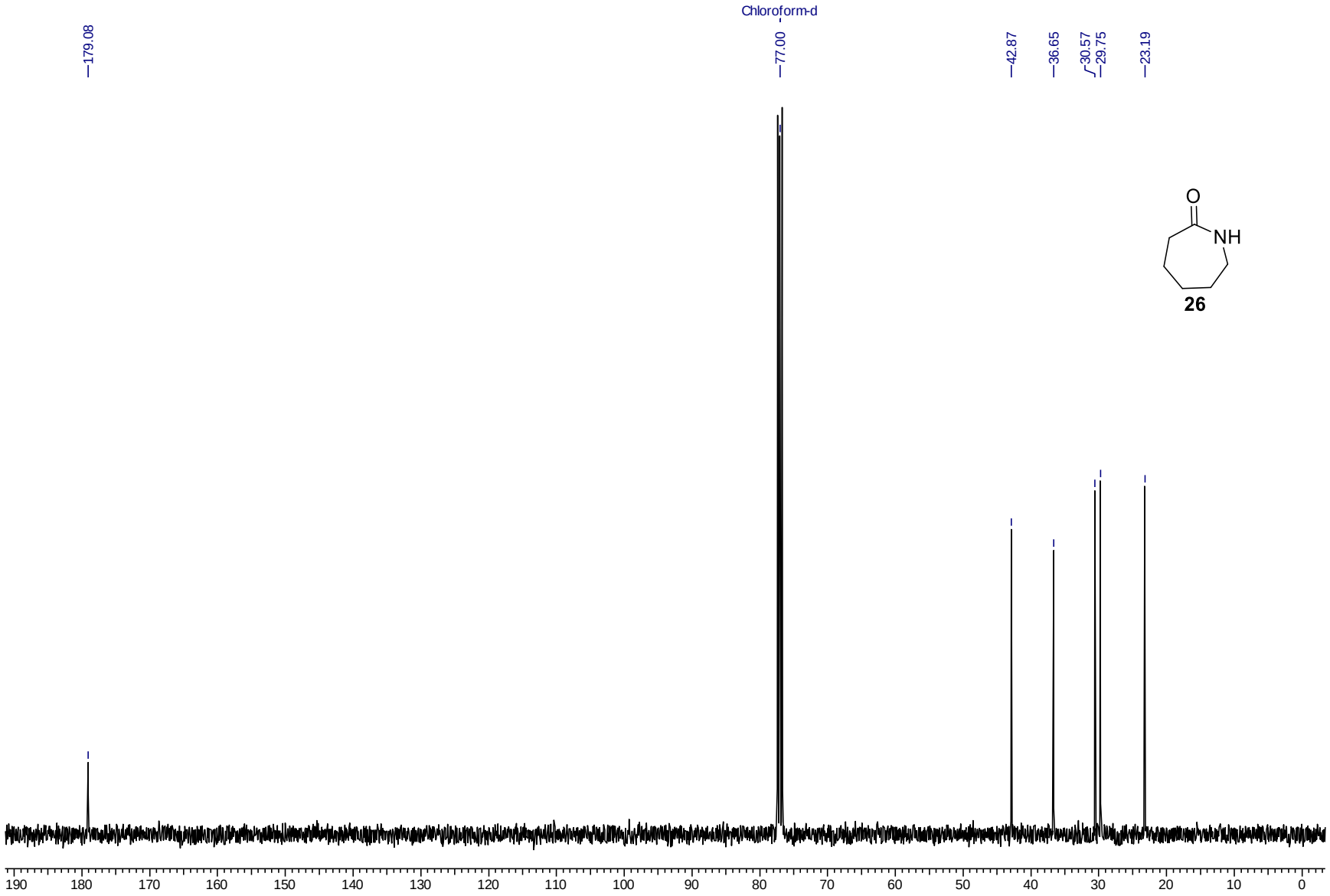
DEPT NMR, 100MHz



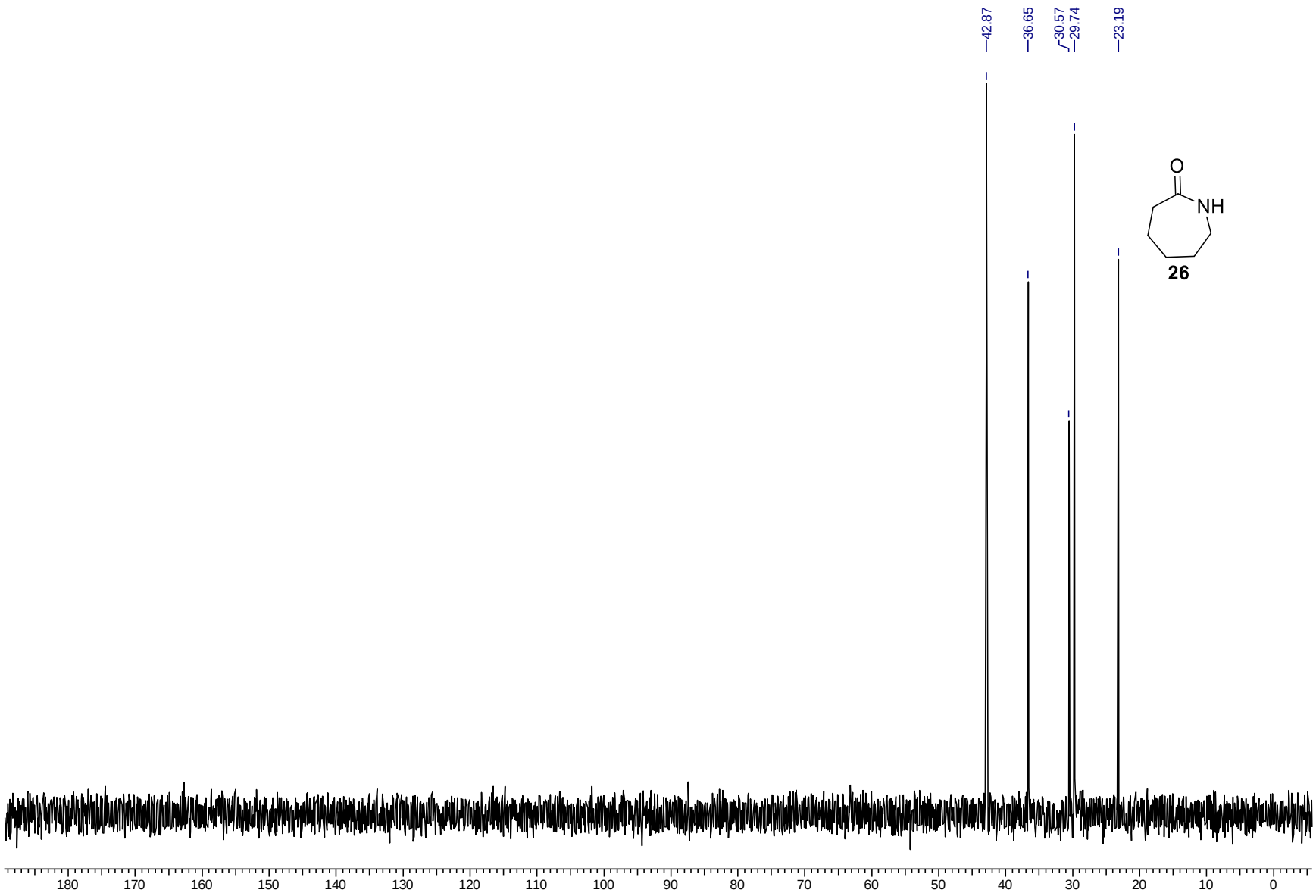
^{1}H NMR, 400MHz



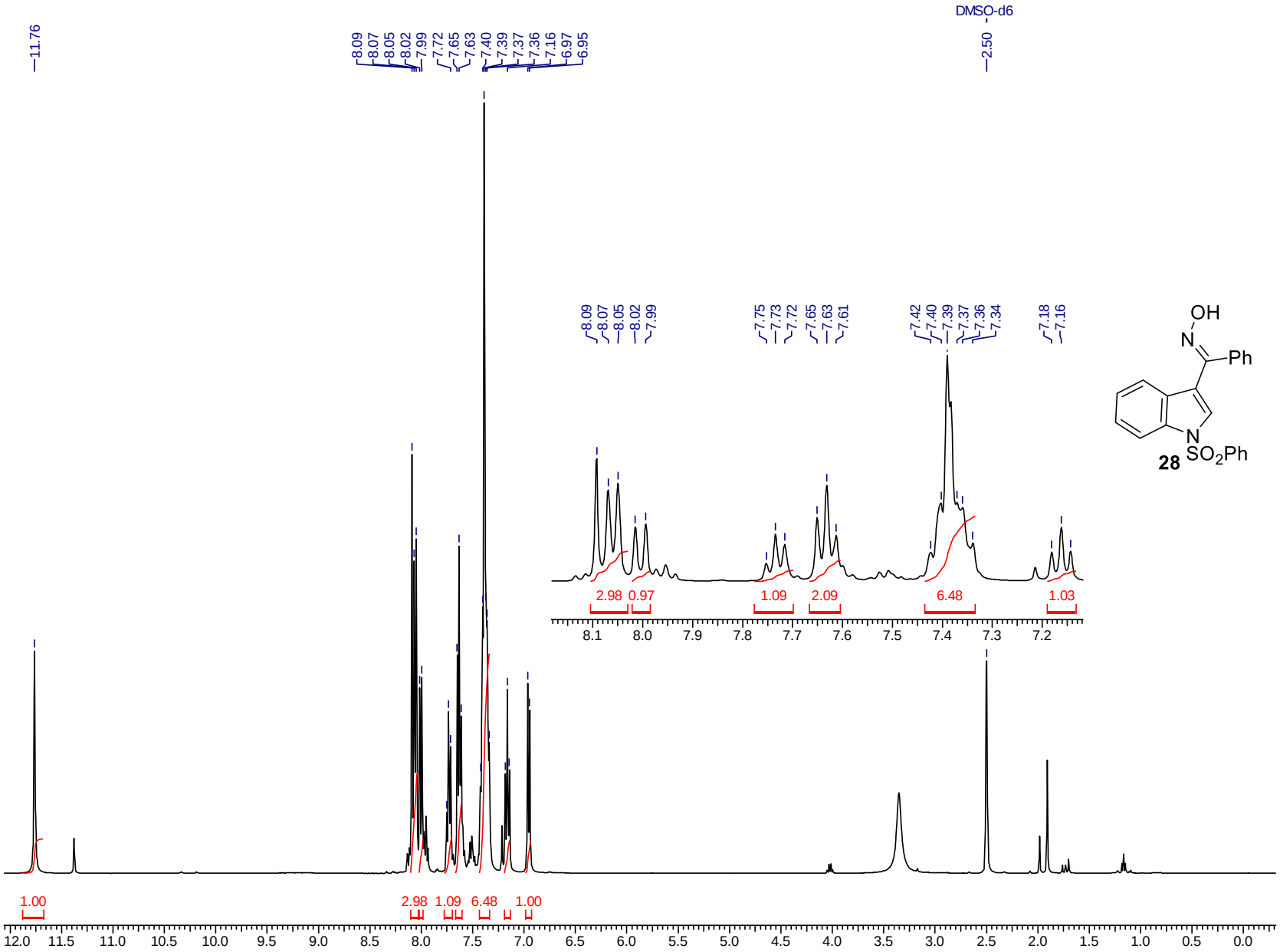
^{13}C NMR, 100MHz



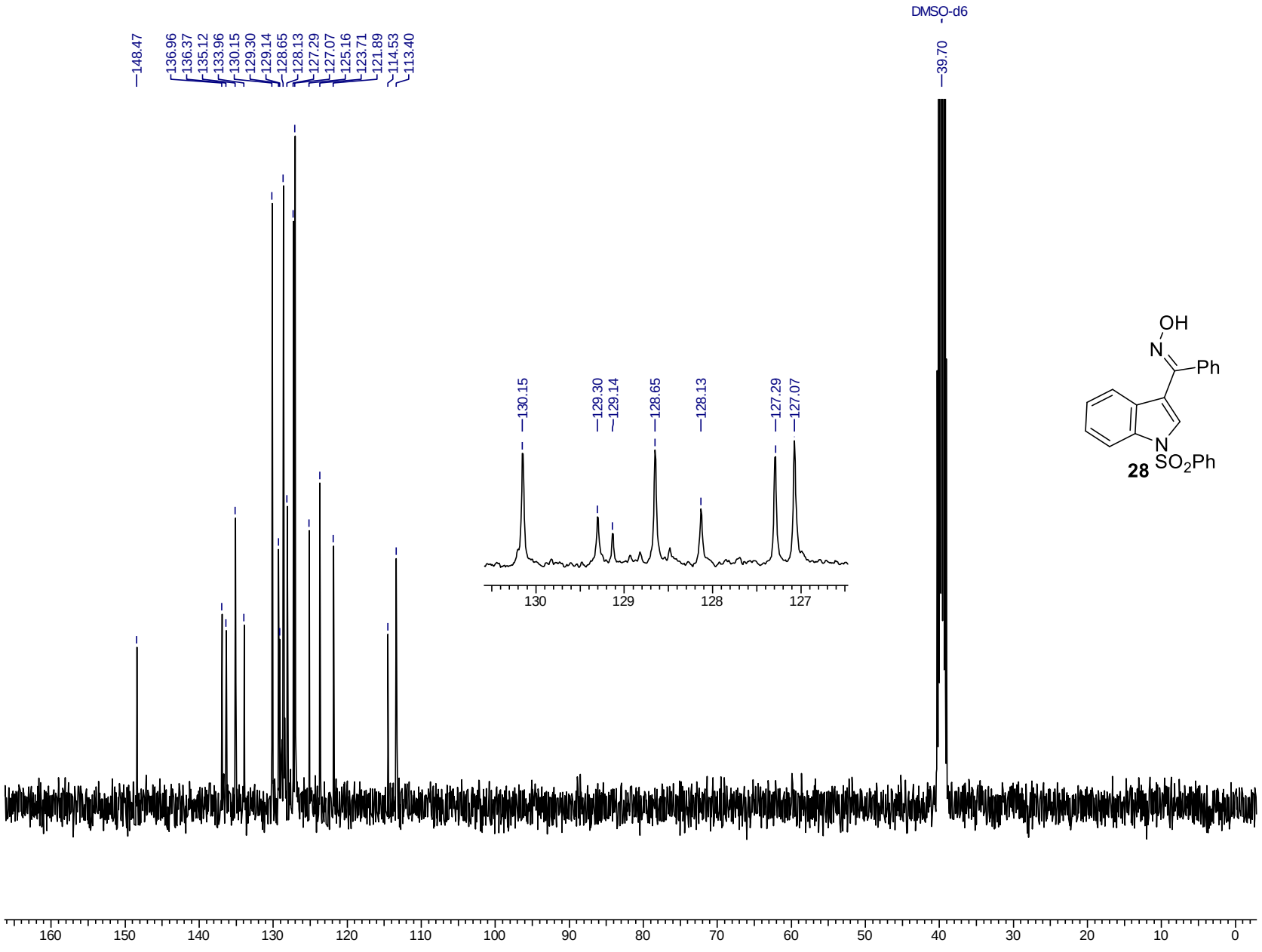
DEPT NMR, 100MHz



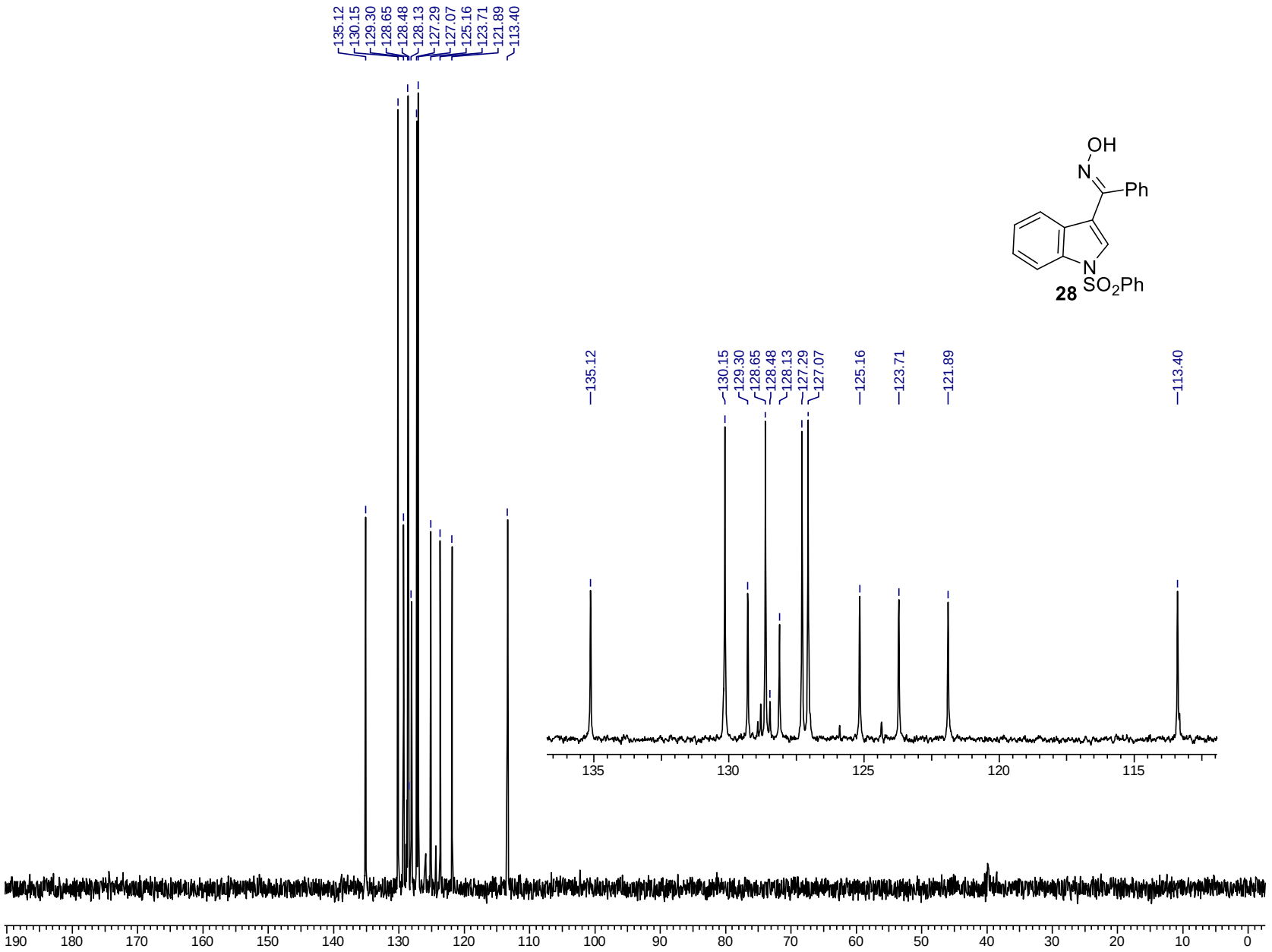
^{1}H NMR 400 MHz



