Solvent-dependent oxidations of 5- and 6-azaindoles to trioxopyrrolopyridines and functionalized azaindoles†

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Electronic Supplementary Information

General

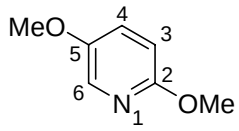
Unless otherwise indicated, all reactions were carried out under a positive pressure of argon and with oven-dried glassware. Melting points were measured on a Barnstead Electrothermal 9200 melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer FT-IR SPECTRUM ONE spectrometer (film or 1% in KBr). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker ALS300 and DRX 300 Fourier transform spectrometers, using an internal deuterium lock, operating at 300 MHz. Chemical shifts are reported in parts per million (ppm) relative to internal standard (tetramethylsilane, δ_H = 0.00; $CDCl_3$, δ_H = 7.26; acetone-d_6, δ_H = 2.05 and DMSO-d_6, δ_H = 2.50).[1] Data are presented as follows: chemical shift (δ, ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br = broad), coupling constant (reported in Hz), assignment. Atom numbering refers to pyridine and indole nomenclatures. Carbon magnetic resonance (^{13}C NMR) spectra were recorded on Bruker AC200 and DRX 300 Fourier transform spectrometers, using an internal deuterium lock, operating at 50 MHz and 75 MHz respectively. Chemical shifts are reported in parts per million (ppm) relative to internal standard (tetramethylsilane, δ_C = 0.00; $CDCl_3$, δ_C = 77.16; acetone-d_6, δ_C = 29.84 and DMSO-d_6, δ_C = 39.52). Carbon multiplicities (indicated in parentheses) were determined by DEPT experiments. Electron-Spray low-resolution mass spectra were recorded on a Thermo ALCQ Advantage spectrometer. Gas chromatography coupled with low-resolution mass spectroscopy (GC-MS) were recorded on a Thermo Focus GC (fused silica column, diameter 0.25 mm, length 15 m, coated with TR5M5, thickness 0.25 µm, initial temperature for 2 min: 70°C, heating rate 15°C/min)-DSQ spectrometer operating at 70 eV. High-resolution mass spectra were recorded on a Thermoquest Finnigan MAT 95 XL spectrometer (for chemical ionisations, isobutane was used). Elemental analyses (Anal.) were performed by the Service Central d'Analyses du CNRS, Solaize, France.

Product purification by flash column chromatography was performed using Merck Kieselgel 60 Å (40-63 µm). Analytical thin layer chromatography (TLC) was carried out using Merck commercial aluminium sheets coated (0.2 mm layer thickness) with Kieselgel 60 F254, with visualization by ultraviolet and anisaldehyde stain solution. *N*,*N*-dimethylformamide (HPLC grade) was used as received without purification. THF (anhydrous analytical grade, stored over molecular sieves) was purchased from Carlo Erba Chemicals. Dichloromethane was distilled over calcium hydride prior to use. Diisopropylamine was distilled over sodium hydride prior to use. Methanol and isopropanol were distilled over sodium prior to use. Petroleum ether (PE) refers to the 40-60°C boiling point fraction. MeLi and *n*-BuLi solutions were titrated using *N*-benzylbenzamide.[2] All other chemical reagents were used as received.

5-hydroxy-2-methoxy-pyridine **7** and 2-methoxy-5-methoxymethoxy-pyridine **8b** were prepared according to known procedures.[3] Methyl- and *tert*-butyl azidoacetate were prepared from methyl- and *tert*-butyl bromoacetate and sodium azide according to a literature procedure.[4]

[1] H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.* 1997, **62**, 7512.
[2] A. F. Burchat, J. M. Chong and N. Nielsen *J. Organomet. Chem.* 1997, **542**, 281.
[3] H. Van de Poël, G. Guillaumet and M.-C. Viaud-Massuard *Heterocycles* 2002, **57**, 55.
[4] A. T. Moore and H. N. Rydon *Org. Synth.* 1965, **45**, 47.

General experimental procedure for the methylation of pyridinols: preparation of 2,5-dimethoxy-pyridine 8a

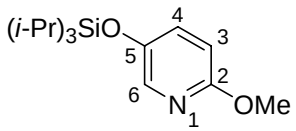


8a

To a solution of 5-hydroxy-2-methoxy-pyridine **7** (1.877 g, 15 mmol) in DMF (45 mL) at room temperature was added K_2CO_3 (3.110 g, 22.5 mmol). The mixture was stirred at 50°C for 10 min, then methyl iodide (935 µL, 15 mmol) was added. The reaction mixture was then stirred for 3h30 at 50°C. After addition of water (50 mL) and EtOAc (100 mL) and decantation, the aqueous phase was extracted with EtOAc (2×100 mL) and the organic phase was dried over Na_2SO_4. After filtration and removal of the solvents under reduced pressure, the residue was purified by flash chromatography (PE/EtOAc 70:30) to afford **8a** (1.790 g, 86%) as a yellow liquid.

ν_{max} (film)/cm^{-1} 3583, 2947, 2838, 1738, 1611, 1576, 1493, 1464, 1382, 1253, 1185, 1039, 828 and 742; δ_H (300 MHz; $CDCl_3$) 3.81 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.69 (1H, d, J = 9.0, ArH3), 7.21 (1H, dd, J = 9.0 and J = 3.0, ArH4) and 7.80 (1H, d, J = 3.0, ArH6); δ_C (75 MHz; $CDCl_3$) 53.43 (CH_3), 56.18 (CH_3), 111.02 (CH), 126.73 (CH), 131.01 (CH), 151.05 (C) and 158.73 (C); GC-MS (retention time: 3.97 min) *m/z* (EI) 139 ($M^{+\bullet}$, 96%), 138 (100), 96 (48) and 54 (44).

2-Methoxy-5-triisopropylsilanyloxy-pyridine 8c

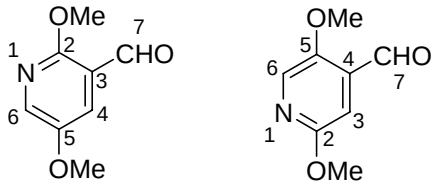


8c

To a solution of 5-hydroxy-2-methoxy-pyridine **7** (2.503 g, 20 mmol) and imidazole (2.859 g, 42 mmol) in DMF (60 mL) at room temperature was added triisopropylsylilchloride (5.2 mL, 24 mmol). The reaction mixture was stirred for 20h, after which water (50 mL) and EtOAc (100 mL) were added. After decantation, the aqueous phase was extracted with EtOAc (2×100 mL) and the organic phase was dried over Na_2SO_4. After filtration and removal of the solvents under reduced pressure, the residue was purified by flash chromatography (PE/EtOAc 90:10) to afford **8c** (6.336 g, quantitative) as a pale yellow liquid.

ν_{max} (film)/cm^{-1} 2945, 2893, 2867, 2727, 1743, 1724, 1607, 1584, 1573, 1488, 1464, 1432, 1378, 1256, 1195, 1115, 1060, 1031, 997, 912, 883, 818 and 688; δ_H (300 MHz; $CDCl_3$) 1.08 (18H, d, J = 6.8, ($CH(CH_3)_2)_3$), 1.16-1.28 (3H, m, ($CH(CH_3)_2)_3$), 3.87 (3H, s, OCH_3), 6.61 (1H, d, J = 8.9, ArH3), 7.1((1H, dd, J = 8.9 and J = 3.0, ArH4) and 7.79 (1H, d, J = 3.0, ArH6); δ_C (75 MHz; $CDCl_3$) 12.55 (CH), 17.76 (CH_3), 53.41 (CH_3), 110.76 (CH), 131.07 (CH), 136.79 (CH), 147.40 (C) and 158.59 (C); GC-MS (retention time: 9.83 min) *m/z* (EI) 281 ($M^{+\bullet}$, 22%), 238 (62), 210 (50), 182 (100) and 168 (58).

Typical experimental procedure for the formylation of 5-substituted 2-methoxypyridines 8: preparation of 5a and 6a



5a and **6a**

To a solution of 2,5-dimethoxy-pyridine **8a** (417 mg, 3.0 mmol) in anhydrous THF (10 mL) was added diisopropylamine (10 µL, 0.06 mmol). The mixture was then cooled to -40°C and MeLi 1.6 M solution in Et_2O (3.4 mL, 5.4 mmol) was slowly added. The resulting mixture was stirred at 0°C for 3 hours, then cooled to -40°C and *N*-formylpiperidine (600 µL, 5.4 mmol) was added. The mixture was stirred at -40°C for 2h then quenched by careful addition of a solution of 37% aqueous HCl (3 mL) in THF (7 mL). The temperature was raised to 20°C, then water (30 mL) and EtOAc (150 mL) were added. The pH of the resulting mixture was then adjusted to 8-9 with solid K_2CO_3. After decantation, the aqueous phase was extracted with EtOAc (2×20 mL). After drying of the combined organic phases with Na_2SO_4 and filtration, the solvents were removed under reduced pressure. The resulting crude product was purified by flash chromatography (PE/EtOAc 96:4 to 80:20).

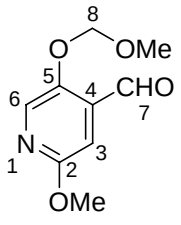
The less polar fraction was 2,5-dimethoxy-pyridine-3-carbaldehyde **5a** (77 mg, 15% yield, colorless solid).

Mp 64-66°C; Anal. found C, 57.4; H, 5.5; N, 8.35. $C_8H_9NO_3$ requires C, 57.5; H, 5.4; N, 8.4; ν_{max} (KBr)/cm^{-1} 3461, 3055, 2953, 2875, 1679, 1611, 1577, 1488, 1445, 1432, 1411, 1382, 1305, 1290, 1258, 1211, 1172, 1044, 1012, 955, 904, 800, 752 and 737; δ_H (300 MHz; $CDCl_3$) 3.84 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 7.66 (1H, d, J = 3.3, ArH), 8.10 (1H, d, J = 3.3, ArH) and 10.35 (1H, s, CHO); δ_C (75 MHz; $CDCl_3$) 53.87 (CH_3), 56.24 (CH_3), 117.90 (C), 121.01 (CH), 140.52 (CH), 151.35 (C), 159.39 (C) and 189.13 (CH).

The more polar fraction was 2,5-dimethoxy-pyridine-4-carbaldehyde **6a** (279 mg, 56% yield, yellow solid).

Mp 98-100°C; ν_{max} (KBr)/cm^{-1} 3362, 2976, 2914, 1697, 1616, 1563, 1485, 1456, 1446, 1436, 1396, 1381, 1314, 1277, 1242, 1220, 1190, 1040, 1011, 930, 883, 873 and 742; δ_H (300 MHz; $CDCl_3$) 3.91 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 7.08 (1H, s, ArH), 8.01 (1H, s, ArH) and 10.43 (1H, s, CHO); δ_C (75 MHz; $CDCl_3$) 53.93 (CH_3), 56.72 (CH_3), 107.83 (CH), 131.51 (CH), 133.28 (C), 151.00 (C), 159.12 (C) and 189.15 (CH); *m/z* (EI) 167 ($M^{+\bullet}$, 100%), 166 (75) and 44 (88); HRMS (EI) found ($M^{+\bullet}$) 167.0580, $C_8H_9NO_3$ requires 167.0582.

2-Methoxy-5-methoxymethoxy-pyridine-4-carbaldehyde 6b



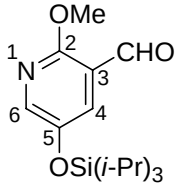
6b

Compound **6b** was prepared according to the same procedure as for compounds **5a**/**6a**, scale: 2-methoxy-5-methoxymethoxypyridine (1.523 g, 9.0 mmol), THF (30 mL), diisopropylamine (30 µL, 0.18 mmol), MeLi 1.6 M in Et_2O (10.2 mL, 16.2 mmol), *N*-formylpiperidine (1.8 mL, 16.2 mmol). The crude product was purified by flash chromatography (PE/EtOAc 90:10 to 80/20) to afford **6b** (1.083 g, 61%) as a yellow solid.

Mp 39-40°C; ν_{max} (KBr)/cm^{-1} 3369, 2973, 2930, 1739, 1699, 1609, 1486, 1380, 1235, 1195, 1155,

1083, 1032, 986 and 930; δ_H (300 MHz; $CDCl_3$) 3.53 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 5.25 (2H, s, C*H*$_2$OCH$_3$), 7.07 (1H, s, ArH), 8.23 (1H, s, ArH), 10.43 (1H, s, CHO); δ_C (75 MHz; $CDCl_3$) 54.10 (CH_3), 56.66 (CH_3), 96.25 (CH_2), 107.64 (CH), 134.28 (C), 136.03 (CH), 148.98 (C), 159.88 (C) and 189.22 (CH); *m/z* (CI) 199 (10%), 198 (MH^+, 100) and 89 (15); HRMS (CI) found (MH^+) 198.0766, $C_9H_{12}NO_4$ requires 198.0766.

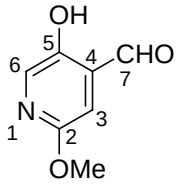
2-Methoxy-5-triisopropylsilanyloxy-pyridine-3-carbaldehyde 5c



5c

Compound **5c** was prepared according to the same procedure as for compounds **5a**/**6a**, scale: 2-methoxy-5-triisopropylsilanyloxypyridine (2.815 g, 10.0 mmol), THF (35 mL), diisopropylamine (30 µL, 0.2 mmol), MeLi 1.5 M in Et_2O (12.0 mL, 18.0 mmol), *N*-formylpiperidine (2.0 mL, 18.0 mmol). The crude product was purified by flash chromatography (PE/EtOAc 98:2 to 96:4) to afford **5c** (1.965 g, 64%) as a yellow oil.
ν_{max} (film)/cm^{-1} 2943, 2893, 2868, 2748, 1742, 1691, 1602, 1569, 1474, 1430, 1383, 1286, 1244, 1211, 1048, 1018, 1003, 910, 882, 844, 801, 755, 690, 665 and 587; δ_H (300 MHz; $CDCl_3$) 1.10 (18H, d, *J* = 6.8, (CH(C*H*$_3$)$_2$)$_3$), 1.18-1.30 (3H, m, (C*H*(CH$_3$)$_2$)$_3$), 4.02 (3H, s, OCH_3), 7.61 (1H, d, *J* = 3.1, ArH), 8.04 (1H, d, *J* = 3.1, ArH) and 10.32 (1H, s, CHO); δ_C (50 MHz; $CDCl_3$) 12.53 (CH), 17.84 (CH_3), 53.85 (CH_3), 118.29 (C), 127.56 (CH), 144.19 (CH), 147.87 (C), 159.26 (C) and 189.27 (CH); *m/z* (CI) 311 (23%) and 310 (MH^+, 100); HRMS (CI) found (MH^+) 310.1838, $C_{16}H_{28}NO_3Si$ requires 310.1838.

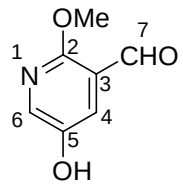
Typical experimental procedure for the acidic deprotection of 6b: 5-hydroxy-2-methoxy-pyridine-4-carbaldehyde 9



9

To a solution of 2-methoxy-5-methoxymethoxy-pyridine-4-carbaldehyde **6b** (986 mg, 5 mmol) in THF (10 mL) was added 3N aqueous HCl (15 mL) and the resulting mixture was stirred at 50°C for 3 hours. After this time, the mixture was cooled to room temperature and water (100 mL) was added followed by neutralisation (pH=7-8) with solid K_2CO_3. The aqueous phase was extracted with EtOAc (3×100 mL). After drying of the organic phase over Na_2SO_4, filtration and removal of the solvents under reduced pressure, the residue was purified by flash chromatography (PE/EtOAc 70:30) to afford **9** (725 mg, 95%) as a yellow powder.
Mp 136-137°C; ν_{max} (KBr)/cm^{-1} 3436, 2925, 2616, 1691, 1677, 1472, 1449, 1424, 1394, 1324, 1298, 1229, 1119, 1048, 921, 854, 830 and 733; δ_H (300 MHz; $CDCl_3$) 3.93 (3H, s, OCH_3), 6.93 (1H, d, *J* = 0.5, ArH3), 8.08 (1H, s, ArH5), 9.46 (1H, s, ArOH) and 9.97 (1H, d, *J* = 0.5, CHO); δ_C (75 MHz; $CDCl_3$) 54.16 (CH_3), 111.62 (CH), 127.71 (C), 137.34 (CH), 148.96 (C), 158.35 (C) and 196.58 (CH); *m/z* (ESI^+) 186 (M+CH$_3$OH+H$^+$, 100%), 168 (46) and 154 (MH^+, 49); HRMS (EI) found ($M^{+\bullet}$) 153.0421, $C_7H_7NO_3$ requires 153.0426.

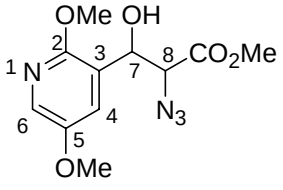
Typical experimental procedure for the fluoride-promoted deprotection of 5c: preparation of 5-hydroxy-2-methoxy-pyridine-3-carbaldehyde 10



10

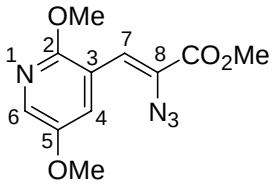
A tetra *n*-butyl-ammonium fluoride 1M solution in THF (15 mL, 15 mmol) was added to a stirred solution of 2-methoxy-5-triisopropylsilanyloxy-pyridine-3-carbaldehyde **5c** (3.095 g, 10 mmol) in anhydrous THF (15 mL) at 0°C. The temperature was allowed to rise to room temperature and the resulting mixture for stirred for 2 hours. After addition of water (15 mL) and EtOAc (50mL) and decantation, the aqueous phase was extracted with EtOAc (2×50 mL). The combined organic phases were washed with water (2×50 mL) and dried over Na_2SO_4. After filtration and removal of the solvents under reduced pressure, the residue was purified by flash chromatography (PE/EtOAc 50:50) to afford **10** (1.408 g, 92%) as a white solid.
Mp 104-105°C; Anal. found C, 54.6; H, 4.6; N, 9.05. $C_7H_7NO_3$ requires C, 54.9; H, 4.6; N, 9.15; ν_{max} (KBr)/cm^{-1} 3466, 3084, 3007, 2962, 2888, 1674, 1312, 1588, 1483, 1460, 1426, 1390, 1323, 1307, 1283, 1226, 1207, 1170, 1132, 1049, 995, 897, 751 and 743; δ_H (300 MHz; $CDCl_3$) 4.03 (3H, s, OCH_3), 5.09 (1H, br s, ArOH), 7.64 (1H, d, *J* = 3.2, ArH), 8.07 (1H, d, *J* = 3.2, ArH) and 10.33 (1H, s, CHO); δ_C (50 MHz; $CDCl_3$) 54.10 (CH_3), 118.17 (C), 124.31 (CH), 140.93 (CH), 148.15 (C), 159.29 (C) and 190.22 (CH); *m/z* (ESI^+) 200 (66%), 186 ($M+CH_3OH+H^+$, 100) and 154 (MH^+, 59); *m/z* (ESI^-) 152 ($M-H^-$, 100%) and 137 (44).

Condensation reaction between 3-formyl pyridine 5a and methyl azidoacetate:



11a

and

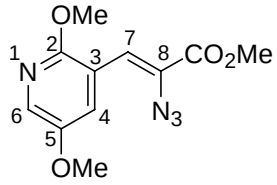


4a

Sodium metal (226 mg, 9.84 mmol) was added to anhydrous methanol (6 mL) at 0°C and the resulting mixture stirred until the metal completely dissolved. To this preformed sodium methoxide solution at 0°C was slowly added (over a 5 min period) a solution in methanol (6 mL) of aldehyde **5a** (401 mg, 2.4 mmol) and methyl azidoacetate (1.055 g, 3.8 mmol). The mixture was stirred at 0°C for 3 hours, then poured onto crushed ice (40 g, in an open beaker) and left for one hour in a refrigerator at 4°C. The product was recovered by filtration on a sintered glass funnel (n°4) and dried under vacuum to give a pale yellow solid (315 mg). This product consisted of a 28:72 mixture (determined by ^1H NMR) of azidoacrylate **4a** and azidoalcohol **11a**, respectively. The crude product was purified by flash chromatography (EP/AcOEt 70:30, the solid was adsorbed onto silica).
The less polar fraction was 2-Azido-3-(2,5-dimethoxy-pyridin-3-yl)-acrylic acid methyl ester **4a** (87 mg, pale yellow powder, 14% yield).
Mp 123-124°C; ν_{max} (KBr)/cm^{-1} 3088, 2986, 2941, 2853, 2120, 1702, 1611, 1571, 1470, 1440, 1400, 1382, 1347, 1303, 1279, 1261, 1214, 1182, 1146, 1082, 1019 and 962. δ_H (300 MHz; DMSO-d_6) 3.81 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 7.03 (1H, s, CH), 7.89 (1H, d, *J* = 3.0, ArH) and 8.13 (1H, d, *J* = 3.0, ArH); δ_C (75 MHz; DMSO-d_6) 53.26 (CH_3), 53.76 (CH_3), 56.21 (CH_3), 115.70 (C), 116.01 (CH), 125.33 (CH), 127.33 (C), 132.66 (CH), 150.40 (C), 155.22 (C) and 162.97 (C); *m/z* (CI) 265 (MH^+, 31%), 238 (14) and 237 (MH^+-N_2, 100); HRMS (CI) found (MH^+) 265.0938, $C_{11}H_{13}N_4O_4$ requires 265.0937.

The more polar fraction was 2-Azido-3-(2,5-dimethoxy-pyridin-3-yl)-3-hydroxy-propionic acid methyl ester **11a (**205 mg, white powder, 20% yield).
Mp 145-146°C; ν_{max} (KBr)/cm^{-1} 3413, 3153, 2965, 2935, 2130, 2098, 1742, 1589, 1484, 1435, 1405, 1351, 1274, 1295, 1214, 1250, 1205, 1068, 1043, 1014, 1008, 947 and 817; δ_H (300 MHz; DMSO-d_6) 3.78 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.17 (1H, d, *J* = 2.3, CHN_3), 5.31 (1H, dd, *J* = 5.0 and *J* = 2.3, C*H*OH), 6.23 (1H, d, *J* = 5.0, disappears after D_2O addition, OH), 7.46 (1H, d, *J* = 3.0, ArH), 7.80 (1H, d, *J* = 3.0, ArH); δ_C (75 MHz; DMSO-d_6) 52.70 (CH_3), 53.39 (CH_3), 56.04 (CH_3), 63.95 (CH), 68.53 (CH), 124.08 (CH), 124.30 (C), 129.58 (CH), 151.08 (C), 153.56 (C) and 169.09 (C); *m/z* (CI) 283 (MH^+, 32%), 265 (MH^+-H_2O, 25), 168 (100) and 88 (37); HRMS (CI) found (MH^+) 283.1044, $C_{11}H_{15}N_4O_5$ requires 283.1042.

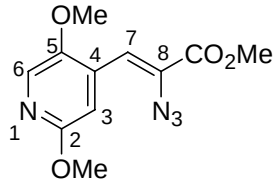
Typical experimental procedure for the preparation of azidoacrylates: 2-Azido-3-(2,5-dimethoxy-pyridin-3-yl)-acrylic acid methyl ester 4a



4a

Sodium metal (189 mg, 8.2 mmol) was added to anhydrous methanol (4 mL) at 0°C and the resulting mixture was stirred until the metal completely dissolved. To this preformed sodium methoxide solution at 30°C was quickly added (in 30 seconds) a solution of aldehyde **5a** (335 mg, 2.0 mmol) and methyl azidoacetate (1.055 g, 7.6 mmol) in methanol (6 mL). The mixture was stirred at 30°C for 2 hours, then poured onto crushed ice (40 g, in an open beaker) and left for one hour in a refrigerator at 4°C. The product was recovered by filtration on a sintered glass funnel (n°4) and dried under vacuum to afford **4a** (315 mg, 57%) as an off-white powder.

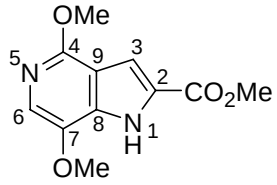
2-Azido-3-(2,5-dimethoxy-pyridin-4-yl)-acrylic acid methyl ester 4b



4b

Compound **4b** was prepared according to the same procedure as for compound **4a**, scale: sodium metal (189 mg, 8.2 mmol), anhydrous methanol (4 mL), methanol (6 mL), aldehyde (335 mg, 2 mmol), methyl azidoacetate (875 mg, 7.6 mmol). (268 mg, 51%, yellow powder).
Mp 117-118°C (decomposed); ν_{max} (KBr)/cm^{-1} 3439, 3108, 2946, 2925, 2851, 2127, 1716, 1602, 1548, 1487, 1463, 1435, 1384, 1322, 1281, 1254, 1214, 1189, 1082, 1044, 1014, 888 and 739; δ_H (300 MHz; acetone-d_6) 3.84 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 7.12 (1H, s, CH), 7.50 (1H, s, ArH), 7.89 (1H, s, ArH); δ_C (75 MHz; acetone-d_6) 53.58 (CH_3), 53.62 (CH_3), 57.15 (CH_3), 111.07 (CH), 116.05 (CH), 130.32 (CH), 130.53 (C), 133.25 (C), 149.30 (C), 159.41 (C) and 164.00 (C); *m/z* (EI) 264 ($M^{+\bullet}$, 53%), 204 (49), 177 (58), 64 (54) and 59 (100); HRMS (EI) found ($M^{+\bullet}$) 264.0856, $C_{11}H_{12}N_4O_4$ requires 264.0859.

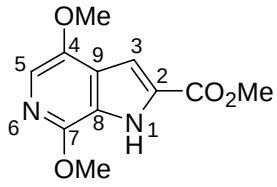
4,7-Dimethoxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid methyl ester 2a



2a

The reaction was carried out in a 100 mL round-bottom flask, open to the atmosphere *via* a condenser and an addition funnel.
To hot xylene (13 mL) at 140°C was slowly added with vigorous stirring a suspension of acrylate **4a** (423 mg, 1.6 mmol) in xylene (27 mL). Once the addition was complete, the mixture was stirred for 1 hour at 140°C, then slowly cooled down to room temperature overnight without stirring. After the complete crystallisation of the solid, the supernatant was removed and the solid dried under high vacuum to give 5-azaindole **2a** (310 mg, 82%) as pale pink crystals.
Mp 192-193°C; Anal. found C, 55.8; H, 5.3; N, 11.65. $C_{11}H_{12}N_2O_4$ requires C, 55.95; H, 5.1; N, 11.85; ν_{max} (KBr)/cm^{-1} 3437, 3300, 2948, 2924, 1702, 1619, 1593, 1537, 1499, 1465, 1446, 1429, 1360, 1307, 1258, 1208, 1157, 1098, 1087, 984, 853 and 754; δ_H (300 MHz; DMSO-d_6) 3.84 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 7.10 (1H, s, ArH), 7.47 (1H, s, ArH) and 12.57 (1H, br s, NH); δ_C (75 MHz; DMSO-d_6) 51.89 (CH_3), 52.79 (CH_3), 56.37 (CH_3), 106.53 (CH), 112.95 (C), 120.41 (CH), 127.46 (C), 134.17 (C), 140.04 (C), 152.78 (C) and 160.91 (C); *m/z* (CI) 238 (12%) and 237 (MH^+, 100); HRMS (CI) found (MH^+) 237.0874, $C_{11}H_{13}N_2O_4$ requires 237.0875.

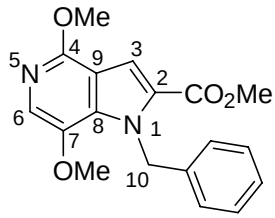
4,7-Dimethoxy-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid methyl ester 2c



2c

The reaction was carried out in a 50 mL round-bottom flask, open to the atmosphere *via* a condenser and an addition funnel.
To hot xylene (8 mL) at 140°C was slowly added with vigorous stirring a solution of acrylate **4b** (264 mg, 1.0 mmol) in xylene (16 mL). Once the addition was complete, the mixture was stirred for 1 hour at 140°C, then cooled down to room temperature over 4 hours and held in a freezer at -20°C overnight. The supernatant was removed and the solid dried under high vacuum to give 6-azaindole **2c** (73 mg, 31%) as a pale yellow powder. The supernatant was purified by flash chromatography (PE/EtOAc 50:50) to afford **2c** (61 mg, 26%) as a pale yellow powder; global yield = 57%.
Mp 169-170°C; ν_{max} (KBr)/cm^{-1} 3306, 2994, 2939, 1713, 1511, 1470, 1448, 1340, 1320, 1288, 1234, 1202, 1097, 992, 827 and 747; δ_H (300 MHz; DMSO-d_6) 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 7.07 (1H, s, ArH), 7.27 (1H, s, ArH) and 12.62 (1H, br s, NH); δ_C (75 MHz; DMSO-d_6) 52.03 (CH_3), 52.81 (CH_3), 55.86 (CH_3), 104.90 (CH), 114.66 (CH), 123.03 (C), 124.81 (C), 128.96 (C), 145.67 (C), 146.37 (C) and 160.98 (C); *m/z* (EI) 236 ($M^{+\bullet}$, 100%), 221 ($M^{+\bullet}$-$CH_3^{\bullet}$, 7), 204 ($M^{+\bullet}$-CH_3OH, 53), 189 ($M^{+\bullet}$-CH_3OH-$CH_3^{\bullet}$, 54); HRMS (EI) found ($M^{+\bullet}$) 236.0798, $C_{11}H_{12}N_2O_4$ requires 236.0797.

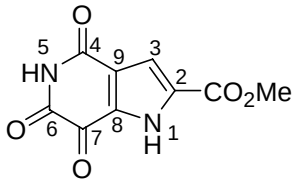
1-Benzyl-4,7-dimethoxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid methyl ester 2b



2b

To a solution of 5-azaindole **2a** (100 mg, 0.42 mmol) in DMF (3 mL) at room temperature, was added in one portion sodium hydride (60% dispersion in mineral oil, 20 mg, 0.50 mmol). The mixture was heated to 50°C and stirred for 3h30. Benzyl bromide (50 µL, 0.42 mmol) was then added and the resulting mixture stirred for an additional two hours at 50°C. After cooling down to room temperature, water (10 mL) was added and the aqueous phase extracted with EtOAc (3×20 mL). The organic phases were dried over Na_2SO_4, filtered and the solvents removed under reduced pressure. The resulting crude product was purified by flash chromatography (PE/EtOAc 70:30) to afford compound **2b** (101 mg, 74%) as a white powder.
Mp 121-122°C; ν_{max} (KBr)/cm^{-1} 3435, 3028, 3008, 2940, 1712, 1657, 1606, 1520, 1483, 1452, 1437, 1400, 1362, 1312, 1269, 1234, 1203, 1101, 1066, 1011, 985, 857, 749 and 727; δ_H (300 MHz; DMSO-d_6) 3.79 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 6.04 (2H, s, C*H*$_2$Ph), 6.93 (2H, d, *J* = 7.0, CH_2*o*-Ar*H*), 7.17-7.29 (3H, m, CH_2Ar*H*), 7.30 (1H, s, ArH) and 7.54 (1H, s, ArH); δ_C (75 MHz; DMSO-d_6) 49.31 (CH_2), 51.97 (CH_3), 52.96 (CH_3), 56.64 (CH_3), 109.44 (CH), 111.93 (C), 121.96 (CH), 125.93 (CH), 126.98 (CH), 127.02 (C), 128.49 (CH), 134.47 (C), 139.19 (C), 140.48 (C), 153.08 (C) and 160.85 (C); *m/z* (ESI$^+$) 328 (19%), 327 (MH$^+$, 100); HRMS (ESI$^+$) found (MH$^+$) 327.1347, $C_{18}H_{19}N_2O_4$ requires 327.1345.

Experimental procedure for the oxidation of 4,7-dimethoxy 5-azaindole 2a: 4,6,7-Trioxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid methyl ester 12a



12a

To a solution of 5-azaindole **2a** (47 mg, 0.2 mmol) in a 1:1 acetonitrile/water mixture (16 mL) at room temperature was added in one portion [Bis(trifluoroacetoxy)iodo]benzene (PIFA) (86 mg, 0.2 mmol). After stirring for one hour, a further portion of PIFA (86 mg, 0.2 mmol) was added. This procedure was repeated twice more, after 2h and 3h reaction time, so that a total of four equivalents (344 mg, 0.8 mmol) of PIFA were used. One hour after the last PIFA addition, the mixture was filtered on a sintered glass funnel filled with a one cm thick pad of silica gel, washing with EtOAc. After evaporation of the filtrate under reduced pressure, the residue was purified by flash chromatography (petroleum ether / EtOAc 50:50) to afford a pink solid. This solid was then washed with dichloromethane to give the trioxo compound **12a** (43 mg, 97%) as a pale yellow solid.
Mp 269-270°C; ν_{max} (KBr)/cm^{-1} 3210, 3137, 2924, 2853, 1690, 1554, 1455, 1432, 1287, 1229, 1138, 1096, 974, 927 and 799; δ_H (300 MHz; DMSO-d_6) 3.85 (3H, s, OCH_3), 7.16 (1H, s, H3), 11.54 (1H, s, H5) and 14.00 (1H, br s, H1); δ_C (75 MHz; DMSO-d_6) 52.38 (CH_3), 113.25 (CH), 123.89 (C), 130.32 (C), 132.77 (C), 158.70 (C), 159.95 (C), 160.69 (C) and 166.45 (C); *m/z* (ESI$^+$) 463 (48%), 445 (54), 427.1 (2M+H$^+$, 29), 222.9 (MH$^+$, 100), 209 (24); HRMS (ESI$^+$) found (M+Na$^+$) 245.0174, $C_9H_6N_2O_5Na$ requires 245.0174.

The monocrystal for the X-ray diffraction analysis was obtained as follows: a solution of

compound **12a** (1 mg) in acetone (0.7 mL) was allowed to stand for three days at room temperature (20°C) in a test tube (without capping). A colorless needle (0.06 × 0.07 × 0.21 mm) was then analyzed on a Nonius Kappa CCD diffractometer at 293K.
The crystal structure data of compound **12a** has been deposited at the Cambridge Crystallographic Data Centre (CCDC 641655).

Crystal data

$C_9H_6N_2O_5$	V = 458.78 (1) Å^3
M_r = 222.16	Z = 2
Triclinic, *P*-1	D_x = 1.608 Mg m^{-3}
a = 5.35 Å	Mo $K\alpha$ radiation
b = 8.79 Å	Cell parameters from 0 reflections
c = 10.58 Å	θ = 0–0°
α = 111.47°	μ = 0.14 mm^{-1}
β = 94.77°	T = 293 K
γ = 94.31°	Needle, colorless

Data collection

Nonius KappaCCD diffractomer	1005 reflections with $I > 2.0\sigma(I)$
ϕ & ω scans	R_{int} = 0.042
Absorption correction: none	θ_{max} = 27.7°
T_{min} = 0.991, T_{max} = 0.992	h = -7 → 6
3192 measured reflections	k = -11 → 11
2078 independent reflections	l = -13 → 13

Refinement

Refinement on *F*	H atoms constrained to parent site
$R[F^2 > 2\sigma(F^2)]$ = 0.047	Calculated weights Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ... + A_{n-1}]*T_{n-1}(x)] where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 0.603 0.477 0.354
$wR(F^2)$ = 0.057	$(\Delta/\sigma)_{max}$ <0.0001
S = 1.06	$\Delta\rho_{max}$ = 0.20 e Å^{-1}
1005 reflections	$\Delta\rho_{min}$ = -0.20 e Å^{-1}
145 parameters	Extinction correction: None

Geometric parameters (Å, °) for CRYSTALS cif

O1—C10	1.203 (4)	O7—C9	1.305 (4)
C13—N4	1.354 (4)	O7—C12	1.450 (4)
C13—C7	1.385 (4)	N4—C11	1.374 (4)
C13—C10	1.439 (4)	C5—C7	1.401 (4)
N3—C6	1.397 (4)	C5—C11	1.379 (4)
N3—C8	1.362 (4)	C6—C7	1.457 (4)
O4—C8	1.213 (3)	C8—C10	1.556 (4)
O2—C6	1.210 (3)	C9—C11	1.476 (5)
O5—C9	1.216 (4)		

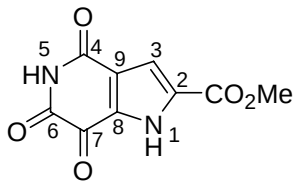
N4—C13—C7	108.7 (3)	N3—C8—O4	123.0 (3)
N4—C13—C10	127.4 (3)	N3—C8—C10	117.5 (3)
C7—C13—C10	123.9 (3)	O4—C8—C10	119.6 (3)
C6—N3—C8	127.8 (3)	O7—C9—O5	125.1 (3)
C9—O7—C12	116.1 (3)	O7—C9—C11	112.2 (3)
C13—N4—C11	107.9 (3)	O5—C9—C11	122.6 (3)
C7—C5—C11	106.2 (3)	C8—C10—C13	114.1 (3)
N3—C6—O2	119.7 (3)	C8—C10—O1	118.9 (3)
N3—C6—C7	115.1 (3)	C13—C10—O1	127.0 (3)
O2—C6—C7	125.1 (3)	C9—C11—C5	131.4 (3)
C6—C7—C5	130.7 (3)	C9—C11—N4	119.1 (3)
C6—C7—C13	121.5 (3)	C5—C11—N4	109.4 (3)
C5—C7—C13	107.8 (3)		

Hydrogen-bond parameters (Å, °) for CRYSTALS cif

	D—H	H...*A*	D...A	*D*—H...*A*
N4—H1...O5^{i}	0.85	2.00	2.843 (2)	170
N3—H2...O4^{ii}	0.88	2.05	2.924 (2)	174

Symmetry codes: (i) 1-x, 1-y, 1-z; (ii) -1-x, 1-y, 2-z.

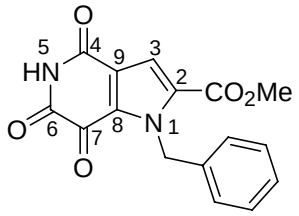
Experimental procedure for the oxidation of 7-hydroxy 4-methoxy 5-azaindole 3a: Preparation of compound 12a.



