Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Novel one-pot method for the stereoselective synthesis of tetrahydropyrimidinones in low melting mixture

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Supporting Information

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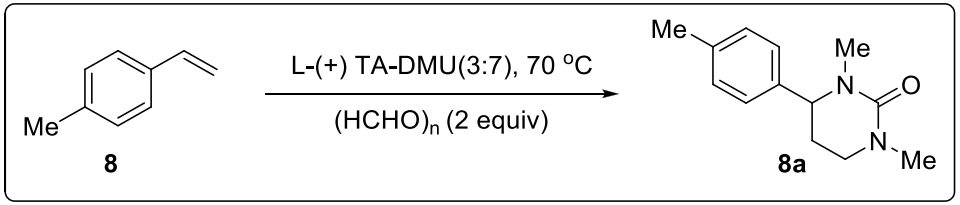
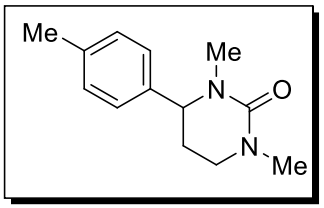
General Considerations: All the solvents were distilled prior to use. Dry solvents were prepared according to the standard procedures. All other reagents were used as received from either Aldrich or Lancaster chemical companies. Reactions requiring inert atmosphere were carried out under argon atmosphere. Infrared (IR) spectra were recorded on a JASCO 4100 FT-IR spectrometer. ^{1}H NMR spectra were measured on Bruker AVANCE 400 MHz and 500 MHz spectrometers. Chemical shifts were reported in ppm relative to solvent signals. ^{13}C NMR spectra were recorded on Bruker 100 MHz and 125 MHz spectrometers with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. The high-resolution mass spectra (HRMS) were performed on Micromass QTOF micro mass spectrometer equipped with a Harvard apparatus syringe pump. The structures were solved by direct methods (SHELXS-97) and refined by full-matrix least squares techniques against *F2* (SHELXL-97). Hydrogen atoms were inserted from geometry consideration using the HFIX option of the program. For thin layer chromatography (TLC) analysis throughout this work, E-Merck precoated TLC plates (silica gel 60 F254 grade, 0.25 mm) were used. Acme (India) silica gel (100-200 mesh) was used for column chromatography.

Synthesis of tetrhydropyrimidinones (THPMs):

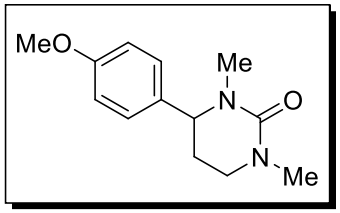
Vinyl arenes were prepared from carbonyl compounds by known procedure.[1]



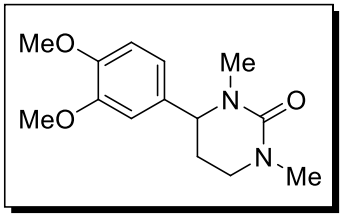
General experimental procedure A: 1.5 g of L - (+)-tartaric acid–DMU (30:70) was heated to 70 °C to obtain a clear melt. To this melt, 1 mmol of vinyl arene and 2 mmol of paraformaldehyde were added at 70 °C. The reaction was monitored by thin layer chromatography. After completion of reaction, the reaction mixture was quenched by adding water while still hot. The reaction mixture was cooled to room temperature and aqueous layer was extracted with EtOAc (3 x 5 mL) and washed with water (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography over silica gel using 30% EtOAc/hexane to afford pure THPMs.



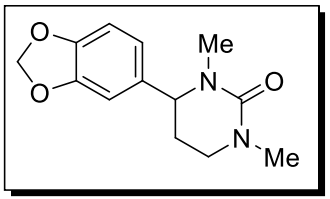
1,3-dimethyl-4-(p-tolyl)tetrahydropyrimidin-2(1H)-one 8a: Following the procedure A, the reaction of 4-methyl styrene (**8**) (118 mg, 1 mmol) and formaldehyde (60 mg, 2 mmol) at 70 °C for 22h afforded compound **8a** in 53% yield (116 mg) as a colourless liquid; **IR** (neat): 2935, 1614, 1515, 1459, 1245, 1032 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 7.16 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 4.42 (t, J = 4.4 Hz, 1H), 3.14 (dt, J = 3.6, 11.6 Hz, 1H), 3.00-3.06 (m, 1H), 2.97 (s, 3H), 2.86 (s, 3H), 2.29-2.38 (m, 4H), 1.86 (ddd, J = 4.0, 8.0, 13.2 Hz, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): **δ** 157.0, 138.6, 137.2, 129.5, 126.2, 61.2, 44.1, 36.0, 34.9, 30.0, 21.1 ppm; **HRMS** (ESI) calculated for $C_{13}H_{18}N_2O$ $[M+Na]^+$ 241.1317, found 241.1328.



Synthesis of 4-(4-methoxyphenyl)-1,3-dimethyltetrahydropyrimidin-2(1H)-one 9a: Following the procedure A, the reaction of 4-methoxy styrene (**9**) (134 mg, 1 mmol) and formaldehyde (60 mg, 2 mmol) at 70 ^{o}C for 22h afforded compound **9a** in 59% yield (138 mg) as a colorless liquid; **IR** (neat): 2935, 1614, 1515, 1459, 1245, 1032 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 7.06 (dd, J = 2.0, 6.8 Hz, 2H), 6.86 (dd, J = 2.0, 6.8 Hz, 2H), 4.39 (t, J = 4.4 Hz, 1H), 3.78 (s, 3H), 3.13 (dt, J = 4.0, 12.0 Hz, 1H), 3.00-3.06 (m, 1H), 2.96 (s, 3H), 2.84 (s, 3H), 2.26-2.35 (m, 1H), 1.83 (ddd, J = 4.0, 8.0, 13.2 Hz, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): **δ** 159.0, 157.0, 133.5, 127.3, 114.1, 60.8, 55.3, 44.0, 35.9, 34.8, 30.0 ppm; **HRMS** (ESI) calculated for $C_{13}H_{18}N_2O_2$ $[M + H]^+$ 235.1441, found 235.1448.

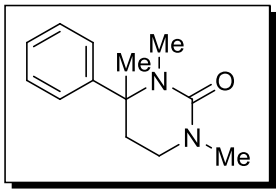


4-(3,4-dimethoxyphenyl)-1,3-dimethyltetrahydropyrimidin-2(1H)-one 10a: Following the procedure A, the reaction of vinyl arene (**10**) (150 mg, 0.91 mmol) and formaldehyde (55 mg, 1.8 mmol) at 70 ^{o}C for 14h afforded compound **10a** in 76% yield (184 mg) as a colorless liquid; **IR** (neat): 2925, 1611, 1517, 1459, 1306, 1240 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 6.83 (d, J = 8.0 Hz, 1H), 6.70 (dd, J = 2.0, 8.0 Hz, 1H), 6.65 (d, J = 2.0Hz, 1H) 4.39 (t, J = 4.8 Hz, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.15 (dt, J = 3.6, 10.4 Hz, 1H), 3.04-3.10 (m, 1H), 2.98 (s, 3H), 2.86 (s, 3H), 2.27-2.35(m, 1H), 1.88 (ddd, J = 4.0, 8.0, 12.4 Hz, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): **δ** 157.1, 149.4, 148.5, 134.2, 118.5, 111.3, 109.3, 61.2, 56.1, 56.0, 44.3, 36.0, 34.9, 30.2 ppm; **HRMS** (ESI) calculated for $C_{14}H_{20}N_2O_3$ $[M+H]^+$ 265.1547, found 265.1543.

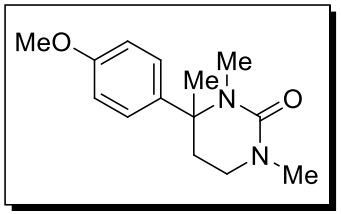


4-(benzo[d][1,3]dioxol-5-yl)-1,3-dimethyltetrahydropyrimidin-2(1H)-one 11a: Following the procedure A, the reaction of vinyl arene (**11**) (148 mg, 1 mmol) and formaldehyde (60 mg, 2 mmol) at 70 ^{o}C for 17h afforded compound **11a** in 68% yield (168 mg) as a colorless liquid; **IR** (neat)**:** 3447, 3037, 2923, 1632, 1302 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$)**: δ** 6.75 (d, J = 8.0 Hz, 1H), 6.62 (d, J = 1.6Hz, 1H), 6.59 (dd, J = 1.6, 7.6 Hz, 1H), 5.93 (s, 2H), 4.35 (t, J = 4.4Hz, 1H), 3.14 (ddd, J = 4.0, 11.2, 23.2 Hz, 1H), 3.04 (ddd, J = 4.0, 8.8, 11.2 Hz, 1H), 2.95 (s, 3H), 2.84 (s, 3H), 2.29 (dddd, J = 5.2, 10.8, 13.2, 14.8 Hz, 1H), 1.82 (ddd, J = 4.0, 8.0,

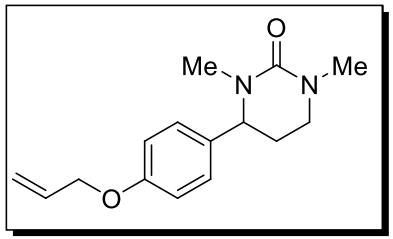
12.0 Hz, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$)**: δ** 156.8, 148.2, 147.0, 135.6, 119.4, 108.4, 106.6, 101.2, 61.1, 44.0, 35.9, 34.8, 30.1 ppm; **HRMS** (ESI) calculated for $C_{13}H_{16}N_2O_3$ $[M+H]^+$ 249.1234, found 249.1226.



1,3,4-trimethyl-4-phenyltetrahydropyrimidin-2(1H)-one 12a: Following the procedure A, the reaction of vinyl arene (**12**) (80 mg, 0.677 mmol) and formaldehyde (41 mg, 1.35 mmol) at 70 ^oC for 21h afforded compound **12a** in 69% yield (102 mg) as a colorless liquid; **IR** (neat)**:** 2923, 1617, 1511, 1349, 1261, 1032 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 7.33-7.37 (m, 2H), 7.21-7.28 (m, 3H), 3.03 (td, J = 4.8, 12.0Hz, 1H), 2.96 (s, 3H), 2.88-2.94 (m, 1H), 2.83 (s, 3H), 2.00-2.14 (m, 2H), 1.69 (s, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): **δ** 157.3, 145.1, 128.7, 127.1, 125.8, 61.0, 43.8, 38.4, 36.2, 30.5, 26.8 ppm; **HRMS** (ESI) calculated for $C_{13}H_{18}N_2O$ $[M+Na]^+$ 241.1311, found 241.1325.



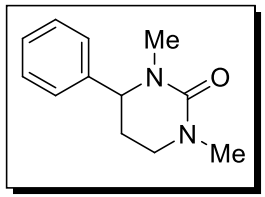
4-(4-methoxyphenyl)-1,3,4-trimethyltetrahydropyrimidin-2(1H)-one 13a: Following the procedure A, the reaction of vinyl arene (**13**) (100 mg, 0.67 mmol) and formaldehyde (40 mg, 1.3 mmol) at 70 ^oC for 23h afforded compound **13a** in 76% yield (127 mg) as a colorless liquid; **IR** (neat): 3454, 2932, 1621, 1511, 1455,1353, 1257 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 7.09 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 8.0 Hz, 2H), 3.76 (s, 3H), 2.98-3.03 (m, 1H), 2.92 (s, 3H), 2.86-2.90 (m, 1H), 2.77 (s, 3H), 1.93-2.08 (m, 2H), 1.62 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): **δ** 158.5, 157.2, 137.0, 126.8, 113.9, 60.4, 55.2, 43.8, 38.4, 36.1, 30.2, 26.9 ppm; **HRMS** (ESI) calculated for $C_{14}H_{20}N_2O_2$ $[M+H]^+$ 249.1598, found 249.1606.

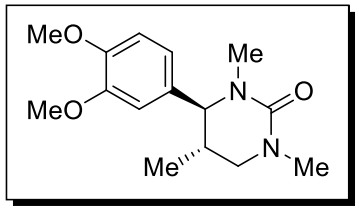


4-(4-(allyloxy)phenyl)-1,3-dimethyltetrahydropyrimidin-2(1H)-one 14a: Following the procedure A, the reaction of styrene (**14**) (80 mg, 0.5 mmol) with formaldehyde (30 mg, 1 mmol) at 70 ^oC for 22h afforded compound **14a** in 73% yield (95 mg) as a colorless liquid; **IR** (neat): 3441, 2927, 1617, 1513, 1411, 1249 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 7.03 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 5.97-6.06 (m, 1H), 5.38 (dd, J = 1.2, 17.2 Hz, 1H), 5.24 (d, J =,10.4 Hz, 1H), 4.49 (d, J = 5.2Hz, 2H), 4.38 (t, J = 4.4Hz, 1H), 3.10 (dt, J = 3.6, 11.6Hz, 1H), 2.99-3.04 (m, 1H), 2.94 (s, 3H), 2.82 (s, 3H), 2.25-2.33

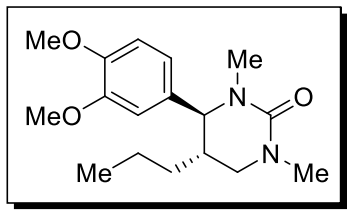
(m, 1H), 1.79-1.85 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): **δ** 157.9, 156.9, 133.6, 133.2, 127.2, 117.7, 114.8, 68.8, 60.7, 43.9, 35.8, 34.7, 29.9 ppm; **HRMS** (ESI) calculated for $C_{15}H_{20}N_2O_2$ $[M+Na]^+$ 283.1417, found 283.1423.

Data for THPM derivative from styrene 1,3-dimethyl-4-phenyltetrahydropyrimidin-2(1H)-one (reference 26)**:** Following the procedure A, the reaction of styrene (104 mg, 1 mmol) and formaldehyde (60 mg, 2 mmol) at 70 °C for 25h afforded compound in 14% yield (29 mg) as a colorless liquid; **IR** (neat): 2927, 2857, 2377, 1617, 1508, 1446, 1402, 1331cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 7.36 (t, J = 6.0 Hz, 2H), 7.26-7.29 (m, 1H), 7.17 (d, J = 6.0 Hz, 2H), 4.47 (t, J = 3.6 Hz, 1H), 3.14 (dt, J = 3.2, 9.2 Hz, 1H), 3.03-3.07 (m, 1H), 2.98 (s, 3H), 2.88 (s, 3H), 2.33-2.40 (m, 1H), 1.89 (ddd, J = 3.2, 6.0, 12.8 Hz, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): **δ** 157.0, 141.7, 128.8, 127.5, 126.3, 61.4, 44.0, 36.0, 34.9, 29.9 ppm; **HRMS** (ESI) calculated for $C_{12}H_{16}N_2O$ $[M + H]^+$ 205.1324, found 205.1324



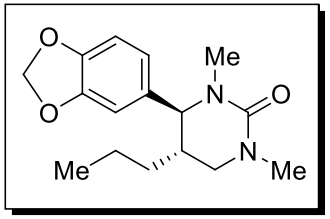


(4S,5S)-4-(3,4-dimethoxyphenyl)-1,3,5-trimethyltetrahydropyrimidin-2(1H)-one 15a: Following the procedure A, the reaction of vinyl arene (**15**) (160 mg, 0.9 mmol) and formaldehyde (56 mg, 1.8 mmol) at 70 °C for 20h afforded compound **15a** in 69% yield (102 mg, dr = 19:1) as a colorless liquid recovered starting material 71mg; **IR** (neat): 2925, 1611, 1517, 1459, 1306, 1277 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl3): **δ** 6.81 (d, J = 8.0 Hz, 1H), 6.69 (dd, J = 2.0, 8.0 Hz, 1H), 6.64 (d, J = 2.0 Hz, 1H), 3.91 (d, J = 6.0Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.18 (dd, J = 4.0, 11.6 Hz, 1H), 2.97 (s, 3H), 2.88 (dd, J = 6.4, 12.0 Hz, 1H), 2.77 (s, 3H), 2.07-2.00 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, CDCl3): **δ** 157.0, 149.4, 148.5, 134.1, 119.1, 111.1, 109.3, 68.4, 56.0, 56.0, 51.4, 36.1, 34.8, 34.7, 17.1 ppm; **HRMS** (ESI) calculated for $C_{15}H_{22}N_2O_3$ $[M+H]^+$ 279.1700, found 279.1703.



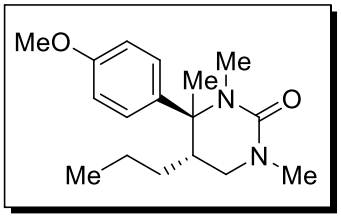
(4S,5S)-4-(3,4-dimethoxyphenyl)-1,3-dimethyl-5-propyltetrahydropyrimidin-2(1H)-one 16a: Following the procedure A, the reaction of vinyl arene (**16**) (150 mg, 0.72 mmol) and formaldehyde (43 mg, 1.44 mmol) at 70 °C for 21h afforded compound **16a** in 73% yield (164 mg, dr = 19:1) as a colorless liquid; **IR** (neat): 2927, 2857, 1617, 1508, 1446, 1402, 1331, 1305 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): **δ**

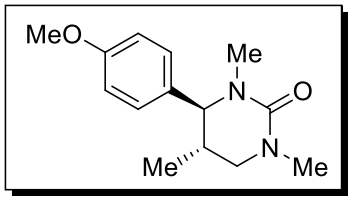
6.83 (d, J = 8.4 Hz, 1H), 6.69 (dd, J = 8.4 Hz, 1H), 6.63 (s, 1H), 4.04 (d, J = 4.0 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.22 (dd, J = 4.0, 12.0 Hz, 1H), 2.97 (s, 3H), 2.83-2.86 (m, 4H), 1.29-1.83 (m, 5H), 0.90 (t, J = 6.8 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): **δ** 156.8, 149.4, 148.4, 134.5, 118.8, 111.2, 109.3, 66.5, 56.1, 56.0, 48.6, 39.4, 36.2, 35.1, 33.4, 20.5, 14.1 ppm; **HRMS** (ESI) calculated for $C_{17}H_{26}N_2O_3$ $[M+H]^+$ 307.2016, found 307.2042.



(4S,5S)-4-(benzo[d][1,3]dioxol-5-yl)-1,3-dimethyl-5-propyltetrahydropyrimidin-2(1H)-one 17a: Following the procedure A, the reaction of vinyl arene (**17**) (100 mg, 0.52 mmol) and formaldehyde (32 mg, 1.05 mmol) at 70 ^oC for 18h afforded compound **17a** in 68% yield (103 mg, dr = 19:1) as a colorless liquid; **IR** (neat): 3002, 2355, 1608, 1266, 1041 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 6.77 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 1.6Hz, 1H), 6.61 (dd, J = 1.6, 8.0 Hz, 1H), 5.96 (s, 2H), 4.02 (d, J = 4.0 Hz, 1H), 3.23 (dd, J = 4.0, 12.0 Hz, 1H), 2.97 (s, 3H), 2.83-2.86 (m, 4H), 1.76-1.82 (m, 1H), 1.29-1.48 (m, 4H), 0.92 (t, J = 7.2Hz, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): **δ** ppm 156.7, 148.2, 147.0, 136.1, 119.7, 108.4, 106.8, 101.3, 66.5, 48.4, 39.4, 36.2, 35.1, 33.4, 20.5, 14.1 ppm; **HRMS** (ESI) calculated for $C_{16}H_{22}N_2O_3$ $[M+H]^+$ 291.1703, found 291.1704.

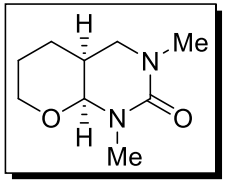
(4S,5S)-4-(4-methoxyphenyl)-1,3,4-trimethyl-5-propyltetrahydropyrimidin-2(1H)-one 18a: Following the procedure A, the reaction of vinyl styrene (**18**) (80 mg, 0.42 mmol) and formaldehyde (26 mg, 0.84 mmol) at 70 ^oC for 24h afforded compound **18a** in 63% yield (84 mg, dr = 19:1) as a colorless liquid; **IR** (neat): 2923, 1617, 1511, 1402, 1345, 1257, 1159 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 7.18 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.0Hz, 2H), 3.80 (s, 3H), 3.00-3.14 (m, 2H), 2.98 (s, 3H), 2.55 (s, 3H), 2.01-2.07 (m, 1H), 1.43 (s, 3H), 1.24-1.28 (m, 2H), 0.98-1.06 (m, 2H), 0.72 (t, J = 7.2 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): **δ** 158.5, 157.4, 136.7, 127.7, 113.7, 63.9, 55.3, 49.1, 44.0, 36.1, 31.2, 30.0, 20.8, 18.2, 14.0 ppm; **HRMS** (ESI) calculated for $C_{17}H_{26}N_2O_2$ $[M+Na]^+$ 313.1886, found 313.1892.





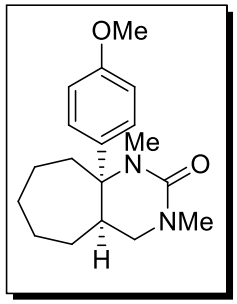
(4S,5S)-4-(3-methoxyphenyl)-1,3,5-trimethyltetrahydropyrimidin-2(1H)-one 19a: Following the procedure A, the reaction of vinyl arene (**19**) (80 mg, 0.54 mmol) and formaldehyde (32 mg, 1.08 mmol) at 70 ^{o}C for 20h afforded compound **19a** in 74% yield (98 mg, dr = 19:1) as a colorless liquid; **IR** (neat): 2925, 1617, 1507, 1454, 1405, 1242, 1174 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl3): δ 7.06 (d, J = 4.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 3.93 (d, J = 5.2 Hz, 1H), 3.78 (s, 3H), 3.16 (dd, J = 4.0, 11.6 Hz, 1H), 2.96 (s, 3H), 2.84 (dd, J = 6.0, 11.6 Hz, 1H), 2.76 (s, 3H), 1.98-2.03 (m, 1H), 1.03 (d, J = 6.8 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, CDCl3): δ 159.0, 156.9, 133.7, 127.7, 114.1, 67.9, 55.3, 51.1, 36.1, 34.7, 17.1 ppm; **HRMS** (ESI) calculated for $C_{14}H_{20}N_2O_2$ $[M+Na]^+$ 271.1417, found 271.1430.

(4S,5S)-4-(3,4-dimethoxyphenyl)-1,3,5-trimethyltetrahydropyrimidin-2(1H)-one 15a from starting material 20: Following the procedure A, the reaction of vinyl arene (**20**) (80 mg, 0.44 mmol) and formaldehyde (27 mg, 0.88 mmol) at 70 ^{o}C for 16h afforded compound **15a** in 81% yield (101 mg, dr = 19:1) as a colorless liquid; **IR** (neat): 2925, 1611, 1517, 1459, 1306, 1277 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl3): **δ** 6.81 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.64 (s, 1H), 3.90 (d, J = 5.2 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.17 (dd, J = 4.0, 11.6 Hz, 1H), 2.96 (s, 3H), 2.87 (dd, J = 6.4, 12.0 Hz, 1H), 2.77 (s, 3H), 2.07-2.01 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, CDCl3): **δ** 156.9, 149.4, 148.5, 134.1, 119.1, 111.0, 109.2, 68.4, 56.0, 56.0, 51.4, 36.1, 34.7, 34.7, 17.0 ppm; **HRMS** (ESI) calculated for $C_{15}H_{22}N_2O_3$ $[M+H]^+$ 279.1700, found 279.1703.

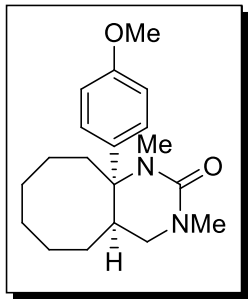


1,3-dimethylhexahydro-1H-pyrano[3,2-d]pyrimidin-2(3H)-one 21a: Following the procedure A, the reaction of 3, 4-dihydropyran (**21**) (84 mg, 1 mmol) and formaldehyde (60 mg, 2 mmol) at 70 ^{o}C for 16h afforded compound **21a** in 65% yield (119 mg) as a colorless liquid; **IR** (neat): 3429, 1637, 1286, 1234, 1103 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 4.40 (d, J = 1.6 Hz, 1H), 3.91-3.95 (m, 1H), 3.57 (t, J = 11.6 Hz, 1H), 3.47 (dt, J = 2.4, 11.6 Hz, 1H), 2.96 (s, 3H), 2.86-2.91 (m, 4H), 2.17-2.22 (m, 1H), 1.63-1.83 (m, 3H), 1.32-1.38 (m, 1H) ppm; **^{13}C NMR** (100

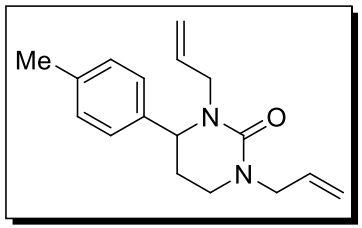
MHz, $CDCl_3$): **δ** ppm 155.6, 87.2, 66.3, 47.2, 35.7, 34.1, 31.3, 24.9, 21.3 ppm; **HRMS** (ESI) calculated for $C_9H_{16}N_2O_2$ $[M+H]^+$ 184.1285, found 185.1297.



9a-(4-methoxyphenyl)-1,3-dimethyldecahydro-2H-cyclohepta[d]pyrimidin-2-one 22a: Following the procedure A, the reaction of vinyl arene (**22**) (80 mg, 0.39 mmol) and formaldehyde (23 mg, 0.79 mmol) at 70 °C for 14h afforded compound **22a** in 80% yield (97 mg) as a colorless liquid; **IR** (neat): 2926, 1620, 1509, 1098, 1035 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 7.07 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 3.77 (s, 3H), 3.03 (dd, J = 2.8, 12.0 Hz, 1H), 2.91 (s, 3H), 2.87 (s, 3H), 2.55 (dd, J = 1.6, 11.6 Hz, 1H), 2.18 (dd, J = 8.8, 15.2 Hz, 1H), 1.80-1.98 (m, 4H), 1.62-1.78 (m, 3H), 1.49-1.54 (m, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): **δ** 158.3, 157.5, 139.9, 126.7, 113.8, 66.6, 55.3, 52.1, 46.2, 37.8, 36.7, 30.1, 29.0, 27.3, 26.7, 21.6 ppm; **HRMS** (ESI) calculated for $C_{18}H_{26}N_2O_2$ $[M+Na]^+$ 325.1886, found 325.1894.

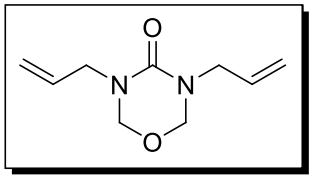


10a-(4-methoxyphenyl)-1,3-dimethyldecahydrocycloocta[d]pyrimidin-2(1H)-one 23a: Following the procedure A, the reaction of vinyl arene (**23**) (70 mg, 0.32 mmol) and formaldehyde (19 mg, 0.64 mmol) at 70 °C for 17h afforded compound **23a** in 74% yield (76 mg) as a colorless liquid; **IR** (neat): 2926, 1620, 1509, 1098, 1035 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 7.18 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 8.0 Hz, 2H), 3.06 (s, 3H), 2.83 (s, 3H), 2.80 (d, J = 2.4 Hz, 1H), 2.47 (d, J = 11.2 Hz, 1H), 2.31 (s, 3H), 2.03-2.16 (m, 4H), 1.49-1.88 (m, 7H), 1.23-1.32 (m, 2H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): **δ** ppm 157.8, 144.9, 136.4, 129.4, 125.1, 66.3, 54.2, 40.6, 36.7, 35.9, 30.3, 29.1, 27.9, 27.6, 23.6, 21.9, 20.9 ppm; **HRMS** (ESI) calculated for $C_{19}H_{28}N_2O_2$ $[M+H]^+$ 317.2224, found 317.2213.

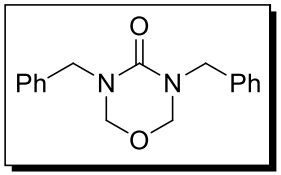


1,3-diallyl-4-p-tolyltetrahydropyrimidin-2(1H)-one 24: Diallylurea prepared by known procedure.[2] 1.5 g of L - (+)-tartaric acid–diallylurea (TA:DAU) (30:70) was heated to 70 °C to obtain a clear melt. To this melt, 4-methyl styrene (**8**) (118 mg, 1 mmol) and paraformaldehyde (60 mg, 2 mmol) were added at 70 °C. After completion of reaction, the reaction mixture was quenched by adding water while

still hot. The reaction mixture was cooled to room temperature and aqueous layer was extracted with EtOAc (3 x 5 mL) and washed with water (2 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography over silica gel to furnish the corresponding bis-allyl THPM derivative **24** along with 3,5-diallyl-1,3,5-oxadiazinan-4-one (**25**). Colorless liquid; yield 19% (52 mg); **IR** (neat): 3441, 2927, 1617, 1513, 1411, 1249 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 7.26 (d, J = 7.6 Hz, 2H), 7.15 (d, J = 7.6 Hz, 2H), 5.79-5.93 (m, 2H), 5.09-5.26 (m, 4H), 4.65 (d, J = 10.0 Hz, 1H), 3.76-3.93 (m, 5H), 3.16 (d, J = 15.2 Hz, 1H), 2.35 (s, 1H), 1.90-1.97 (m, 1H), 1.76-1.82 (m, 1H)ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): **δ** 159.0, 141.3, 136.9, 135.5, 133.6, 129.1, 125.7, 116.9, 115.5, 70.1, 49.6, 43.9, 43.4, 37.9, 21.2 ppm; **HRMS** (ESI) calculated for $C_{17}H_{22}N_2O$ $[M+H]^+$ 271.1806, found 271.1805.



3,5-diallyl-1,3,5-oxadiazinan-4-one 25: Colorless liquid; yield 33% (59 mg); **IR** (neat): 2927, 1617, 1513, 1411, 1249 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 5.74-5.83 (m, 2H), 5.15-5.21 (m, 4H), 4.75 (s, 4H), 3.95 (d, J = 5.6 Hz, 4H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): **δ** ppm 153.7, 133.5, 117.2, 78.3, 47.0 ppm; **HRMS** (ESI) calculated for $C_{17}H_{18}N_2O_2$ $[M+Na]^+$ 205.0947, found 205.0948.

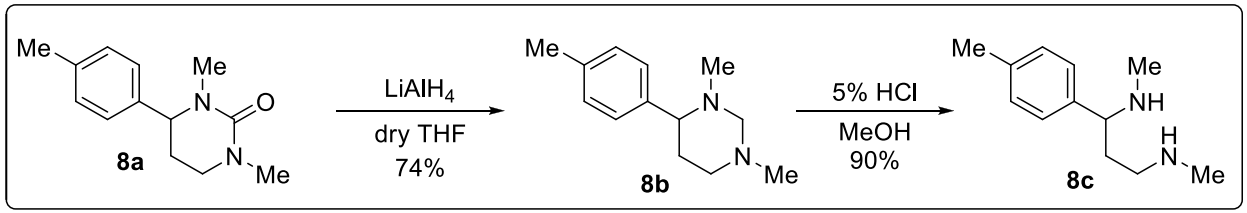


3,5-dibenzyl-1,3,5-oxadiazinan-4-one 26: Dibenzylurea prepared by known procedure.[3] 1.5 g of L -(+)-tartaric acid-choline chloride (1:2) was heated to 70 ^oC to obtain a clear melt. To this melt, 4-methyl styrene (**8**) (59 mg, 0.5 mmol) and dibenzylurea (120 mg, 0.5 mmol) and paraformaldehyde (30 mg, 1 mmol) were added. After completion of reaction, the reaction mixture was quenched by adding water while still hot, cooled to room temperature and extracted with EtOAc (3x 5 mL). The organic layer was washed with water (2 x 5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography over silica gel to give 3,5-dibenzyl-1,3,5-oxadiazinan-4-one (**27**) as a colorless liquid (102 mg) in 72% yield. **IR** (neat): 2926, 1620, 1509, 1098, 1035 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 7.28-7.39 (m, 10H), 4.76 (s, 4H), 4.62 (s, 4H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): **δ** ppm 154.2, 137.5, 128.8, 127.8, 127.5, 78.5, 48.1 ppm; **HRMS** (ESI) calculated for $C_{17}H_{18}N_2O_2$ $[M+Na]^+$ 305.1260, found 305.1262.

Gram scale synthesis of THPMs derivative 8a: 9.0 g of L -(+)-tartaric acid–DMU (30:70) was heated to 70 ^{o}C to obtain a clear melt. To this melt, 1 g of 4-methyl styrene (**8**) and 508 mg of paraformaldehyde were added at 70 ^{o}C. The reaction was monitored by thin layer chromatography. After completion of reaction, the reaction mixture was quenched by adding water while still hot. The reaction mixture was cooled to room temperature and aqueous layer was extracted with EtOAc (3 x 40 mL) and washed with water (2 x 40 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography over silica gel using 30% EtOAc/hexane to afford pure **8a** (1.04g**)** THPM derivative in 56% yield.

Recovery and recycle of melt mixture: To recover the melt, aqueous layer was concentrated under reduced pressure. The recovered melt mixture was reused in the next cycle without any further purification. The recovered melt was azotropically dried with toluene. To perform the reaction in recovered melt 1 mmol DMU was added and allowed to stirr 70 ^{o}C to obtain a clear melt. To this melt, 1 mmol of 4-methyl styrene (**8**) and 60 mg of paraformaldehyde were added at 70 ^{o}C. The reaction progress was monitored by thin layer chromatography. After completion of reaction, the reaction mixture was quenched by adding water while still hot. The reaction mixture was cooled to room temperature and aqueous layer was extracted with EtOAc (3 x 40 mL) and washed with water (2 x 40 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography over silica gel using 30% EtOAc/hexane to afford pure THPM derivative **8a** (107 mg**)** in 49% yield.

Synthesis of 1,3-diamine:



A mixture of lithium aluminum hydride (186 mg, 5.04 mmol) and **8a** (220 mg, 1.09 mmol) in anhydrous THF (5.0 mL) was stirred for 4 h. The reaction was quenched with water (3.0 mL), and 10% aqueous sodium hydroxide (3.0 mL) was added. After being

stirred for 15 minutes, the mixture was diluted with ethyl acetate, filtered through celite pad. The filtrate was extracted with ethyl acetate three times. The combined organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give the crude product, which was was purified by silica gel chromatography.

1,3-dimethyl-4-(p-tolyl)hexahydropyrimidine 8b: 156 mg, colourless liquid, yield 74%; **IR** (neat): 2941, 2783, 2374, 2349, 1513, 1447, 1387, 1283 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 7.16 (d, J = 7.6 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 3.67 (d, J = 8.8 Hz, 1H), 2.86 (d, J = 11.6 Hz, 2H), 2.67 (dd, J = 2.4, 11.2 Hz, 1H), 2.46 (d, J = 9.2 Hz, 1H), 2.25 (s, 6H), 2.06 (dt, J = 2.4, 12.0 Hz, 1H), 1.80-1.88 (m, 4H), 1.52 (dd, J = 2.0, 13.2 Hz, 1H) ppm; **^{13}C NMR** (100 MHz, MeOH-d^4): **δ** 140.6, 136.7, 129.1, 127.4, 80.1, 68.6, 54.7, 42.9, 40.6, 34.3, 21.1 ppm; **HRMS** (ESI) calculated for $C_{13}H_{20}N_2$ $[M+H]^+$ 205.1699, found 205.1700.

N^1,N^3-dimethyl-1-(p-tolyl)propane-1,3-diamine 8c: To the product (100 mg, 0.49 mmol) obtained above was added 5% HCl in methanol (3.0 mL). The mixture was stirred at 50 °C until TLC revealed complete conversion. and concentrated under reduced pressure to give 1,3-diamine 87 mg, white solid (moisture sensitive), yield 90%; **IR** (neat): 3403, 2978, 2743, 1465, 1267 cm^{-1}; **^{1}H NMR** (400 MHz, MeOH-d^4): **δ** 7.34 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 7.6 Hz, 2H), 4.23 (dd, J = 4.0, 10.8 Hz, 1H), 3.19 (d, J = 1.2 Hz, 1H), 2.90 (dd, J = 4.4, 11.2 Hz, 1H), 2.51-2.59 (m, 4H), 2.44 (s, 3H), 2.35 (dd, J = 4.8, 11.6 Hz, 1H), 2.28 (s, 3H) ppm; **^{13}C NMR** (100 MHz, MeOH-d^4): **δ** 141.9, 131.5, 130.9, 129.6, 61.9, 46.7, 33.7, 31.6, 30.2, 21.3 ppm; **HRMS** (ESI) calculated for $C_{12}H_{20}N_2$ $[M+H]^+$ 193.1699`, found 193.1700.

References:

1. (a) L. J. Rono, H. G. Yayla, D. Y. Wang, M. F. Armstrong, and R. R. Knowles, *J. Am. Chem. Soc.*, 2013, **135**, 17735; (b) T.-Q. Wang, Y.-Y. Hu, and S.-L. Zhang, *Org. Biomol. Chem.*, 2010, **8**, 2312; (c) A. M. Del Hoyo, A. G. Herraiz and M. G. Suero, *Angew. Chem., Int. Ed.*, 2017, **56**, 1610.

2. C. Iacobucci, C. Piotrowski, A. Rehkamp, C. H. Ihling and A. Sinz, *J. Am. Soc. Mass Spectrom.*, 2019, **30**, 139-148.