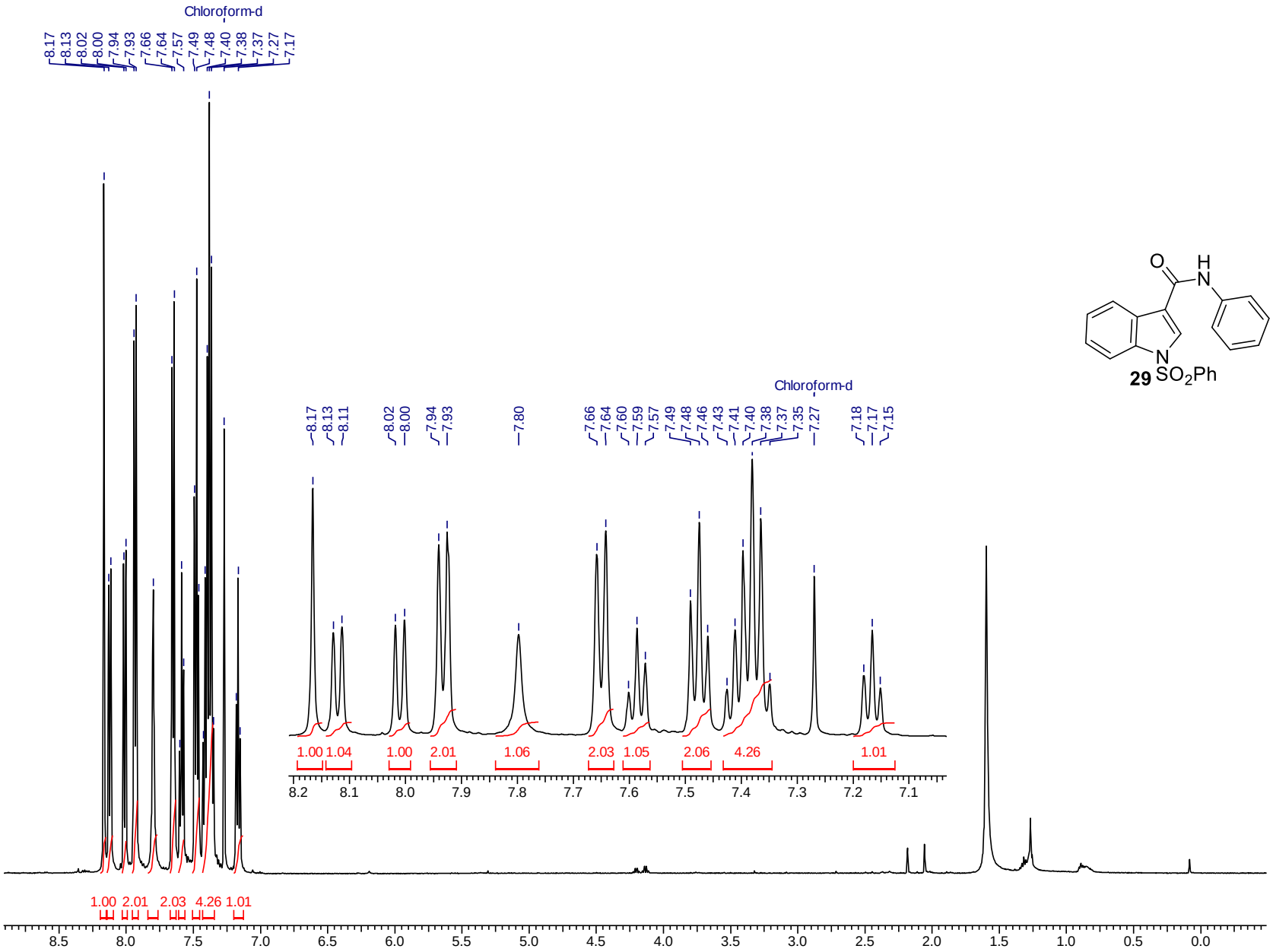
^{13}C NMR, 100MHz



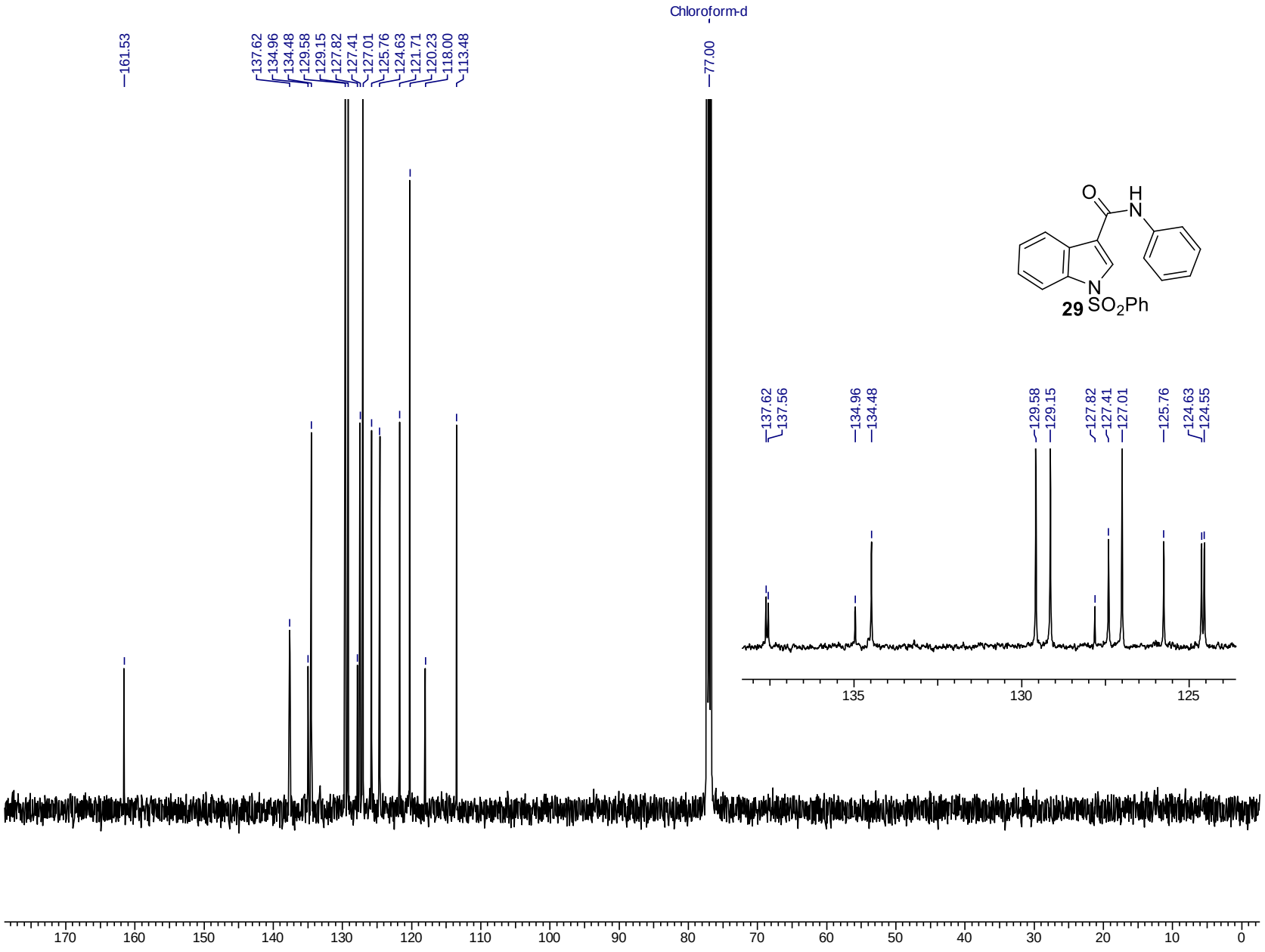
DEPT NMR, 100MHz



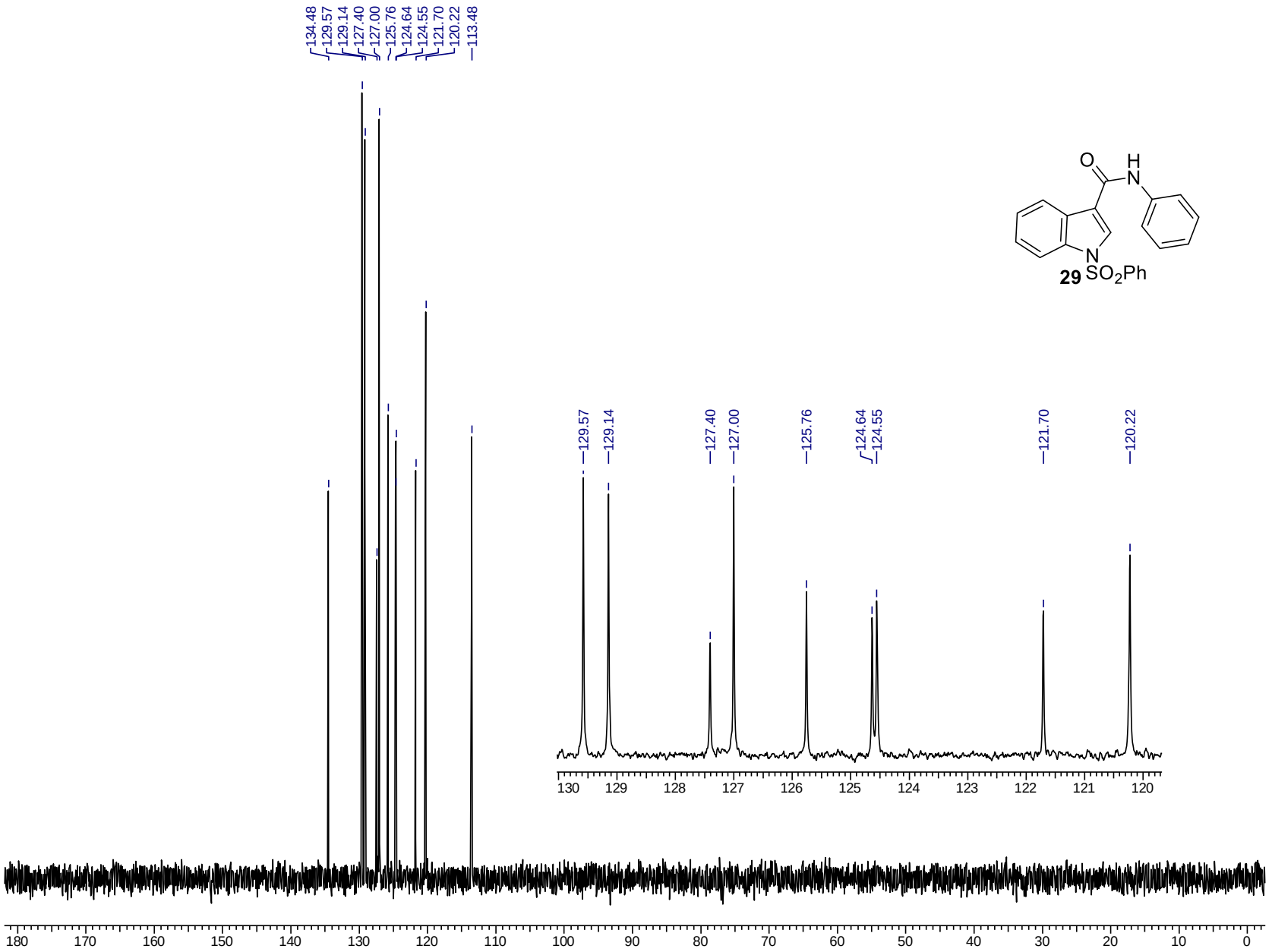
^{1}H NMR 500 MHz



^{13}C NMR, 125 MHz



DEPT NMR, 125 MHz



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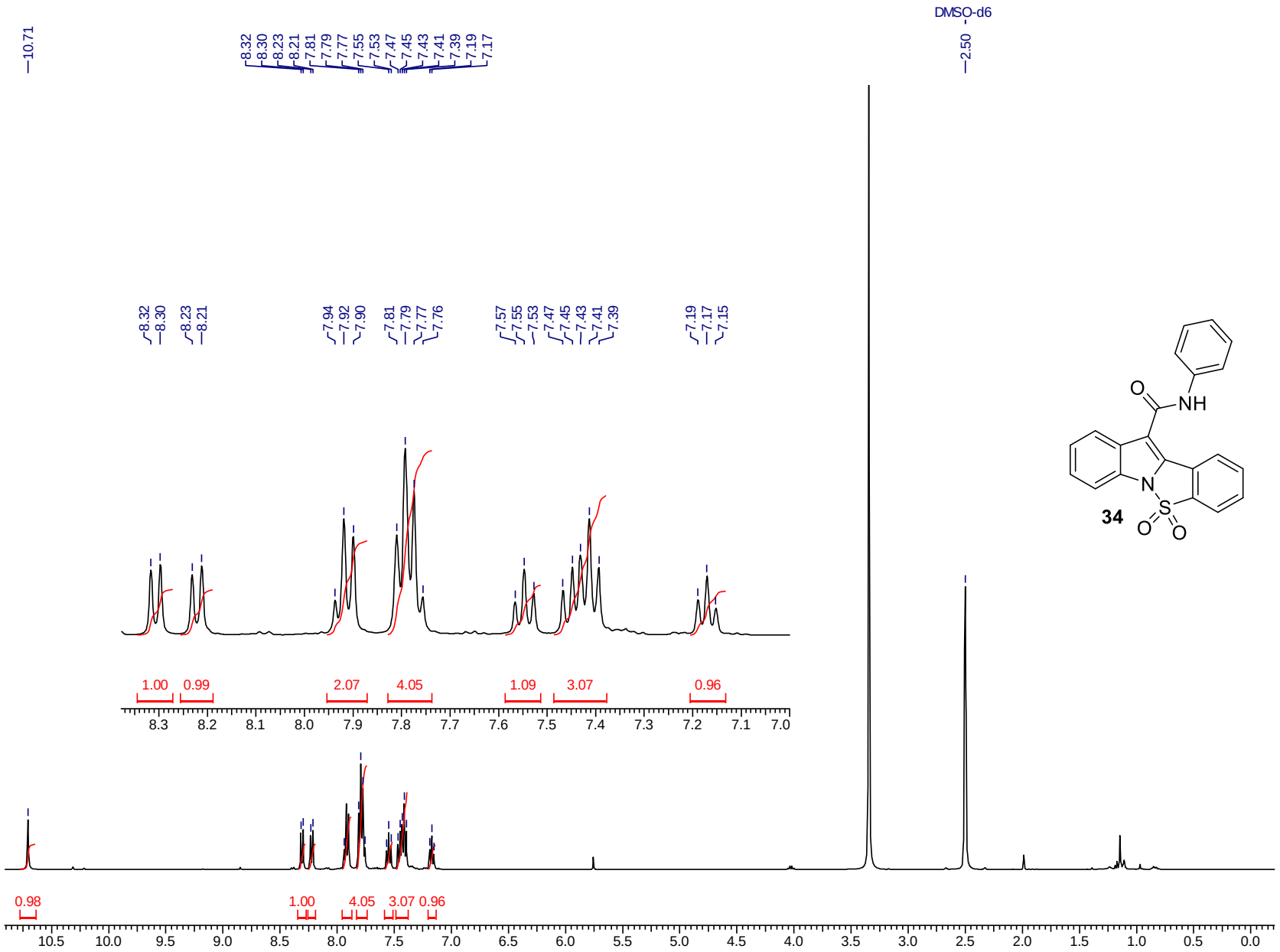