12a

To a solution of 5-azaindole **3a** (22 mg, 0.1 mmol) in a 1:1 acetonitrile/water mixture (8 mL) at room temperature was added in one portion [Bis(trifluoroacetoxy)iodo]benzene (PIFA) (44 mg, 0.1 mmol). After stirring for one hour, the resulting mixture was filtered off on a sintered glass funnel filled with a one cm thick pad of silica gel, washing with EtOAc. After evaporation of the filtrate under reduced pressure, the residue was purified by flash chromatography (PE/EtOAc 50:50) to afford the trioxo compound **12a** (19 mg, 95%) as an orange solid.

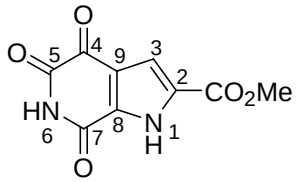
Typical experimental procedure for the oxidation of *N*-benzyl 4,7-dimethoxy 5-azaindole 2b: Preparation of 1-Benzyl-4,6,7-trioxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid methyl ester 12b



12b

To a solution of *N*-benzyl 5-azaindole **2b** (68 mg, 0.21 mmol) in a 1:1 acetonitrile/water mixture (23 mL) at room temperature was added in one portion [Bis(trifluoroacetoxy)iodo]benzene (PIFA) (359 mg, 0.84 mmol). After stirring for four hours, the resulting mixture was filtered off on a sintered glass funnel filled with a one cm thick pad of silica gel, washing with EtOAc. After evaporation of the filtrate under reduced pressure, the residue was purified by flash chromatography (PE/EtOAc 70:30) to afford compound **12b** (53 mg, 81%) as a pale brown solid.
Mp 208-209°C; ν_{max} (KBr)/cm^{-1} 3205, 3120, 2924, 2853, 1728, 1710, 1674, 1526, 1489, 1454, 1425, 1382, 1255, 1186, 1119, 1078, 945, 737 and 707; δ_H (300 MHz; DMSO-d$_6$) 3.79 (3H, s, OCH_3), 5.99 (2H, s, C*H*$_2$Ph), 7.13 (2H, d, *J* = 6.4, CH_2*o*-Ar*H*), 7.25-7.30 (3H, m, CH_2Ar*H*), 7.32 (1H, s, H3) and 11.70 (1H, s, H5); δ_C (75 MHz; DMSO-d$_6$) 49.73 (CH_2), 52.50 (CH_3), 115.27 (CH), 123.45 (C), 126.66 (CH), 127.43 (CH), 128.47 (CH), 129.52 (C), 132.00 (C), 136.79 (C), 158.52 (C), 159.74 (C), 160.26 (C) and 167.13 (C); *m/z* (ESI$^+$) 648 (32%), 647 (2M+Na$^+$, 100), 335 (M+Na$^+$, 11), 313 (MH$^+$, 8); HRMS (ESI$^+$) found (M+Na$^+$) 335.0647, $C_{16}H_{12}N_2O_5Na$ requires 335.0644.

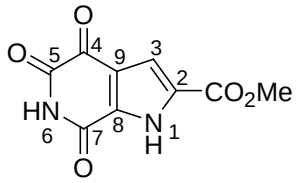
Preparation of compound 12c from 4,7-dimethoxy 6-azaindole 2c: 4,5,7-Trioxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid methyl ester 12c



12c

Compound **12c** was prepared according to the same procedure as for compound **12b**, scale: 6-azaindole **2c** (50 mg, 0.21 mmol), [Bis(trifluoroacetoxy)iodo]benzene (PIFA) (365 mg, 0.85 mmol), 1:1 acetonitrile/water mixture (16 mL). The crude product was purified by flash chromatography (PE/EtOAc 50:50) to afford **12c** (27 mg, 57%) as a yellow powder.
Mp 261-262°C; ν_{max} (KBr)/cm^{-1} 3436, 3203, 3124, 2925, 2854, 1691, 1561, 1503, 1483, 1425, 1395, 1331, 1276, 1234, 1140, 1101, 990, 932, 809 and 774; δ_H (300 MHz; DMSO-d$_6$) 3.84 (3H, s, OCH_3), 7.18 (1H, s, H3), 11.73 (1H, br s, H6) and 14.06 (1H, very br s, H1); δ_C (75 MHz; DMSO-d$_6$) 52.21 (CH_3), 112.51 (CH), 124.31 (C), 129.69 (C), 132.73 (C), 157.28 (C), 159.22 (C), 160.20 (C) and 171.10 (C); *m/z* (ESI$^+$) 468 (22%), 467 (2M+Na$^+$, 100), 245 (M+Na$^+$, 15); *m/z* (ESI$^-$) for $C_9H_5N_2O_5$ 221 (M-H$^-$, 100%); HRMS (ESI$^+$) found (M+Na$^+$) 245.0177, $C_9H_6N_2O_5Na$ requires 245.0174.

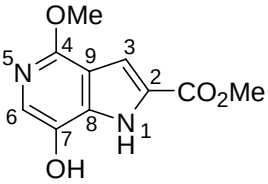
Preparation of compound 12c from 4-hydroxy 7-methoxy 6-azaindole 3c.



12c

Compound **12c** was also prepared according to the same procedure as for compound **12a** (from 7-hydroxy 4-methoxy 5-azaindole **3a**), scale: 6-azaindole **3c** (30 mg, 0.134 mmol), [Bis(trifluoroacetoxy)iodo]benzene PIFA (59 mg, 0.137 mmol), 1:1 acetonitrile/water mixture (8 mL). The crude product was purified by flash chromatography (PE/EtOAc 40:60) to afford **12c** (29.5 mg, 99%) as an orange powder.

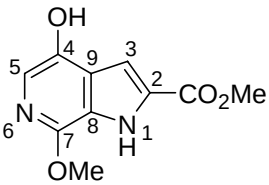
Typical experimental procedure for the BBr_3 monodemethylation of 4,7-dimethoxy azaindole 2a: preparation of 7-hydroxy-4-methoxy 5-azaindole 7-Hydroxy-4-methoxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid methyl ester 3a



3a

To a cooled (-78°C) solution of dimethoxy 5-azaindole **2a** (25 mg, 0.10 mmol) in dichloromethane (2 mL) was added dropwise a 1M solution of BBr_3 in dichloromethane (535 µL, 0.53 mmol). The mixture was then stirred at room temperature for 16 hours. Methanol (2 mL) was added dropwise and the solvent was removed *in vacuuo*. Water (4 mL) was added to the residue and the pH of this solution was carefully adjusted to pH=7 (controlled with a calibrated pH meter) with 0.5 M sodium hydroxide solution. The aqueous phase was extracted with EtOAc (3×10 mL) and, after drying over Na_2SO_4, the solvent was removed under reduced pressure. The resulting crude product was purified by flash chromatography (PE/Et_2O 20:80) to afford compound **3a** (13.5 mg, 57%) as a yellow solid.
Mp 183-184°C (decomposed); ν_{max} (KBr)/cm^{-1} 3315, 2924, 2854, 1711, 1628, 1601, 1541, 1497, 1442, 1389, 1327, 1278, 1208, 1161, 1093, 1071, 989, 936, 829, 749 and 708; δ_H (300 MHz; DMSO-d_6) 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 7.09 (1H, s, ArH), 7.34 (1H, s, ArH), 9.28 (1H, br s, ArOH) and 12.07 (1H, br s, NH); δ_C (50 MHz; DMSO-d_6) 51.90 (CH_3), 52.62 (CH_3), 106.34 (CH), 113.10 (C), 122.95 (CH), 126.84 (C), 133.98 (C), 136.70 (C), 151.77 (C) and 161.02 (C); *m/z* (CI) 223 (MH^+, 100%), 85 (10), 79 (20); HRMS (CI) found (MH^+) 223.0720, $C_{10}H_{11}N_2O_4$ requires 223.0719.

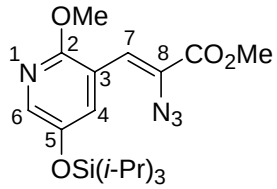
Preparation of 4-hydroxy-7-methoxy 6-azaindole 3c from monodemethylation of 4,7-dimethoxy azaindole 2c. 4-Hydroxy-7-methoxy-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid methyl ester 3c



3c

Compound **3c** was prepared according to the same procedure as for compound **3a**, scale: 6-azaindole **2c** (25 mg, 0.10 mmol), dichloromethane (2 mL), 1M solution BBr_3 in CH_2Cl_2 (266 µL, 0.26 mmol). The crude product was purified by flash chromatography (PE/Et_2O 30:70) to afford **3c** (13 mg, 55%) as a yellow powder.
Mp 203-204°C (decomposed); ν_{max} (KBr)/cm^{-1} 3325, 2924, 2852, 1709, 1512, 1449, 1413, 1333, 1262, 1199, 1090, 1063, 820, 776 and 747; δ_H (300 MHz; DMSO-d_6) 3.86 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 7.16 (1H, s, ArH), 7.17 (1H, s, ArH), 9.41 (1H, s, ArOH) and 12.42 (1H, br s, NH); δ_C (75 MHz; DMSO-d_6) 51.98 (CH_3), 52.65 (CH_3), 105.52 (CH), 117.58 (CH), 123.21 (C), 124.88 (C), 128.48 (C), 143.11 (C), 145.19 (C) and 161.13 (C); *m/z* (ESI^+) 223 (MH^+, 100%), 209 (24), 191 (23); *m/z* (ESI^-) 425 (100%), 237 (27), 221 (M-H^-, 30); HRMS (ESI^+) found (MH^+) 223.0717, $C_{10}H_{11}N_2O_4$ requires 223.0719.

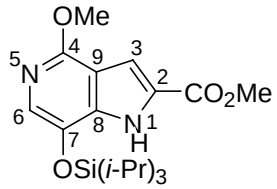
2-Azido-3-(2-methoxy-5-triisopropylsilanyloxy-pyridin-3-yl)-acrylic acid methyl ester 13



13

Sodium metal (540 mg, 23.5 mmol) was dissolved in anhydrous methanol (17 mL) at 0°C under argon. To this preformed sodium methoxide solution at 0°C was quickly added a solution of aldehyde **5c** (1.77 g, 5.7 mmol) and methyl azidoacetate (2.50 g, 21.7 mmol) in methanol (17 mL). The mixture was stirred at 25°C for two hours, then poured onto crushed ice (120 g) and held for one hour at 4°C. After addition of dichloromethane (100 mL) and decantation, the aqueous phase was extracted with dichloromethane (3×150 mL). The organic phases were washed with water (2×150 mL) and dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the residue was purified by flash chromatography (PE/EtOAc 70:30) to afford acrylate **13** (457 mg, 20%) as an orange solid.
Mp 61-63°C (decomposed); ν_{max} (KBr)/cm^{-1} 3409, 3093, 2946, 2892, 2867, 2123, 1716, 1612, 1589, 1564, 1468, 1437, 1425, 1403, 1379, 1290, 1277, 1260, 1227, 1141, 1086, 1026, 1009, 901, 883, 864, 834, 748, 740 and 692; δ_H (300 MHz; $CDCl_3$) 1.12 (18H, br d, J = 6.8, ($CH(CH_3)_2)_3$), 1.26 (3H, m, ($CH(CH_3)_2)_3$), 3.91 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 7.18 (1H, s, CH), 7.77 (1H, d, J = 3.0, ArH) and 8.15 (1H, d, J = 3.0, ArH); δ_C (50 MHz; $CDCl_3$) 12.57 (CH), 17.87 (CH_3), 52.99 (CH_3), 53.79 (CH_3), 116.23 (C), 117.98 (CH), 126.66 (C), 130.30 (CH), 138.23 (CH), 147.08 (C), 156.00 (C) and 163.80 (C); *m/z* (ESI) 407 (MH^+, 12%), 380 (23), 379 (MH^+-N_2, 100).

4-Methoxy-7-triisopropylsilanyloxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid methyl ester 14

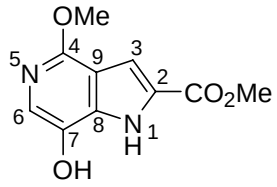


14

A solution of azidoacrylate **13** (369 mg, 0.9 mmol) in dry xylene (32 mL) was added dropwise onto hot (140°C) xylene (18 mL). After addition, the mixture was heated at 140°C for one hour and then cooled down to room temperature. The xylene solution was then chromatographed over silica gel (eluent PE/EtOAc 90:10) to give 5-azaindole **14** (266 mg, 77%) as a pale yellow solid.
Mp 134-135°C; ν_{max} (KBr)/cm^{-1} 3423, 3114, 2969, 2943, 2866, 1723, 1606, 1546, 1497, 1460,

1432, 1382, 1352, 1309, 1296, 1275, 1239, 1215, 1189, 1178, 1083, 1011, 885, 850 and 833; δ_H (300 MHz; $CDCl_3$) 1.13 (18H, d, J = 7.2, ($CH(CH_3)_2)_3$), 1.33 (3H, m, ($CH(CH_3)_2)_3$), 3.95 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 7.27 (1H, d, J = 2.3, H3), 7.50 (1H, s, H6) and 8.91 (1H, br s, NH); δ_C (50 MHz; $CDCl_3$) 12.81 (CH), 17.98 (CH_3), 52.20 (CH_3), 53.25 (CH_3), 107.98 (CH), 114.12 (C), 126.46 (C), 126.81 (CH), 135.60 (C), 135.88 (C), 153.70 (C) and 161.80 (C); *m/z* (ESI^+) 380 (24%), 379 (MH^+, 100), 365 (13); *m/z* (ESI^-) 378 (31%), 377 ($M\text{-}H^-$, 100); HRMS (ESI^+) found (MH^+) 379.2052, $C_{19}H_{31}N_2O_4Si$ requires 379.2053.

Fluoride promoted deprotection of the TIPS-protected 5-azaindole 14: preparation of 7-hydroxy-4-methoxy 5-azaindole 3a.

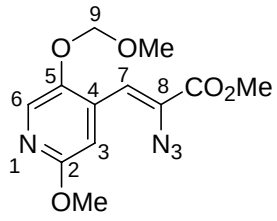


3a

A tetra *n*-butyl-ammonium fluoride 1M solution in THF (1.15 mL, 1.15 mmol) was added to a stirred solution of 5-azaindole **7** (290 mg, 0.76 mmol) in anhydrous THF (1.2 mL) at 0°C under argon. The temperature was allowed to raise to room temperature and the resulting mixture for stirred for 35 minutes. After addition of water (1.5 mL) and EtOAc (10mL), the aqueous phase was extracted with EtOAc (2×10 mL). The organic phases was washed with water (2×10 mL) and dried over Na_2SO_4. After filtration and removal of the solvents under reduced pressure, the residue was purified by flash chromatography (PE/EtOAc 40:60) to afford **3a** as an orange solid (157 mg, 92%).

Spectral data of the product were similar to those of compound **3a** which was obtained after BBr_3-mediated demethylation of 4,7-dimethoxy 5-azaindole **2a**.

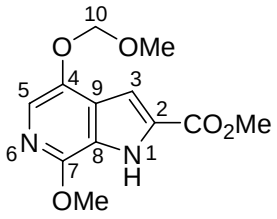
2-Azido-3-(2-methoxy-5-methoxymethoxy-pyridin-4-yl)-acrylic acid methyl ester 15a



15a

Sodium metal (95 mg, 4.1 mmol) was dissolved in anhydrous methanol (3 mL) at 0°C under argon. To this preformed sodium methoxide solution at 0°C was quickly added a solution of aldehyde **6b** (199 mg, 1.0 mmol) and methyl azidoacetate (440 mg, 3.8 mmol) in methanol (3 mL). The mixture was stirred at 30°C for one hour, then poured onto crushed ice (20 g) and held for one hour at 4°C. The product **15a** was recovered by filtration on a sintered glass funnel as a pale yellow solid (60.6 mg, 21%).
Mp 78-79°C (decomposed); ν_{max} (KBr)/cm^{-1} 3418, 3105, 2956, 2856, 2129, 1716, 1618, 1606, 1546, 1482, 1434, 1381, 1319, 1275, 1260, 1219, 1202, 1155, 1084, 1039, 989 and 962; δ_H (300 MHz; $CDCl_3$) 3.51 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 5.15 (2H, s, CH_2OCH_3), 7.15 (1H, s, CH), 7.55 (1H, s, ArH), 8.04 (1H, s, ArH); δ_C (50 MHz; $CDCl_3$) 53.4 (CH_3), 53.67 (CH_3), 56.38 (CH_3), 96.42 (CH_2), 110.61 (CH), 116.04 (CH), 129.49 (C), 133.76 (CH), 134.05 (C), 146.50 (C), 159.50 (C) and 163.46 (C); *m/z* (ESI) 295 (MH^+, 7%), 267 (MH^+-N_2, 69), 223 (41), 191 (100), 177 (36).

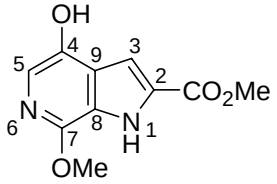
7-Methoxy-4-methoxymethoxy-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid methyl ester 16a



16a

Compound **16a** was prepared according to the same procedure as for compound **2a**, scale: azidoacrylate **15a** (36.6 mg, 0.12 mmol), xylene (11 mL). The crude product was purified by flash chromatography (PE/EtOAc 70:30) to afford **16a** (yellow powder, 10.1 mg, 31%).
Mp 119-120°C; ν_{max} (KBr)/cm^{-1} 3322, 3299, 1716, 1706, 1510, 1443, 1333, 1314, 1299, 1274, 1227, 1206, 1163, 1149, 1092, 1055, 979, 917, 779 and 750; δ_H (300 MHz; $CDCl_3$) 3.55 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.07 (3H, s, OCH_3), 5.26 (2H, s, CH_2OCH$_3$), 7.25 (1H, d, J = 2.3, H3), 7.54 (1H, s, H5) and 9.21 (1H, br s, NH); δ_C (50 MHz; $CDCl_3$) 52.32 (CH_3), 53.32 (CH_3), 56.27 (CH_3), 96.06 (CH_2), 105.83 (CH), 120.93 (CH), 123.06 (C), 126.54 (C), 128.46 (C), 143.72 (C), 147.40 (C) and 161.69 (C); *m/z* (ESI$^+$) 268 (13%), 267 (MH$^+$, 100), 223 (15); HRMS (CI) found (MH$^+$) 267.0987, $C_{12}H_{15}N_2O_5$ requires 267.0981.

Acidic deprotection of the MOM-protected 6-azaindole 16a: preparation of 4-hydroxy-7-methoxy 6-azaindole 3c



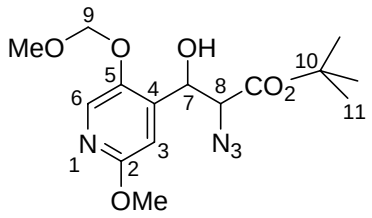
3c

To a solution of 6-azaindole **16a** (80 mg, 0.30 mmol) in THF (1 mL) was added 3N aqueous HCl (1.1 mL) and the resulting mixture was stirred at 50°C for 3 hours. After this time, the mixture was cooled to room temperature and water (10 mL) was added followed by neutralisation (pH=7-8) with solid K_2CO_3. The aqueous phase was then extracted with EtOAc (3×10 mL). After drying of the organic phase over Na_2SO_4, filtration and removal of the solvents under reduced pressure, the residue was purified by flash chromatography (PE/EtOAc 40:60) to afford **3c** (52 mg, 77%) as an orange solid.

Spectral data of the product were similar to those of compound **3c** which was obtained after BBr_3-mediated demethylation of 4,7-dimethoxy 5-azaindole **2c**.

2-Azido-3-(2-methoxy-5-methoxymethoxy-pyridin-4-yl)-acrylic acid *tert*-butyl ester 15b

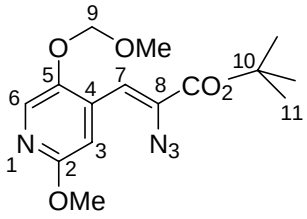
Formation of the azidoalcohol 11b:



11b

Sodium hydride (60% dispersion in oil, 60 mg, 1.52 mmol) was added portionwise to cold (-30°C) isopropanol (4.5 mL). To the resulting sodium isopropoxide solution was then added solid aldehyde **6b** (150 mg, 0.76 mmol) until completely dissolved. A solution of *tert*-butyl azidoacetate (477 mg, 3.04 mmol) in isopropanol (0.8 mL) was then added dropwise to the reaction mixture. After stirring for four hours at -30°C, water (15 mL) was added. The mixture was allowed to warm to room temperature, then the aqueous phase was extracted with EtOAc (3×15 mL) and the combined organic phases dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the residue was purified by flash chromatography (PE/EtOAc 70:30) to afford azidoalcohol **11b** (170 mg, 63%) as a yellow oil.
This compound **11b** was obtained as a 1:1 mixture of two diastereomers: dia1 and dia2.
δ_H (300 MHz; DMSO-d_6) 1.20 (9H, s, *t*-Bu dia1), 1.48 (9H, s, *t*-Bu dia2), 3.39 (3H, s, OCH_3 dia 1), 3.42 (3H, s, OCH_3 dia 2), 3.80 (3H, s, OCH_3 dia 1), 3.81 (3H, s, OCH_3 dia 2), 3.93-3.97 (2H, m, CHN_3 for both dia), 5.14-5.24 (5H, m, C*H*$_2$OCH$_3$ for both dia + C*H*OH for dia1), 5.39 (dd, *J* = 5.3-2.6, 1H, C*H*OH for dia2), 6.24 (1H, d, *J* = 5.3, disappears after D_2O addition, OH for dia1), 6.37 (1H, d, *J* = 5.3, disappears after D_2O addition, OH for dia2), 6.83(1H, s, ArH for dia1), 6.90(1H, s, ArH for dia2), 7.88 (1H, s, ArH for dia1) and 7.90 (1H, s, ArH for dia2); δ_C (75 MHz; DMSO-d_6) 27.32 (CH_3), 27.69 (CH_3), 53.16 (CH_3), 53.19 (CH_3), 55.88 (CH_3), 56.04 (CH_3), 63.26 (CH), 64.13 (CH), 68.85 (CH), 69.40 (CH), 82.03 (C), 82.37 (C), 95.08 (CH_2), 95.58 (CH_2), 108.40 (CH), 108.50 (CH), 131.79 (CH), 132.41 (CH), 143.25 (C), 143.92 (C), 144.83 (C), 145.26 (C), 158.71 (C), 158.77 (C), 166.62 (C) and 167.37 (C). (It was impossible to assign with certitude signals for both diastereomers); *m/z* (ESI$^+$) 731 (2M+Na$^+$, 14%), 377 (M+Na$^+$, 54), 355 (MH$^+$, 100), 299 (MH$^+$-isobutene $(CH_3)_2C{=}CH_2$, 36).

Formation and *in situ* elimination of the mesylate of compound 11b: formation of azidoacrylate 15b:

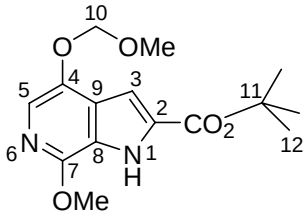


15b

To a solution of **11b** (649 mg, 1.83 mmol) in dichloromethane (50 mL) at 45°C was added quickly methanesulfonyl chloride (710 µl, 9.19 mmol) and then triethylamine (2.6 ml, 18.30 mmol). The reaction mixture was stirred at 45°C for one hour then cooled to room temperature. After addition of a saturated aqueous solution of $NaHCO_3$ (50 mL) and decantation, the aqueous phase was extracted with CH_2Cl_2 (3×100 mL). The organic phases were washed with brine (2×100 mL) and dried over Na_2SO_4. After filtration and removal of of the solvent under reduced pressure, the residue was purified by flash chromatography (PE/EtOAc 80:20) to afford azidoacrylate **15b** (527 mg, 85%) as a yellow solid.
Mp 63-64°C; ν_{max} (KBr)/cm^{-1} 3435, 2924, 2116, 1712, 1605, 1484, 1384, 1277, 1217, 1200, 1153, 1078, 1037, 995 and 886; δ_H (300 MHz; DMSO-d_6) 1.54 (9H, s, *t*-Bu), 3.43 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 5.20 (2H, s, C*H*$_2$OCH$_3$), 6.99 (1H, s, CH), 7.44 (1H, s, ArH) and 8.02 (1H, s,

ArH); δ_C (75 MHz; DMSO-d_6) 27.55 (CH_3), 53.28 (CH_3), 56.10 (CH_3), 83.84 (C), 96.45 (CH_2), 109.50 (CH), 114.10 (CH), 130.91 (C), 133.79 (C), 134.59 (CH), 145.85 (C), 158.70 (C) and 161.03 (C); *m/z* (ESI^+): 359 (MNa^+, 12%), 337 (MH^+, 26), 309 (MH^+-N_2, 26), 253 (MH^+-N_2-isobutene $(CH_3)_2C{=}CH_2$, 100), 177 (43).

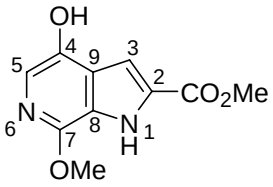
7-Methoxy-4-methoxymethoxy-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid tert-butyl ester 16b



16b

Compound **16b** was prepared according to the same procedure as for compound **2a**, scale: azidoacrylate **15b** (72 mg, 0.21 mmol), xylene (7.2 mL), reaction time 2 hours. The crude product was purified by flash chromatography (PE/EtOAc 70:30) to afford **16b** (47 mg, 72%) as a yellow powder.
Mp 93-94°C; ν_{max} (KBr)/cm^{-1} 3307, 2979, 2936, 1713, 1620, 1587, 1506, 1445, 1408, 1370, 1336, 1300, 1278, 1227, 1208, 1154, 1093, 1059, 973 and 923; δ_H (300 MHz; DMSO-d_6) 1.56 (9H, s, *t*-Bu), 3.43 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 5.24 (2H, s, CH_2OCH_3), 7.03 (s, 1H, ArH), 7.40 (1H, s, ArH) and 12.44 (1H, br s, NH); δ_C (75 MHz; DMSO-d_6) 27.88 (CH_3), 52.89 (CH_3), 55.78 (CH_3), 81.55 (C), 95.37 (CH_2), 104.48 (CH), 119.66 (CH), 122.83 (C), 125.74 (C), 130.98 (C), 142.92 (C), 147.04 (C) and 159.84 (C); *m/z* (ESI^+) 308 (MH^+, 46%), 252 (100), 222 (48); HRMS (EI) found ($M^{+\bullet}$) 308.1370, $C_{15}H_{20}N_2O_5$ requires 308.1372.

Acidic deprotection and *in situ* transesterification of the MOM-protected 6-azaindole 16b: preparation of 4-hydroxy-7-methoxy 6-azaindole 3c.

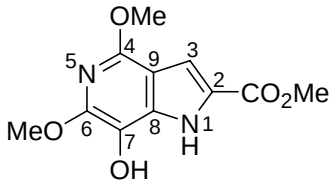


3c

To a solution of 6-azaindole **16b** (48 mg, 0.16 mmol) in methanol (4 mL) was added 3N aqueous HCl (1 mL) and the resulting mixture stirred at 25°C for 4h30: after this time, TLC analysis showed the complete consumption of the starting material. The reaction was then heated to 50°C for 20 hours. A new product was formed whose Rf matched that of compound **3c**. After this time, the mixture was evaporated to dryness. Water (4 mL) was then added to the residue and the pH of this solution was carefully adjusted to pH=7 (controled with a calibrated pH meter) with 0.5M sodium hydroxide solution. The aqueous phase was then extracted with EtOAc (4×15 mL) and, after drying over Na_2SO_4, the solvent was removed under reduced pressure. The resulting crude product was purified by flash chromatography (cyclohexane/EtOAc 60:40) to afford compound **3c** (17 mg, 49%) as a light brown solid.

Spectral data of the product were similar to those of compound **3c** which was obtained after BBr_3-mediated demethylation of 4,7-dimethoxy 5-azaindole **2c**.

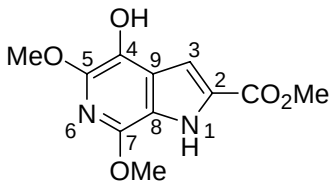
Typical experimental procedure for the oxidation of 7-hydroxy-4-methoxy 5-azaindole 3a: Preparation of 7-Hydroxy-4,6-dimethoxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid methyl ester 17a



17a

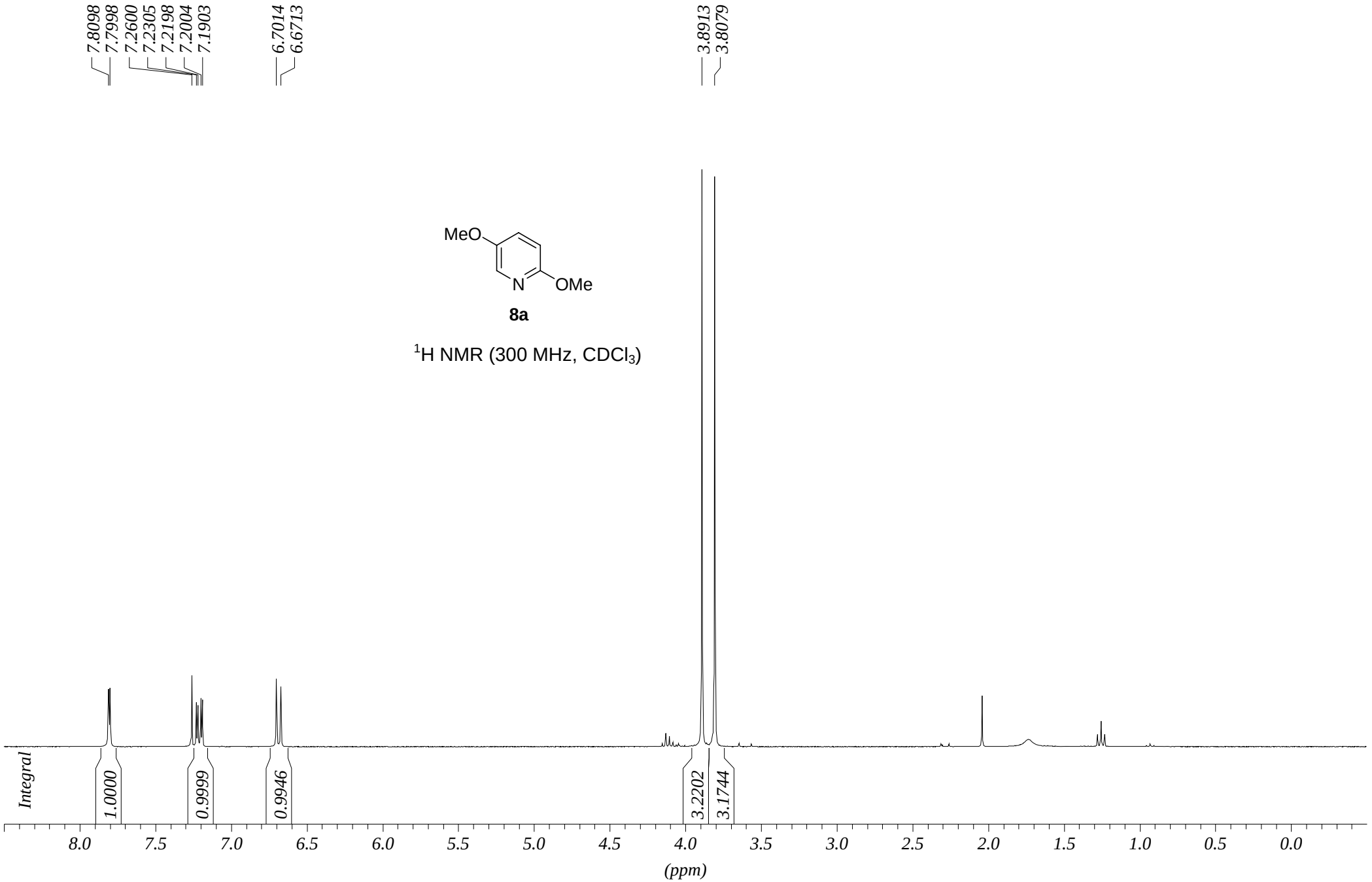
To a solution of **3a** (26 mg, 0.11 mmol) in a 1:1 acetonitrile/methanol mixture (18 mL) at room temperature was added in one portion [Bis(trifluoroacetoxy)iodo]benzene (PIFA) (50 mg, 0.11 mmol). After stirring at room temperature for four hours, the resulting mixture was filtered off on a sintered glass funnel filled with a one cm thick pad of silica gel, washing with EtOAc. After evaporation of the filtrate under reduced pressure, the residue was purified by flash chromatography (cyclohexane/EtOAc 70:30) to afford **17a** (25 mg, 85%) as a yellow powder.
Mp 199-200°C; ν_{max} (KBr)/cm^{-1} 3501, 3373, 2951, 2853, 1702, 1675, 1653, 1612, 1537, 1497, 1470, 1446, 1416, 1377, 1329, 1310, 2289, 2211, 1228, 1042, 977 and 748; δ_H (300 MHz; DMSO-d_6) 3.83 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 7.02 (1H, d, J = 2.0, H3), 8.41 (1H, s, ArOH) and 11.63 (1H, s, NH); δ_C (75 MHz; DMSO-d_6) 51.80 (CH_3), 52.83 (CH_3), 53.63 (CH_3), 106.42 (CH), 108.64 (C), 119.49 (C), 126.73 (C), 136.46 (C), 145.53 (C), 148.19 (C) and 161.07 (C); *m/z* (CI) 254 (13%), 253 (MH^+, 100); HRMS (CI) found (MH^+) 253.0820, $C_{11}H_{13}N_2O_5$ requires 253.0824.

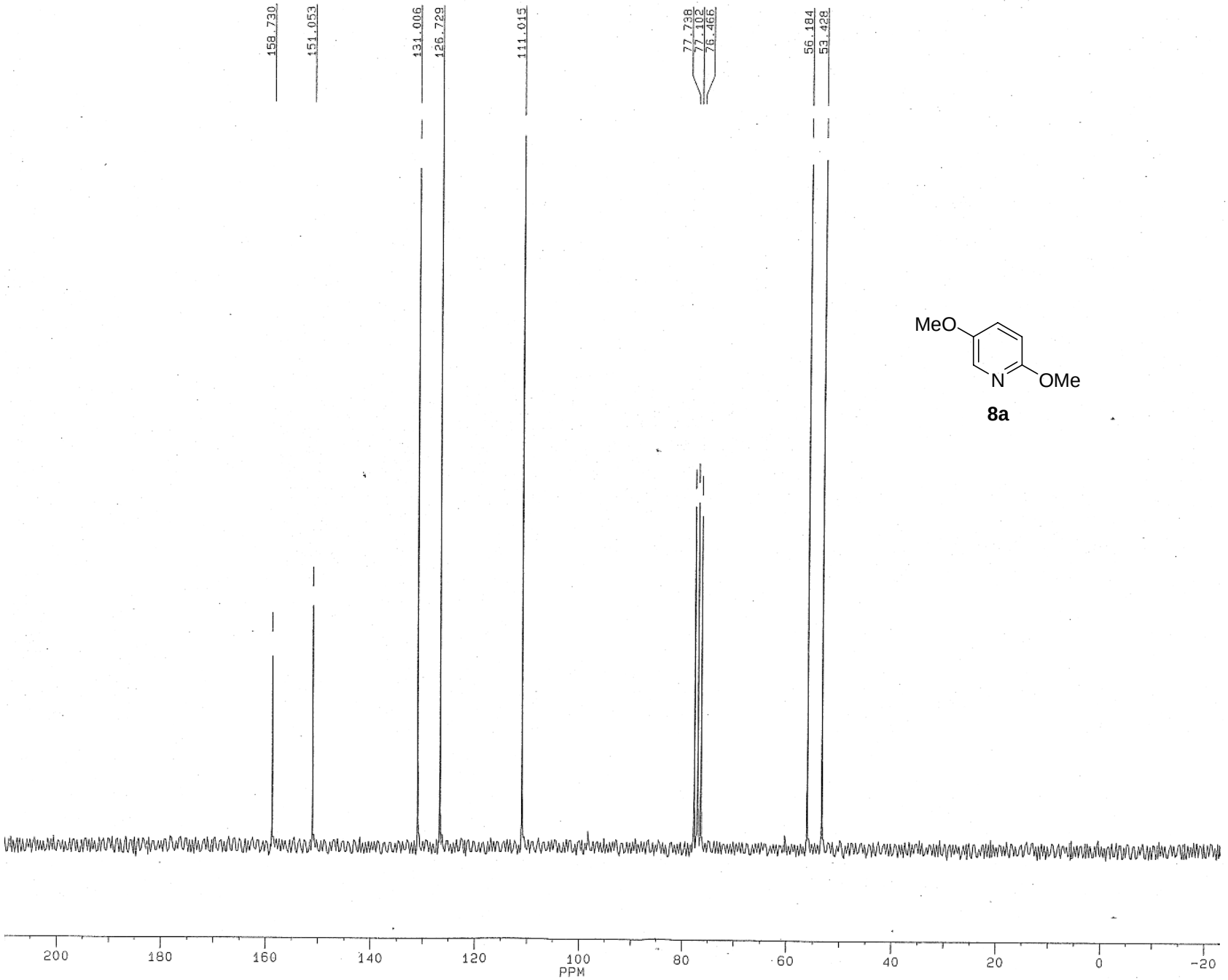
Oxidation of 4-hydroxy-7-methoxy 6-azaindole 3c: Preparation of 4-Hydroxy-5,7-dimethoxy-1*H*-pyrrolo[2,3-*c*]pyridine-2-carboxylic acid methyl ester 17c



17c

Compound **17c** was prepared according to the same procedure as for compound **17a**, scale: azaindole **3c** (50 mg, 0.22 mmol), PIFA (97 mg, 0.22 mmol), 1:1 acetonitrile/methanol mixture (18 mL). The crude product was purified by flash chromatography (cyclohexane/EtOAc 60:40) to afford **17c** (30 mg, 53%) as a yellow powder.
Mp 176-177°C; ν_{max} (KBr)/cm^{-1} 3435, 3323, 2951, 1715, 1644, 1598, 1526, 1507, 1451, 1416, 1354, 1328, 1291, 1250, 1210, 1184, 1125, 1095, 1039, 1000, 977, 907 and 770; δ_H (300 MHz; DMSO-d_6) 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 7.08 (1H, d, J = 2.0, H3), 8.63 (1H, s, ArOH) and 12.10 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): 51.98 (CH_3), 52.86 (CH_3), 53.96 (CH_3), 104.72 (CH), 119.11 (C), 125.78 (C), 127.81 (C), 129.86 (C), 140.43 (C), 140.89 (C) and 161.19 (C); *m/z* (ESI^+) 293 (21%), 253 (MH^+, 100), 238 (27), 223 (28), 209 (25); HRMS (ESI^+) found (MH^+) 253.0822, $C_{11}H_{13}N_2O_5$ requires 253.0824.