3. M. A. Pasha and V. P. Jayashankara, *Synth. Commun.*, 2006, **36**, 1787-1793.

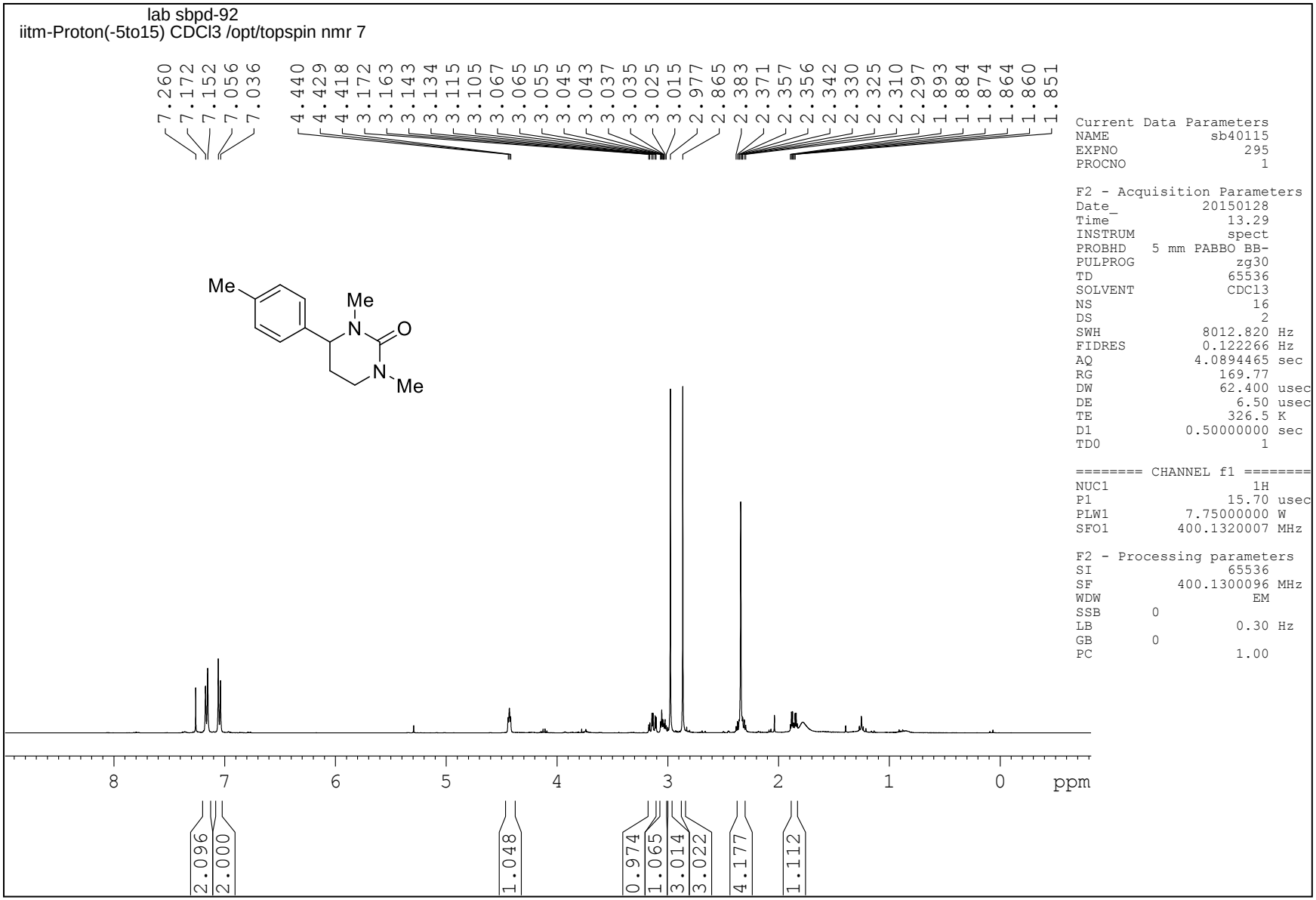


Figure 1 ^{1}H NMR spectrum of compound 8a

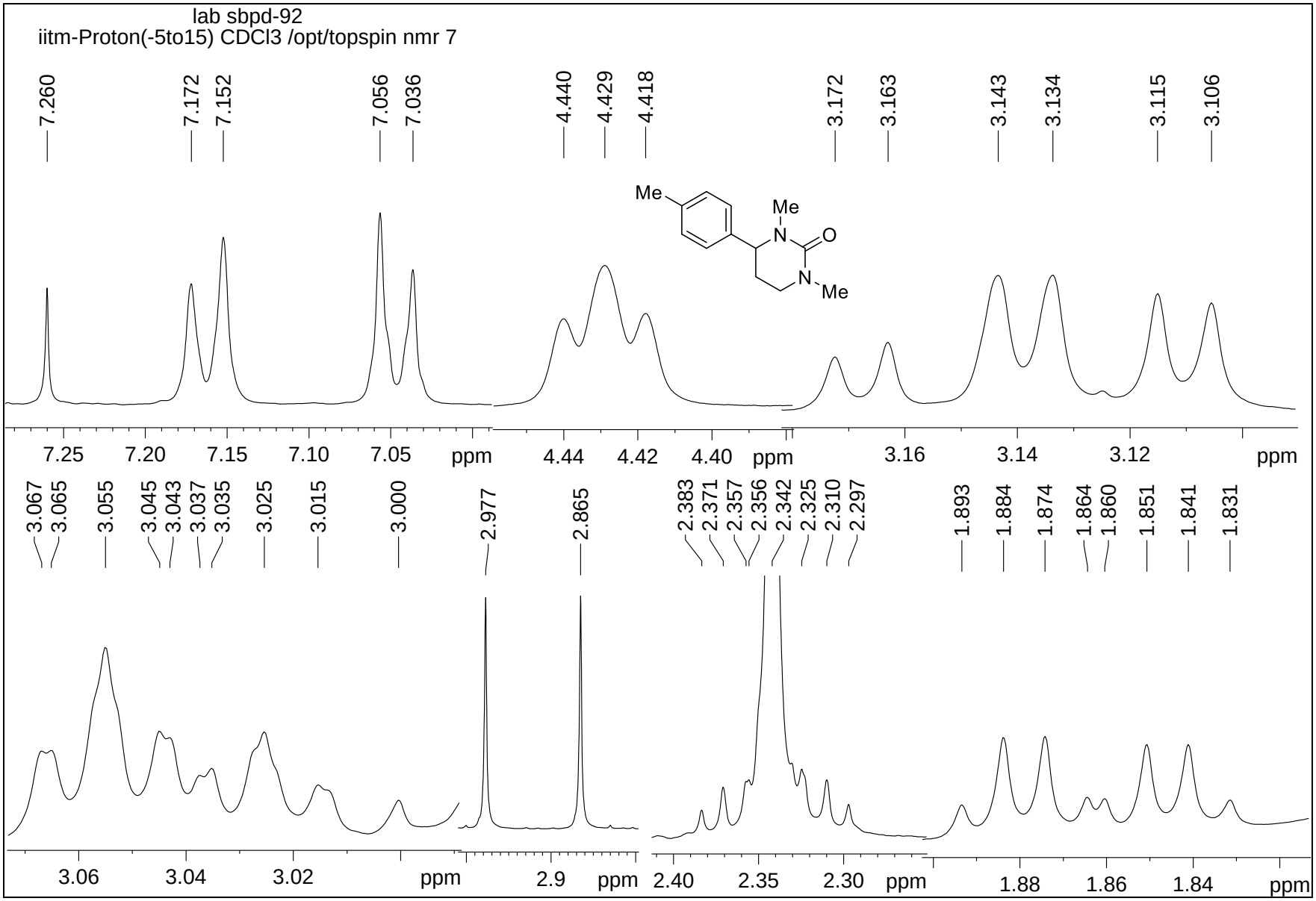


Figure 2 Expanded ^{1}H NMR spectrum of compound 8a

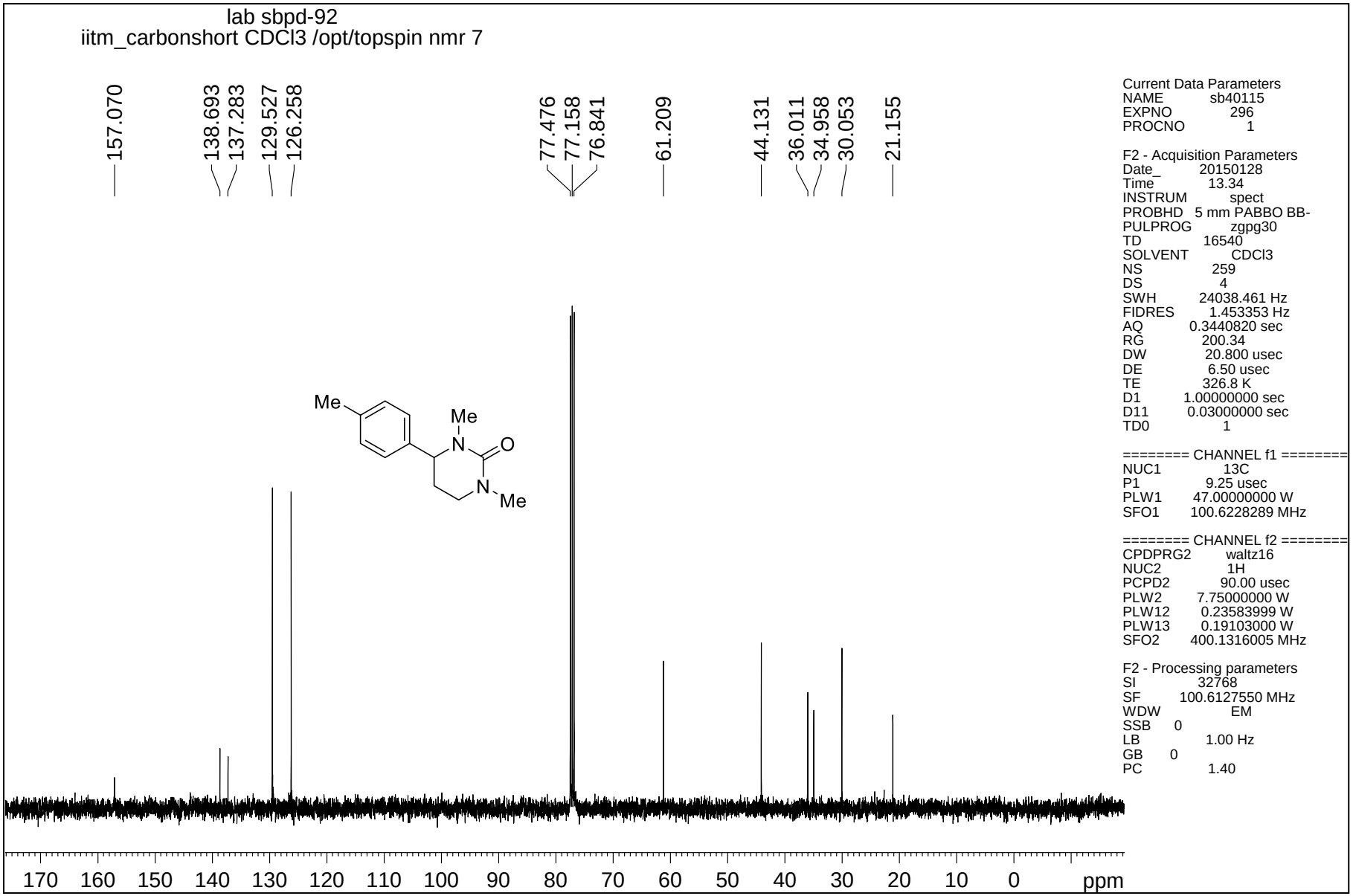


Figure 3 ^{13}C NMR spectrum of compound 8a

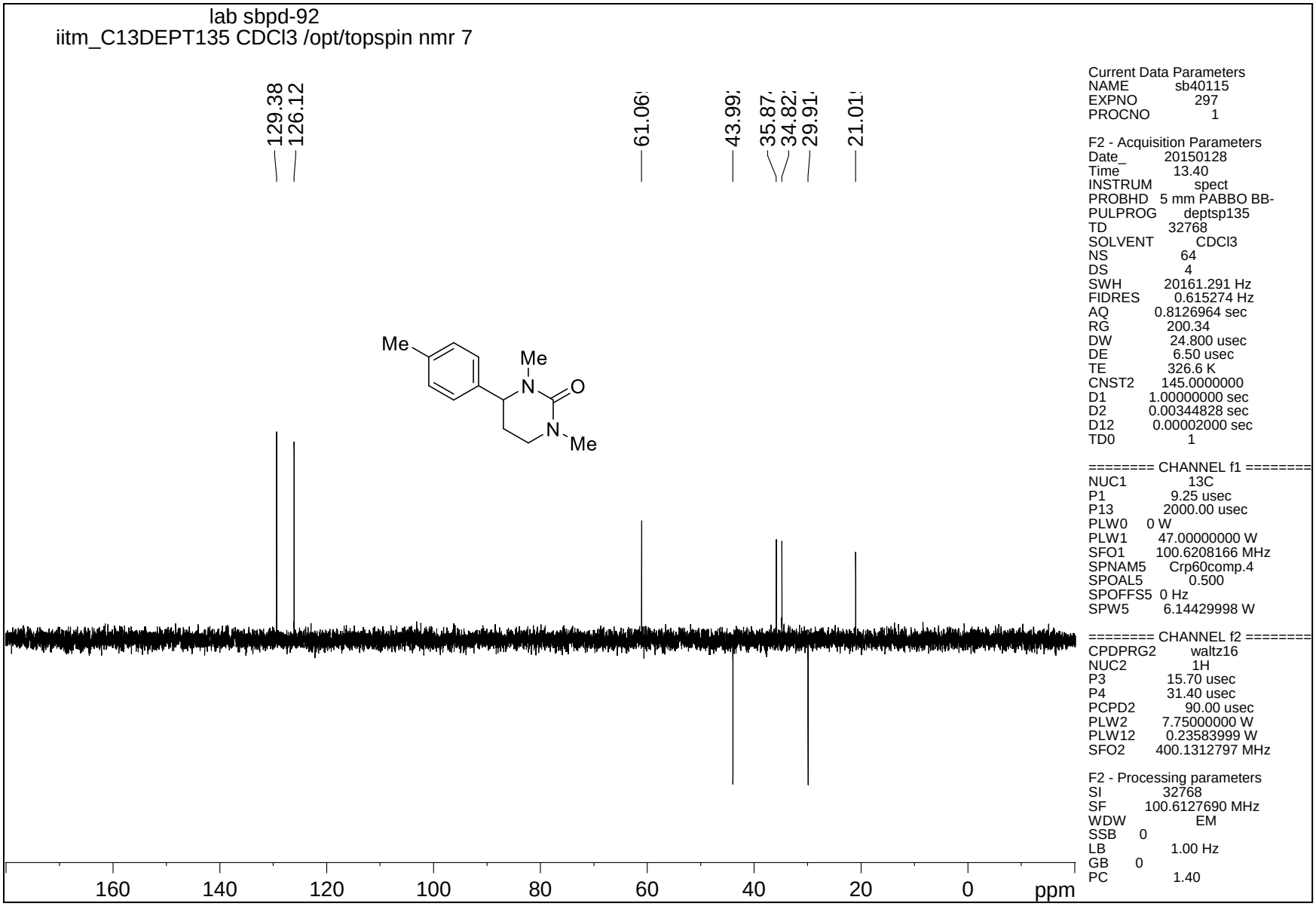


Figure 4 DEPT-135 NMR spectrum of compound 8a

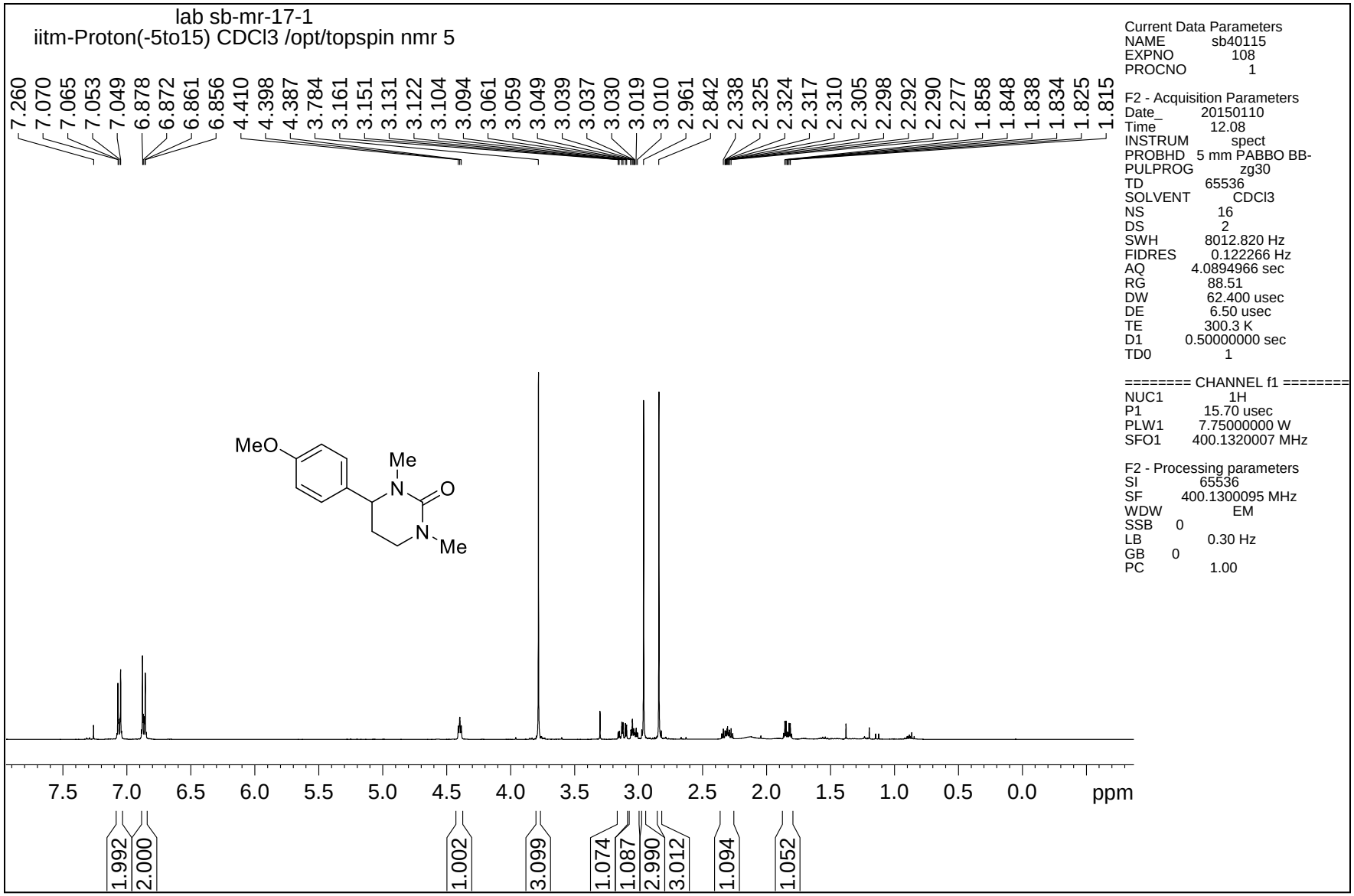


Figure 5 ^{1}H NMR spectrum of compound 9a

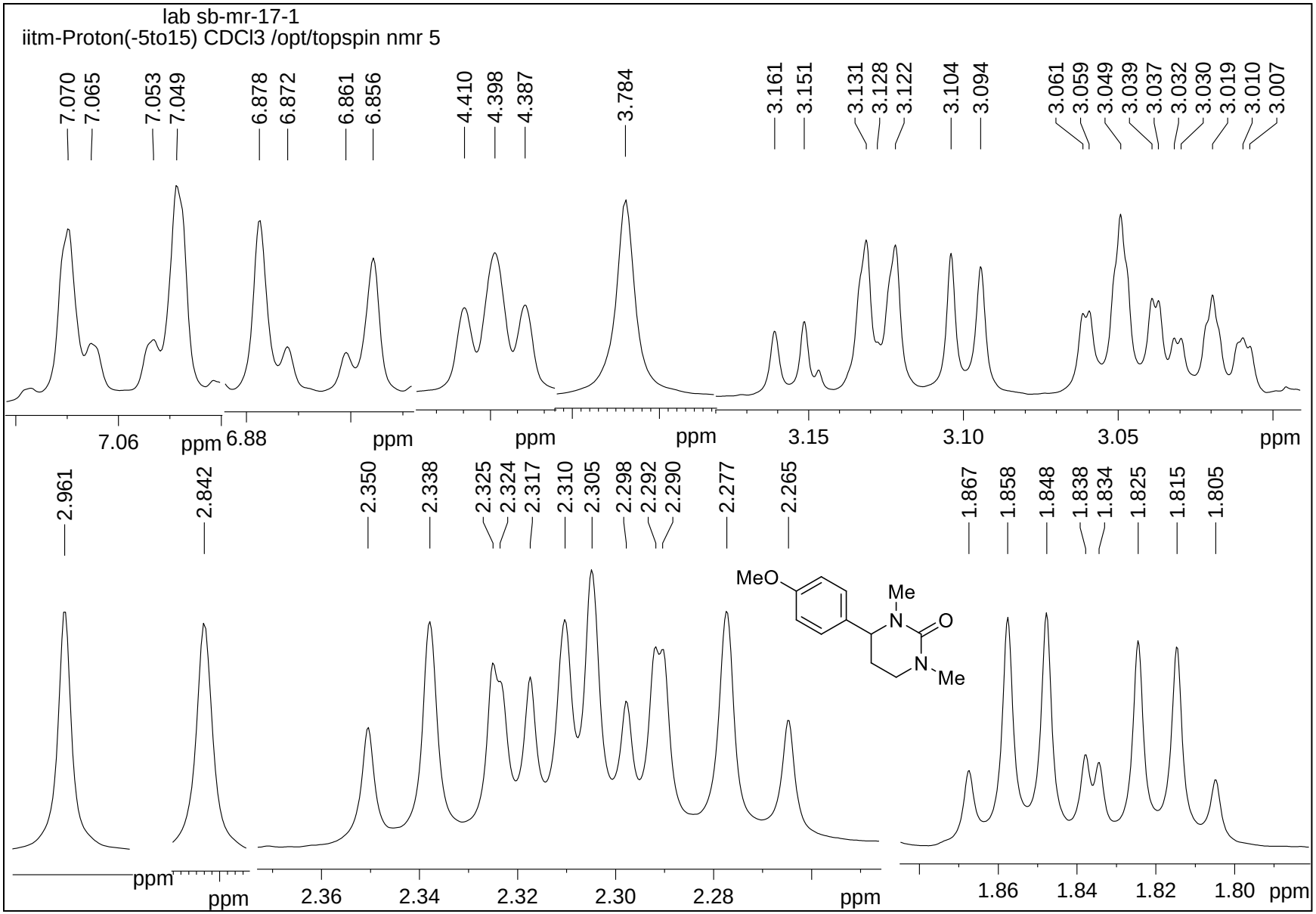


Figure 6 Expanded ^{1}H NMR spectrum of compound 9a

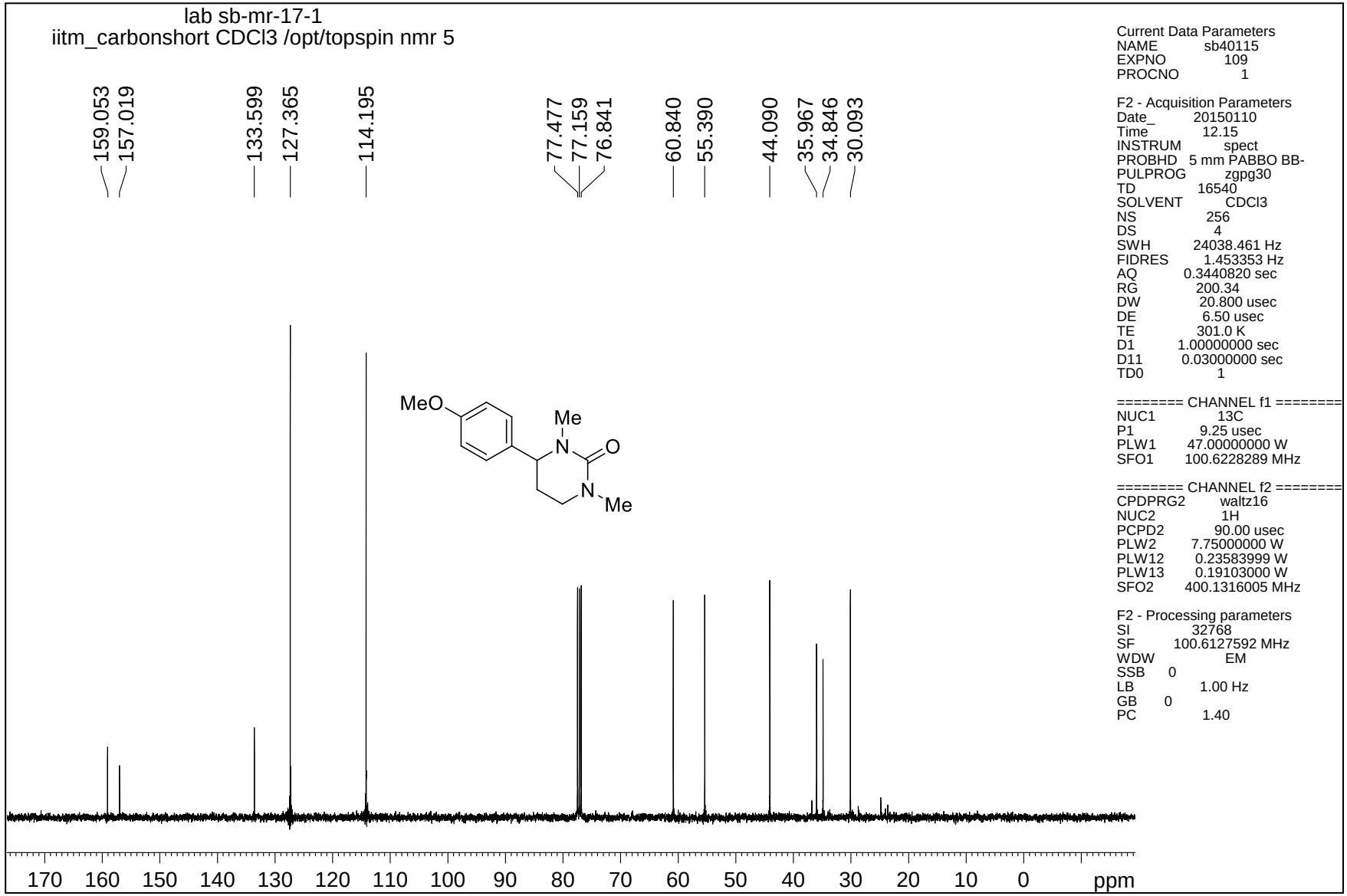


Figure 7 ^{13}C NMR spectrum of compound 9a

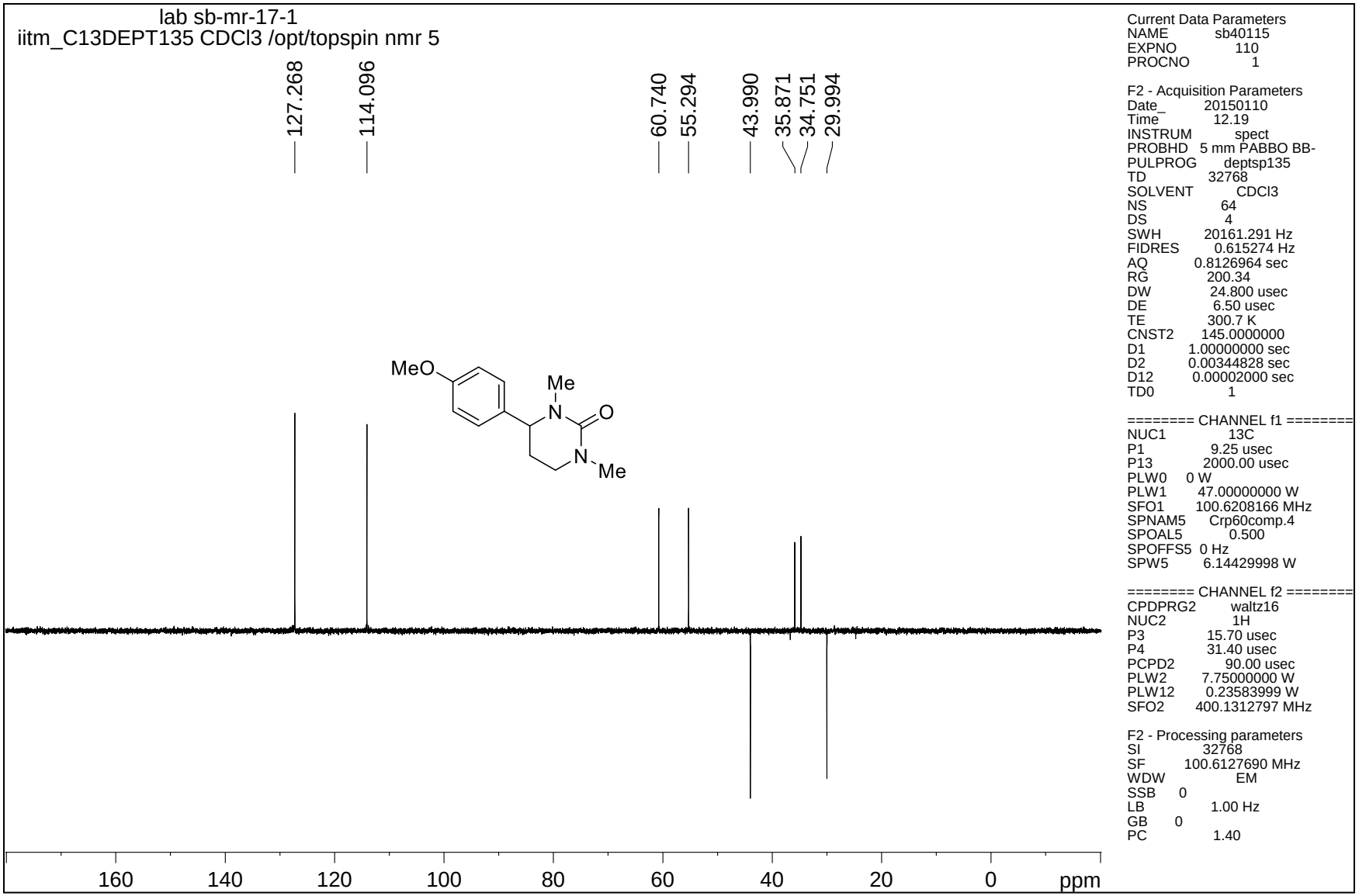


Figure 8 DEPT-135 NMR spectrum of compound 9a

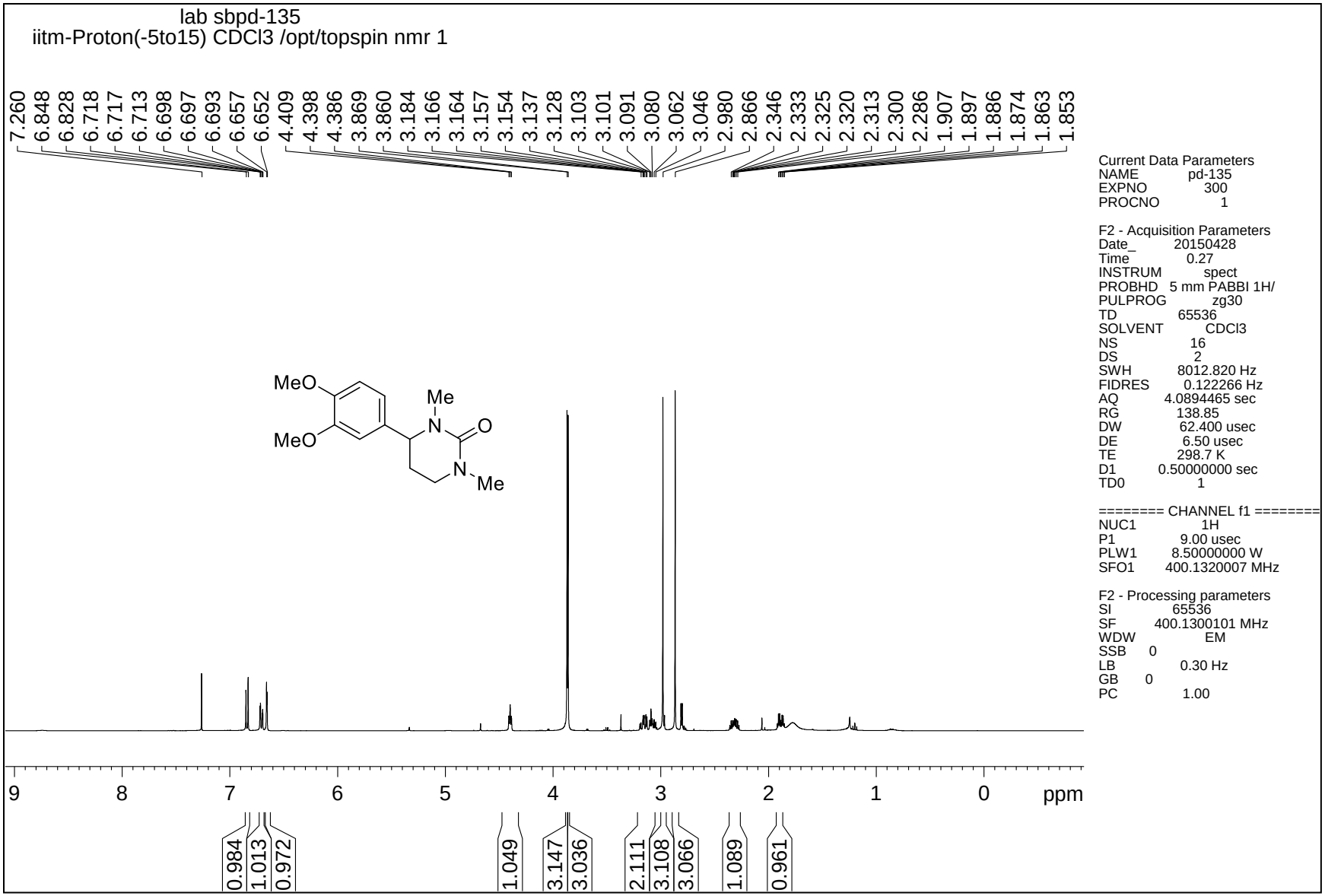


Figure 9 ^{1}H NMR spectrum of compound 10a

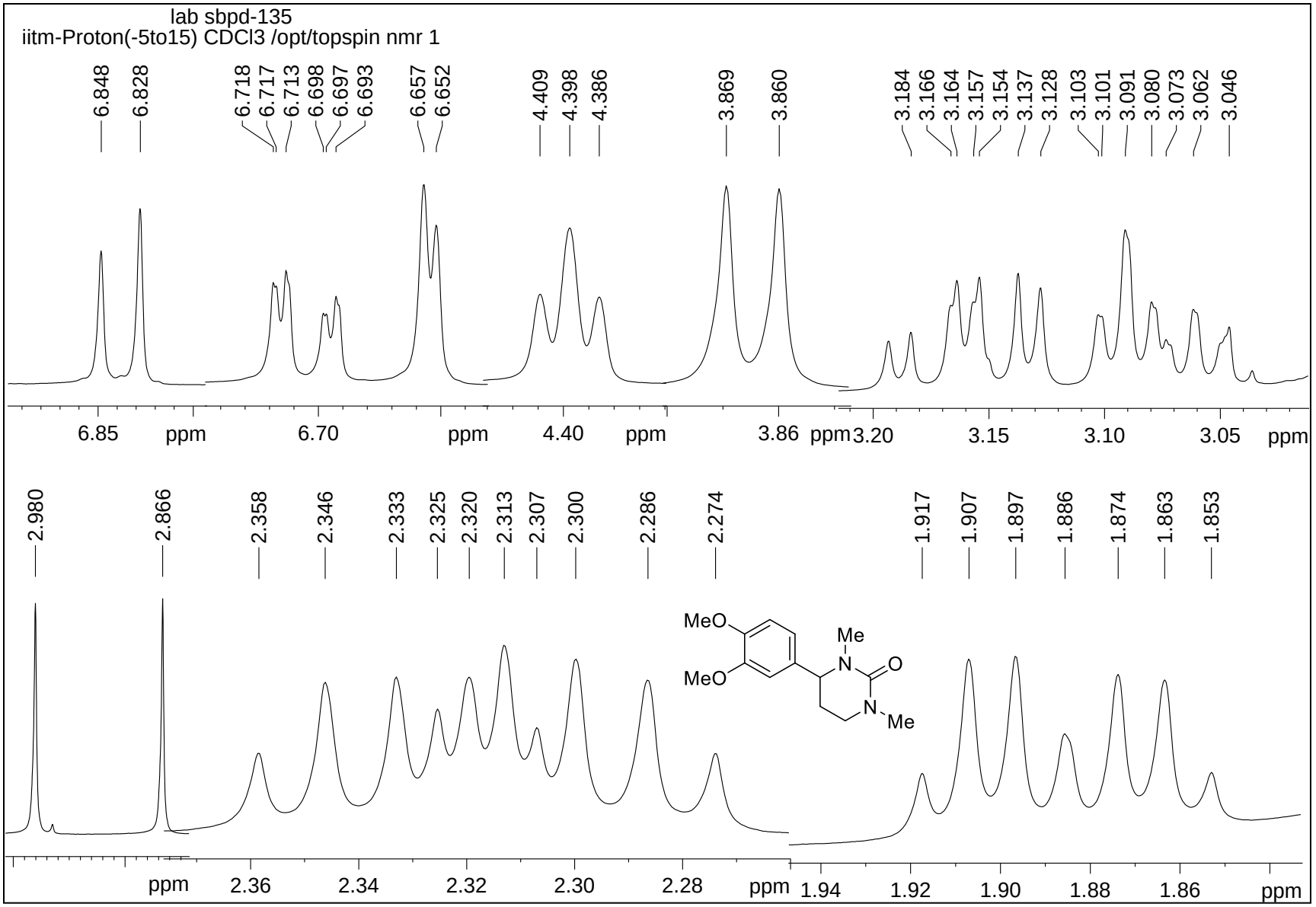


Figure 10 Expanded ^{1}H NMR spectrum of compound 10a

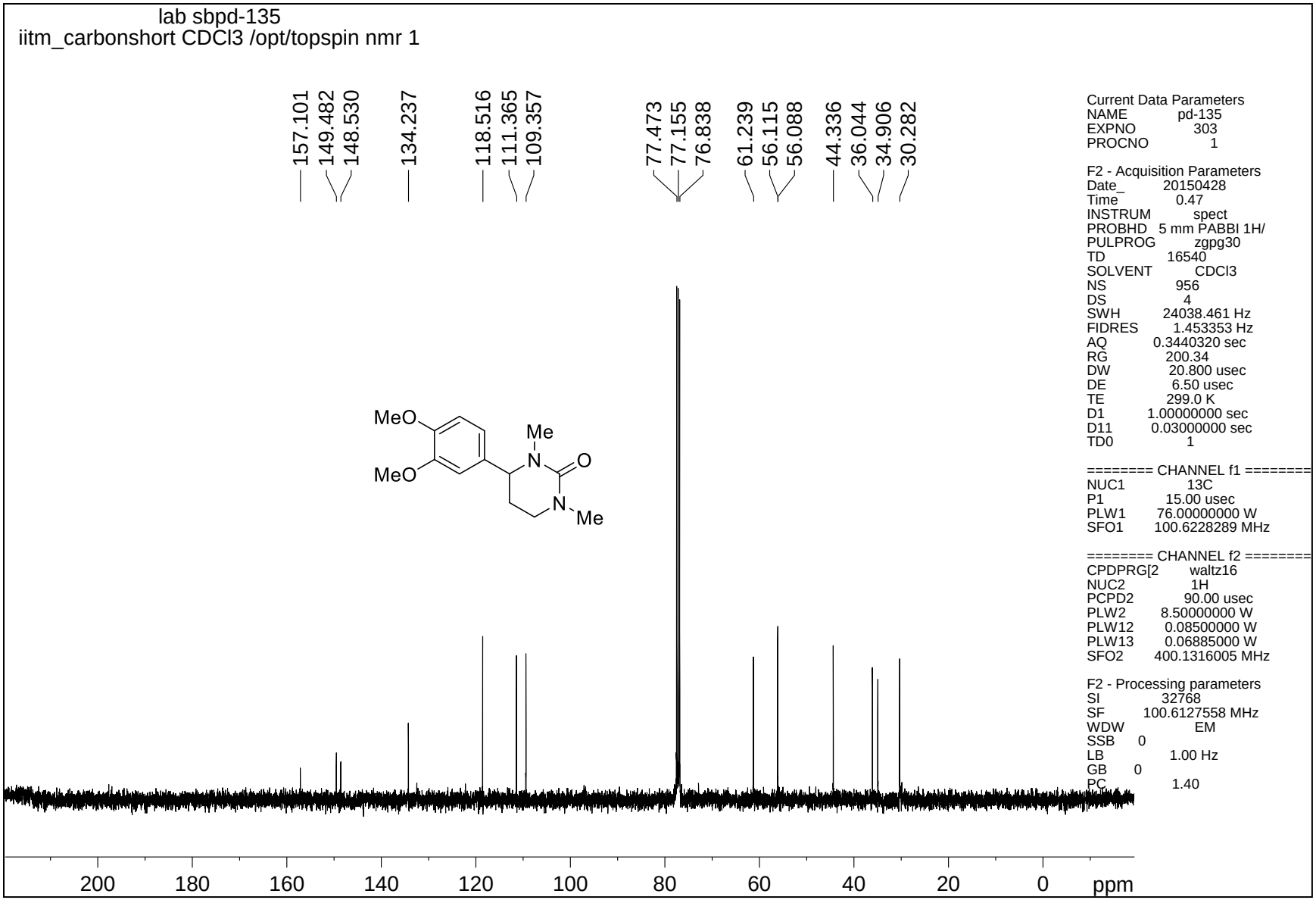


Figure 11 ^{13}**C NMR spectrum of compound 10a**

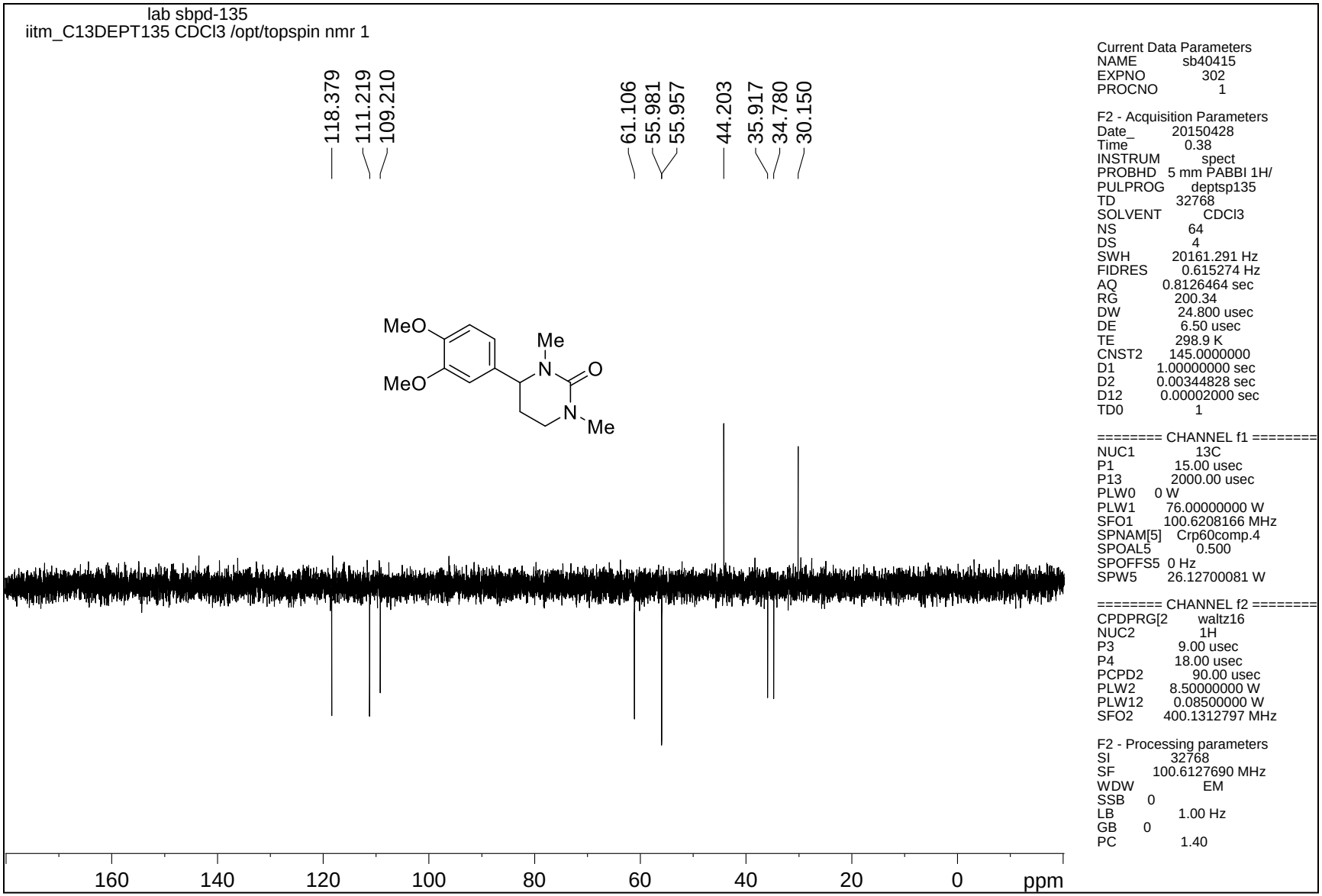


Figure 12 DEPT-135 NMR spectrum of compound 10a

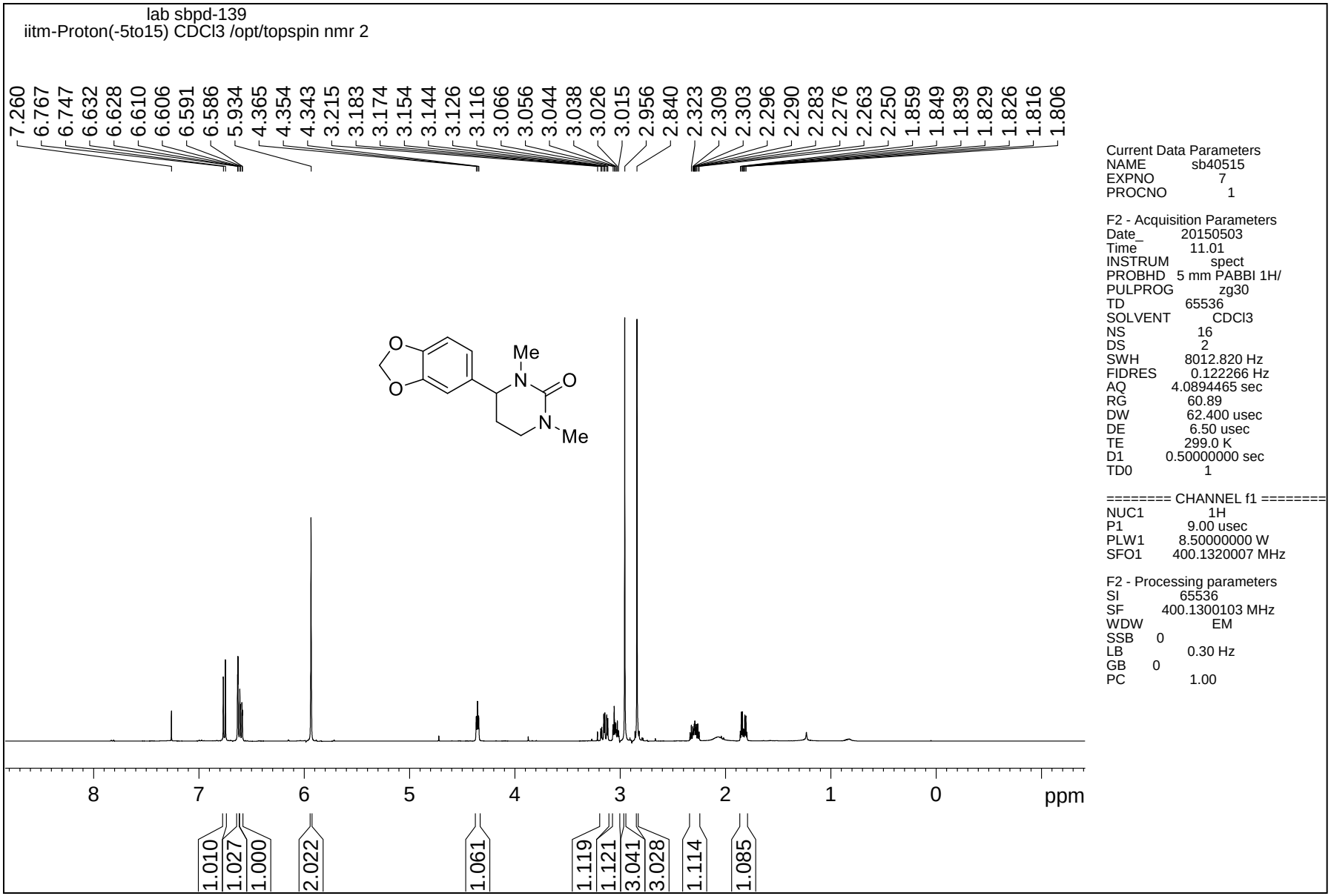


Figure 13 ^{1}H NMR spectrum of compound 11a

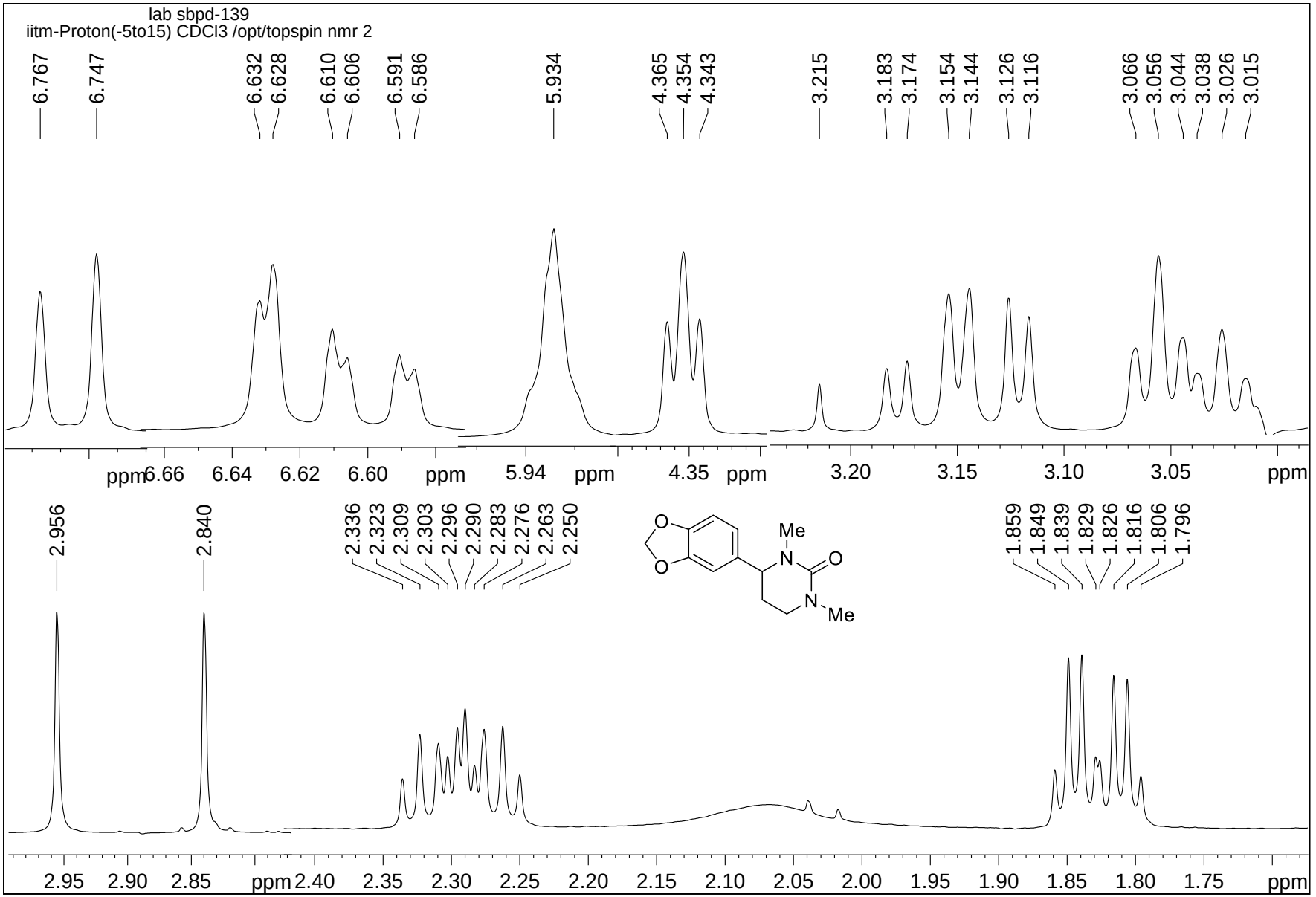


Figure 14 Expanded ^{1}H NMR spectrum of compound 11a

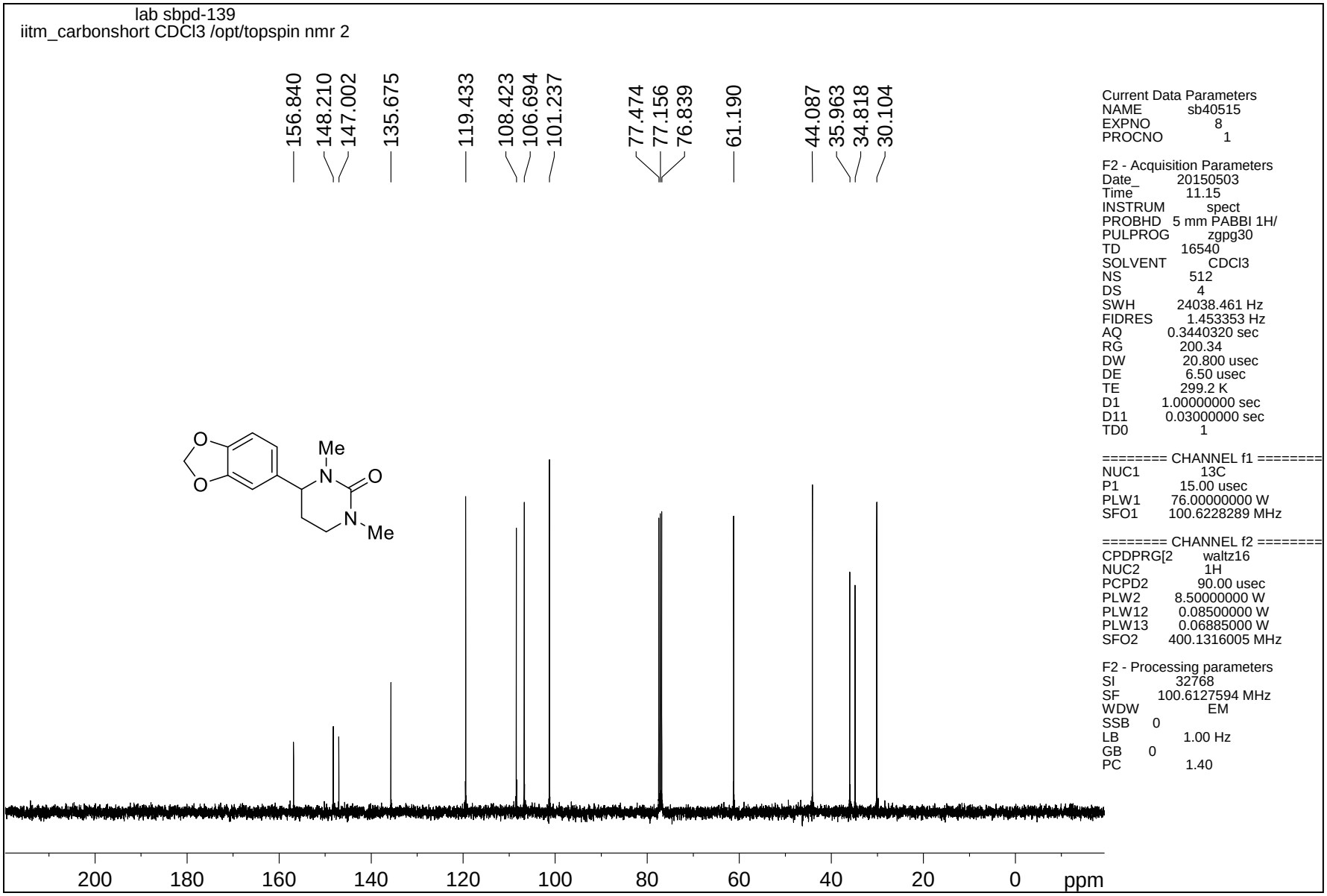


Figure 15 ^{13}**C NMR spectrum of compound 11a**

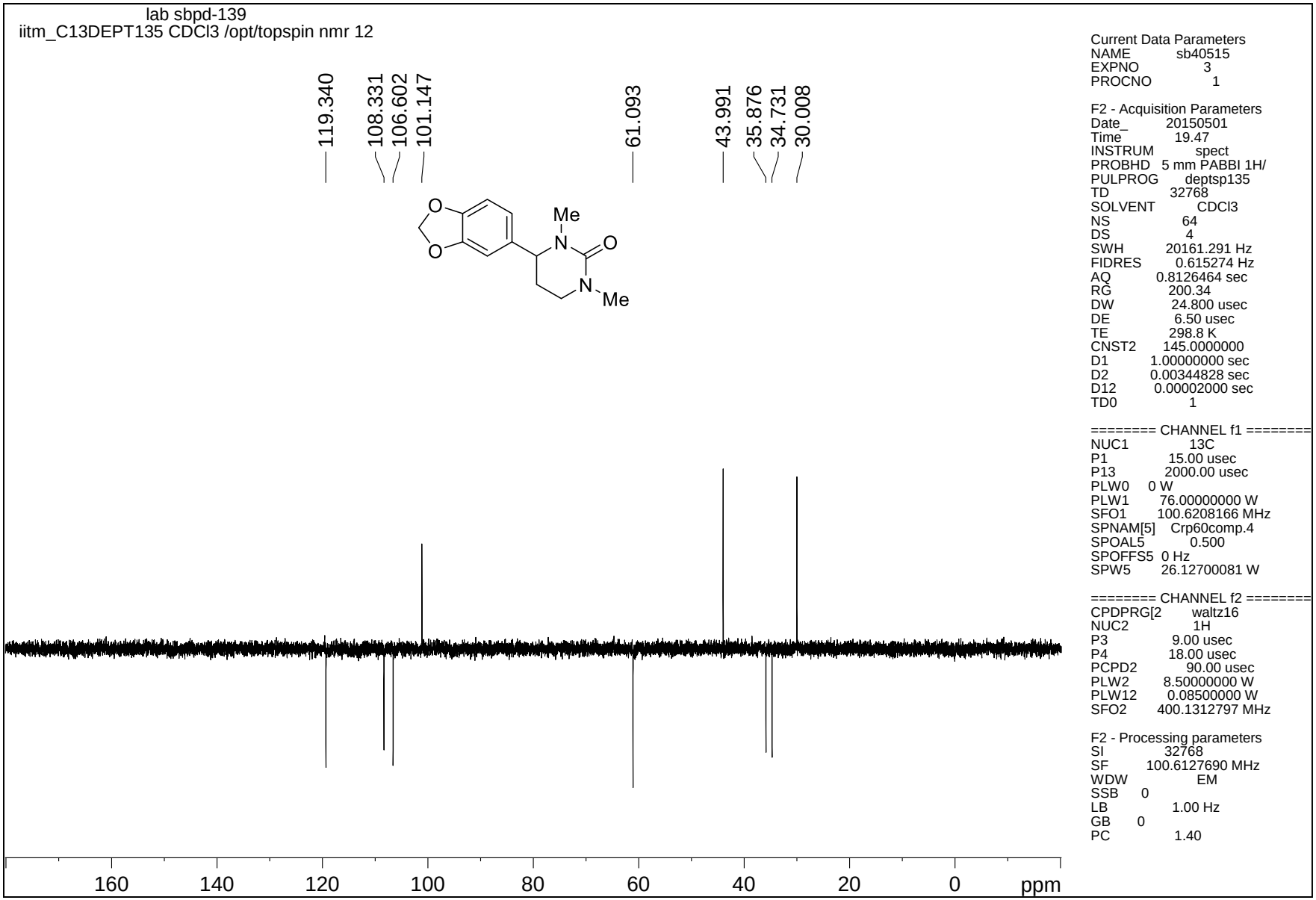