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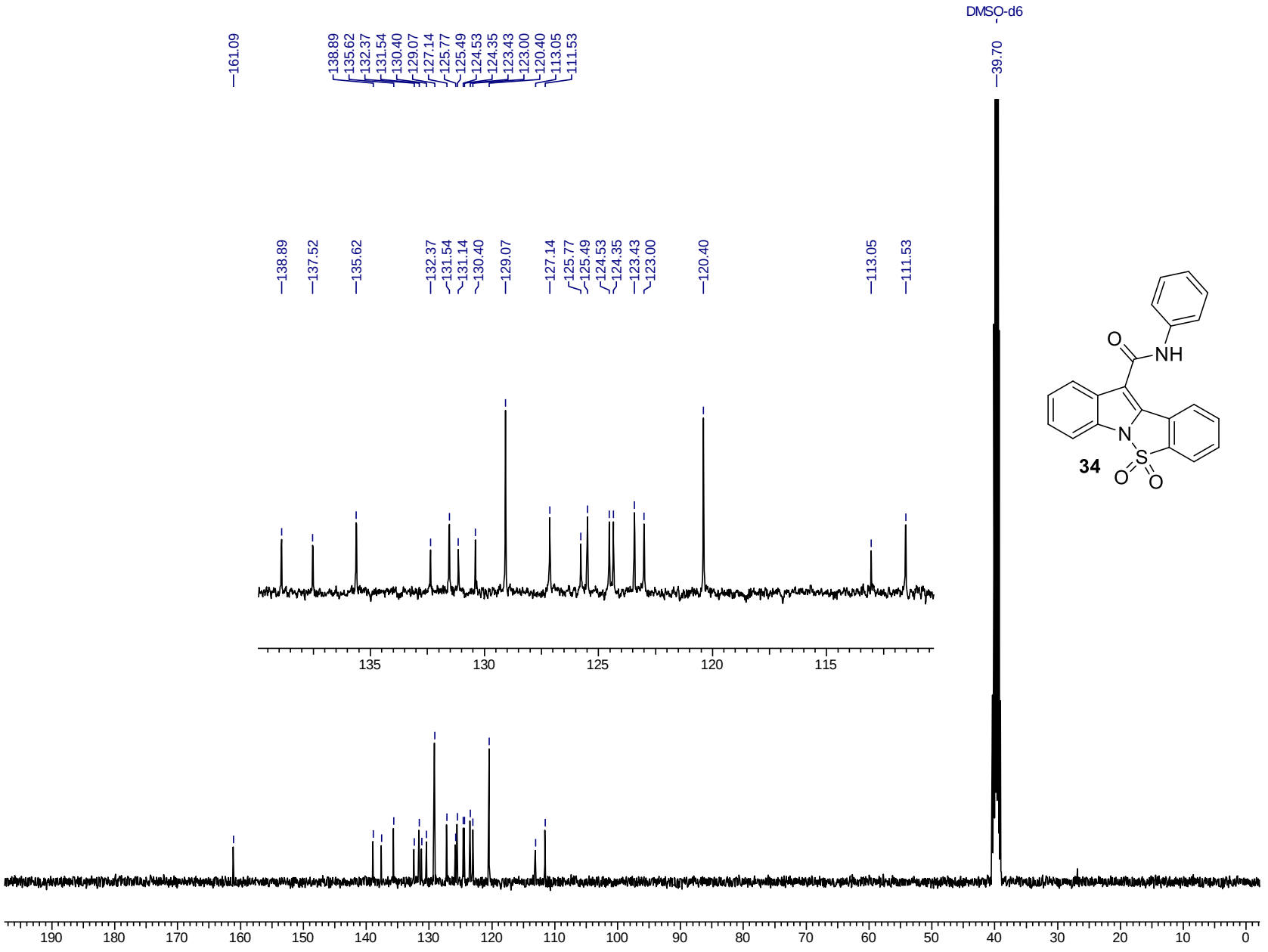
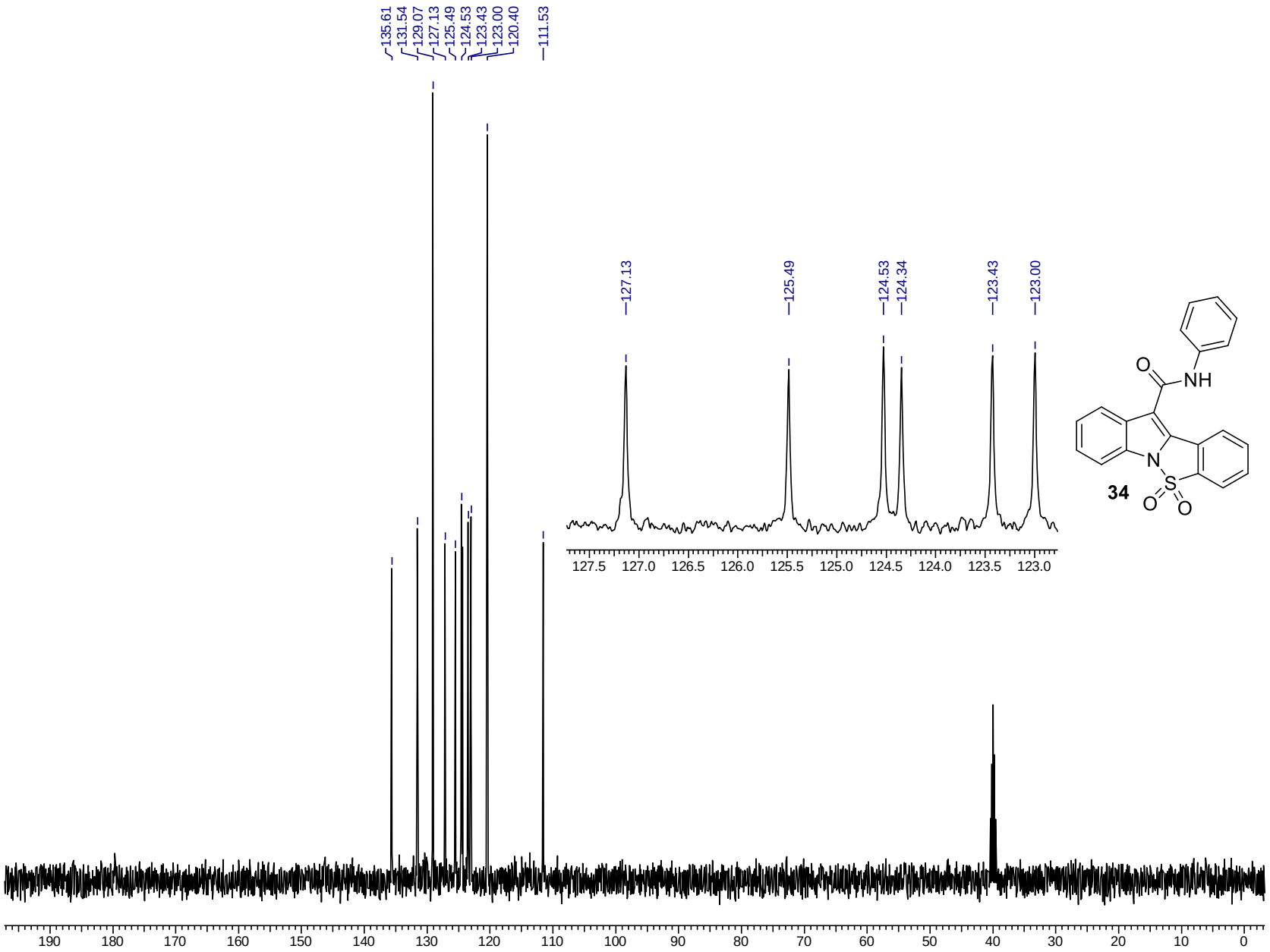


DEPT NMR, 100MHz



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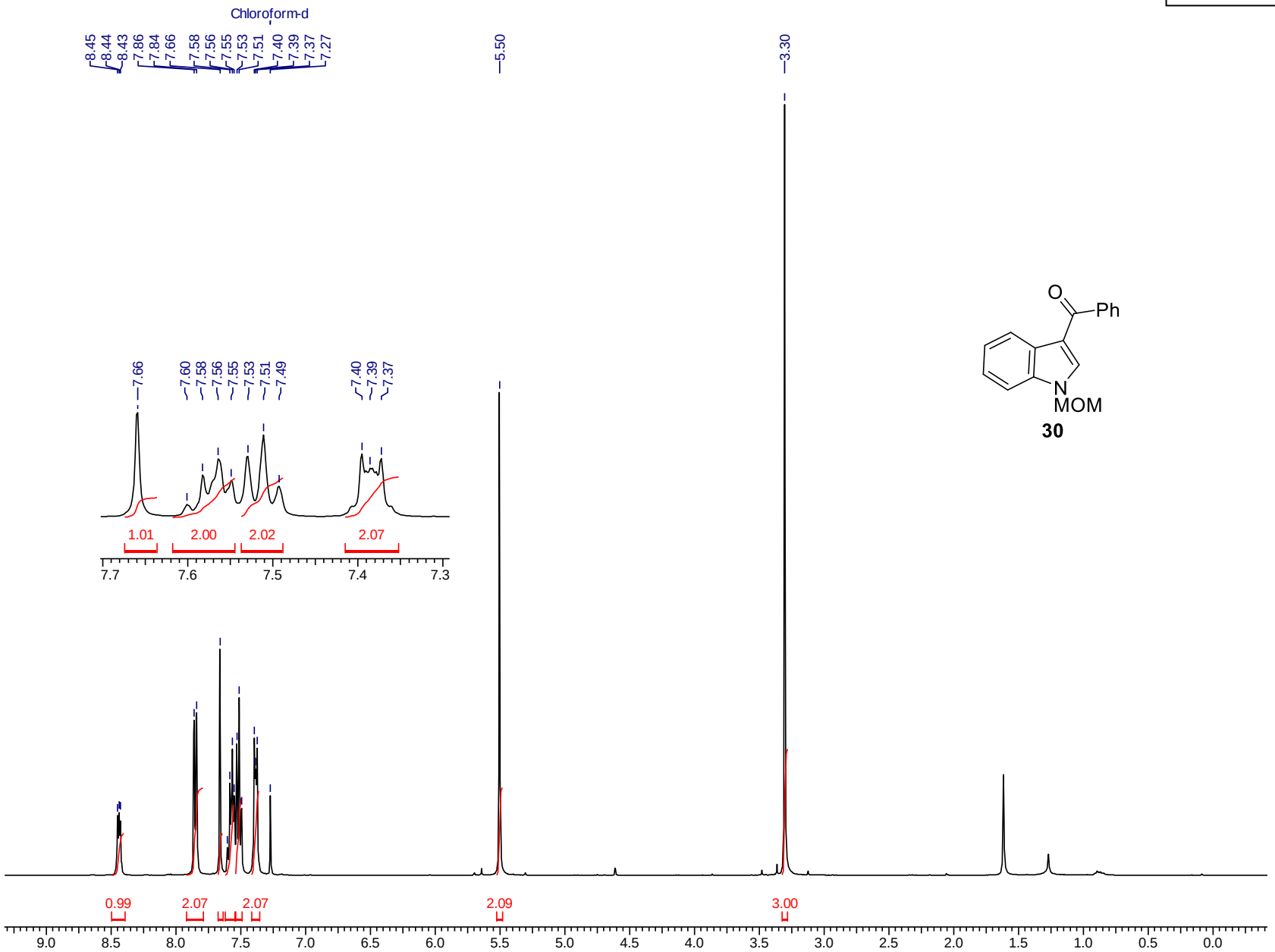
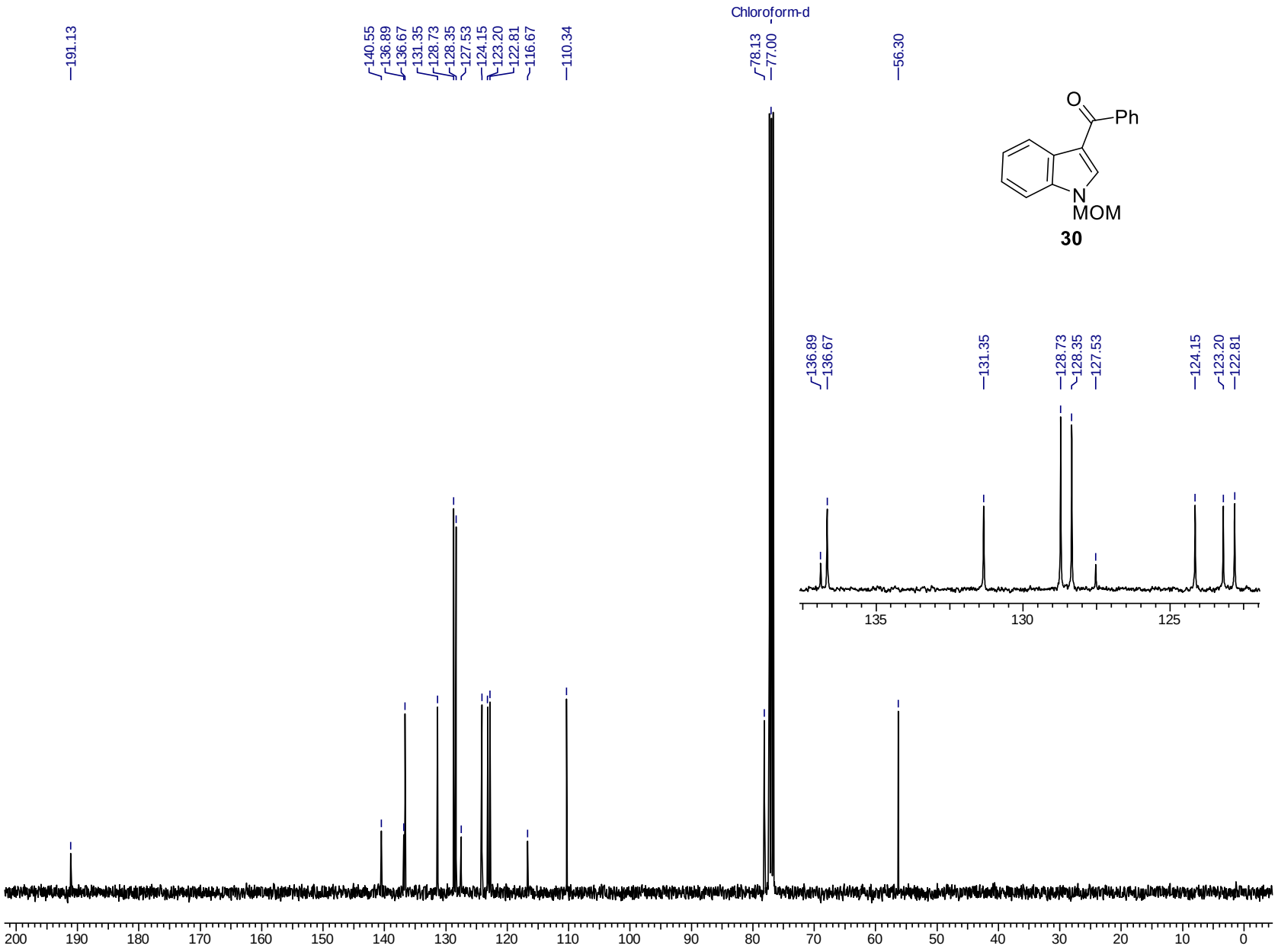
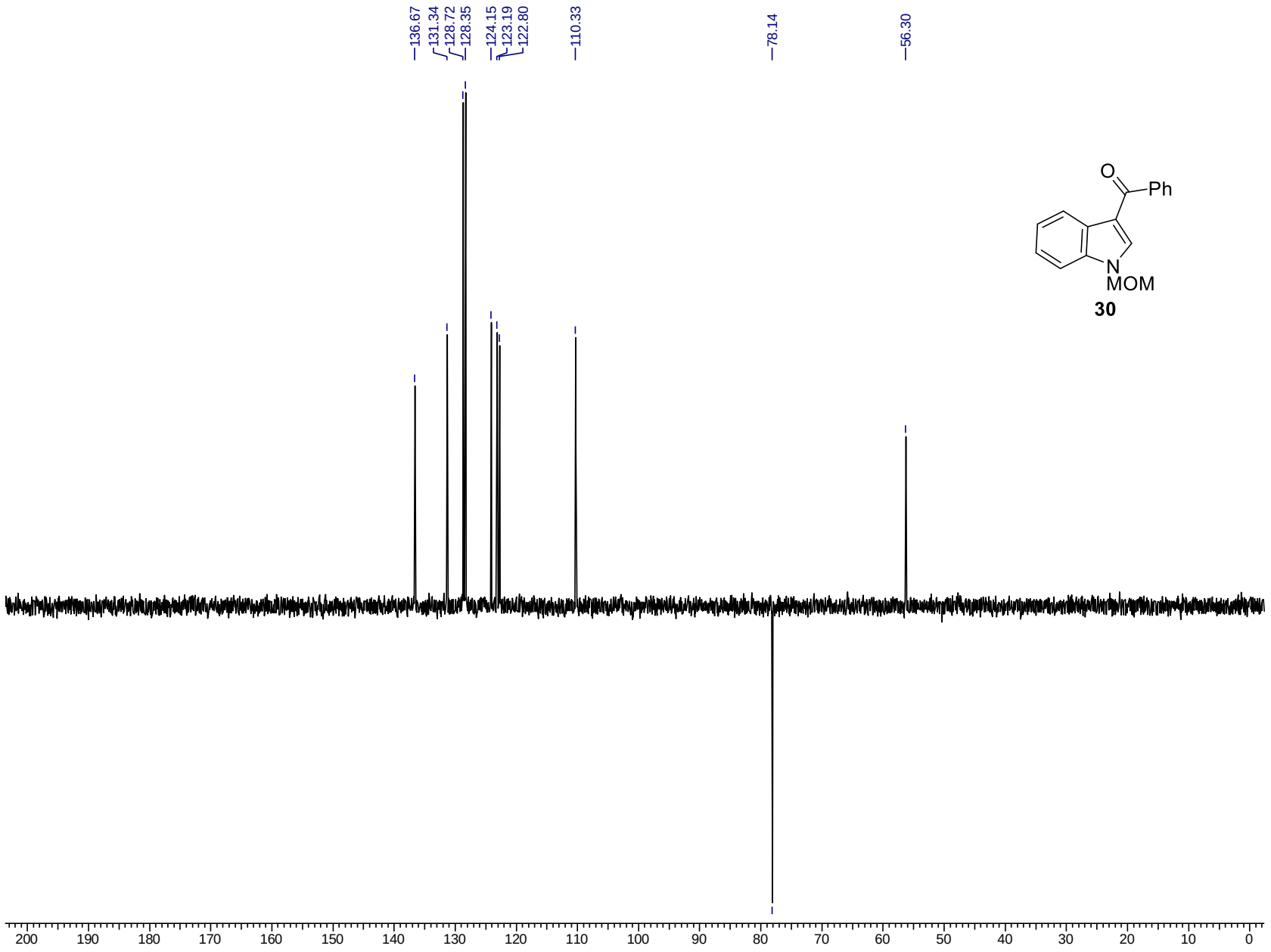