7.8098
7.7998
7.2600
7.2305
7.2198
7.2004
7.1903
6.7014
6.6713
3.8913
3.8079
MeO
N
OMe
8a
1H NMR (300 MHz, CDCl3)
Integral
1.0000
0.9999
0.9946
3.2202
3.1744
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
(ppm)



8a

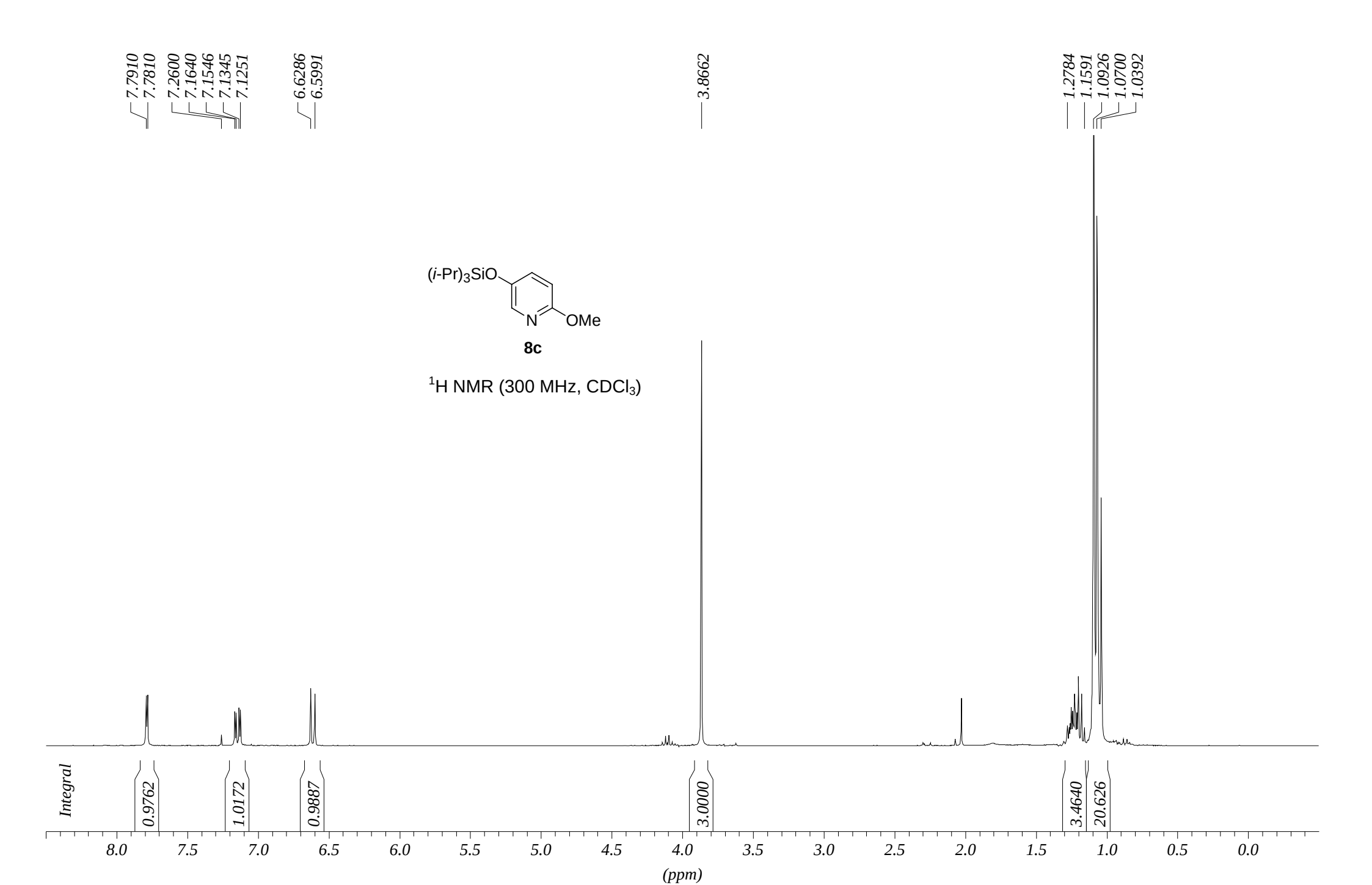
AV061F.113
AU PROG:
X02.AU
DATE 7-4-4
TIME 4:04

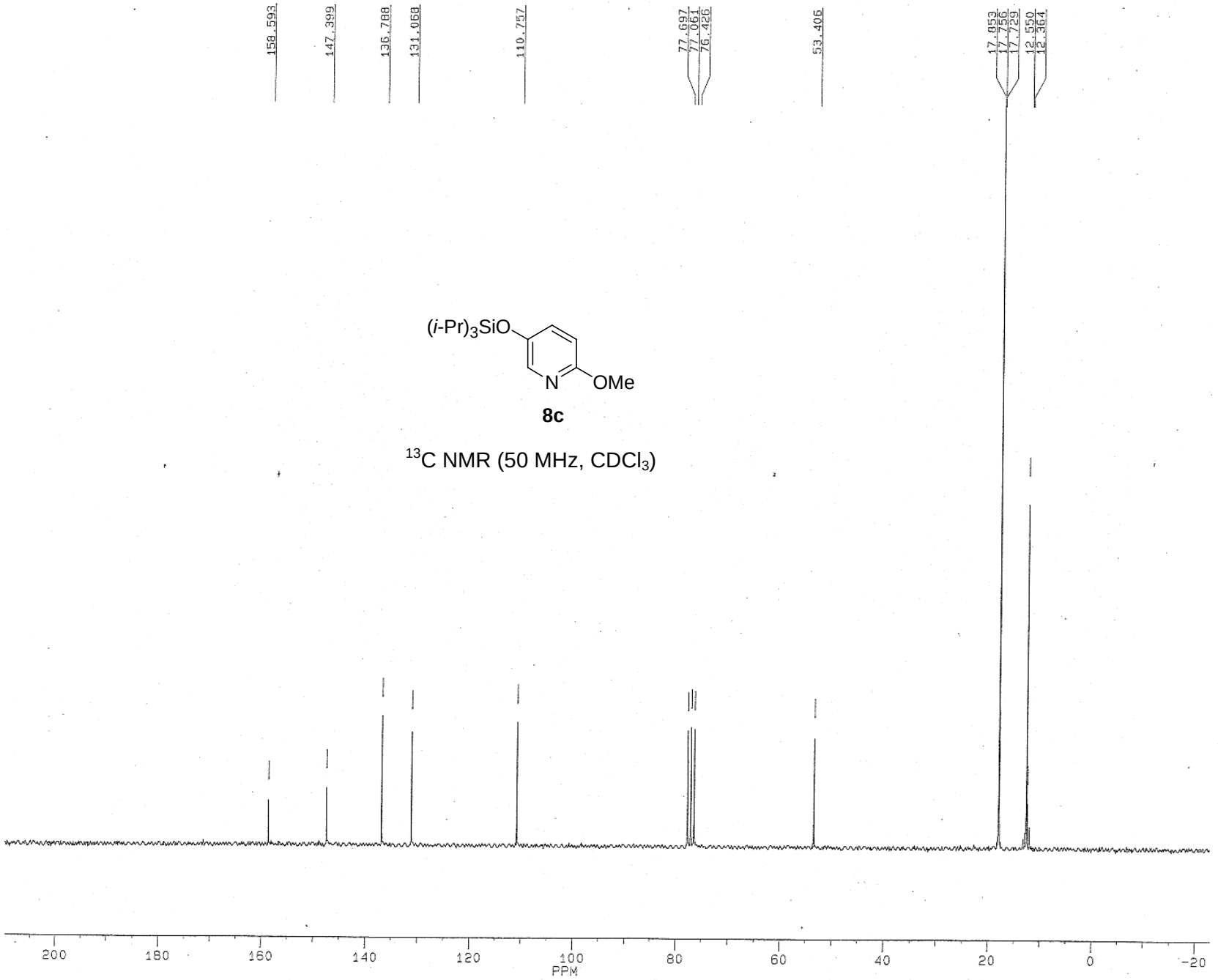
SF 50.323
SY 50.0
O1 8396.387
SI 65536
TD 65536
SW 12500.000
HZ/PT .381

PW 0.0
RD 0.0
AQ 2.621
RG 400
NS 800
TE 297

FW 15700
O2 3154.531
DP 15H DO

LB 1.000
GB 0.0
CX 35.00
CY 20.00
F1 225.342P
F2 -23.044P
HZ/CM 357.132
PPM/CM 7.097
SR 3314.07


7.7910
7.7810
7.2600
7.1640
7.1546
7.1345
7.1251
6.6286
6.5991
3.8662
1.2784
1.1591
1.0926
1.0700
1.0392
(i-Pr)3SiO
N
OMe
8c
1H NMR (300 MHz, CDCl3)
Integral
0.9762
1.0172
0.9887
3.0000
3.4640
20.626
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
(ppm)



BRUKER

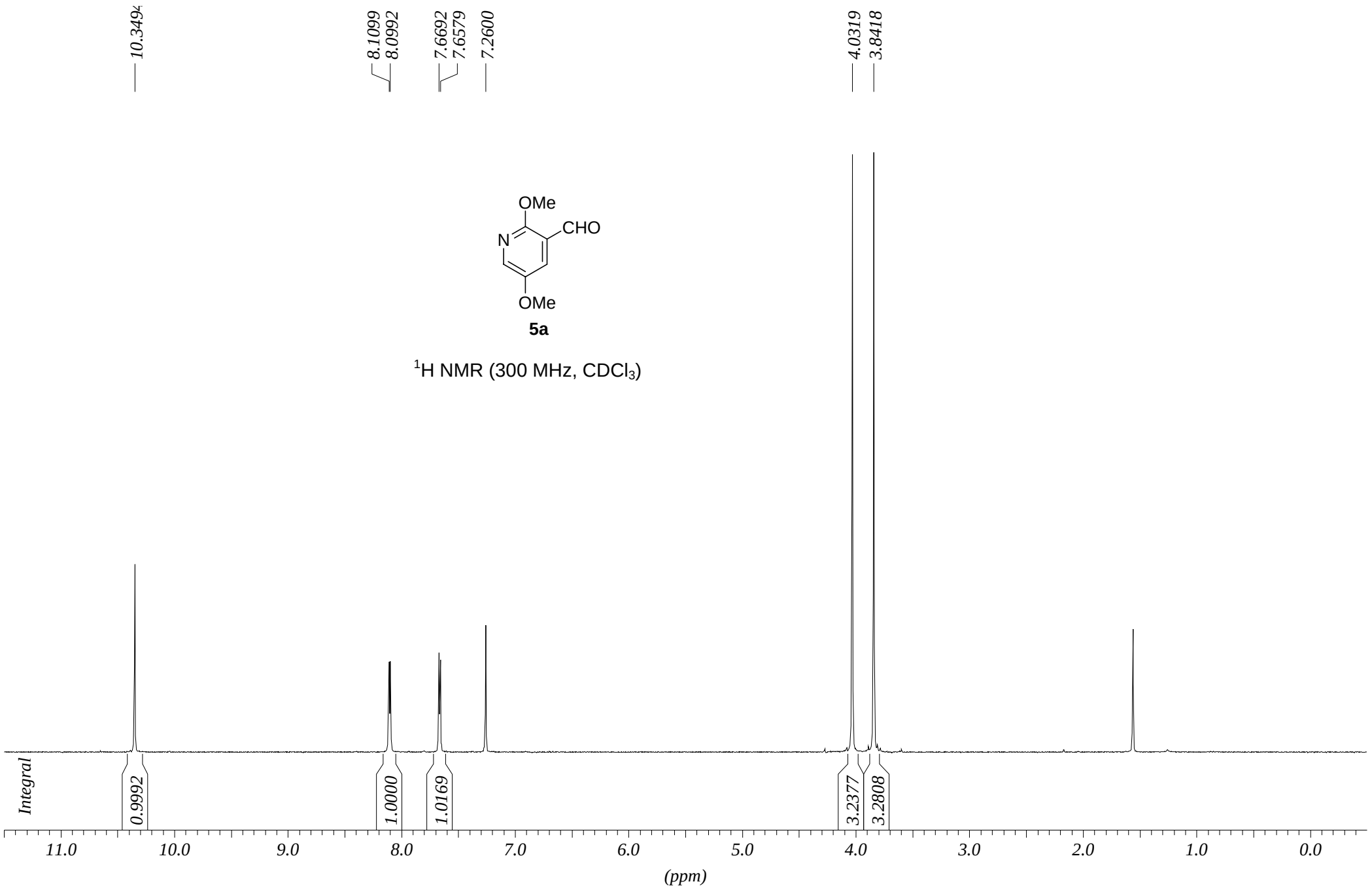
AV060F.114
AU PROG:
X02.AU
DATE 7-4-4
TIME 5:12

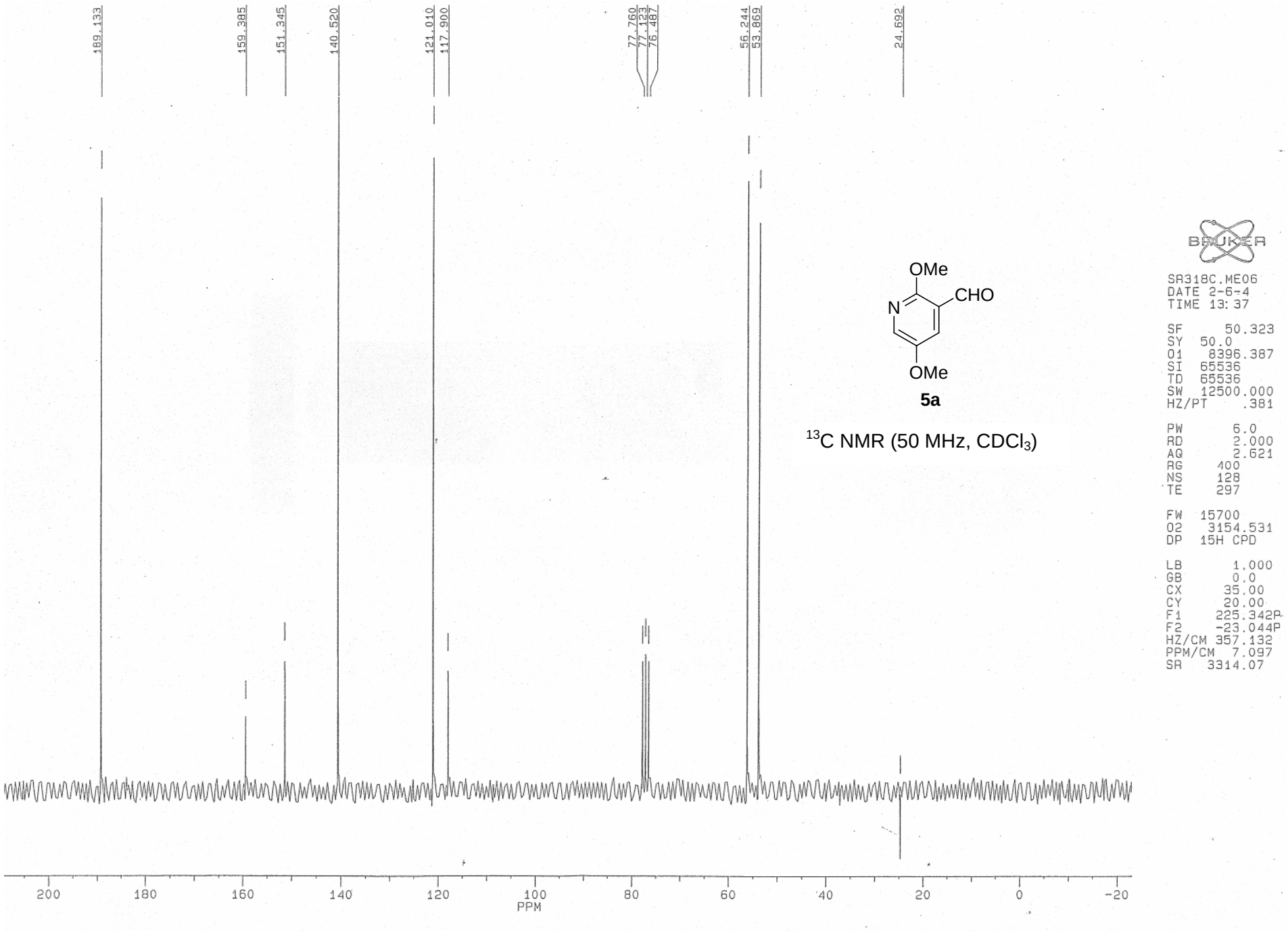
SF 50.323
SY 50.0
O1 8396.387
SI 65536
TD 65536
SW 12500.000
HZ/PT .381

PW 0.0
RD 0.0
AQ 2.621
RG 400
NS 800
TE 297

FW 15700
O2 3154.531
DP 15H D0

LB 1.000
GB 0.0
CX 35.00
CY 20.00
F1 225.221P
F2 -22.923P
HZ/CM 356.783
PPM/CM 7.090
SR 3314.07


10.3494
8.1099
8.0992
7.6692
7.6579
7.2600
4.0319
3.8418
OMe
CHO
N
OMe
5a
1H NMR (300 MHz, CDCl3)
Integral
0.9992
1.0000
1.0169
3.2377
3.2808
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)



5a

^{13}C NMR (50 MHz, $CDCl_3$)

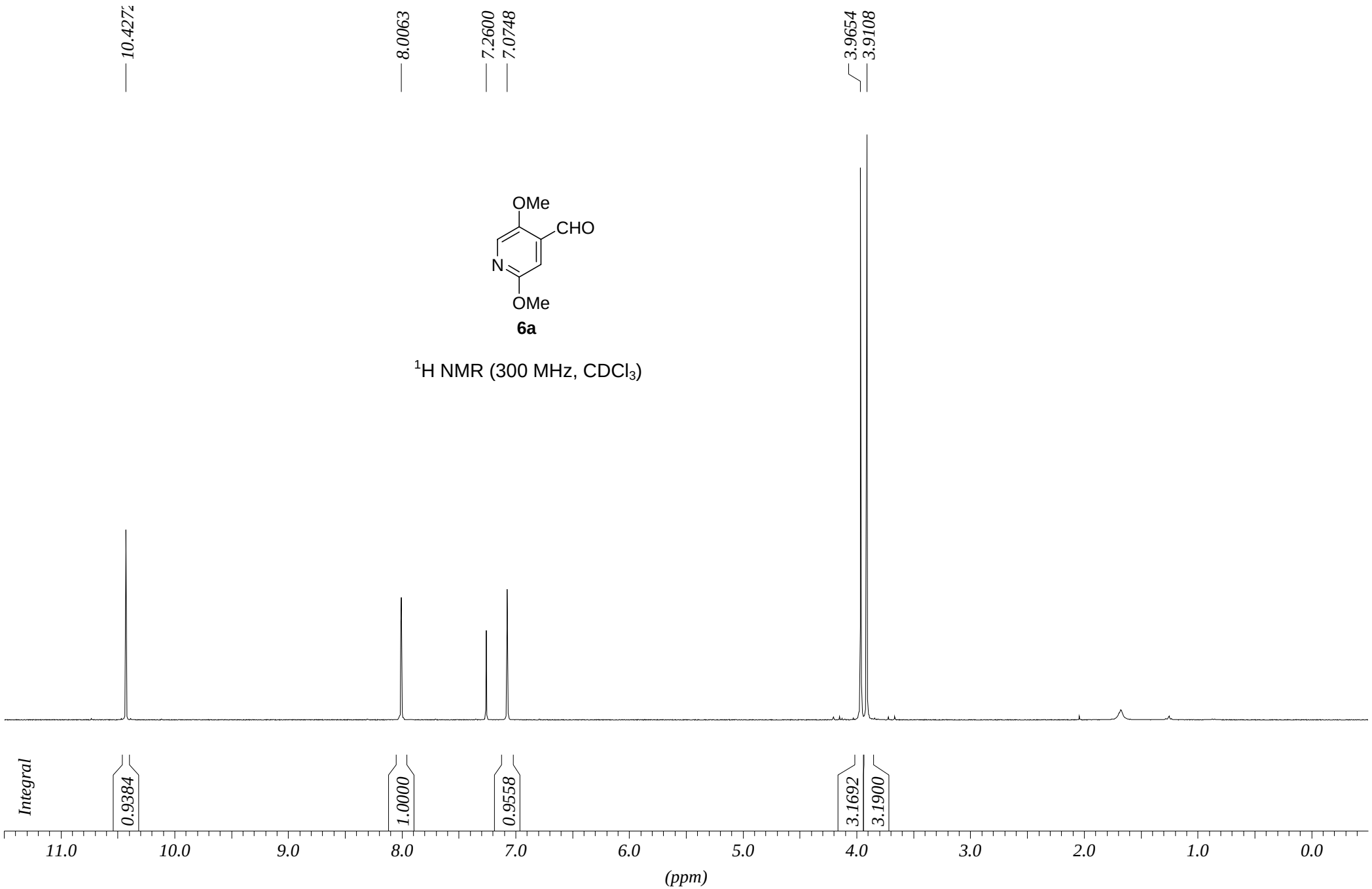
SR318C.ME06
DATE 2-6-4
TIME 13:37

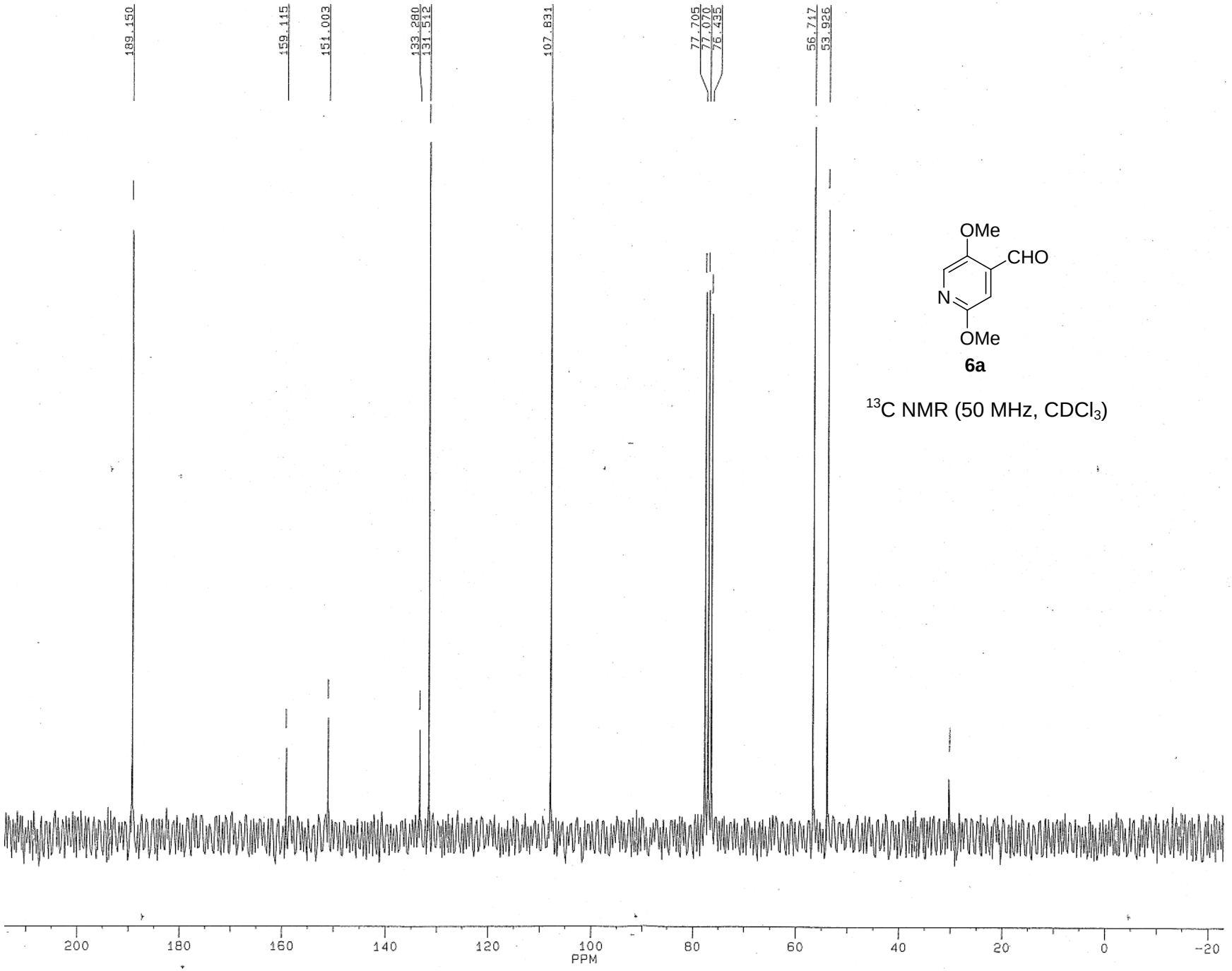
SF 50.323
SY 50.0
O1 8396.387
SI 65536
TD 65536
SW 12500.000
HZ/PT .381

PW 6.0
RD 2.000
AQ 2.621
RG 400
NS 128
TE 297

FW 15700
O2 3154.531
DP 15H CPD

LB 1.000
GB 0.0
CX 35.00
CY 20.00
F1 225.342P
F2 -23.044P
HZ/CM 357.132
PPM/CM 7.097
SR 3314.07


10.4272
8.0063
7.2600
7.0748
3.9654
3.9108
OMe
CHO
N
OMe
6a
1H NMR (300 MHz, CDCl3)
Integral
0.9384
1.0000
0.9558
3.1692
3.1900
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

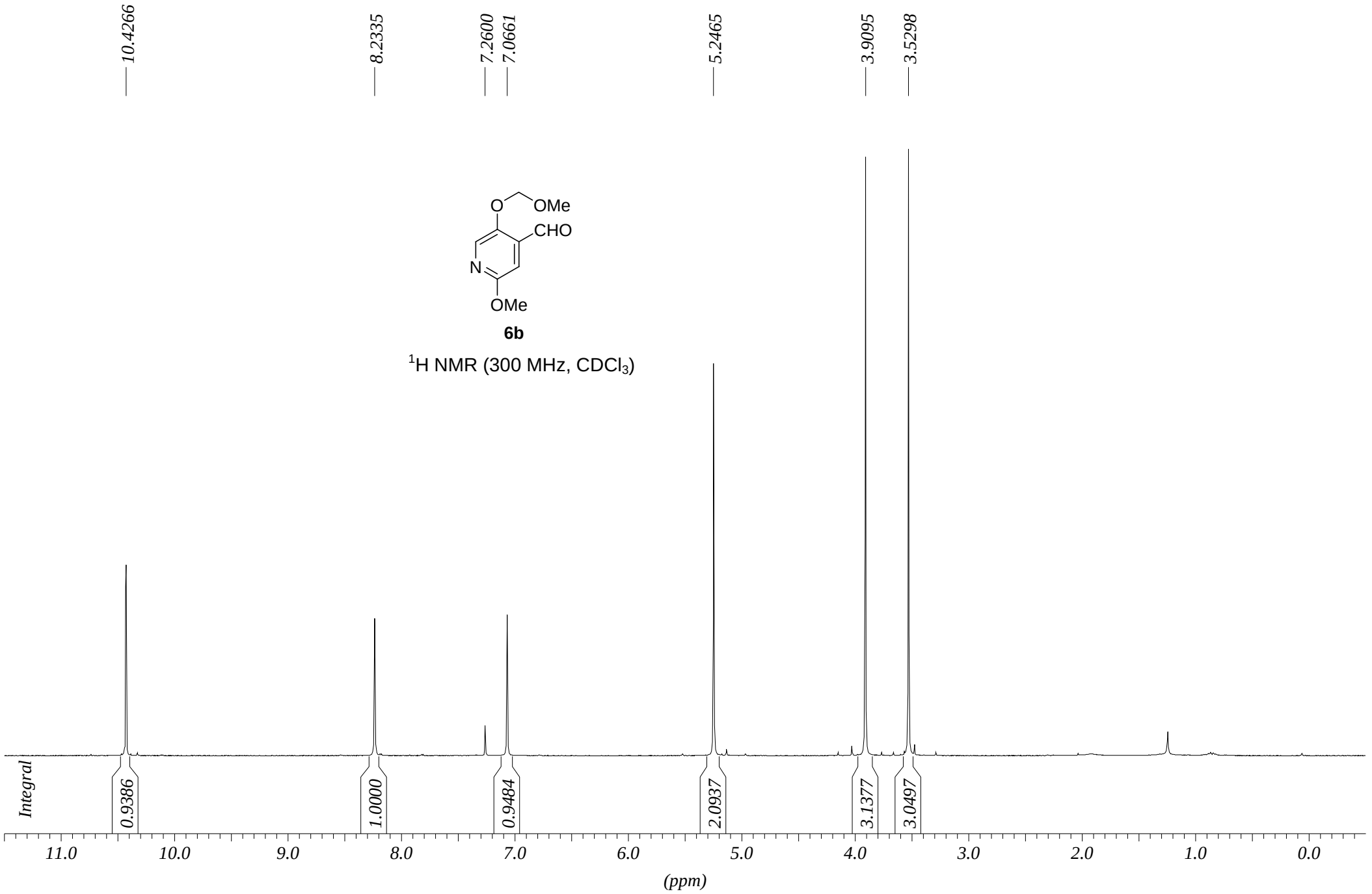


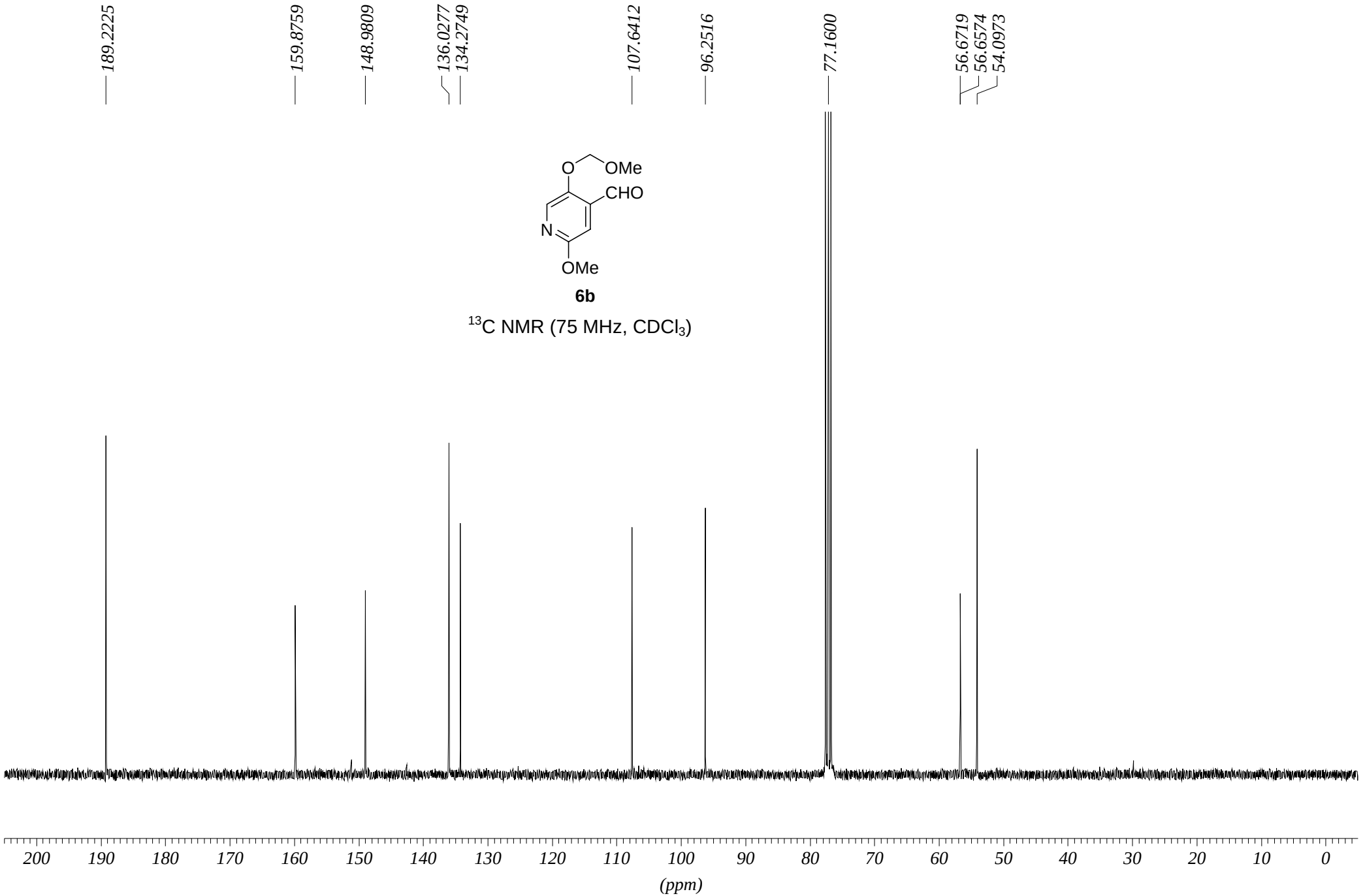
6a

^{13}C NMR (50 MHz, $CDCl_3$)

SR336F2C.07ME
DATE 7-7-4
TIME 15:12

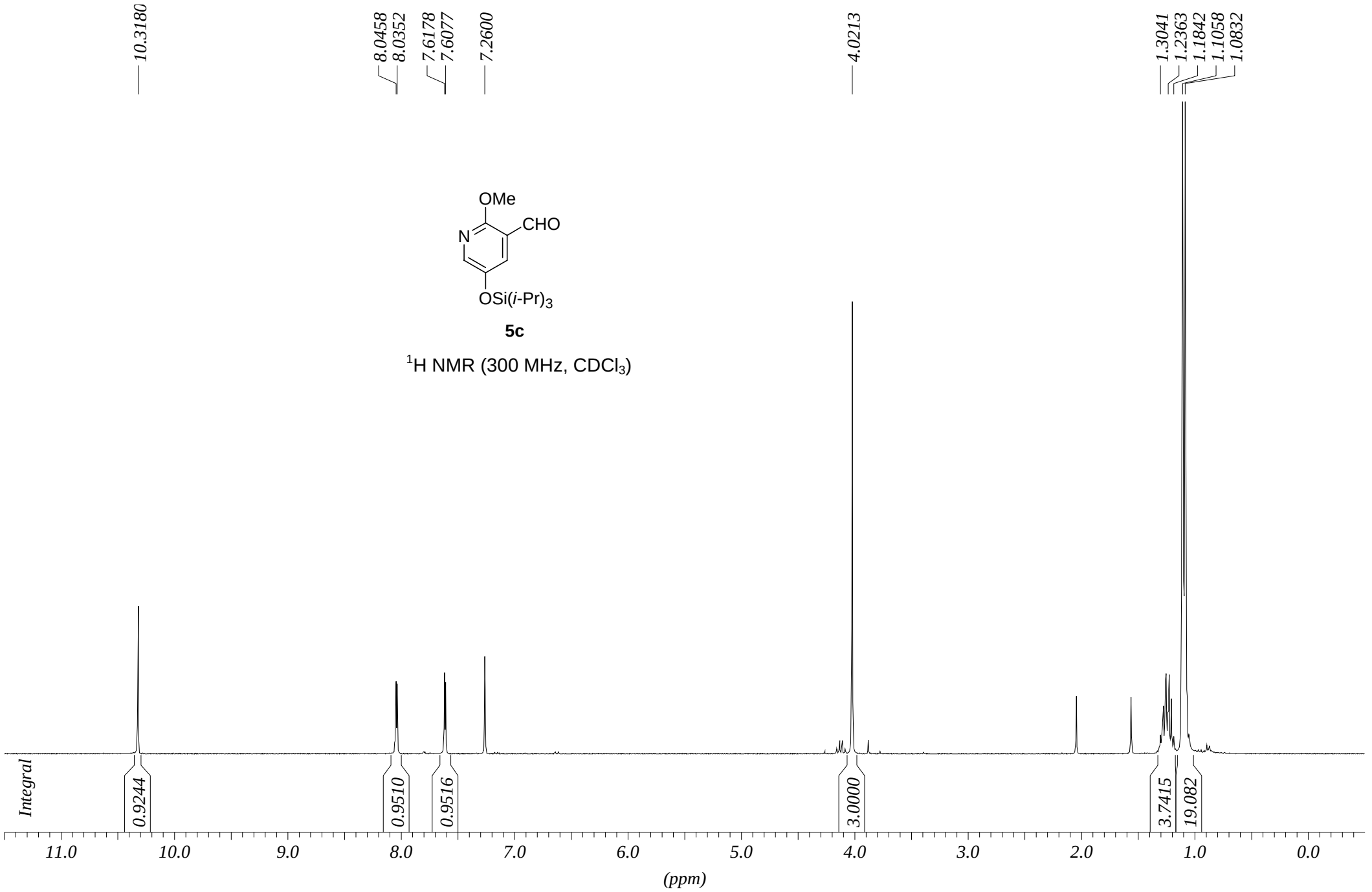
SF	50.323
SY	50.0
O1	8396.387
SI	65536
TD	65536
SW	12500.000
HZ/PT	.381
PW	6.0
RD	2.000
AQ	2.621
RG	400
NS	560
TE	297
FW	15700
O2	3154.531
DP	15H CPD
LB	1.000
GB	0.0
CX	35.00
CY	20.00
F1	225.342P
F2	-23.044P
HZ/CM	357.132
PPM/CM	7.097
SR	3314.07