Figure 16 DEPT-135 NMR spectrum of compound 11a

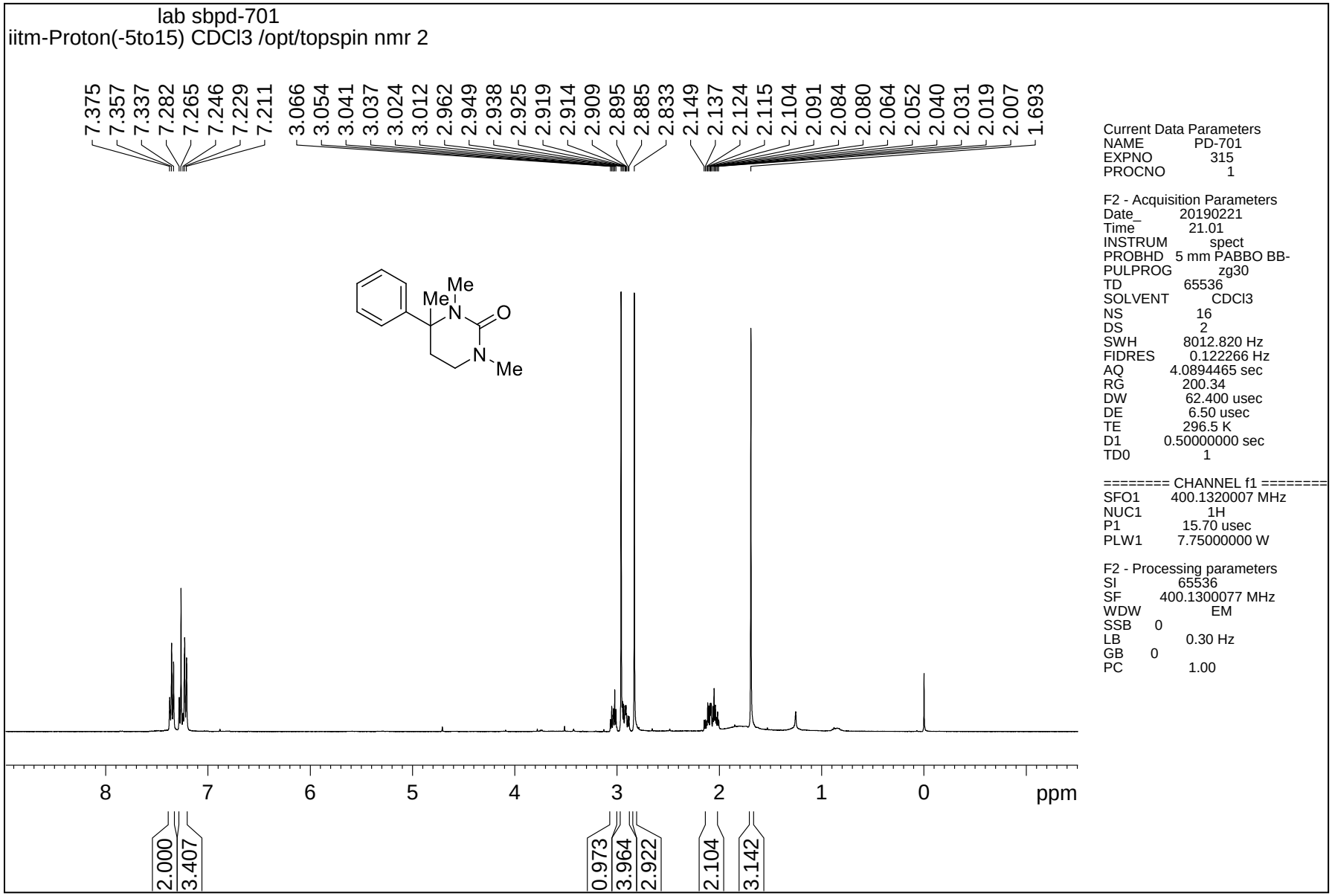


Figure 17 ^{1}H NMR spectrum of compound 12a

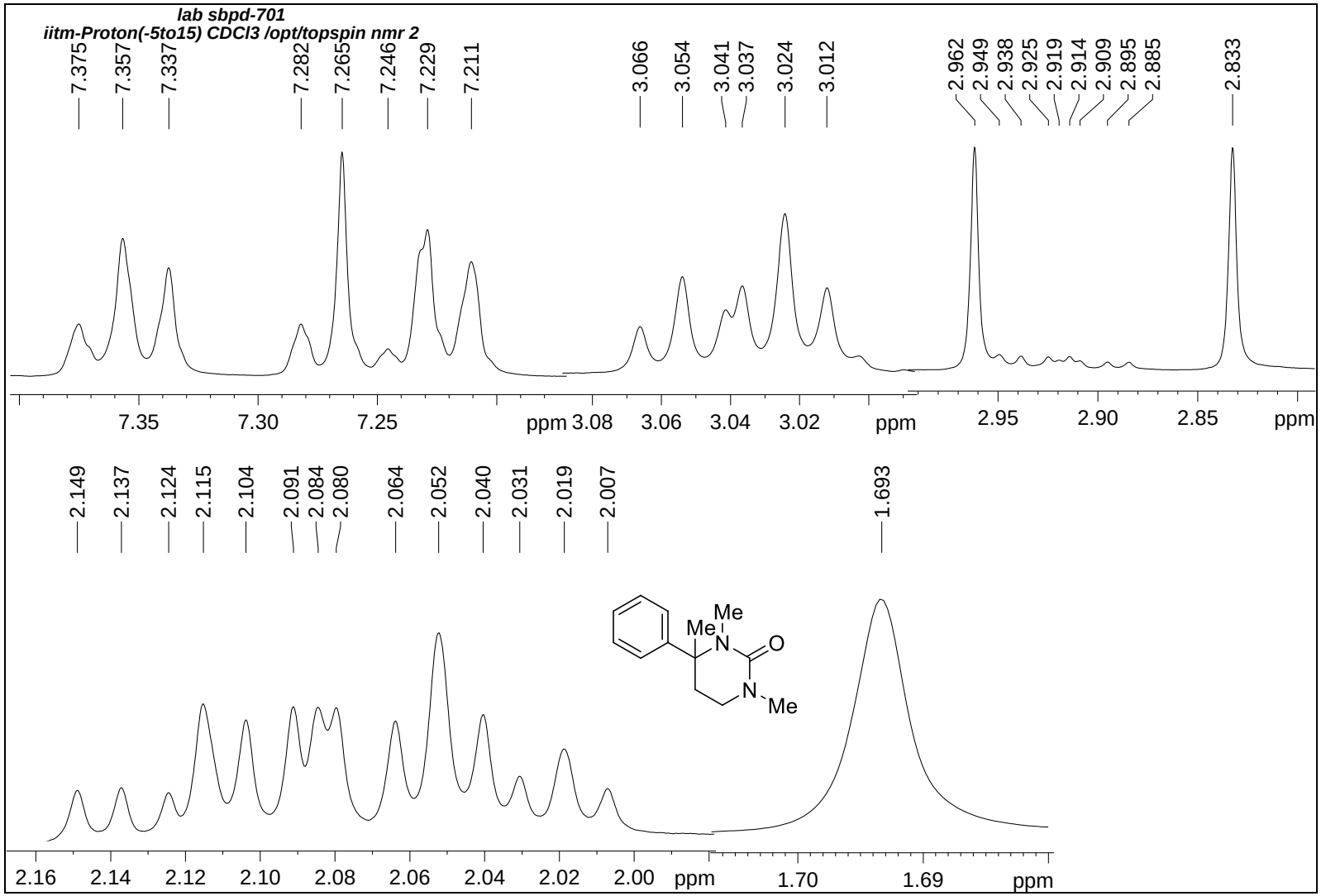


Figure 18 Expanded ^{1}H NMR spectrum of compound 12a

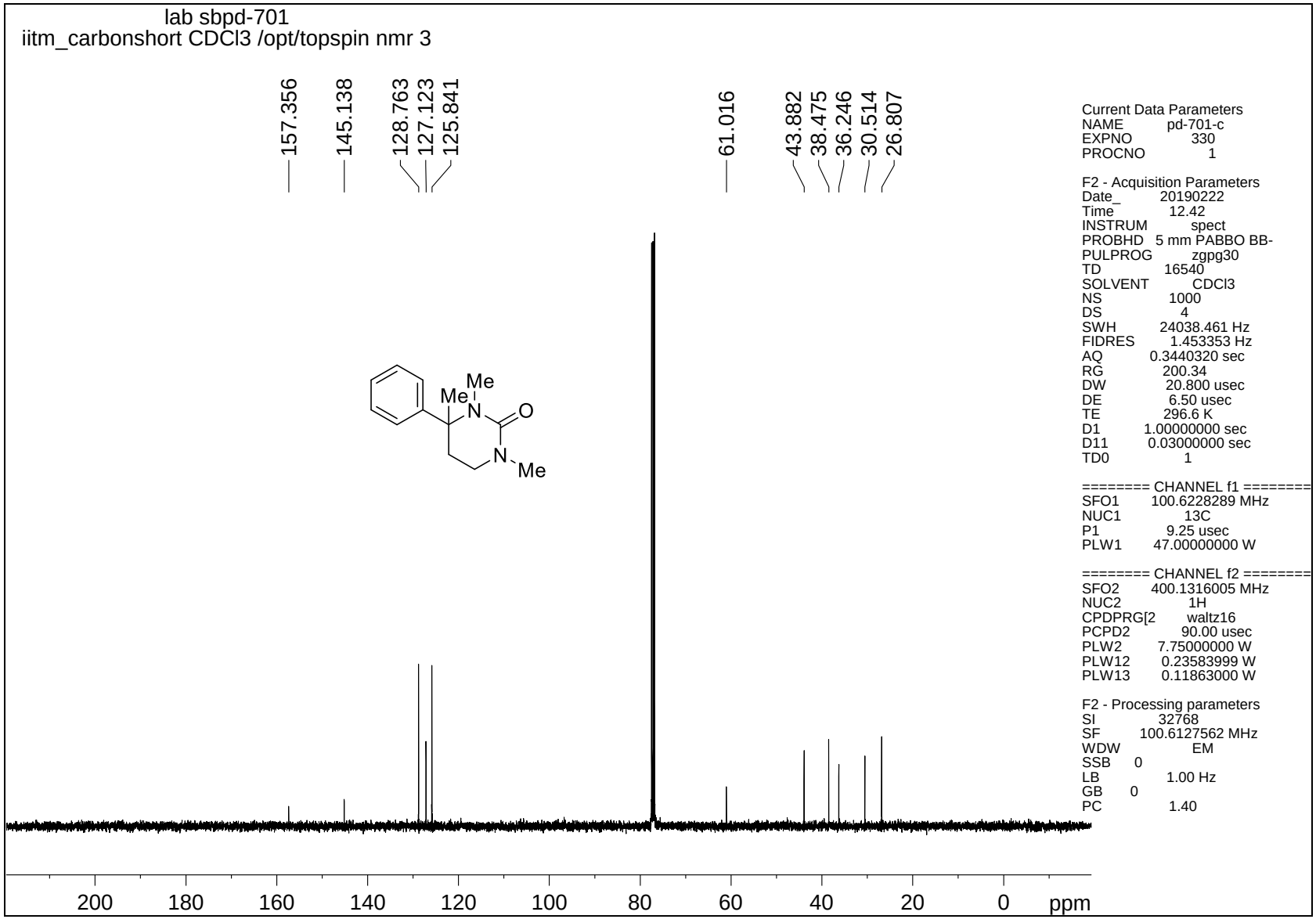


Figure 19 ^{13}**C NMR spectrum of compound 12a**

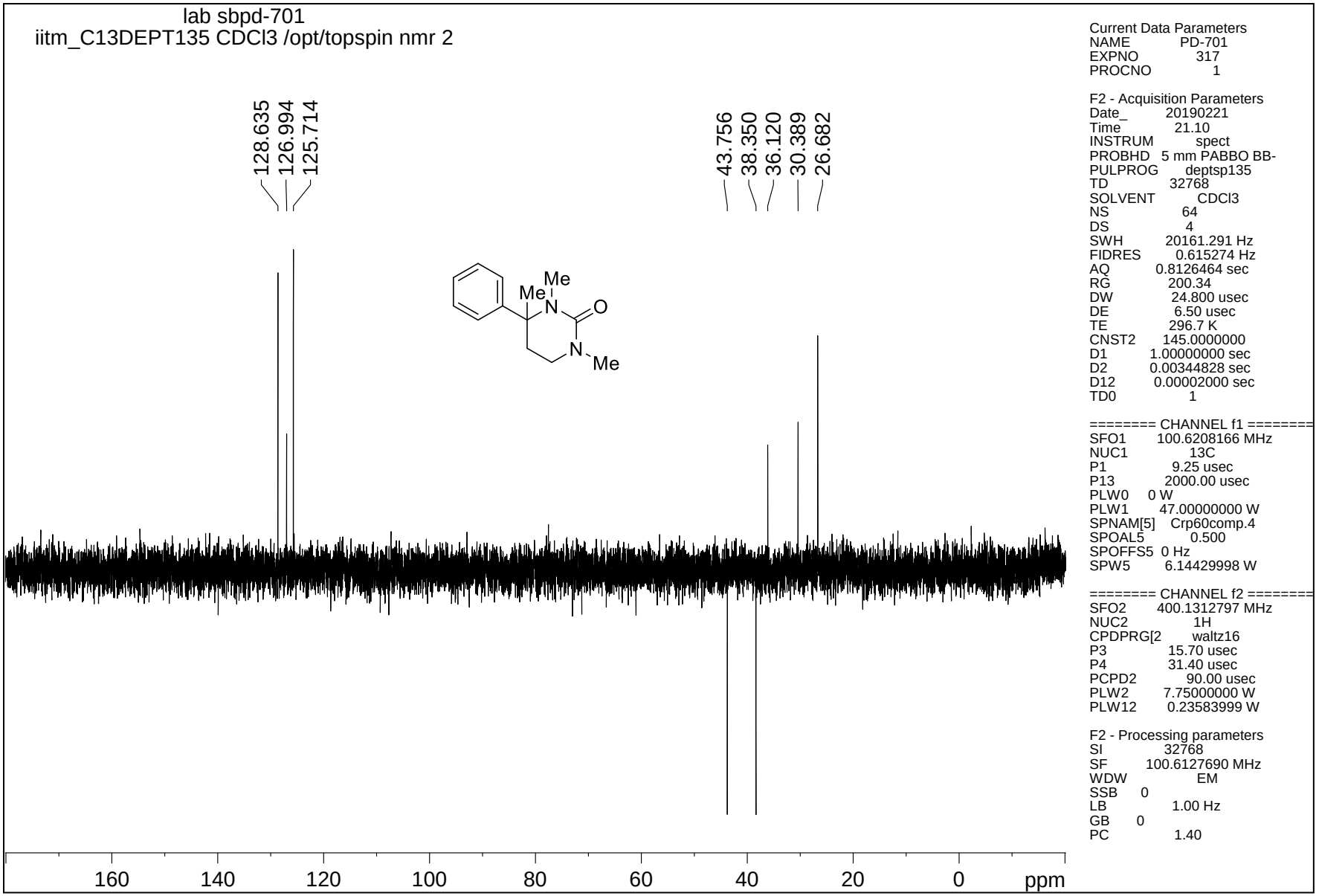


Figure 20 DEPT-135 NMR spectrum of compound 12a

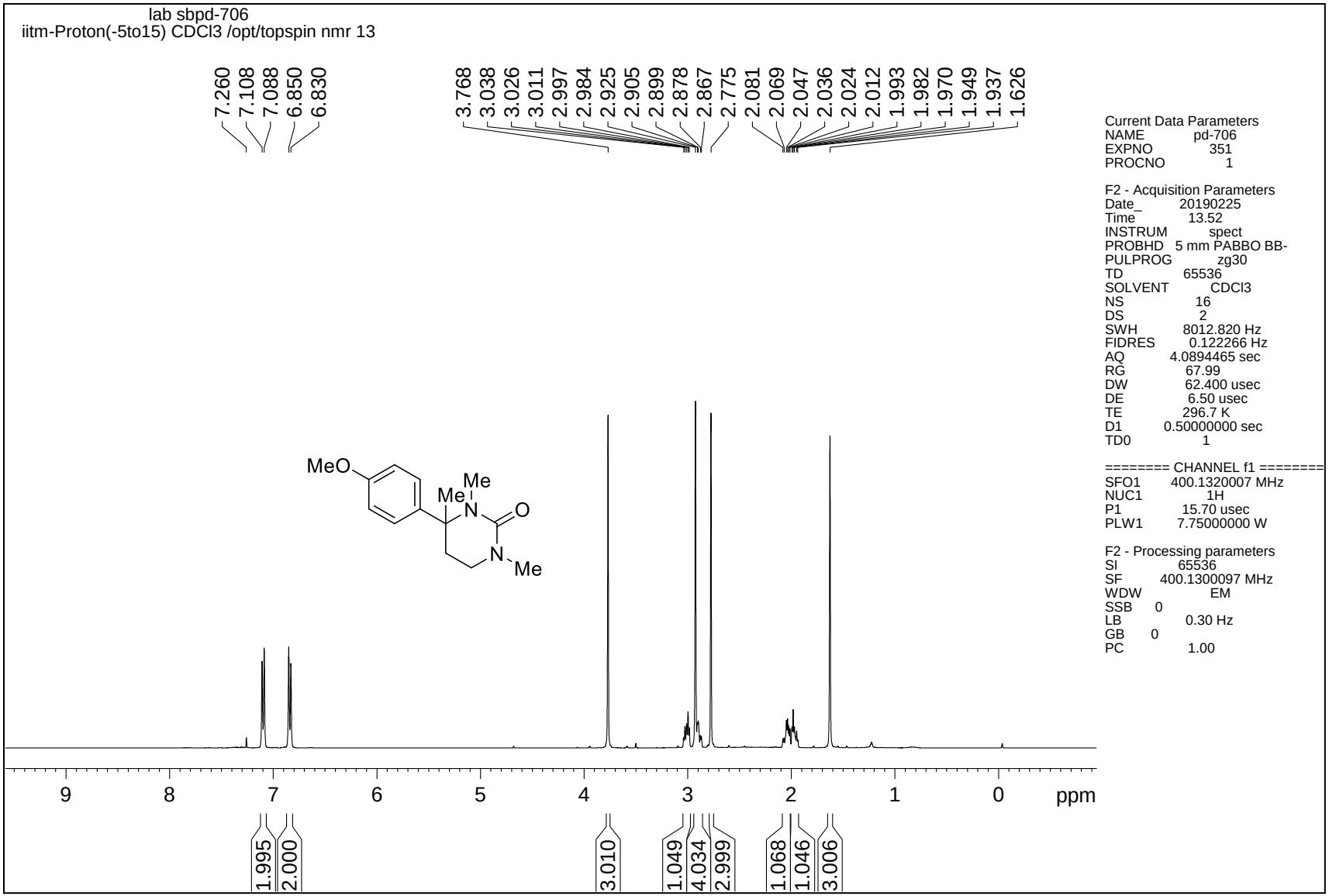


Figure 21 ^{1}H NMR spectrum of compound 13a

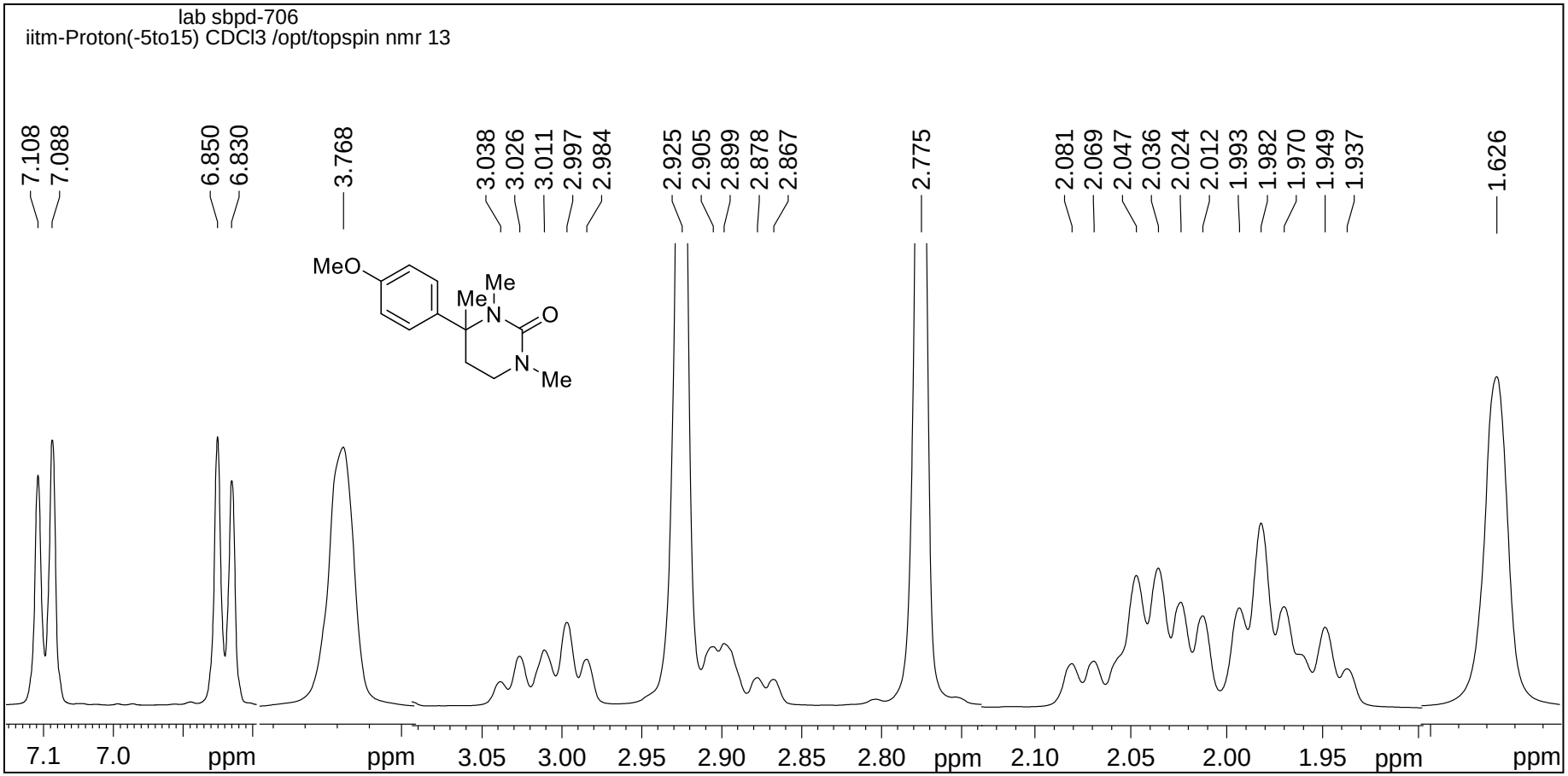


Figure 22 Expanded ^{1}H NMR spectrum of compound 13a

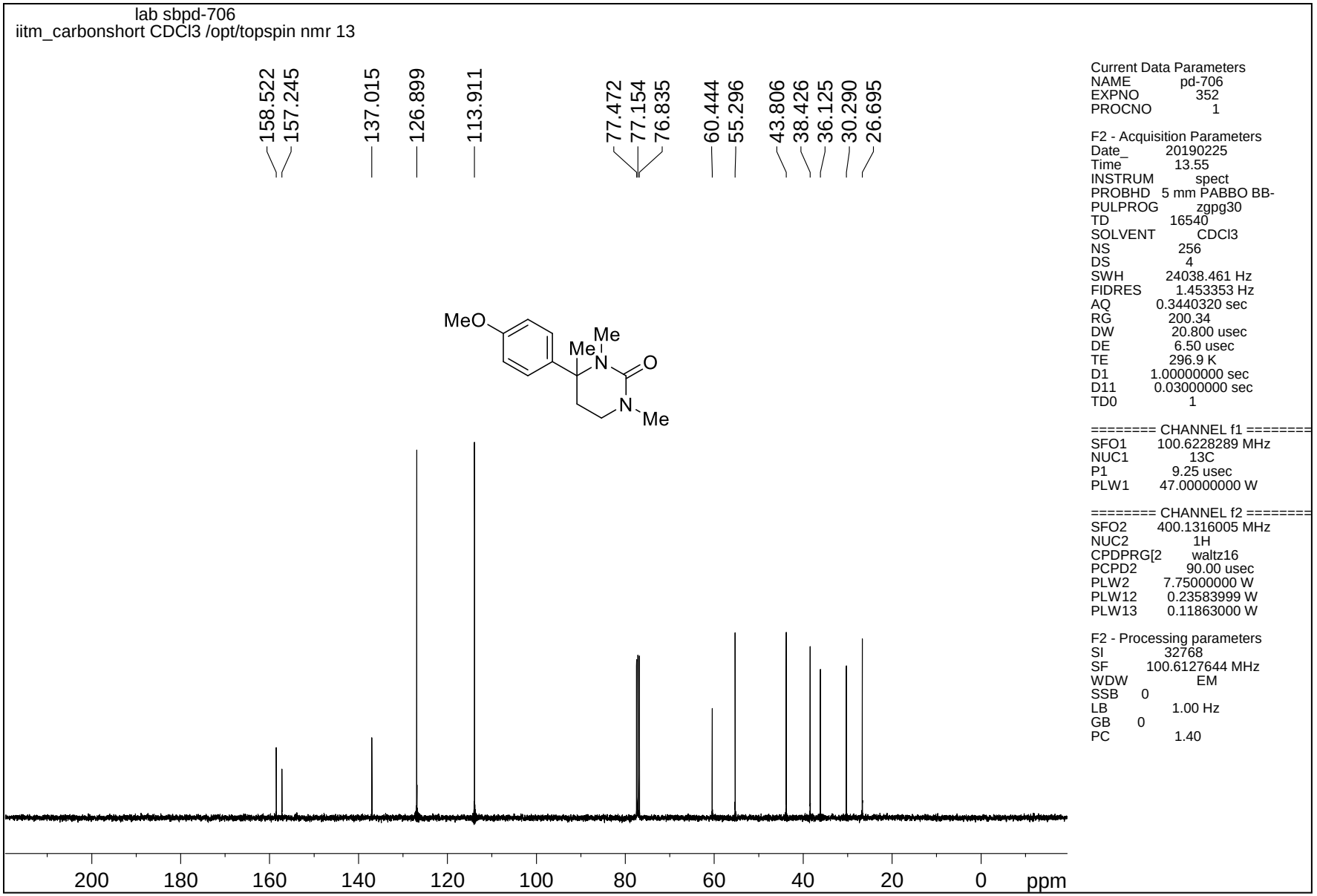


Figure 23 ^{13}C NMR spectrum of compound 13a

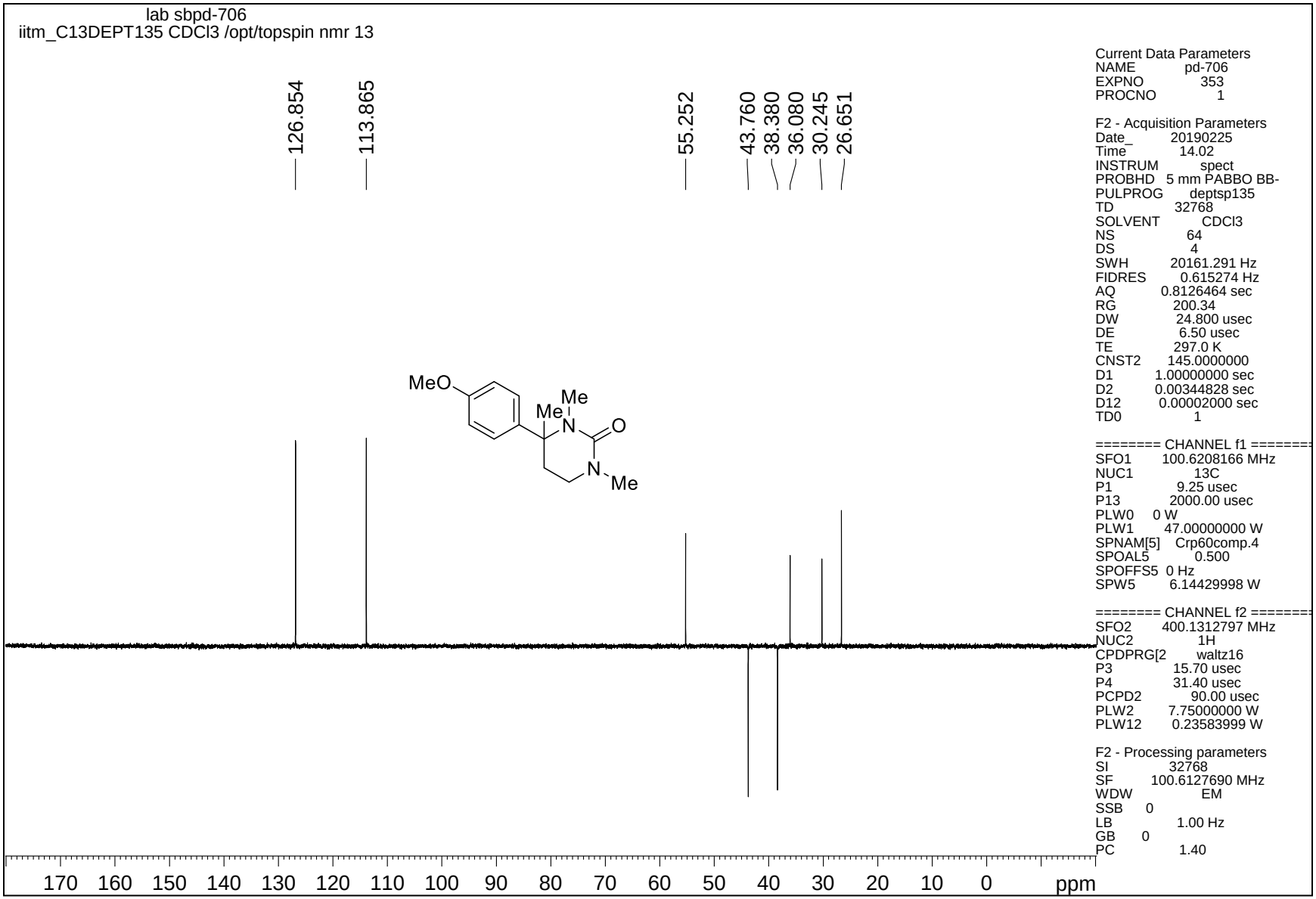


Figure 24 DEPT-135 NMR spectrum of compound 13a

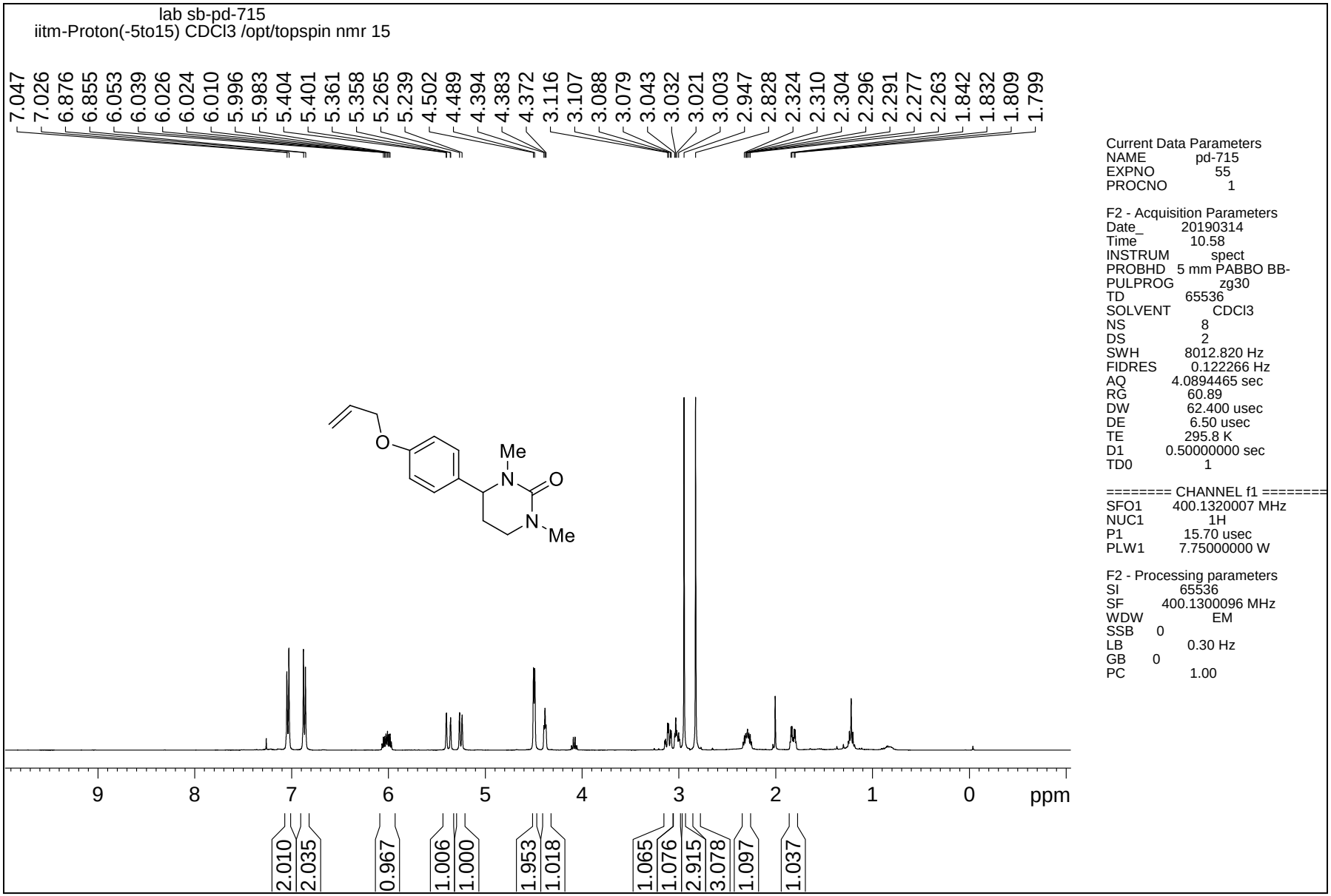


Figure 25 ^{1}H NMR spectrum of compound 14a

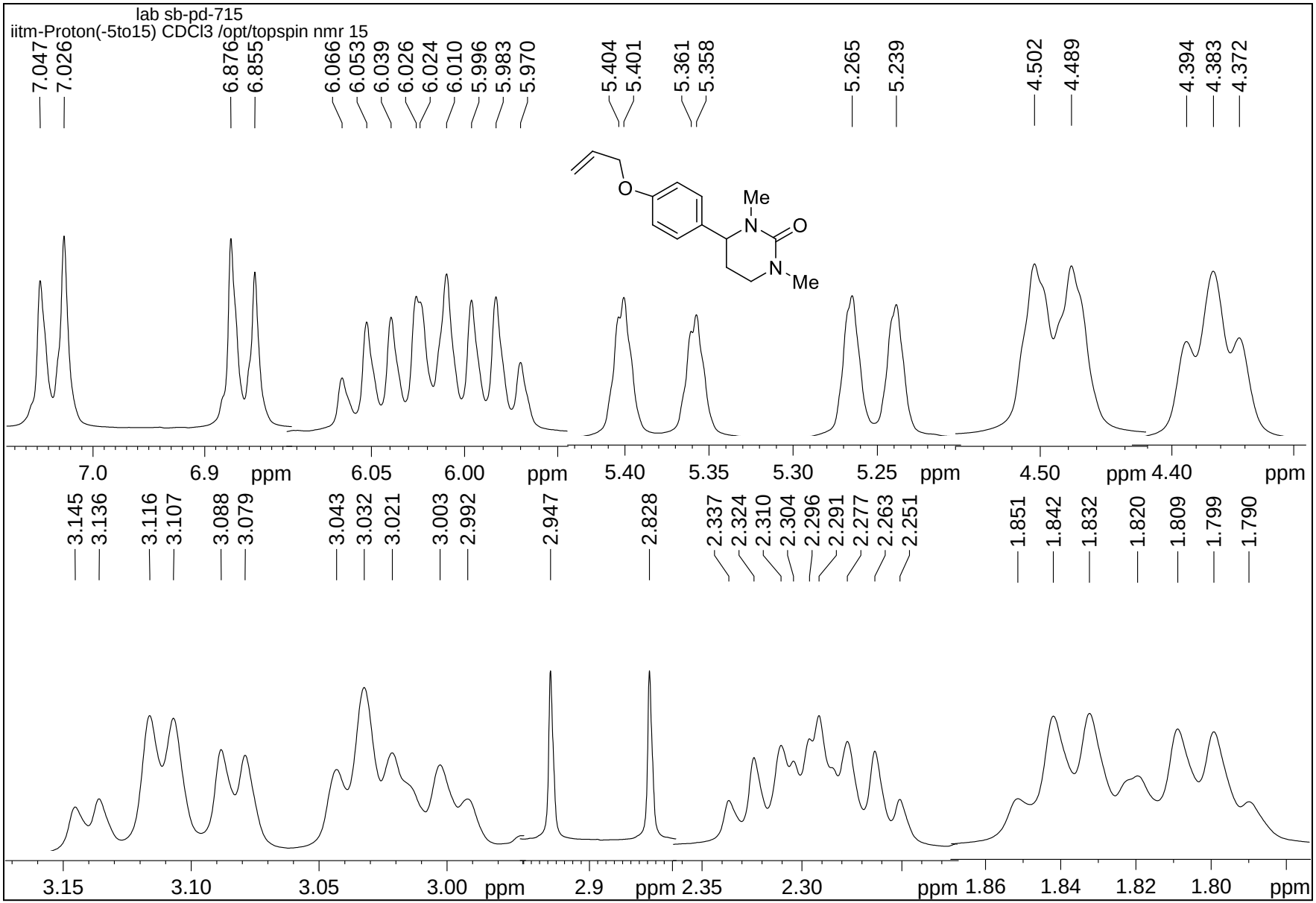


Figure 26 Expanded ^{1}H NMR spectrum of compound 14a

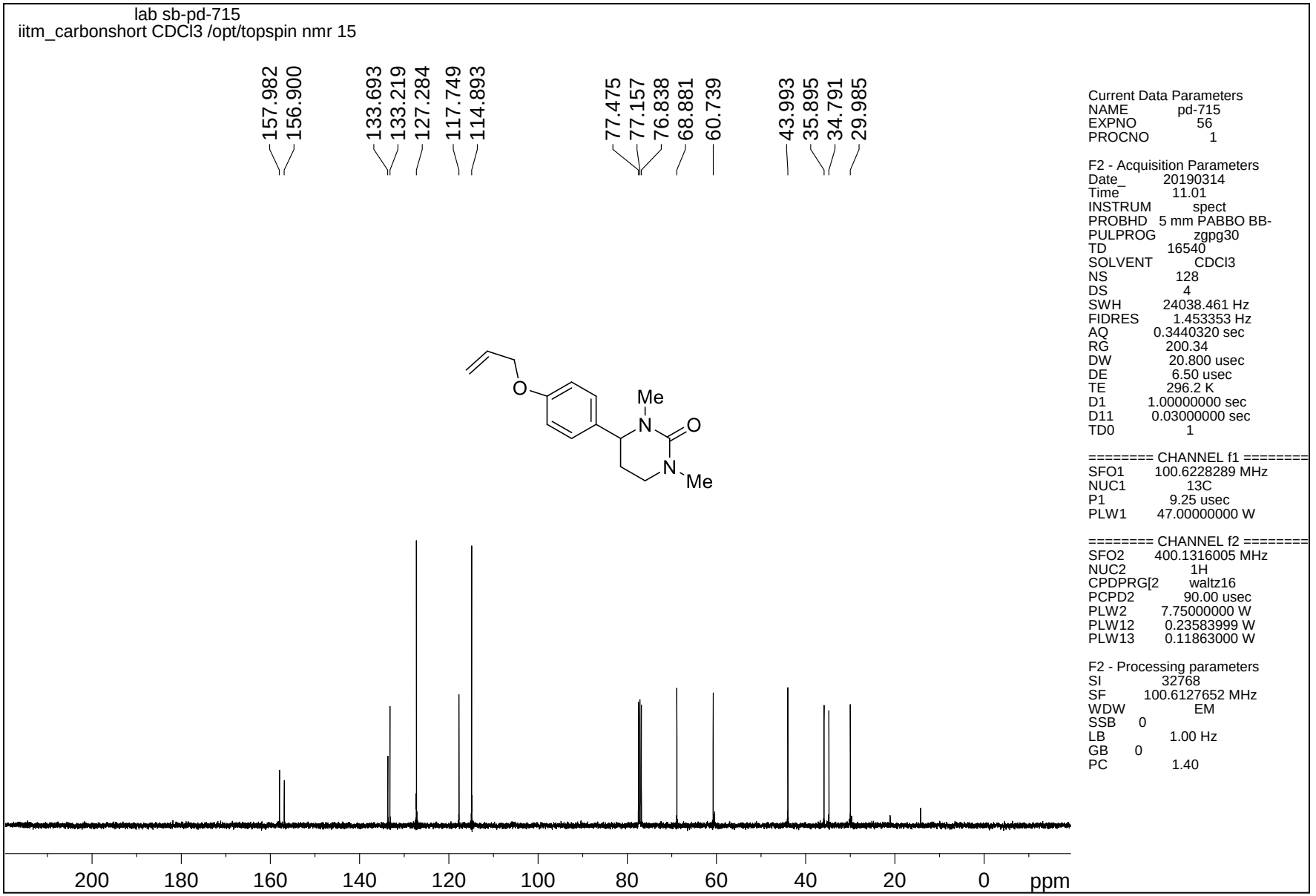


Figure 27 ^{13}C NMR spectrum of compound 14a

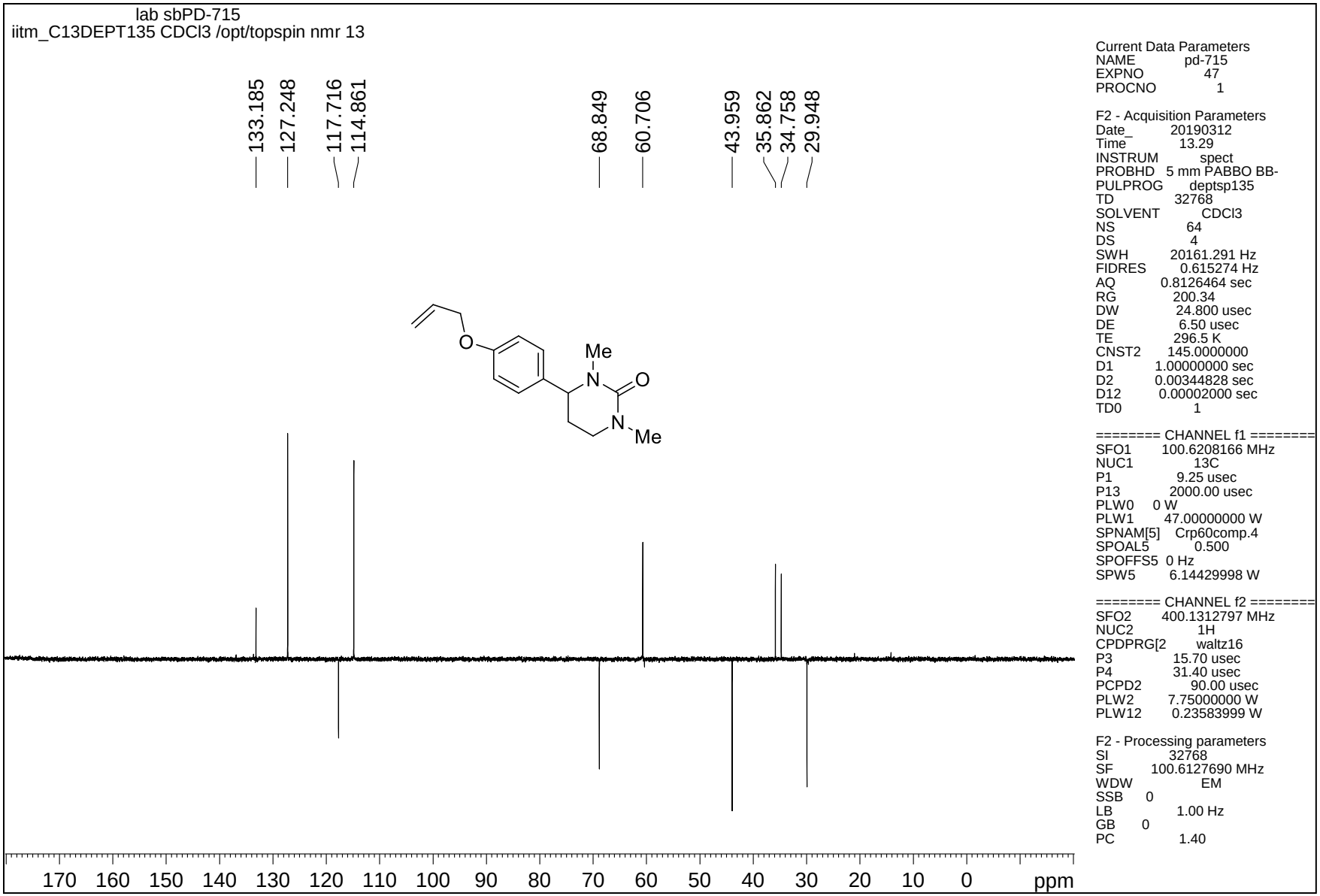


Figure 28 DEPT-135 NMR spectrum of compound 14a

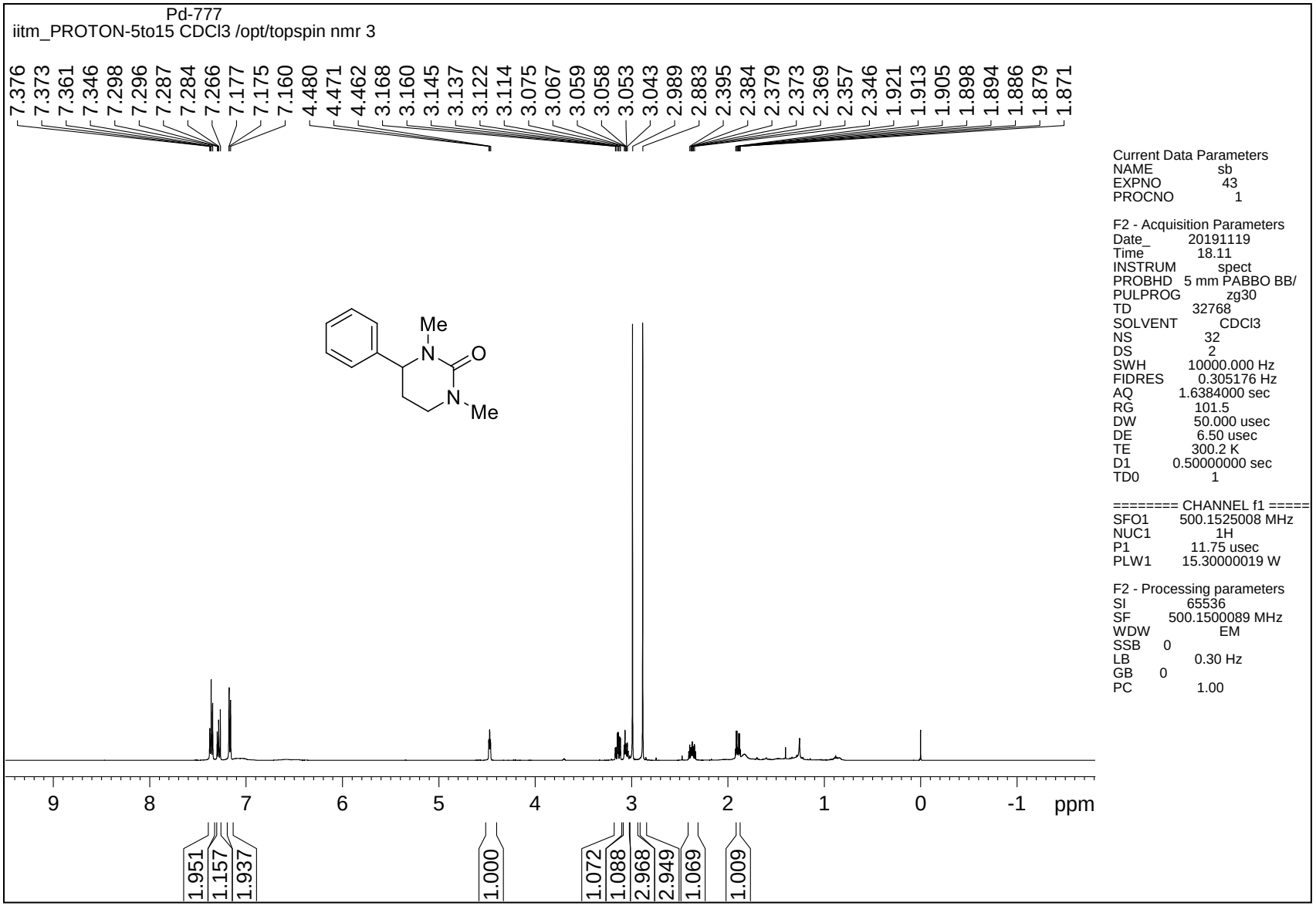


Figure 29 ^{1}H NMR spectrum of THPM from styrene (reference 26)

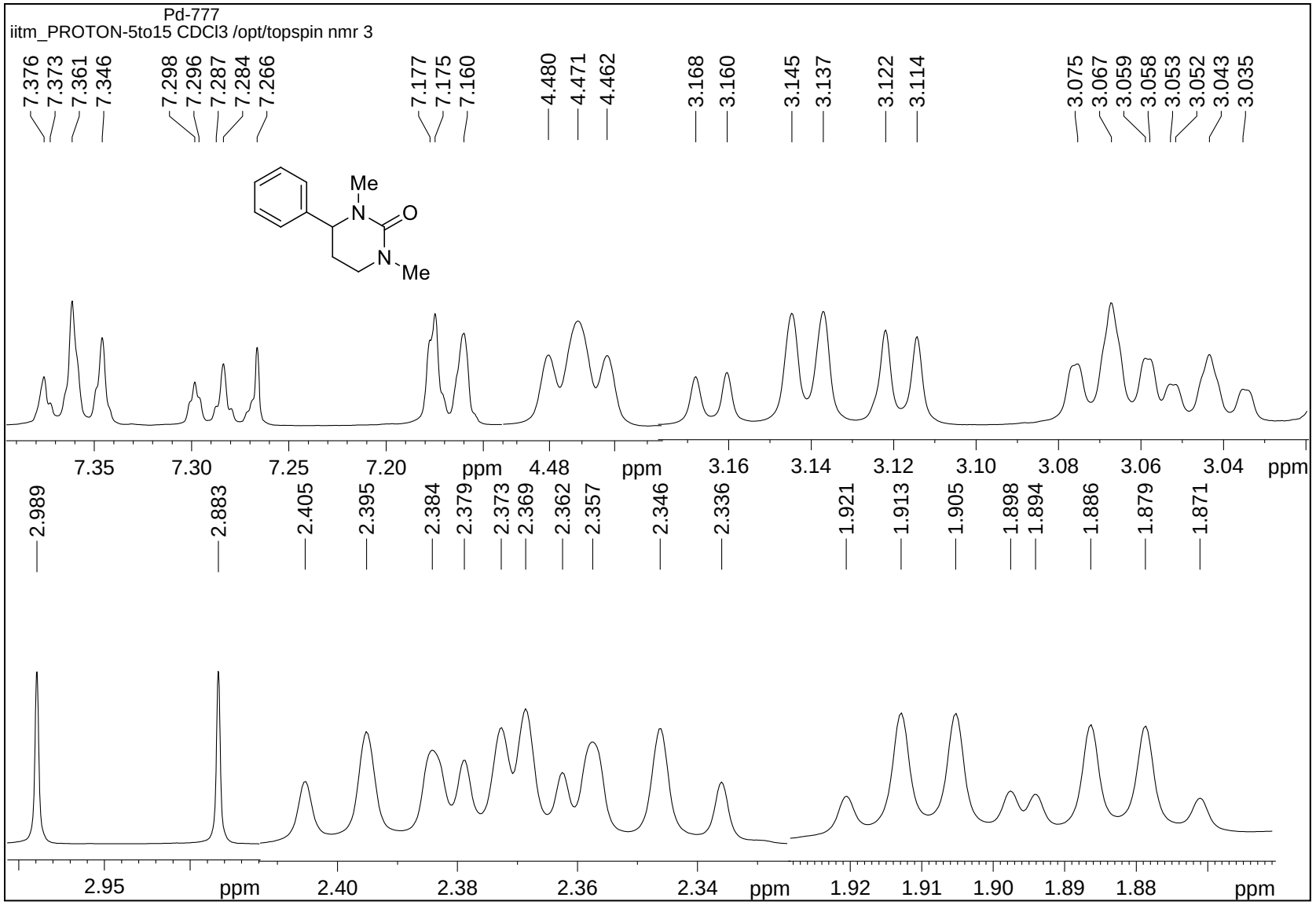


Figure 30 Expanded ^{1}H NMR spectrum of THPM from styrene (reference 26)

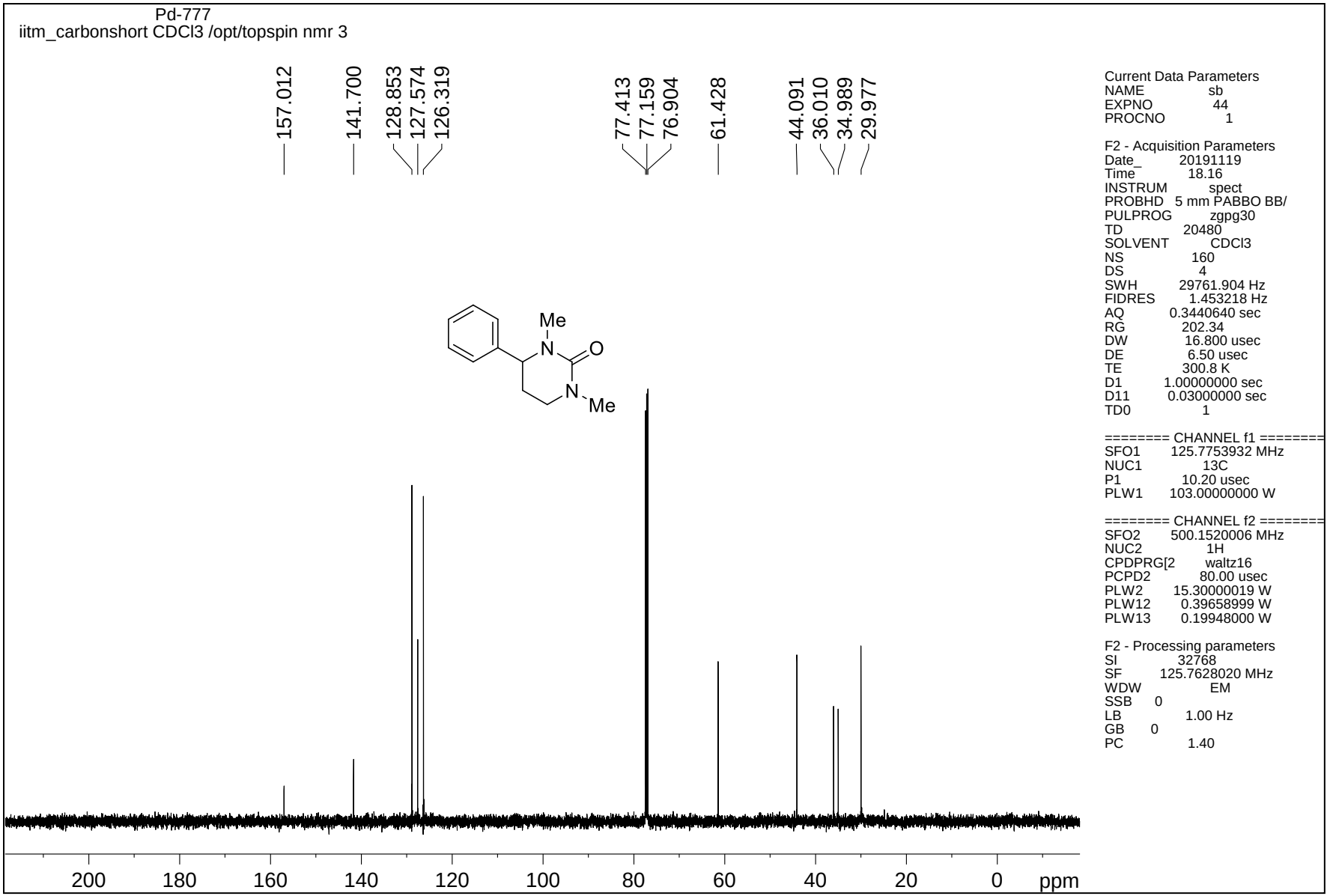


Figure 31 ^{13}**C NMR spectrum of THPM from styrene** (reference 26)

