Synthesis of 3,3-Dichloroindolin-2-ones from Isatin-3-hydrazones and (Dichloroiodo)benzene

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Supporting Information:
Experimental Details and Characterization Data: S1 – S8.
^{1}H and ^{13}C NMR Spectra of New Compounds: S9 – S54.

Experimental Details and Characterization Data General: Reactions were carried out in flame-dried glassware under a positive nitrogen atmosphere, however the chlorination reactions have been found to proceed equally well under an air atmosphere. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes. Solvents were dried and purified using a JC Meyer solvent purification system, and were used without further purification. Thin layer chromatography was performed on glass plates pre-coated with 0.25 mm Kieselgel 60 F_{254} (Silicycle). Flash chromatography columns were packed with 230-400 mesh silica gel (Silicycle). Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrum Two with UATR Two. Proton NMR spectra (^{1}H NMR) were recorded at 300 or 500 MHz, and are are reported (ppm) relative to the residual chloroform peak (7.26 ppm) or dimethylsulfoxide peak (2.50 ppm), and coupling constants (*J*) are reported in hertz (Hz). Carbon NMR spectra (^{13}C NMR) were recorded at 125 or 75 MHz and are reported (ppm) relative to the center line of the triplet from chloroform-*d* (77.16 ppm) or the center line of the septet of dimethylsulfoxide-d_6 (39.52 ppm). Fluorine NMR spectra (^{19}F NMR) were recorded at 282 or 470 MHz, and are reported (ppm) relative to the peak of trifluoroacetic acid (-76.53 ppm). Positive ion Electrospray (ESI) experiments were performed on a ThermoFisher Scientific Q-Exactive hybrid mass spectrometer. Accurate mass determinations were performed at a mass resolution of 70,000. Samples were infused at 5 mL/min in 1:1 CH_3OH:H_2O + 0.1% formic acid.

Characterization Data: Isatin Synthesis: Isatins **8a**, **8i**, **8k-o**, **8q-r** were purchased from Aldrich, Chem-Impex (USA) or Oakwood Chemical (USA), and were used without further purification. Isatins **8b-h** were prepared according to the *N*-alkylation procedure (Method B) of Muthusamy,[1] and their spectra were consistent with literature values. Isatins **8j**, **8p-r** were prepared according to the procedure of Liu (Procedure 4.1.2.),[2] and their spectra were consistent with literature values.[3] Isatin **8s** was prepared form **8a** according to the standard nitration procedure.[4]

Iodobenzene dichloride:[5] Iodobenzene (2.0 g, 9.8 mmol), was suspended in 5% sodium hypochorite (commercial household bleach, 60 ml) in a 300 mL round bottom flask equipped with a magnetic stir bar at rt. The mixture was stirred vigorously as conc. HCl (20 mL) was added dropwise over a few minutes. The yellow suspension was allowed to

stir for 5 minutes, then the suspension was filtered, washed with H_2O (200 mL) then petroleum ether (50 mL). The yellow solid is spread thinly on a watch glass or beaker (with a rubber spatula) and allowed to air-dry in the dark overnight in a desiccator. $PhICl_2$ is recovered as a pale yellow solid (2.5 g, 93% yield). The product with a melting point of 110 – 112 °C was used in the chlorination reactions. Note: The reaction occurred with better reproducibility when bleach formulations that do not contain sodium hydroxide were used.

General procedure for the synthesis of the 3-hydrazono-2-oxindoles 13a-13s: Isatin **12a** (500 mg, 3.03 mmol, 1 eq) was dissolved in absolute methanol (7.6 mL, 0.4 M) and stirred vigorously. To this solution was added hydrazine hydrate, reagent grade 98% (300 μL, 2.0 eq) in one portion and the solution was heated to reflux. After consumption of **12a** as determined by TLC the solution was allowed to cool to RT. Any precipitate formed at this stage was isolated by filtration and washed with a small quantity of cold methanol. Additional product was isolated and purified from the filtrate by silica gel chromatography after concentration by rotary evaporation. The hydrazones were often isolated as a mixture of (E) and (Z) isomers.

3-Hydrazono-2-oxindole 13a: Prepared according to the general procedure above starting with 3.75 g of Isatin **12a** to give **13a** (3.97 g, 97%) as a yellow solid. R_f: 0.43 (40% EtOAc/hexanes, UV active); m.p. 231-232 °C (Lit.[6] 221 °C); IR (ATR) 3352, 3147, 1680, 1655, 1585, 1546, 1464, 1189 cm^{-1}; HRMS (ESI) calcd for $C_8H_8N_3O$ $(M+H)^+$ 162.0662; found 162.0662. NMR spectral data is consistent with literature values.[7]

1-Methyl-3-Hydrazono-2-oxindole 13b: Prepared according to the general procedure above starting with 440 mg of N-Methylisatin **12b** to give **13b** (402 mg, 84%) as an orange solid. R_f: 0.43 (40% EtOAc/hexanes, UV active); m.p: 88-90 °C; IR (ATR) 3325, 3225, 2925, 1674, 1468, 1234 cm^{-1}; HRMS (ESI) calcd for $C_9H_{10}ON_3$ $(M+H)^+$ 176.0818; found 176.0816. NMR spectral data is consistent with literature values.[7]

1-*i*-Propyl-3-hydazono-2-oxindole 13c: Prepared according to the general procedure above starting with 500 mg of N-*i*-Propylisatin **12c** to give **13c** (301 mg, 56%) as a yellow solid. R_f: 0.42 (30% EtOAc/hexanes, UV active); m.p. 111-112 °C; IR (ATR) 3349, 3217, 3159, 1672, 1592, 1566, 1466, 1101 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J*=7.4 Hz, 1H), 7.33 (app. t, *J*=7.8 Hz, 1H), 7.06 (m, 2H), 6.93 (br. s, 1H), 4.76 (sept., *J*=7.0 Hz, 1H), 1.62 (br. s, 1H), 1.49 (d, *J*=7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 142.0, 132.5, 129.9, 123.3, 121.9, 117.0, 110.4, 43.7, 19.7; HRMS (ESI) calcd for $C_{11}H_{14}N_3O$ $(M+H)^+$ 204.1131; found 204.1131.