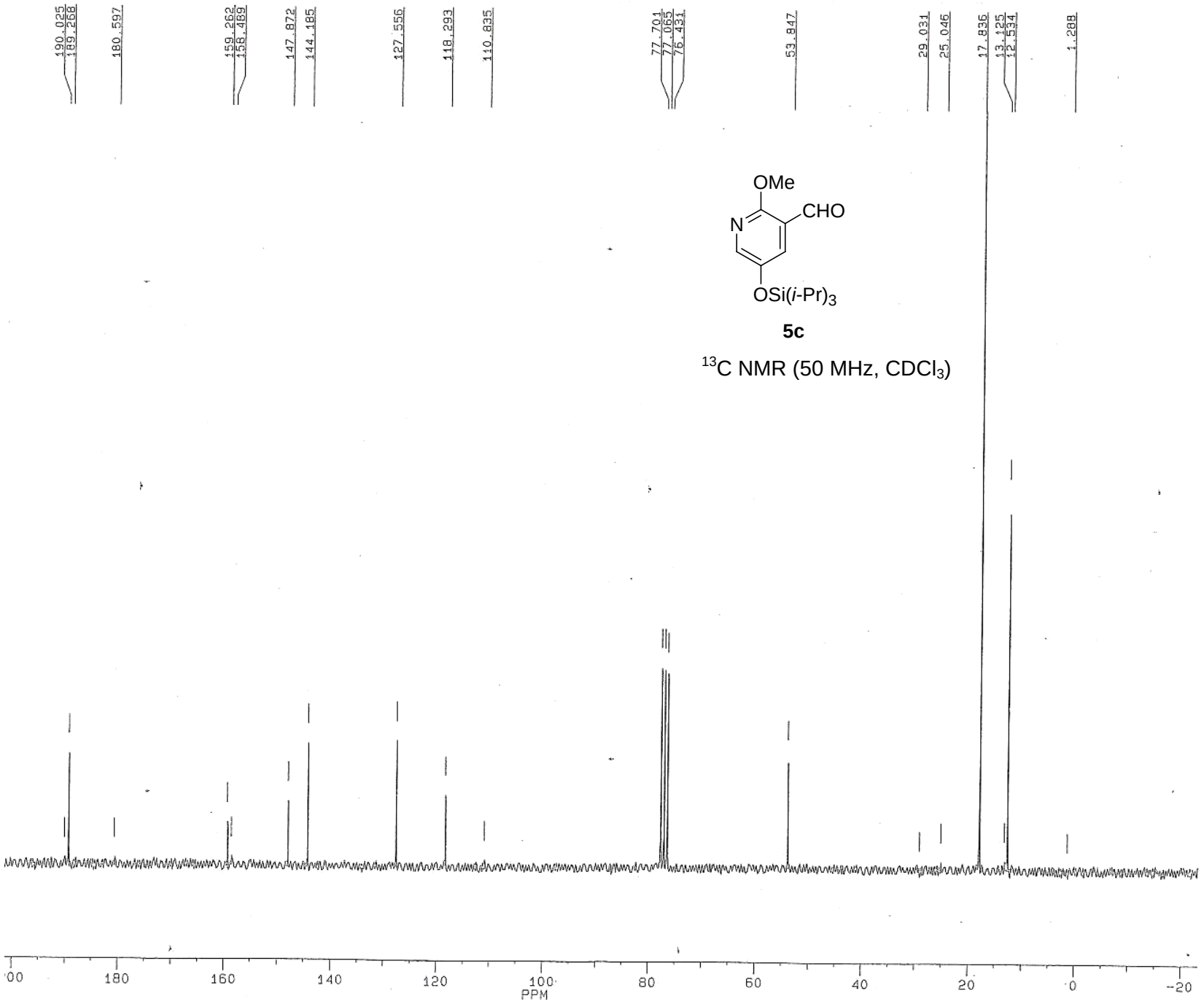

10.4266
8.2335
7.2600
7.0661
5.2465
3.9095
3.5298
O
OMe
CHO
N
OMe
6b
1H NMR (300 MHz, CDCl3)
Integral
0.9386
1.0000
0.9484
2.0937
3.1377
3.0497
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

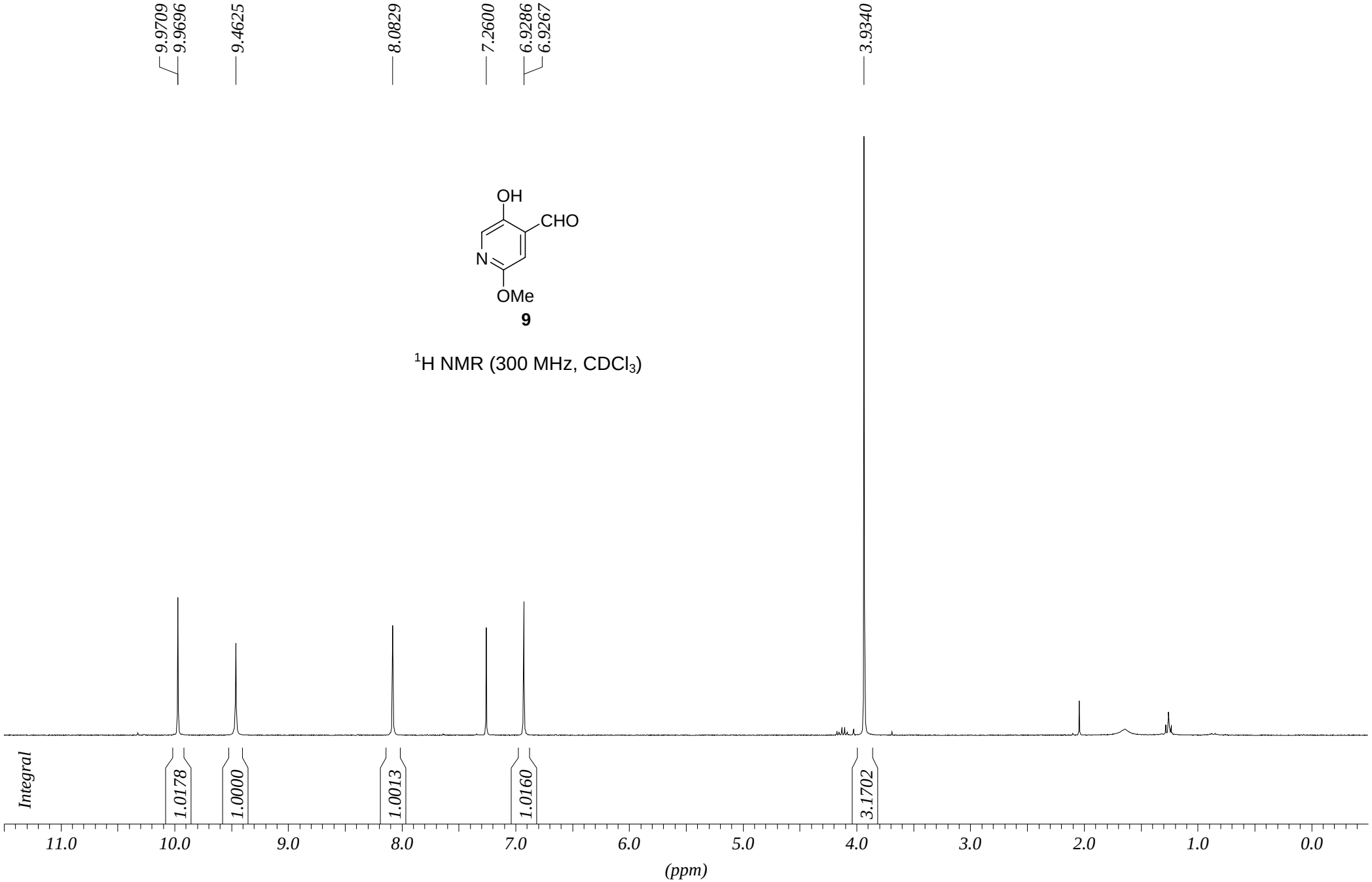


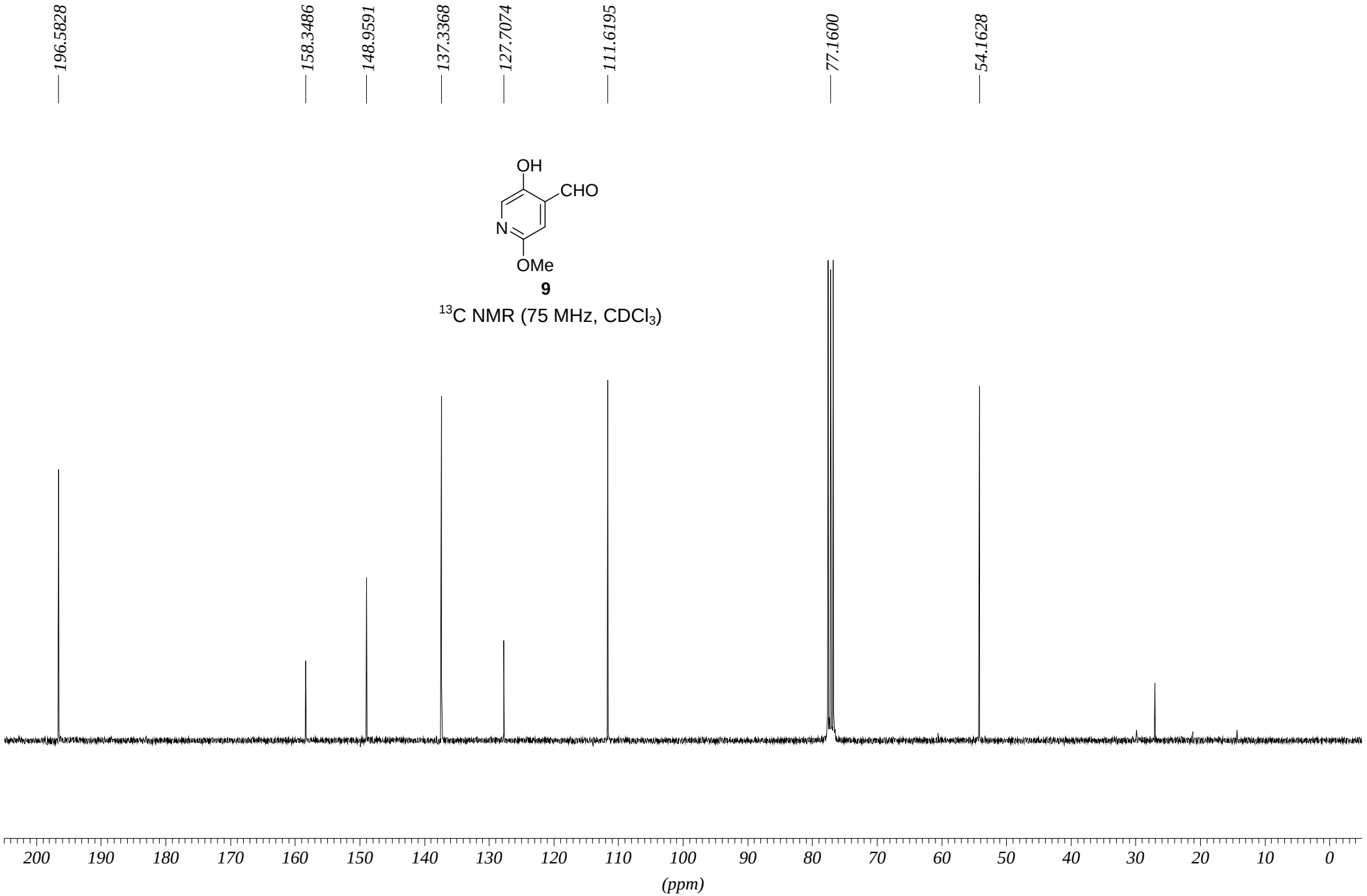
6b

^{13}C NMR (75 MHz, $CDCl_3$)


10.3180
8.0458
8.0352
7.6178
7.6077
7.2600
4.0213
1.3041
1.2363
1.1842
1.1058
1.0832
OMe
CHO
N
OSi(i-Pr)3
5c
1H NMR (300 MHz, CDCl3)
Integral
0.9244
0.9510
0.9516
3.0000
3.7415
19.082
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

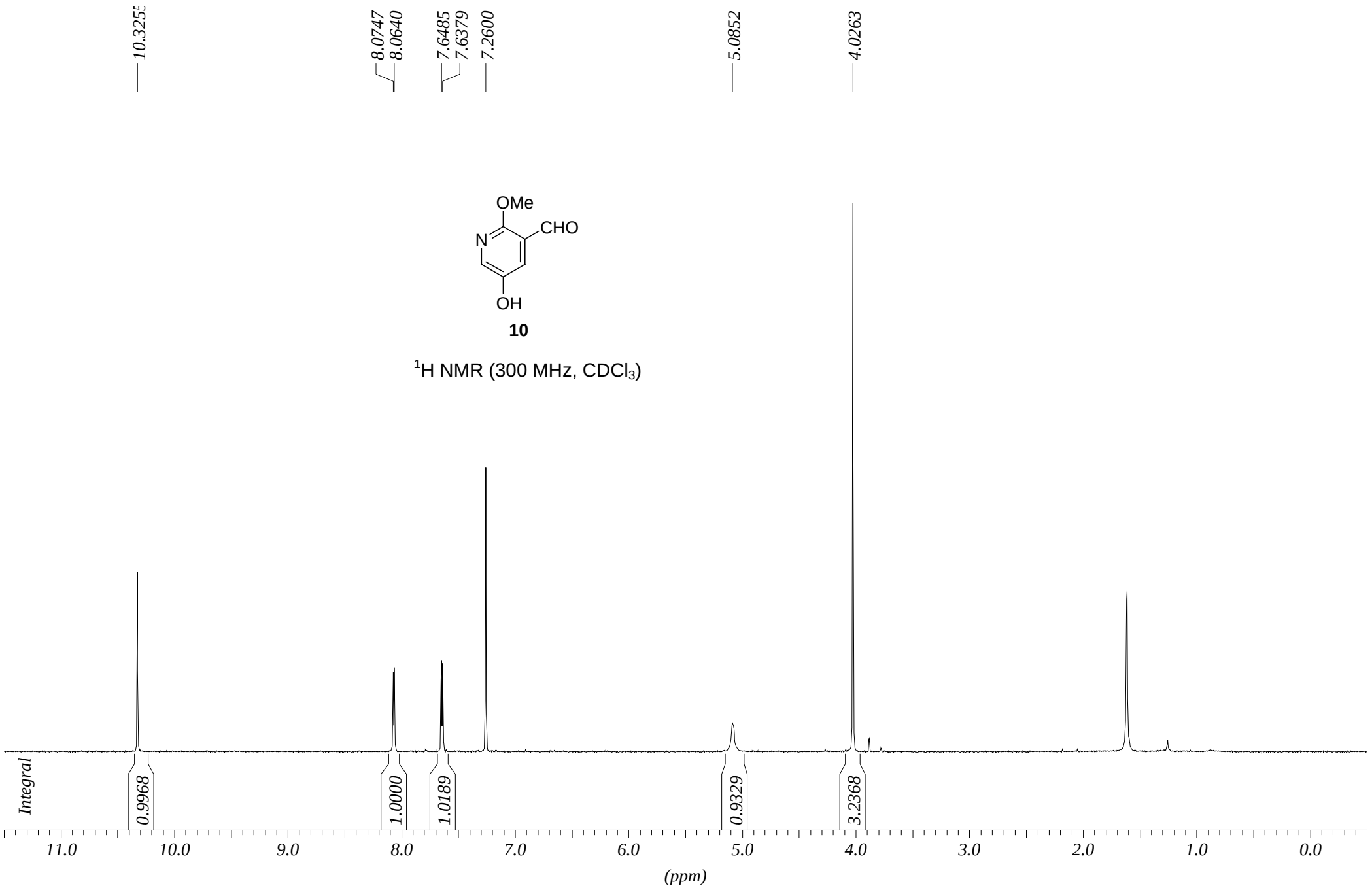

190.025
189.268
180.597
159.262
158.469
147.872
144.185
127.556
118.293
110.835
77.701
77.065
76.431
53.847
29.031
25.046
17.836
13.125
12.534
1.288
OMe
CHO
N
OSi(i-Pr)3
5c
13C NMR (50 MHz, CDCl3)
BRUKER
AV210F.110
AU PROG:
X02.AU
DATE 21-4-4
TIME 14:30
SF 50.323
SY 50.0
O1 8396.387
SI 65536
TD 65536
SW 12500.000
HZ/PT .381
PW 0.0
RD 0.0
AQ 2.621
RG 640
NS 512
TE 297
FW 15700
O2 3154.531
DP 15H D0
LB 1.000
GB 0.0
CX 35.00
CY 20.00
F1 225.463
F2 -23.166
HZ/CM 357.481
PPM/CM 7.104
SR 3314.07
200
180
160
140
120
100
80
60
40
20
0
-20
PPM

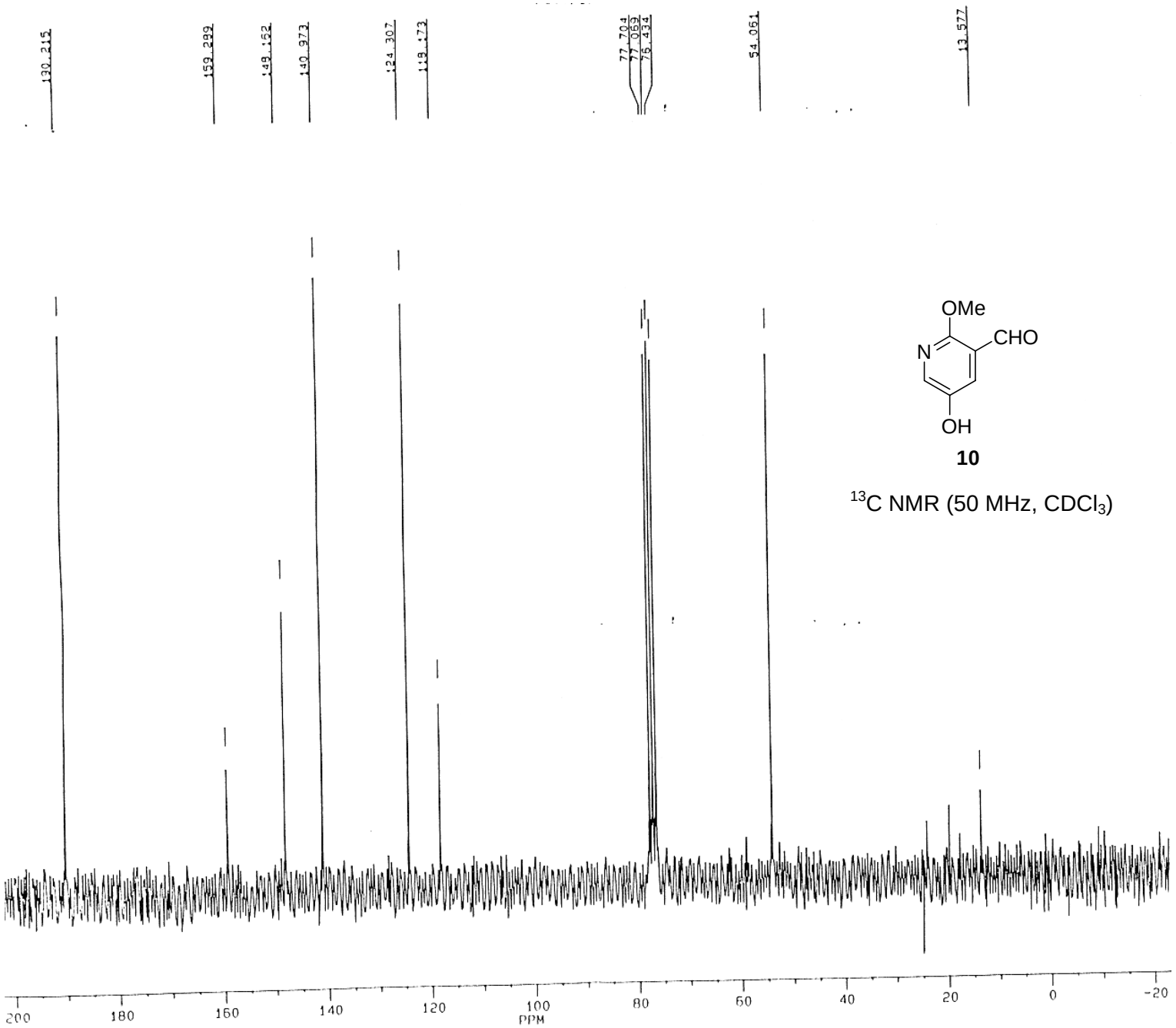

9.9709
9.9696
9.4625
8.0829
7.2600
6.9286
6.9267
3.9340
OH
CHO
N
OMe
9
1H NMR (300 MHz, CDCl3)
Integral
1.0178
1.0000
1.0013
1.0160
3.1702
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

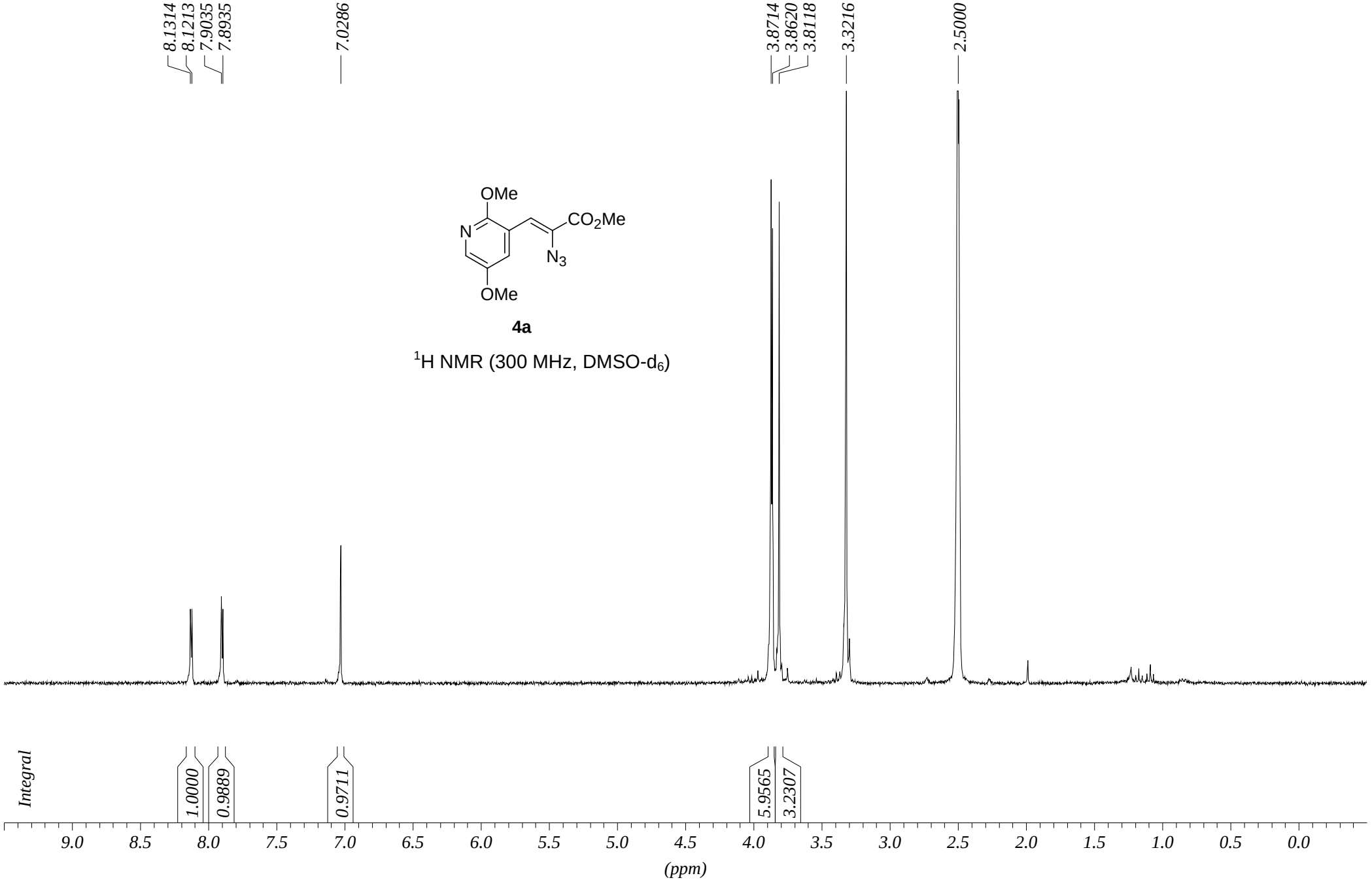


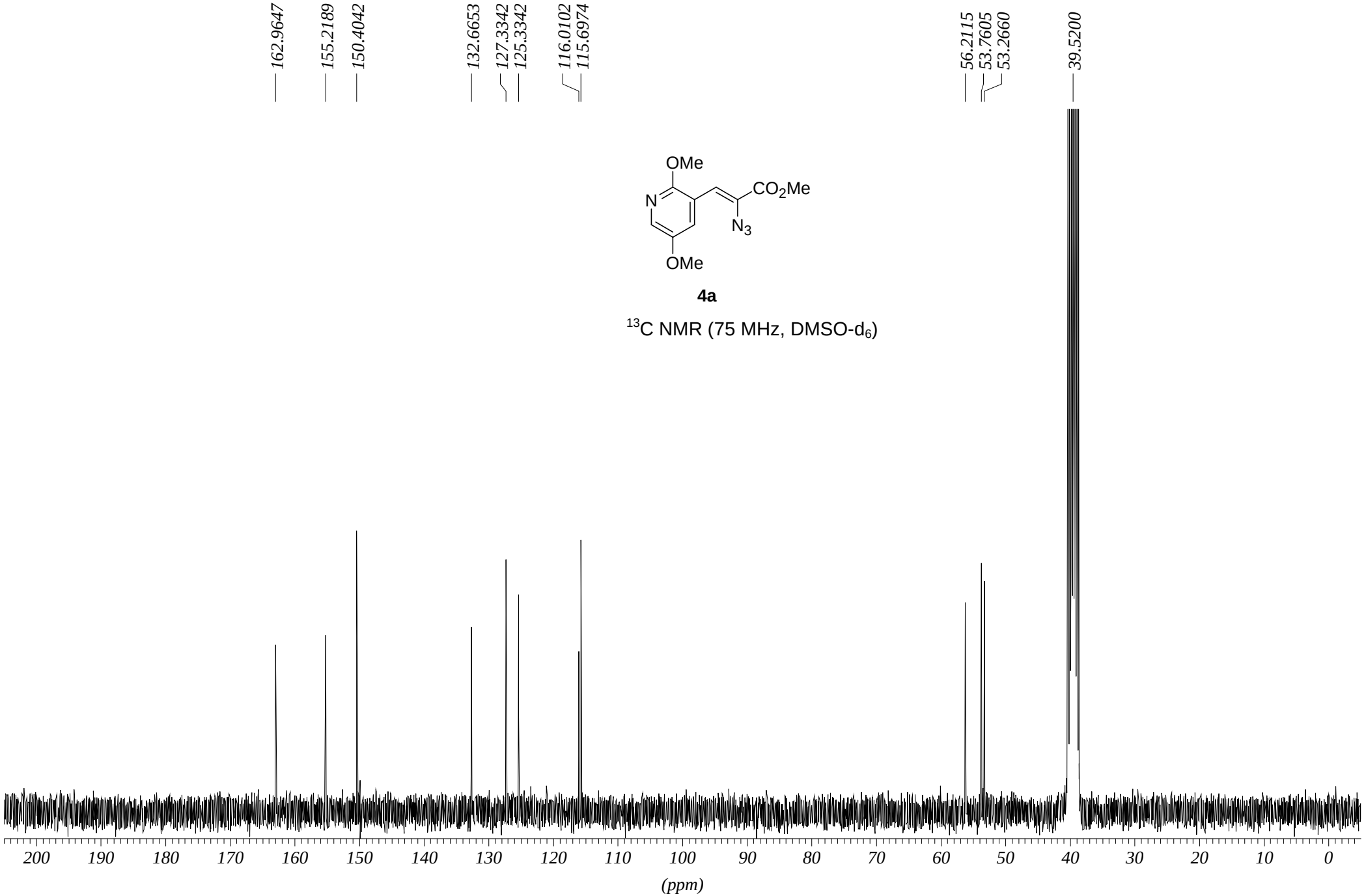
9

^{13}C NMR (75 MHz, $CDCl_3$)


10.3255
8.0747
8.0640
7.6485
7.6379
7.2600
5.0852
4.0263
OMe
CHO
N
OH
10
1H NMR (300 MHz, CDCl3)
Integral
0.9968
1.0000
1.0189
0.9329
3.2368
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

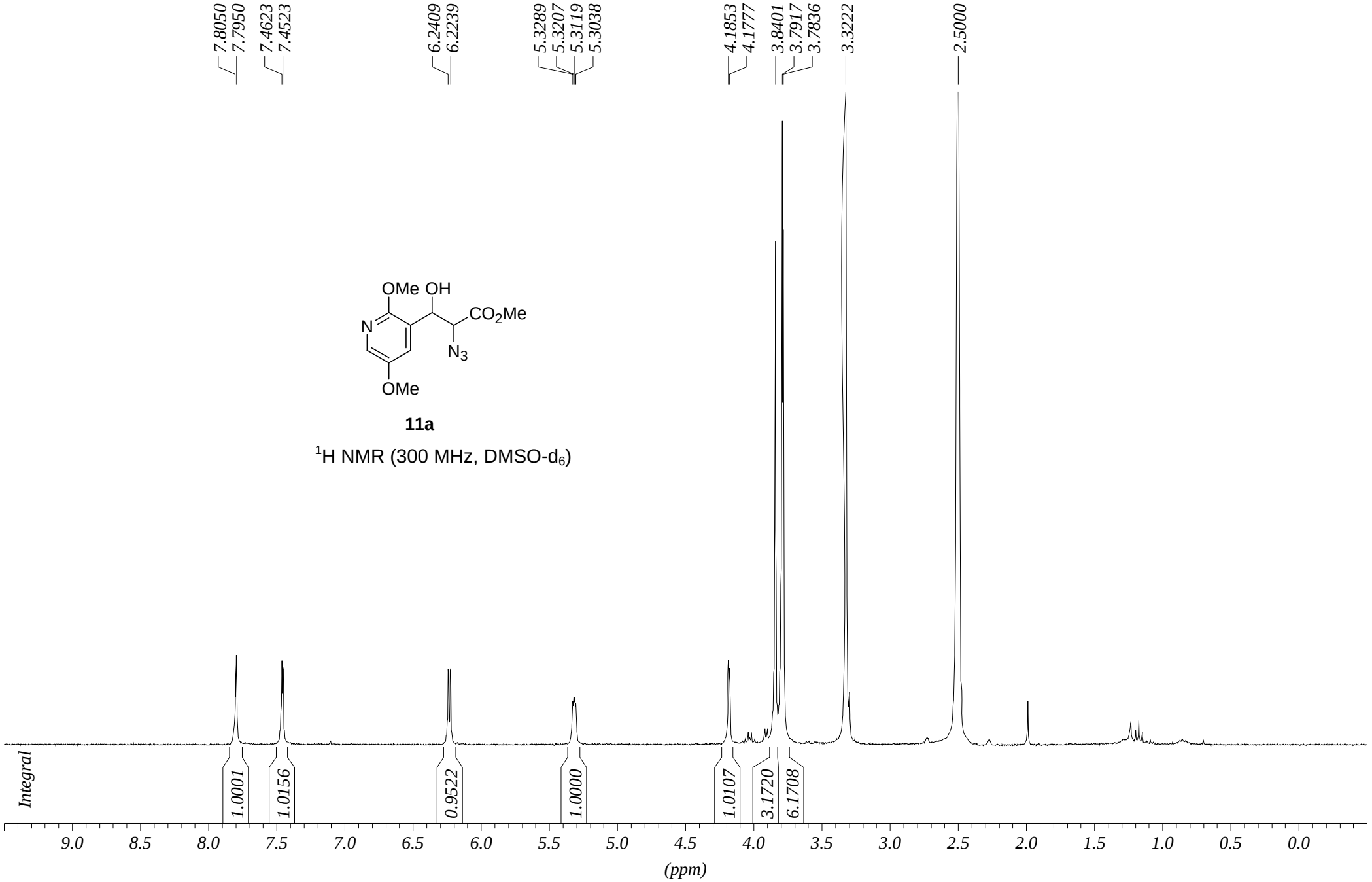

130.215
159.299
149.152
140.973
124.307
118.173
77.704
77.062
76.434
54.061
13.577
OMe
CHO
N
OH
10
^{13}C NMR (50 MHz, $CDCl_3$)
BRUKER
DATE 28-3-4
TIME 16:12
SF 50.323
SY 50.0
O1 8396.387
SI 65536
TD 65536
SW 12500.000
HZ/PT .381
PW 6.0
RD 2.000
AQ 2.621
RG 400
NS 512
TE 297
FW 15700
O2 3154.531
DP 15H CPD
LB 1.000
GB 0.0
CX 35.00
CY 15.00
F1 225.342P
F2 -23.044P
HZ/CM 357.132
PPM/CM 7.097
SR 3314.07
200
180
160
140
120
100
80
60
40
20
0
-20
PPM


8.1314
8.1213
7.9035
7.8935
7.0286
3.8714
3.8620
3.8118
3.3216
2.5000
OMe
N
CO2Me
N3
OMe
4a
1H NMR (300 MHz, DMSO-d6)
Integral
1.0000
0.9889
0.9711
5.9565
3.2307
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
(ppm)



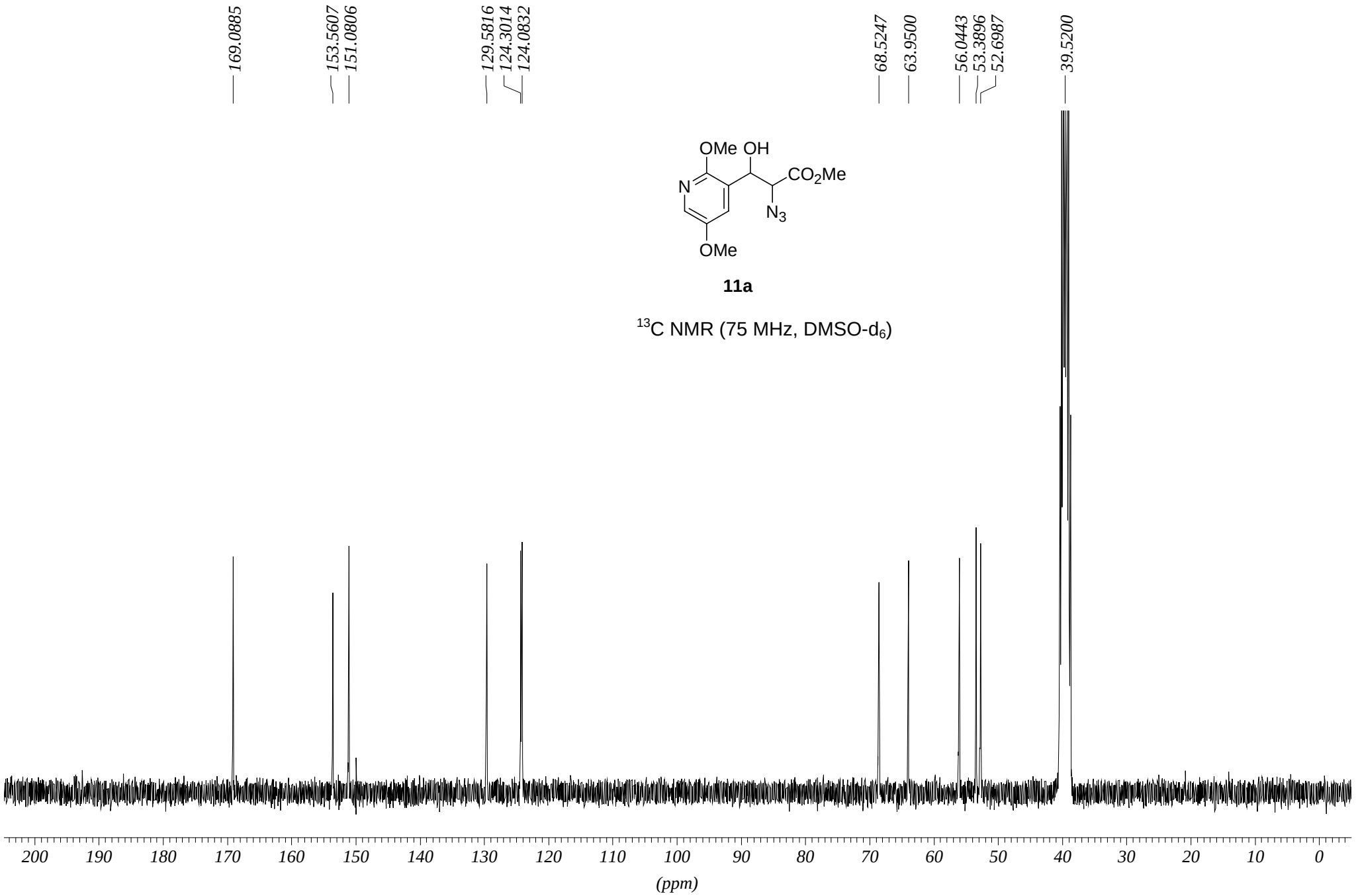
4a

^{13}C NMR (75 MHz, DMSO-d_6)