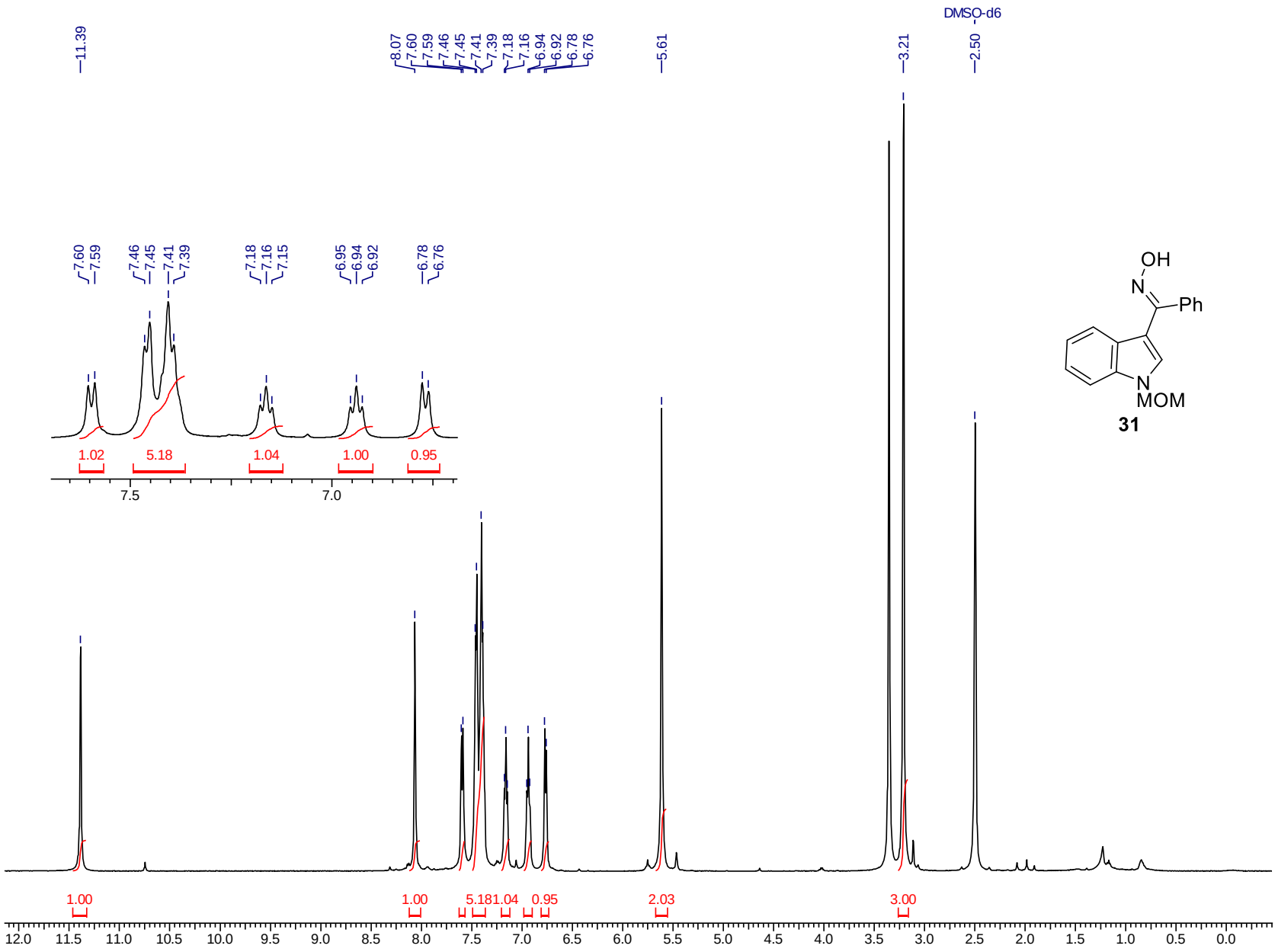
^{13}C NMR, 100 MHz



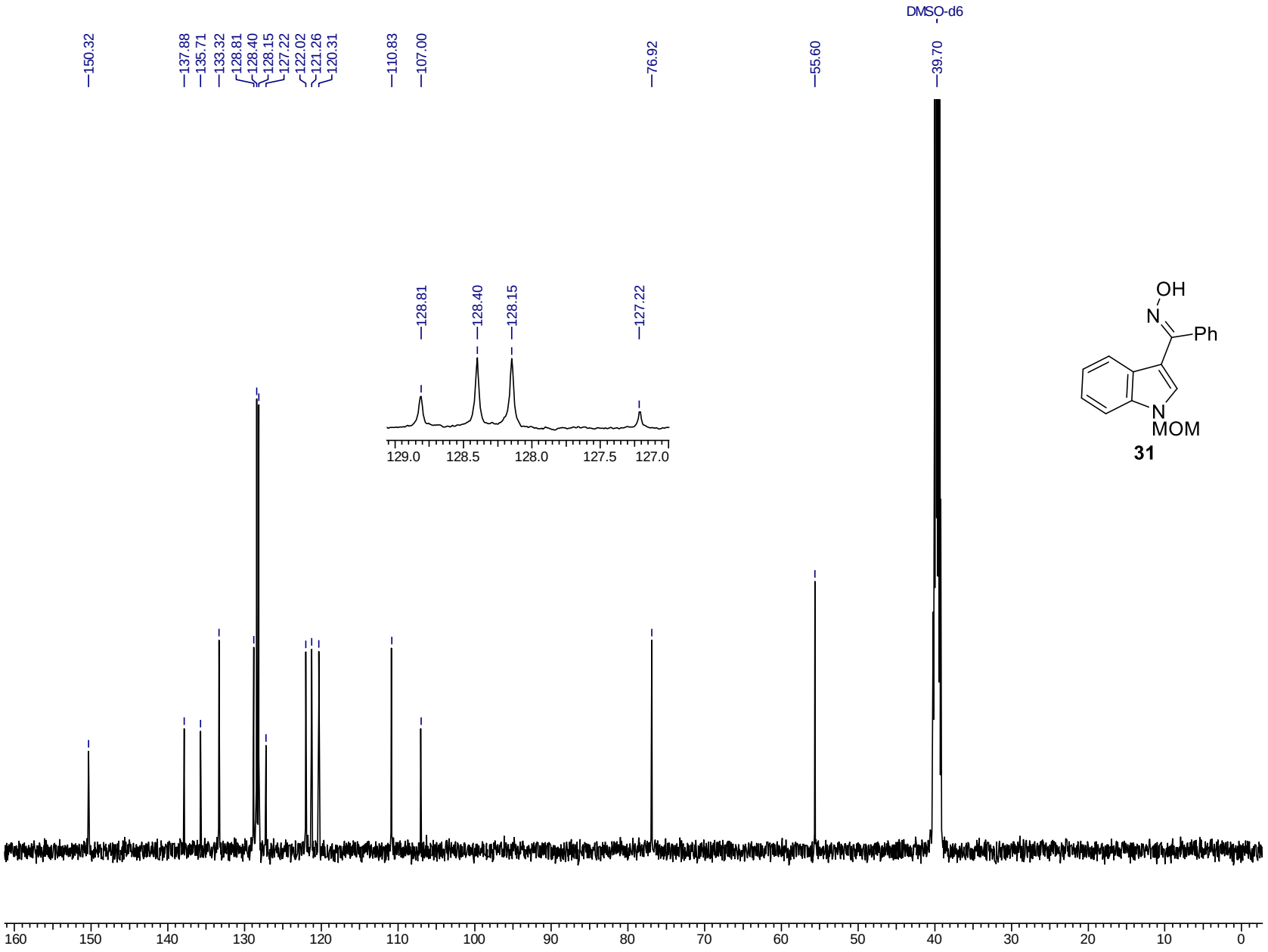
DEPT NMR, 100MHz



^{1}H NMR 500 MHz

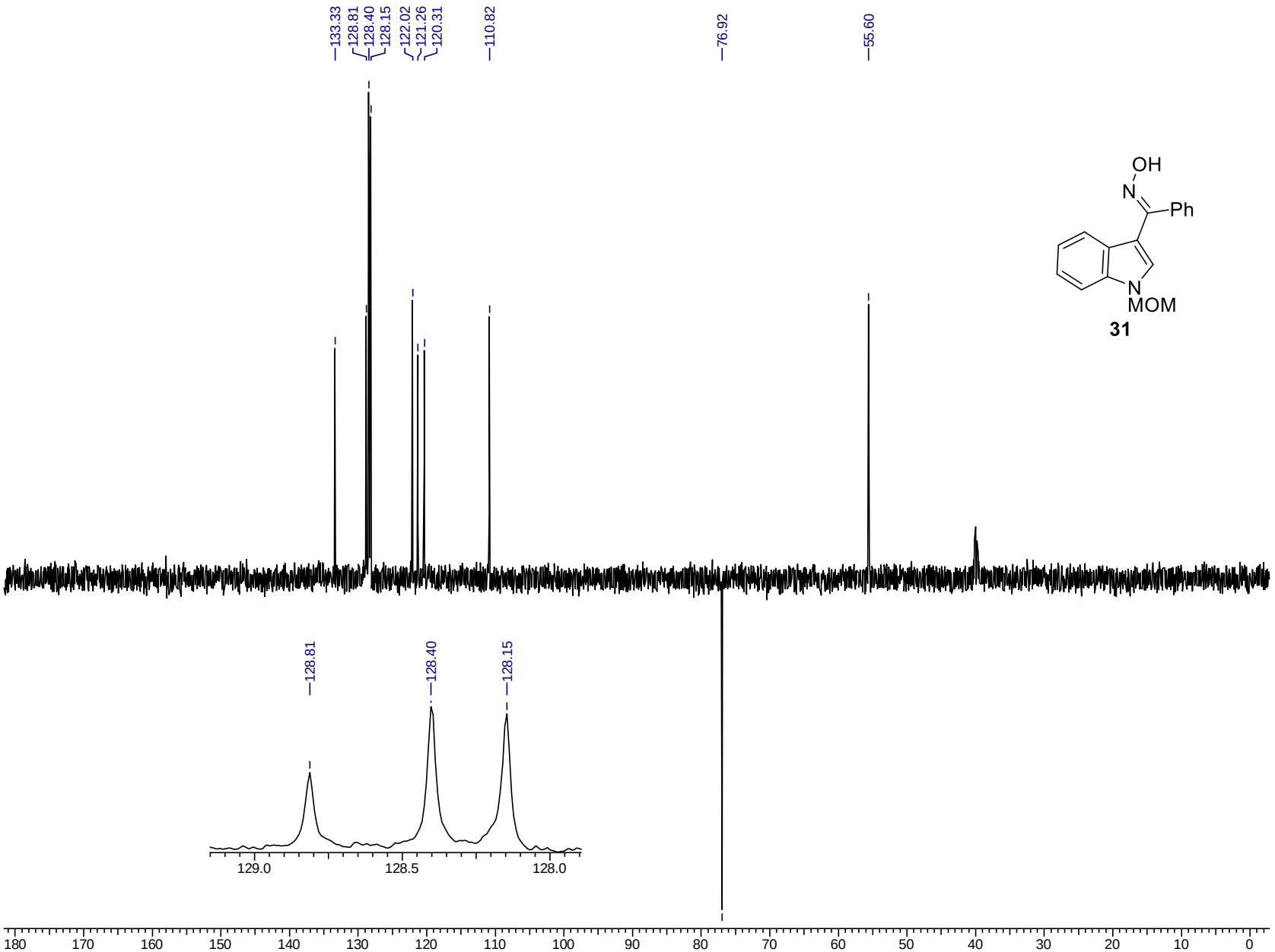


^{13}C NMR, 125 MHz

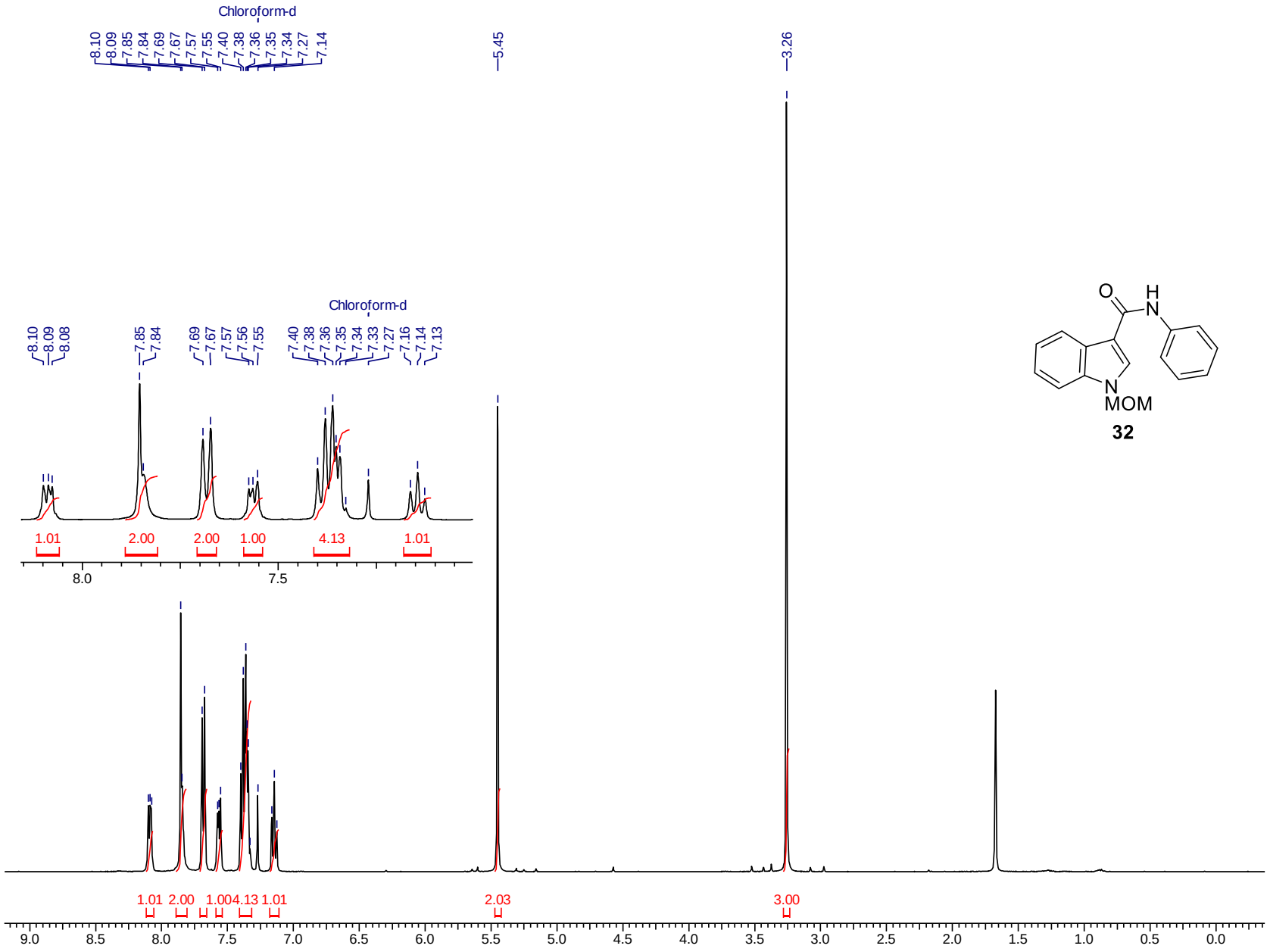


31

DEPT NMR, 125 MHz

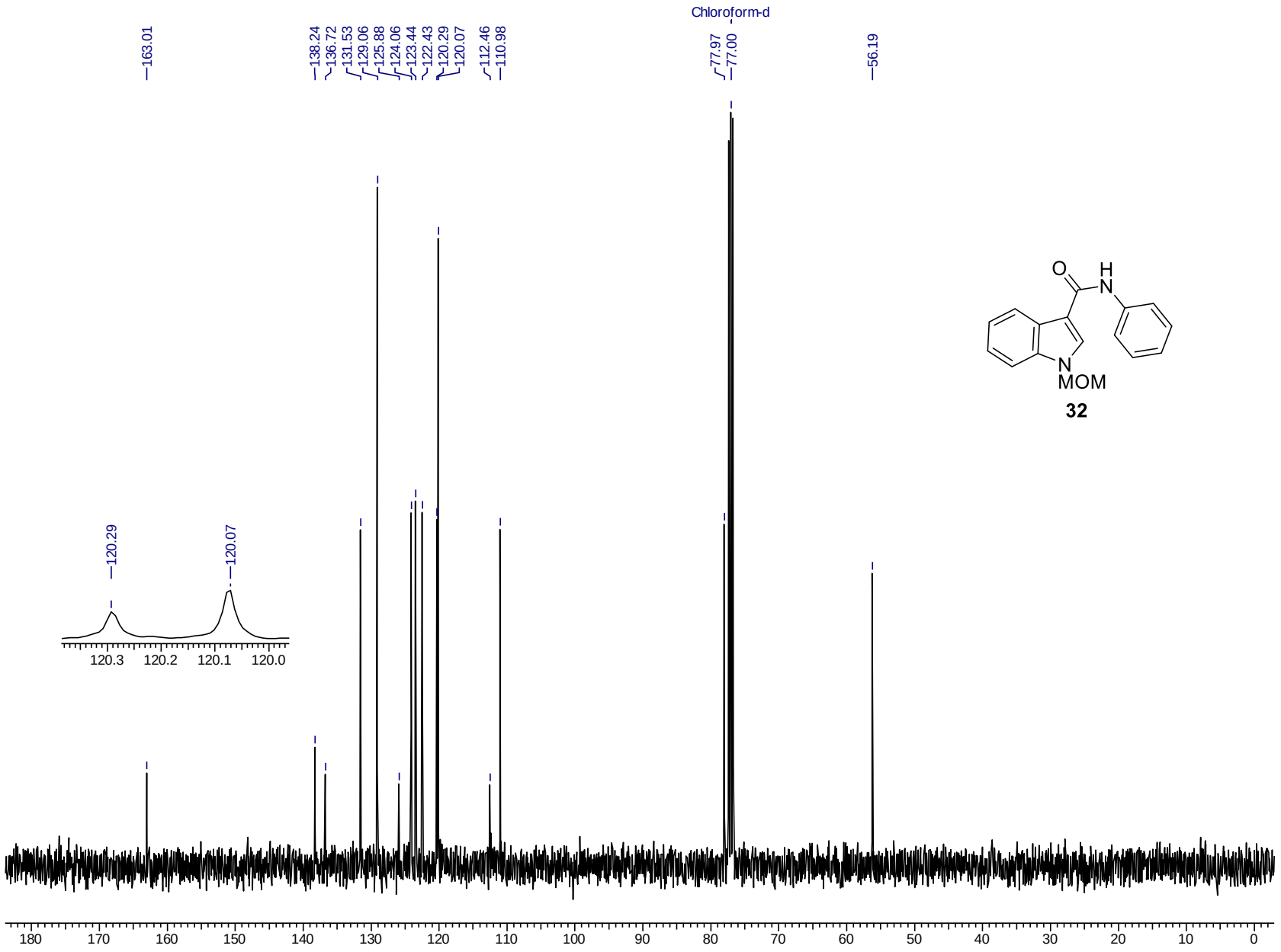