1-Hexyl-3-hydrazono-2-oxindole 13d: Prepared according to the general procedure above starting with 500 mg of N-Hexylisatin **12d** to give **13d** (233 mg, 44%) as an orange solid. R_f: 0.17 (40% EtOAc/hexanes, UV active); m.p. 108-109 °C; IR (ATR) 3376, 3213, 2924, 1682, 1590, 1557, 1464, 1101 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) d 7.54 (d, *J*=7.5 Hz, 1H), 7.35 (app. t, *J*=7.6 Hz, 1H), 7.07 (app. t, *J*=7.6 Hz, 1H), 6.90-6.96 (m, 3H), 3.76 (t, *J*=7.4 Hz, 2H), 1.68 (m, 2H), 1.20-1.50 (m, 6H), 0.87 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 142.3, 131.6, 129.7, 123.0, 122.1, 116.5,

108.7, 39.9, 31.5, 27.7, 26.6, 22.5, 14.0; HRMS (ESI) calcd for $C_{14}H_{20}N_3O$ $(M+H)^+$ 246.1601; found 246.1600.

1-Allyl-3-hydrazono-2-oxindole 13e: Prepared according to the general procedure above starting with 225 mg of N-Allylisatin **12e** to give **13e** (201 mg, 83%) as a yellow solid. R_f: 0.29 (20% EtOAc/hexanes, UV active); m.p. 105-106 °C (Lit.[8] 108-109 °C); IR (ATR) 3346, 3202, 3155, 1673, 1593, 1566, 1464, 1177 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J*=7.4 Hz, 1H), 7.24 (ddd, *J*=1.2, 7.7 Hz, 1H), 7.08 (ddd, *J*=0.85, 7.6 Hz, 1H), 6.85 (d, *J*=7.8 Hz, 1H), 5.88 (ddt, *J*=17.4, 10.3, 5.2 Hz, 1H), 5.25 (m, 1H), 5.20 (m, 1H), 4.42 (ddd, *J*=6.2, 1.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5 140.3, 131.6, 128.7, 128.0, 122.6, 121.6, 118.7, 117.7, 109.2, 41.7; HRMS (ESI) calcd for $C_{11}H_{12}N_3O$ $(M+H)^+$ 202.0975; found 202.0975.

1-Benzyl-3-hydrazono-2-oxindole 13f: Prepared according to the general procedure above starting with 500 mg of N-Benzylisatin **12f** to give **13f** (340 mg, 64%) as a yellow solid. R_f: 0.43 (40% EtOAc/hexanes, UV active); m.p. 162-163 °C; IR (ATR) 3489, 3397, 3260, 3035, 1681, 1562, 1476, 1150 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.69 (d, *J*=14.4 Hz, 1H), 10.00 (d, *J*=14.5 Hz, 1H), 7.20-7.35 (m, 7H), 6.95 (m, 2H), 4.97 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 140.1, 135.9, 128.8, 128.5, 127.9, 127.7, 127.3, 122.6, 121.7, 118.6, 109.2, 43.0; HRMS (ESI) calcd for $C_{15}H_{14}N_3O$ $(M+H)^+$ 252.1131; found 252.1131.

1-Propargyl-3-hydrazono-2-oxindole 13g: Prepared according to the general procedure above starting with 1.85 g N-Propargylisatin **12g** to give **13g** (1.51 g, 75%) as an orange solid. R_f: 0.74 (50% EtOAc/hexanes, UV active); m.p. 137-139 °C; IR (ATR) 3387, 3362, 3295, 2117, 1678, 1557, 1465, 1173 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.49 (d, *J*=13.9 Hz, 1H), 9.81 (d, *J*=13.8 Hz, 1H), 7.43 (d, *J*=7.3 Hz, 1H), 7.28 (app. t, *J*=7.4 Hz, 1H), 7.05-7.14 (m, 2H), 4.60 (s, 2H), 3.27 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.8, 138.0, 126.9, 124.6, 122.3, 121.5, 117.3, 109.3, 78.2, 74.2, 27.9; HRMS (ESI) calcd for $C_{11}H_{10}N_3O$ $(M+H)^+$ 200.0818; found 200.0818.

1-Methoxymethyl-3-hydrazono-2-oxindole 13h: Prepared according to the general procedure above starting with 500 mg N-Methoxymethylisatin **12h** to give **13h** (230 mg, 43%) as a yellow-orange solid. R_f: 0.47 (40% EtOAc/hexanes, UV active); m.p. 108-109 °C; IR (ATR) 3358, 3161, 2927, 1677, 1597, 1560, 1222, 1075 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ Major: 10.54 (br. s, 1H), 7.6 (br. s, 1H), 7.50 (d, *J*=7.5 Hz, 1H), 7.24 (app. t, *J*=7.8 Hz, 1H), 7.08 (app. t, *J*=7.6 Hz, 1H), 7.03 (d, *J*=7.9 Hz, 1H), 5.16 (s, 2H), 3.33 (s, 3H); ^{13}C NMR (125 MHz) δ 162.0, 139.3, 128.0, 123.0, 121.1, 119.7, 118.6, 109.6, 70.7, 56.3; HRMS (ESI) calcd for $C_{10}H_{12}N_3O_2$ $(M+H)^+$ 206.0924; found 206.0925.