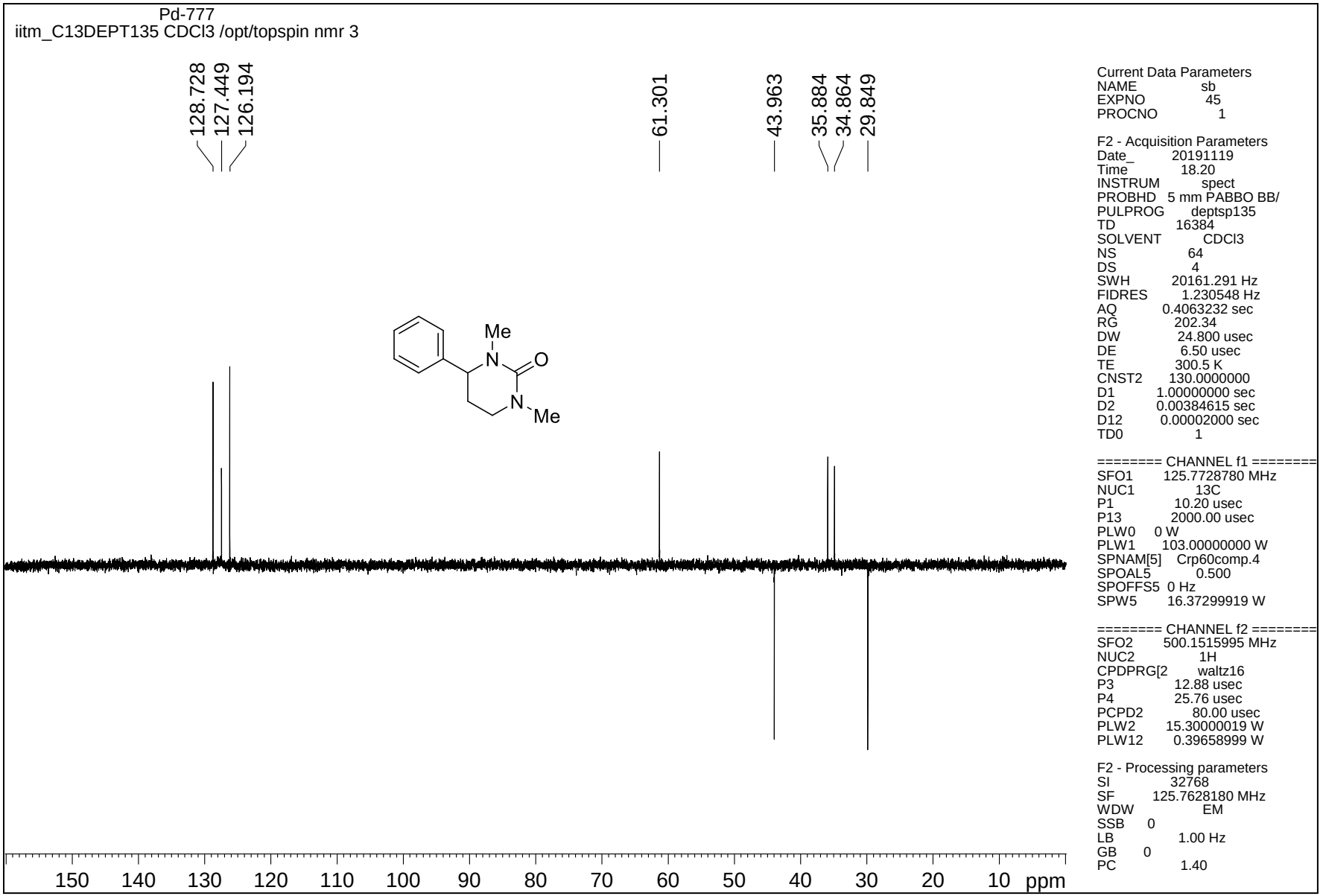


Figure 32 DEPT-135 NMR spectrum of THPM from styrene (reference 26)