^{1}H NMR 400 MHz

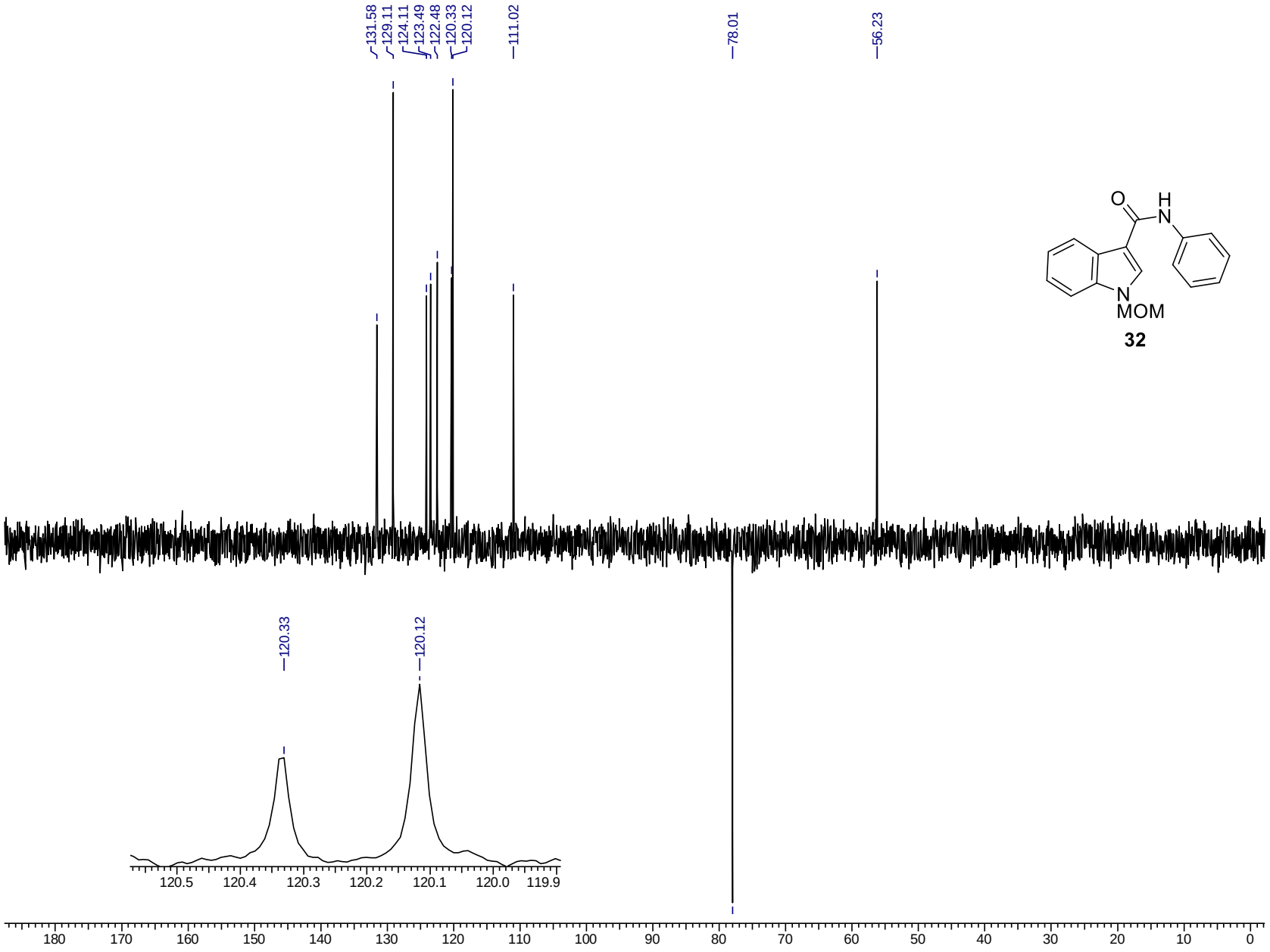


32

^{13}C NMR, 100 MHz



DEPT NMR, 100MHz



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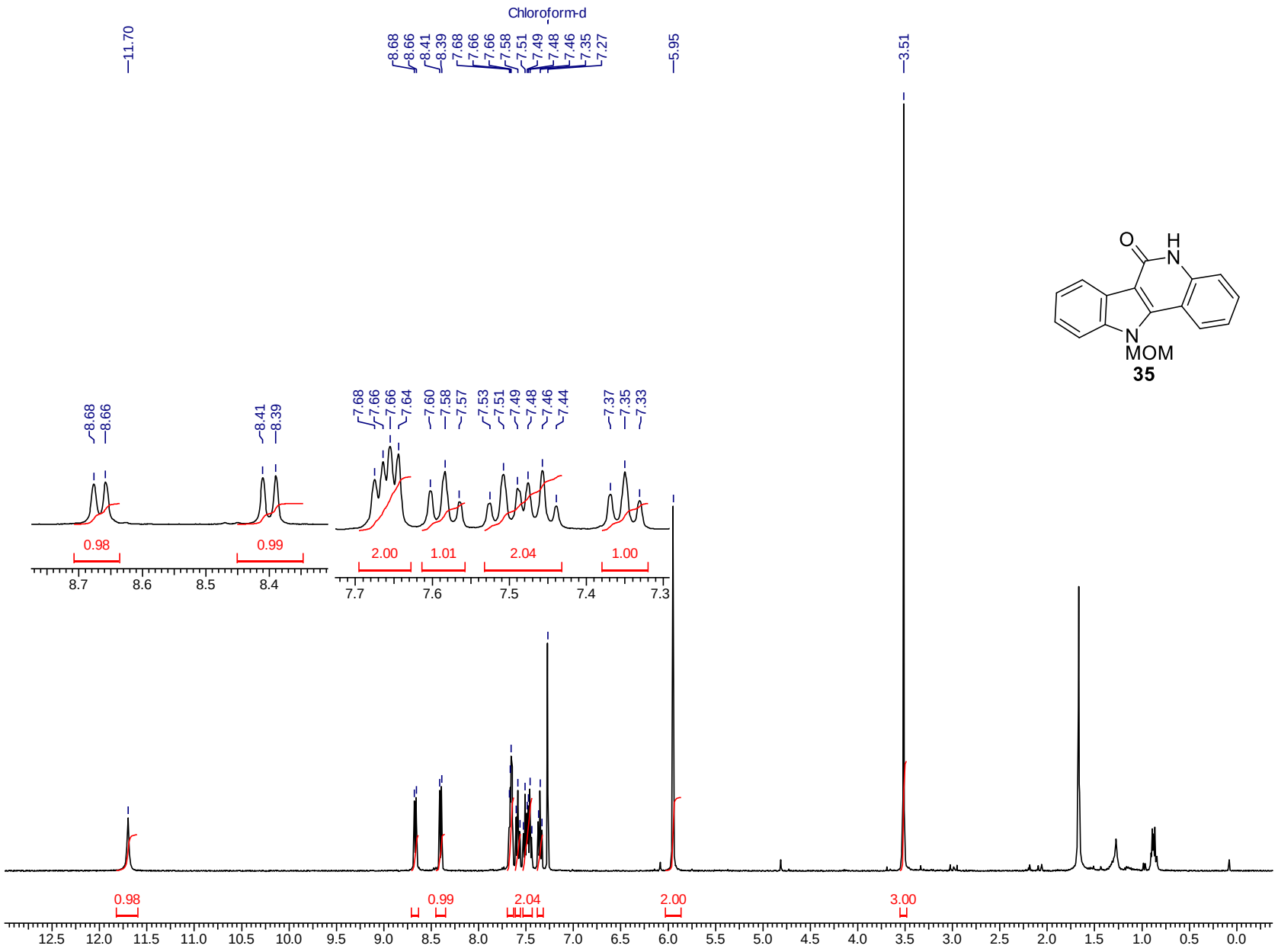
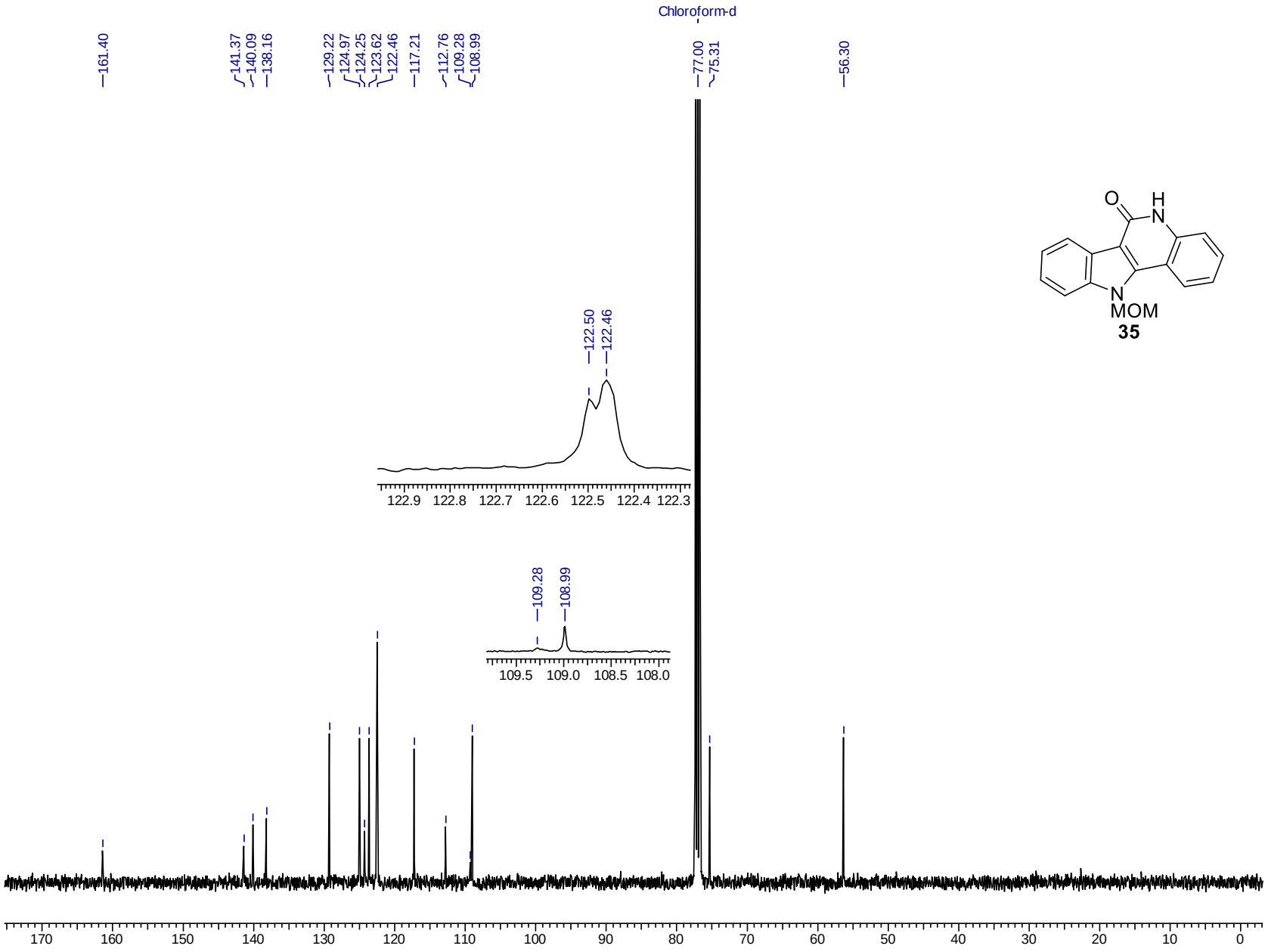
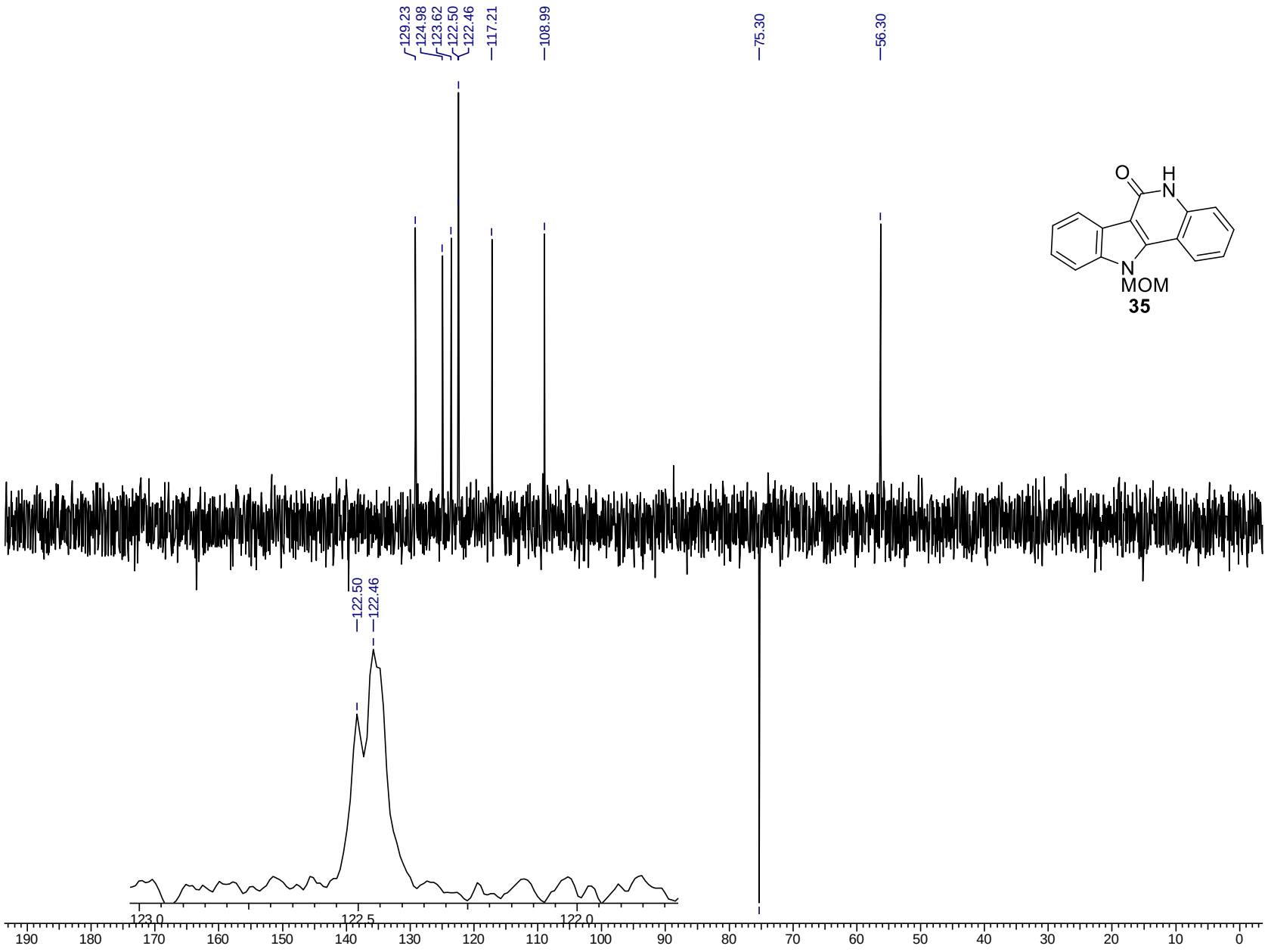