5-Methyl-3-hydrazono-2-oxindole 13i: Prepared according to the general procedure above starting with 500 mg of 5-Methylisatin **12i** to give **13i** (300 mg, 55%) as an orange-yellow solid. R_f: 0.31 (40% EtOAc/hexanes, UV active); m.p. 207-210 °C; IR (ATR) 3386, 3177, 1697, 1572, 1478, 1176 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.23 (br. s, 1H), 8.70 (br. s, 2H), 7.77 (s, 1H), 7.01 (d, *J*=7.5 Hz, 1H), 6.72 (d, *J*=7.4

Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) 166.0, 138.3, 129.9, 129.0, 128.8, 123.5, 117.0, 109.3, 20.7 ; HRMS (ESI) calcd for $C_9H_{10}N_3O$ $(M+H)^+$ 176.0818; found 176.0816.

5-t-Butyl-3-hydrazono-2-oxindole 13j: Prepared according to the general procedure above starting with 750 mg of 5-t-Butylisatin **12j** to give **13j** (603 mg, 75%) as an orange solid. Rf: 0.49 (40% EtOAc/hexanes, UV active); m.p. 187-190 °C; IR (ATR) 3318, 3211, 2955, 1736, 1697, 1562, 1481, 1215 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.59 (br. s, 1H), 10.48 (br. d, *J*=14.1 Hz, 1H), 9.46 (br. d, *J*=13.8 Hz, 1H), 7.36 (s, 1H), 7.19 (d, *J*=8.2 Hz, 1H), 6.78 (d, *J*=8.1 Hz, 1H), 1.27 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.1, 143.8, 136.5, 126.6, 124.0, 121.9, 114.2, 109.5, 34.2, 31.5; HRMS (ESI) calcd for $C_{12}H_{16}ON_3$ $(M+H)^+$ 218.1288; found 218.1288.

5-Fluoro-3-hydrazono-2-oxindole 13k: Prepared according to the general procedure above starting with 500 mg of 5-Fluoroisatin **12k** to give **13k** (500 mg, 92%) as a yellow solid. R_f: 0.23 (40% EtOAc/hexanes, UV active); m.p. 239-241 °C (Lit.[9] 183-185 °C for mixture of (E) and (Z) isomers); IR (ATR) 3372, 3190, 1684, 1621, 1551, 1471, 1207 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) Major: δ 10.36 (br. s, 1H), 8.98 (br. s, 2H), 7.88 (d, *J*=9.2 Hz, 1H), 7.03 (app.t, *J*=8.4 Hz, 1H), 6.80 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) Major: δ 166.0, 157.5 (d, *J*=234 Hz), 136.6, 127.6, 117.2 (d, *J*=7.5 Hz), 114.4 (d, *J*=23.7 Hz), 110.1, 109.8 (d, *J*=15.2 Hz); ^{19}F NMR (282 MHz, DMSO-d_6) Major: δ −122.84; Minor: δ −122.84; HRMS (ESI) calcd for $C_8H_7N_3OF$ $(M+H)^+$ 180.0568; found 180.0567. ^{1}H and ^{13}C NMR spectra for minor isomer match literature values.[10]

5-Chloro-3-hydrazono-2-oxindole 13l: Prepared according to the general procedure above starting with 500 mg of 5-Chloroisatin **12l** to give **13l** (450 mg, 83%) as a yellow solid. R_f: 0.32 (40% EtOAc/hexanes, UV active); m.p. 228-230 °C (Lit.[11] 252-254°C for (E) and (Z) isomeric mixture); IR (ATR) 3401, 3177, 1712, 1632, 1576, 1464, 1198 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) Major: δ 10.5 (br. s, 1H), 9.05 (br. s, 2H), 8.06 (s ,1H), 7.18 (d, *J*=8.1 Hz, 1H), 6.83 (d, *J*=8.4 Hz, 1H), Minor: δ 10.68 (br. s, 1H), 10.66 (br. d, *J*=14.8 Hz, 1H), 9.86 (br. d, *J*=14.8 Hz, 1H), 7.32 (d, *J*=1.3 Hz, 1H), 7.15 (dd, *J*=8.1, 1.7 Hz, 1H), 6.86 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) Major: δ 165.7, 139.1, 127.9, 126.9, 125.2, 122.2, 118.0, 110.8; HRMS (ESI) calcd for $C_8H_7N_3OCl$ $(M+H)^+$ 196.0272; found 196.0272.

5-Bromo-3-hydrazono-2-oxindole 13m: Prepared according to the general procedure above starting with 500 mg of 5-Bromoisatin **12m** to give **13m** (401 mg, 76% yield, 1:1 mixture of isomers) as a yellow solid. R_f: (40% EtOAc/hexanes, UV active); m.p. 230-232 °C (Lit.[12] 252-254 °C for (E) and (Z) isomeric mixture); IR (ATR) 3394, 3178, 1711, 1633, 1573, 1461, 1199 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) Major: δ 10.81 (br. s, 1H), 10.64 (br. d, *J*=14.6 Hz, 1H), 9.84 (br. d, *J*=14.5 Hz, 1H), 7.34 (d, *J*=7.7 Hz, 1H), 6.8 (m, 1H), Minor: 10.49 (s, 1H), 9.04 (s, 1H), 7.44 (s, 1H), 7.34 (d, *J*=7.4 Hz, 1H), 6.79 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.0, 162.9, 139.9, 138.0, 131.2, 129.6, 127.2, 125.3, 125.2, 125.0, 120.2, 119.0, 113.8, 113.5, 112.4, 111.8; HRMS (ESI) calcd for $C_8H_7N_3OBr$ $(M+H)^+$ 239.9767; found 239.9767.

7-Bromo-3-hydrazono-2-oxindole 13n: Prepared according to the general procedure above starting with 330 mg of 7-Bromoisatin **12n** to give **13n** (340 mg, 97%) as an orange solid. R_f: 0.27 (30% EtOAc/hexanes, UV active); m.p. 226-228 °C; IR (ATR) 3426, 3161, 1681, 1587, 1546, 1176 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) Major: δ 10.99 (s, 1H), 10.68 (d, *J*=14.8 Hz, 1H), 9.88 (d, *J*=14.7 Hz, 1H), 7.34 (m, 2H), 6.92 (dd, *J*=7.7, 7.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.6, 137.3, 129.4, 125.5, 124.3, 123.0, 116.3, 102.6; HRMS (ESI) calcd for $C_8H_7N_3OBr$ $(M+H)^+$ 239.9767; found 239.9766.