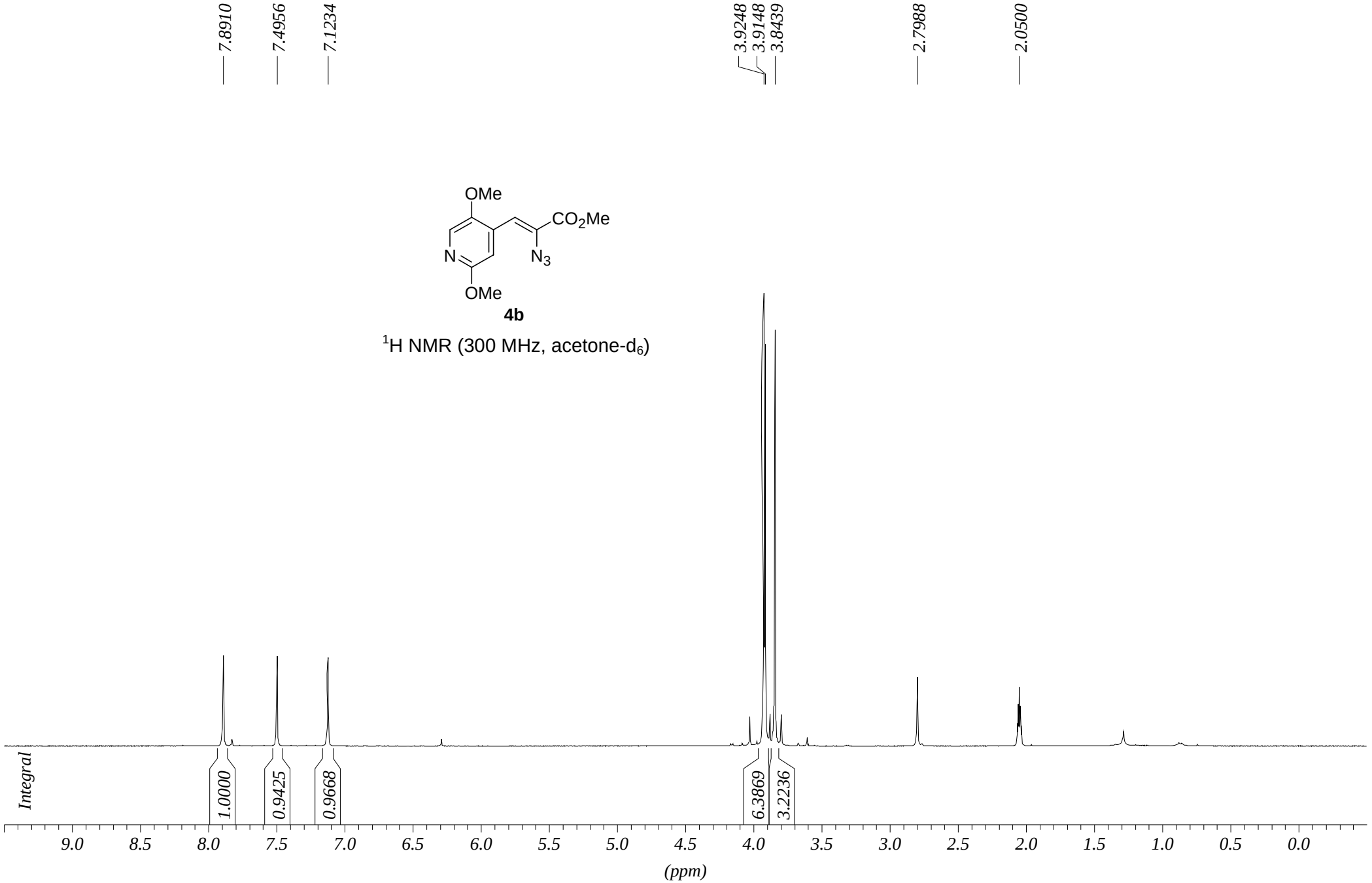
11a

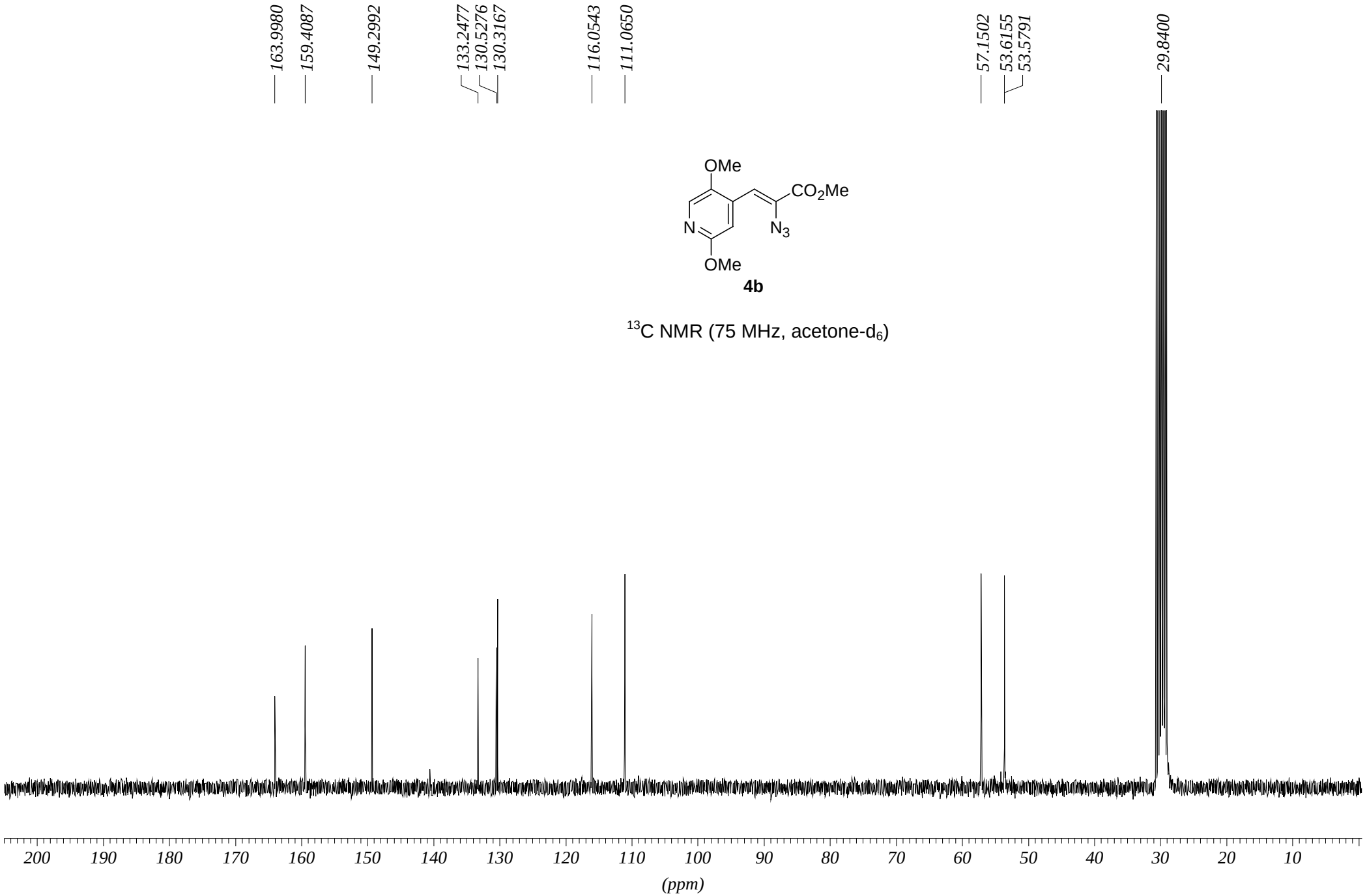
^{1}H NMR (300 MHz, DMSO-d_6)



11a

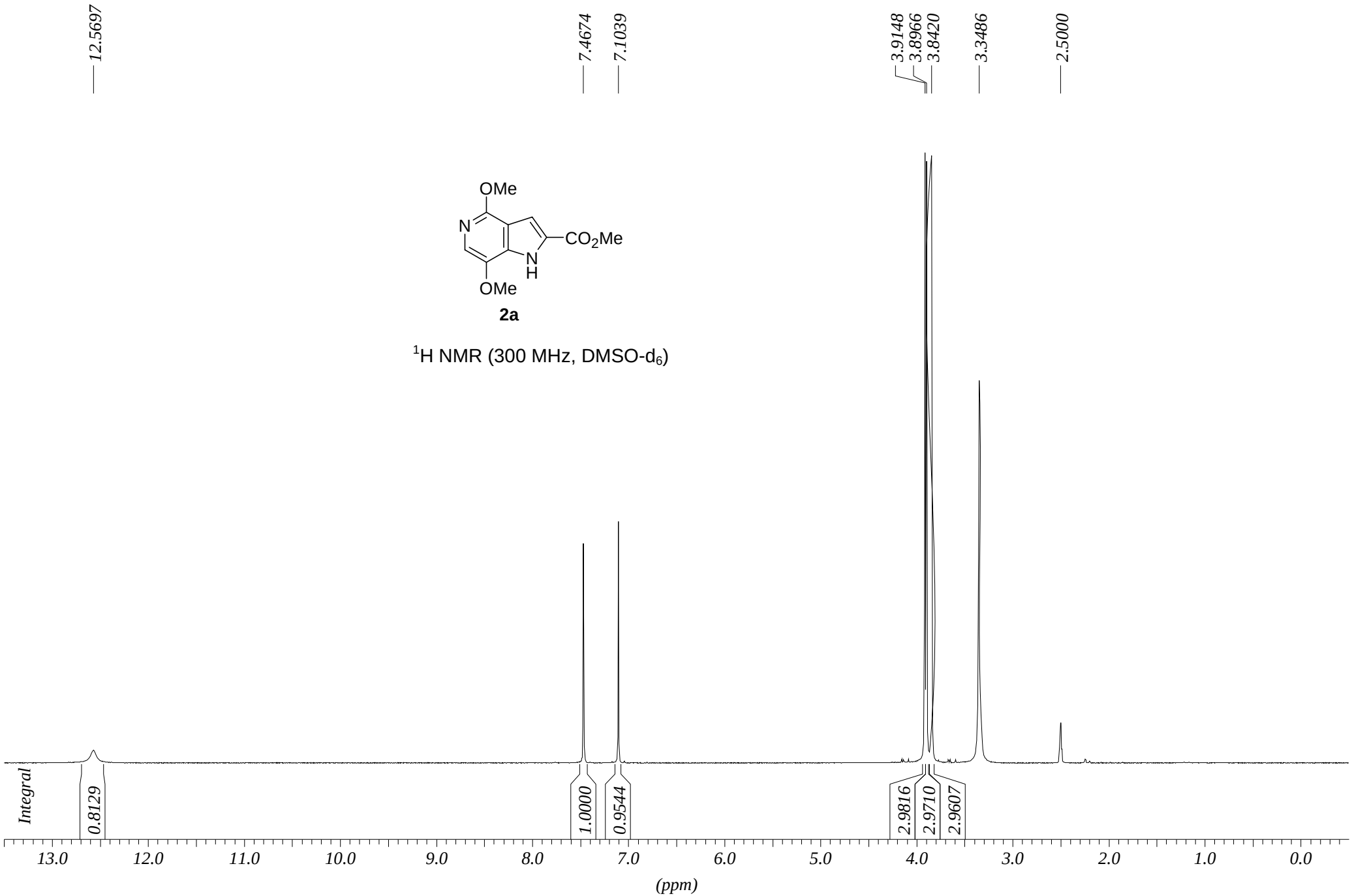
^{13}C NMR (75 MHz, DMSO-d_6)

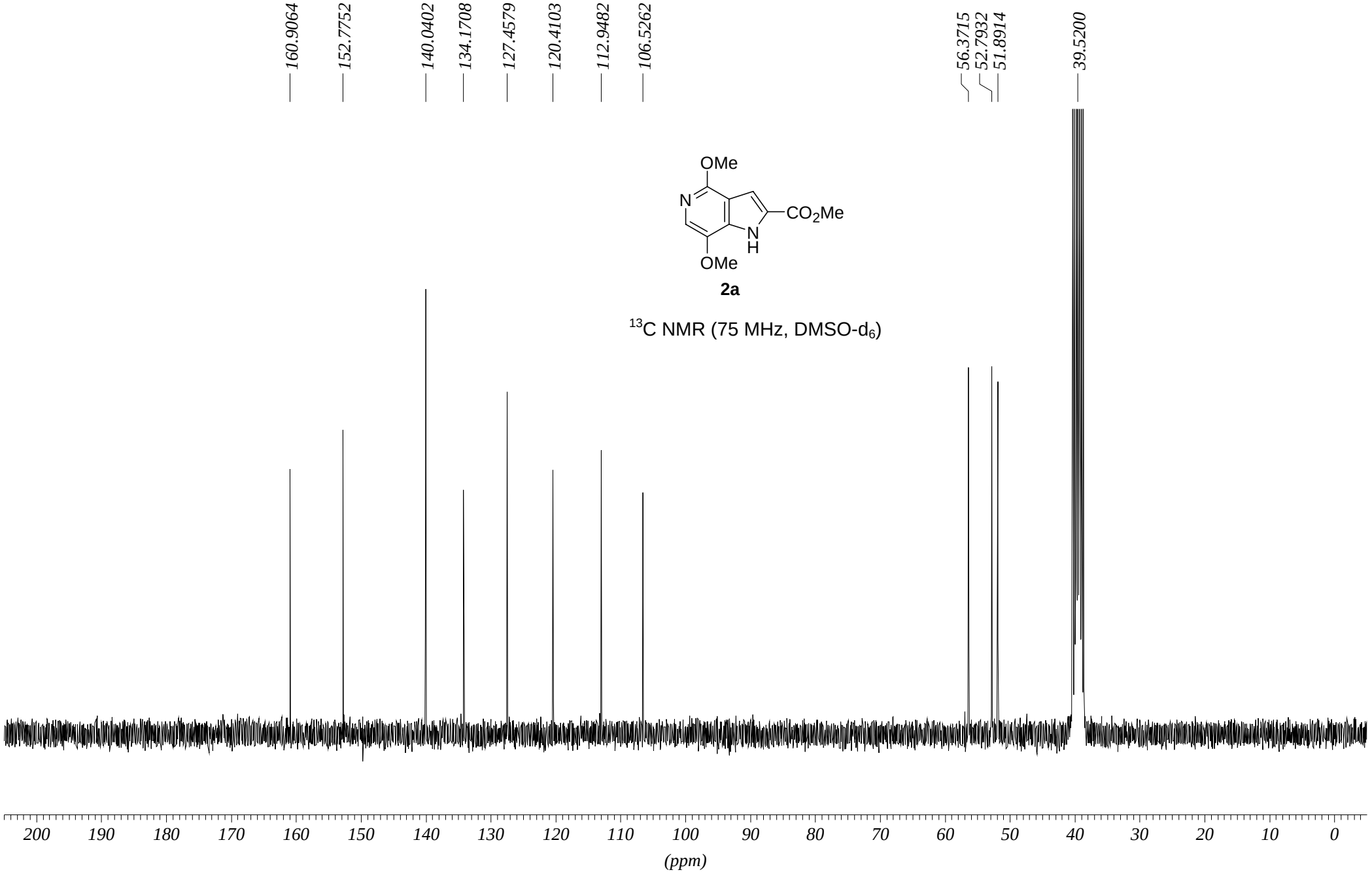

7.8910
7.4956
7.1234
3.9248
3.9148
3.8439
2.7988
2.0500
OMe
CO2Me
N
N3
OMe
4b
1H NMR (300 MHz, acetone-d6)
Integral
1.0000
0.9425
0.9668
6.3869
3.2236
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)



4b

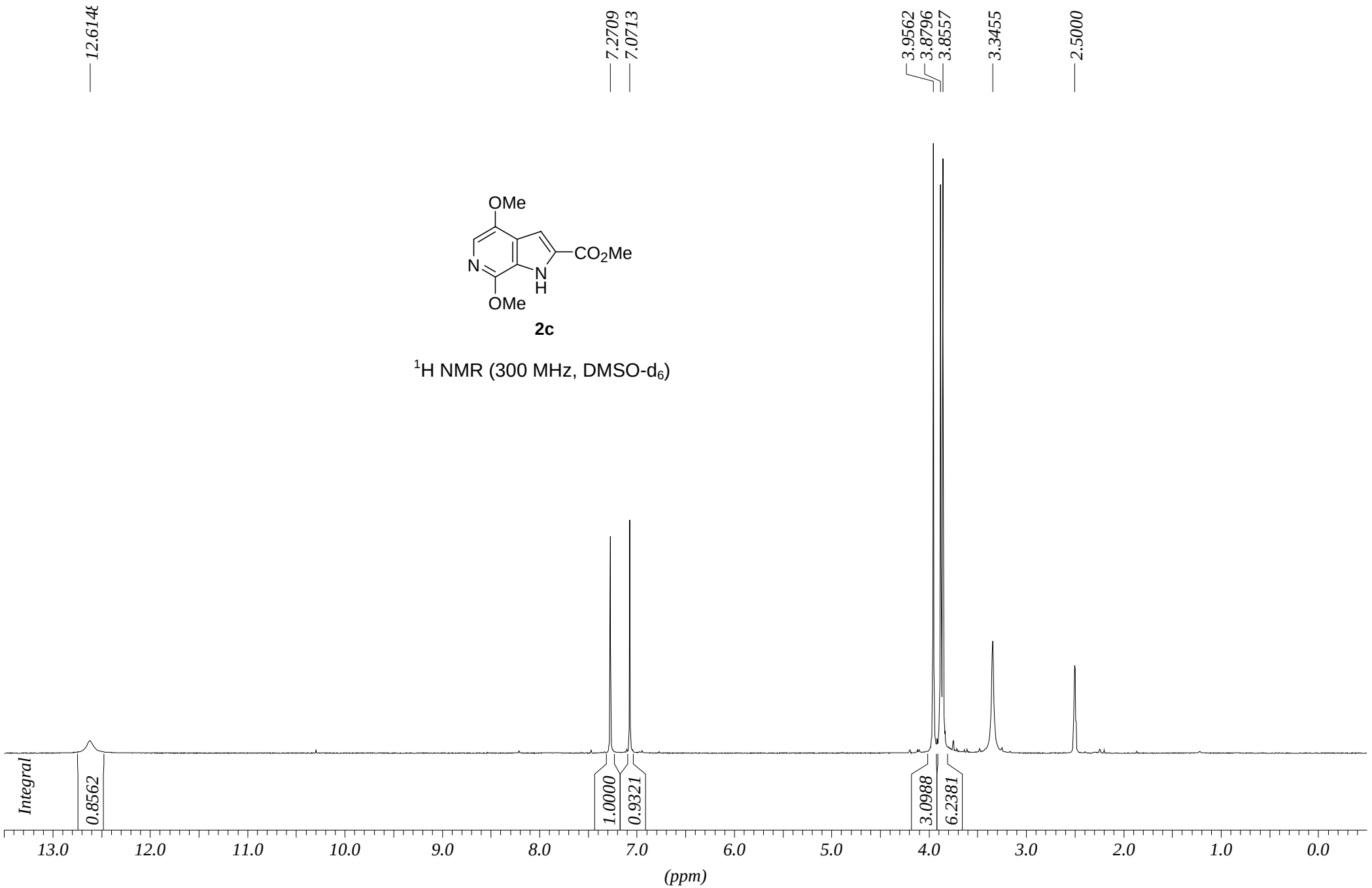
^{13}C NMR (75 MHz, acetone-d_6)

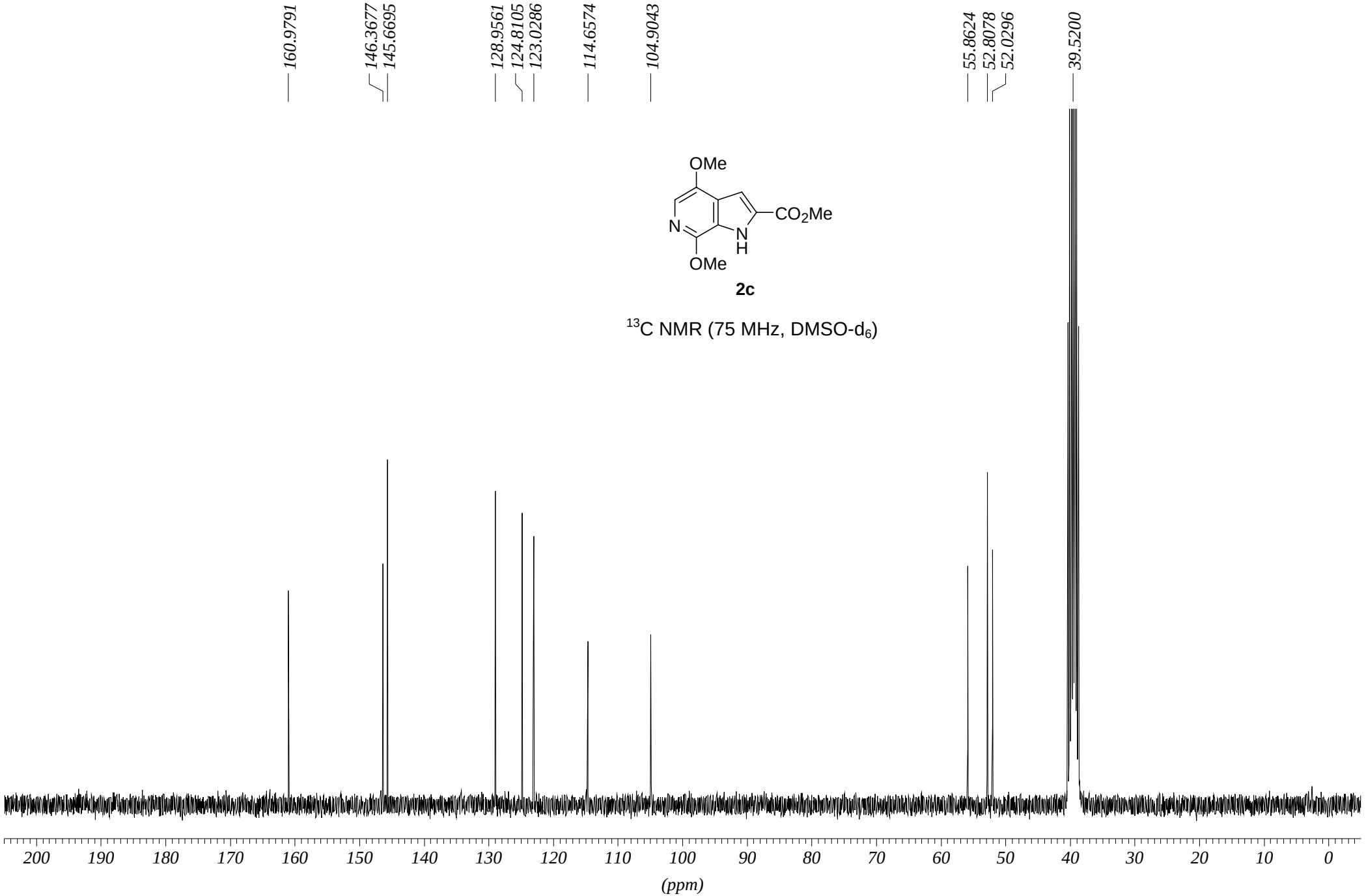

12.5697
7.4674
7.1039
3.9148
3.8966
3.8420
3.3486
2.5000
OMe
N
CO2Me
N
H
OMe
2a
1H NMR (300 MHz, DMSO-d6)
Integral
0.8129
1.0000
0.9544
2.9816
2.9710
2.9607
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)



2a

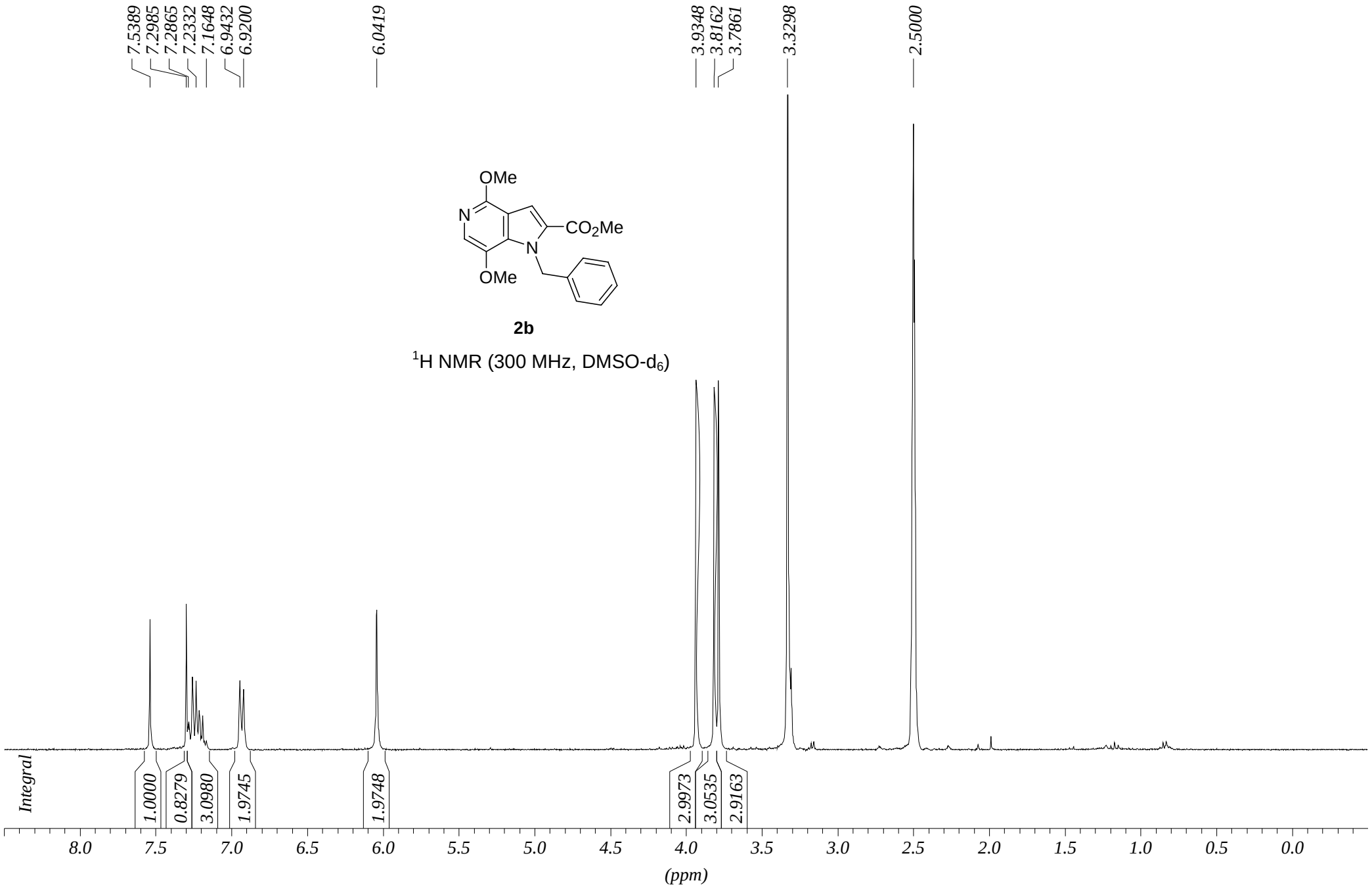
^{13}C NMR (75 MHz, DMSO-d_6)

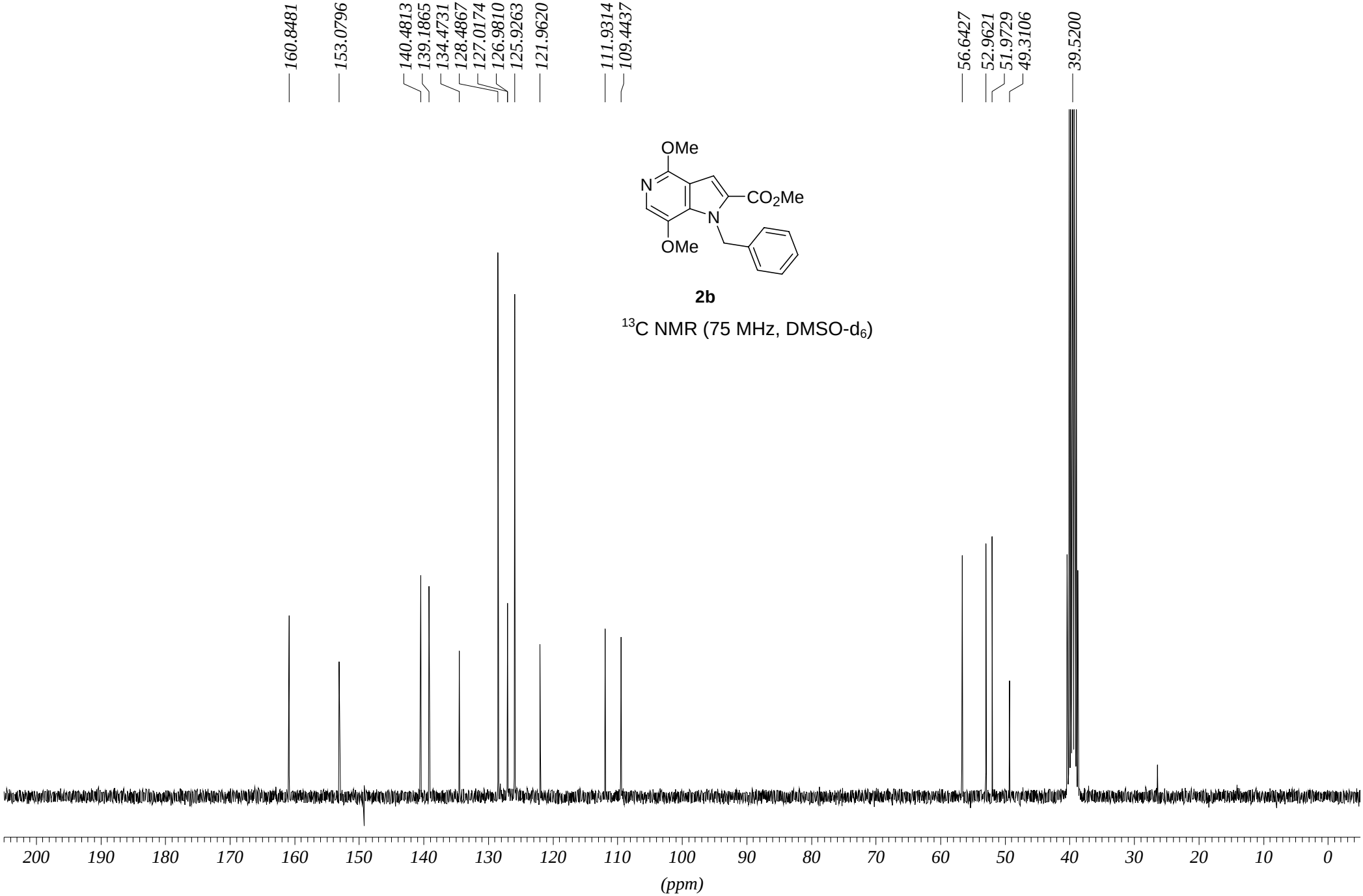

12.6148
7.2709
7.0713
3.9562
3.8796
3.8557
3.3455
2.5000
OMe
CO2Me
N
N
H
OMe
2c
1H NMR (300 MHz, DMSO-d6)
Integral
0.8562
1.0000
0.9321
3.0988
6.2381
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)



2c

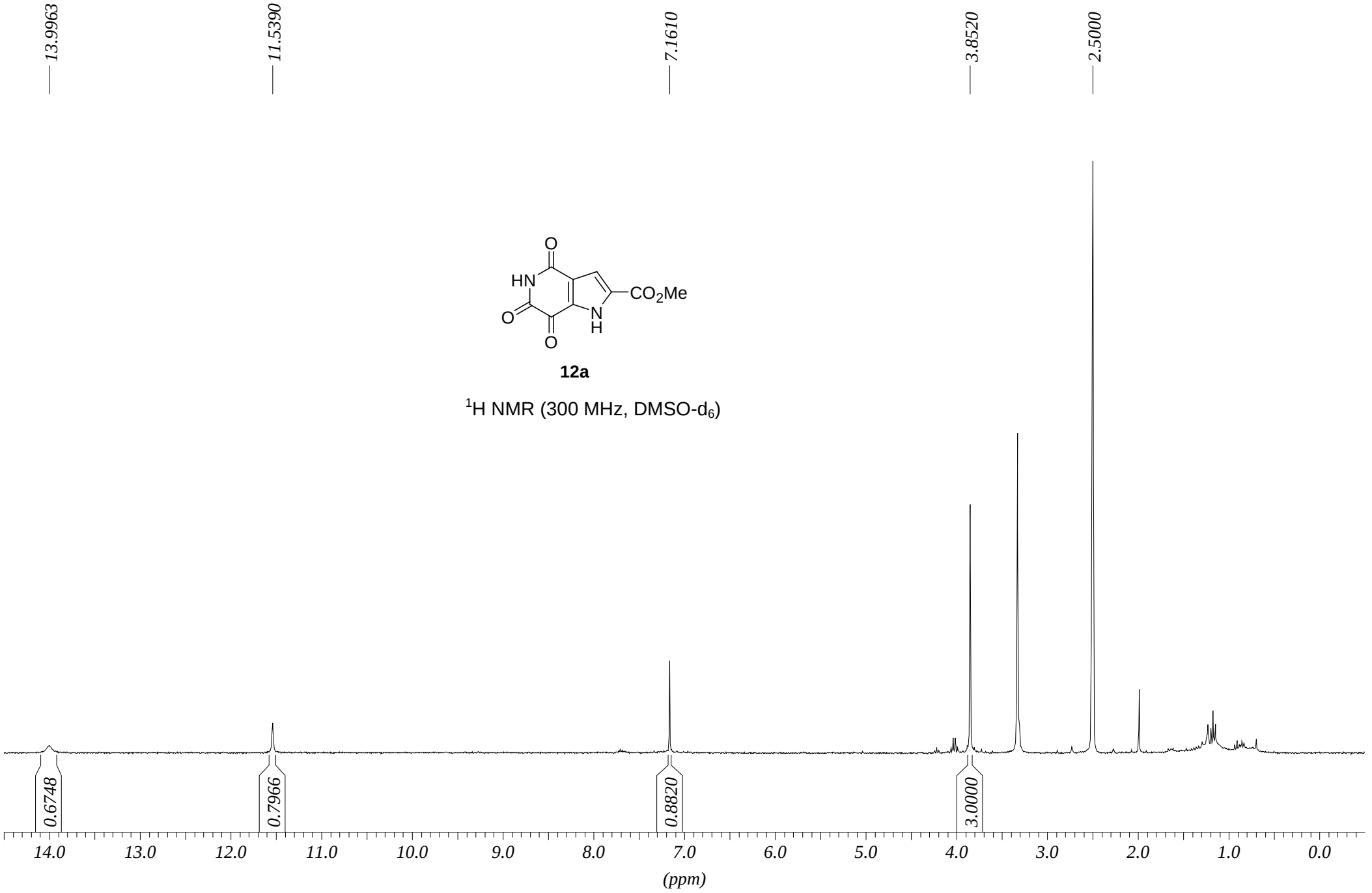
^{13}C NMR (75 MHz, DMSO-d_6)

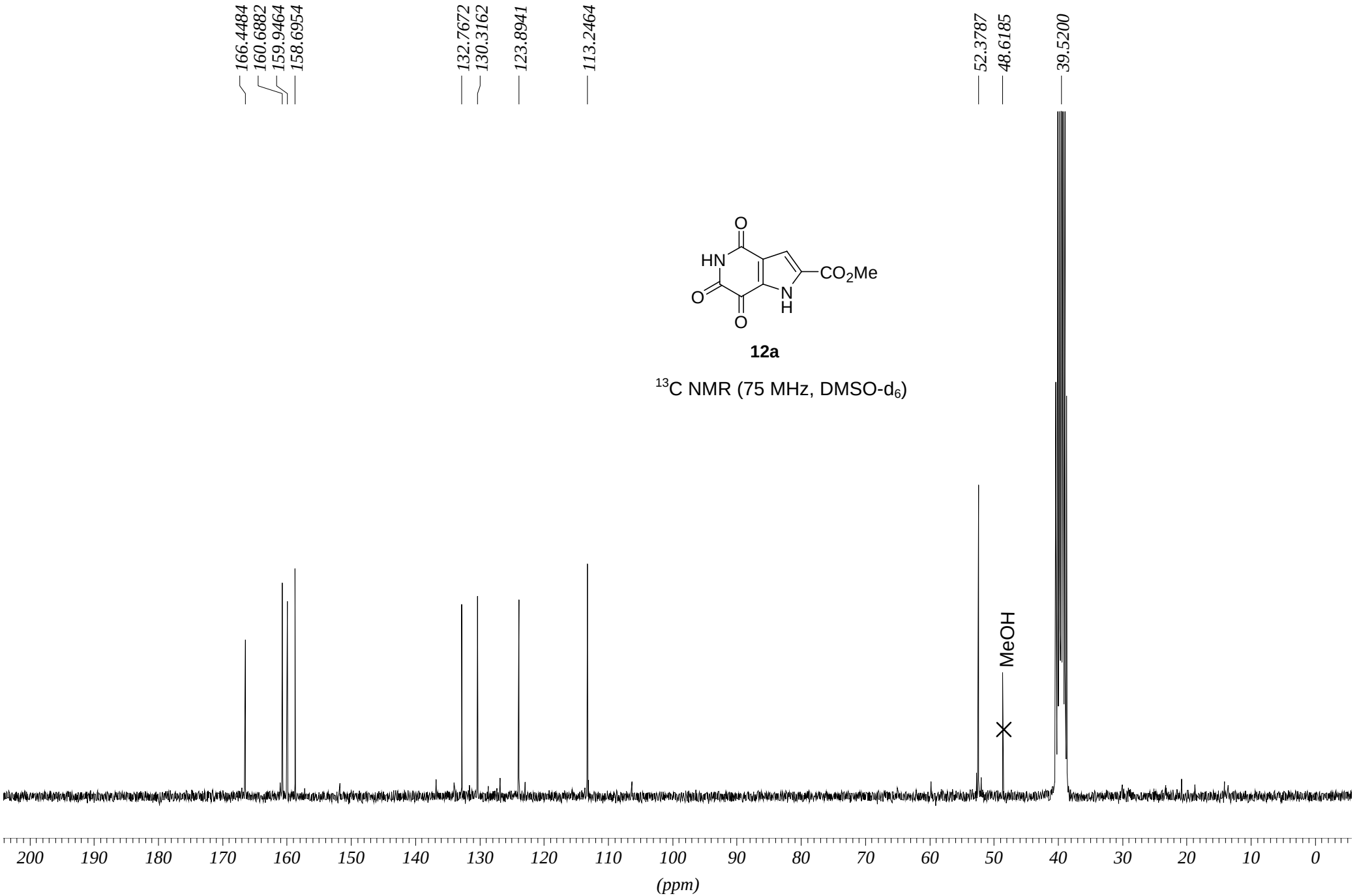

7.5389
7.2985
7.2865
7.2332
7.1648
6.9432
6.9200
6.0419
3.9348
3.8162
3.7861
3.3298
2.5000
OMe
N
CO2Me
N
OMe
2b
1H NMR (300 MHz, DMSO-d6)
Integral
1.0000
0.8279
3.0980
1.9745
1.9748
2.9973
3.0535
2.9163
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)