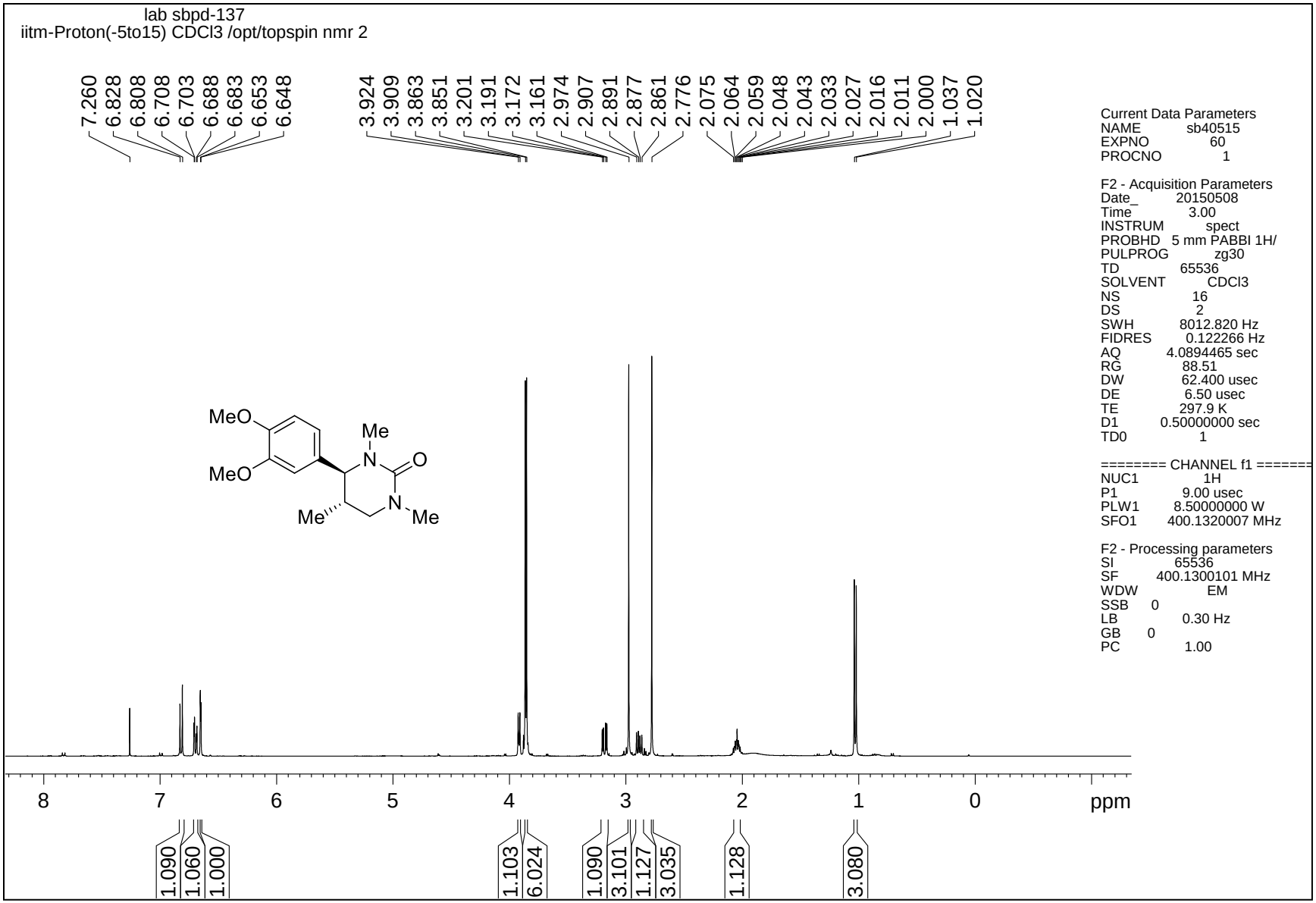


Figure 33 ^{1}H NMR spectrum of compound 15a

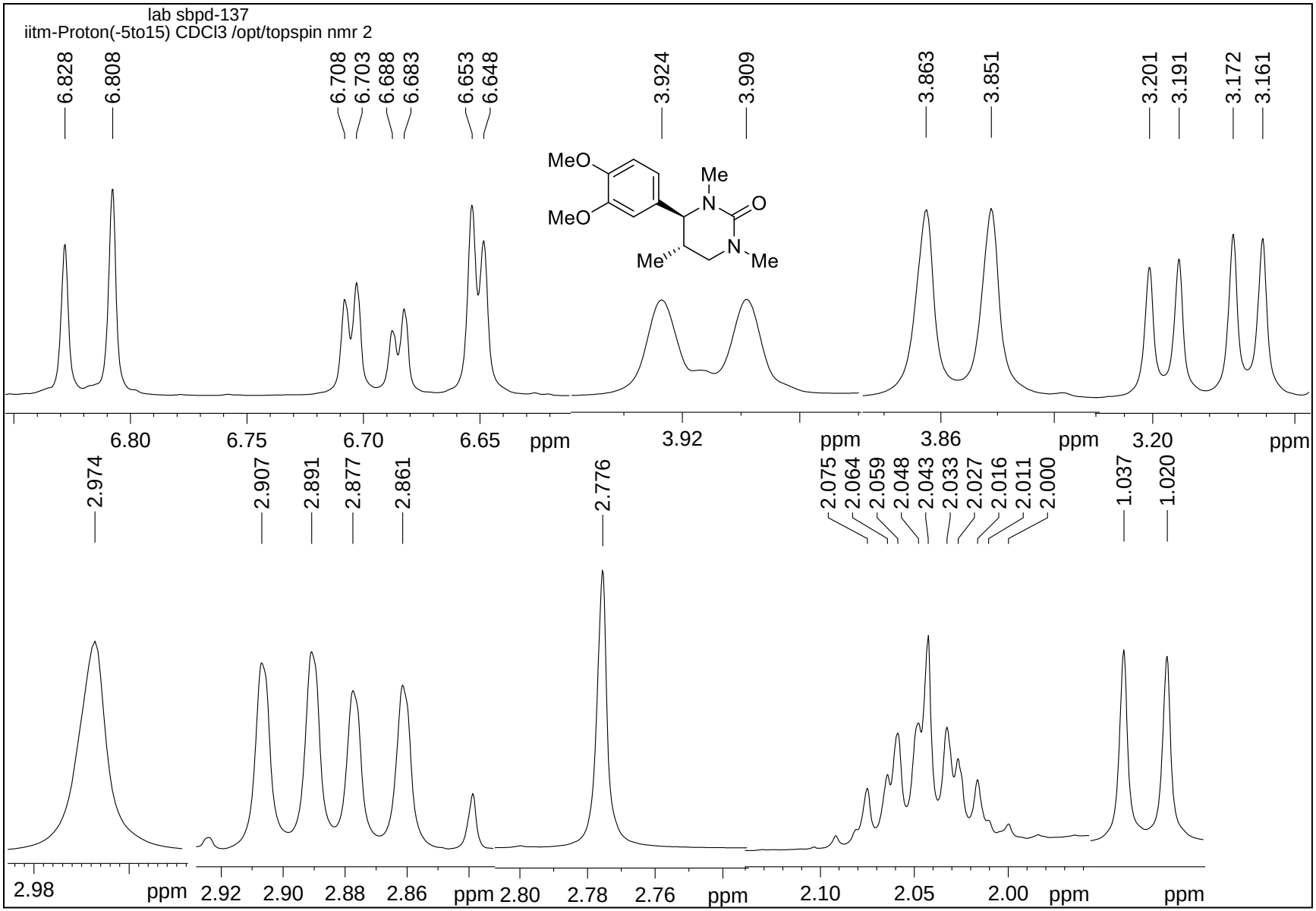


Figure 34 Expanded ^{1}H NMR spectrum of compound 15a

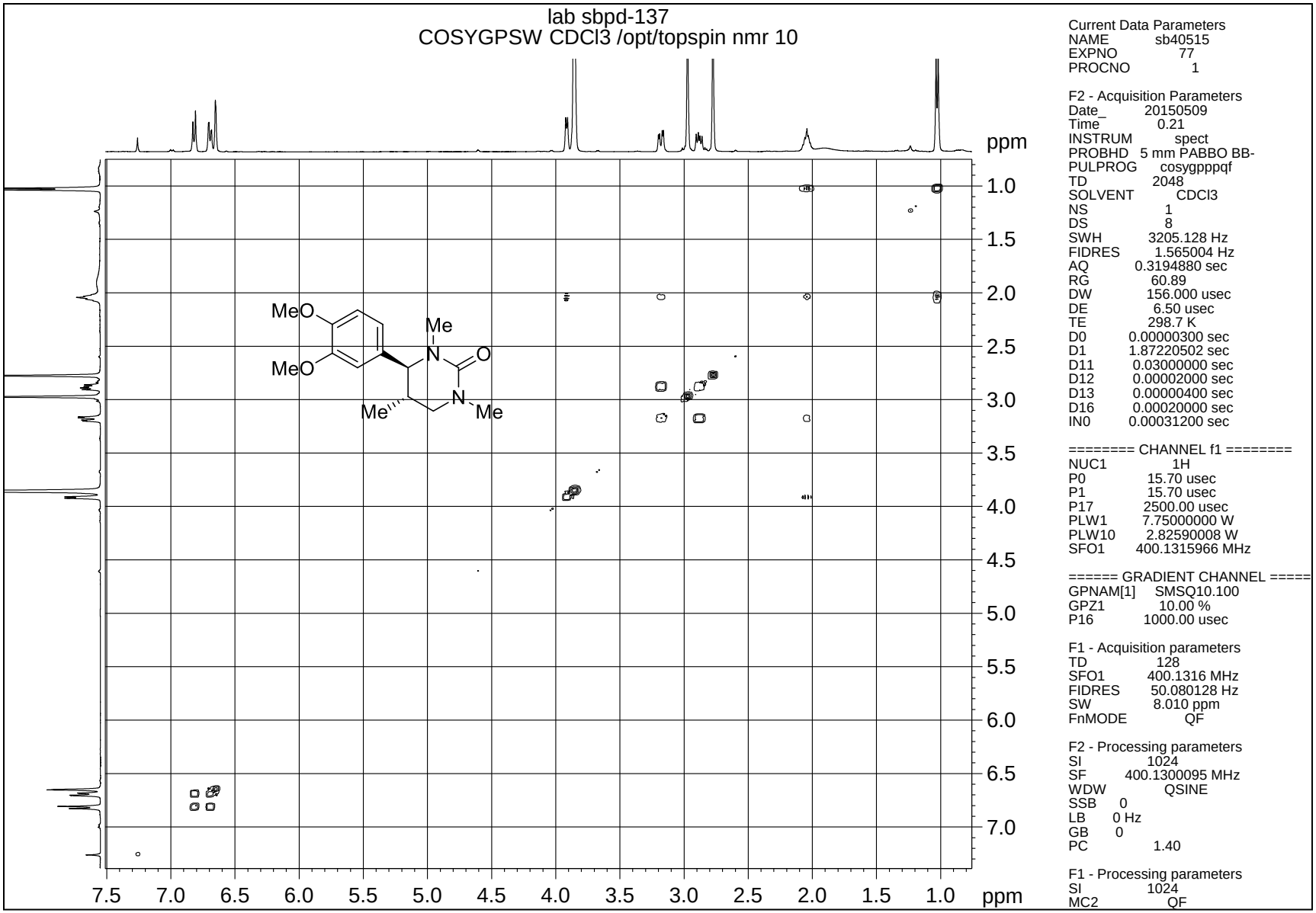


Figure 35 ^{1}H-^{1}H COSY NMR spectrum of compound 15a

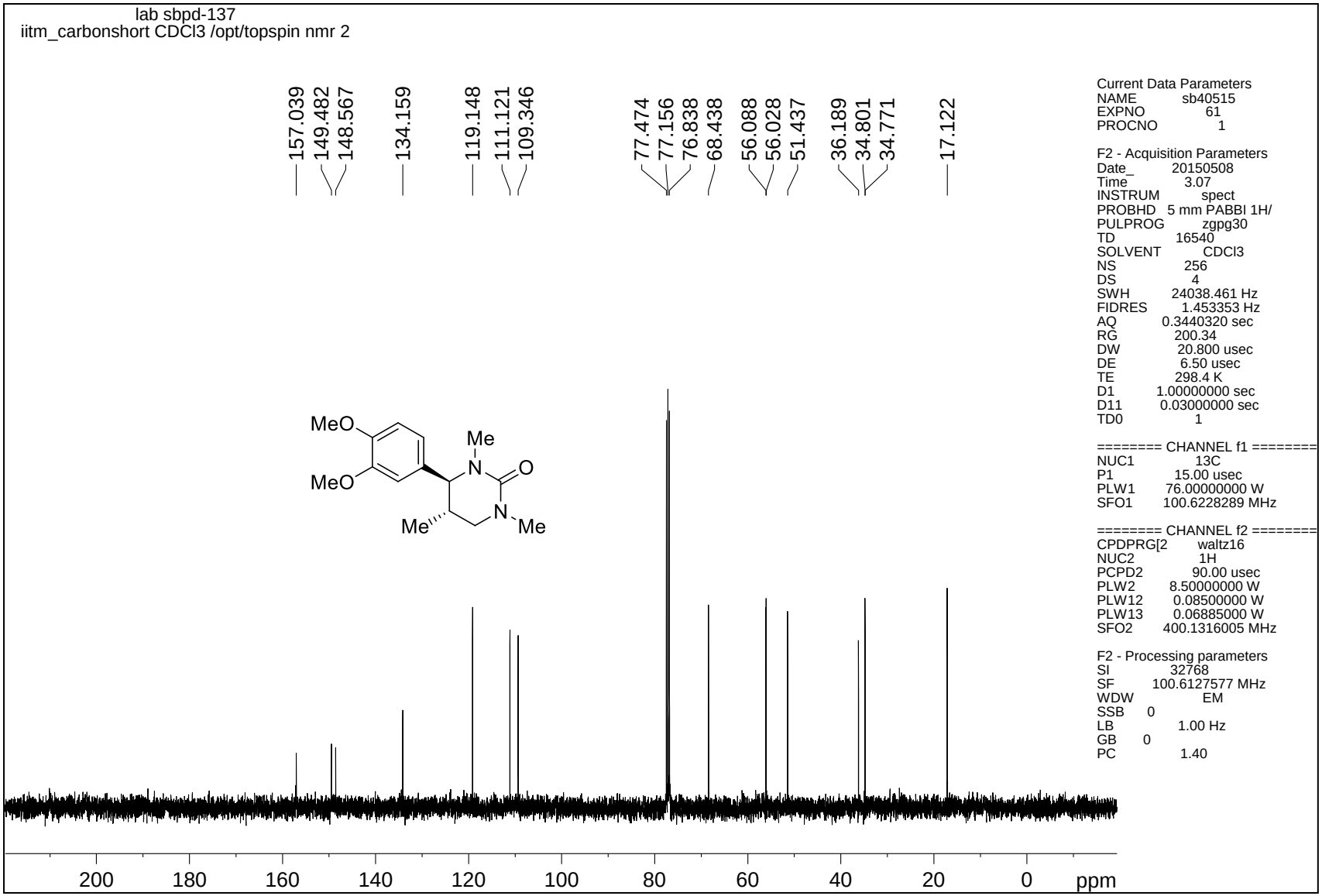


Figure 36 ^{13}C NMR spectrum of compound 15a

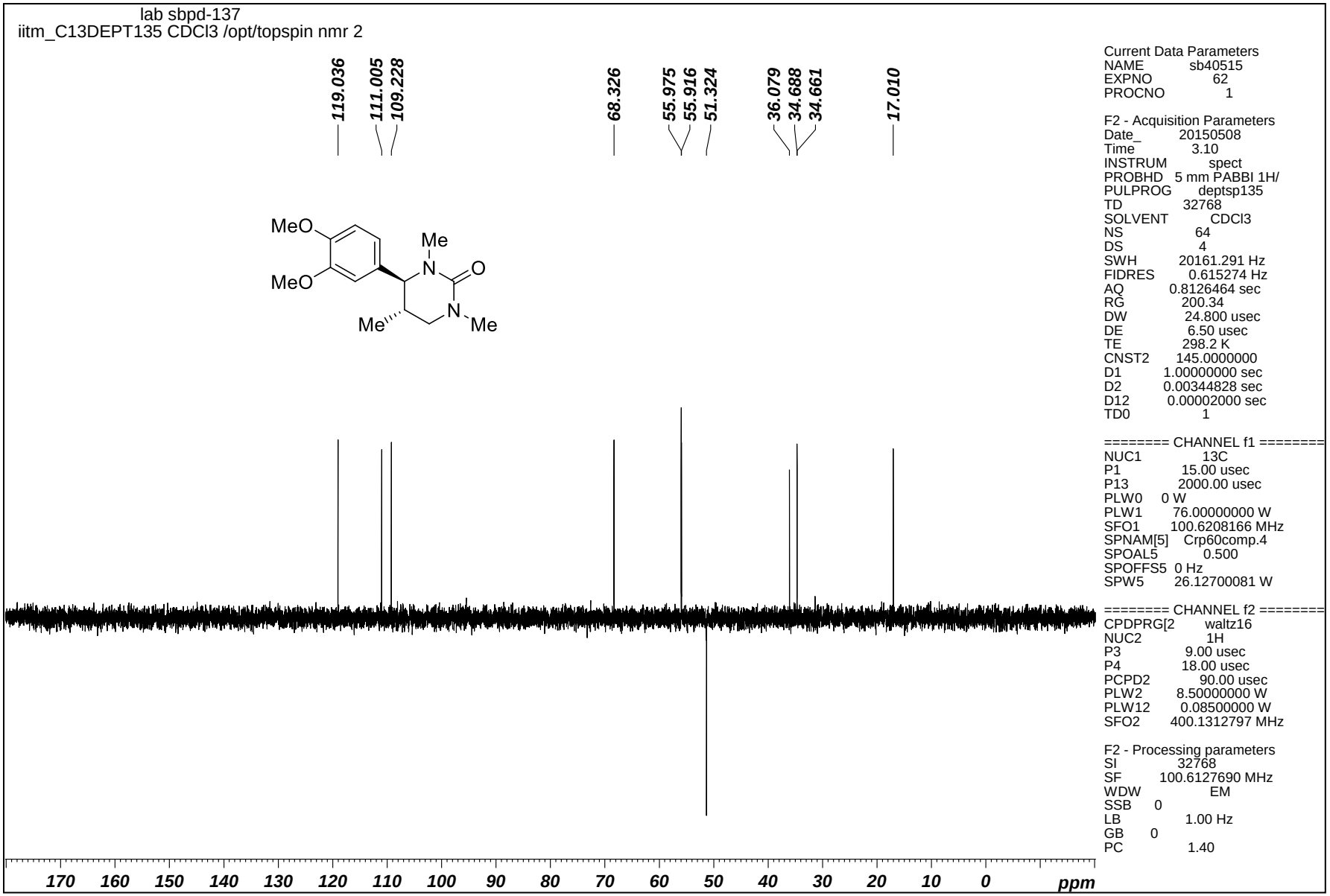


Figure 37 DEPT-135 NMR spectrum of compound 15a

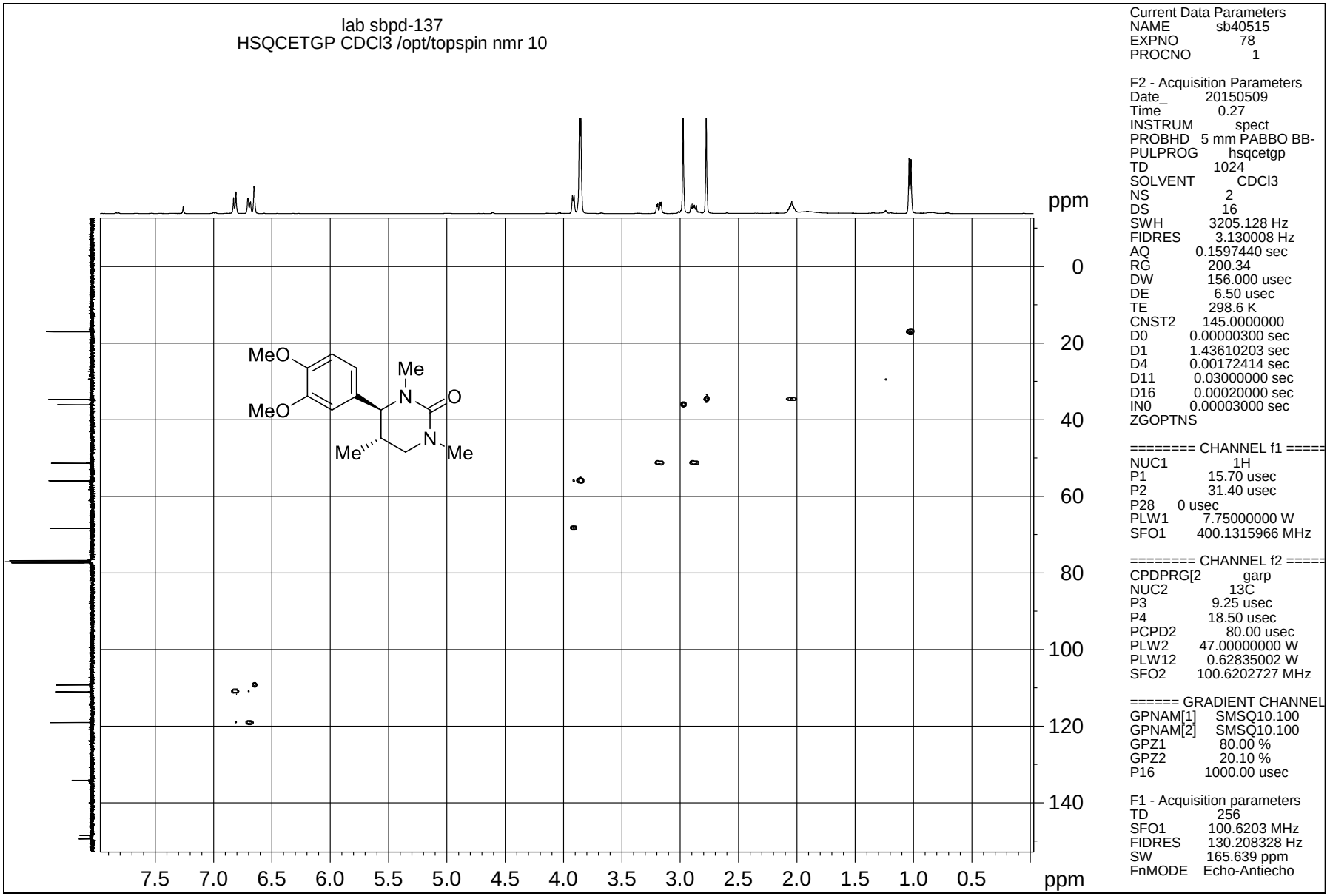


Figure 38 ^{1}H-^{13}C HSQC NMR spectrum of compound 15a

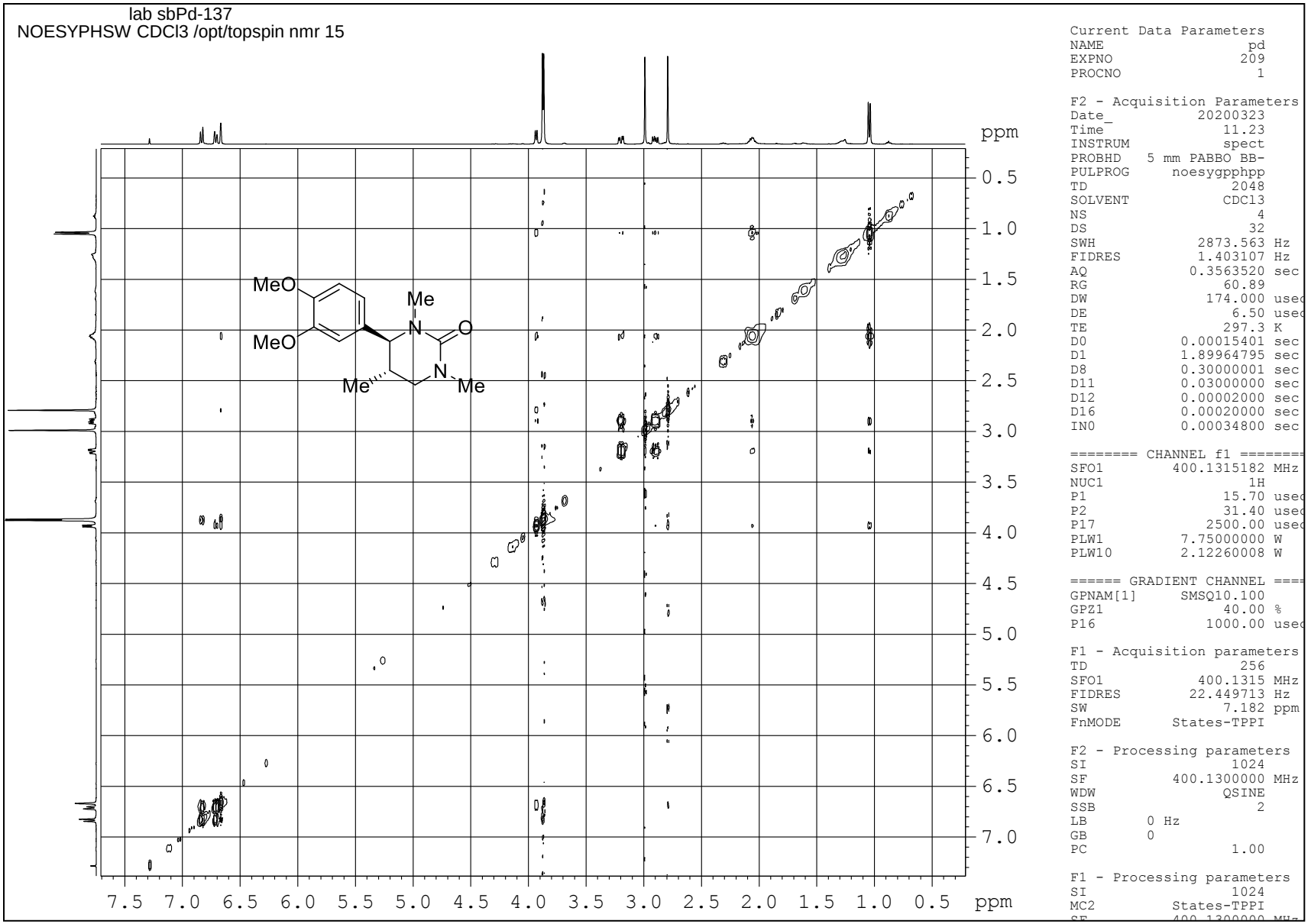


Figure 39 ^{1}H-^{1}H 2D-NOESY spectrum of compound 15a

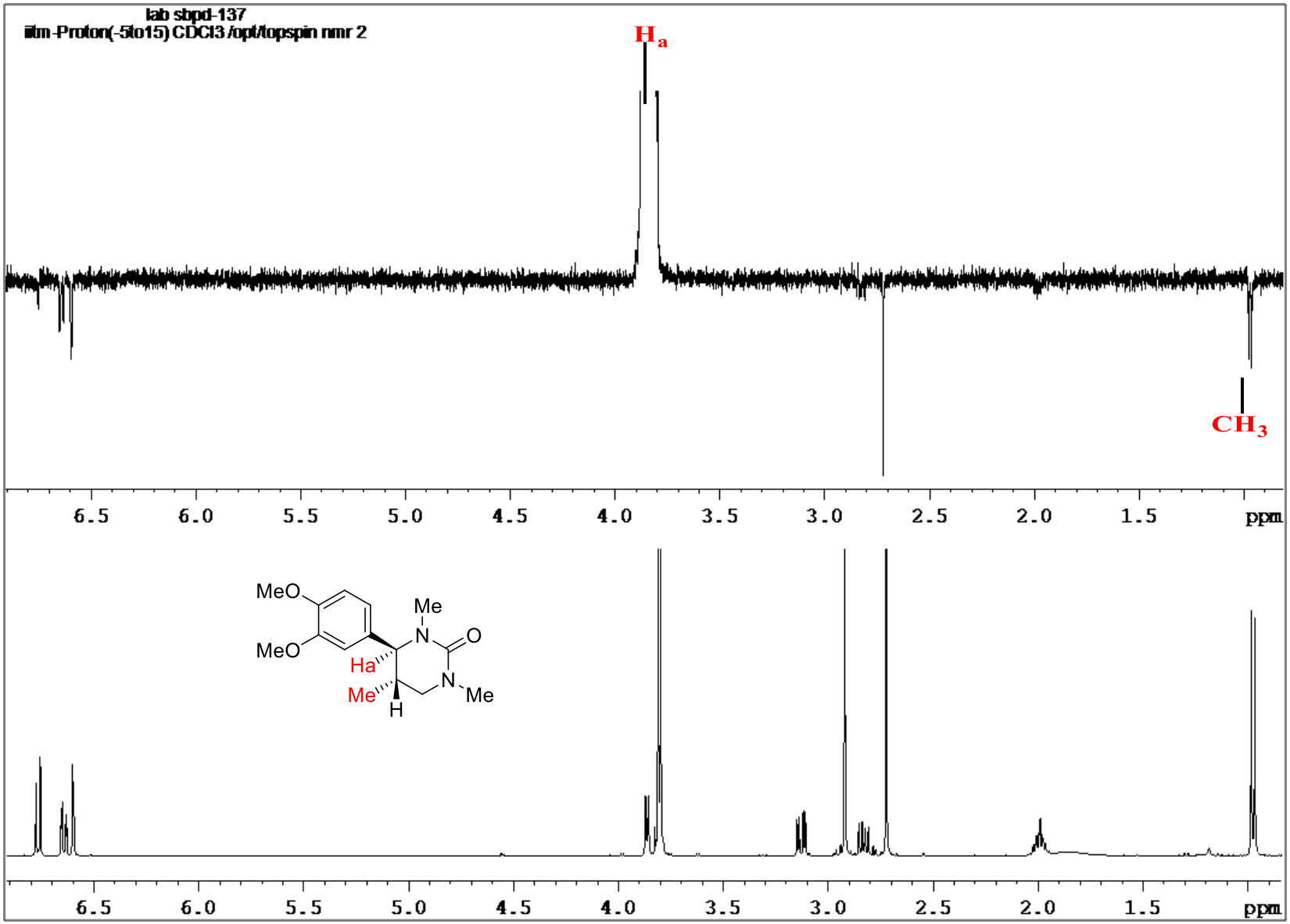


Figure 40 ^{1}H-^{1}H 1D-NOE NMR spectrum of compound 15a

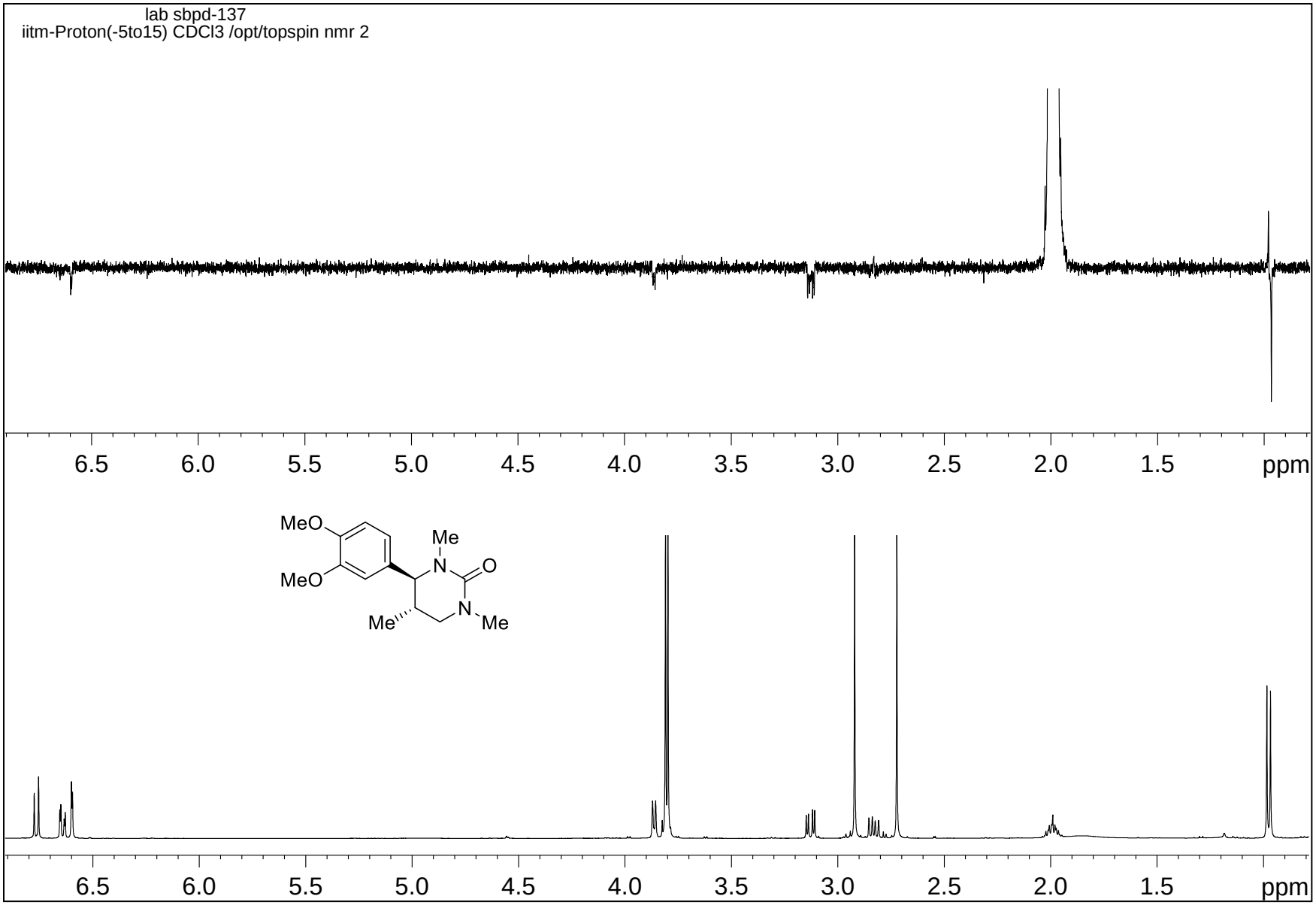


Figure 41 ^{1}H-^{1}H 1D-NOE NMR spectrum of compound 15a

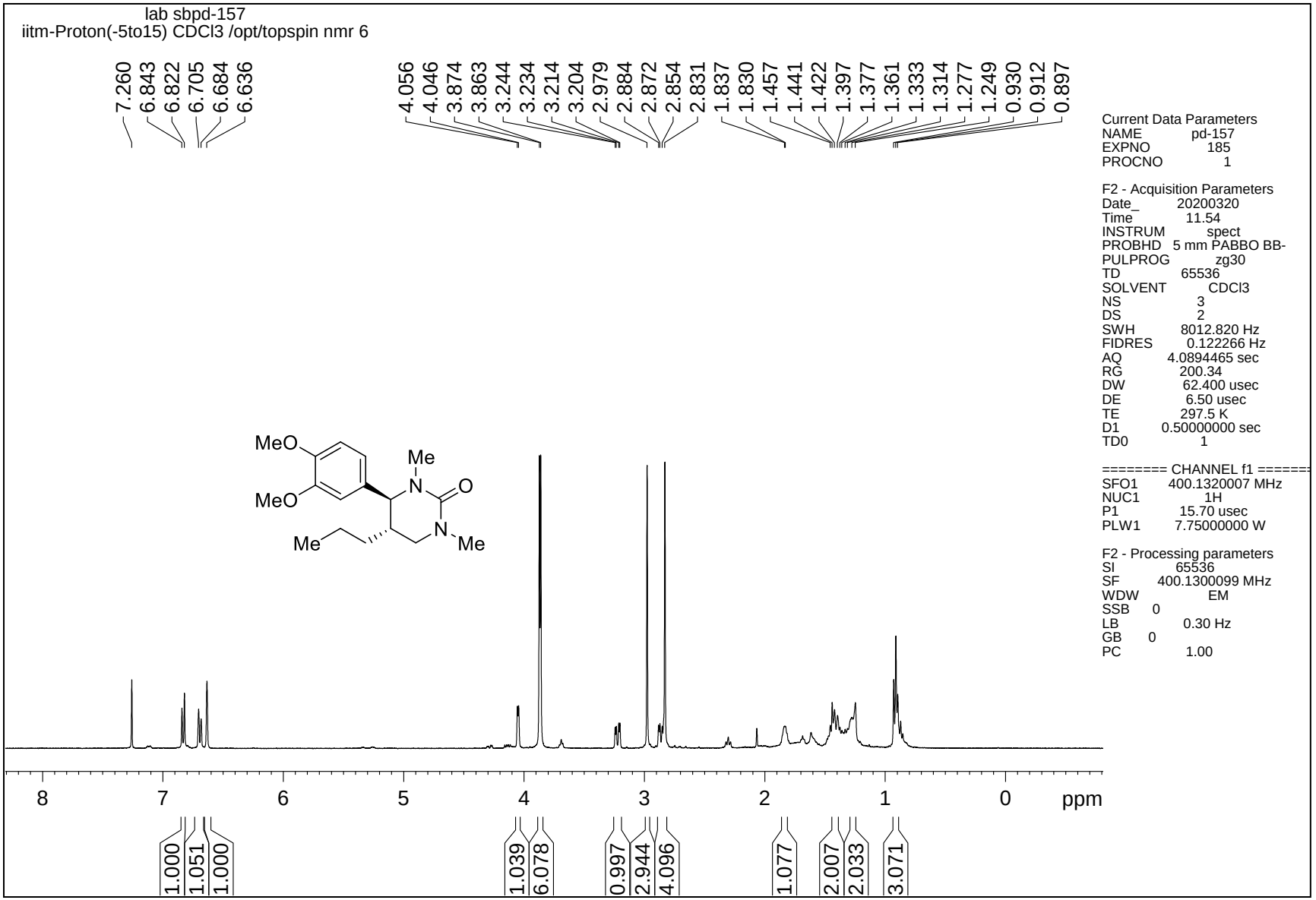


Figure 42 ^{1}H NMR spectrum of compound 16a

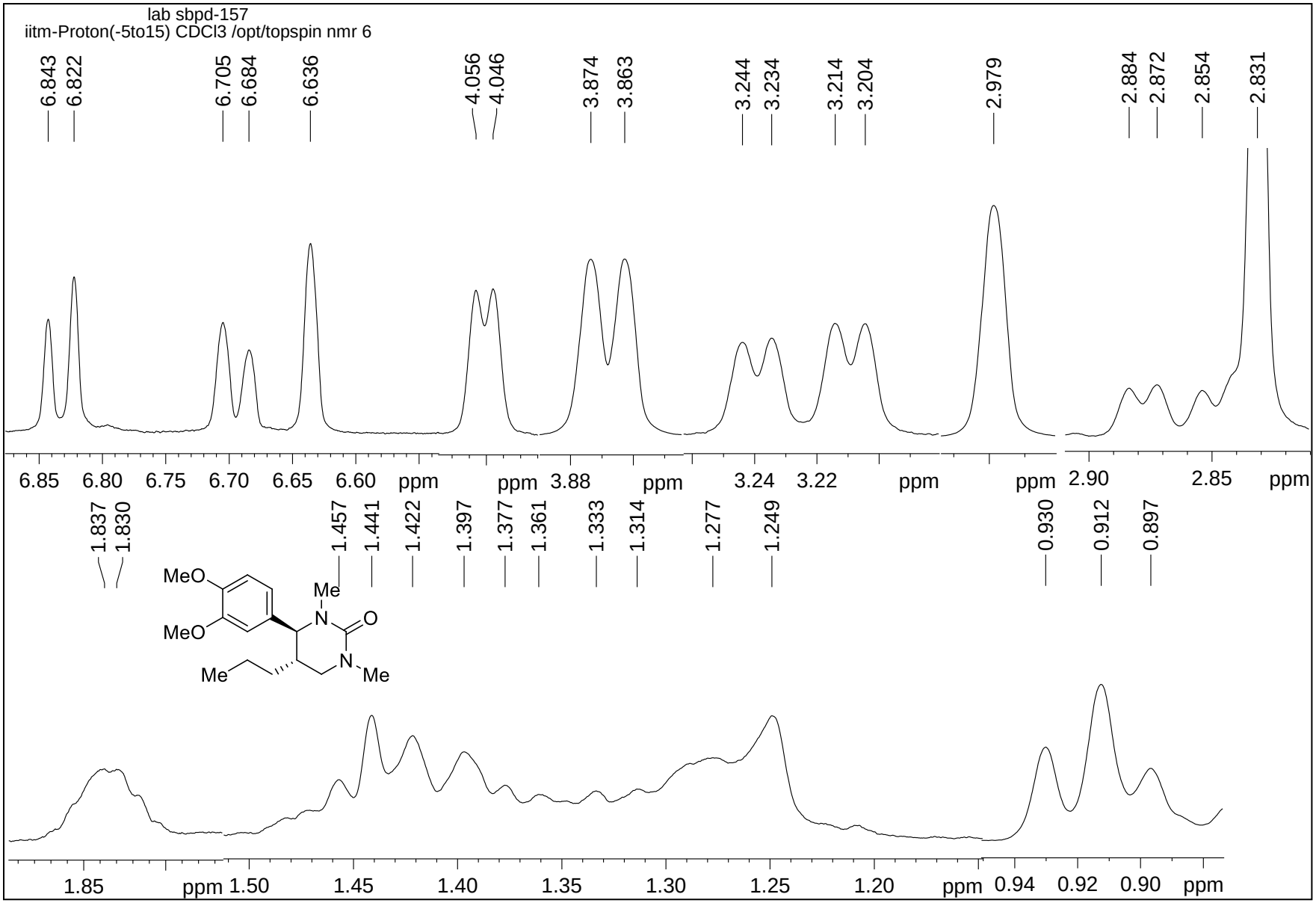


Figure 43 Expanded ^{1}H NMR spectrum of compound 16a

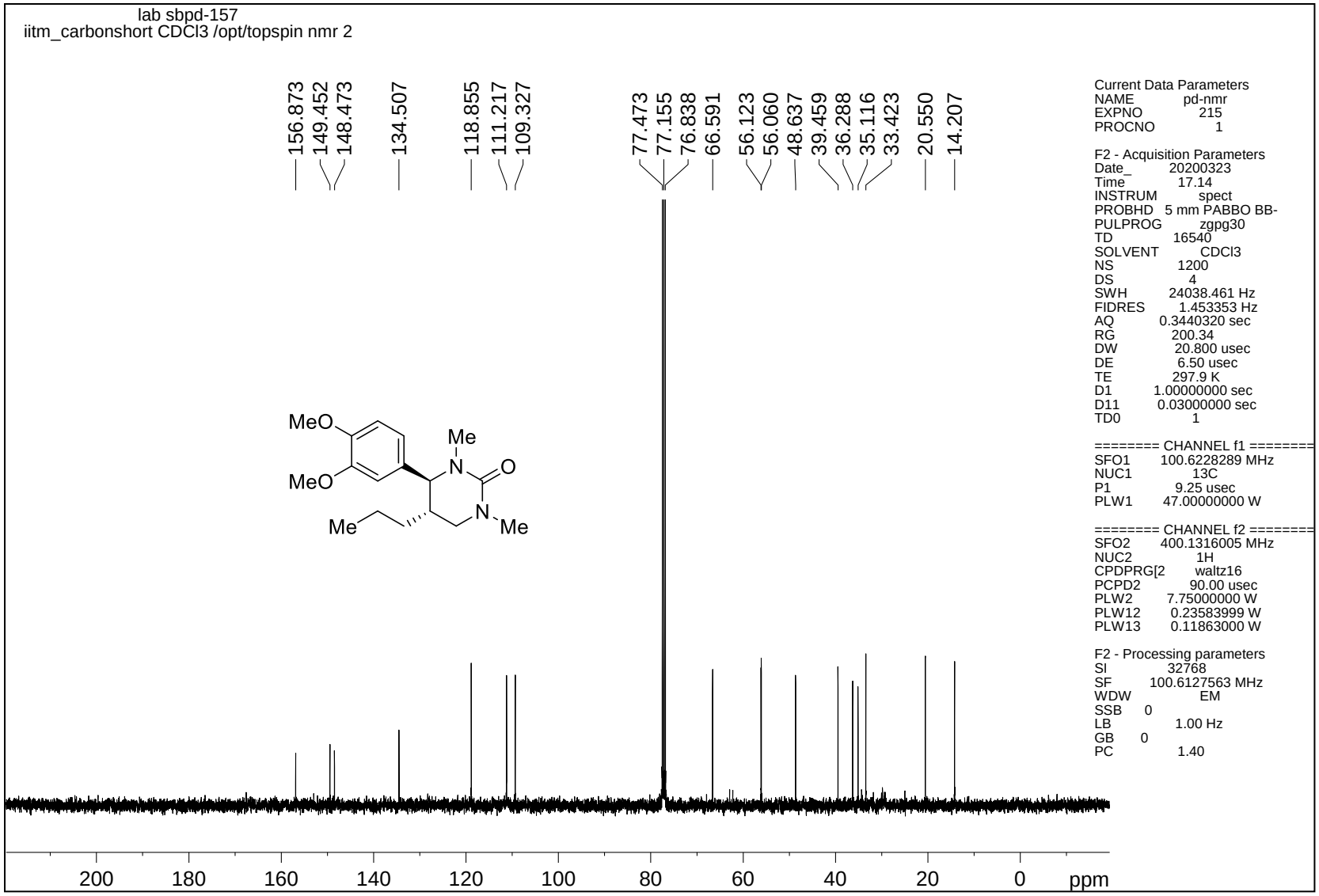


Figure 44 ^{13}C NMR spectrum of compound 16a

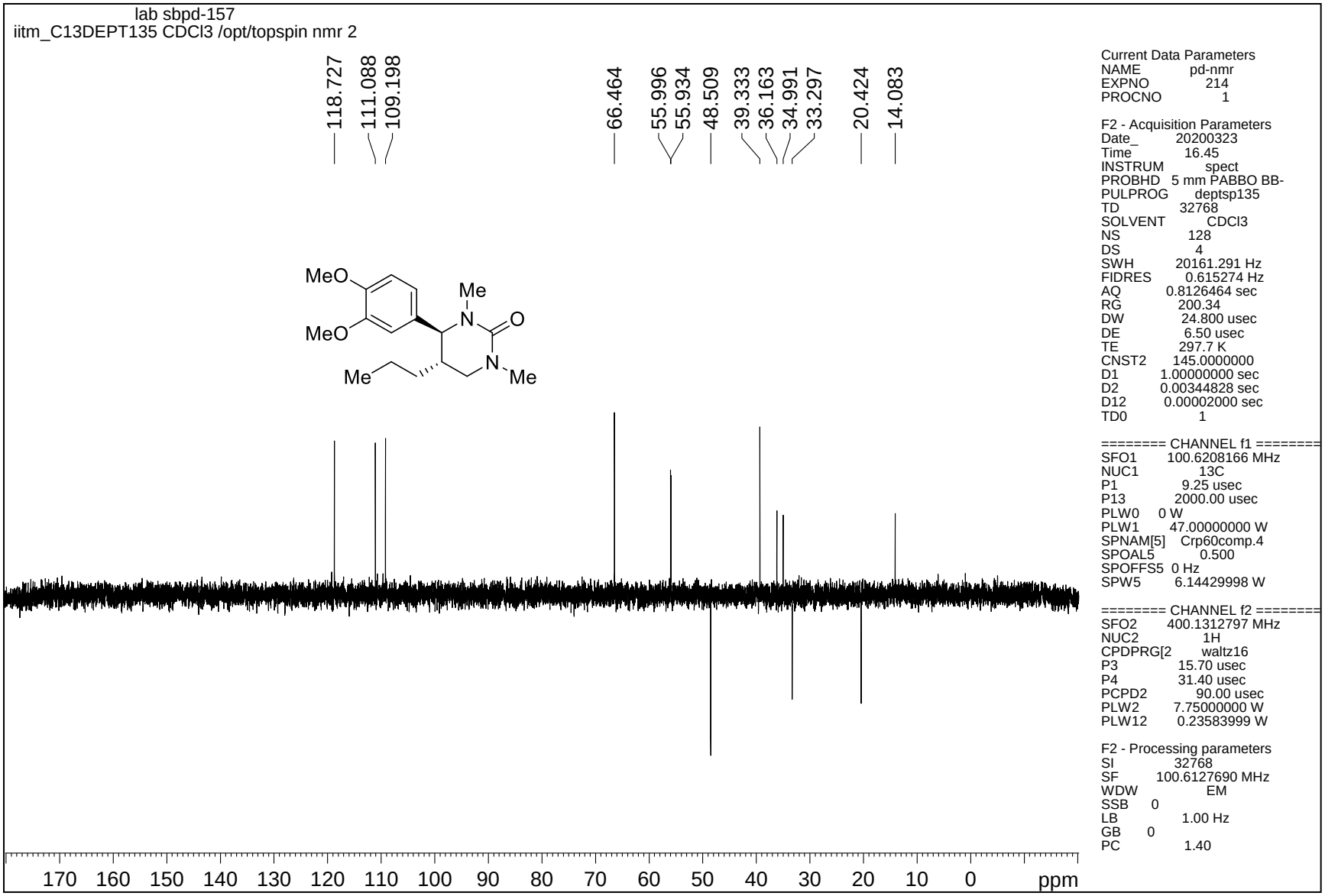


Figure 45 DEPT-135 NMR spectrum of compound 16a

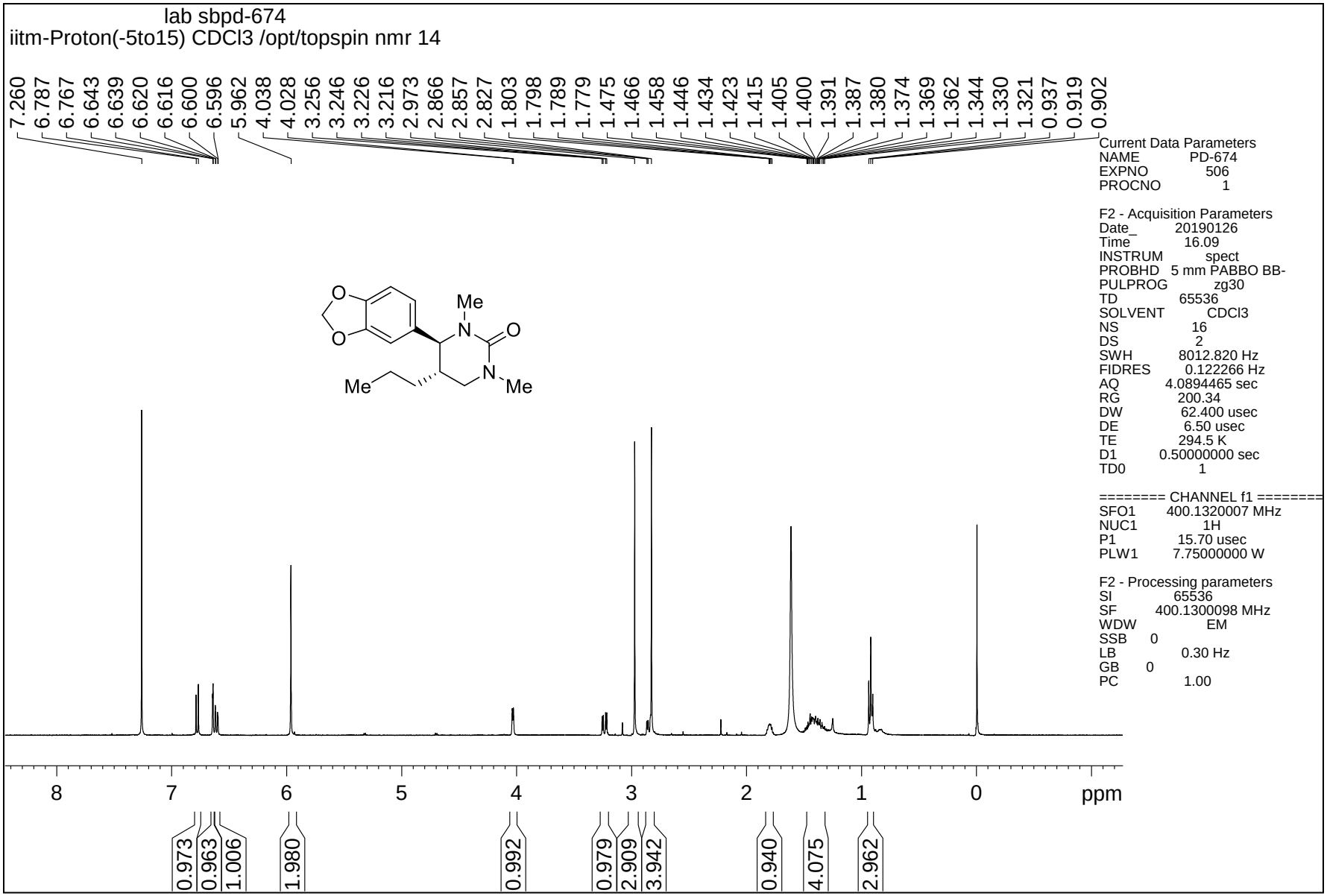


Figure 46 ^{1}H NMR spectrum of compound 17a

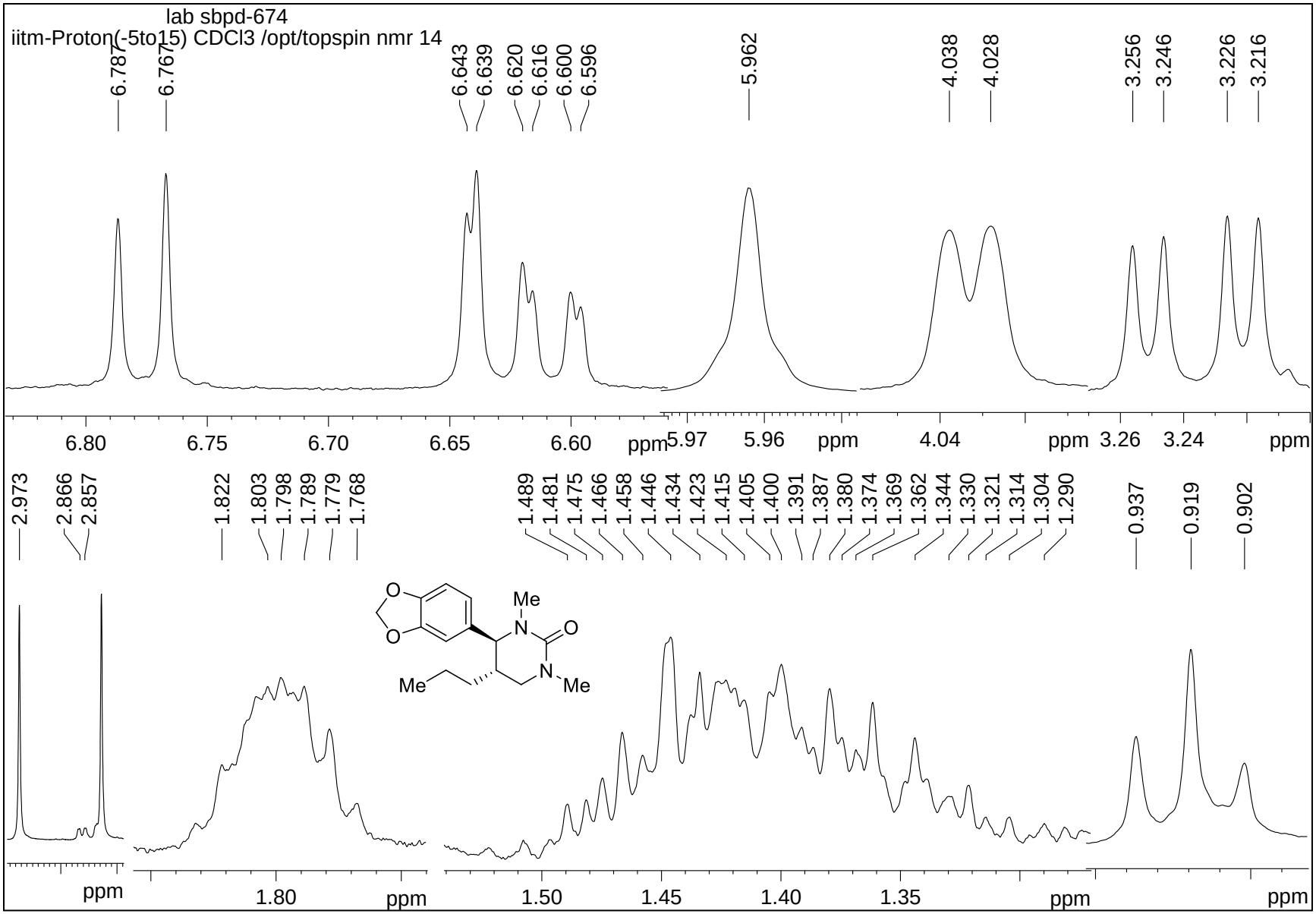


Figure 47 Expanded ^{1}H NMR spectrum of compound 17a

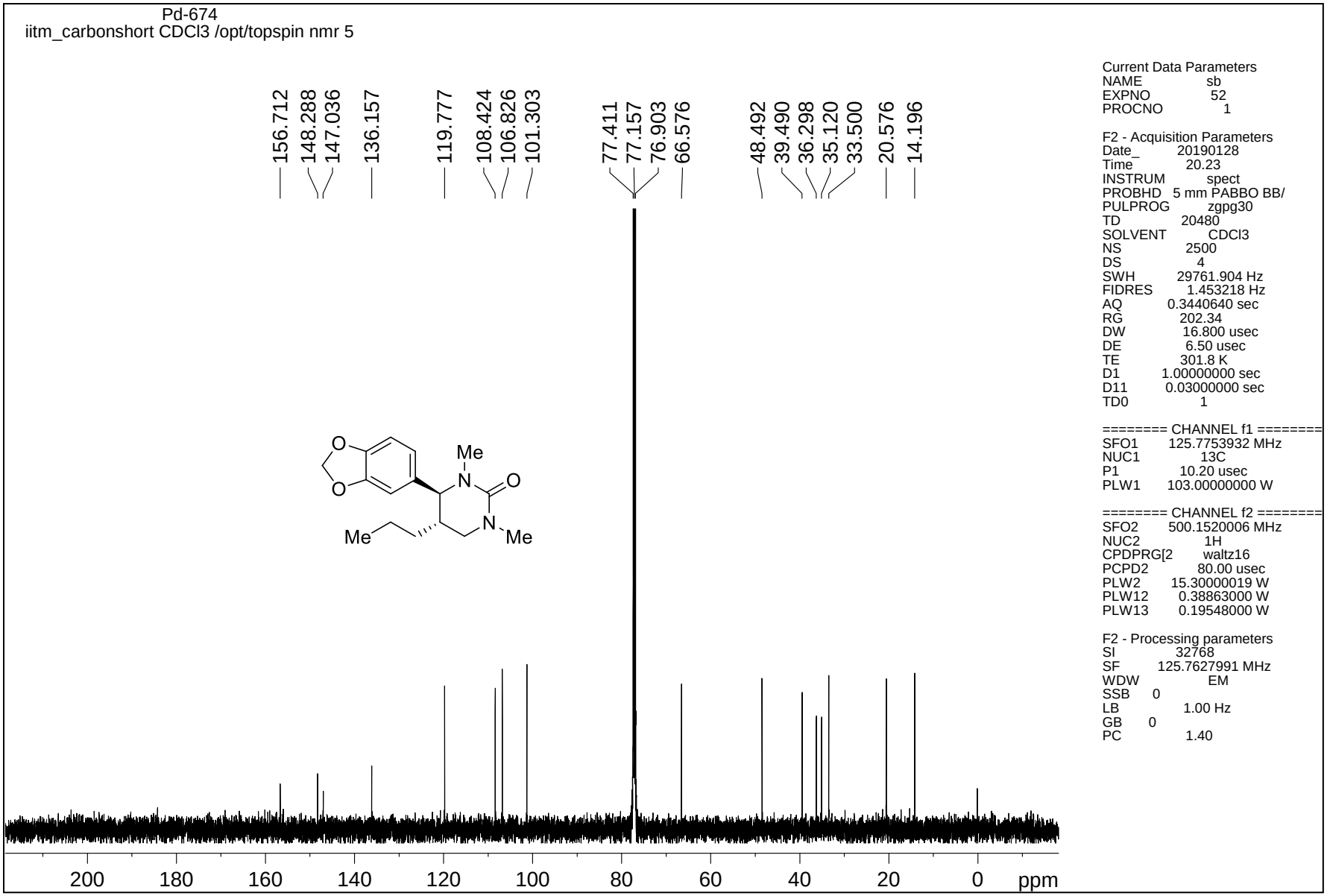


Figure 48 ^{13}C NMR spectrum of compound 17a

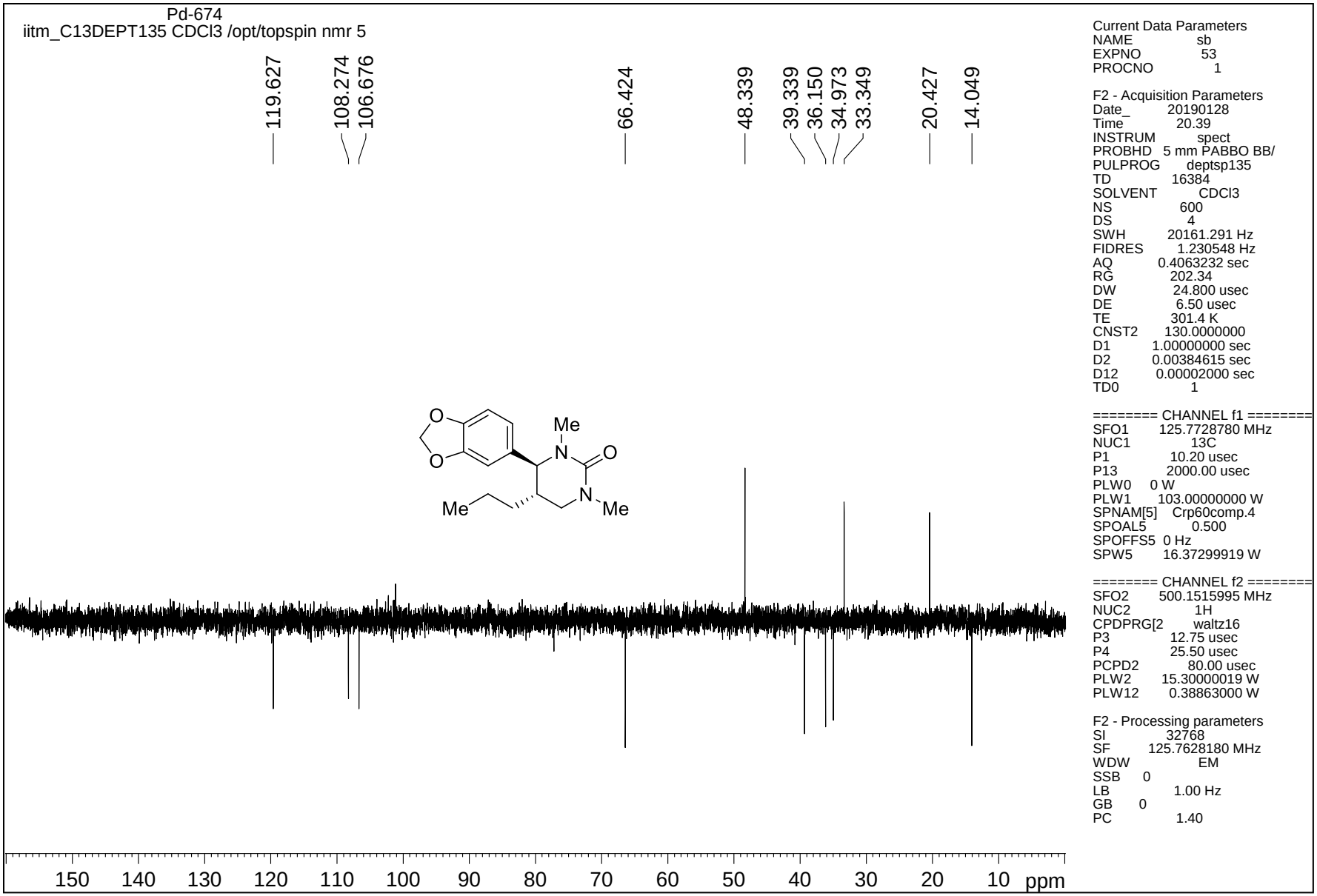


Figure 49 DEPT-135 NMR spectrum of compound 17a