5-Methoxy-3-hydrazono-2-oxindole 13o: Prepared according to the general procedure above starting with 500 mg of 5-Methoxyisatin **12o** to give **13o** (300 mg, 56%) as an orange solid. R_f: 0.22 (40% EtOAc/hexanes, UV active); m.p. 186-188 °C; IR (ATR) 3384, 3322, 3155, 2833, 1697, 168, 1479, 1203 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.17 (br. s, 1H), 8.81 (br. s, 2H), 7.57 (s, 1H), 6.7-6.8 (m, 2H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.0, 154.5, 134.2, 128.6, 117.4, 113.7, 109.9, 109.7, 55.8; HRMS (ESI) calcd for $C_9H_{10}N_3O_2$ $(M+H)^+$ 192.0768; found 192.0766.

5,6,7-Trimethoxy-3-hydrazono-2-oxindole 13p: Prepared according to the general procedure above starting with 300 mg 5,6,7-Trimethoxyisatin **12p** to give **13p** (200 mg, 63%) as a yellow solid. RF: 0.15 (50% EtOAc/hexanes, UV active); m.p. 188-189 °C; IR (ATR) 3269, 2939, 1696, 152, 1474, 1130 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.5-10.7 (m, 2H), 9.31 (br. d, *J*=13.5 Hz, 1H), 6.30 (s, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.0, 153.2, 147.4, 136.7, 135.4, 126.1, 106.6, 91.5, 60.9, 60.1, 56.0; HRMS (ESI) calcd for $C_{11}H_{14}N_3O_4$ $(M+H)^+$ 246.0485; found 246.0485.

5-(Trifluoromethoxy)-3-hydrazono-2-oxindole 13q: Prepared according to the general procedure above starting with 300 mg of 5-(Trifluoromethoxy)isatin **12q** to give **13q** (240 mg, 75% yield) as an orange-yellow solid. R_f: 0.22 (40% EtOAc/hexanes, UV active); m.p. 195-198 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.86 (br. s, 1H), 10.68 (br. d, *J*=14.8 Hz, 1H), 9.90 (br. d, *J*=14.6 Hz, 1H), 7.27 (s, 1H) 7.13 (d, *J*=8.5 Hz, 1H), 6.93 (d, *J*=8.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.9, 143.2 (q, *J*=2.0 Hz), 137.3, 125.1, 126.3, 123.5 (q, *J*=255 Hz), 119.7, 110.8, 110.4; ^{19}F NMR (282 MHz, DMSO-d_6) δ –57.5; HRMS (ESI) calcd for $C_9H_7N_3O_2F_3$ $(M+H)^+$ 246.0485; found 246.0485.

5-(Trifluoromethyl)-3-hydrazono-2-oxindole 13r: Prepared according to the general procedure above starting with 420 mg of 5-(Trifluoromethyl)isatin **12r** to give **13r** (400 mg, 89% yield) as an orange-yellow solid. R_f: 0.11 (30% EtOAc/hexanes, UV active); m.p. 166-168 °C; IR (ATR) 3395, 3233, 1711, 1698, 1552, 1311, 1111 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.09 (br. s, 1H), 10.69 (br. d, *J*=15.1 Hz, 1H), 9.99 (br. d, *J*=14.9 Hz, 1H), 7.59 (s, 1H), 7.50 (d, *J*=8.0 Hz, 1H), 7.03 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.8, 163.4, 142.5, 129.3, 125.6, 124.3, 122.7, 118.7, 110.2; ^{19}F NMR (282 MHz, DMSO-d_6) δ –60.0; HRMS (ESI) calcd for $C_9H_7N_3OF_3$ $(M+H)^+$ 230.0536; found 230.0536.

5-Nitro-3-hydrazono-2-oxindole 13s: Prepared according to the general procedure

above starting with 500 mg of 5-Nitroisatin **12s** to give **13s** (460 mg, 86%) as a yellow solid. Purification by column chromatography (100% EtOAc) gave an analytically pure sample of the *Z*-isomer for characterization. R_f: 0.44 (100% EtOAc, UV active); m.p. 166-168 °C; IR (ATR) 3460, 3413, 3308, 1705, 1622, 1593, 1322 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 11.38 (br. s, 1H), 10.75 (d, *J*=14.9 Hz, 1H), 10.22 (d, *J*=14.8 Hz, 1H), 8.13-8.09 (m, 2H), 7.07 (d, 9.3 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.4, 144.1, 142.6, 124.5, 123.6, 123.5, 112.7, 110.5; HRMS (ESI) calcd for $C_8H_9N_4O_4$ $(M+H_3O^+)^+$ 225.0618; found 225.0618.

General procedure for the chlorination of 3-Hydrazono-2-oxindole derivatives at reflux: Into a flame-dried round bottom flask was added 3-hydrazono-2-oxindoles **13** (0.3 mmol, 1.0 eq.) and to this was added DCE (0.2 M, 1.5 mL) and pyridine (5 mol%, as a 10% solution in CH_2Cl_2). The reaction was heated to reflux and $PhICl_2$ (1.1 eq., 91 mg) was added in one portion while quickly removing the condenser. The reaction was stirred and followed by TLC analysis until starting material was consumed. The reaction mixture was partially concentrated by rotary evaporation and then purified by gradient column chromatography providing analytically pure samples of dichlorides **9**. Spectral data for compounds **9a-f**, **i-m**, **o**, **q**, **s** are consistent with literature values.[13]

3,3-Dichloro-2-oxindole 9a: Compound **13a** (49 mg) was subjected to the general chlorination procedure to give **9a** (61 mg, 97% yield) as an off-white solid. NMR spectra and melting point (162-163 °C) were consistent with those reported in the literature.