2b

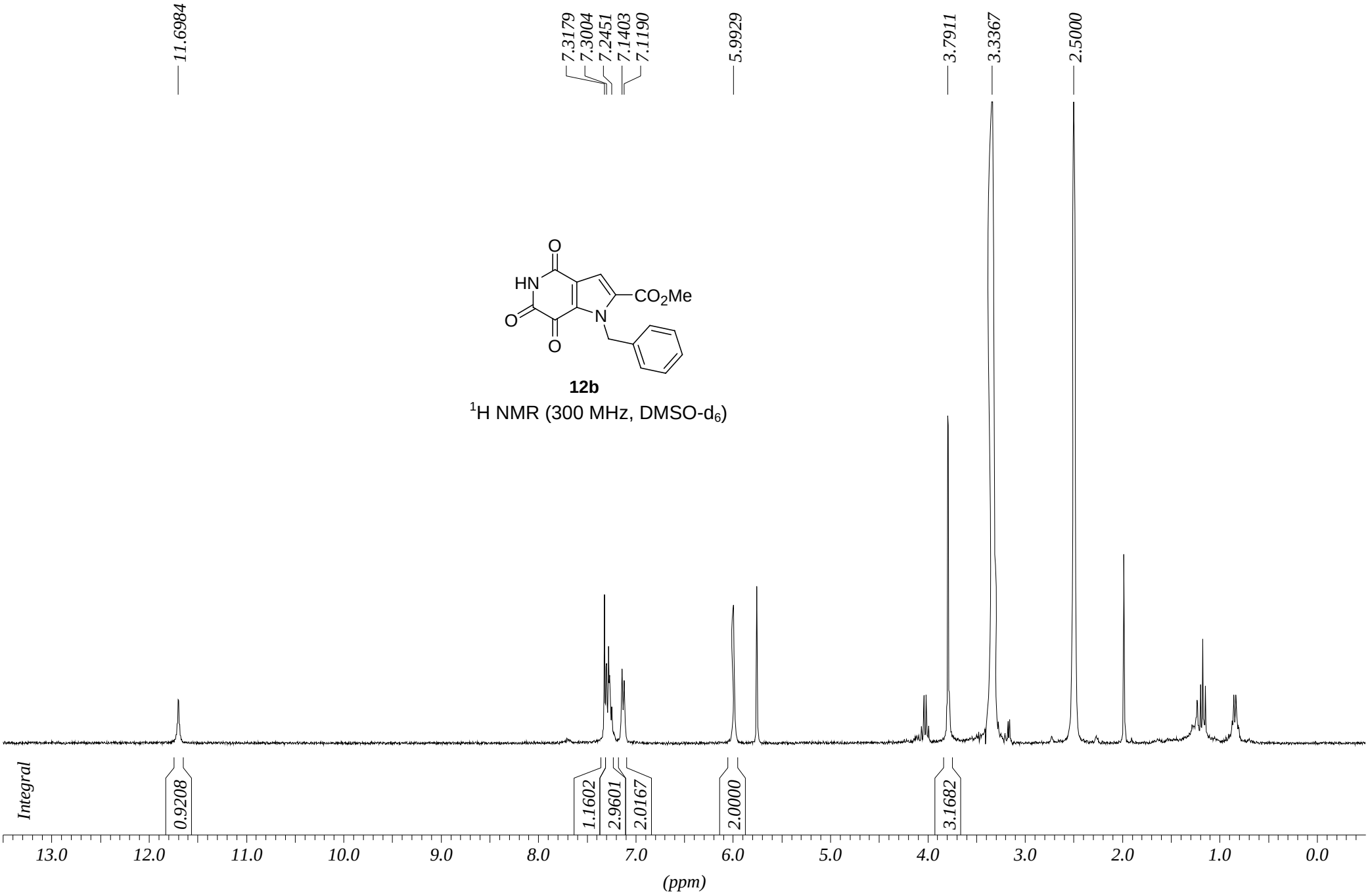
^{13}C NMR (75 MHz, DMSO-d_6)

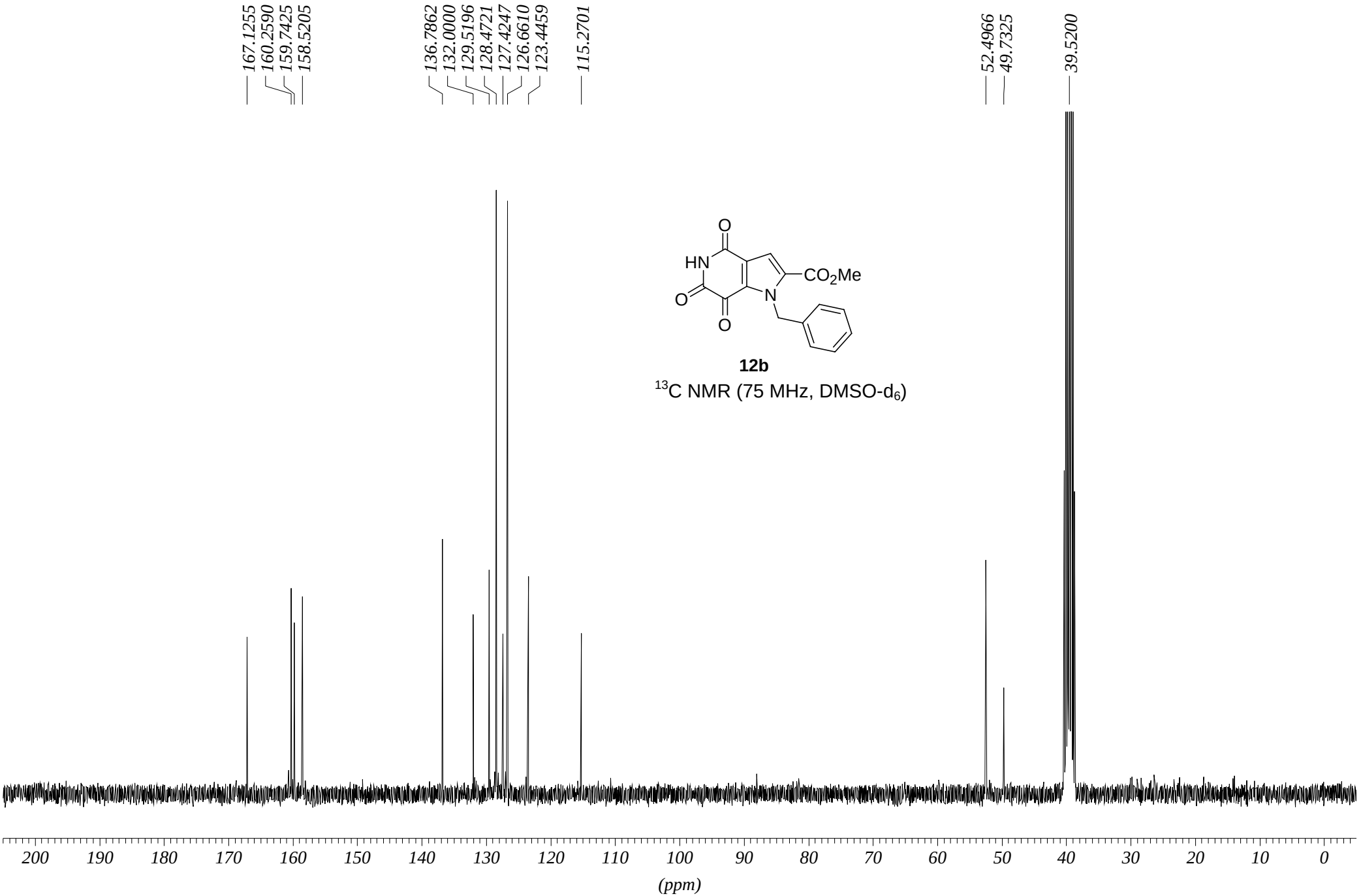

13.9963
11.5390
7.1610
3.8520
2.5000
HN
O
O
O
N
H
CO2Me
12a
1H NMR (300 MHz, DMSO-d6)
0.6748
0.7966
0.8820
3.0000
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)



12a

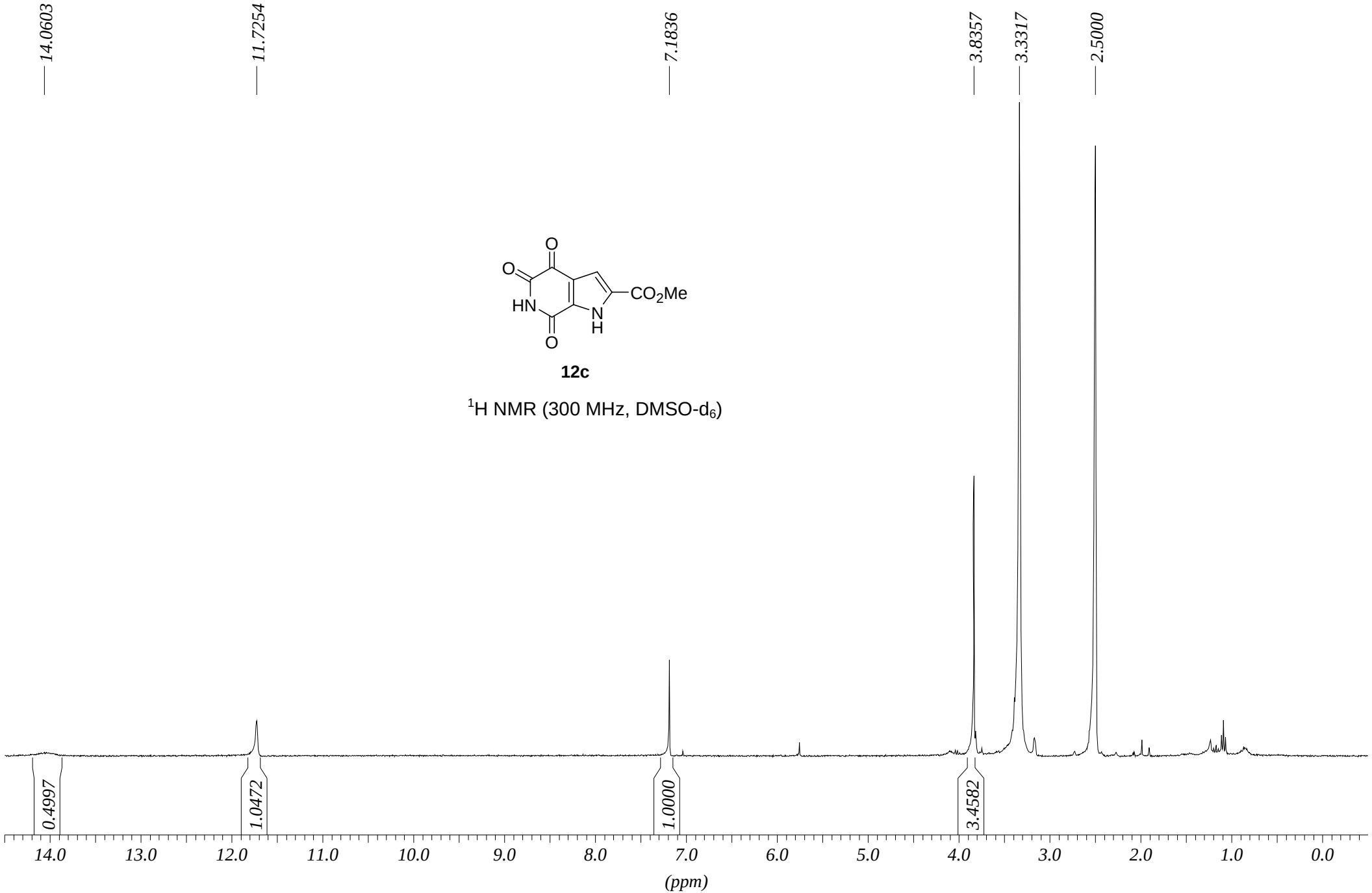
^{13}C NMR (75 MHz, DMSO-d_6)

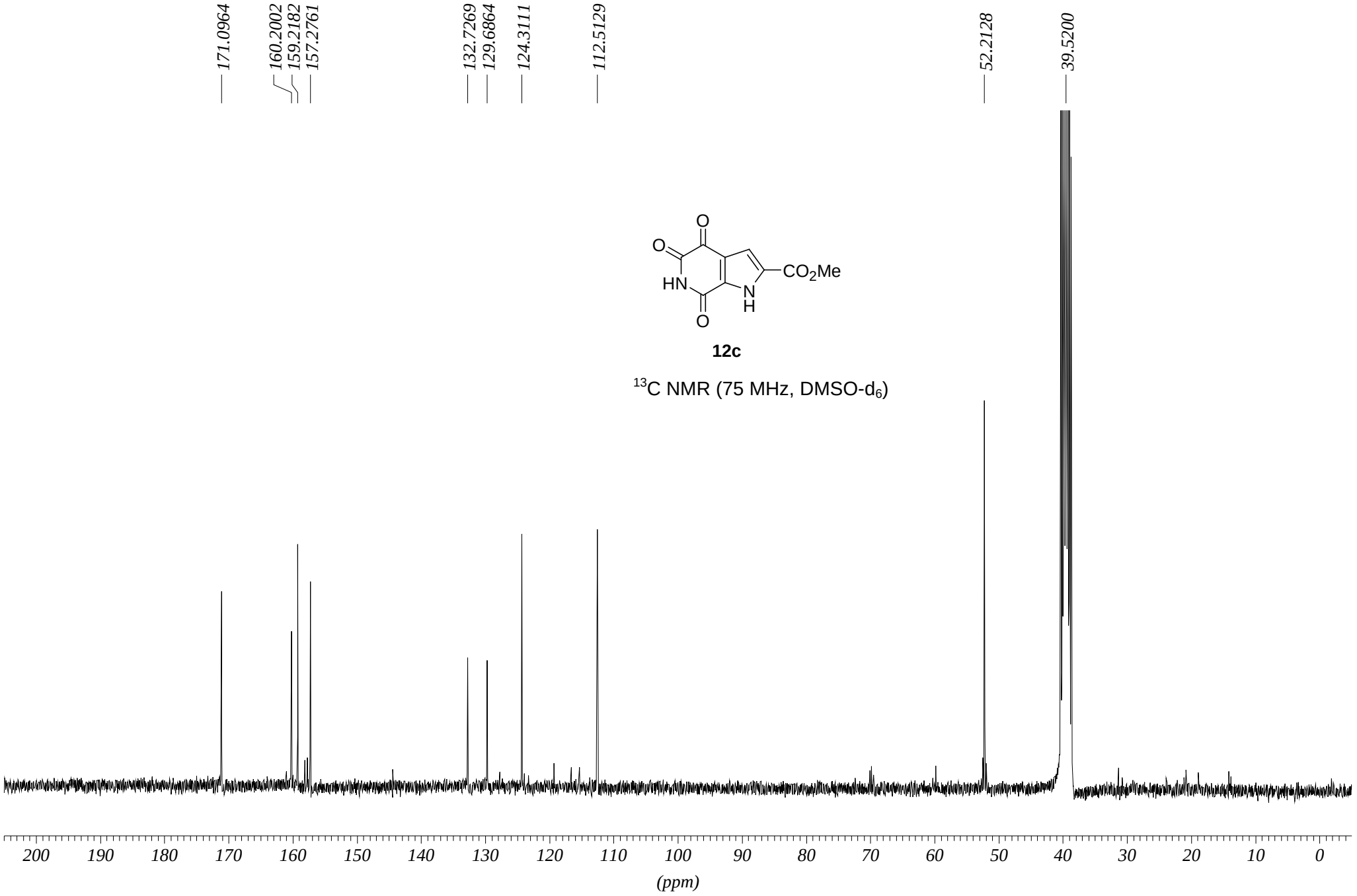

11.6984
7.3179
7.3004
7.2451
7.1403
7.1190
5.9929
3.7911
3.3367
2.5000
HN
O
O
O
N
CO2Me
12b
1H NMR (300 MHz, DMSO-d6)
Integral
0.9208
1.1602
2.9601
2.0167
2.0000
3.1682
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

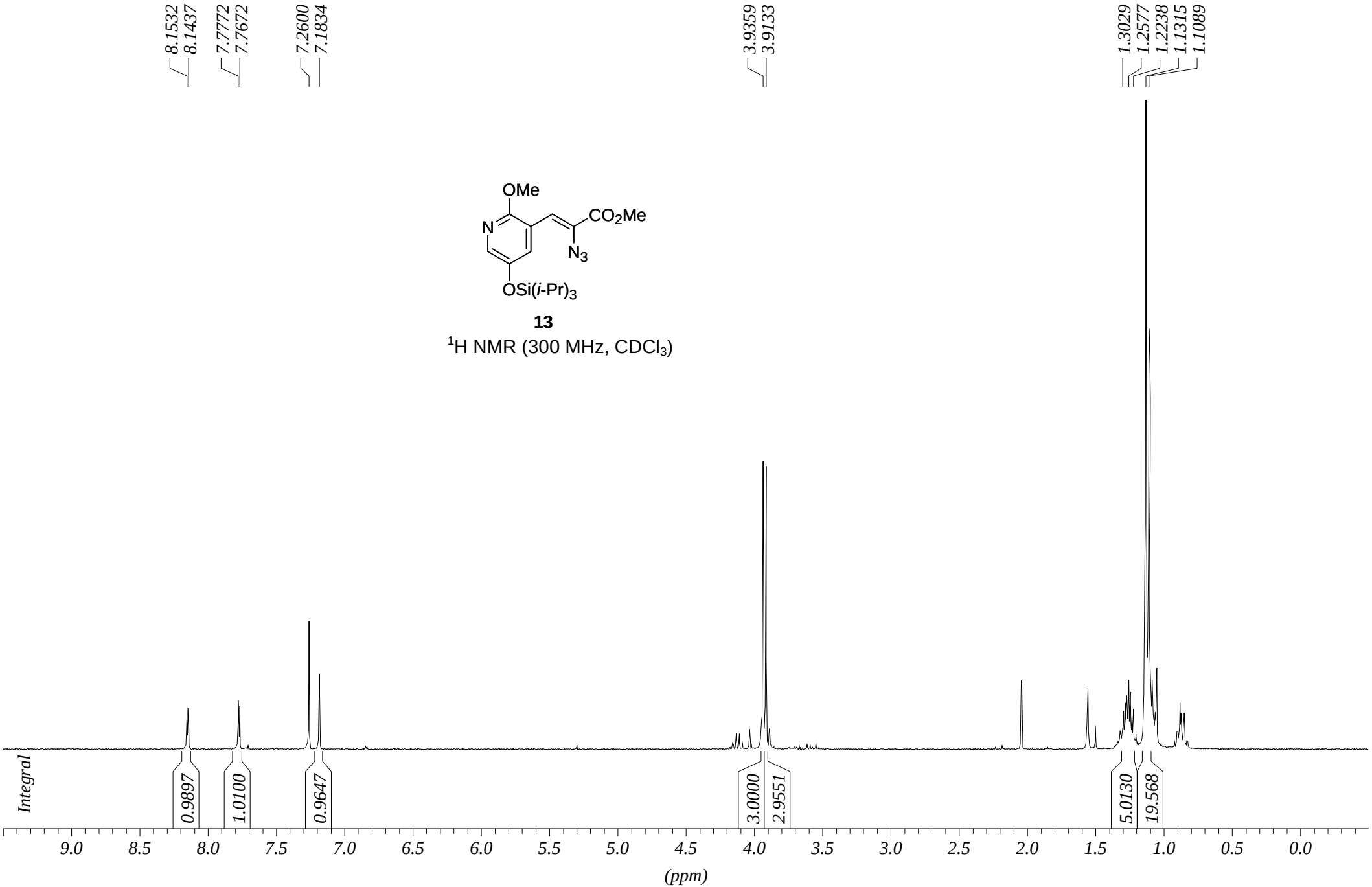


12b

^{13}C NMR (75 MHz, DMSO-d_6)

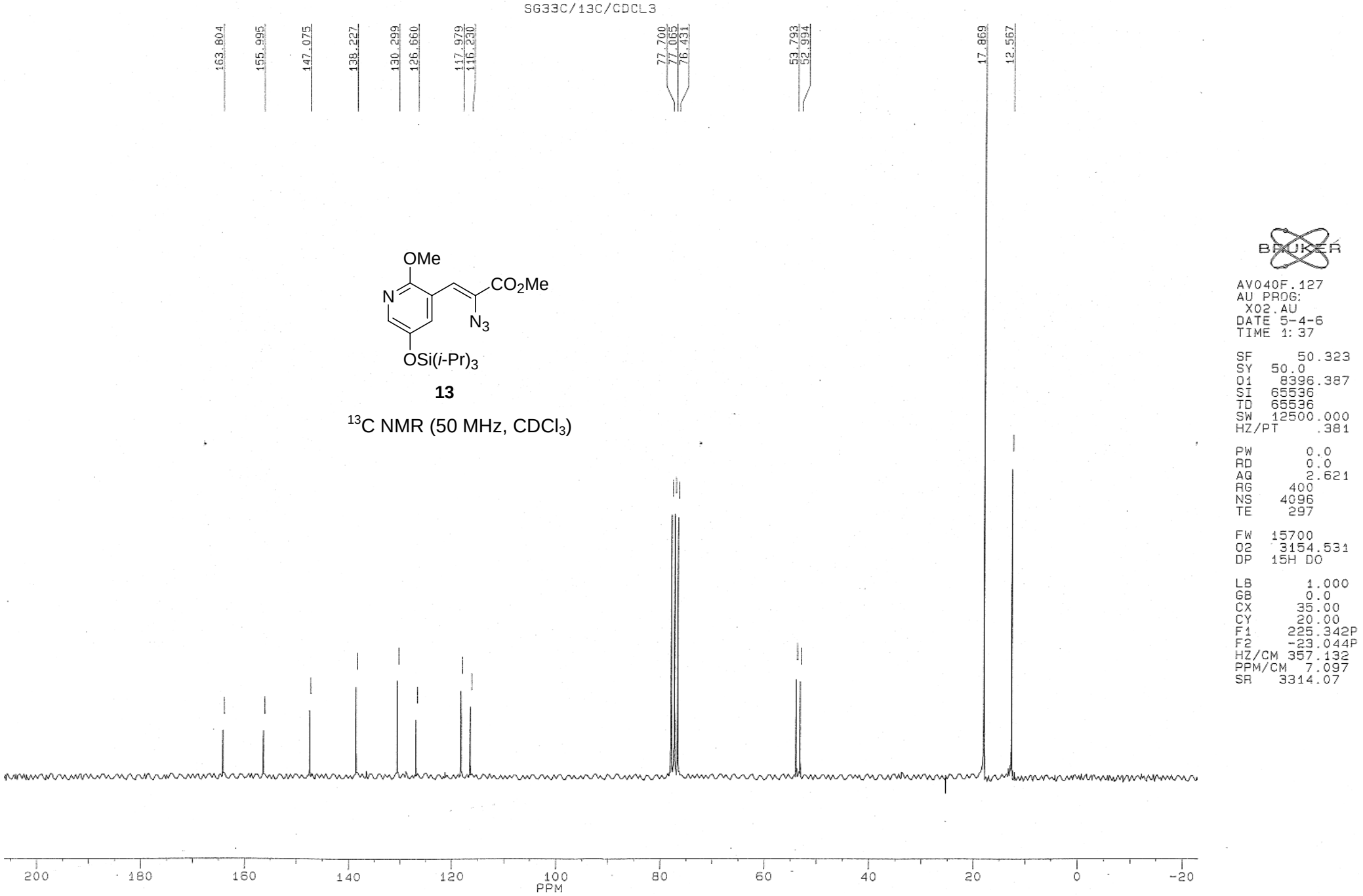

14.0603
11.7254
7.1836
3.8357
3.3317
2.5000
O
O
HN
N
H
O
CO2Me
12c
1H NMR (300 MHz, DMSO-d6)
0.4997
1.0472
1.0000
3.4582
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

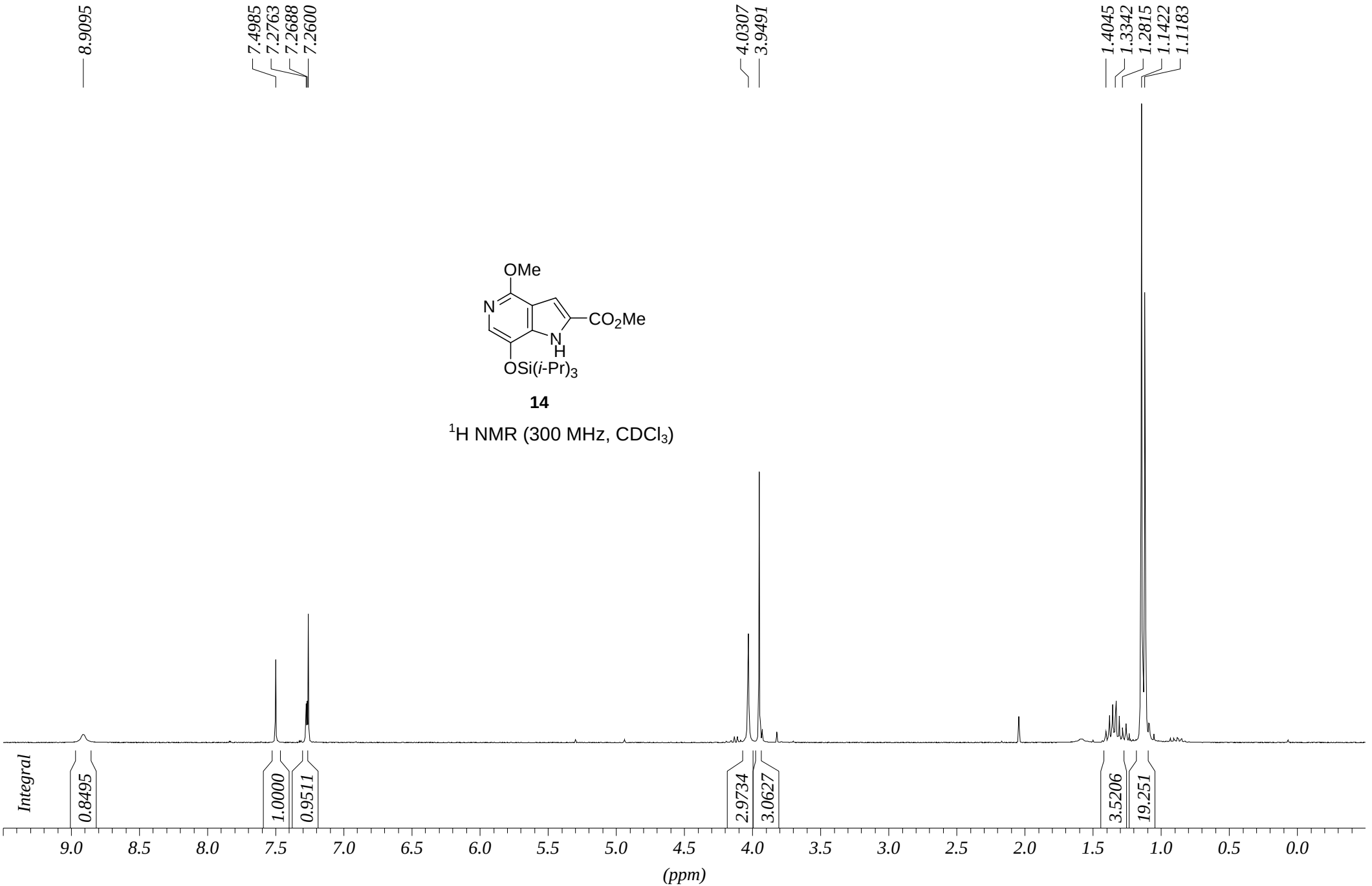

171.0964
160.2002
159.2182
157.2761
132.7269
129.6864
124.3111
112.5129
52.2128
39.5200
O
O
HN
N
H
O
CO2Me
12c
13C NMR (75 MHz, DMSO-d6)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)



13

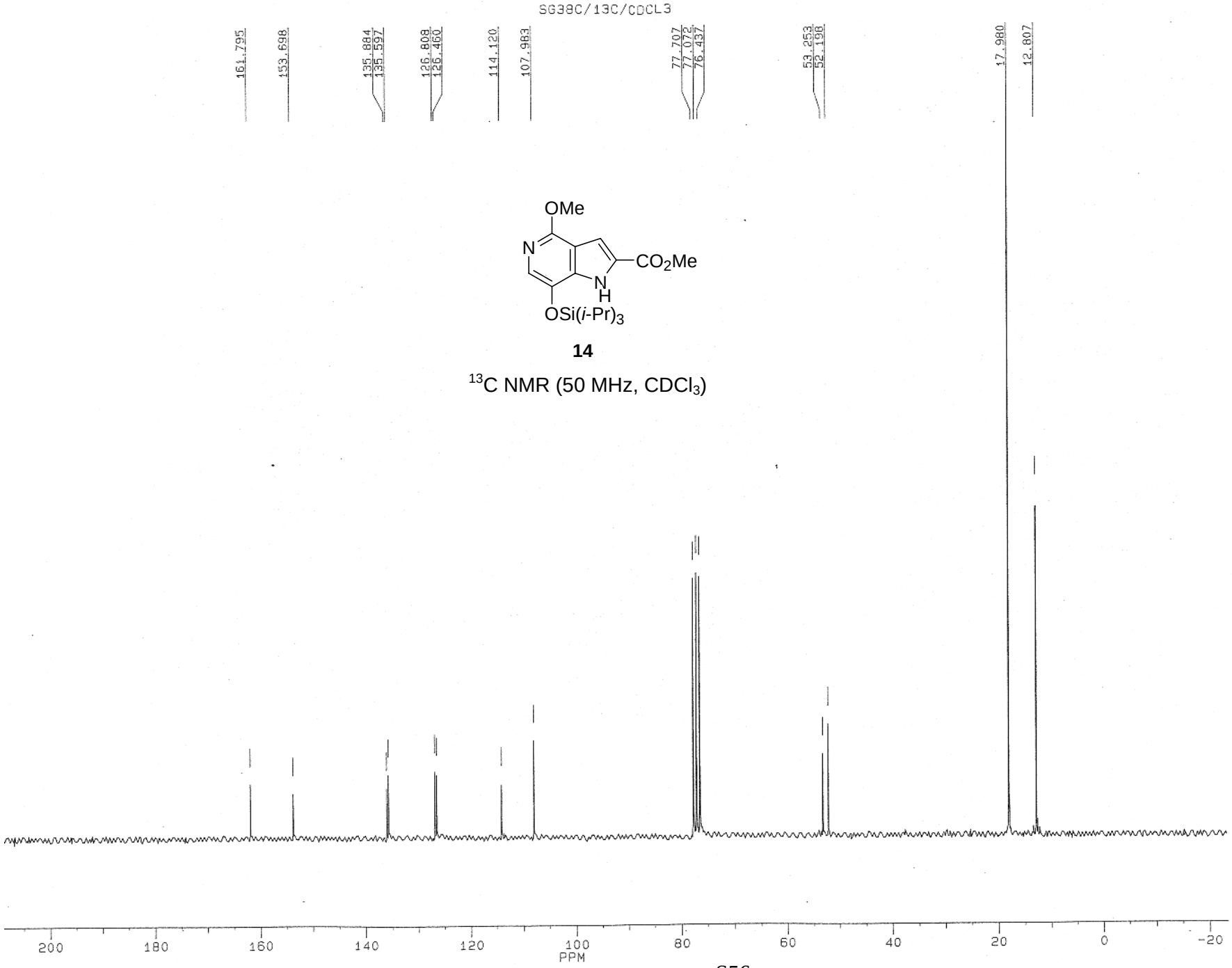
^{1}H NMR (300 MHz, $CDCl_3$)

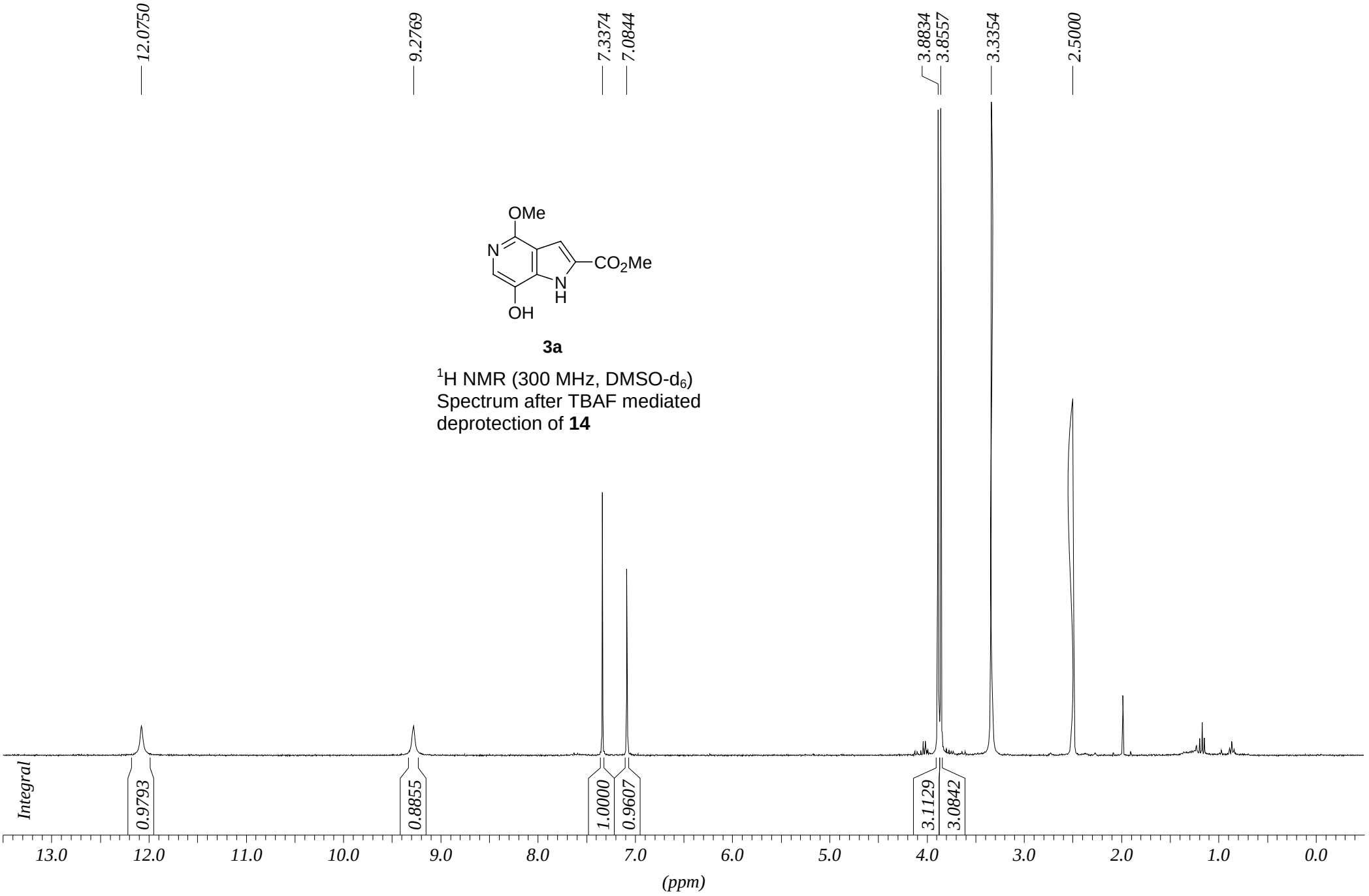

SG33C/13C/CDCL3
163.804
155.995
147.075
138.227
130.299
126.660
117.979
116.230
77.700
77.065
76.431
53.793
52.994
17.869
12.567
OMe
N
CO2Me
N3
OSi(i-Pr)3
13
13C NMR (50 MHz, CDCl3)
BRUKER
AV040F.127
AU PROG:
X02.AU
DATE 5-4-6
TIME 1:37
SF 50.323
SY 50.0
O1 8396.387
SI 65536
TD 65536
SW 12500.000
HZ/PT .381
PW 0.0
RD 0.0
AQ 2.621
RG 400
NS 4096
TE 297
FW 15700
O2 3154.531
DP 15H DO
LB 1.000
GB 0.0
CX 35.00
CY 20.00
F1 225.342P
F2 -23.044P
HZ/CM 357.132
PPM/CM 7.097
SR 3314.07
200
180
160
140
120
100
80
60
40
20
0
-20
PPM