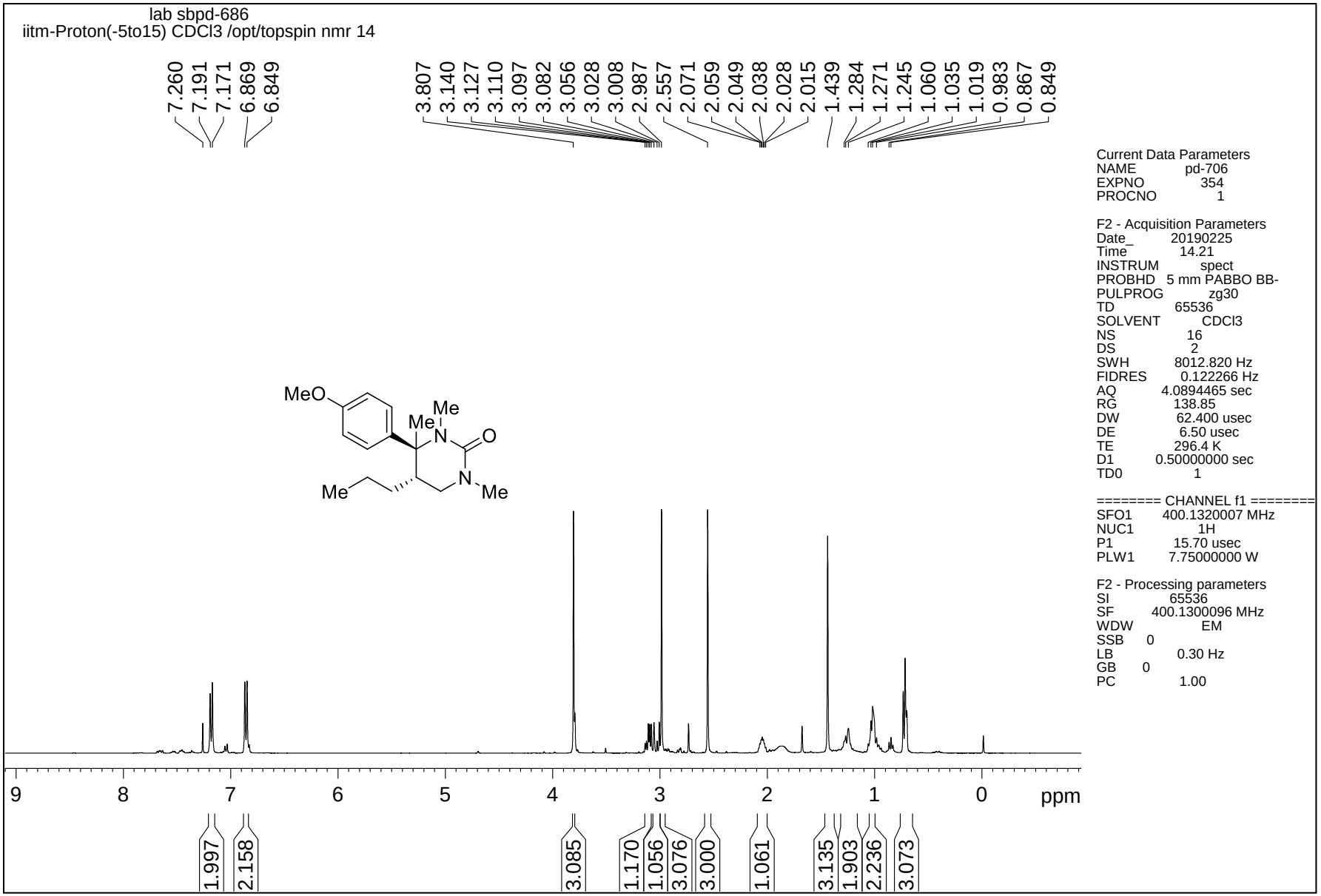


Figure 50 ^{1}H NMR spectrum of compound 18a

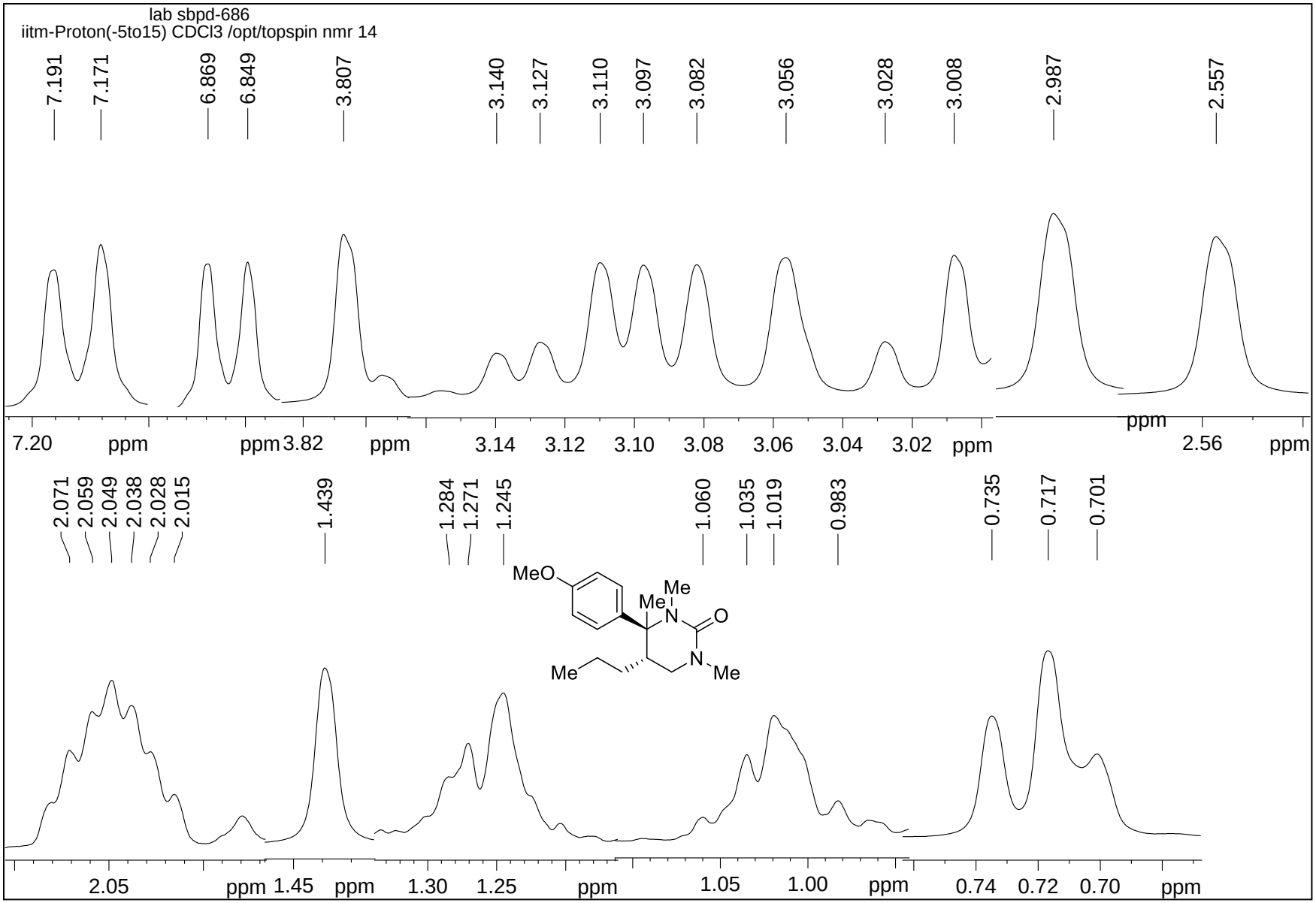


Figure 51 Expanded ^{1}H NMR spectrum of compound 18a

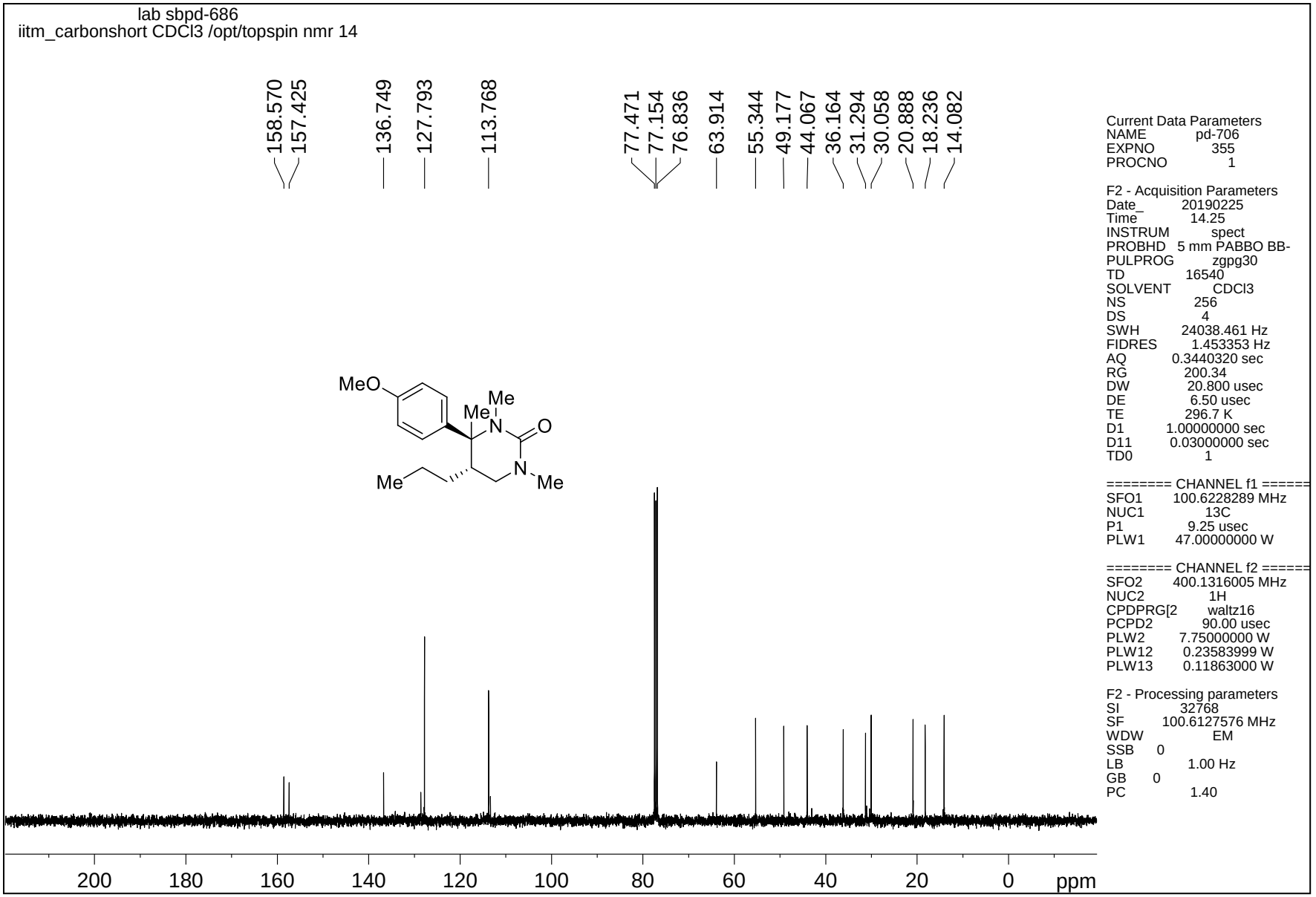


Figure 52 ^{13}C NMR spectrum of compound 18a

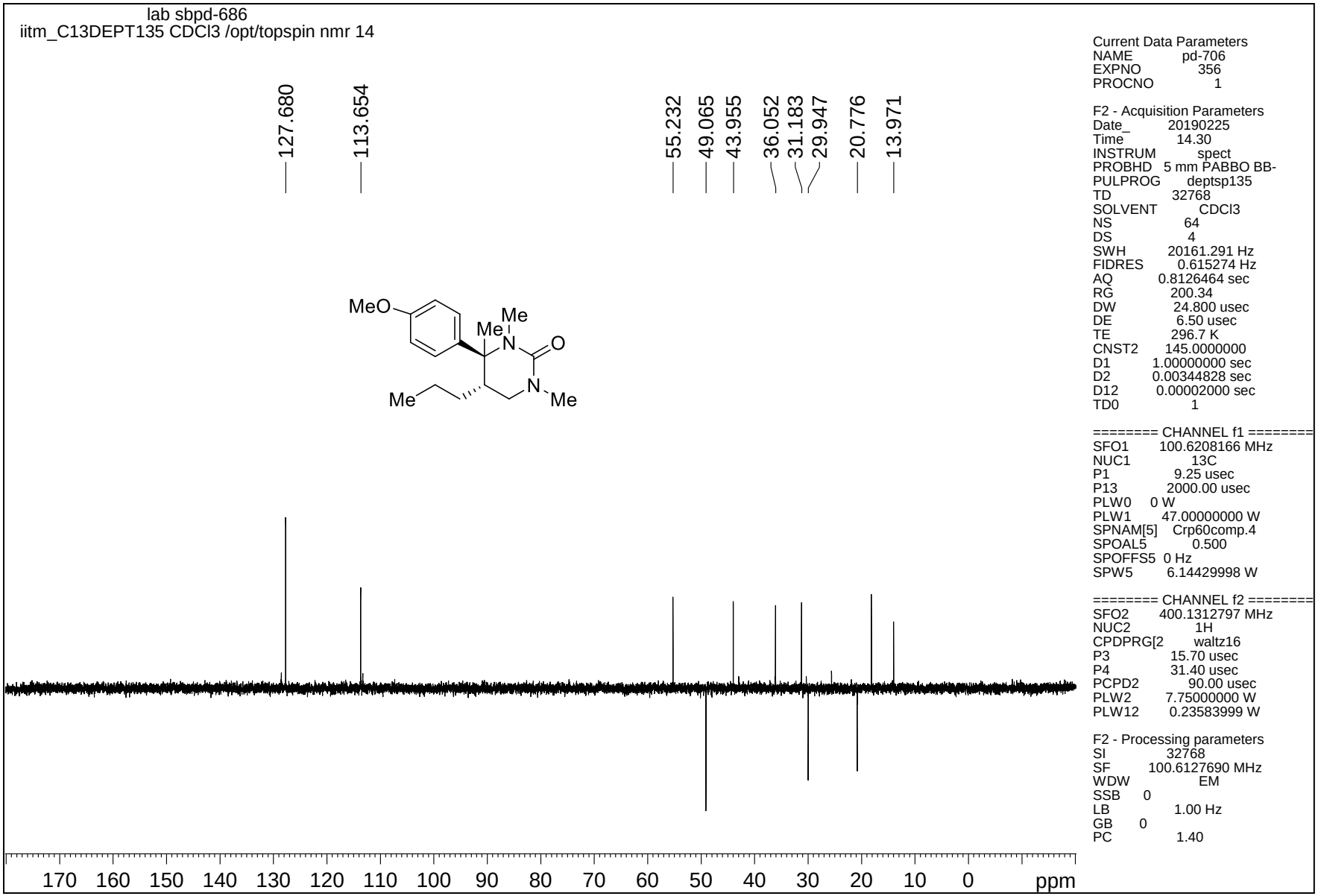


Figure 53 DEPT-135 NMR spectrum of compound 18a

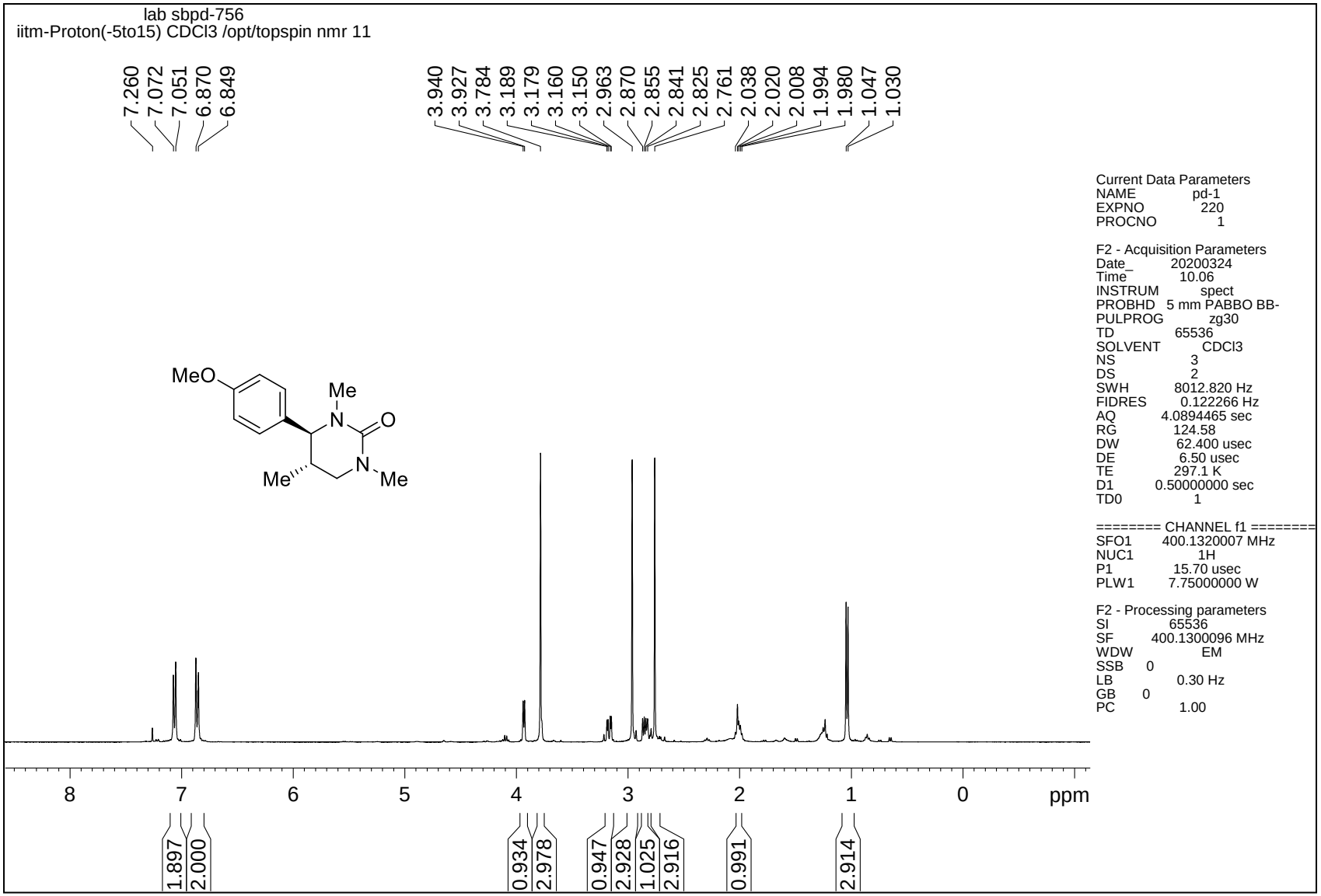


Figure 54 ^{1}H NMR spectrum of compound 19a

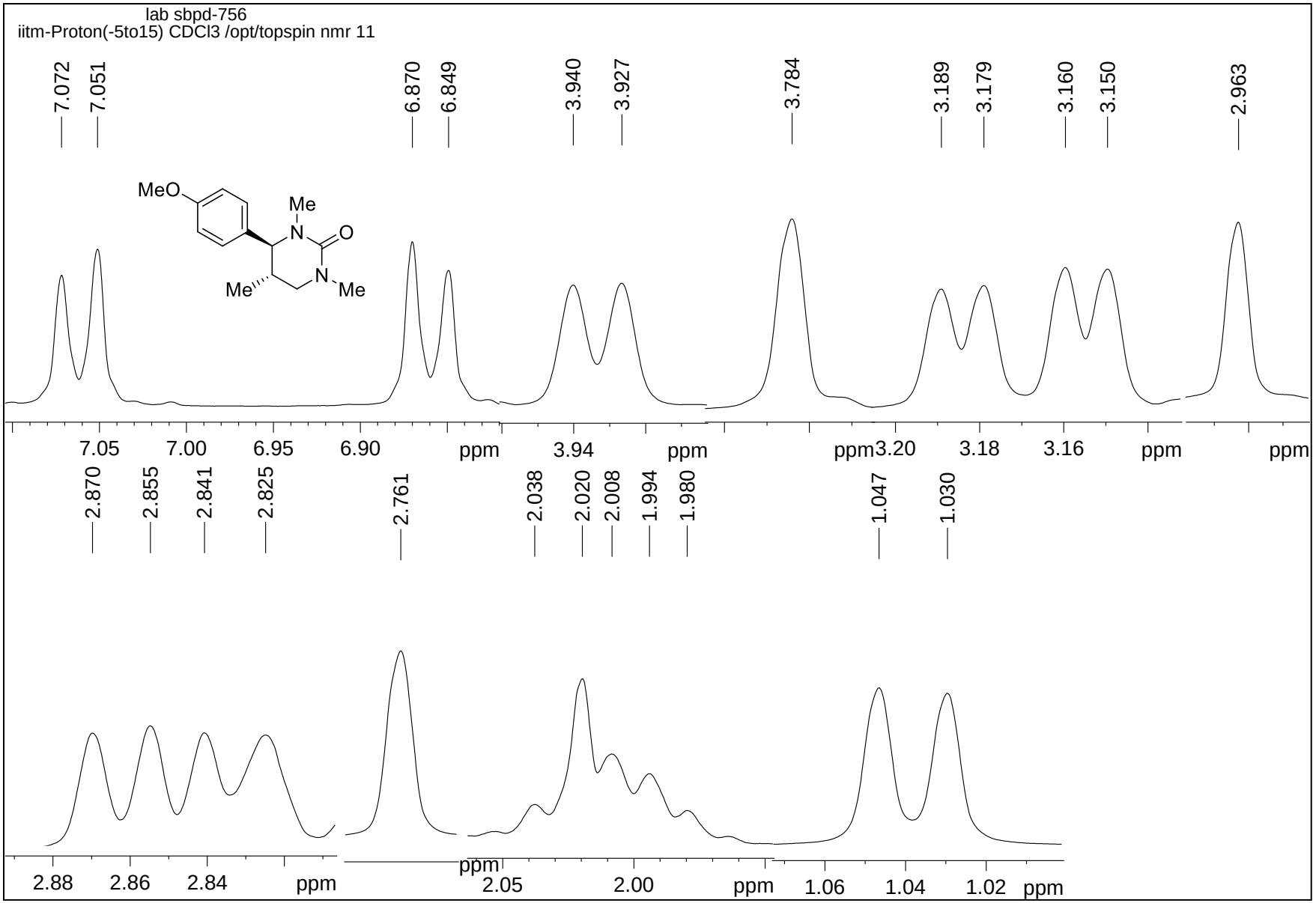


Figure 55 Expanded ^{1}H NMR spectrum of compound 19a

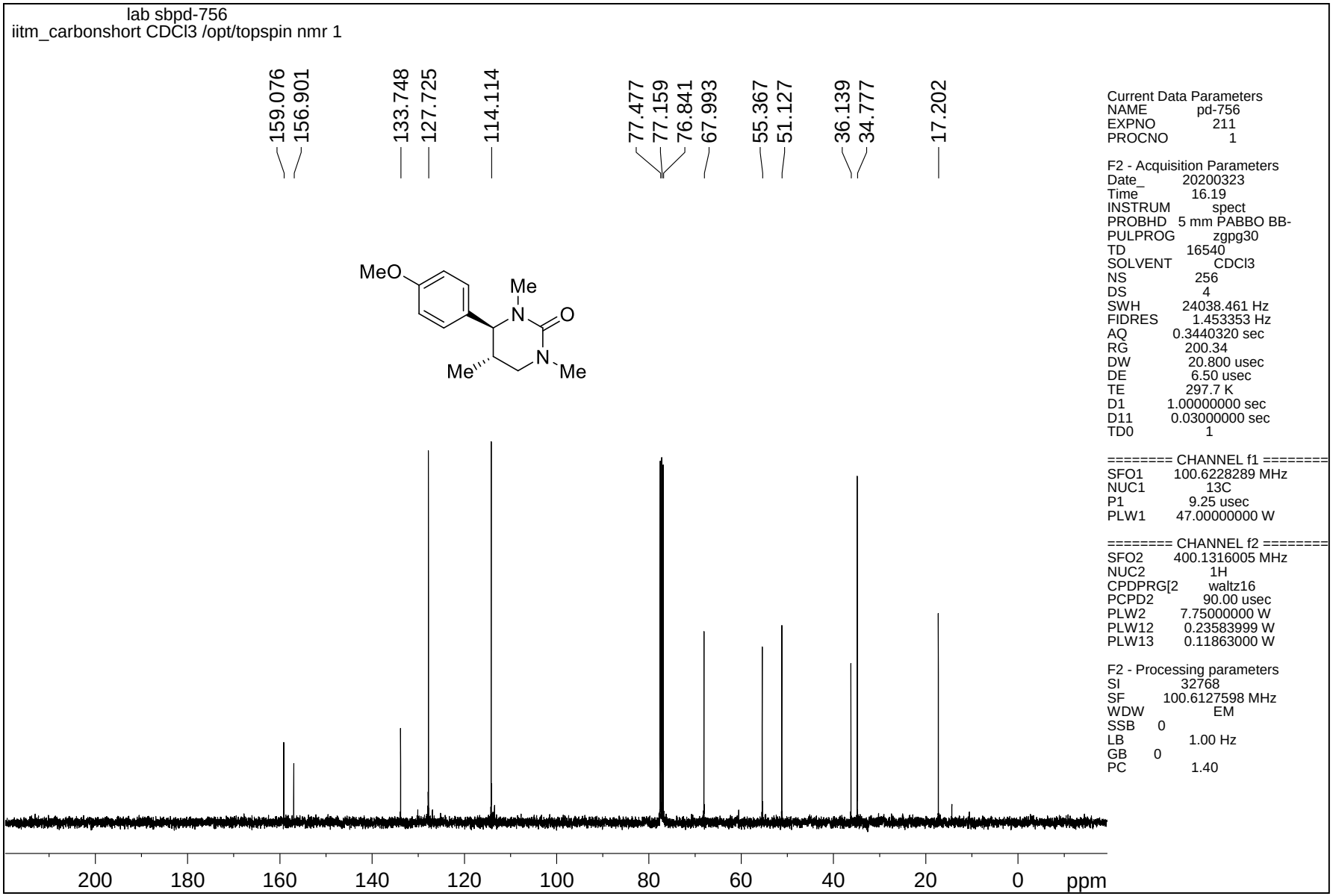


Figure 56 ^{13}C NMR spectrum of compound 19a

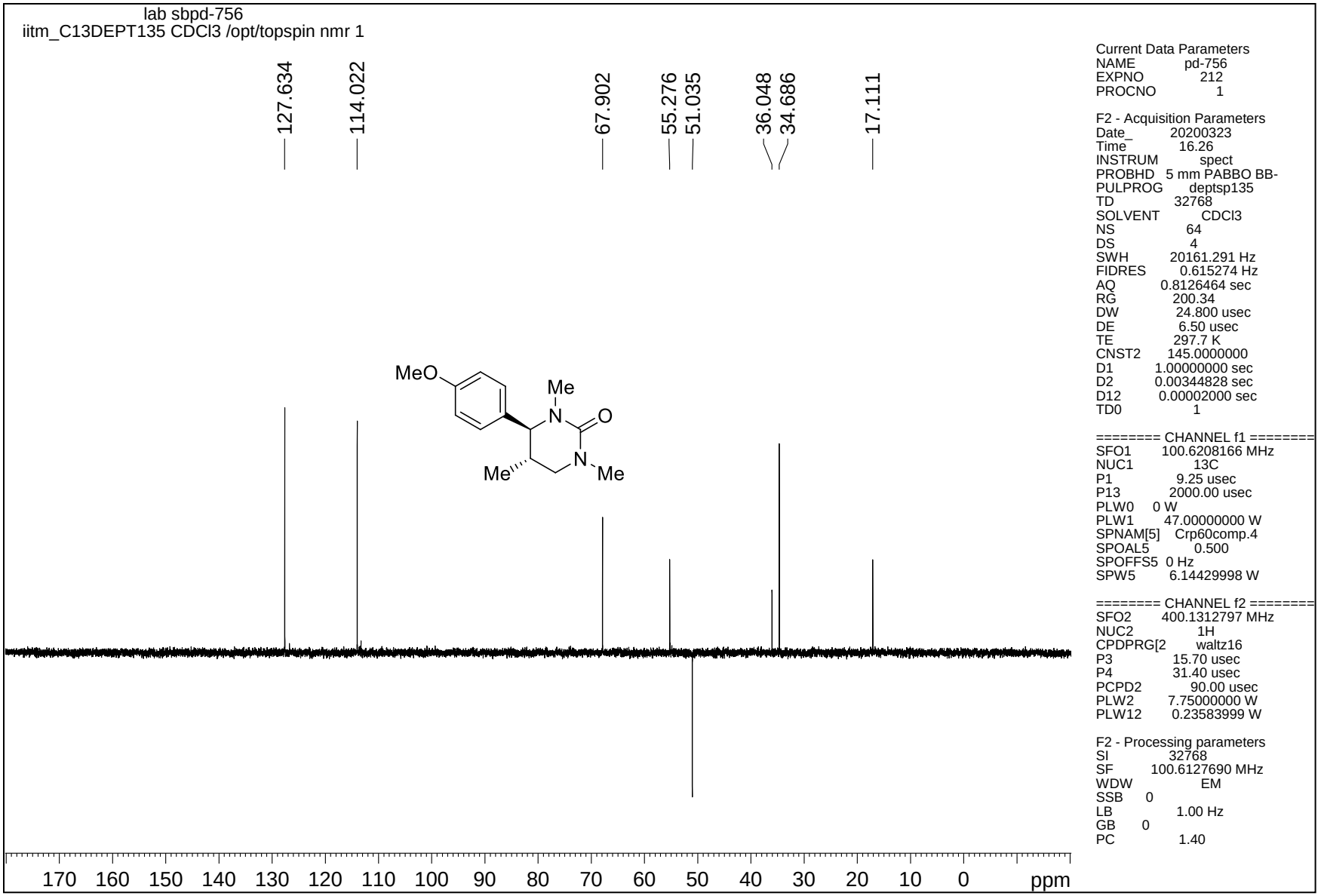


Figure 57 DEPT-135 NMR spectrum of compound 19a

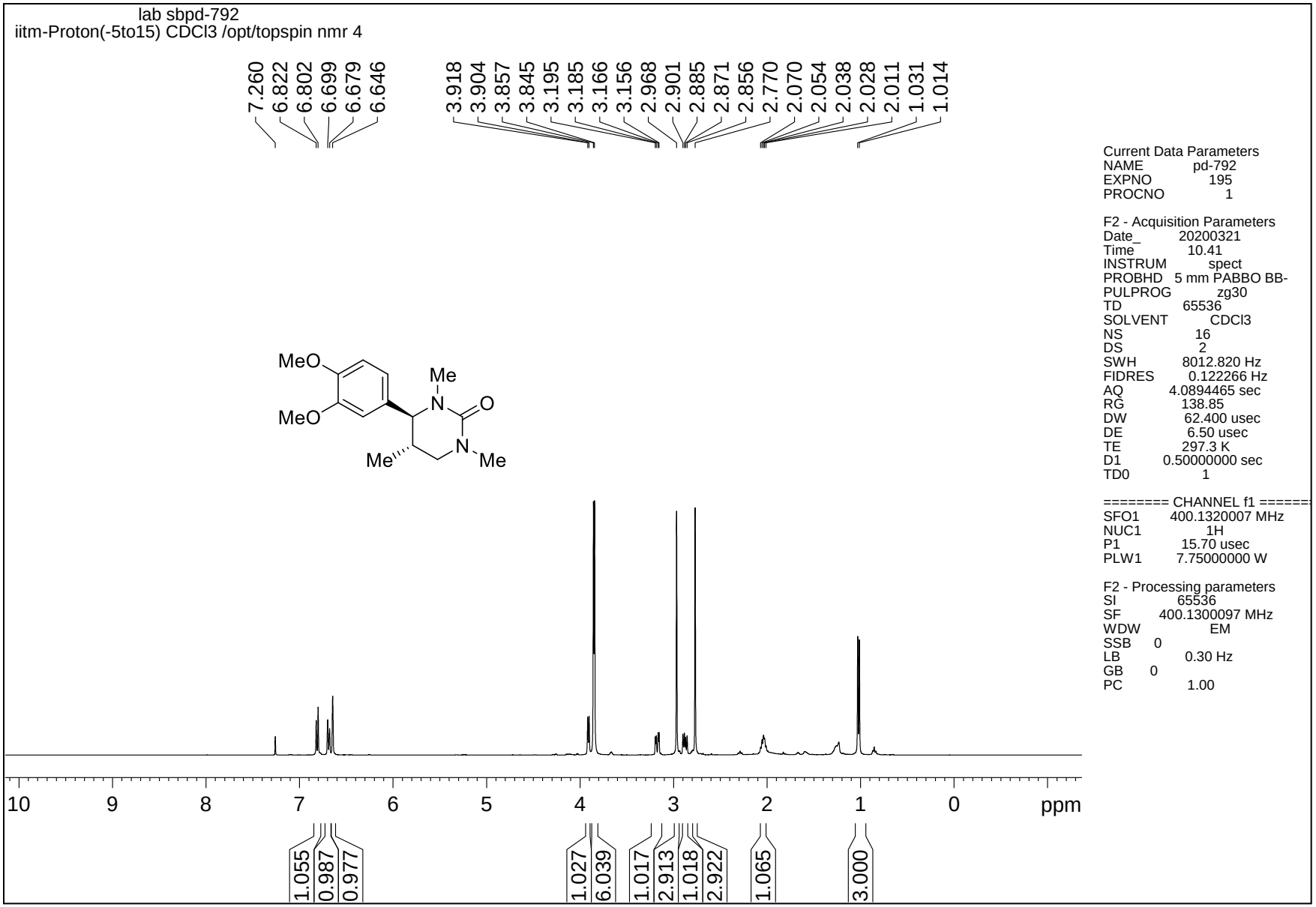


Figure 58 ^{1}H NMR spectrum of compound 15a from 20

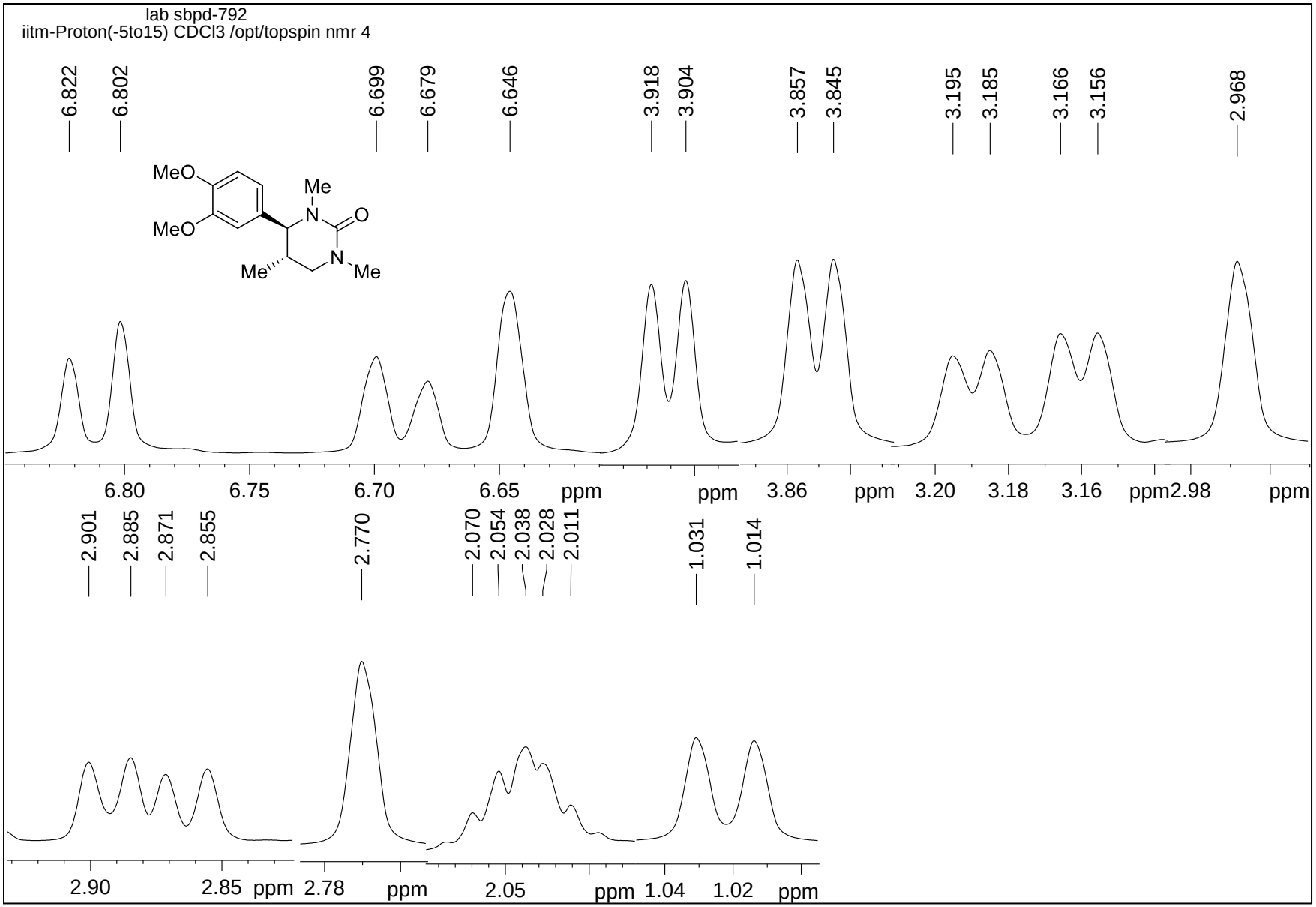


Figure 59 Expanded ^{1}H NMR spectrum of compound 15a from 20

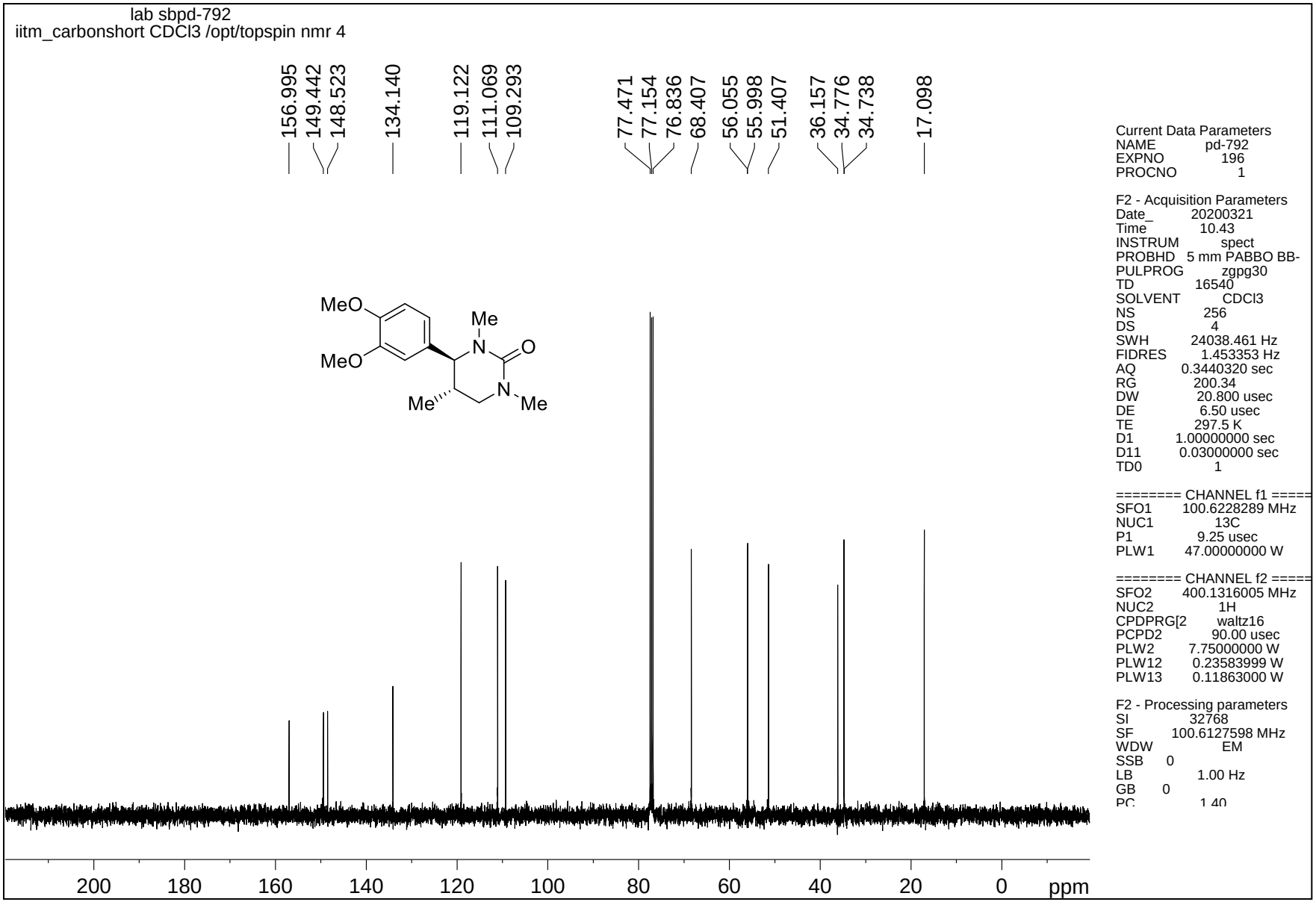


Figure 60 ^{13}C NMR spectrum of compound 15a from 20

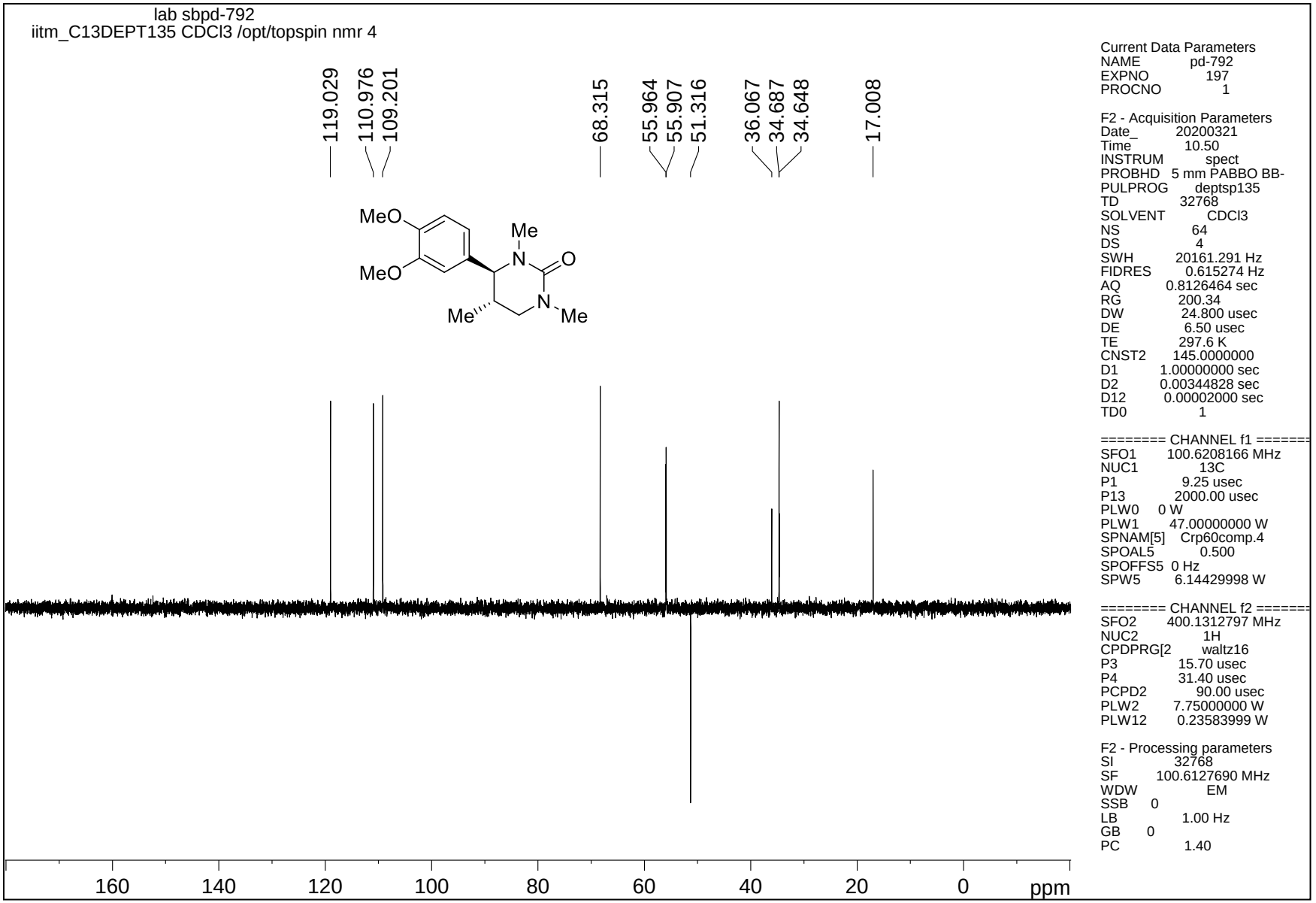


Figure 61 DEPT-135 NMR spectrum of compound 15a from 20

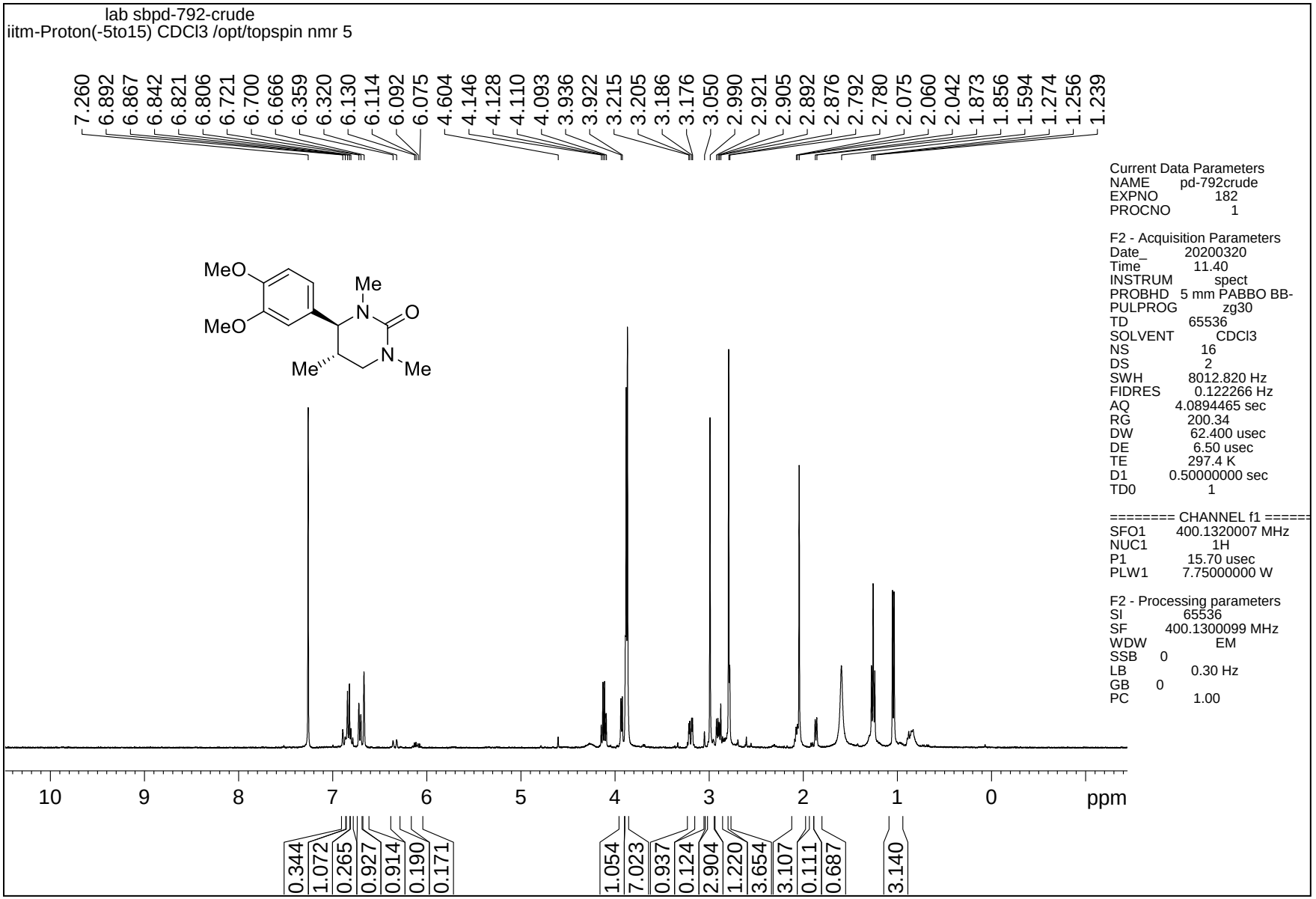


Figure 62 ^{1}H NMR spectrum of crude compound15a

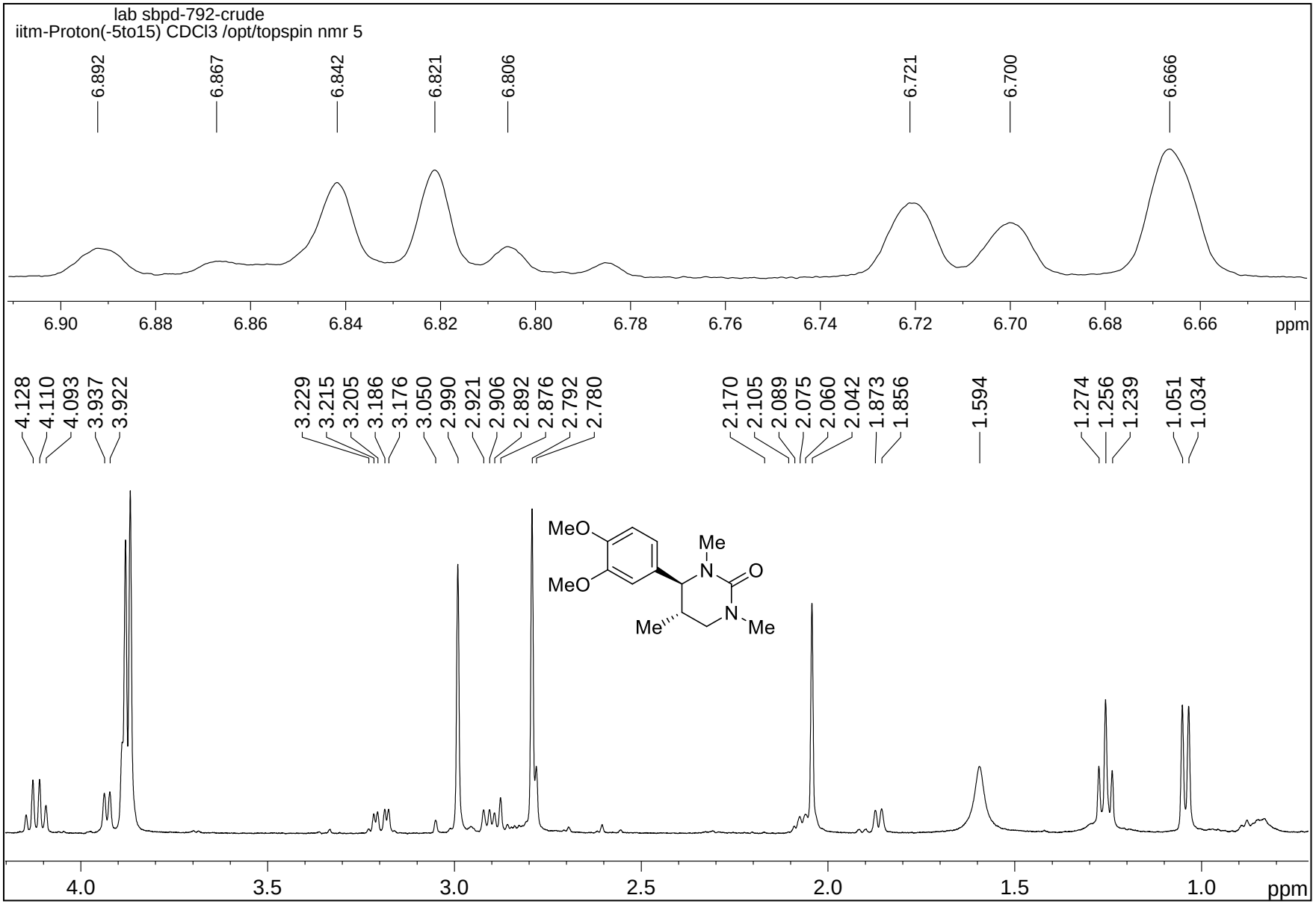


Figure 63 Expanded ^{1}H NMR spectrum of crude compound 15a

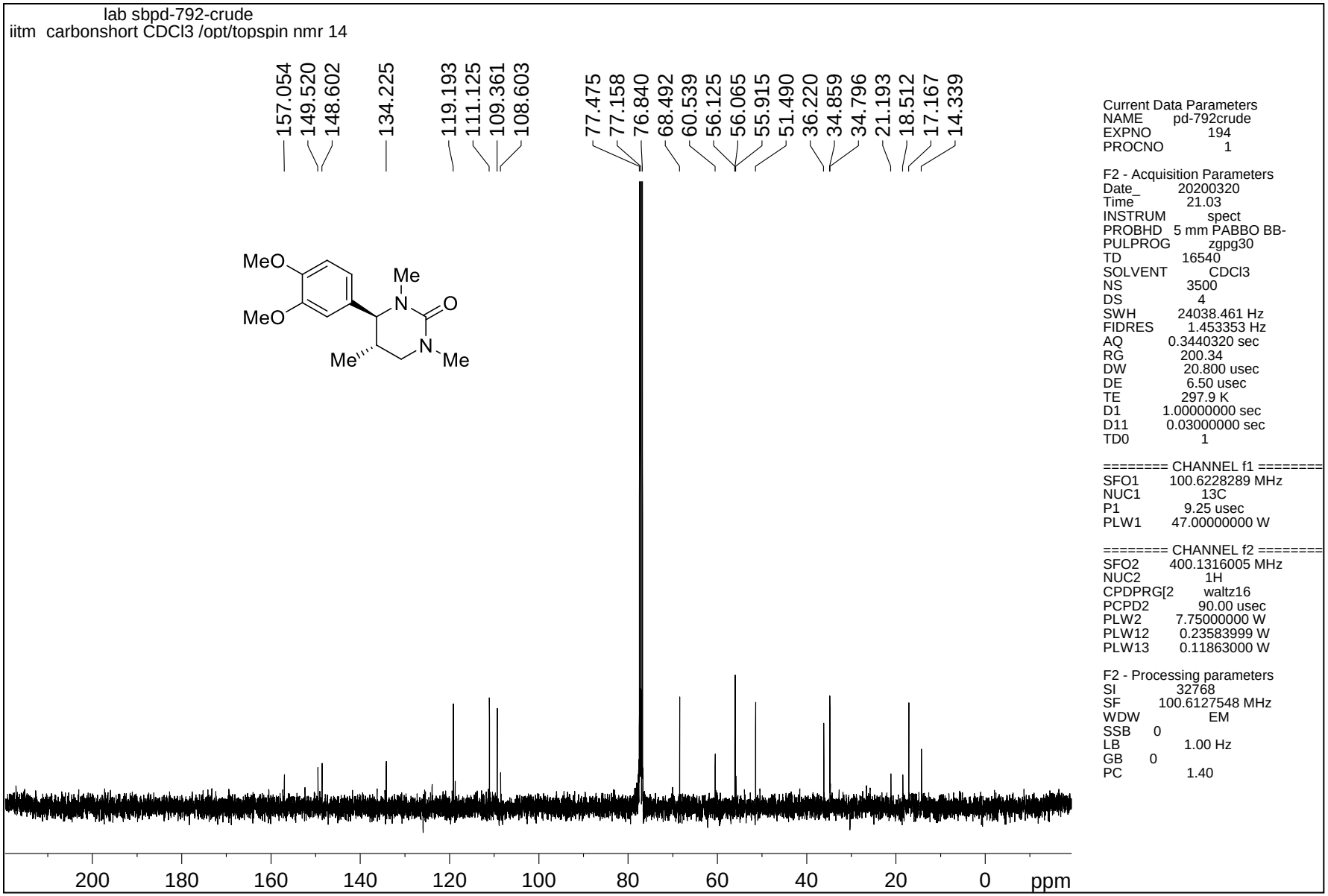


Figure 64 ^{13}C NMR spectrum of crude compound 15a

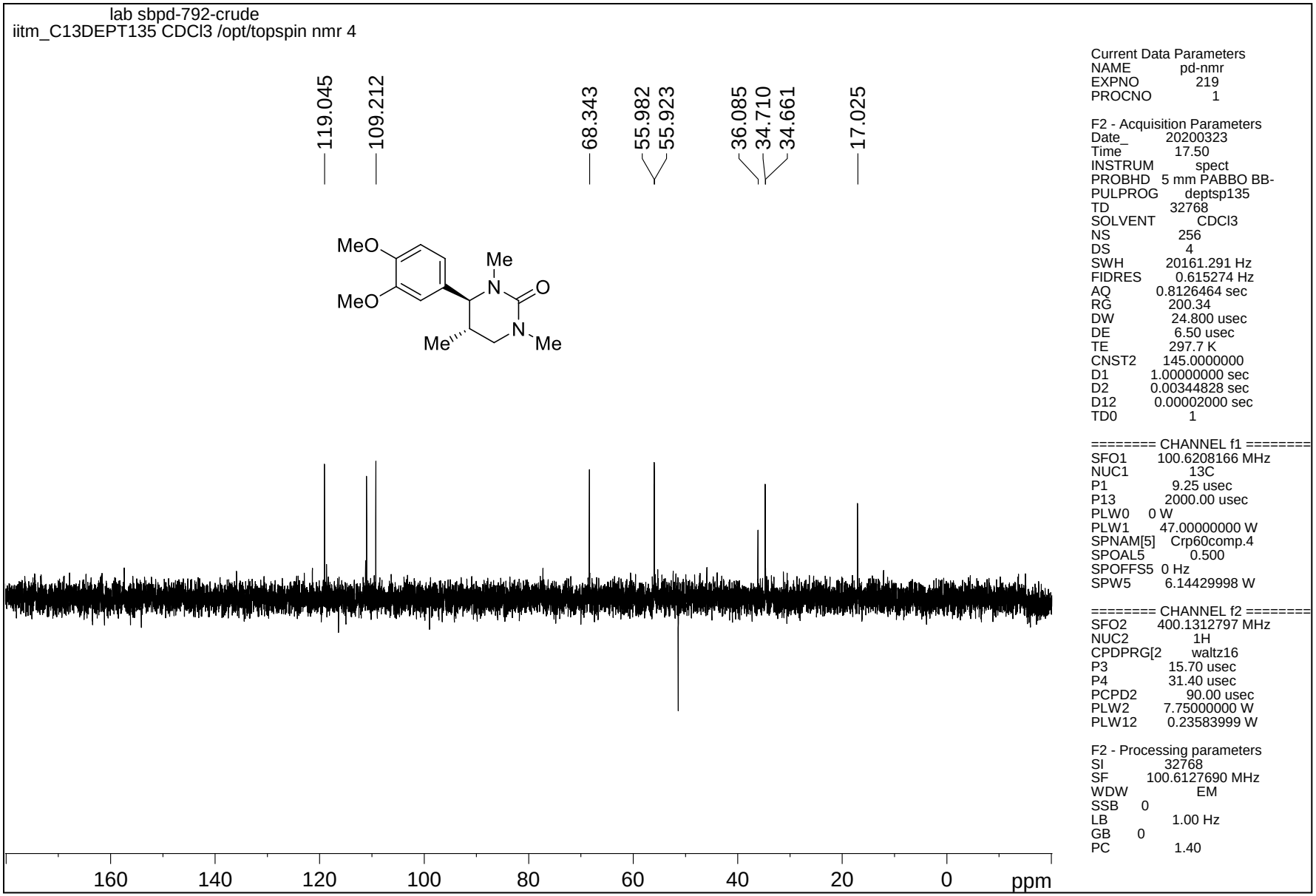


Figure 65 DEPT-135 NMR spectrum of crude compound 15a

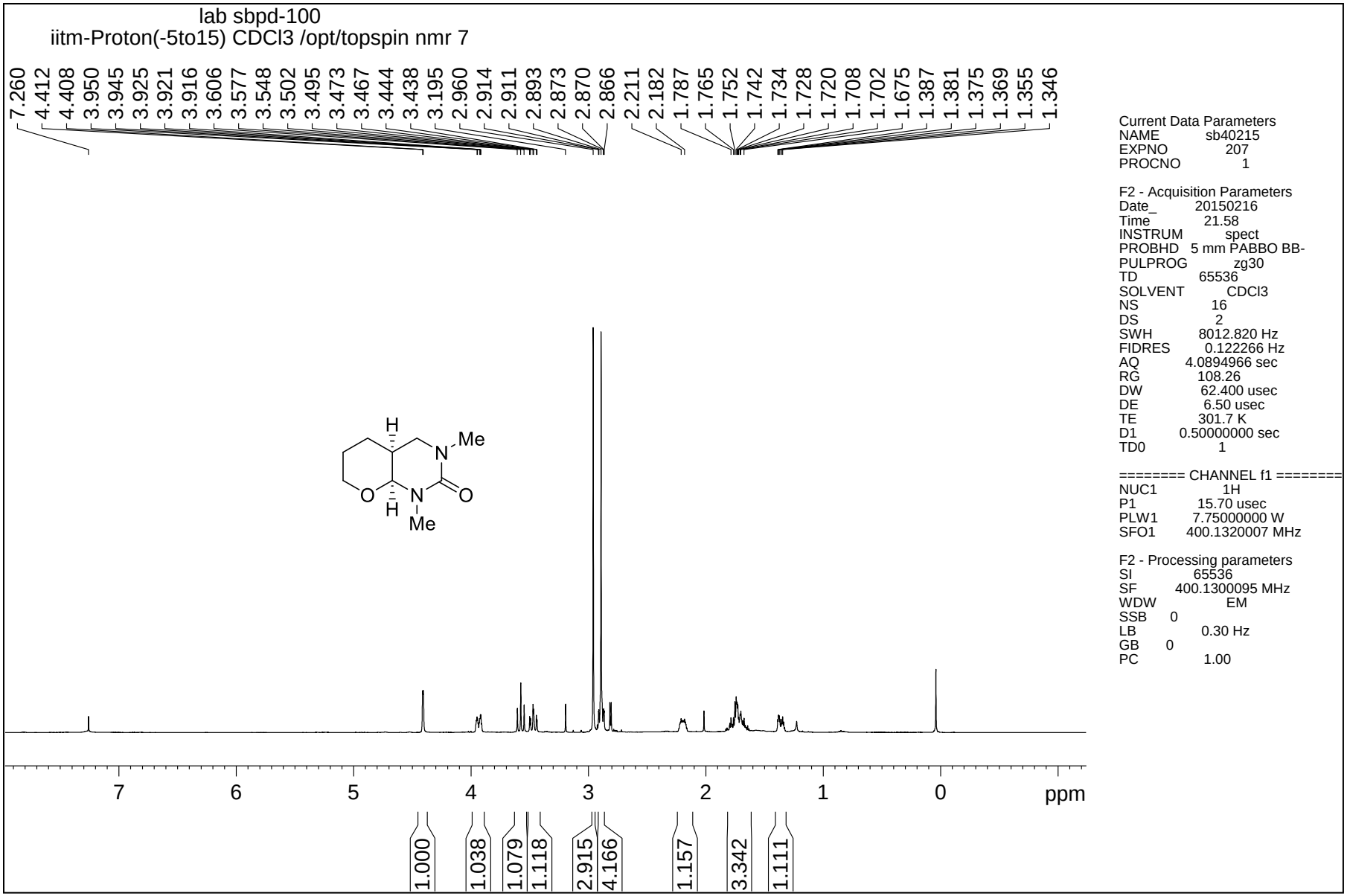