***N*-Methyl-3,3-Dichloro-2-oxindole 9b**: Compound **13b** (35mg) was subjected to the general chlorination procedure to give **9b** (34 mg, 78% yield) as a red solid. NMR spectra were consistent with those reported in the literature.

***N*-*i*-Propyl-3,3-Dichloro-2-oxindole 9c**: Compound **13c** (61 mg) was subjected to the general chlorination procedure to give **9c** (73 mg, 99% yield) as a yellow solid. NMR spectra were consistent with those reported in the literature.

***N*-Hexyl-3,3-Dichloro-2-oxindole 9d**: Compound **13d** (76 mg) was subjected to the general chlorination procedure to give **9d** (76 mg, 85% yield) as a red oil. NMR spectra were consistent with those reported in the literature.

***N*-Allyl-3,3-Dichloro-2-oxindole 9e**: Compound **13e** (60 mg) was subjected to the general chlorination procedure to give **9e** (51 mg, 70% yield) as a red oil. NMR spectra were consistent with those reported in the literature.

***N*-Benzyl-3,3-Dichloro-2-oxindole 9f**: Compound **13f** (75 mg) was subjected to the general chlorination procedure to give **9f** (74 mg, 85% yield) as clear crystals. NMR spectra were consistent with those reported in the literature.

***N*-Propargyl-3,3-Dichloro-2-oxindole 9g**: Compound **13g** (60 mg) was subjected to the general chlorination procedure to give **9g** (60 mg, 82% yield) as pale red crystals. R_f: 0.79 (50% EtOAc/hexanes, UV active); m.p. 87-90 °C; IR (ATR) 3295, 2126 (weak),

1743, 1609, 1173 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.65 (d, *J*=7.6 Hz, 1H), 7.43 (app. t, *J*=7.7 Hz, 1H), 7.22 (app. t, *J*=7.6 Hz, 1H), 7.09 (d, *J*=7.9 Hz, 1H), 4.53 (d, *J*=1.6 Hz, 2H), 2.32 (t, *J*=2.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.0, 138.9, 132.0, 129.2, 125.0, 124.7, 110.3, 74.2, 74.1, 73.7, 30.4; HRMS (ESI) calcd for $C_{11}H_8ONCl_2$ $(M+H)^+$ 239.9978; found 239.9975.

***N*-Methoxymethyl-3,3-Dichloro-2-oxindole 9h**: Compound **13h** (62 mg) was subjected to the general chlorination procedure to give **9h** (60 mg, 81% yield) as a red solid. R_f: 0.66 (40% EtOAc/hexanes, UV active); m.p. 188-189 °C; IR (ATR) 1726, 1662, 1343cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.66 (d, *J*=7.6 Hz, 1H), 7.42 (app. t, *J*=7.7 Hz, 1H), 7.23 (app. t, *J*=7.6 Hz, 1H), 7.06 (d, *J*=7.9 Hz, 1H), 5.17 (s, 2H), 3.37 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.6, 139.0, 132.1, 129.0, 125.0, 124.8, 110.8, 74.5, 72.4, 56.6; HRMS (ESI) calcd for $C_{10}H_{11}O_2NCl_2$ $(M+ H)^+$ 246.0083; found 246.0083.

5-Methyl-3,3-dichloro-2-oxindole 9i: Prepared according to the general chlorination procedure above starting with 53 mg of **13i** to give **9i** (39 mg, 60% yield) as a clear yellow solid. NMR spectra were consistent with those reported in the literature.

5-*t*-Butyl-3,3-dichloro-2-oxindole 9j: Prepared according to the general chlorination procedure above starting with 66 mg of **13j** to give **9j** (49 mg, 63% yield) as an orange solid. NMR spectra were consistent with those reported in the literature.

5-Fluoro-3,3-dichloro-2-oxindole 9k: Prepared according to the general procedure above starting with 54 mg of **13k** to give **9k** (64 mg, 88% yield) as a clear brown solid. NMR spectra were consistent with those reported in the literature.

5-Chloro-3,3-dichloro-2-oxindole 9l: Prepared according to the general procedure above starting with 59 mg of **13l** to give **9l** (57 mg, 80% yield) as a clear yellow solid. NMR spectra were consistent with those reported in the literature.

5-Bromo-3,3-dichloro-2-oxindole 9m: Prepared according to the general procedure above starting with 74 mg of **13m** to give **9m** (73 mg, 87% yield) as pale yellow crystals. NMR spectra were consistent with those reported in the literature.

7-Bromo-3,3-dichloro-2-oxindole 9n: Prepared according to the general procedure above starting with 74 mg of **13n** to give **9n** (61 mg, 73% yield) as an off white-solid. R_f: 0.47 (30% EtOAc/hexanes, UV active); m.p. 198-200 °C (dec.); IR (ATR) 3166, 1738, 1609, 1469, 1158 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.70 (br. s, 1H), 7.68 (d, *J*=7.6 Hz, 1H), 7.62 (d, *J*=8.2 Hz, 1H), 7.12 (app. t, *J*=7.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.9, 138.7, 135.2, 130.2, 125.3, 124.0, 103.2, 75.0; HRMS (ESI) calcd for $C_8H_5ONBrCl_2$ $(M+H)^+$ 279.8926, found 279.8927.

5-Methoxy-3,3-dichloro-2-oxindole 9o: Prepared according to the general procedure above starting with 58 mg of **13o** to give **9o** (41 mg, 59% yield) as a yellow solid. NMR spectra were consistent with those reported in the literature.

5-(Trifluoromethoxy)-3,3-dichloro-2-oxindole 9q: Prepared according to the general procedure above starting with 74 mg of **13q** to give **9q** (77 mg, 89% yield) as pale pink crystals. NMR spectra were consistent with those reported in the literature.