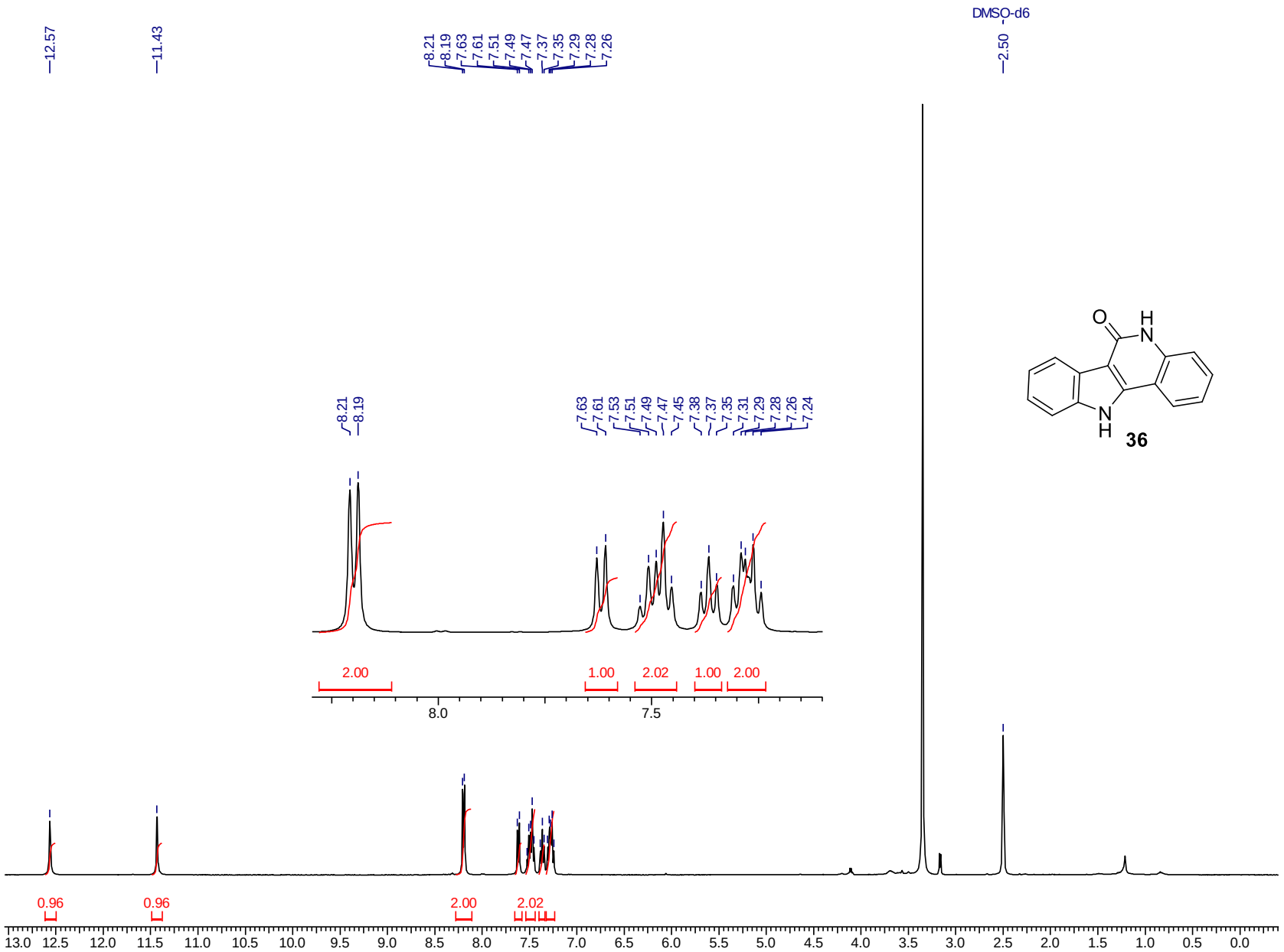
^{13}C NMR, 100 MHz

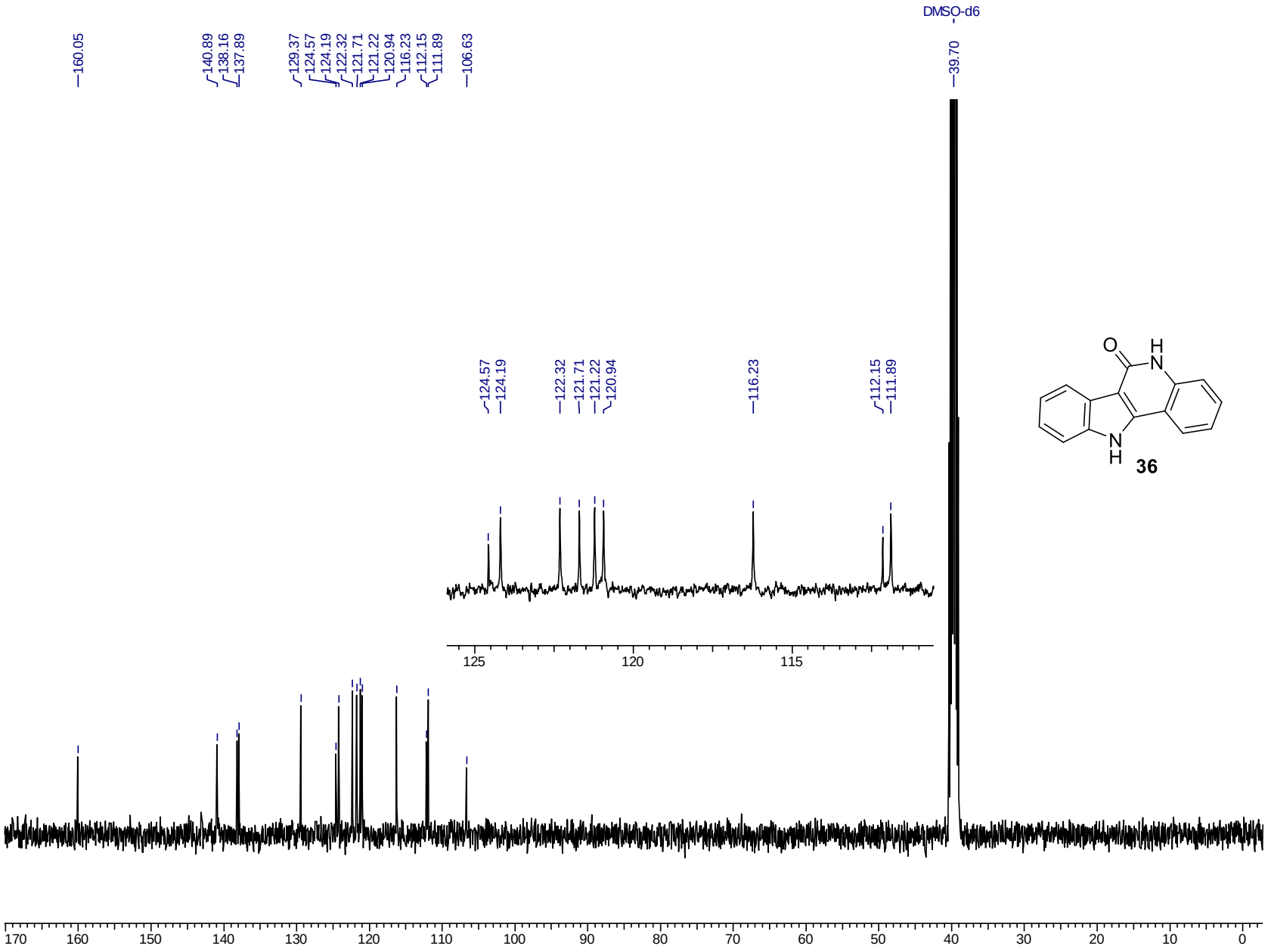


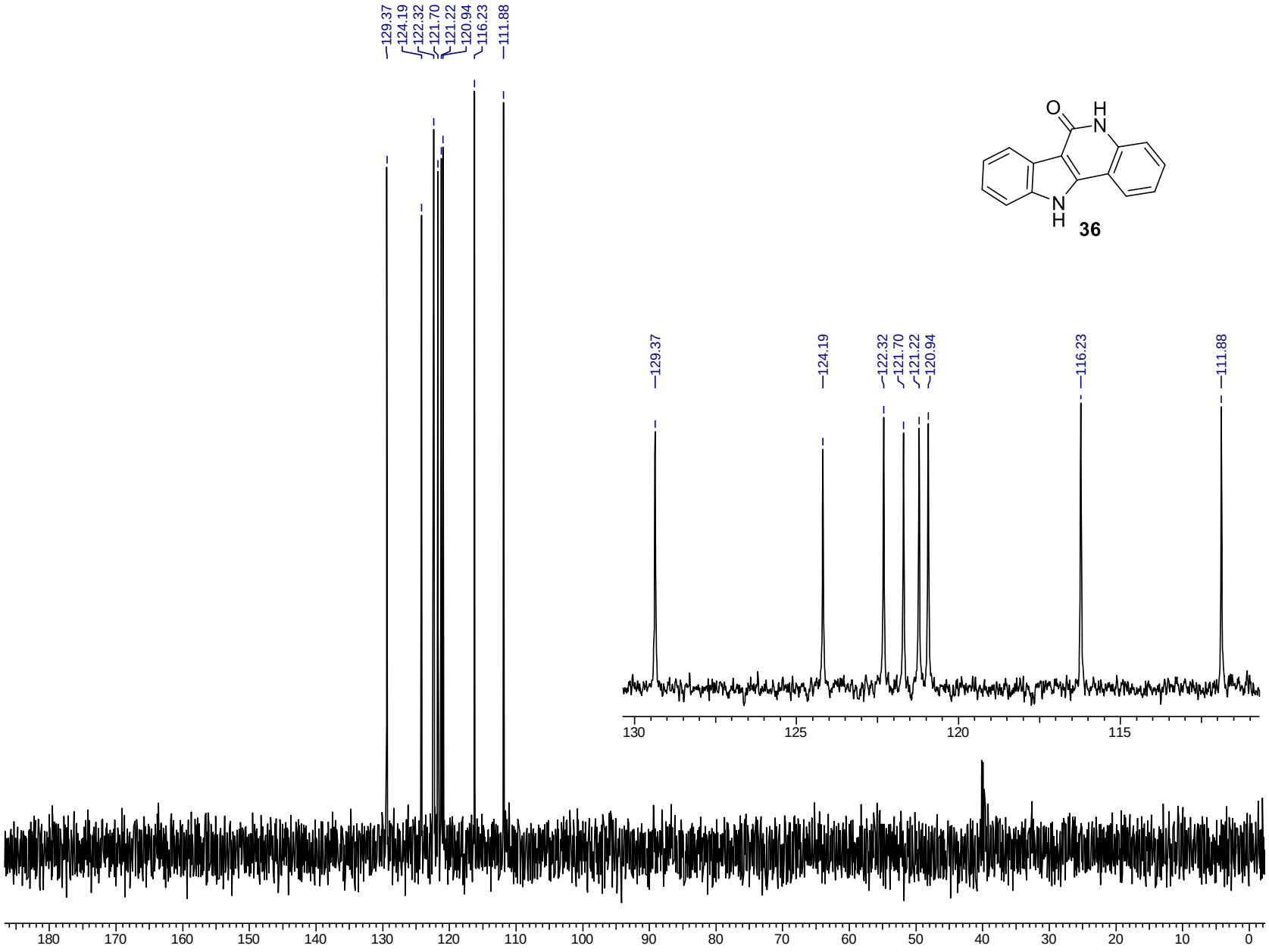
35

DEPT NMR, 100MHz

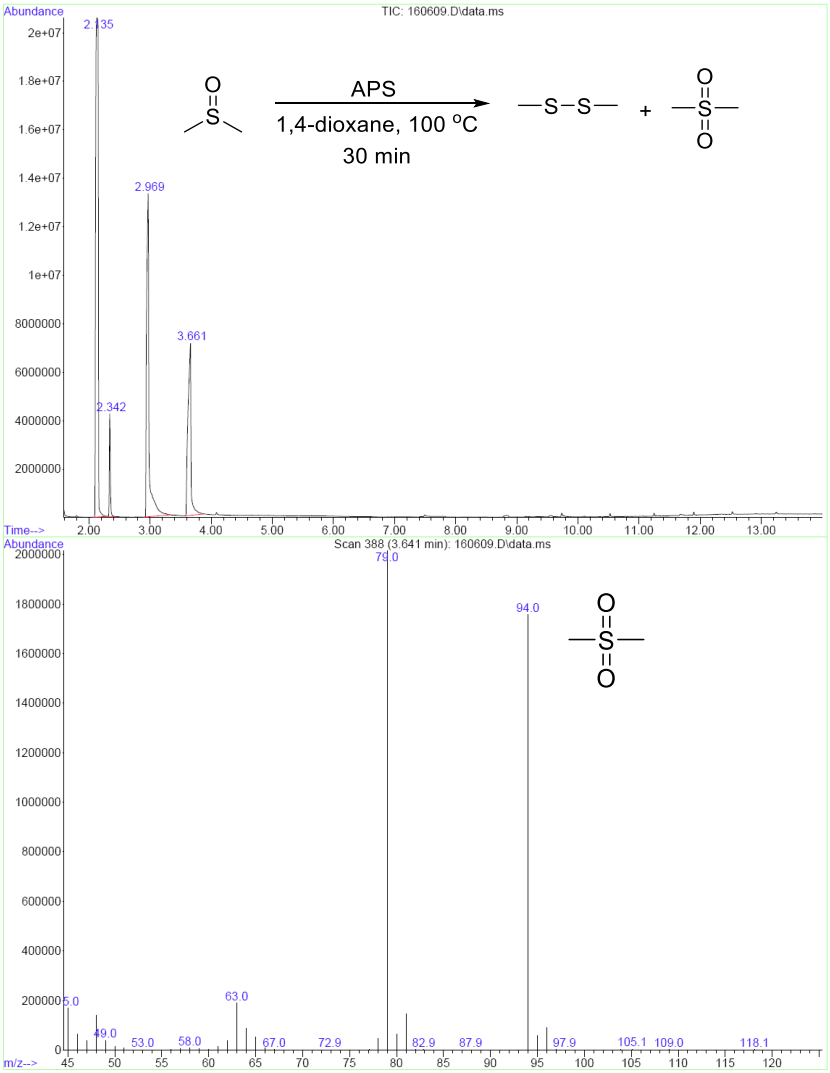


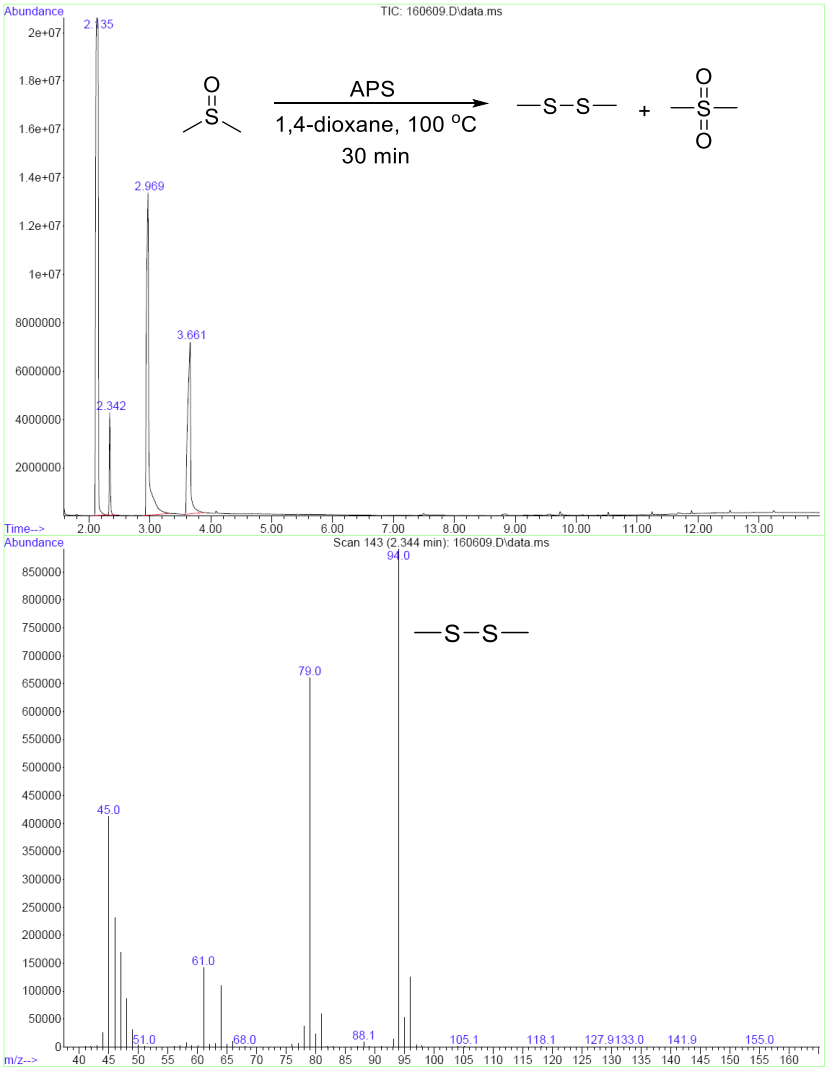

12.57
11.43
8.21
8.19
7.63
7.61
7.51
7.49
7.47
7.37
7.35
7.29
7.28
7.26
DMSO-d6
2.50
8.21
8.19
7.63
7.61
7.53
7.51
7.49
7.47
7.45
7.38
7.37
7.35
7.31
7.29
7.28
7.26
7.24
2.00
1.00
2.02
1.00
2.00
8.0
7.5
O
H
N
N
H
36
0.96
0.96
2.00
2.02
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