Figure 66 ^{1}H NMR spectrum of compound 21a

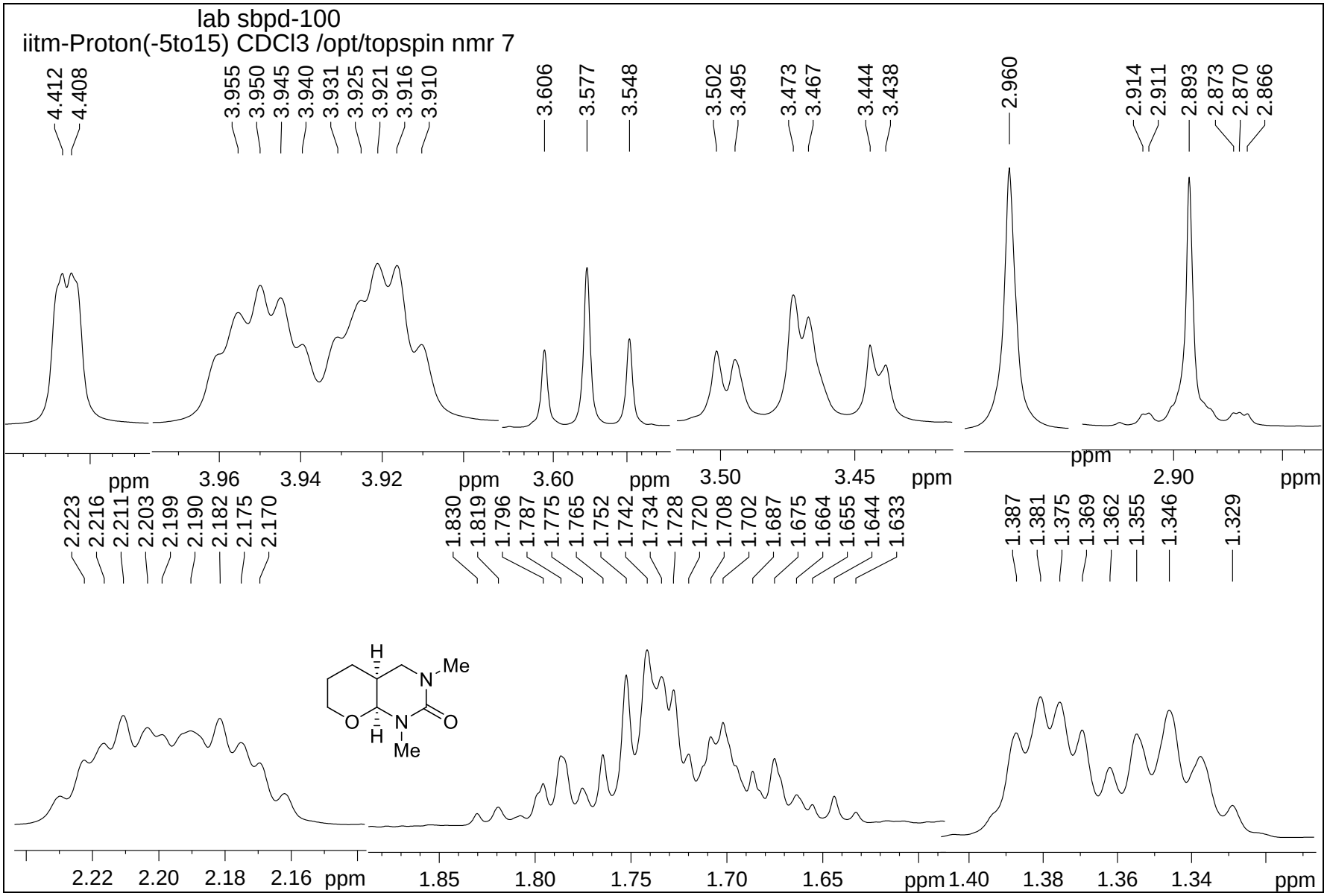


Figure 67 Expanded ^{1}H NMR spectrum of compound 21a

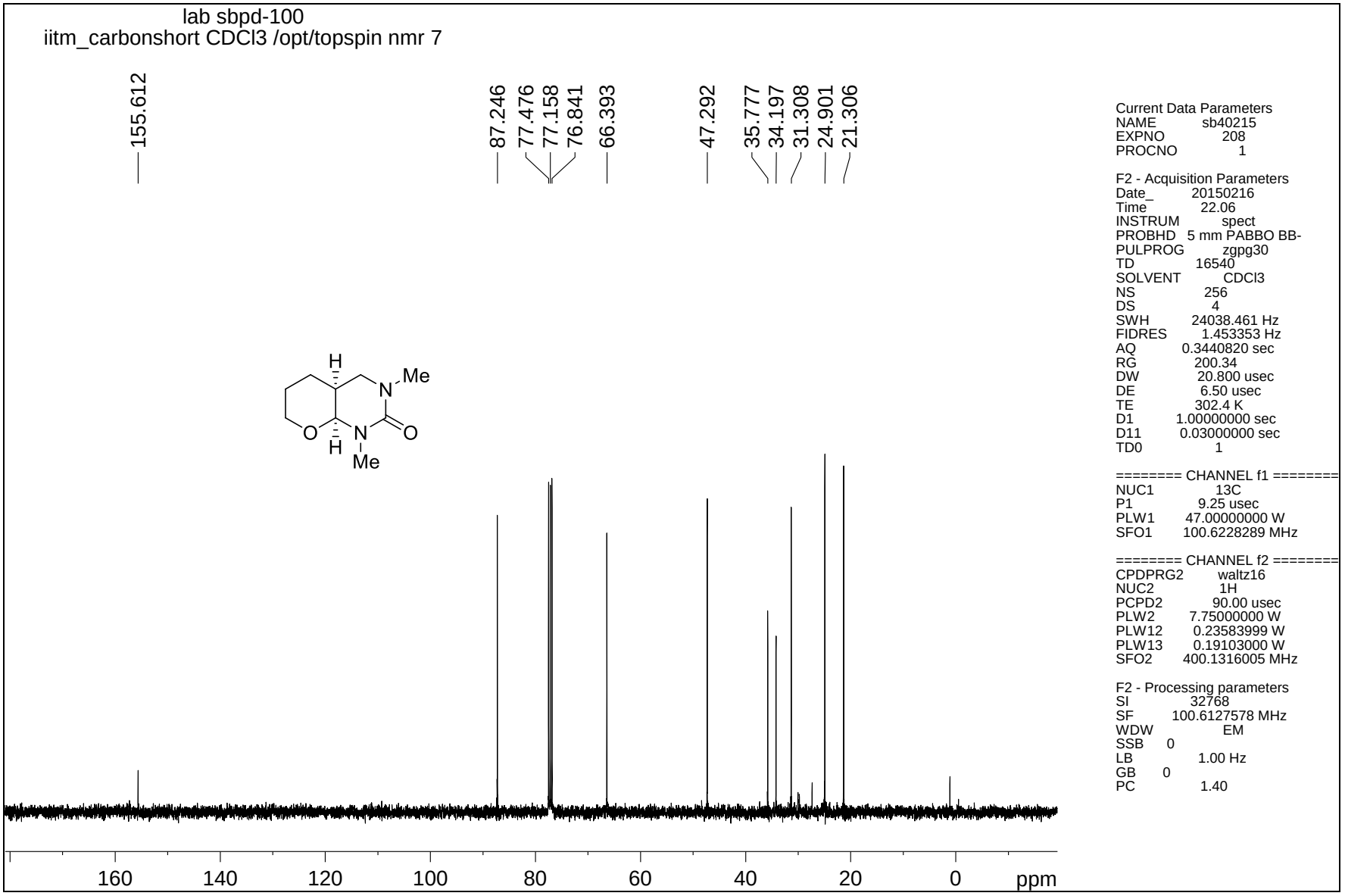


Figure 68 ^{13}C NMR spectrum of compound 21a

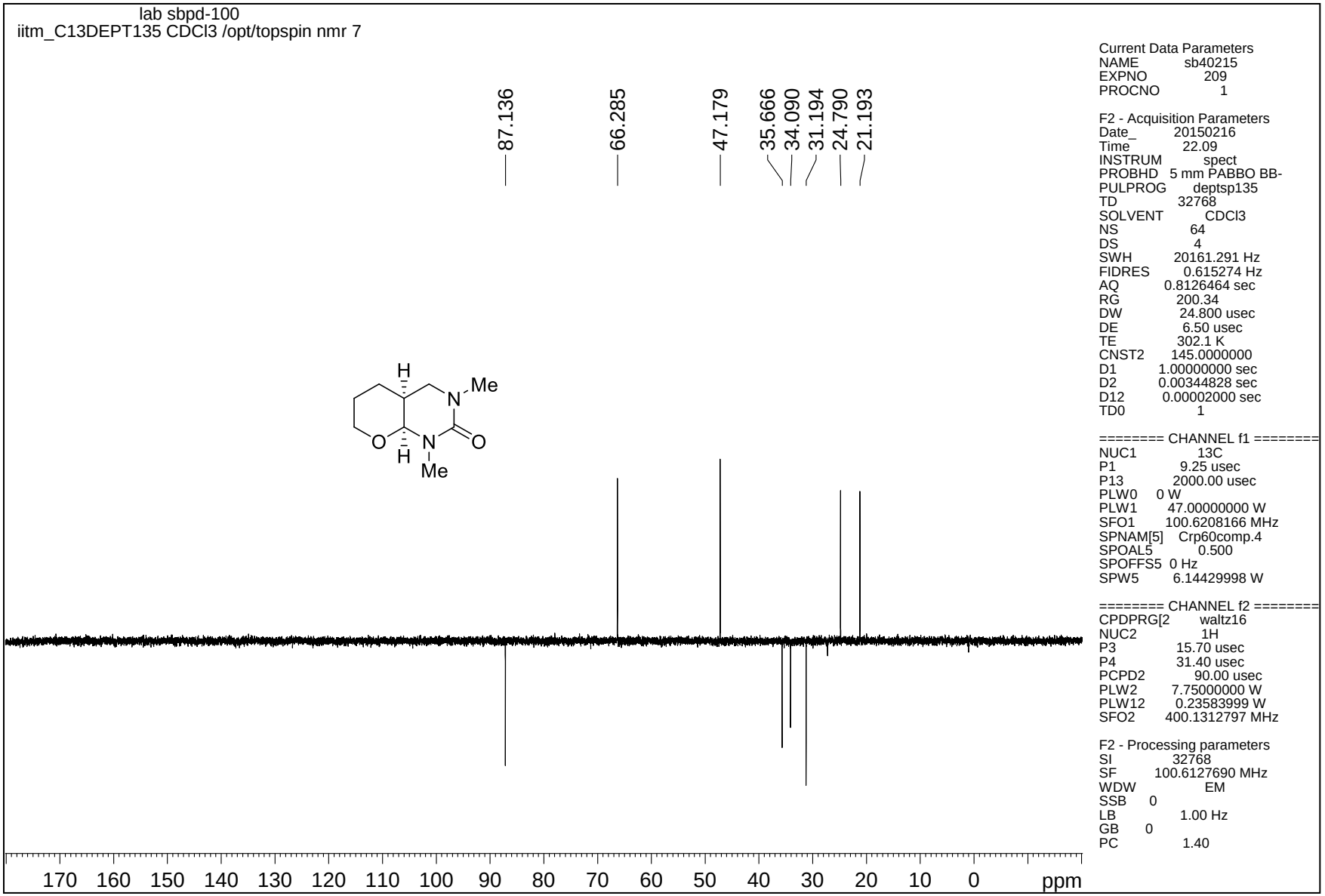


Figure 69 DEPT-135 NMR spectrum of compound 21a

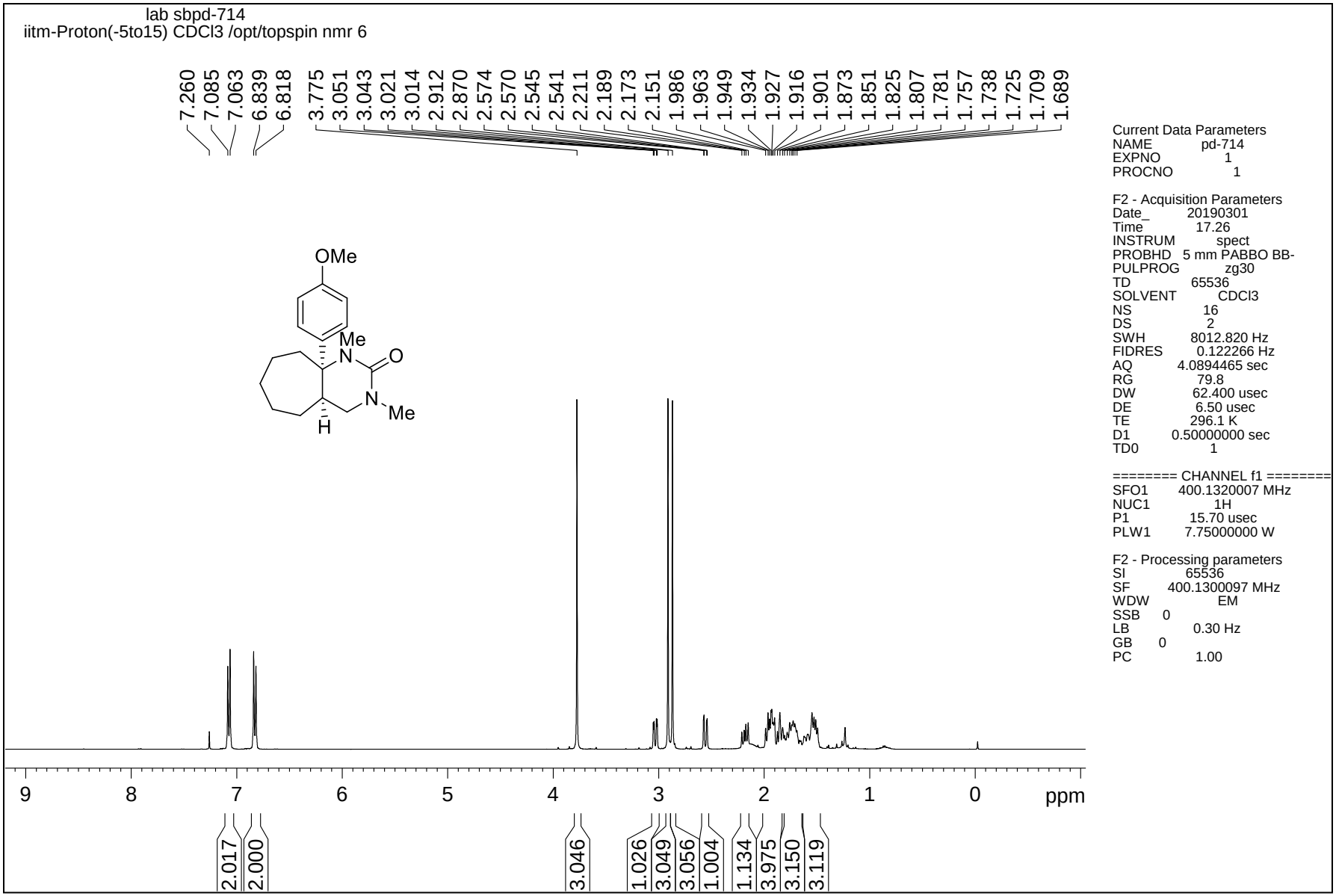


Figure 70 ^{1}H NMR spectrum of compound 22a

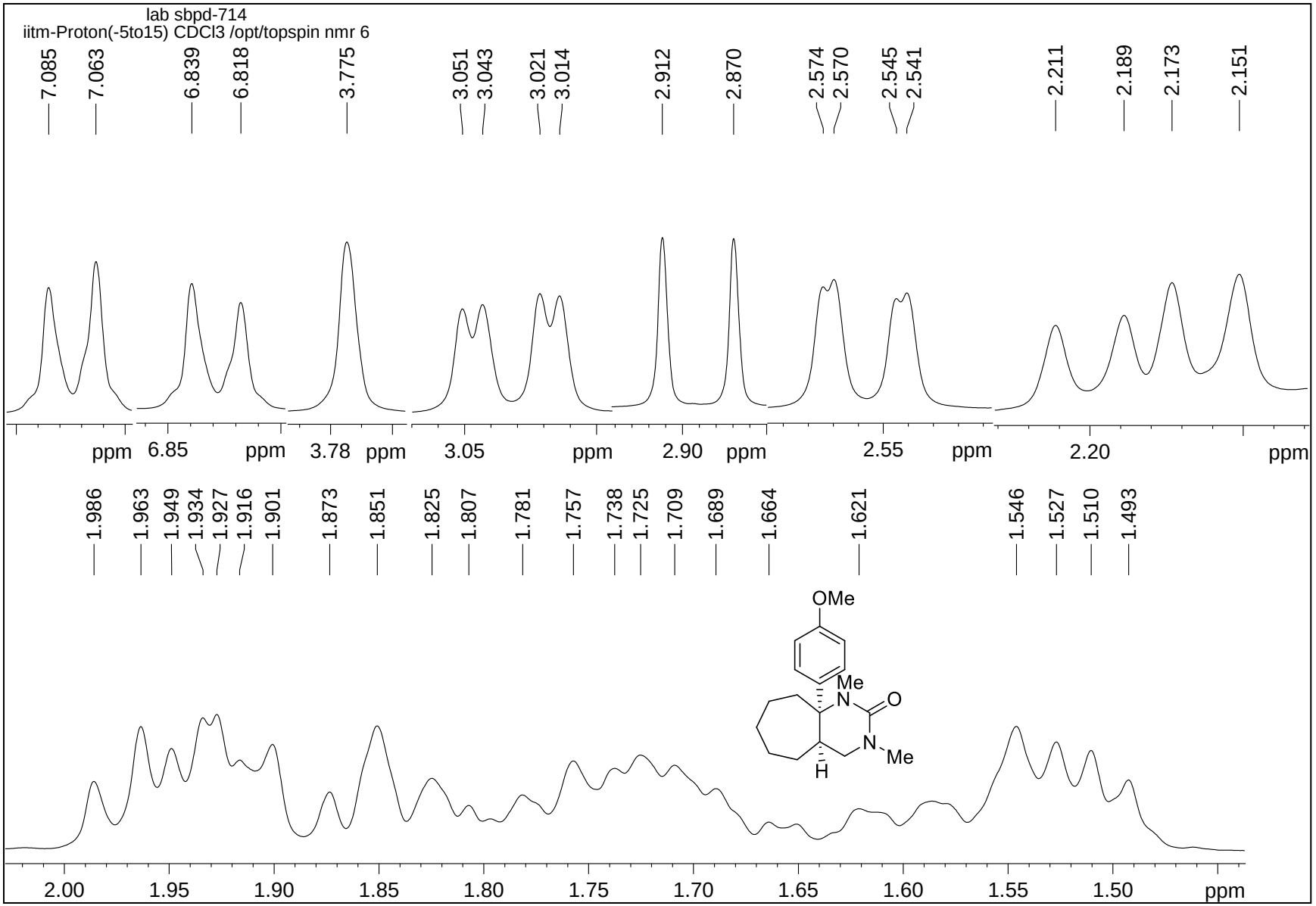


Figure 71 Expanded ^{1}H NMR spectrum of compound 22a

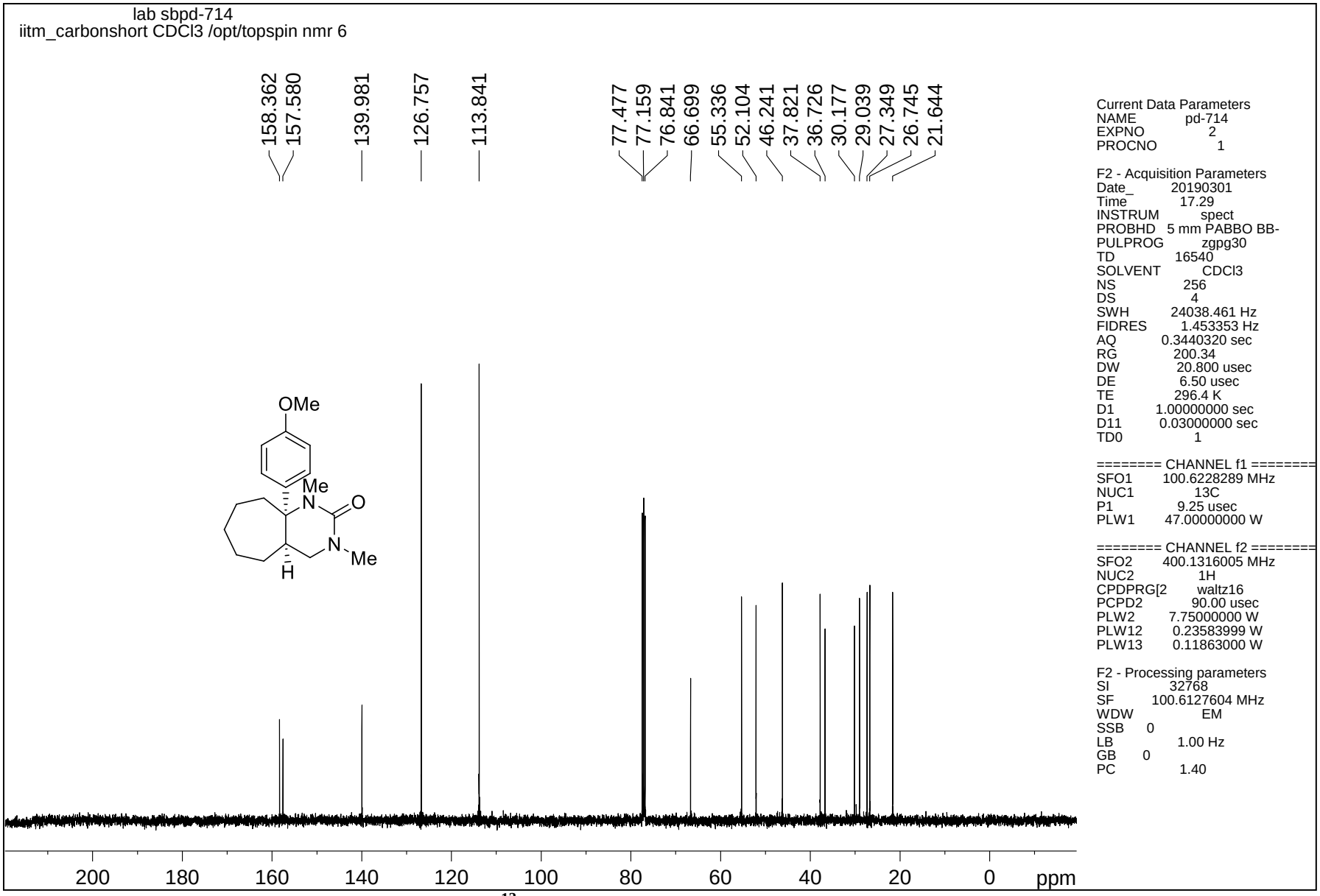


Figure 72 ^{13}C NMR spectrum of compound 22a

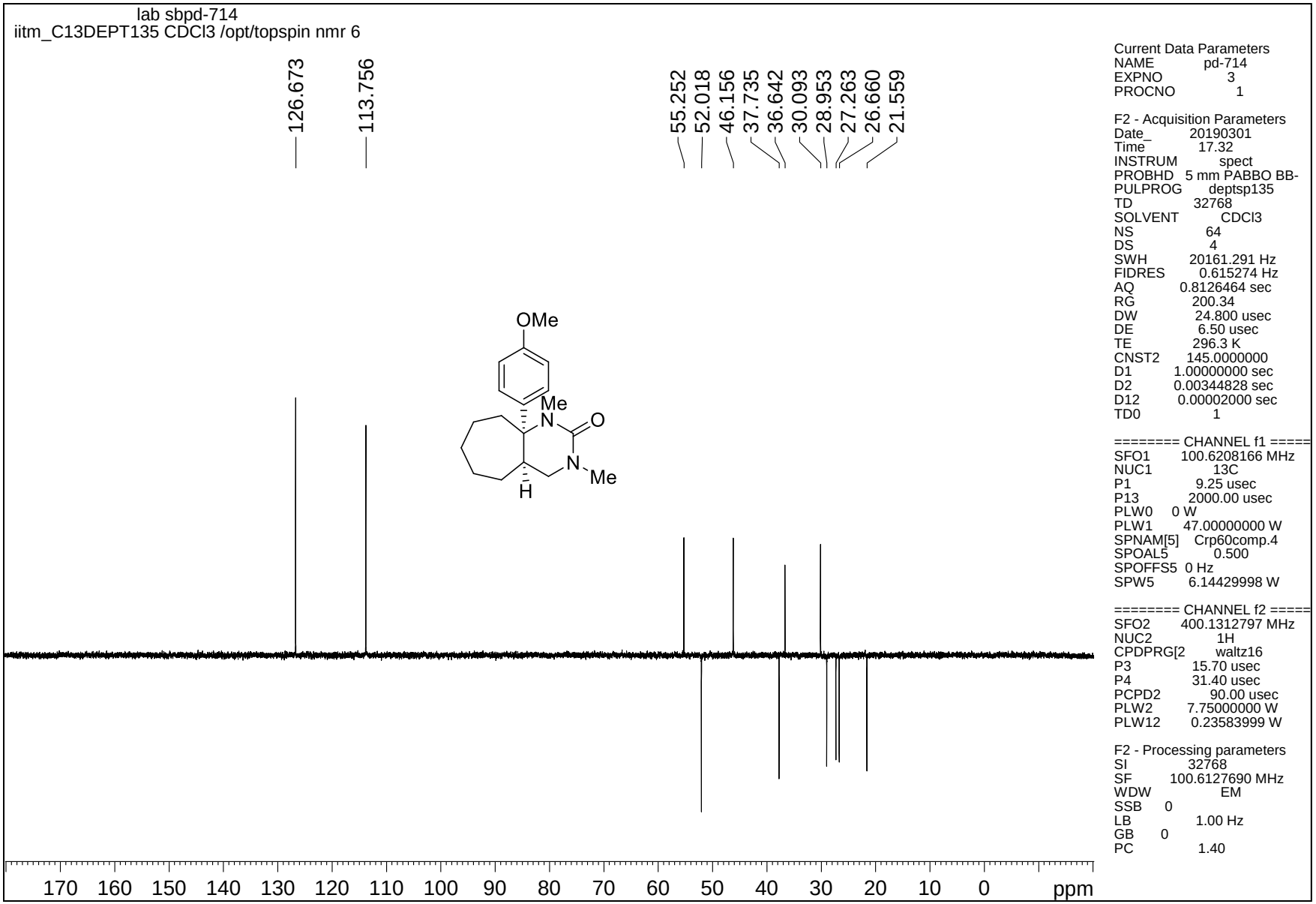


Figure 73 DEPT-135 NMR spectrum of compound 22a

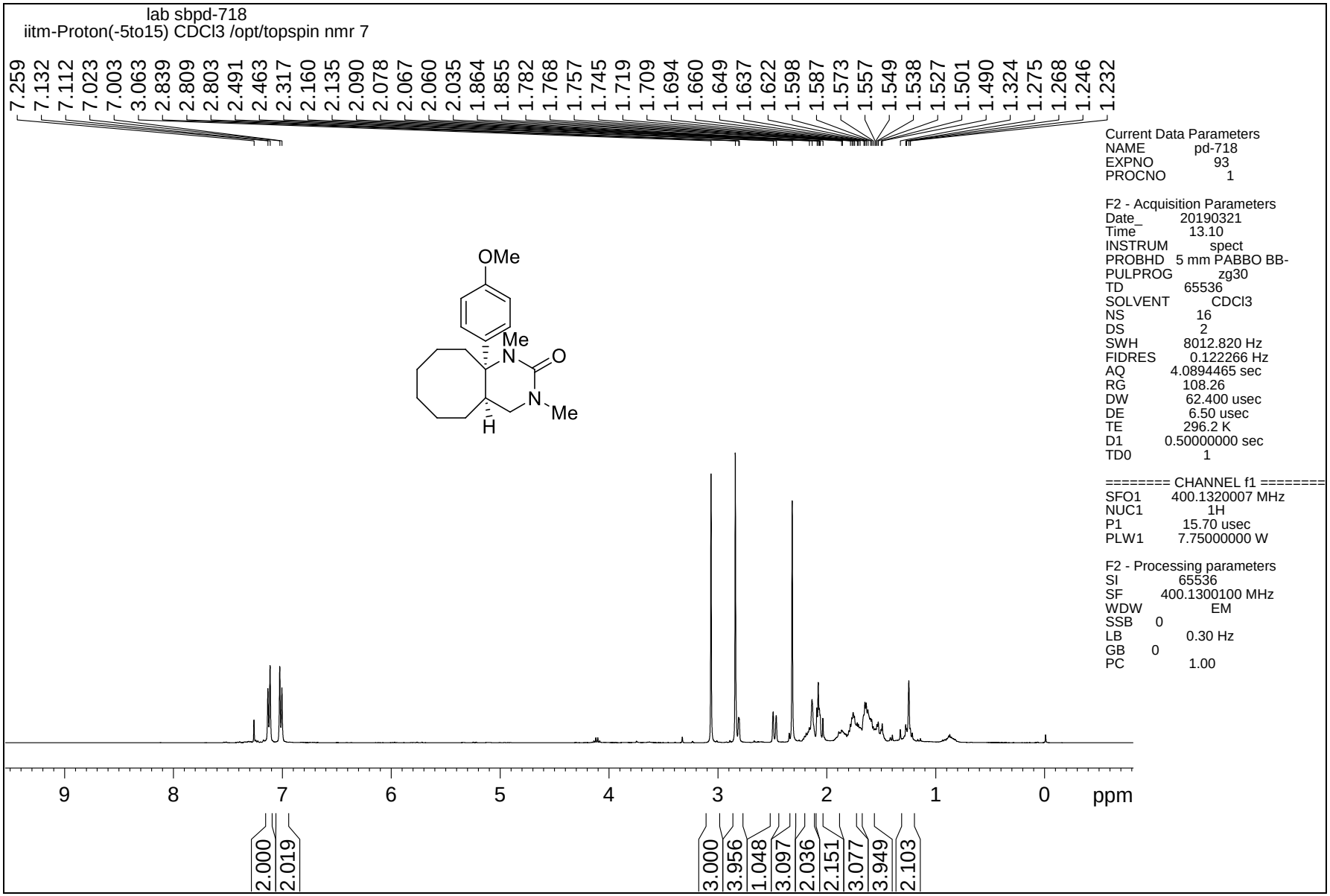


Figure 74 ^{1}H NMR spectrum of compound 23a

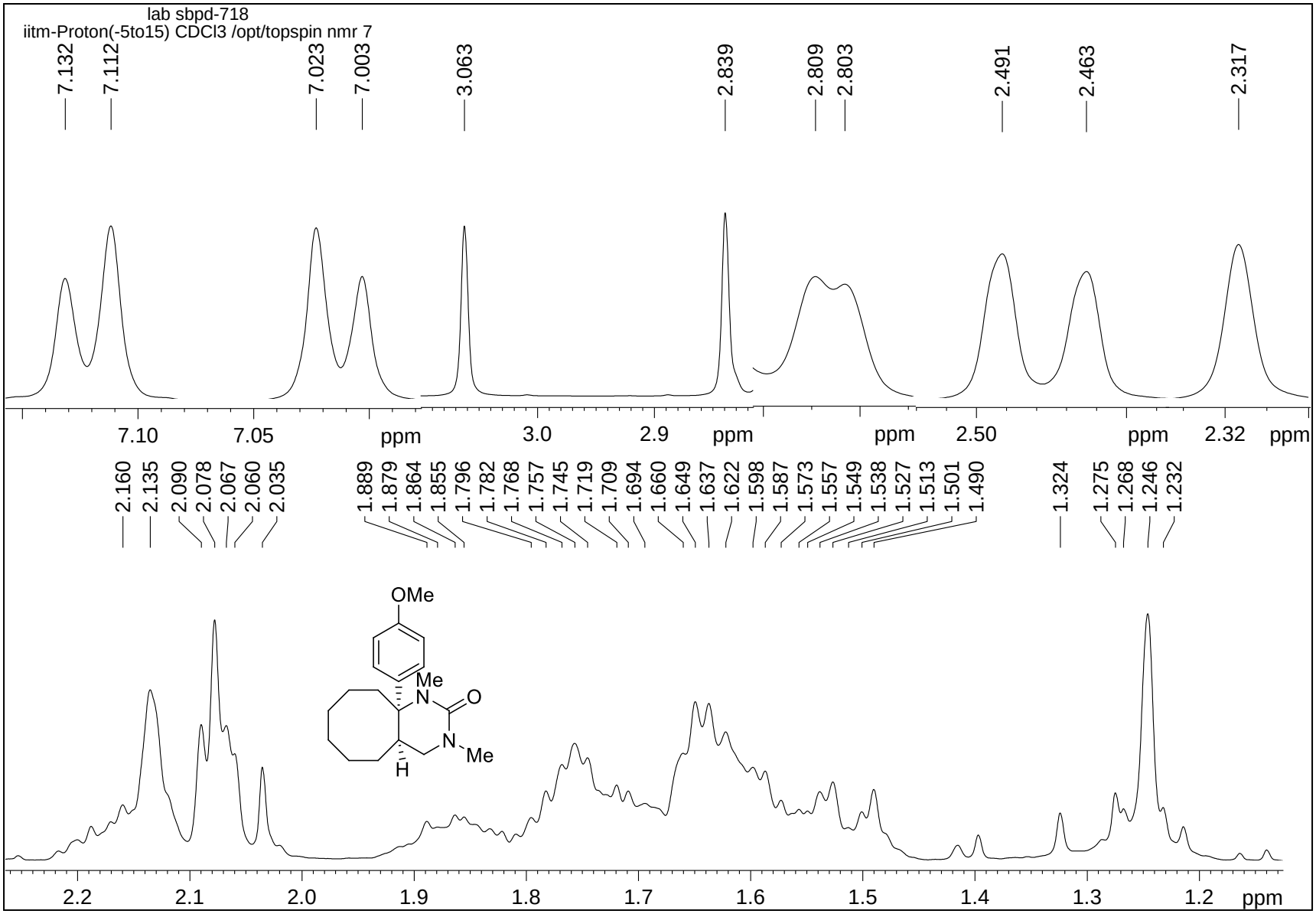


Figure 75 Expanded ^{1}H NMR spectrum of compound 23a

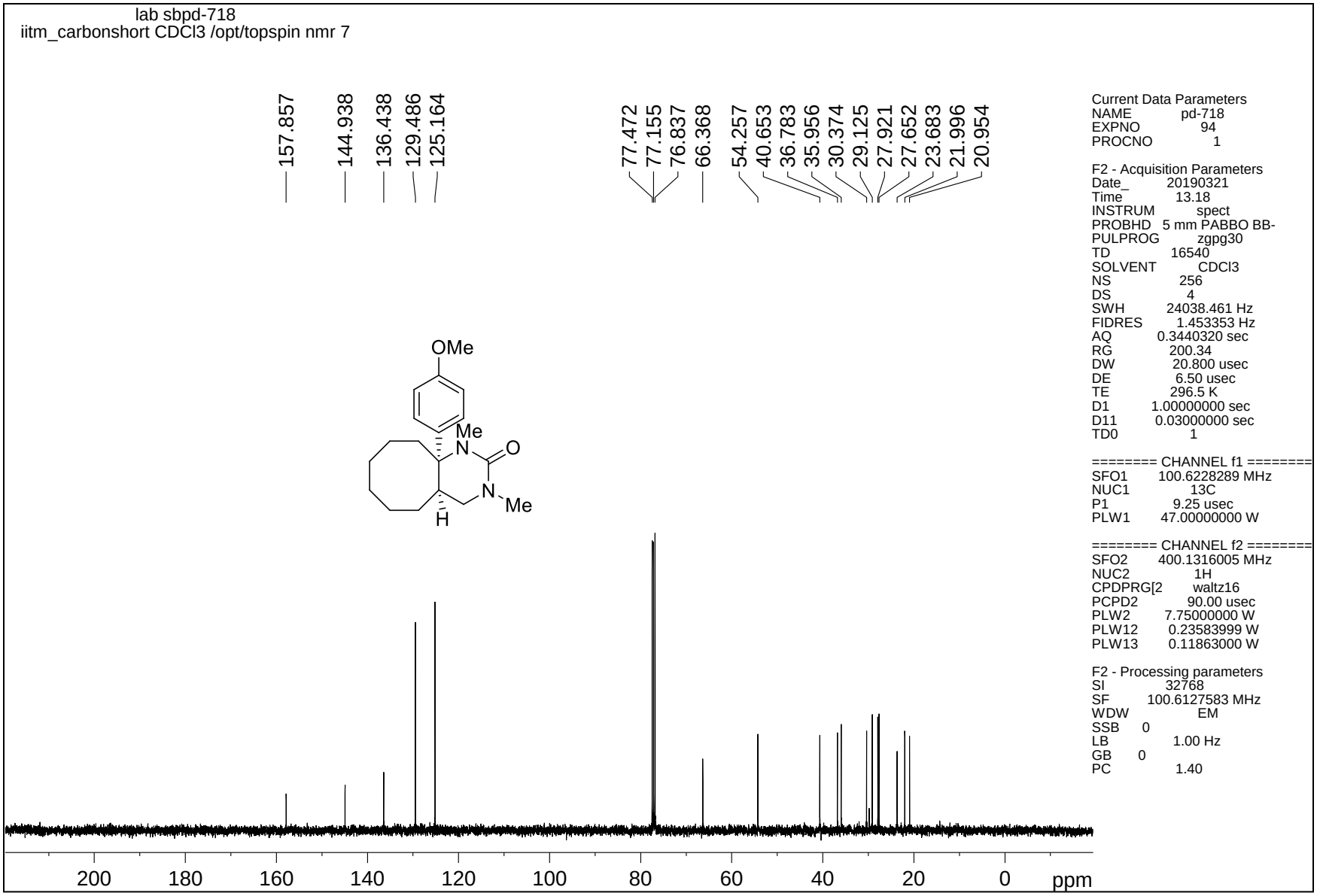


Figure 76 ^{13}C NMR spectrum of compound 23a

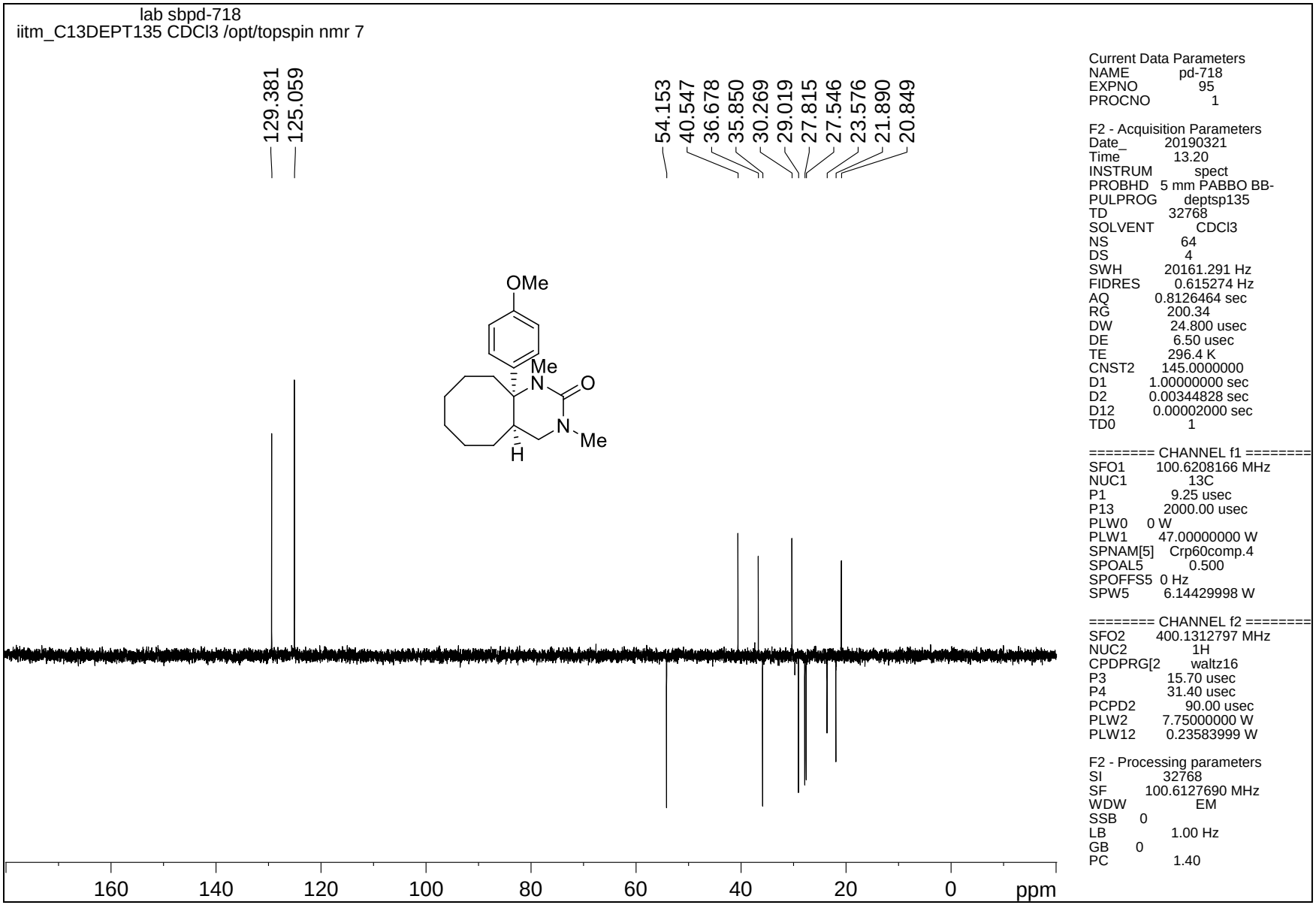


Figure 77 DEPT-135 NMR spectrum of compound 23a

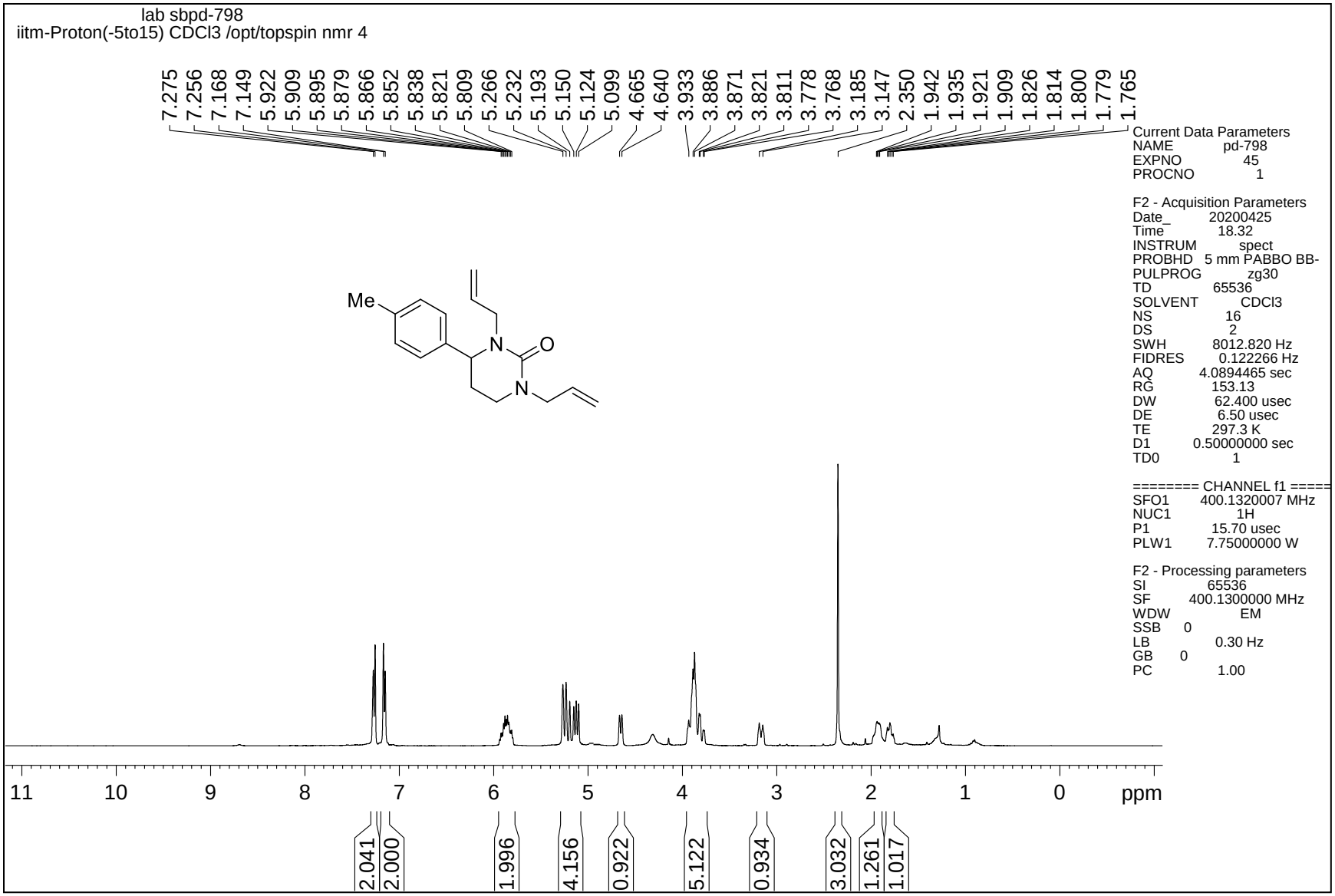


Figure 78 ^{1}H NMR spectrum of compound 24

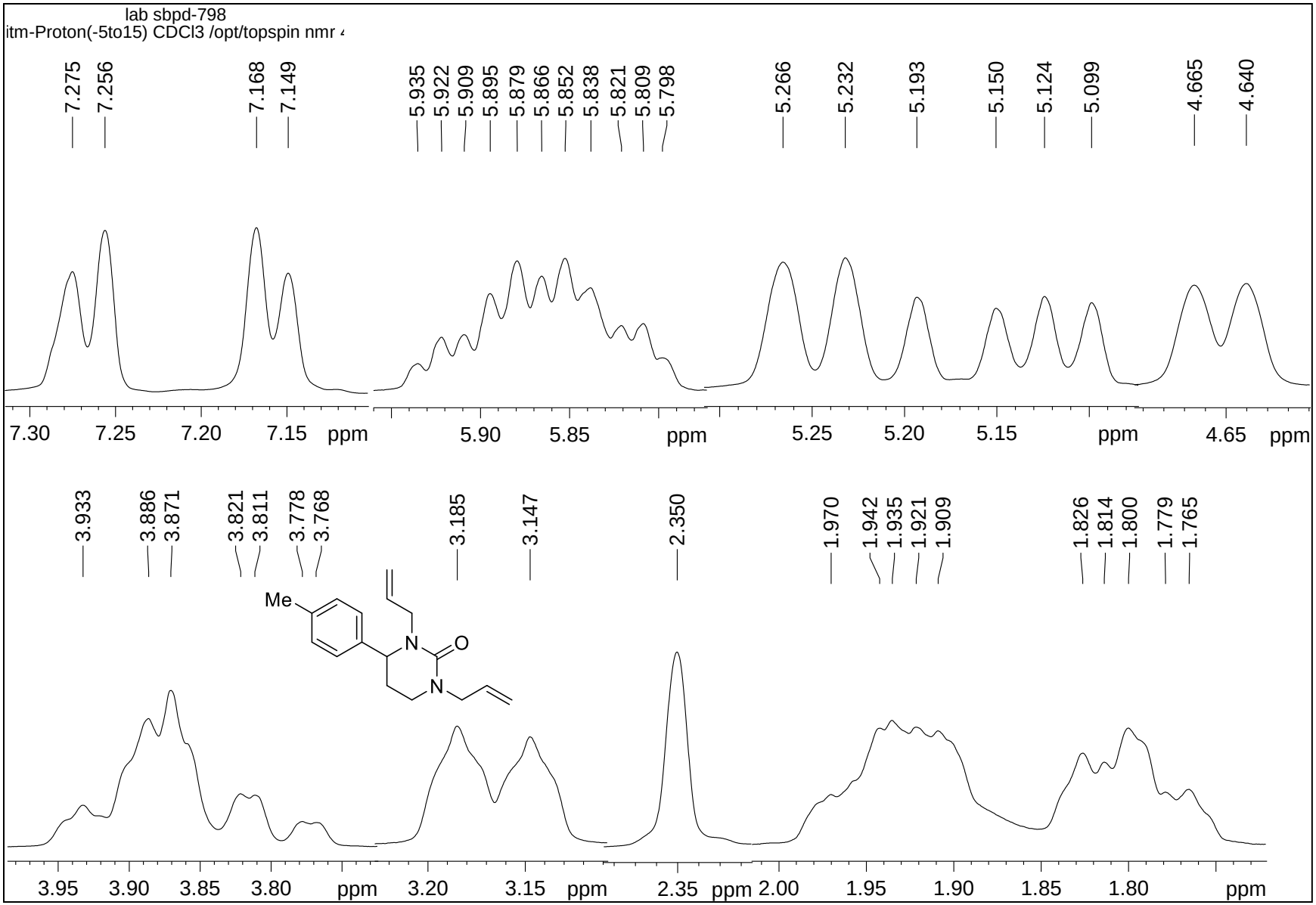


Figure 79 Expanded ^{1}H NMR spectrum of compound 24

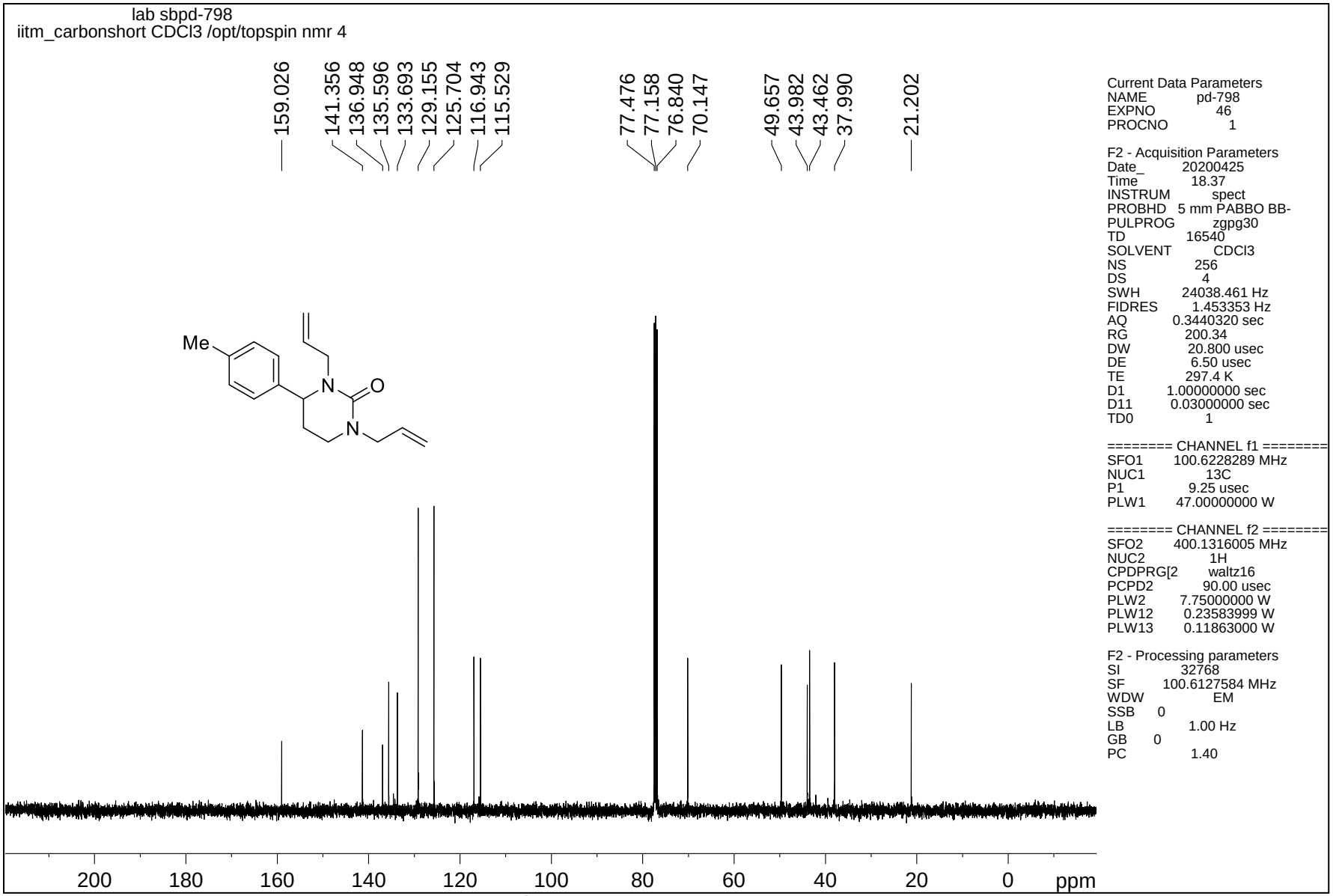


Figure 80 ^{13}C NMR spectrum of compound 24

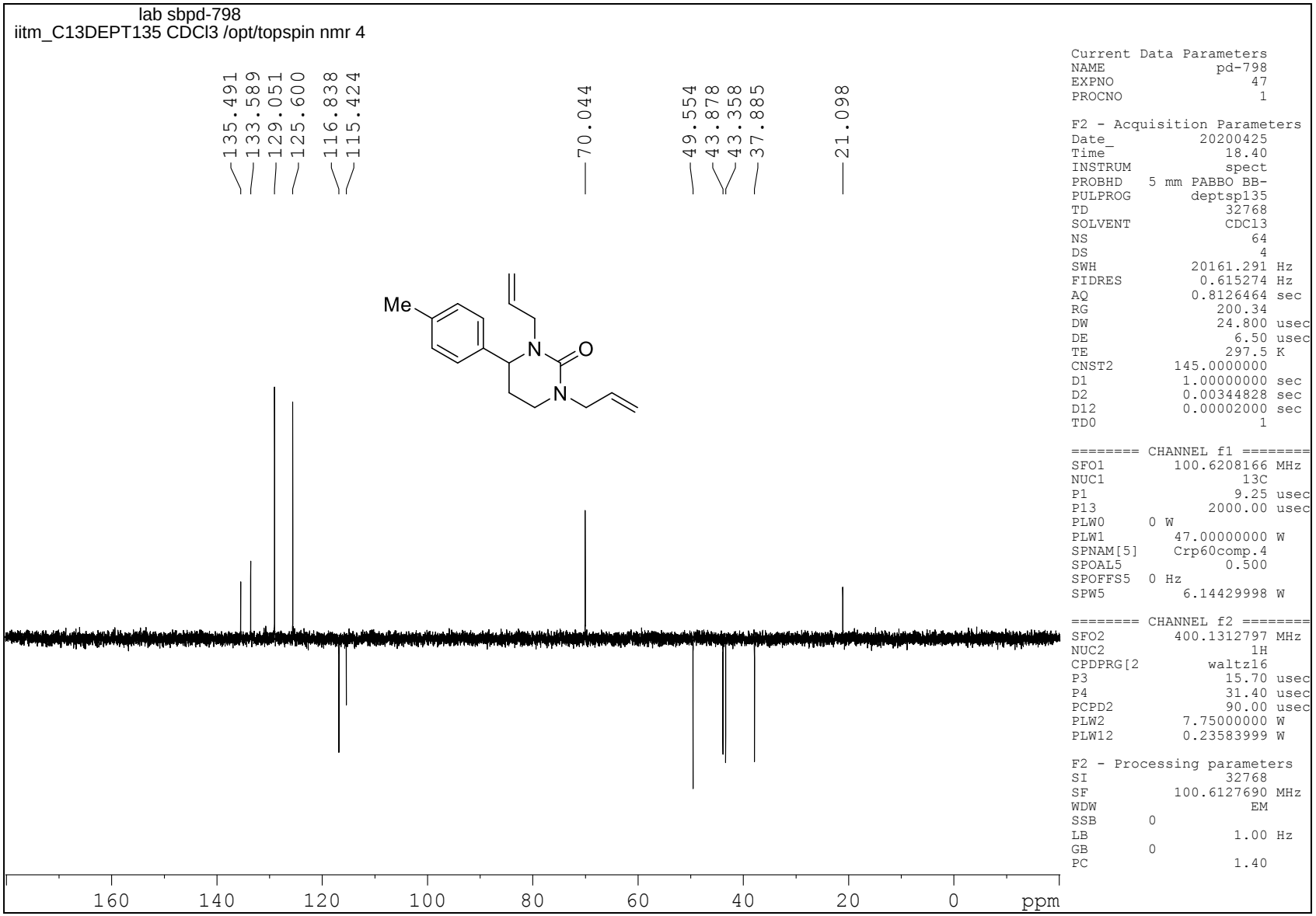


Figure 81 DEPT-135 NMR spectrum of compound 24

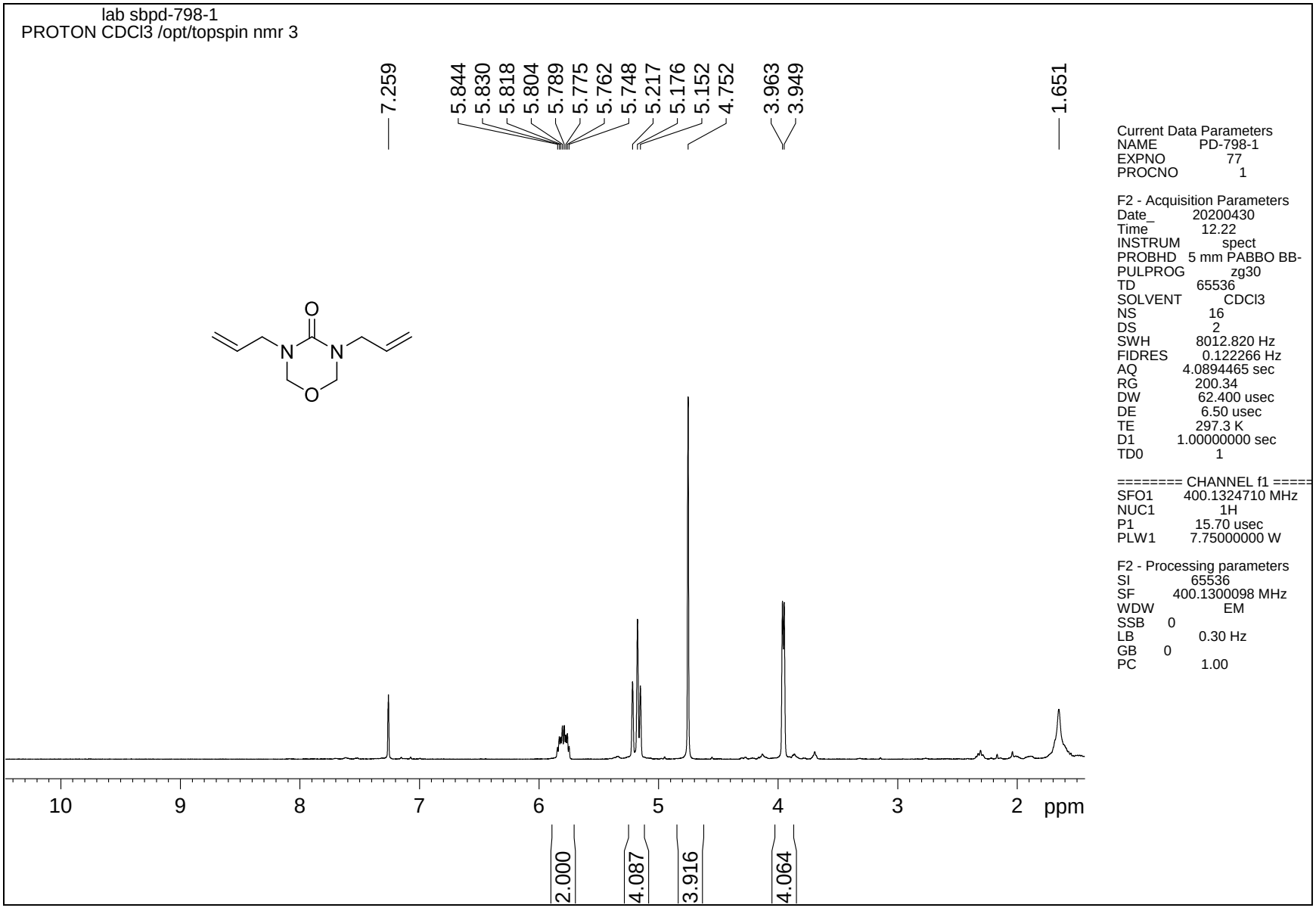


Figure 82 ^{1}H NMR spectrum of compound 25

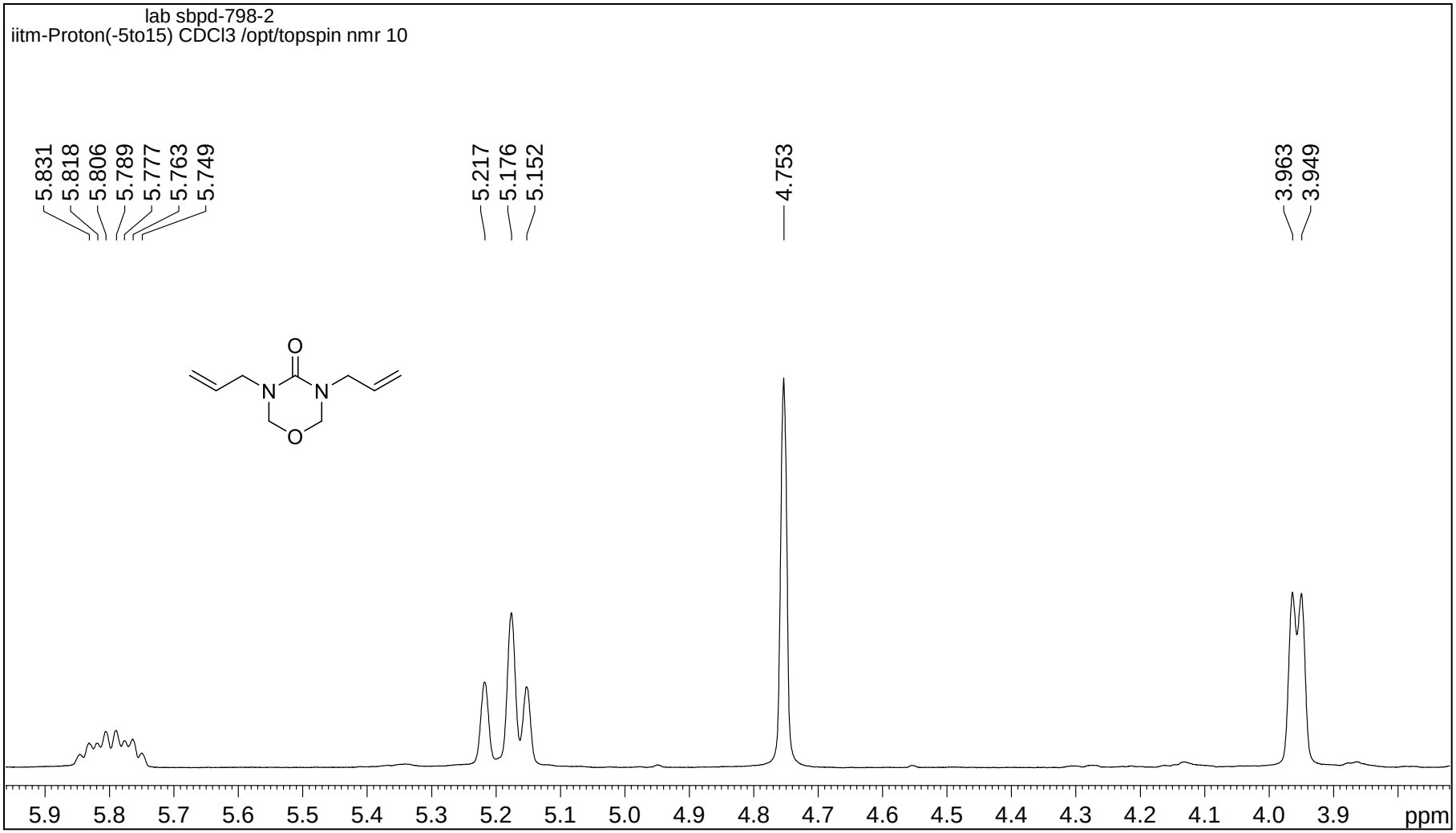


Figure 83 Expanded ^{1}H NMR spectrum of compound 25