14

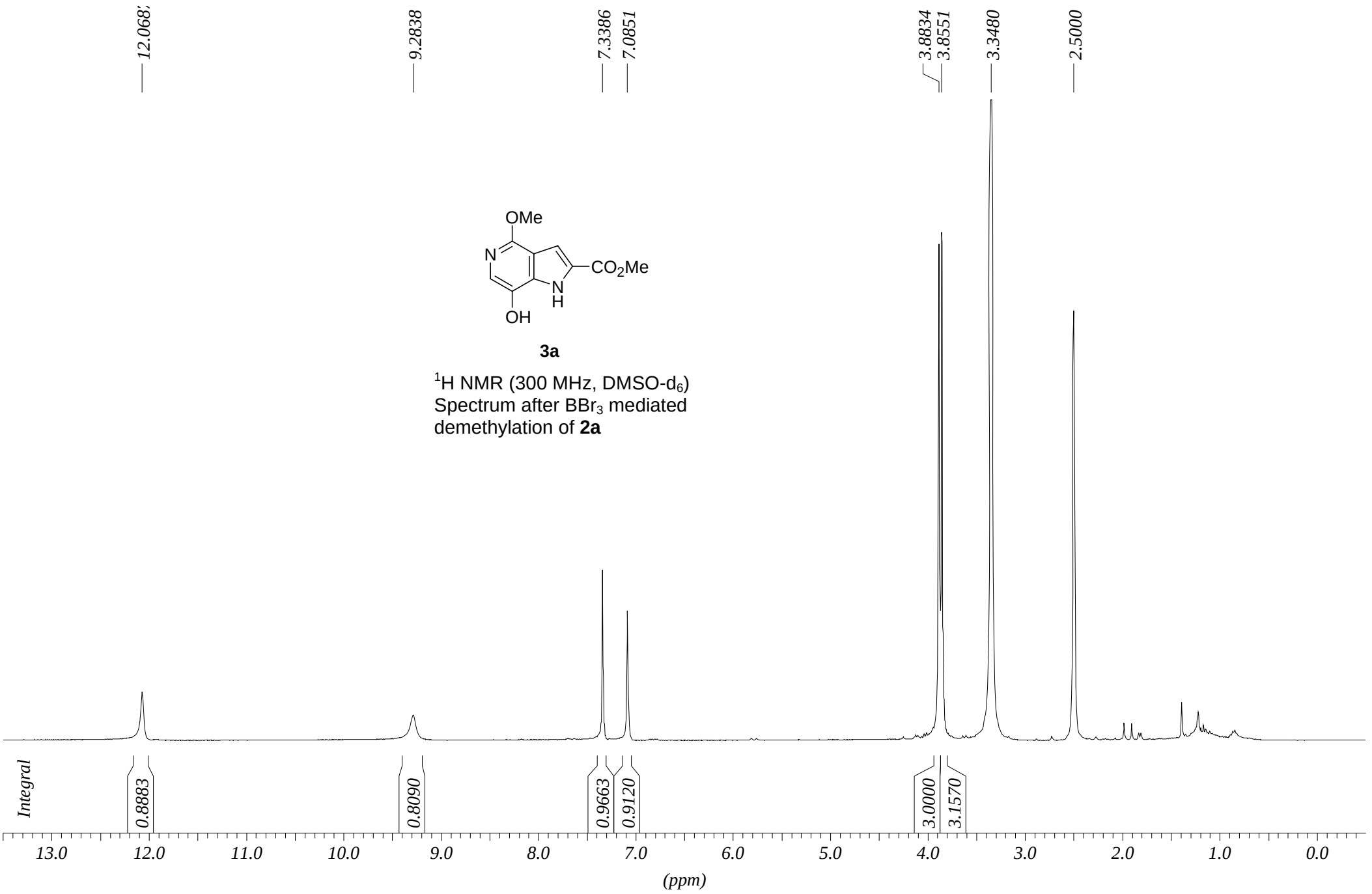
^{1}H NMR (300 MHz, $CDCl_3$)


SG38C/13C/CDCL3
161.795
153.698
135.884
135.597
126.808
126.460
114.120
107.983
77.707
77.072
76.437
53.253
52.198
17.980
12.807
OMe
N
CO2Me
N
H
OSi(i-Pr)3
14
13C NMR (50 MHz, CDCl3)
BRUKER
AV110F.130
AU PROG:
X02.AU
DATE 11-4-6
TIME 23:39
SF 50.323
SY 50.0
O1 8396.387
SI 65536
TD 65536
SW 12500.000
HZ/PT .381
PW 0.0
RD 0.0
AQ 2.621
RG 400
NS 3200
TE 297
FW 15700
O2 3154.531
DP 15H D0
LB 1.000
GB 0.0
CX 35.00
CY 20.00
F1 225.069P
F2 -23.317P
HZ/CM 357.132
PPM/CM 7.097
SR 3314.07
200
180
160
140
120
100
80
60
40
20
0
-20
PPM



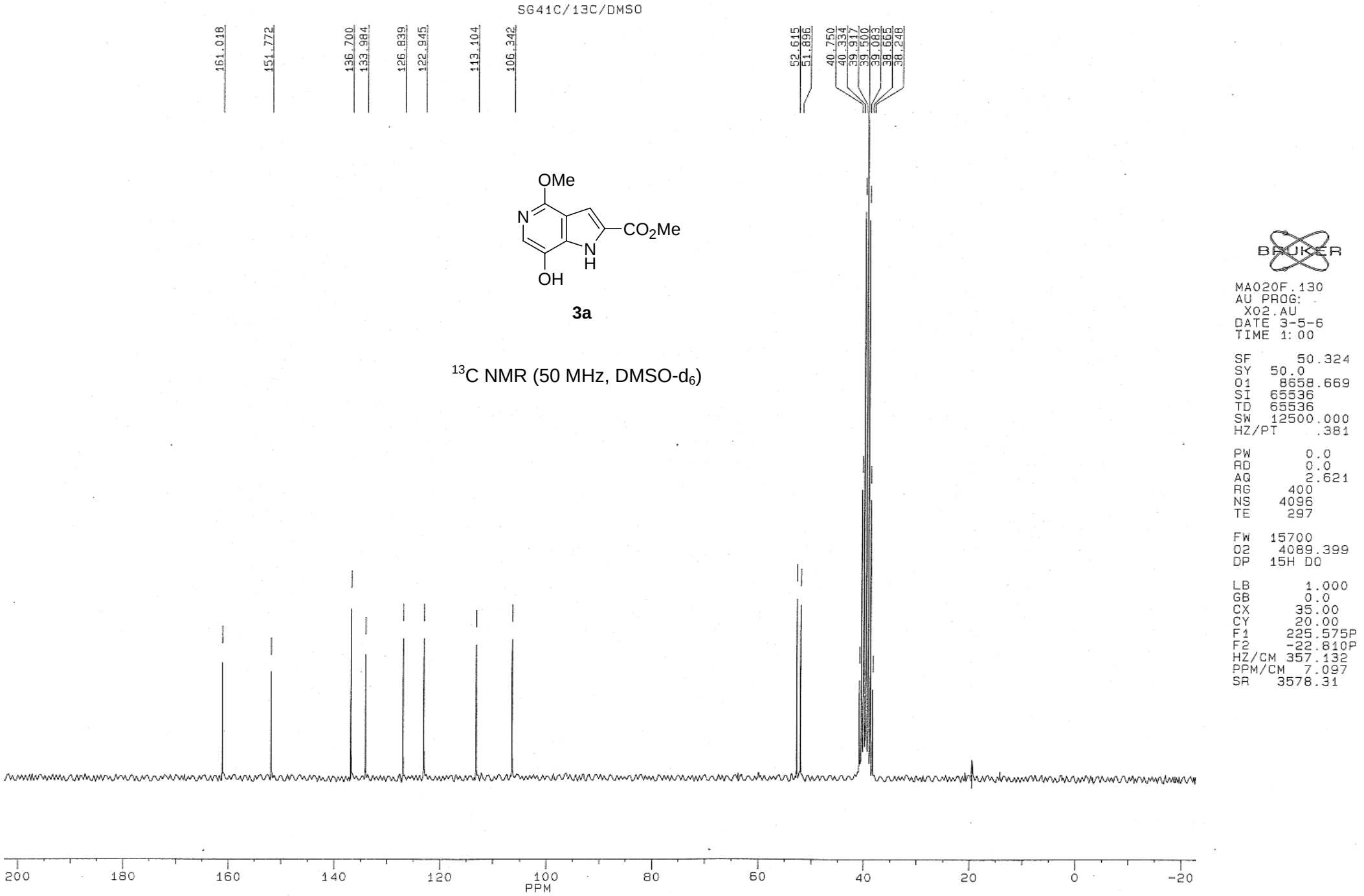
3a

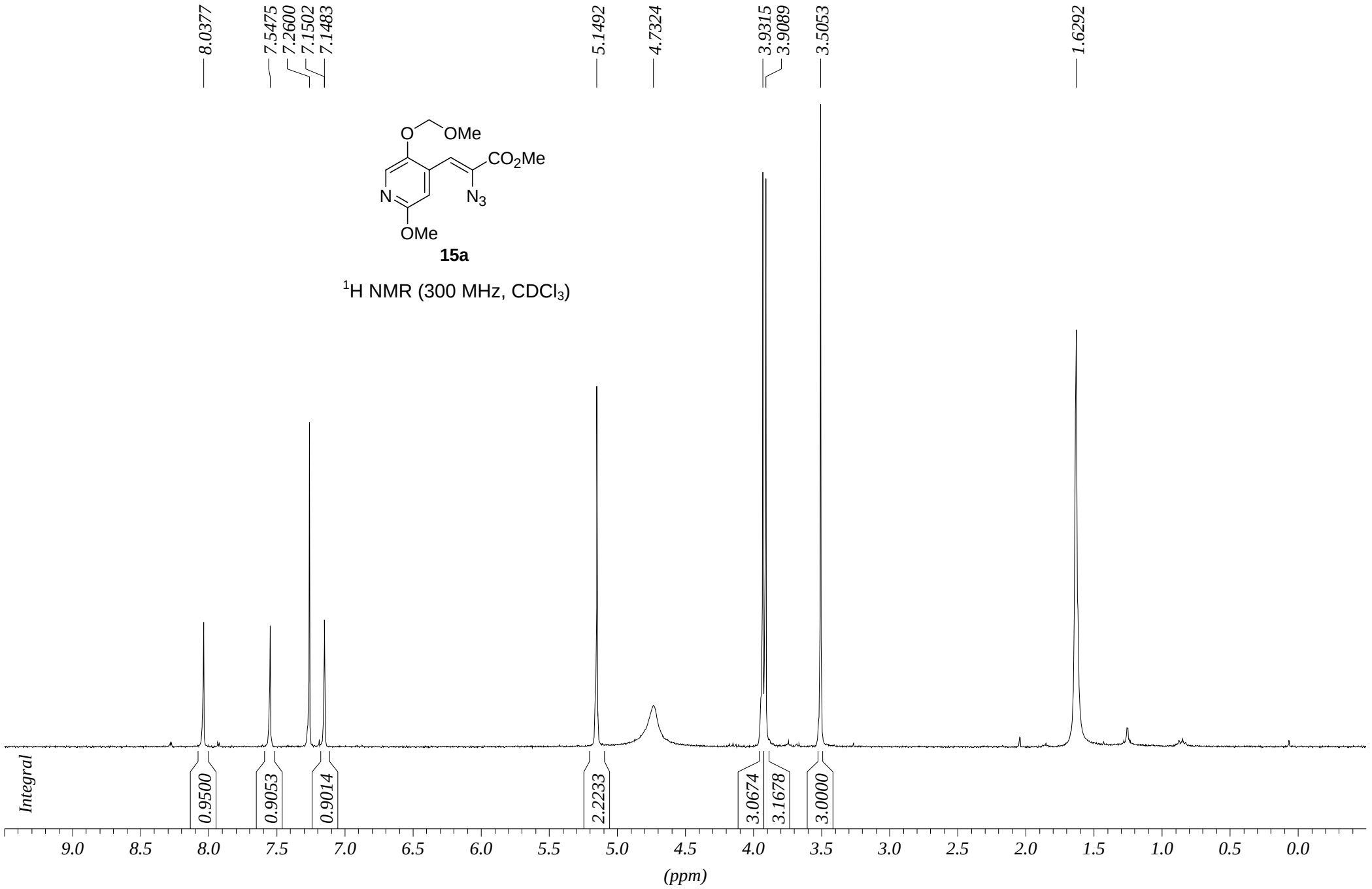
^{1}H NMR (300 MHz, DMSO-d_6)
Spectrum after TBAF mediated deprotection of **14**

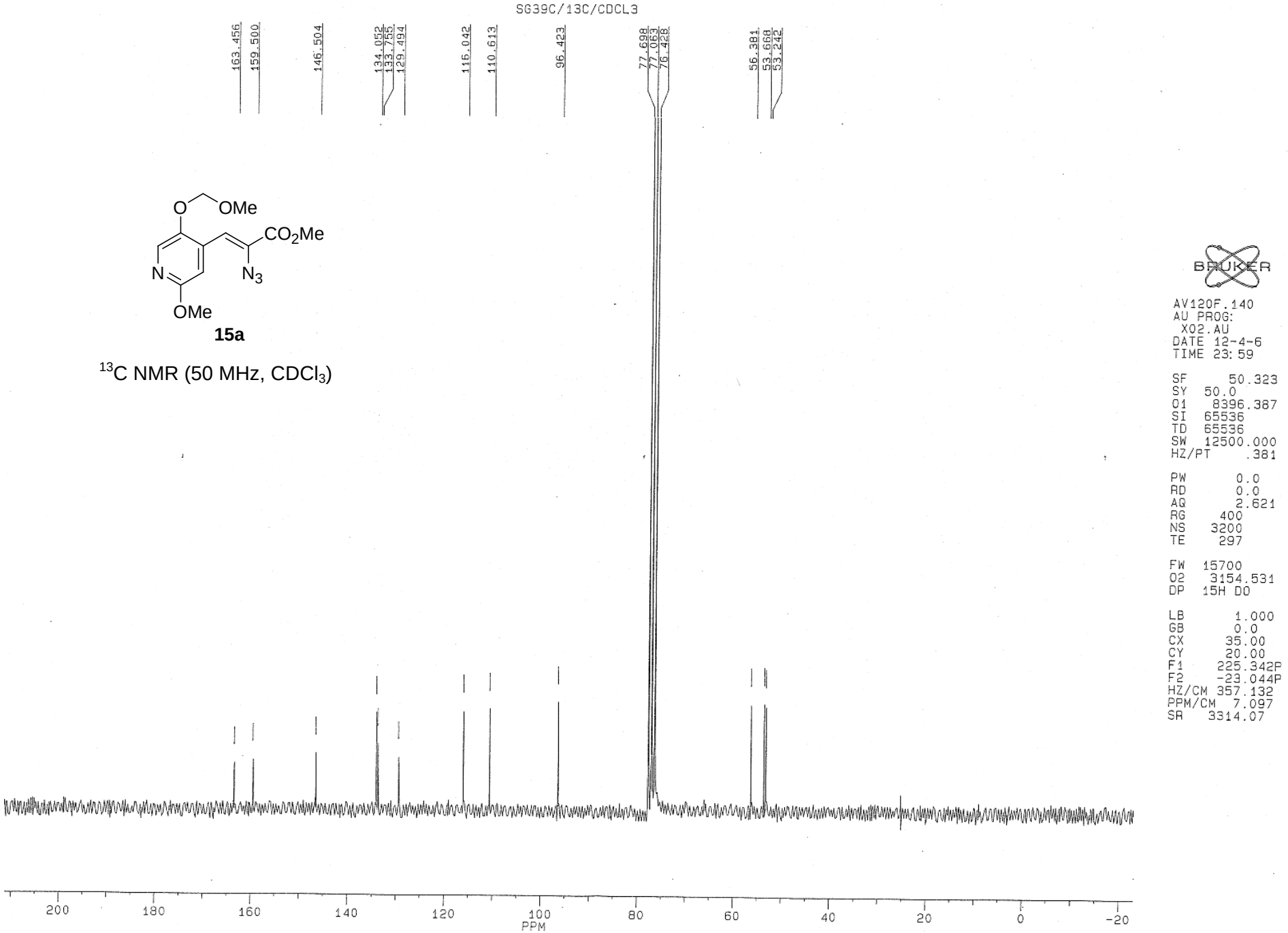


3a

^{1}H NMR (300 MHz, DMSO-d_6)
Spectrum after BBr_3 mediated demethylation of **2a**


SG41C/13C/DMSO
161.018
151.772
136.700
133.984
126.839
122.945
113.104
106.342
52.615
51.896
40.750
40.334
39.917
39.500
39.083
38.665
38.248
OMe
N
CO2Me
N
H
OH
3a
13C NMR (50 MHz, DMSO-d6)
MA020F.130
AU PROG:
X02.AU
DATE 3-5-6
TIME 1:00
SF 50.324
SY 50.0
O1 8658.669
SI 65536
TD 65536
SW 12500.000
HZ/PT .381
PW 0.0
RD 0.0
AQ 2.621
RG 400
NS 4096
TE 297
FW 15700
O2 4089.399
DP 15H DO
LB 1.000
GB 0.0
CX 35.00
CY 20.00
F1 225.575P
F2 -22.810P
HZ/CM 357.132
PPM/CM 7.097
SR 3578.31
200
180
160
140
120
100
80
60
40
20
0
-20
PPM


8.0377
7.5475
7.2600
7.1502
7.1483
5.1492
4.7324
3.9315
3.9089
3.5053
1.6292
O
OMe
CO2Me
N
N3
OMe
15a
1H NMR (300 MHz, CDCl3)
Integral
0.9500
0.9053
0.9014
2.2233
3.0674
3.1678
3.0000
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
(ppm)



15a

^{13}C NMR (50 MHz, $CDCl_3$)

BRUKER

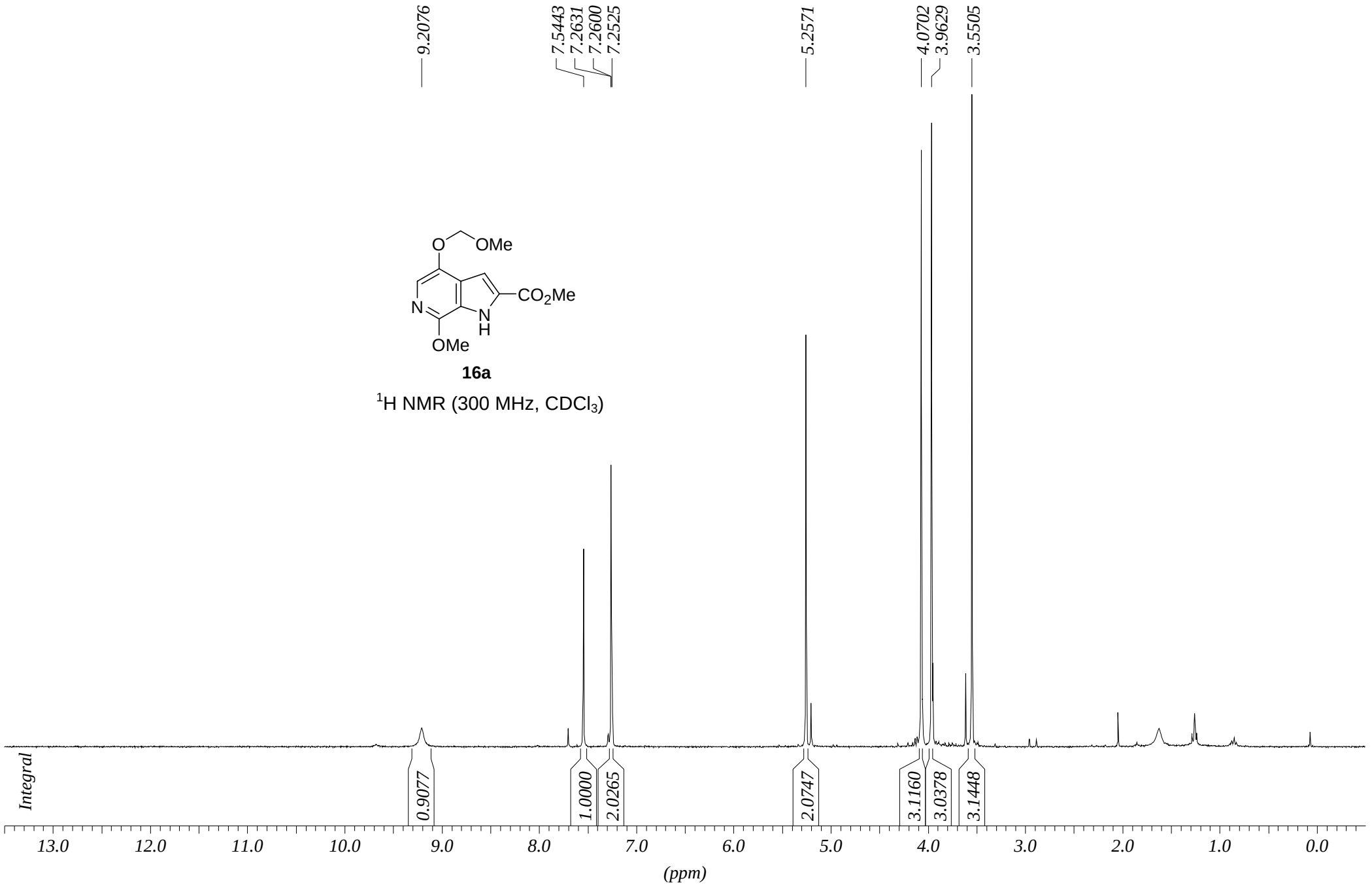
AV120F.140
AU PROG:
X02.AU
DATE 12-4-6
TIME 23:59

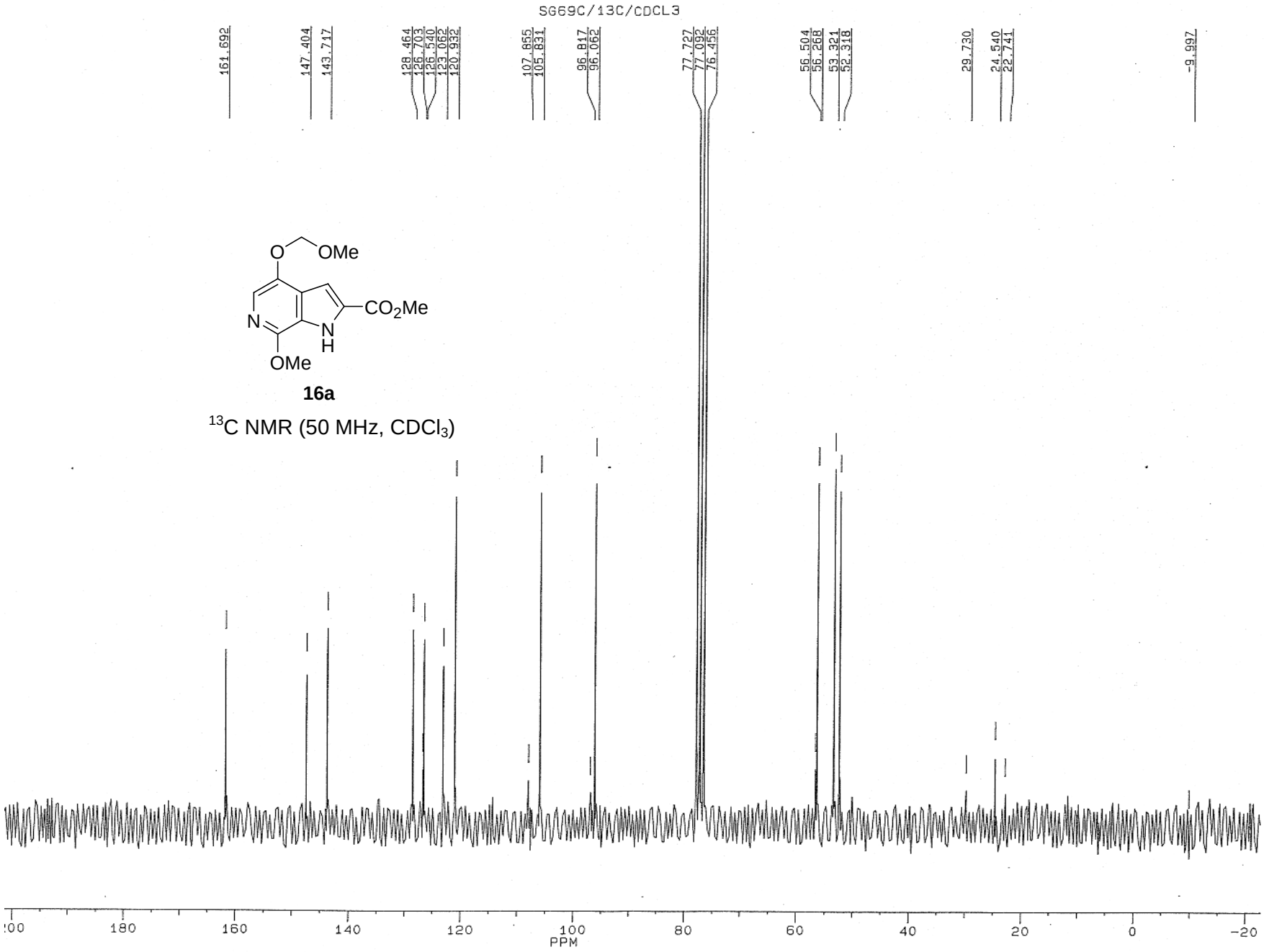
SF 50.323
SY 50.0
O1 8396.387
SI 65536
TD 65536
SW 12500.000
HZ/PT .381

PW 0.0
RD 0.0
AQ 2.621
RG 400
NS 3200
TE 297

FW 15700
O2 3154.531
DP 15H DO

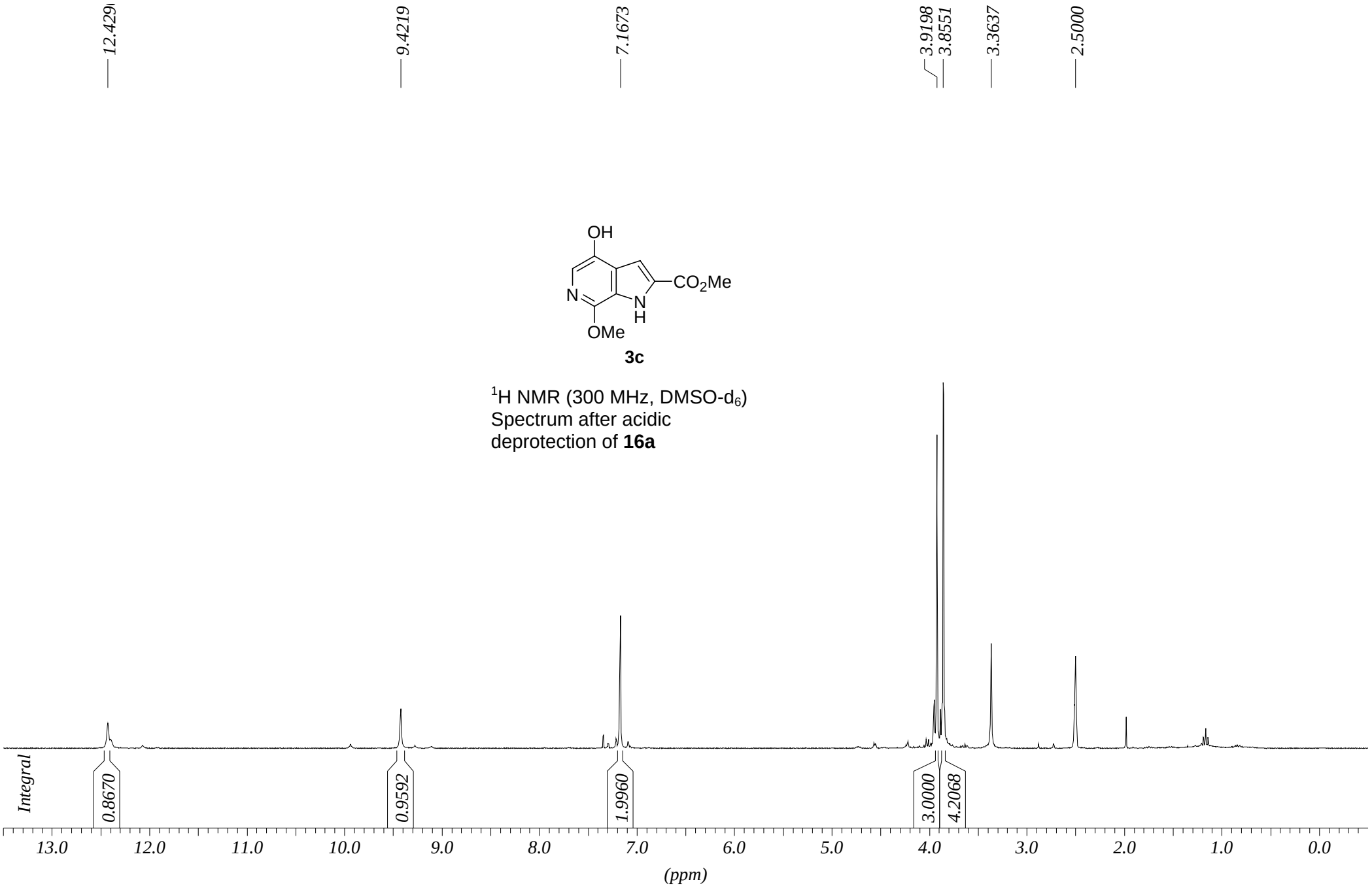
LB 1.000
GB 0.0
CX 35.00
CY 20.00
F1 225.342P
F2 -23.044P
HZ/CM 357.132
PPM/CM 7.097
SR 3314.07

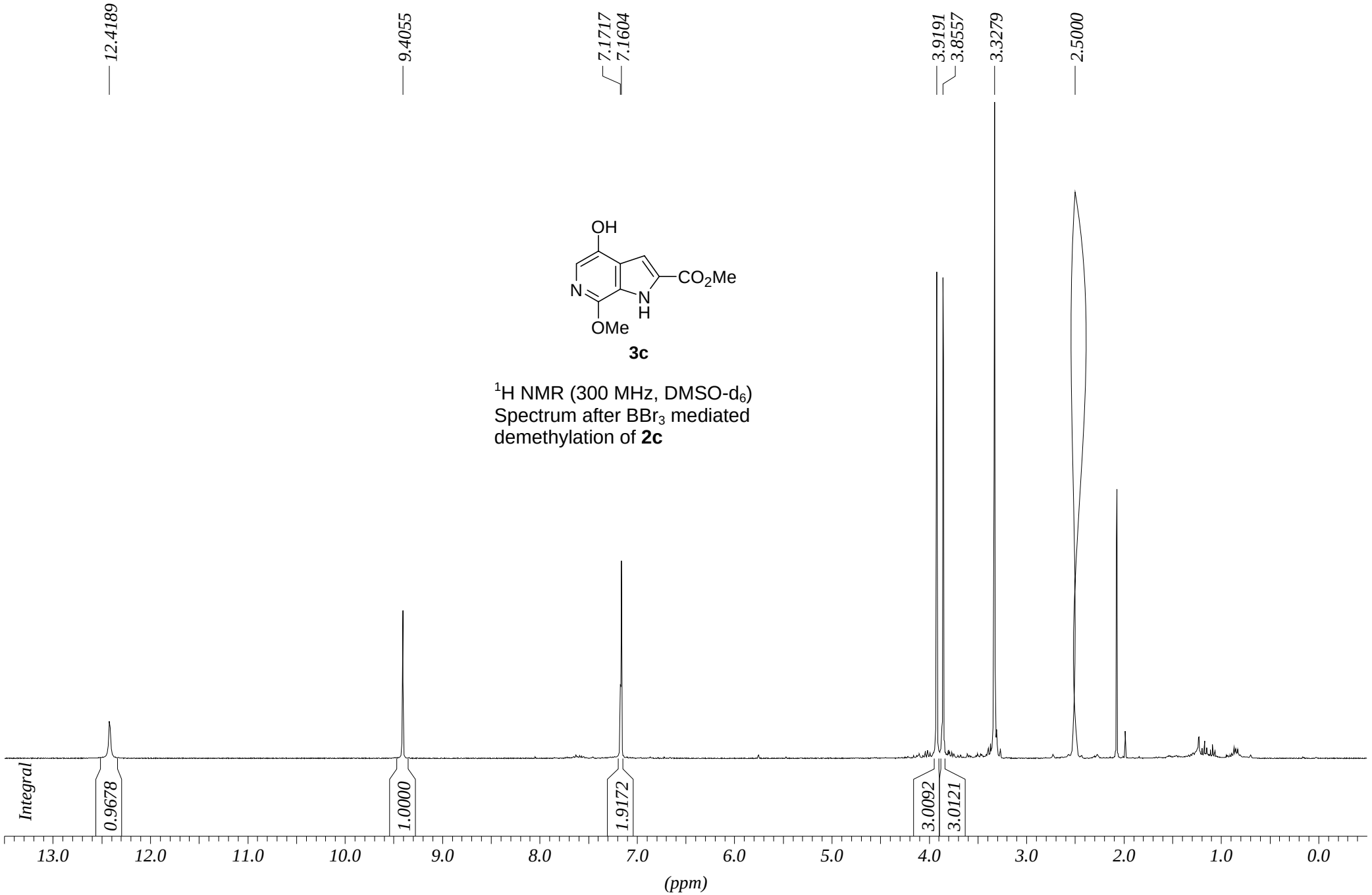

9.2076
7.5443
7.2631
7.2600
7.2525
5.2571
4.0702
3.9629
3.5505
O
OMe
CO2Me
N
N
H
OMe
16a
1H NMR (300 MHz, CDCl3)
Integral
0.9077
1.0000
2.0265
2.0747
3.1160
3.0378
3.1448
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

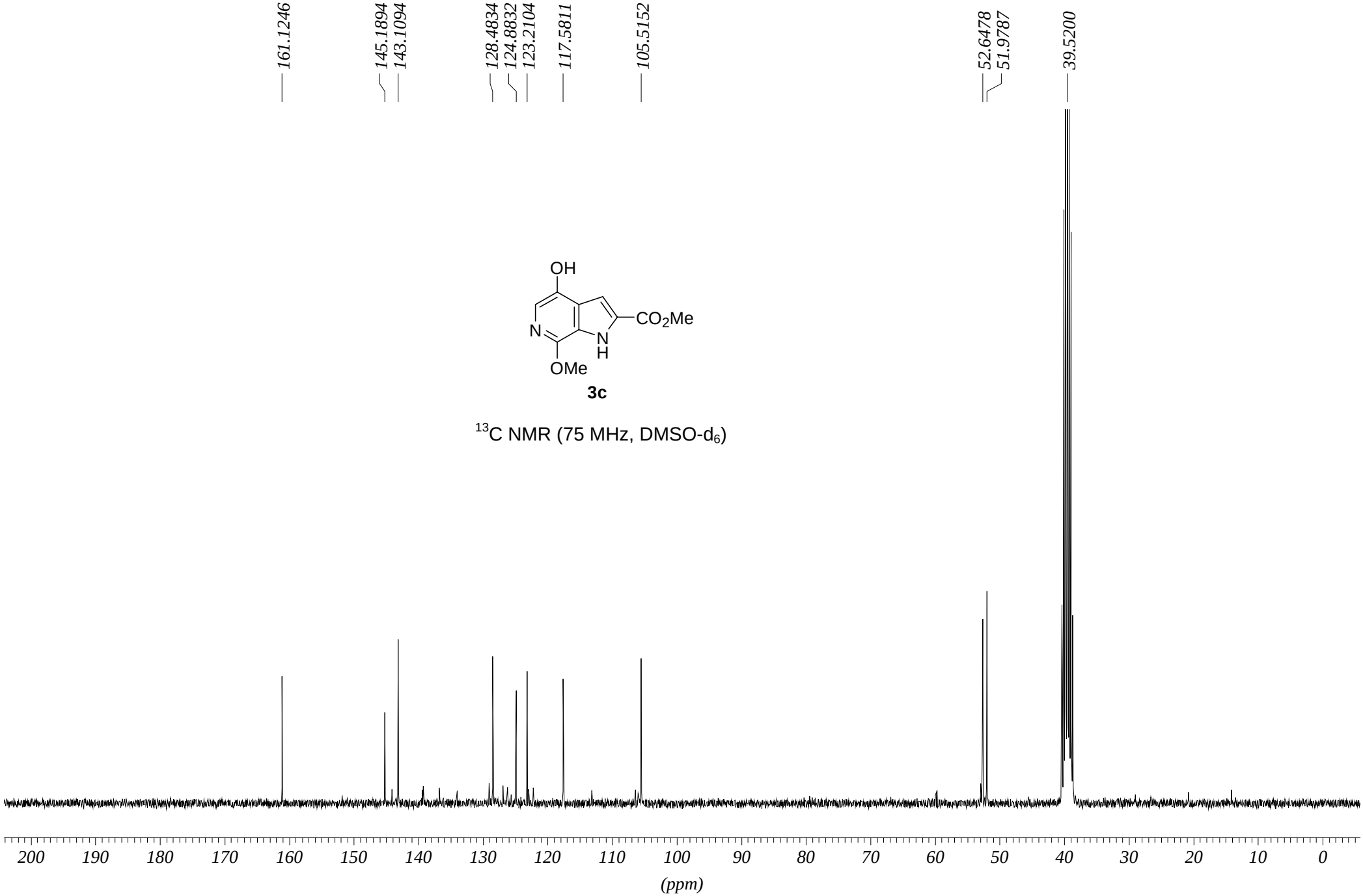


16a

^{13}C NMR (50 MHz, $CDCl_3$)

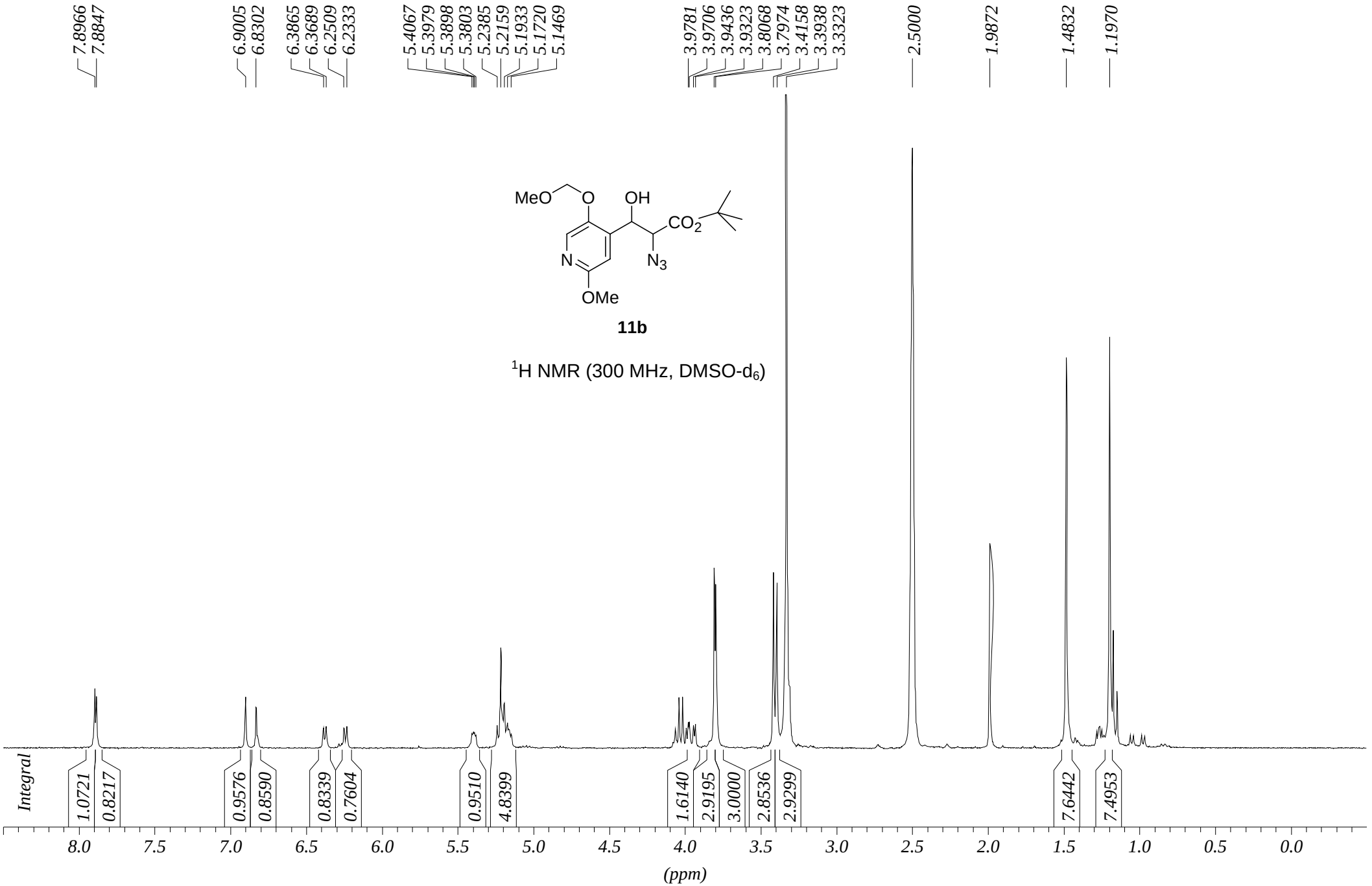

12.4291
9.4219
7.1673
3.9198
3.8551
3.3637
2.5000
OH
N
N
H
CO2Me
OMe
3c
1H NMR (300 MHz, DMSO-d6)
Spectrum after acidic
deprotection of 16a
Integral
0.8670
0.9592
1.9960
3.0000
4.2068
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)