DMSO-d6
160.05
140.89
138.16
137.89
129.37
124.57
124.19
122.32
121.71
121.22
120.94
116.23
112.15
111.89
106.63
39.70
O
H
N
N
H
36
125
120
115
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

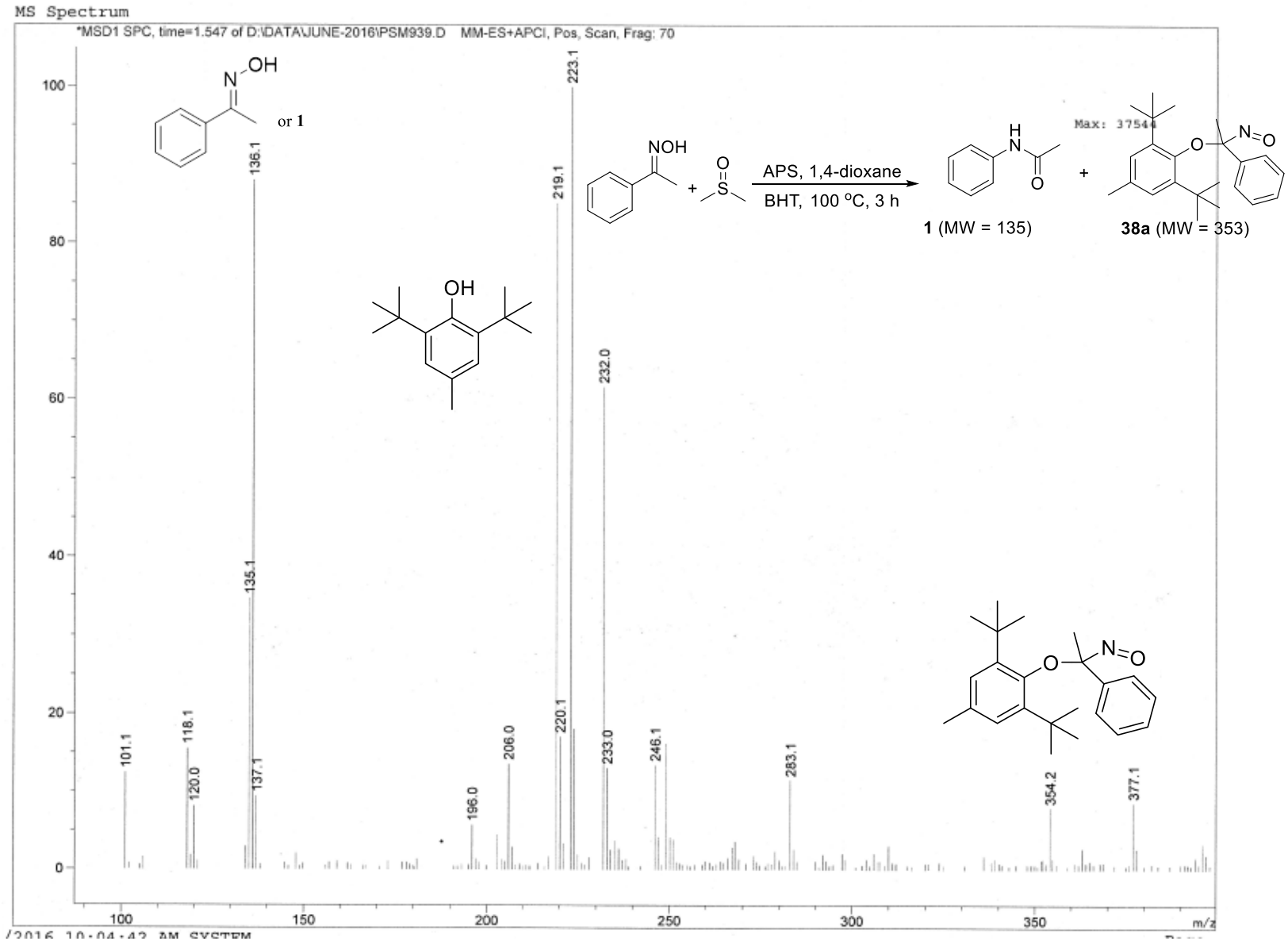

129.37
124.19
122.32
121.70
121.22
120.94
116.23
111.88
O
H
N
N
H
36
129.37
124.19
122.32
121.70
121.22
120.94
116.23
111.88
130
125
120
115
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Blank reaction to detect reactive intermediates:

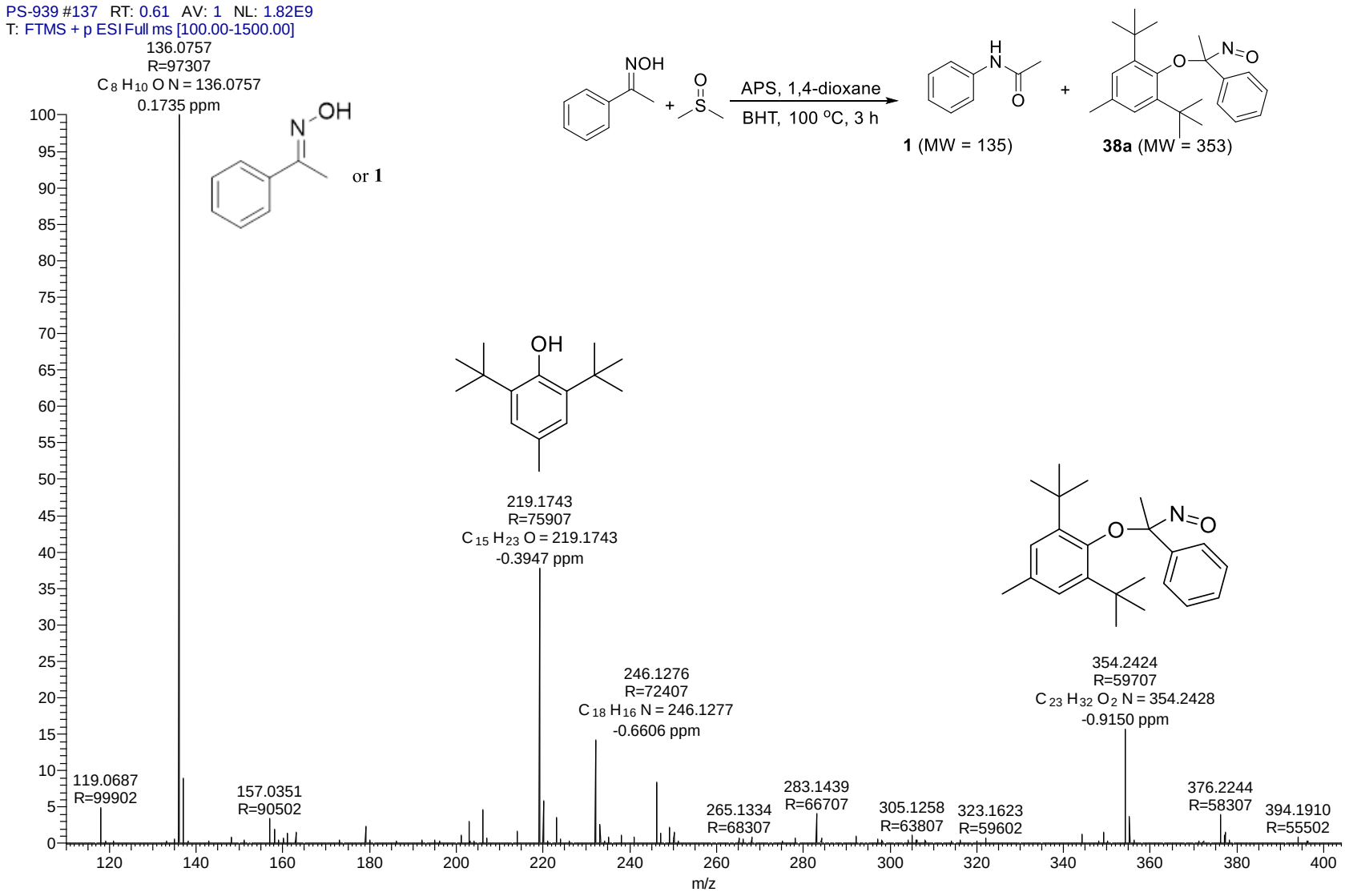




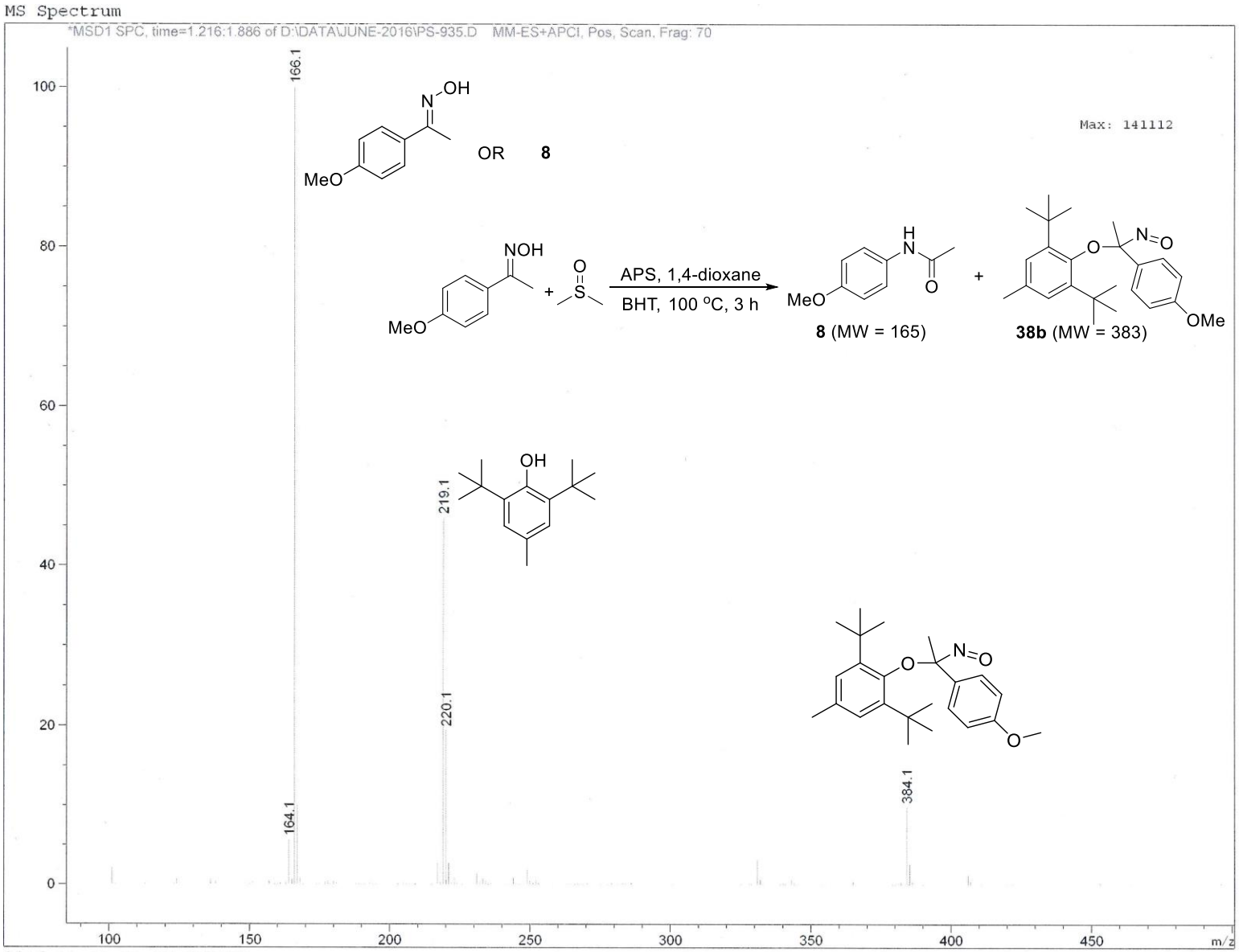
Trapping of intermediate 38a by ESI-LCMS:



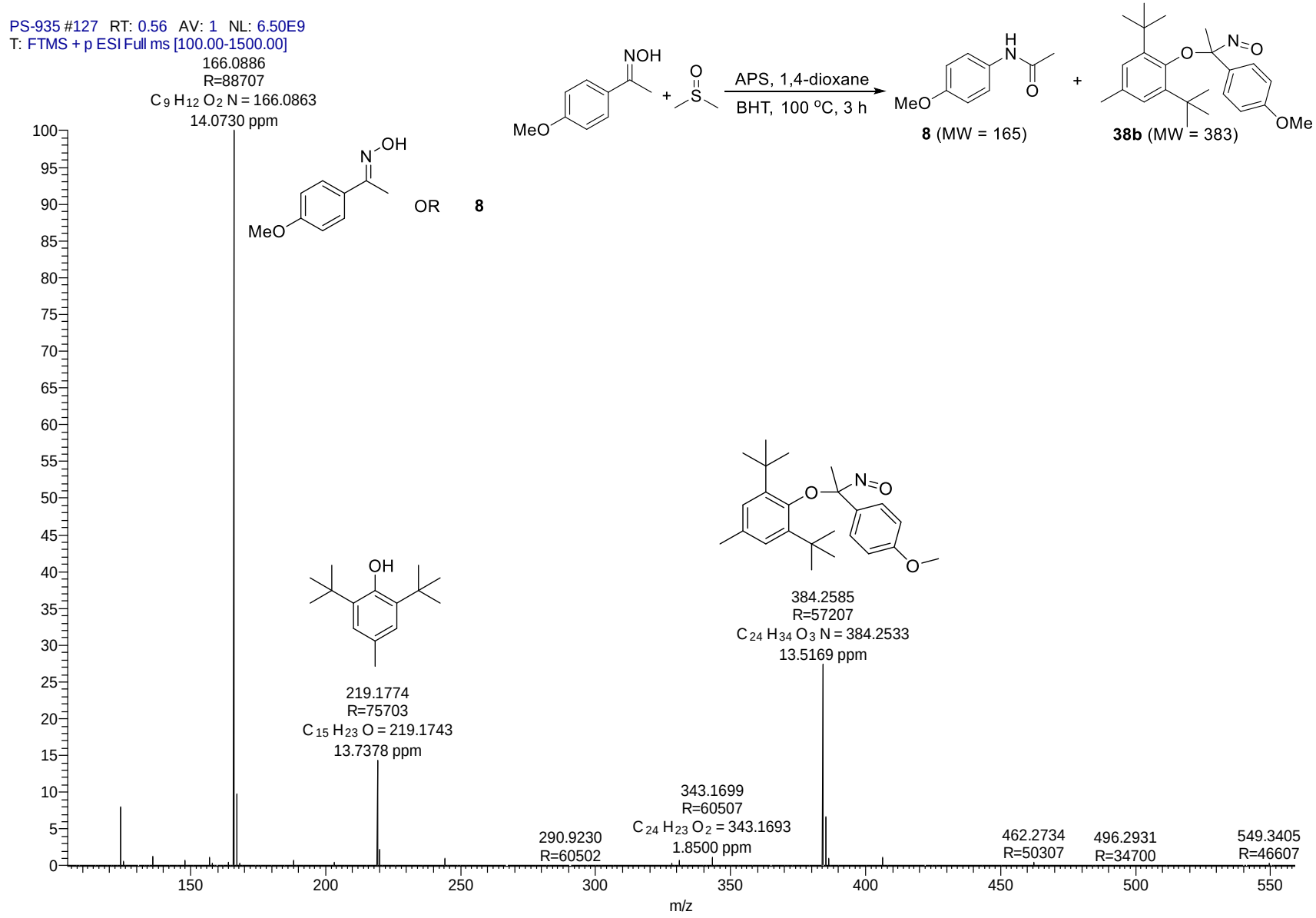
Trapping of intermediate 38a by ESI-HRMS:



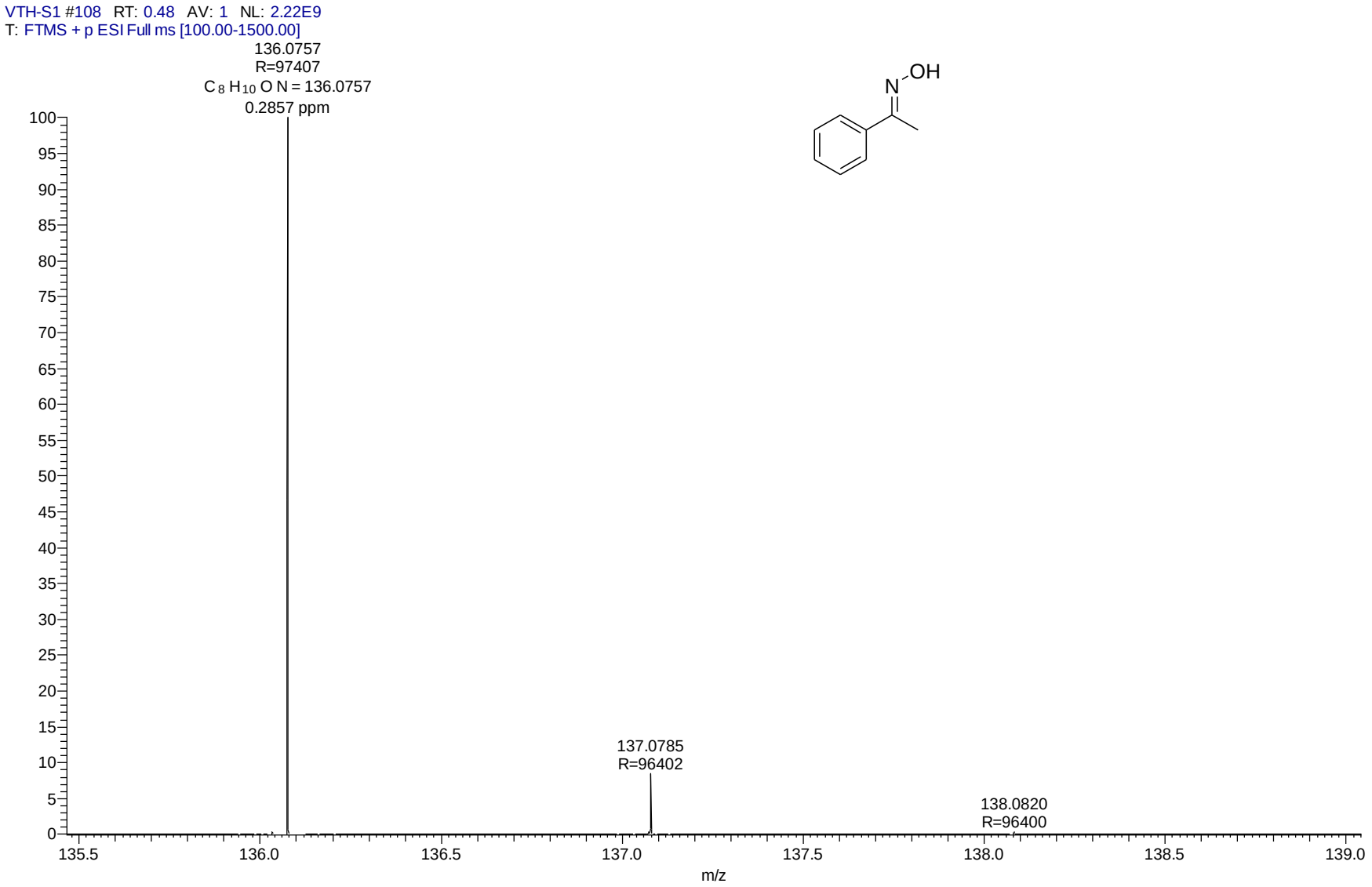
Trapping of intermediate 38b by ESI-LCMS:

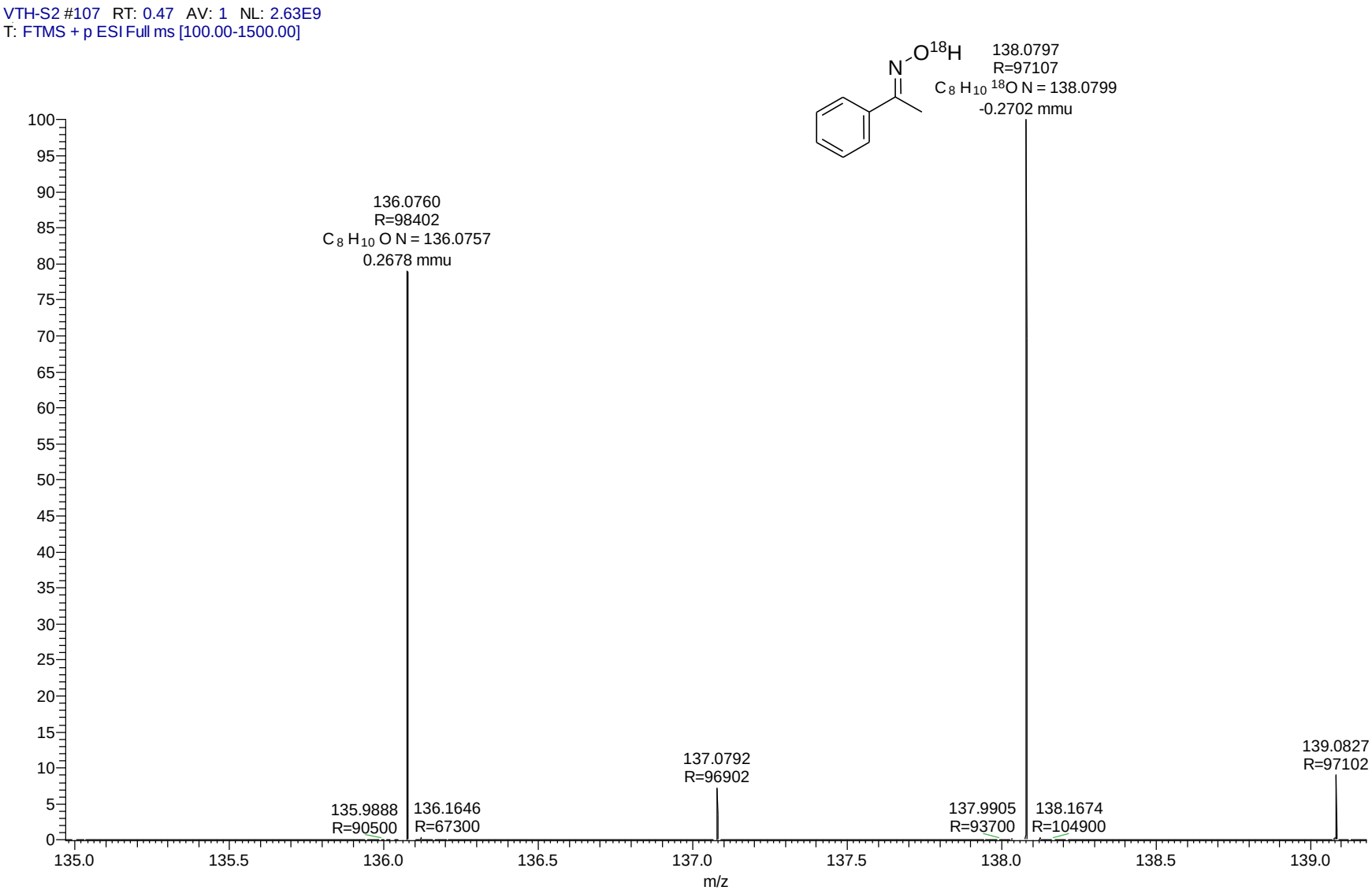


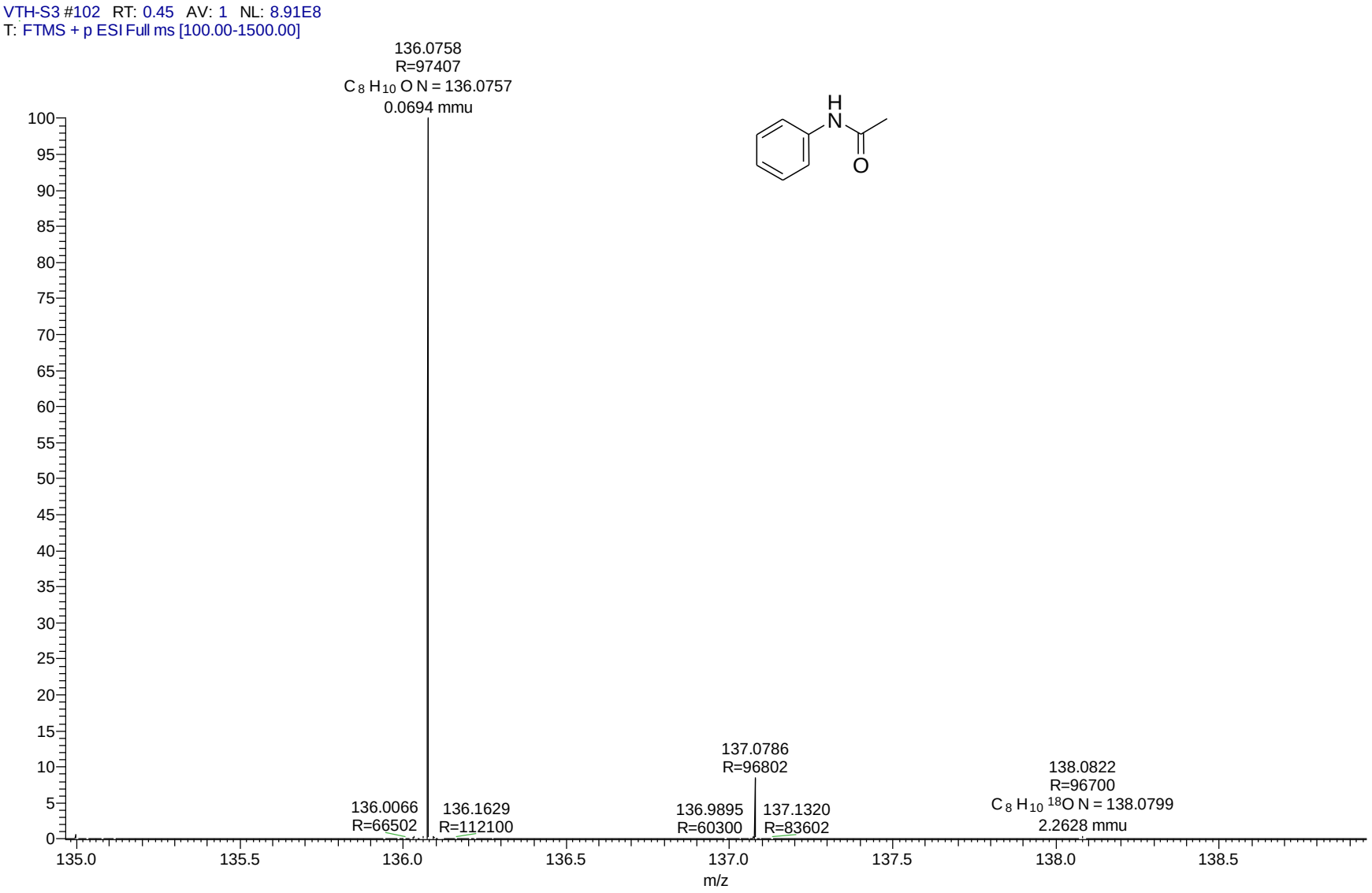
Trapping of intermediate 38b by ESI-LCMS:

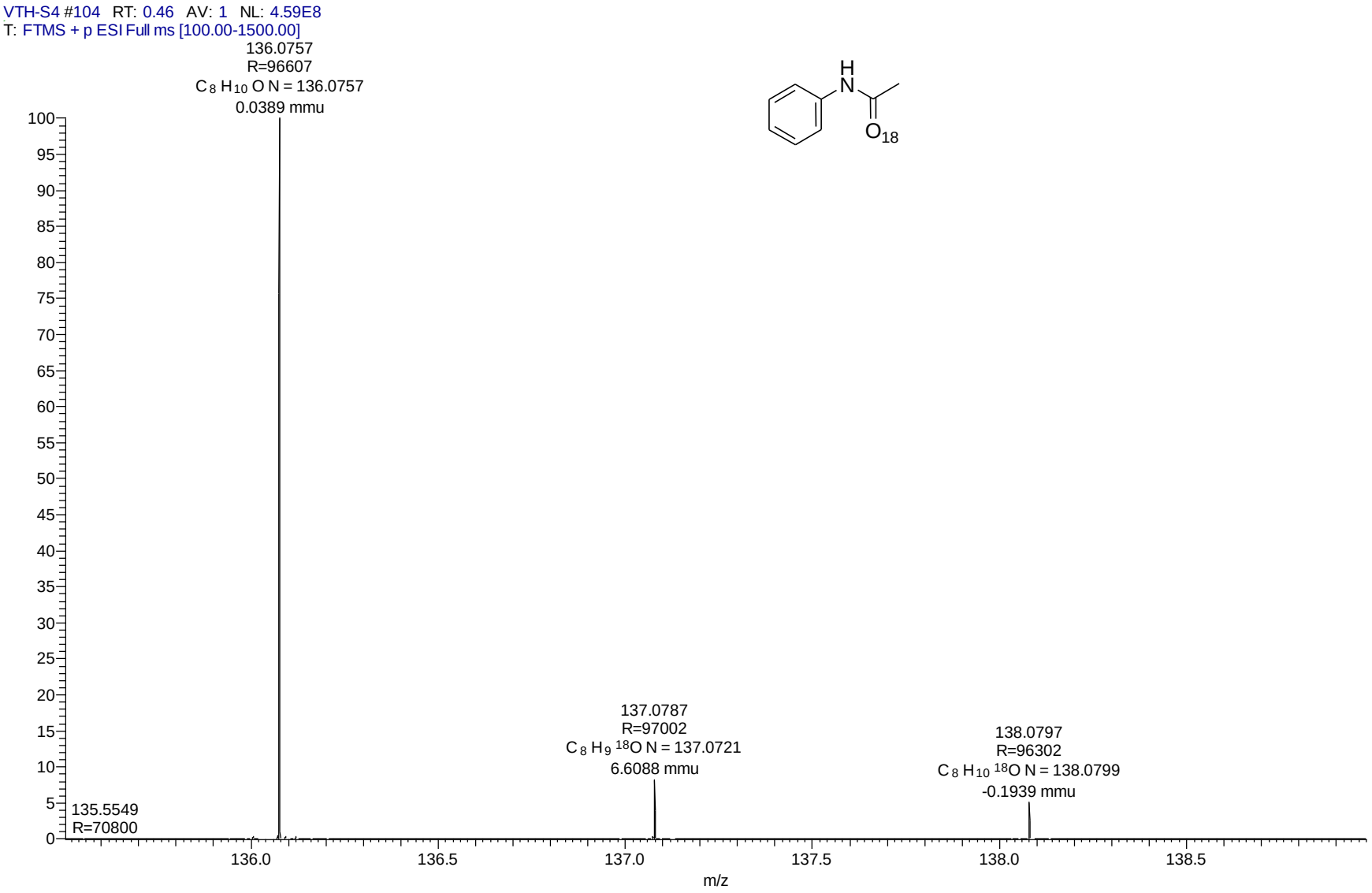


Labeling Experiment:




VTH-S2 #107 RT: 0.47 AV: 1 NL: 2.63E9
T: FTMS + p ESI Full ms [100.00-1500.00]
N
O18H
138.0797
R=97107
C8 H10 18O N = 138.0799
-0.2702 mmu
136.0760
R=98402
C8 H10 O N = 136.0757
0.2678 mmu
135.9888
R=90500
136.1646
R=67300
137.0792
R=96902
137.9905
R=93700
138.1674
R=104900
139.0827
R=97102
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
135.0
135.5
136.0
136.5
137.0
137.5
138.0
138.5
139.0
m/z


VTH-S3 #102 RT: 0.45 AV: 1 NL: 8.91E8
T: FTMS + p ESI Full ms [100.00-1500.00]
136.0758
R=97407
C 8 H 10 O N = 136.0757
0.0694 mmu
H
N
O
136.0066
R=66502
136.1629
R=112100
137.0786
R=96802
136.9895
R=60300
137.1320
R=83602
138.0822
R=96700
C 8 H 10 18O N = 138.0799
2.2628 mmu
m/z


VTH-S4 #104 RT: 0.46 AV: 1 NL: 4.59E8
T: FTMS + p ESI Full ms [100.00-1500.00]
136.0757
R=96607
C 8 H 10 O N = 136.0757
0.0389 mmu
H
N
O 18
135.5549
R=70800
137.0787
R=97002
C 8 H 9 18 O N = 137.0721
6.6088 mmu
138.0797
R=96302
C 8 H 10 18 O N = 138.0799
-0.1939 mmu
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
136.0
136.5
137.0
137.5
138.0
138.5
m/z