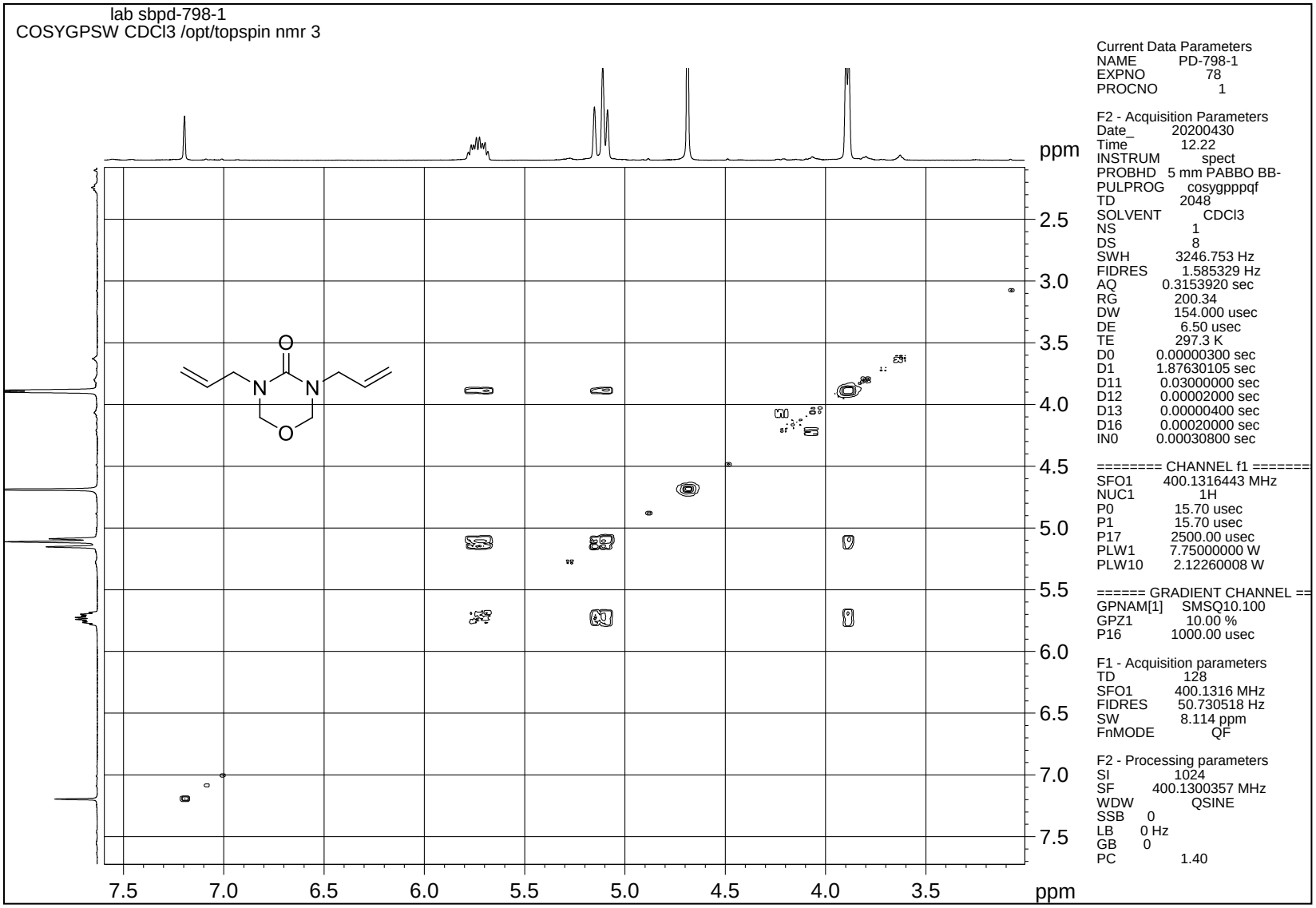


Figure 84 ^{1}H-^{1}H COSY NMR spectrum of compound 25

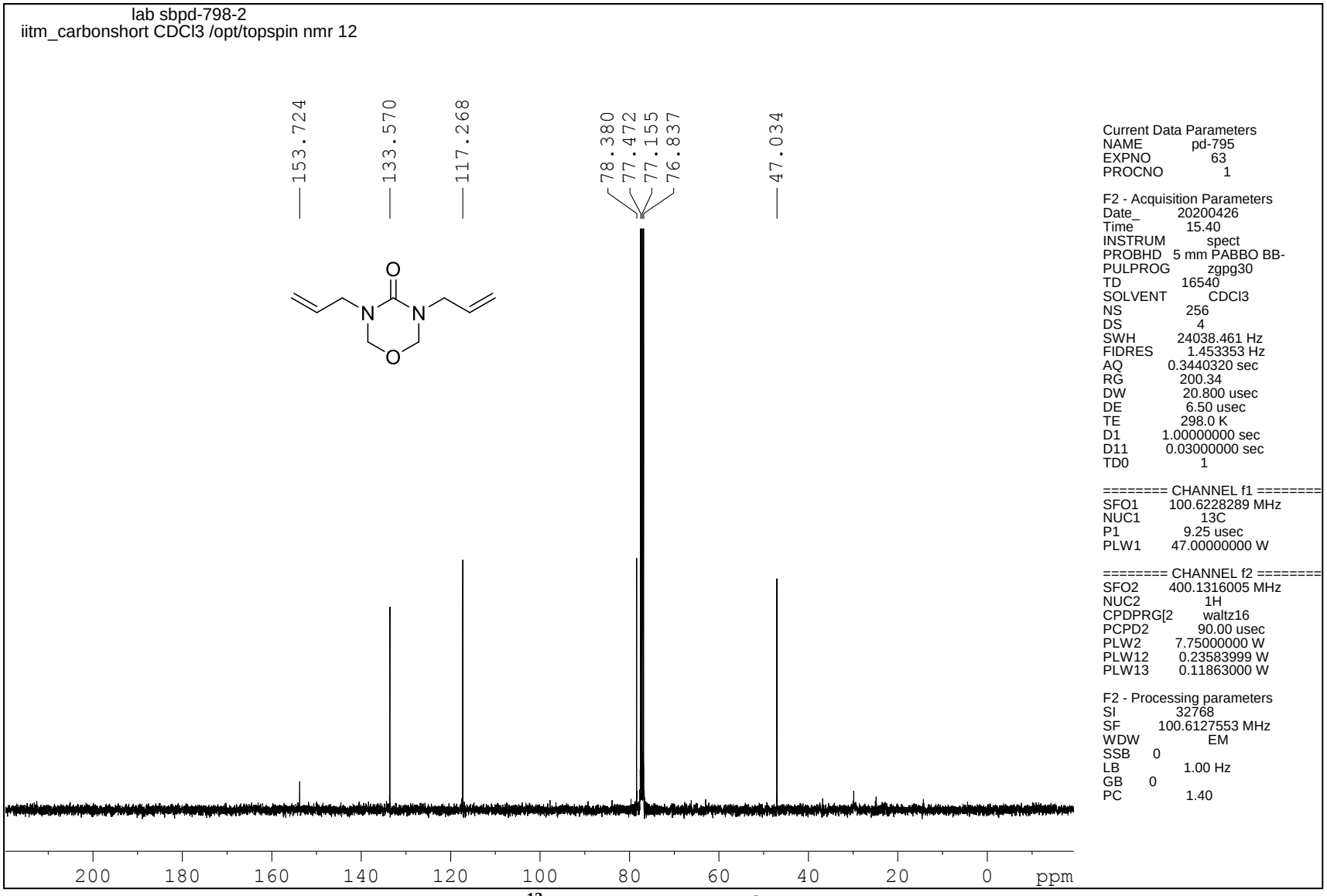


Figure 85 ^{13}C NMR spectrum of compound 25

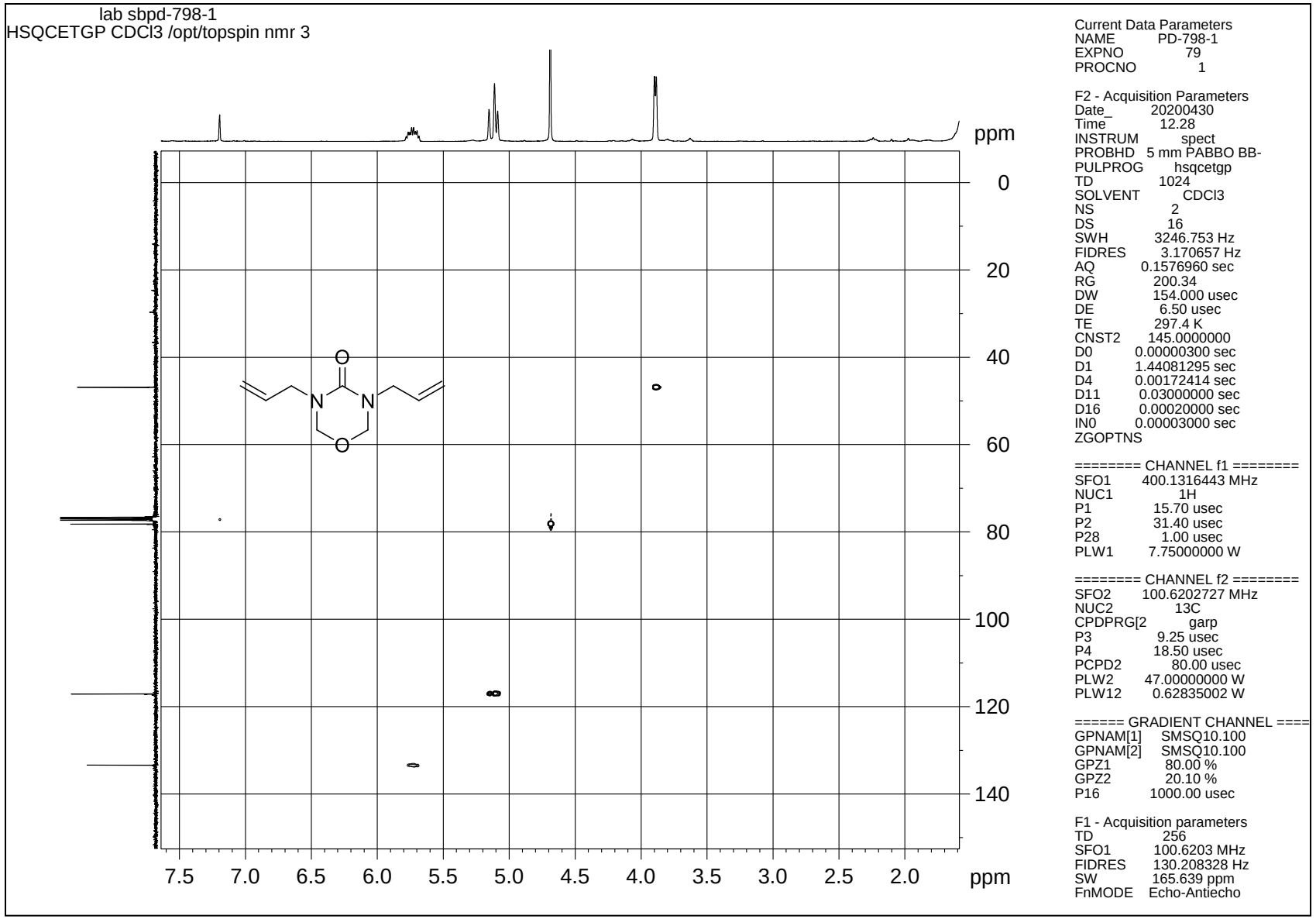


Figure 86 ^{1}H-^{13}C HSQC NMR spectrum of compound 25

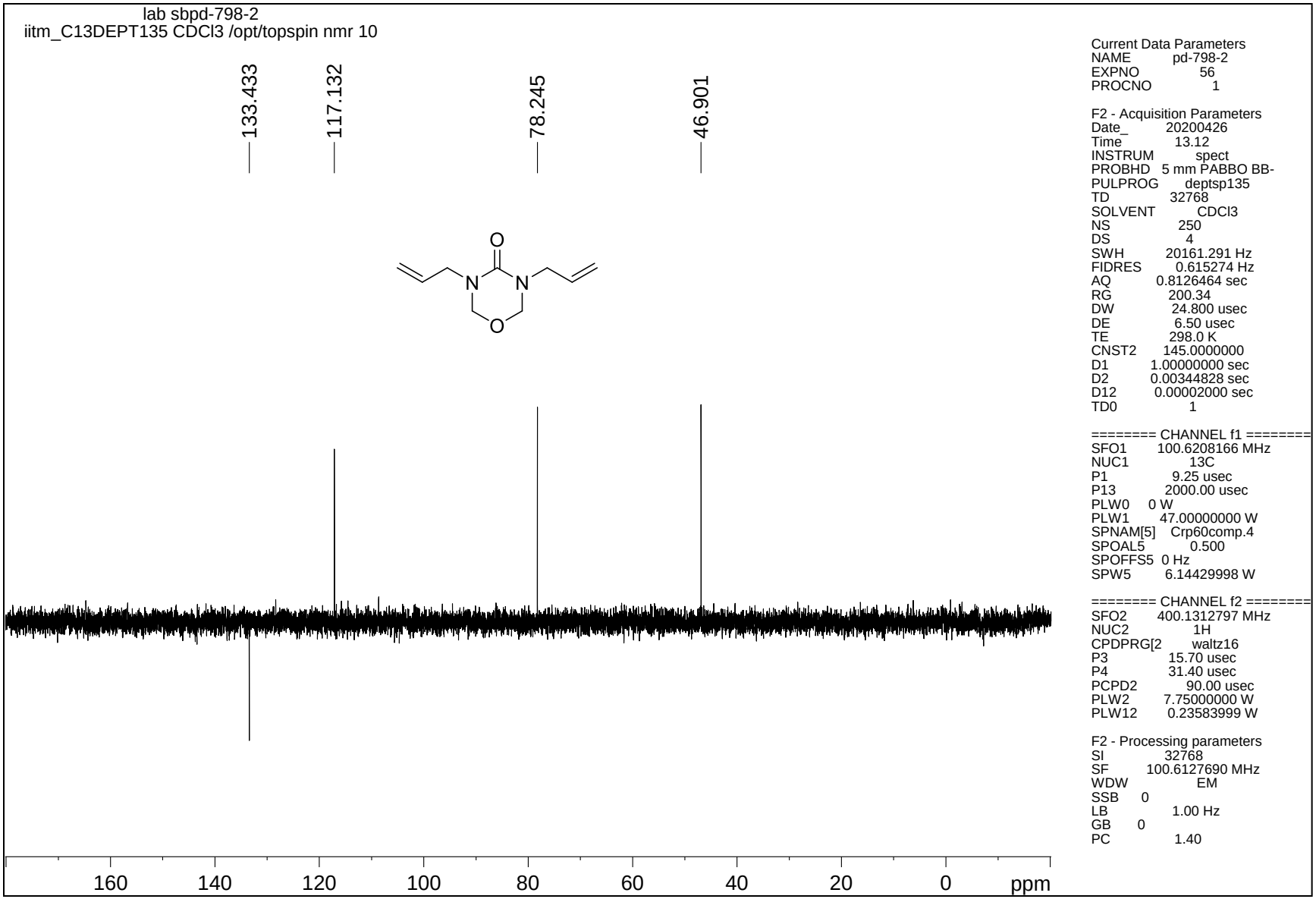


Figure 87 DEPT-135 NMR spectrum of compound 25

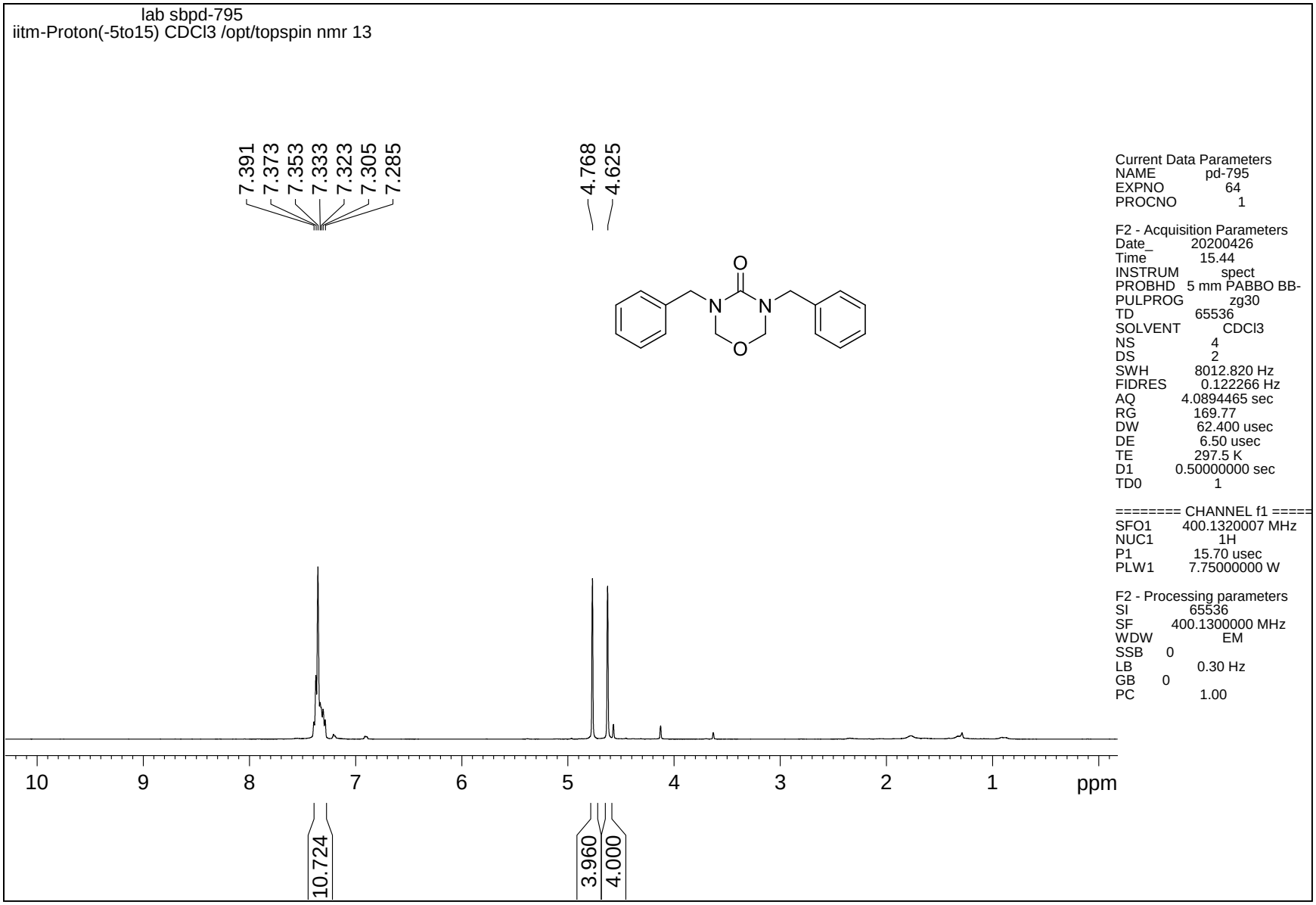


Figure 88 ^{1}H NMR spectrum of compound 27

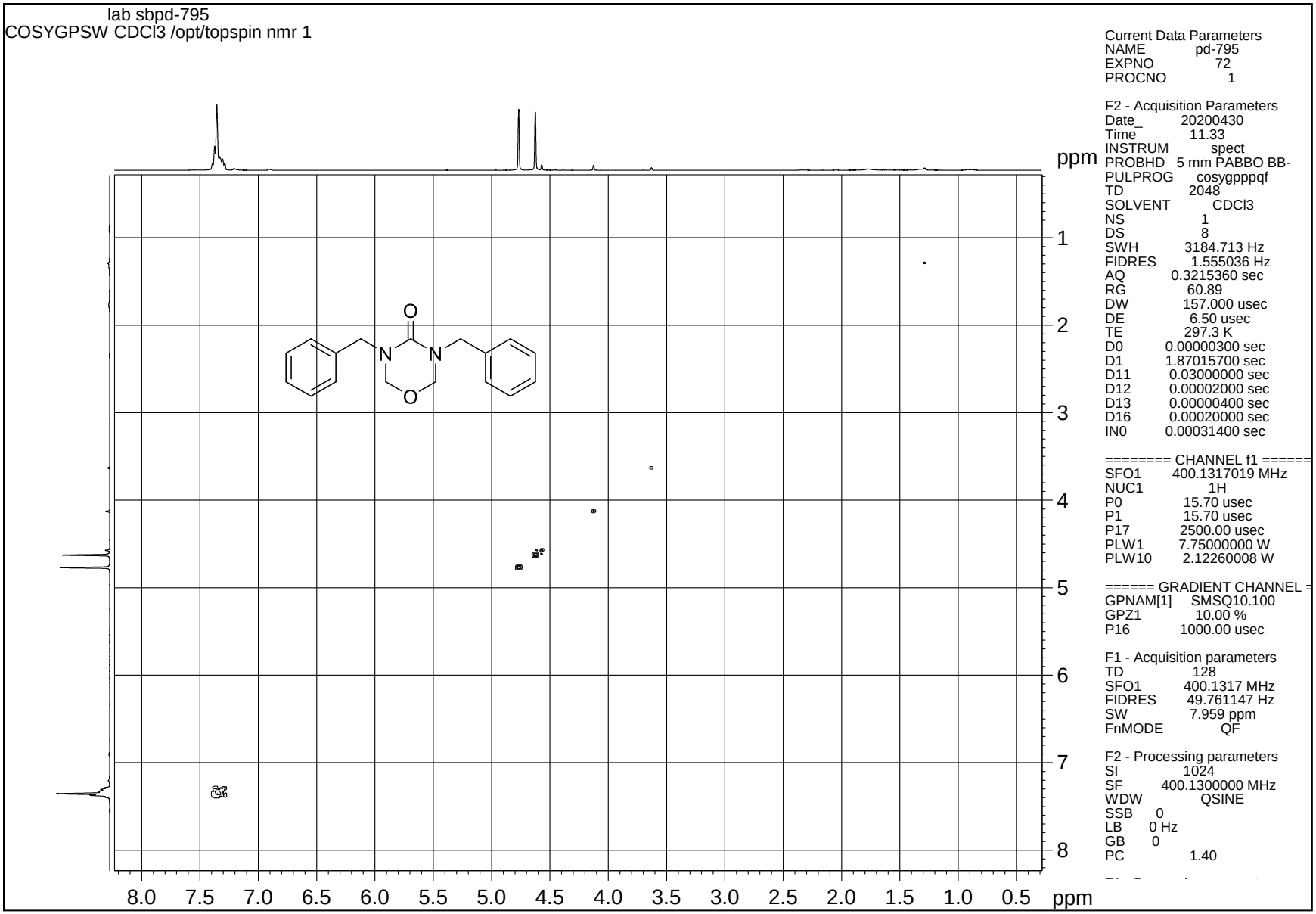


Figure 89 ^{1}H-^{1}H COSY NMR spectrum of compound 27

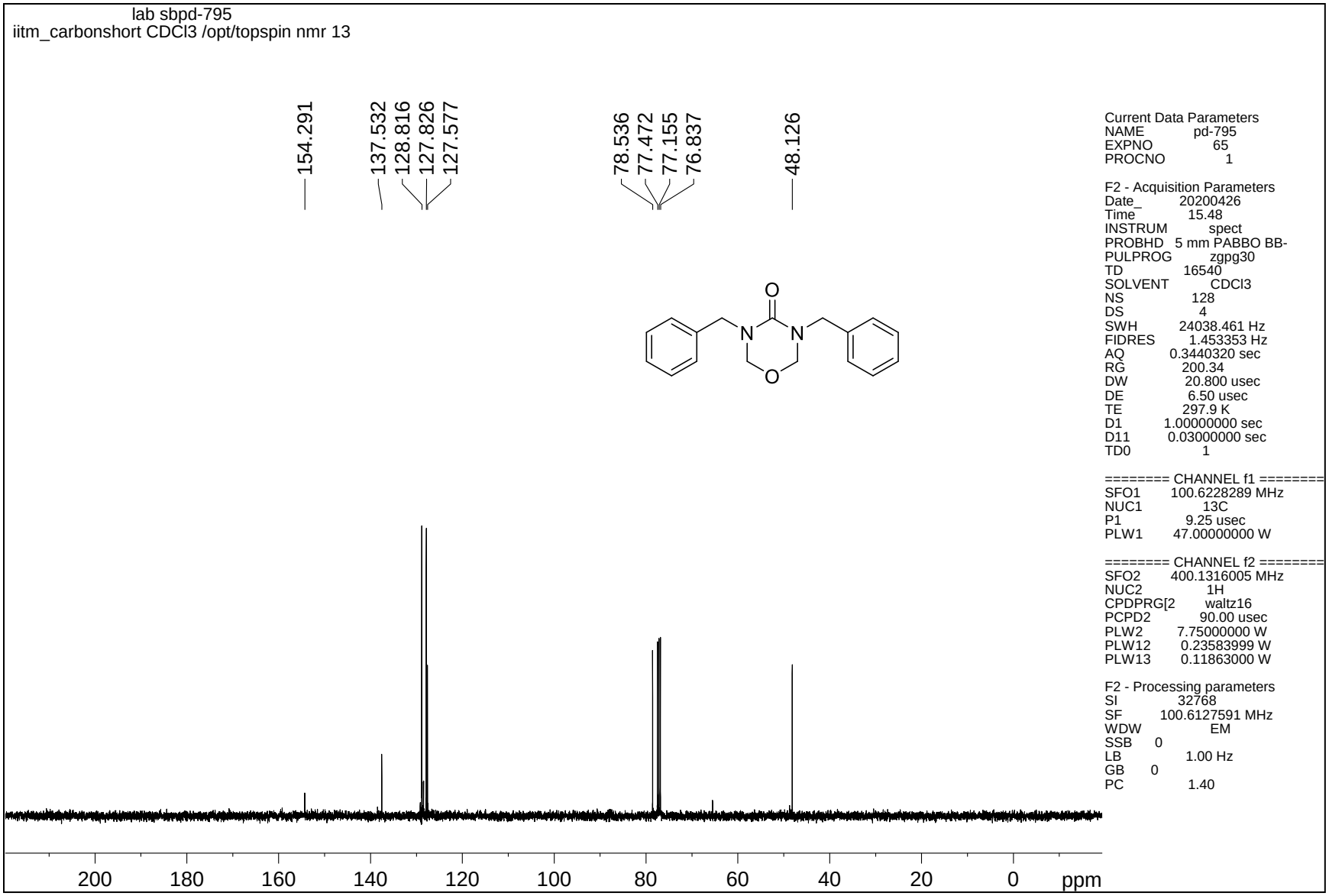


Figure 90 ^{13}C NMR spectrum of compound 27

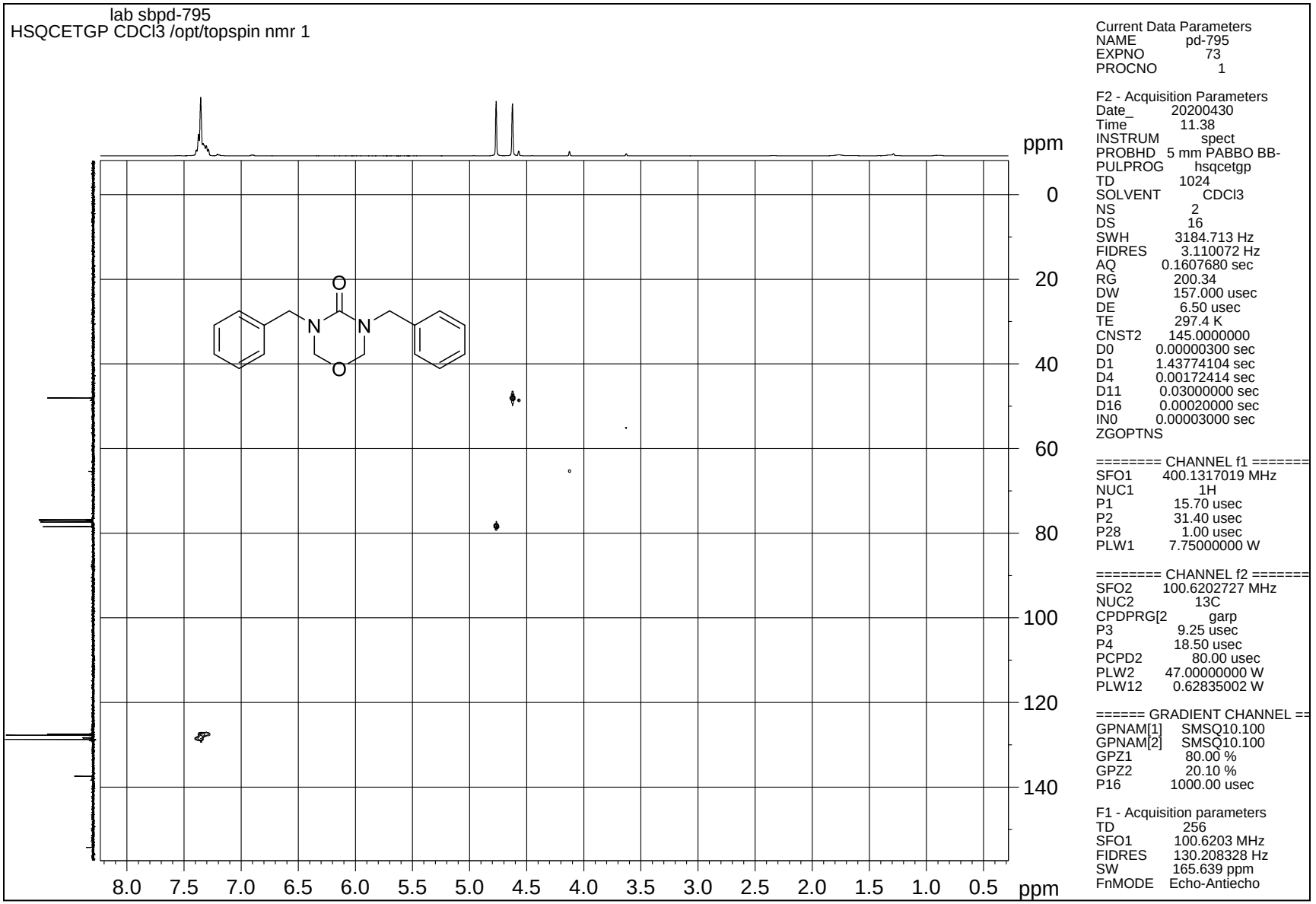


Figure 91 ^{1}H-^{13}C HSQC NMR spectrum of compound 27

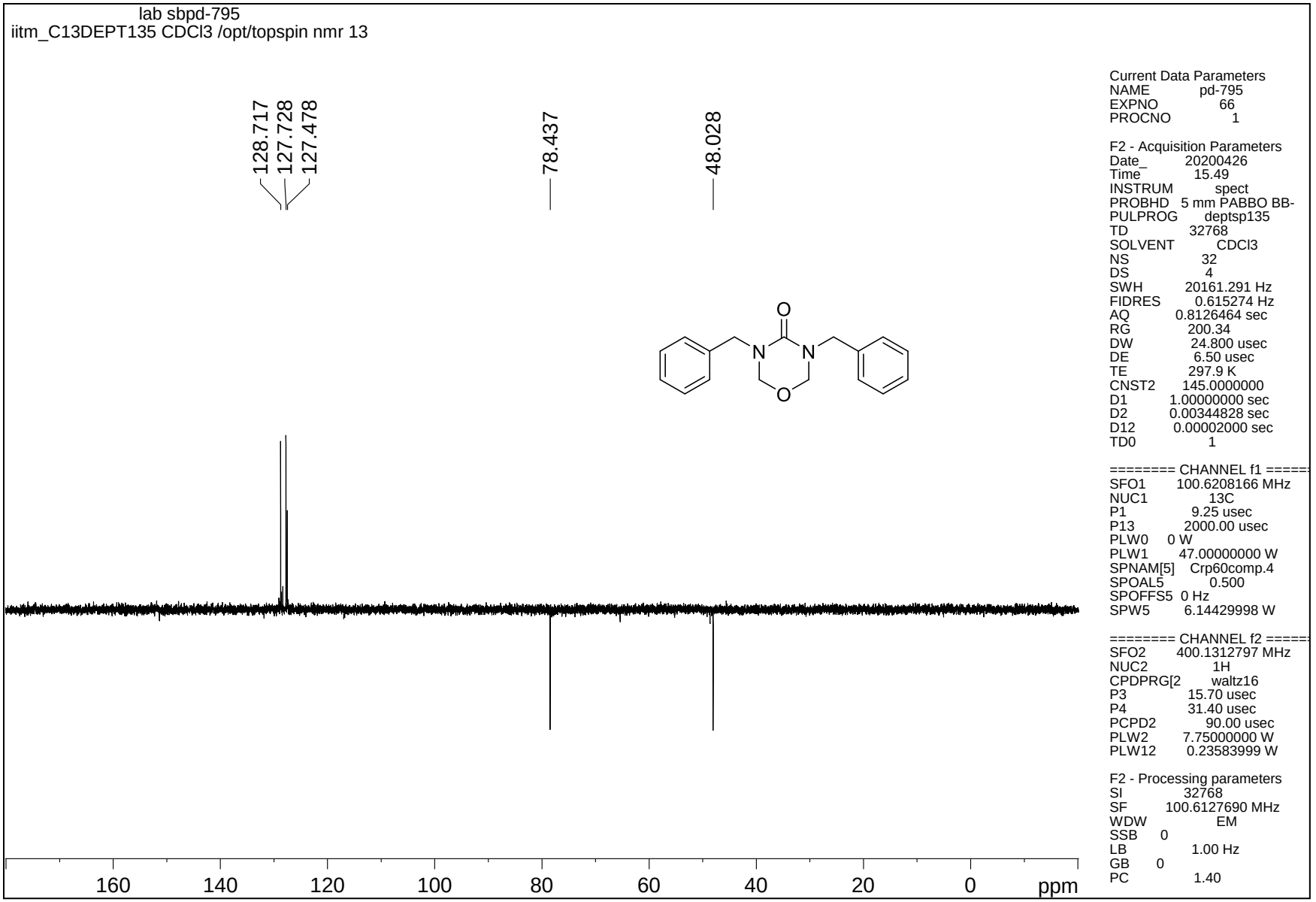


Figure 92 DEPT-135 NMR spectrum of compound 27

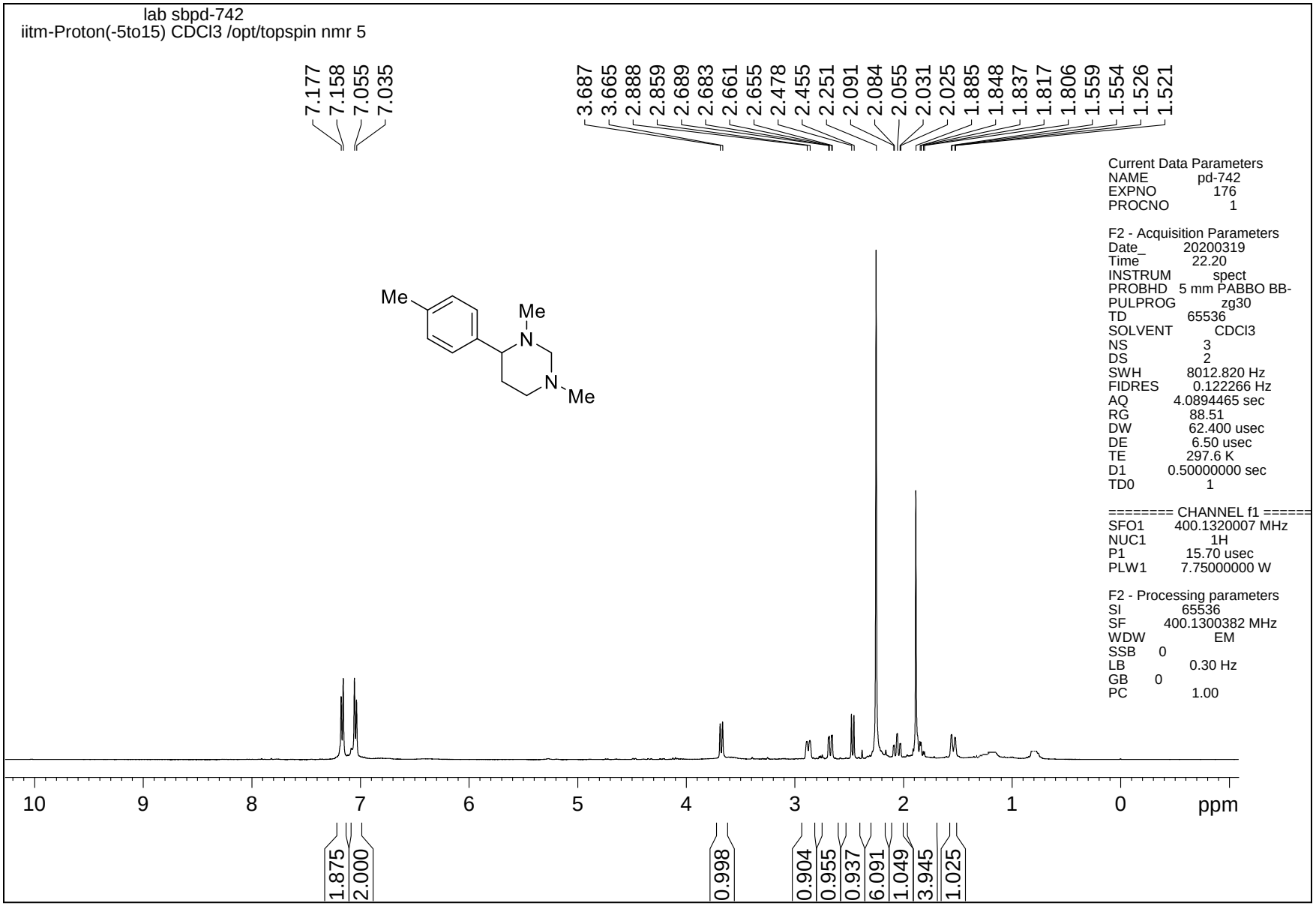


Figure 93 ^{1}H NMR spectrum of compound 8b

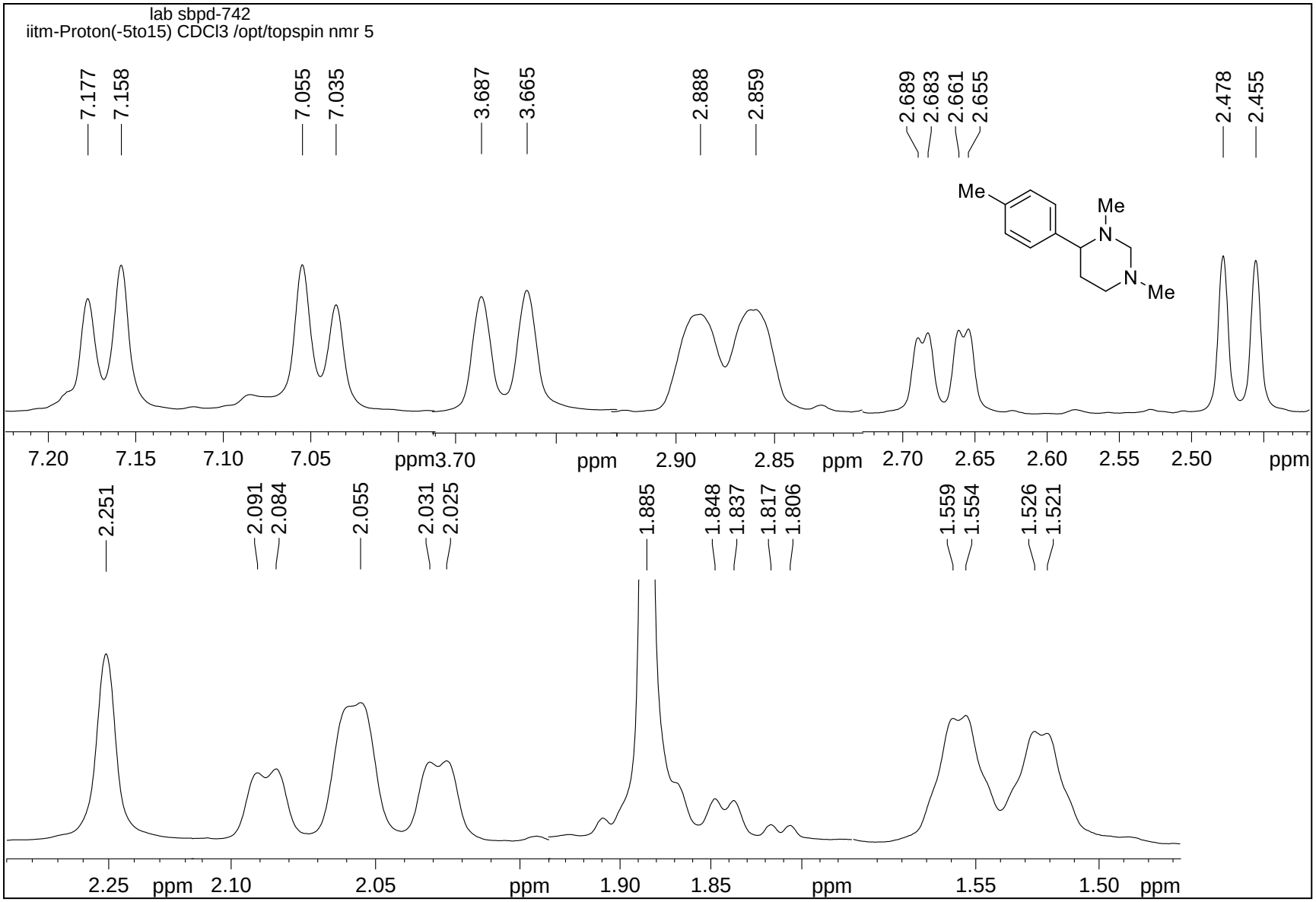


Figure 94 Expanded ^{1}H NMR spectrum of compound 8b

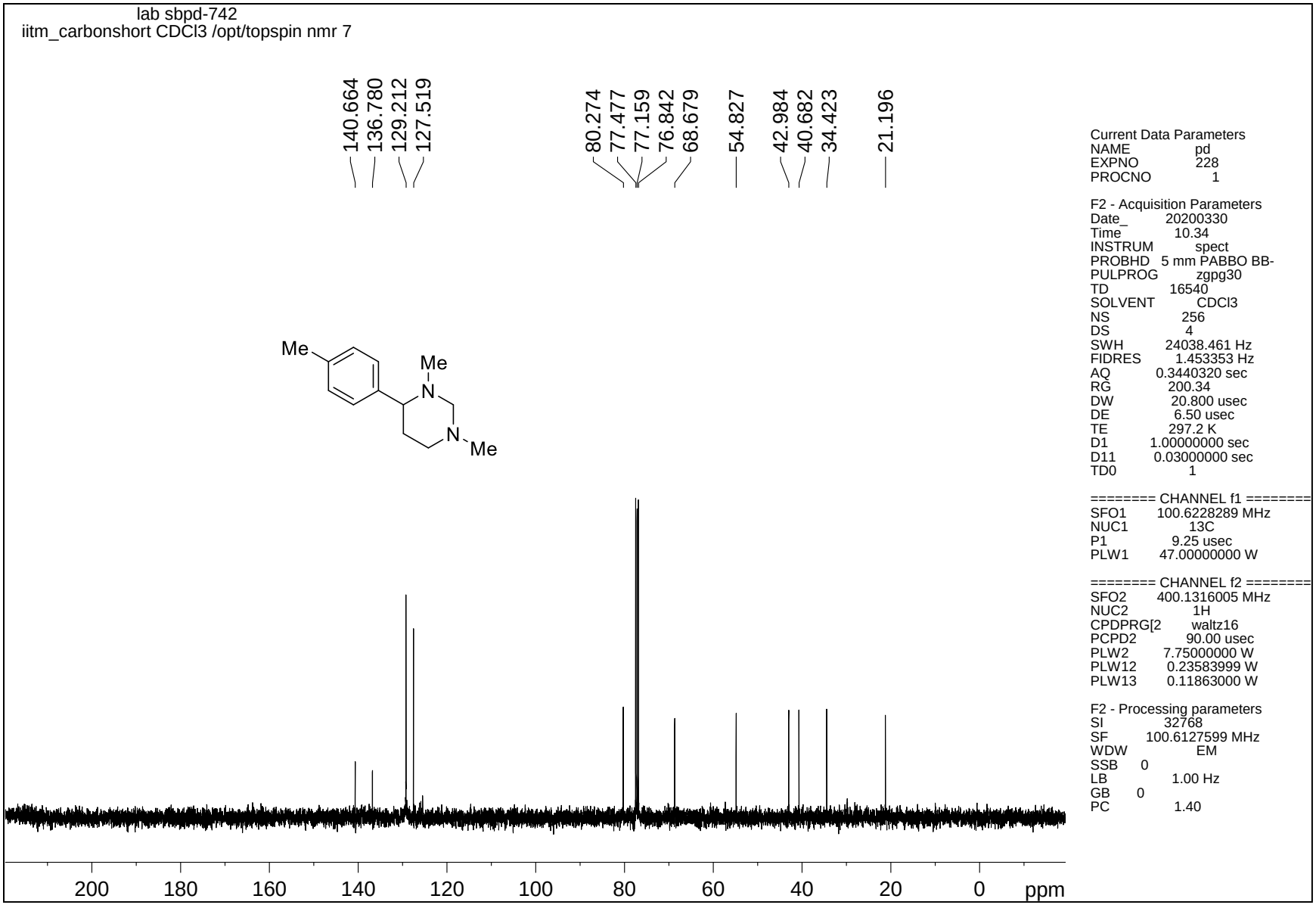


Figure 95 ^{13}C NMR spectrum of compound 8b

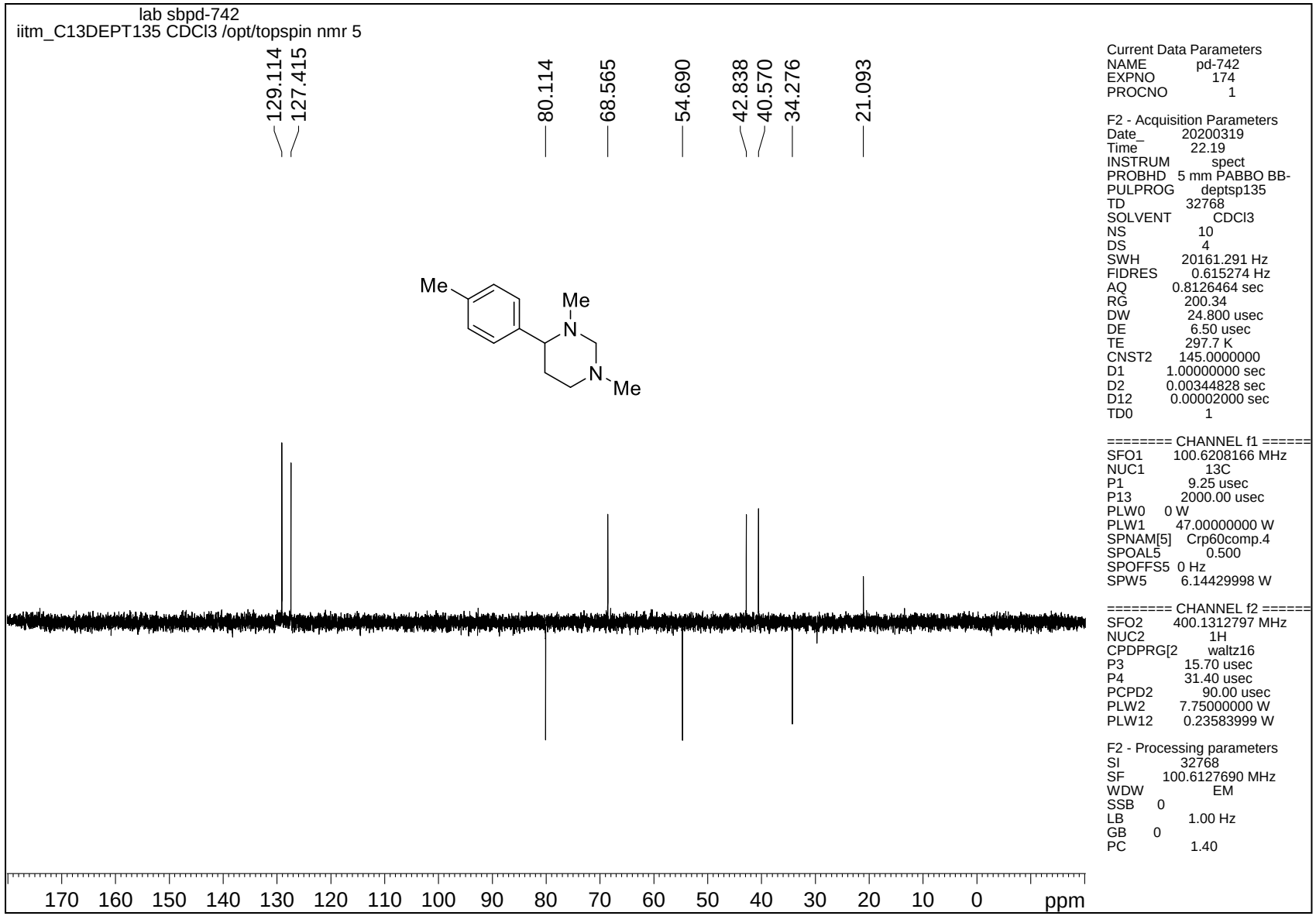


Figure 96 DEPT-135 NMR spectrum of compound 8b

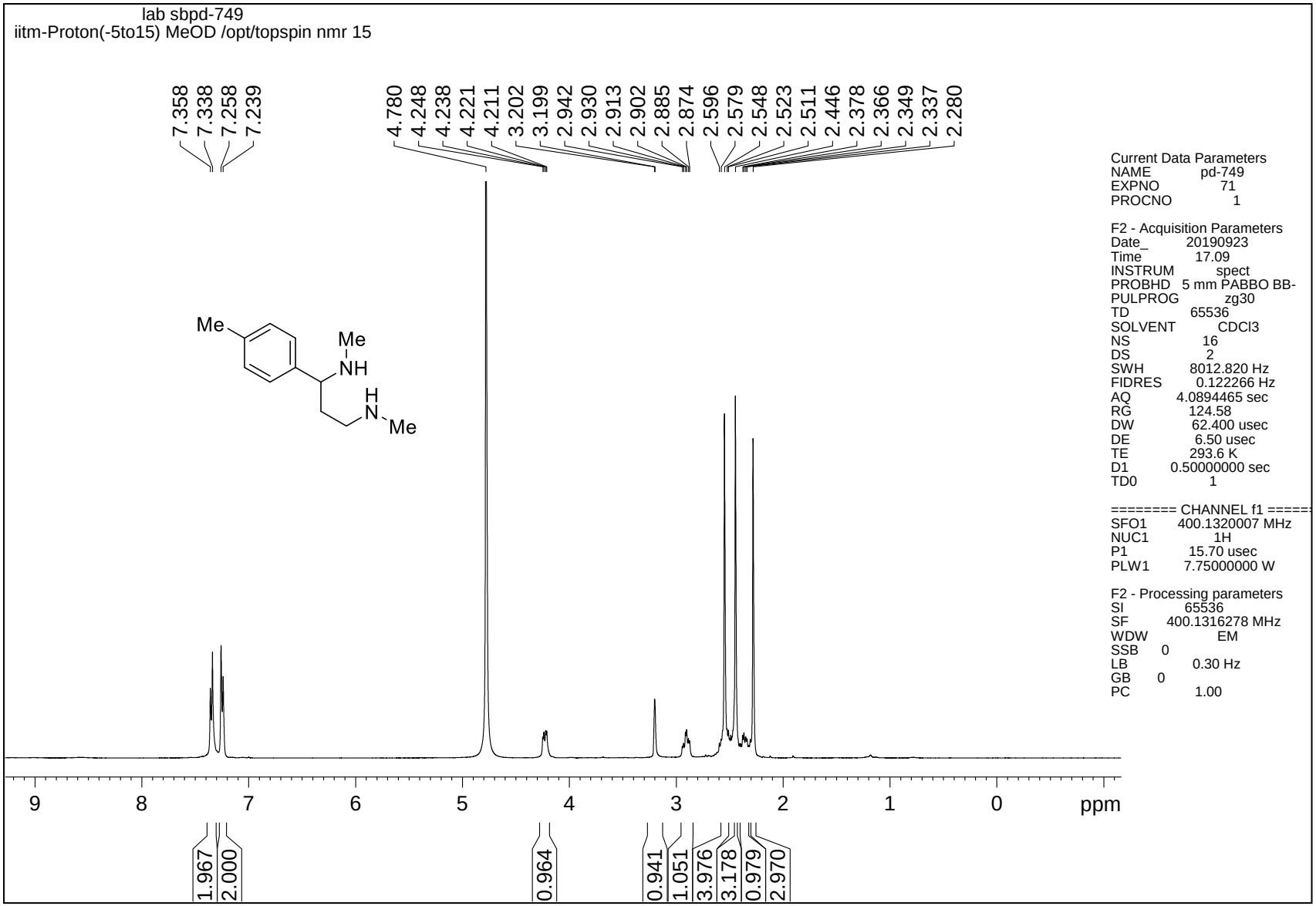


Figure 97 ^{1}H NMR spectrum of compound 8c

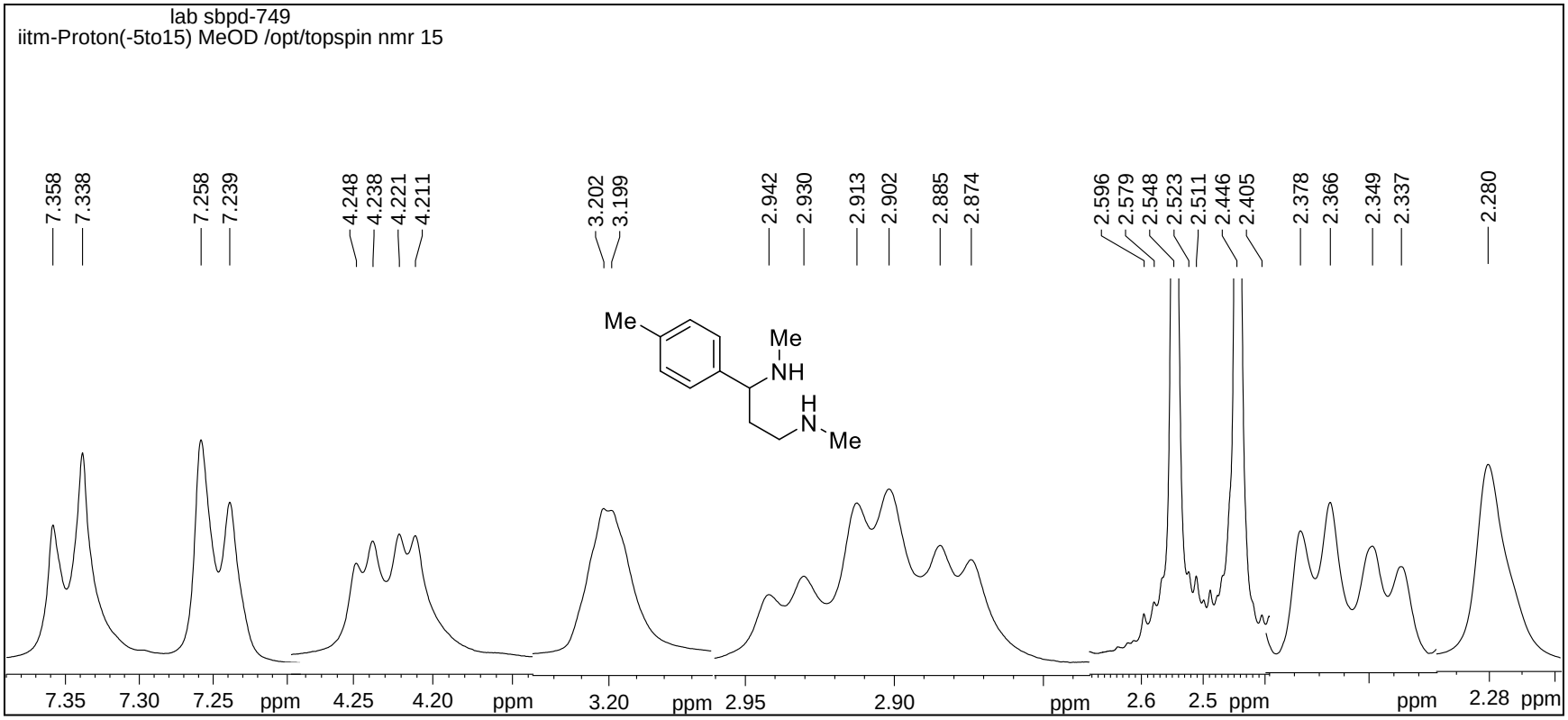


Figure 98 Expanded ^{1}H NMR spectrum of compound 8c

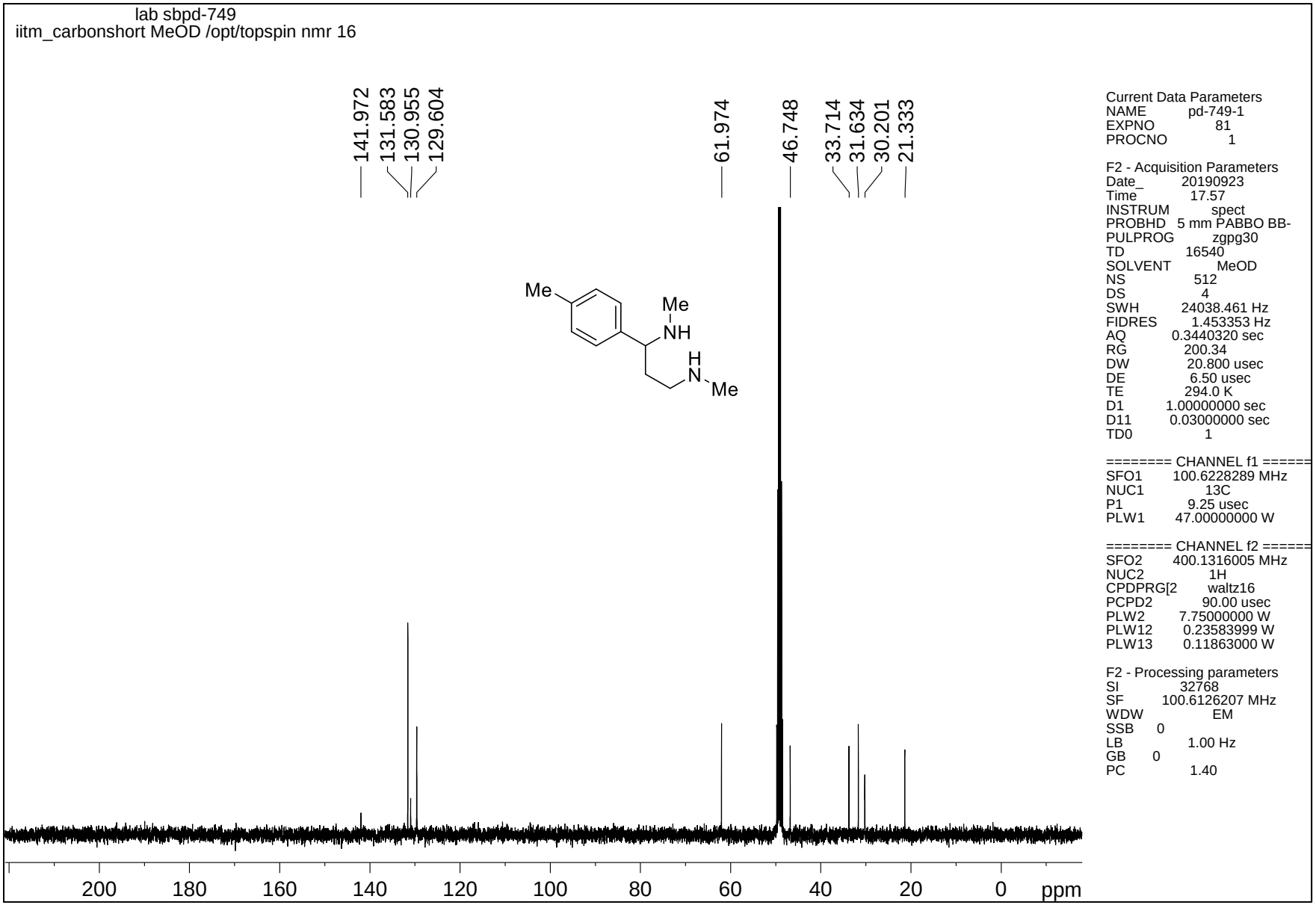


Figure 99 ^{13}C NMR spectrum of compound 8c

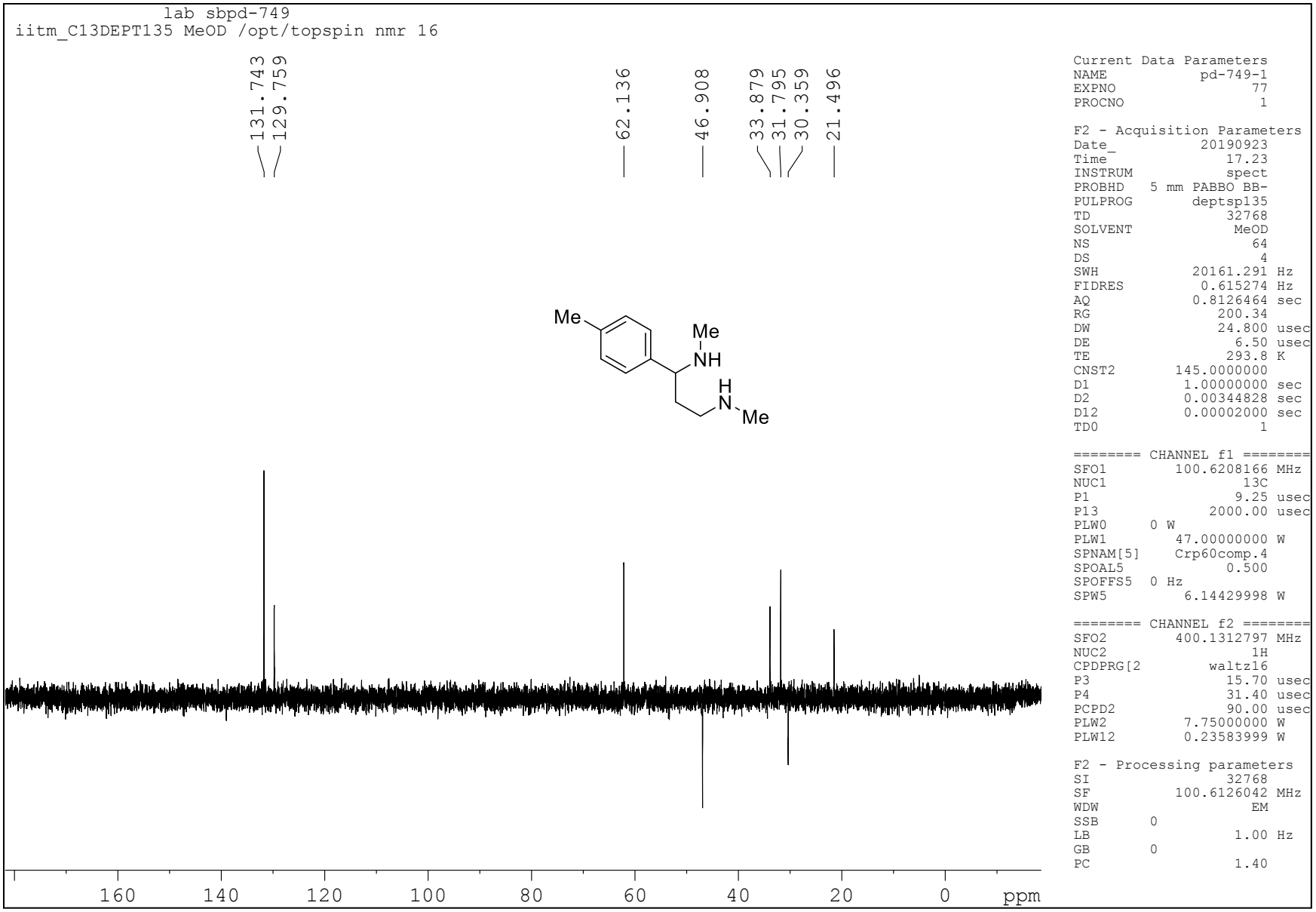


Figure 100 DEPT-135 NMR spectrum of compound 8c