12.4189
9.4055
7.1717
7.1604
3.9191
3.8557
3.3279
2.5000
OH
CO2Me
N
N
H
OMe
3c
1H NMR (300 MHz, DMSO-d6)
Spectrum after BBr3 mediated
demethylation of 2c
Integral
0.9678
1.0000
1.9172
3.0092
3.0121
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)



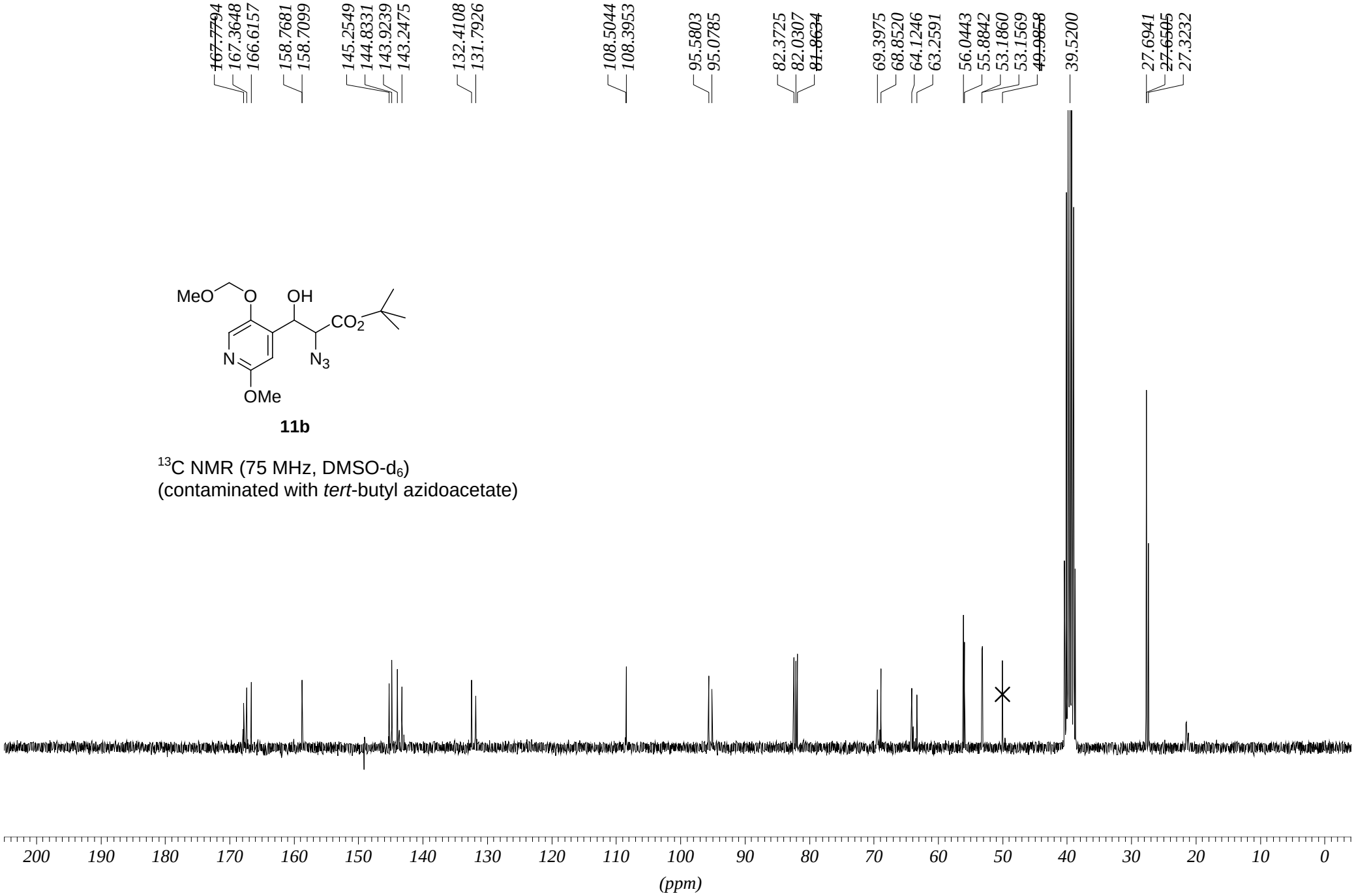
3c

^{13}C NMR (75 MHz, DMSO-d_6)



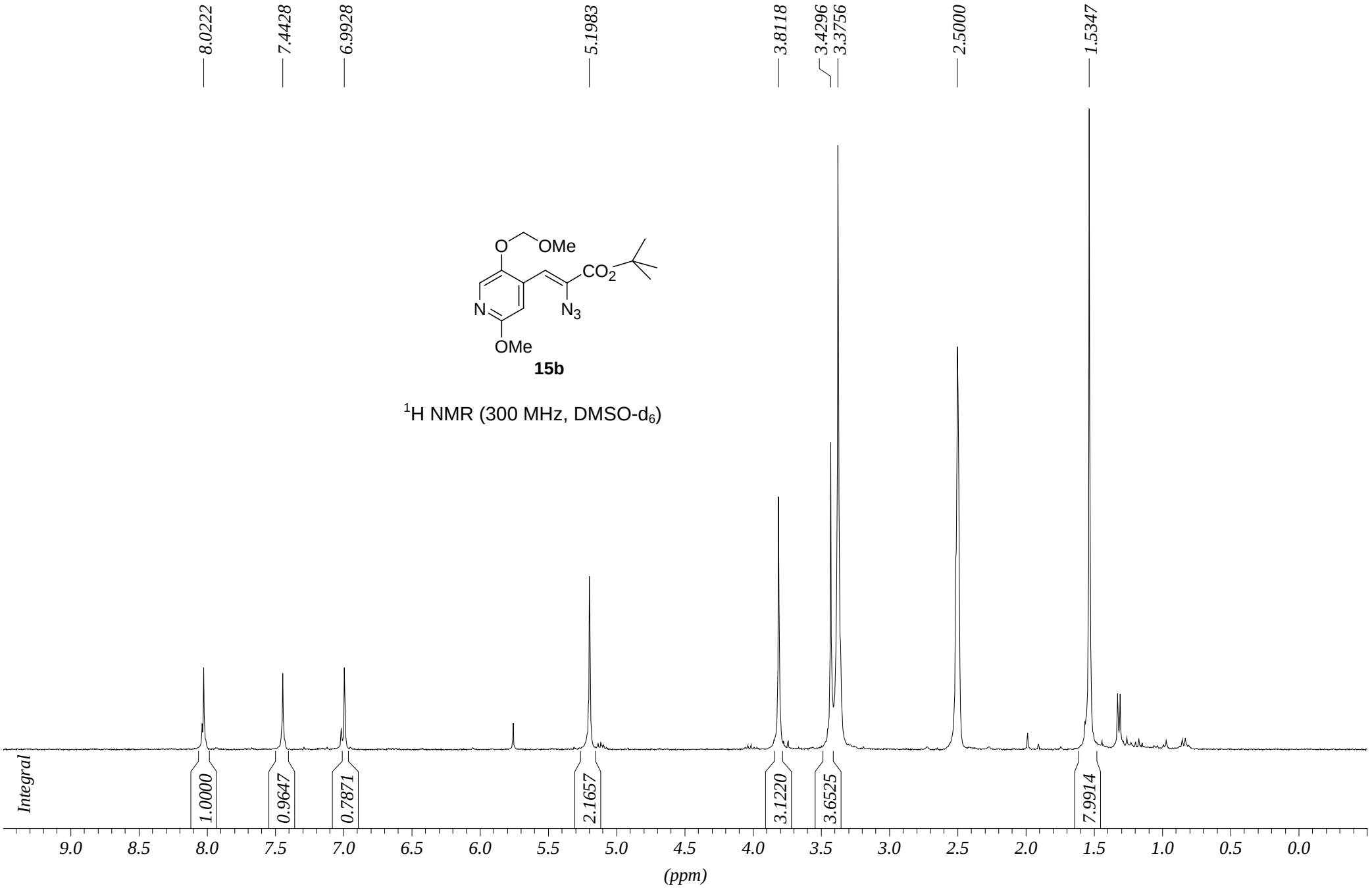
11b

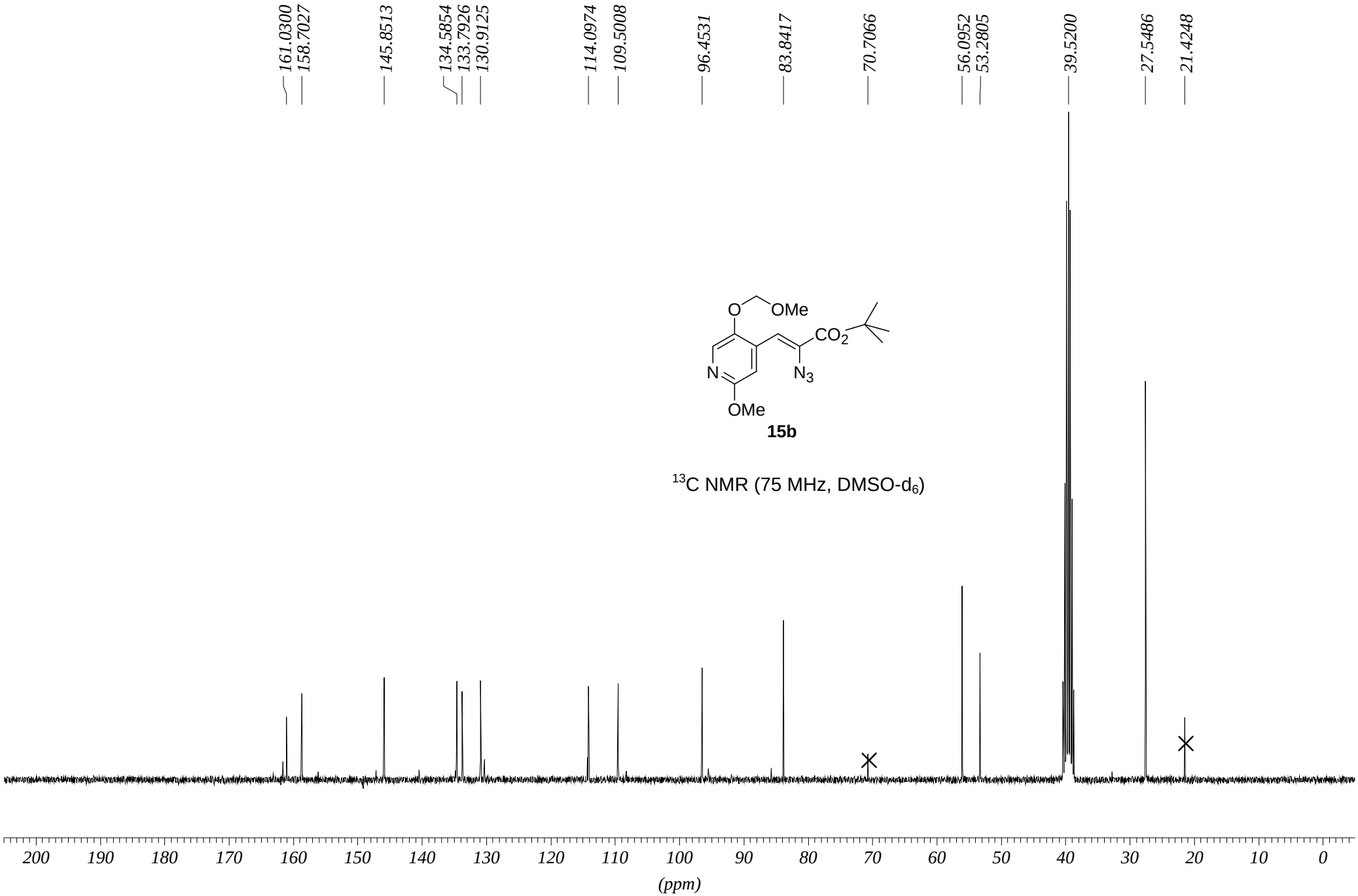
^{1}H NMR (300 MHz, DMSO-d_6)



11b

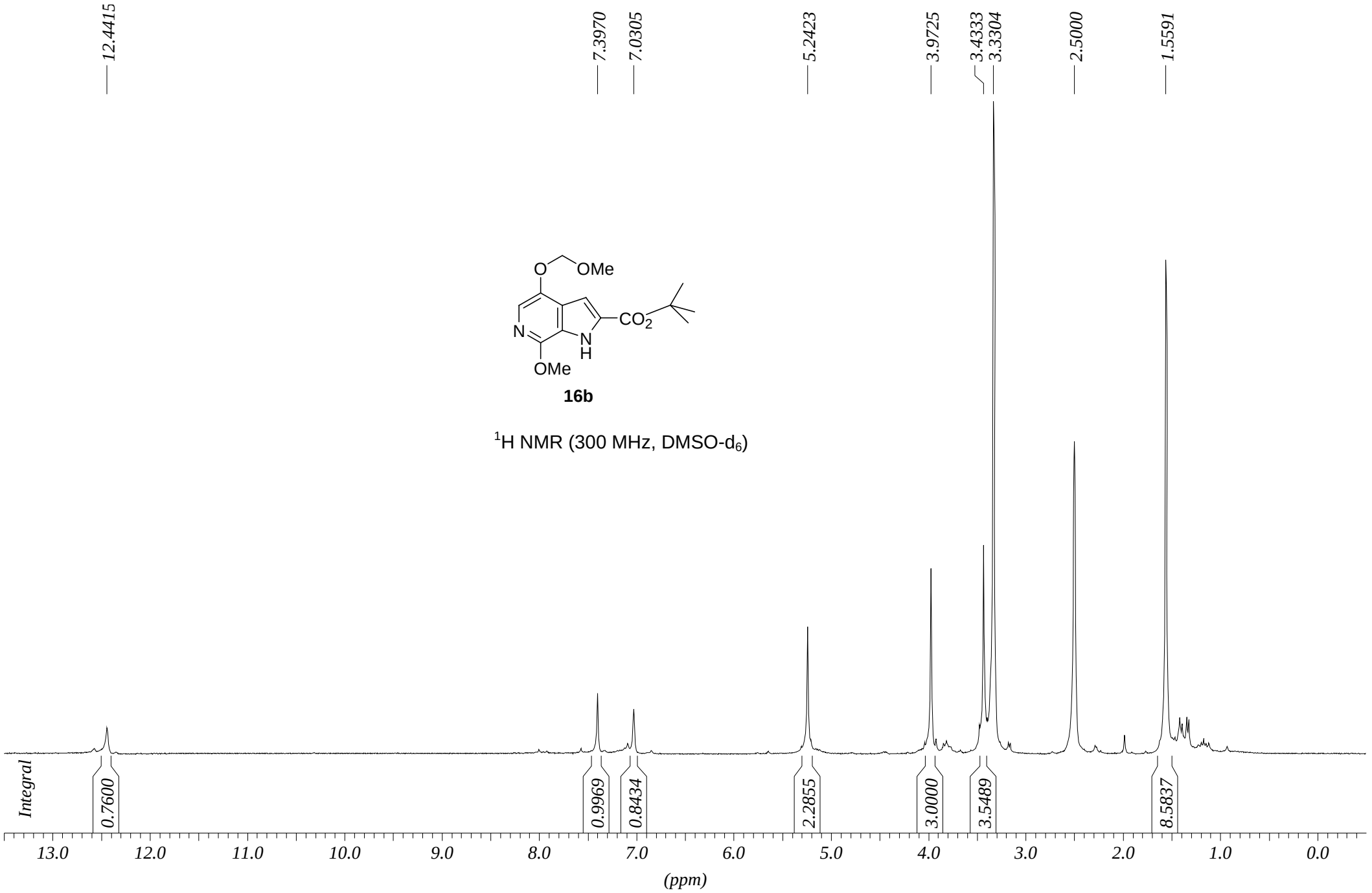
^{13}C NMR (75 MHz, DMSO-d_6)
(contaminated with *tert*-butyl azidoacetate)

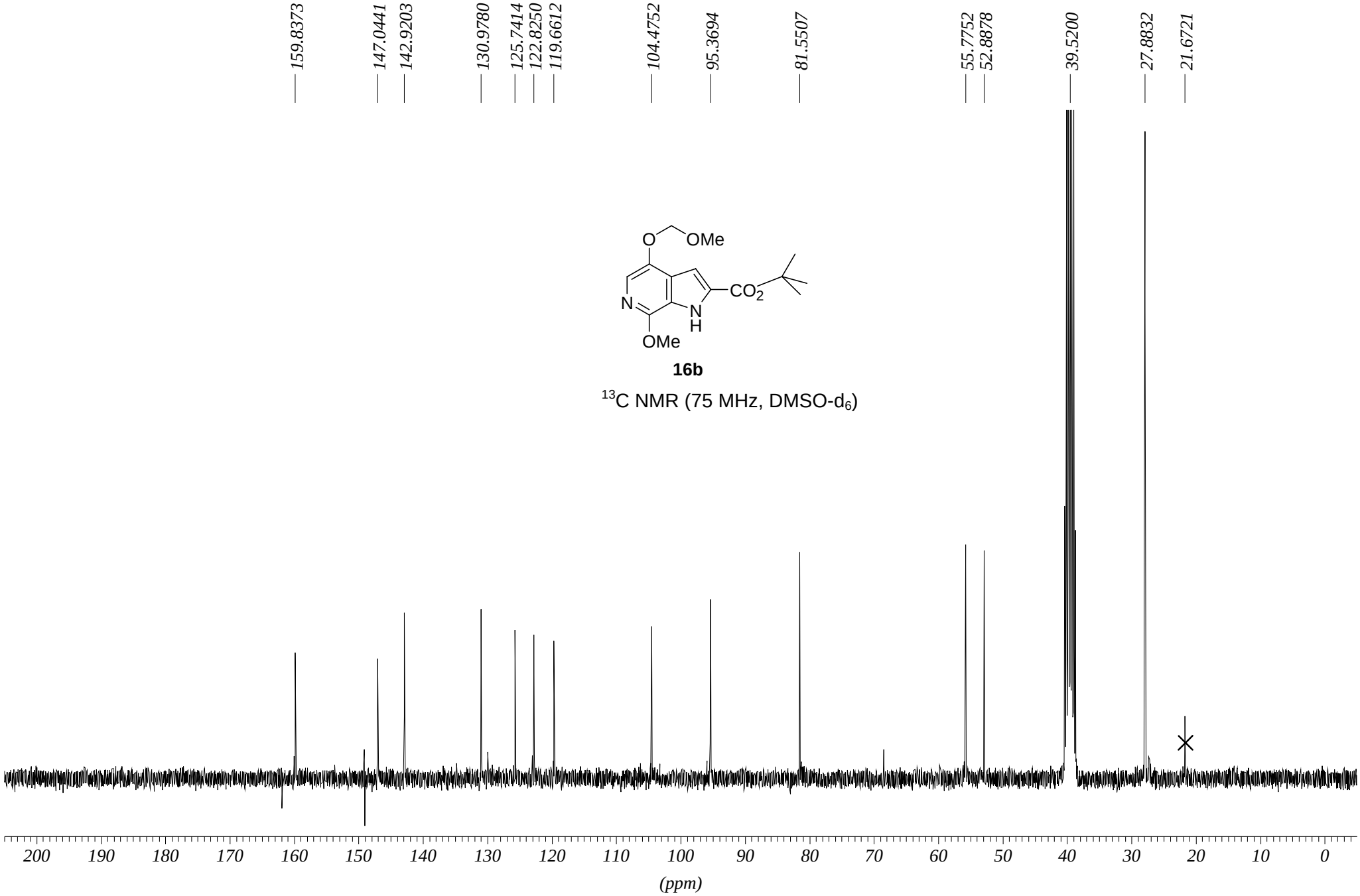

8.0222
7.4428
6.9928
5.1983
3.8118
3.4296
3.3756
2.5000
1.5347
O
OMe
CO2
N
N3
OMe
15b
1H NMR (300 MHz, DMSO-d6)
Integral
1.0000
0.9647
0.7871
2.1657
3.1220
3.6525
7.9914
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)



15b

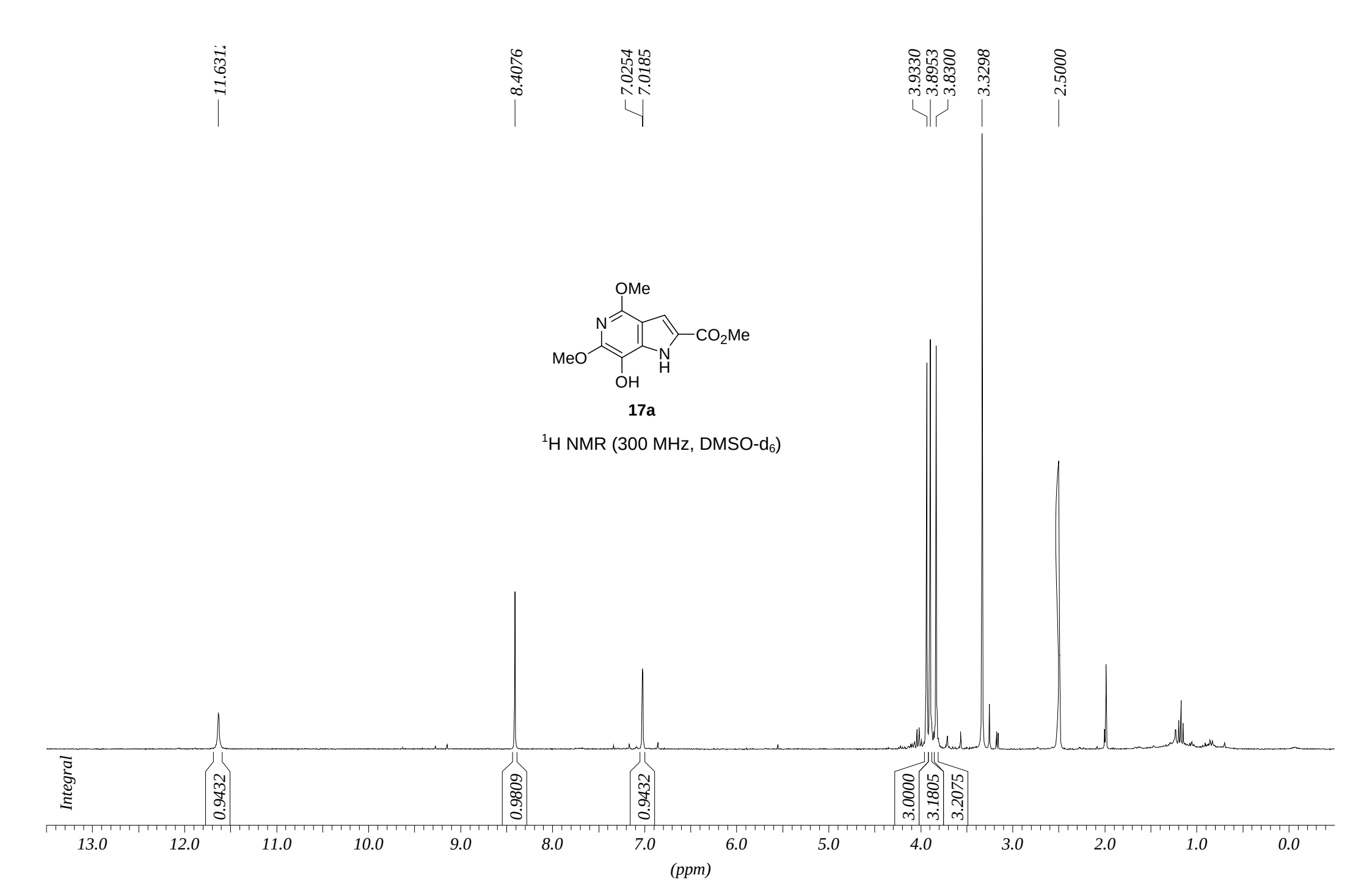
^{13}C NMR (75 MHz, DMSO-d_6)

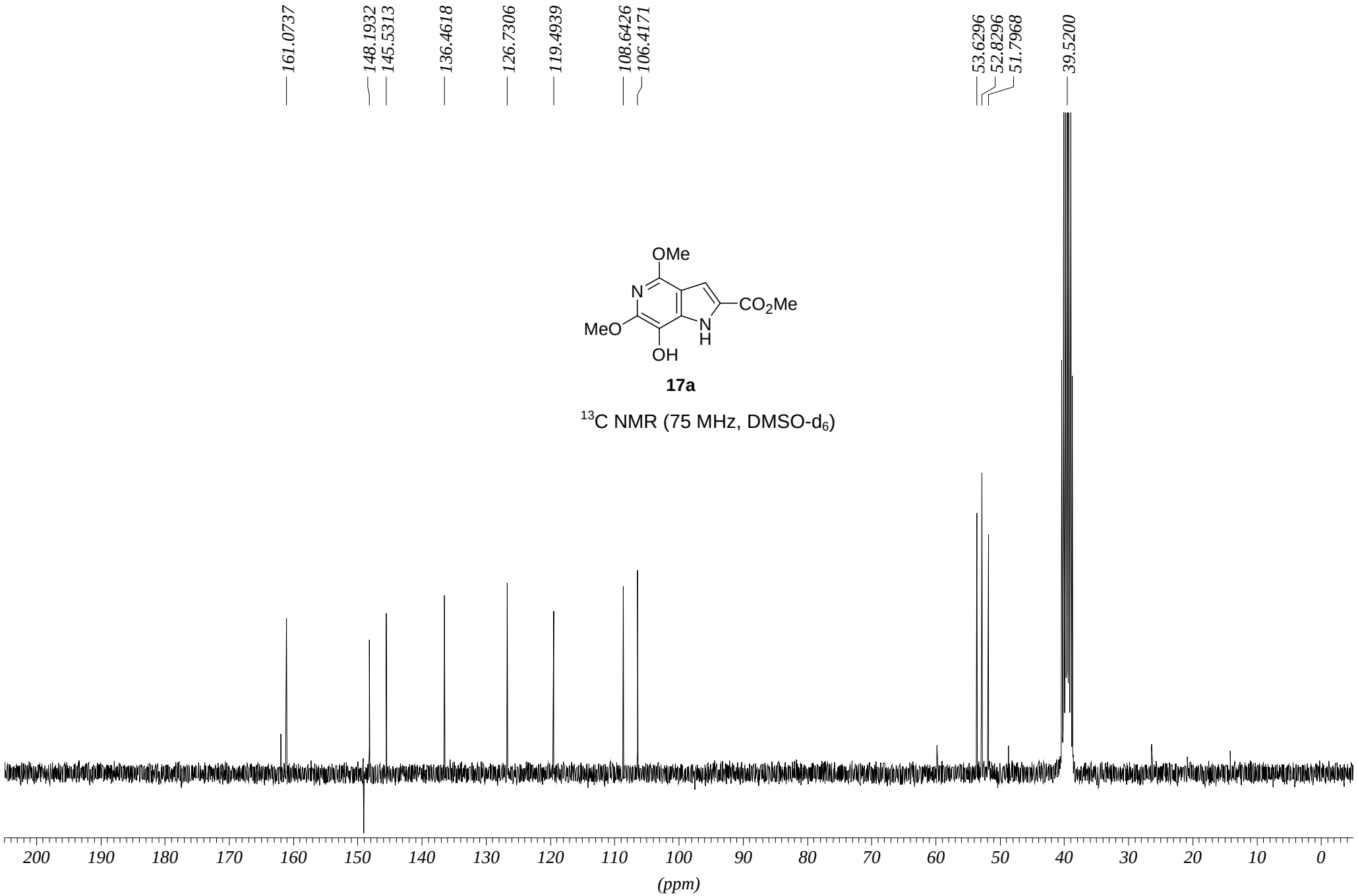

12.4415
7.3970
7.0305
5.2423
3.9725
3.4333
3.3304
2.5000
1.5591
O
OMe
N
N
H
CO2
OMe
16b
1H NMR (300 MHz, DMSO-d6)
Integral
0.7600
0.9969
0.8434
2.2855
3.0000
3.5489
8.5837
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)



16b

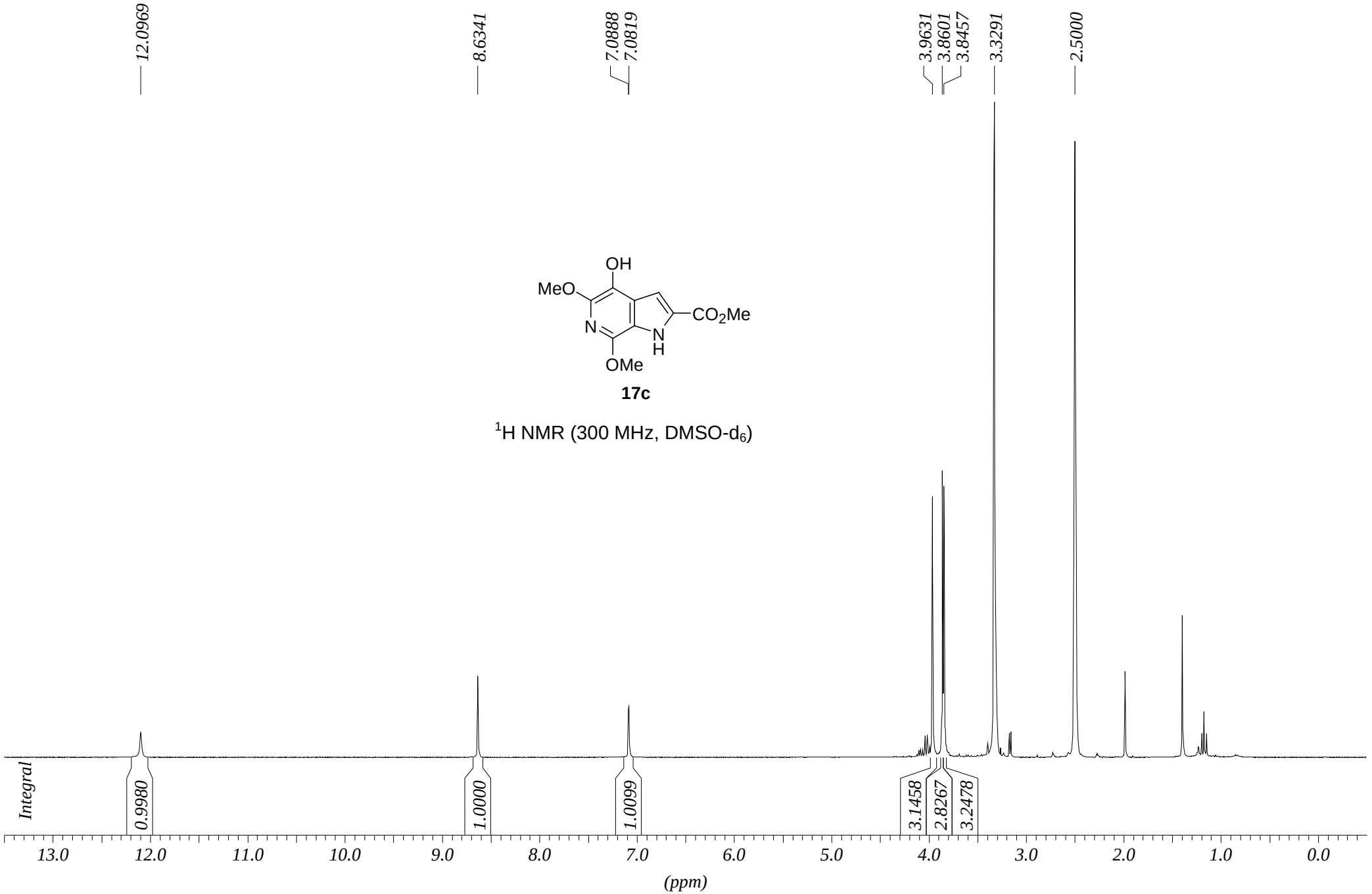
^{13}C NMR (75 MHz, DMSO-d_6)

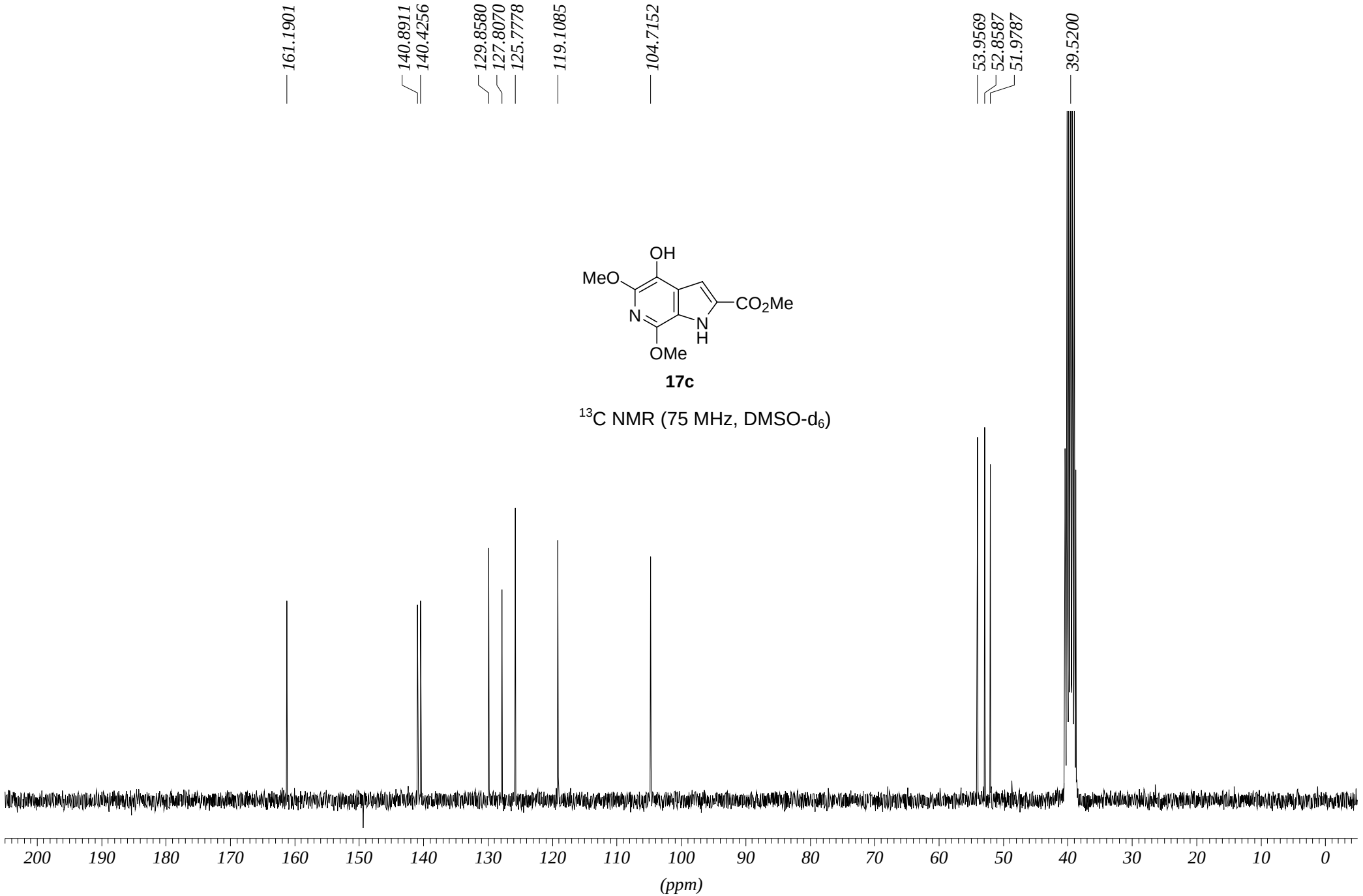

11.631
8.4076
7.0254
7.0185
3.9330
3.8953
3.8300
3.3298
2.5000
OMe
N
CO2Me
MeO
N
H
OH
17a
1H NMR (300 MHz, DMSO-d6)
Integral
0.9432
0.9809
0.9432
3.0000
3.1805
3.2075
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)



17a

^{13}C NMR (75 MHz, DMSO-d_6)


12.0969
8.6341
7.0888
7.0819
3.9631
3.8601
3.8457
3.3291
2.5000
OH
MeO
N
N
H
CO2Me
OMe
17c
1H NMR (300 MHz, DMSO-d6)
Integral
0.9980
1.0000
1.0099
3.1458
2.8267
3.2478
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)



17c

^{13}C NMR (75 MHz, DMSO-d_6)