5-(Trifluoromethyl)-3,3-dichloro-2-oxindole 9r: Prepared according to the general procedure above starting with 69 mg of **13r** to give **9r** (67 mg, 83% yield) as pale red crystals. R_f: 0.28 (30% EtOAc/hexanes, UV active); m.p. 188-189 °C; IR (ATR) 3147, 1768, 1736, 1632, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.69 (br. s, 1H), 7.89 (s, 1H), 7.66 (d, *J*=8.3 Hz, 1H), 7.10 (d, *J*=8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 140.8, 130.3, 129.7 (q, *J*=3.8 Hz), 127.2, (q, *J*=33.4 Hz), 123.6 (q, *J*=272.1 Hz), 122.7 (q, *J*=3.7 Hz), 111.7, 73.5; ^{19}F NMR (282 MHz) δ -62.30; HRMS (ESI) calcd for $C_9H_7N_3OCl_2F_3$ $(M+H)^+$ 269.9695; found 269.9694.

5-Nitro-3,3-dichloro-2-oxindole 9s: Prepared according to the general procedure above starting with 22 mg of **13s** to give **9s** (13 mg, 49% yield) as a clear yellow solid. NMR spectra were consistent with those reported in the literature.

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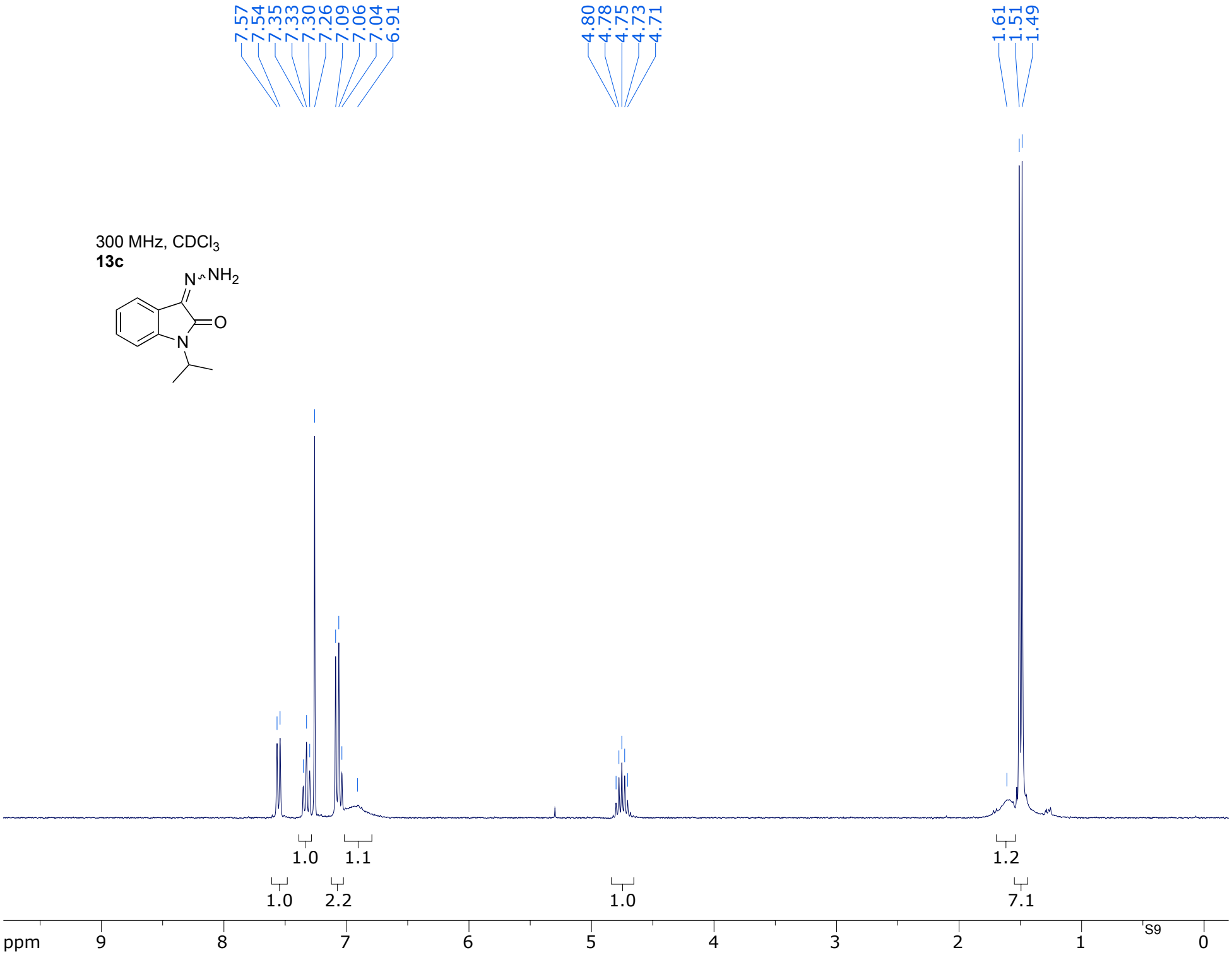
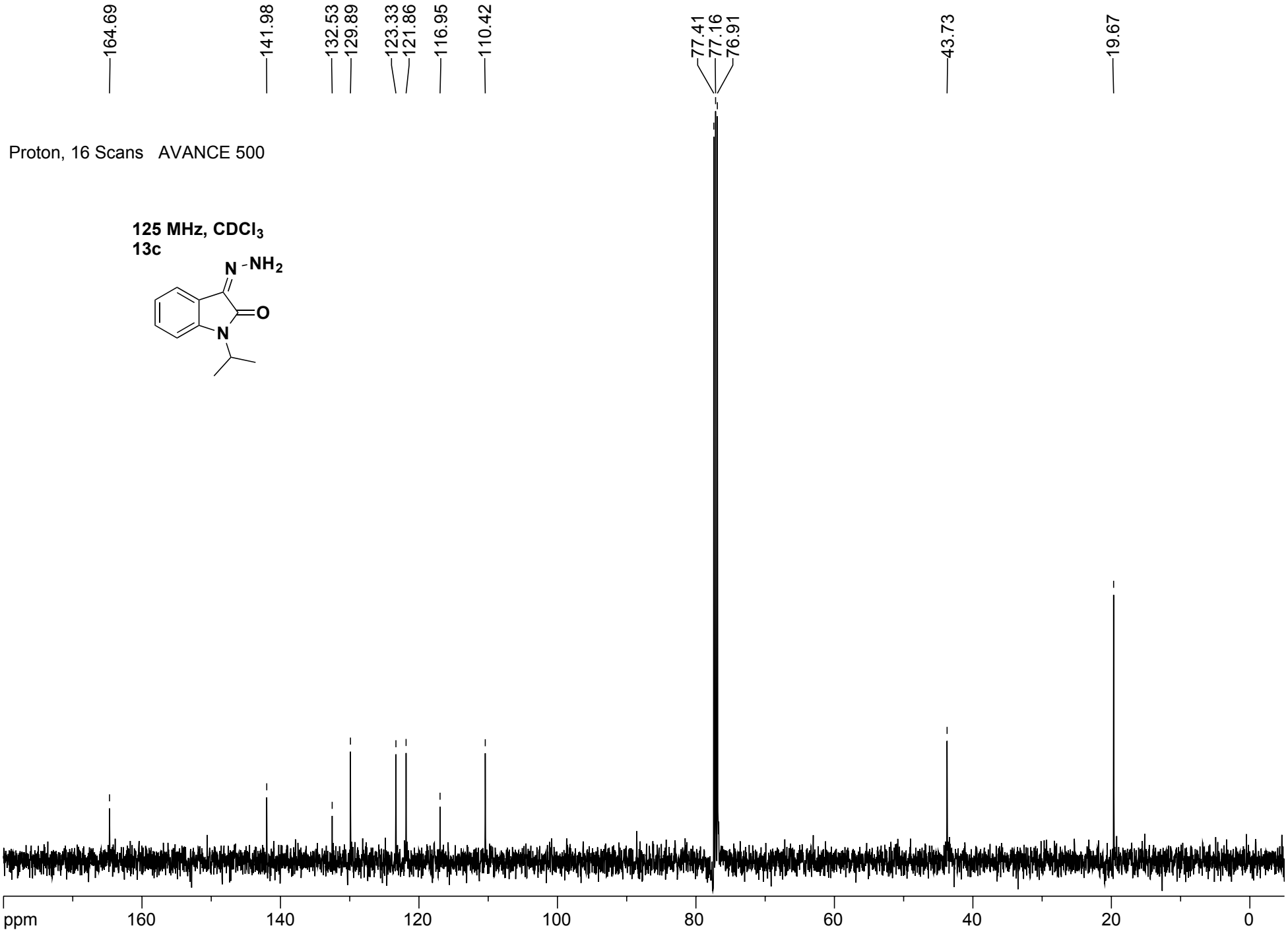
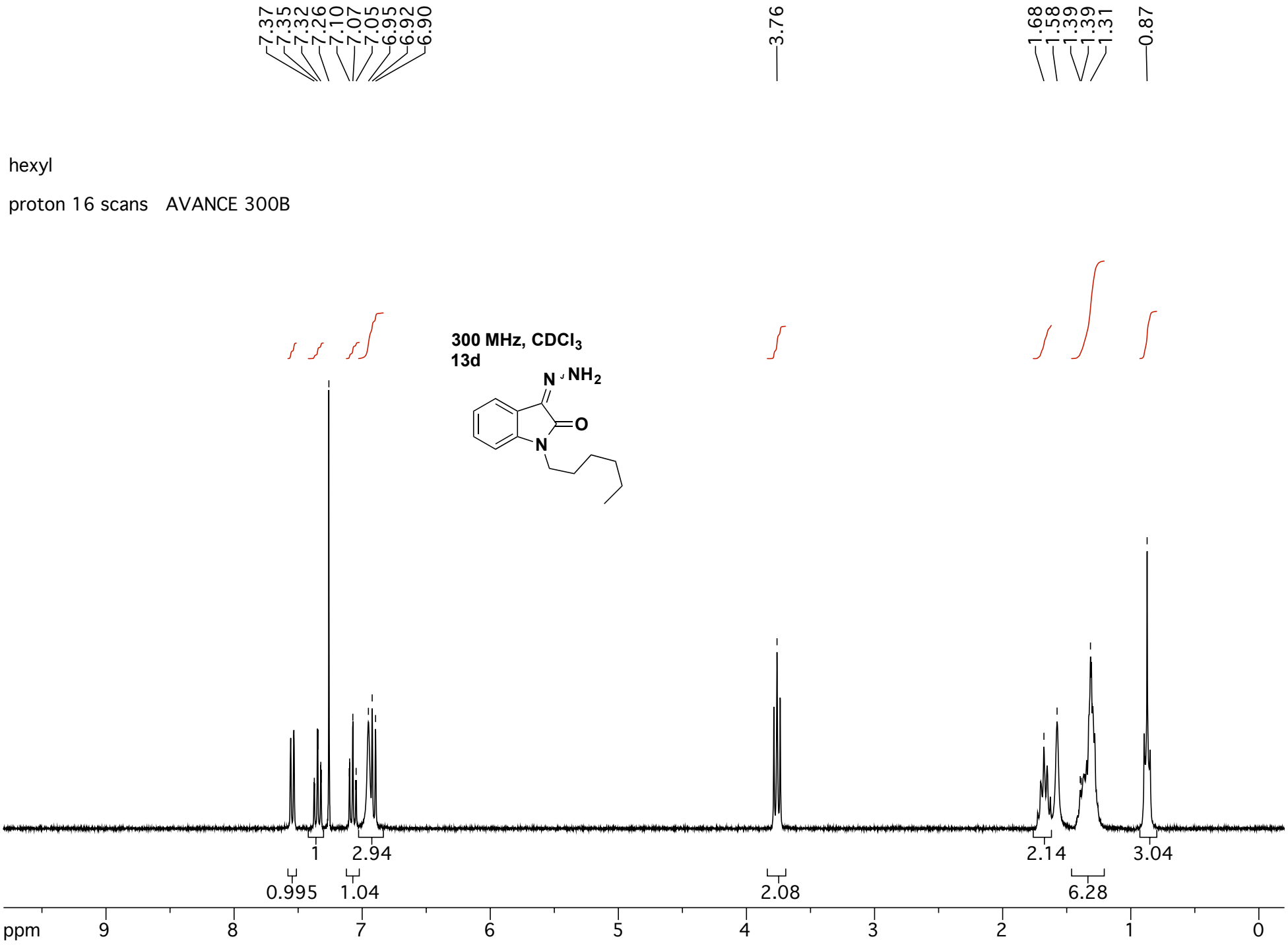
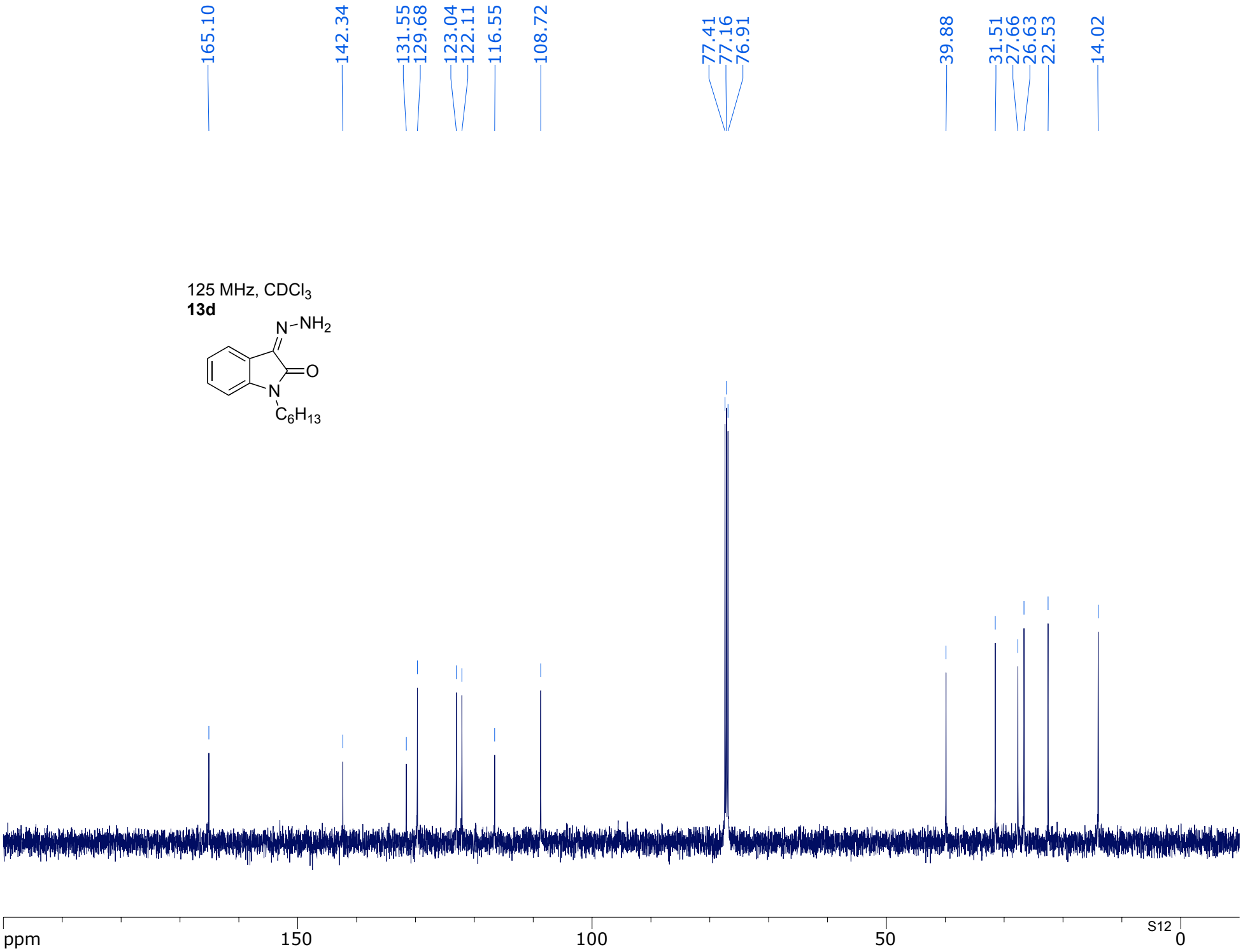

7.57
7.54
7.35
7.33
7.30
7.26
7.09
7.06
7.04
6.91
4.80
4.78
4.75
4.73
4.71
1.61
1.51
1.49
300 MHz, CDCl3
13c
N
NH2
O
N
1.0
1.1
1.2
1.0
2.2
1.0
7.1
ppm
9
8
7
6
5
4
3
2
1
0


164.69
141.98
132.53
129.89
123.33
121.86
116.95
110.42
77.41
77.16
76.91
43.73
19.67
Proton, 16 Scans AVANCE 500
125 MHz, CDCl3
13c
N
NH2
O
N
ppm
160
140
120
100
80
60
40
20
0


7.37
7.35
7.32
7.26
7.10
7.07
7.05
6.95
6.92
6.90
3.76
1.68
1.58
1.39
1.39
1.31
0.87
hexyl
proton 16 scans AVANCE 300B
300 MHz, CDCl3
13d
N
NH2
O
N
1
2.94
0.995
1.04
2.08
2.14
3.04
6.28
ppm
9
8
7
6
5
4
3
2
1
0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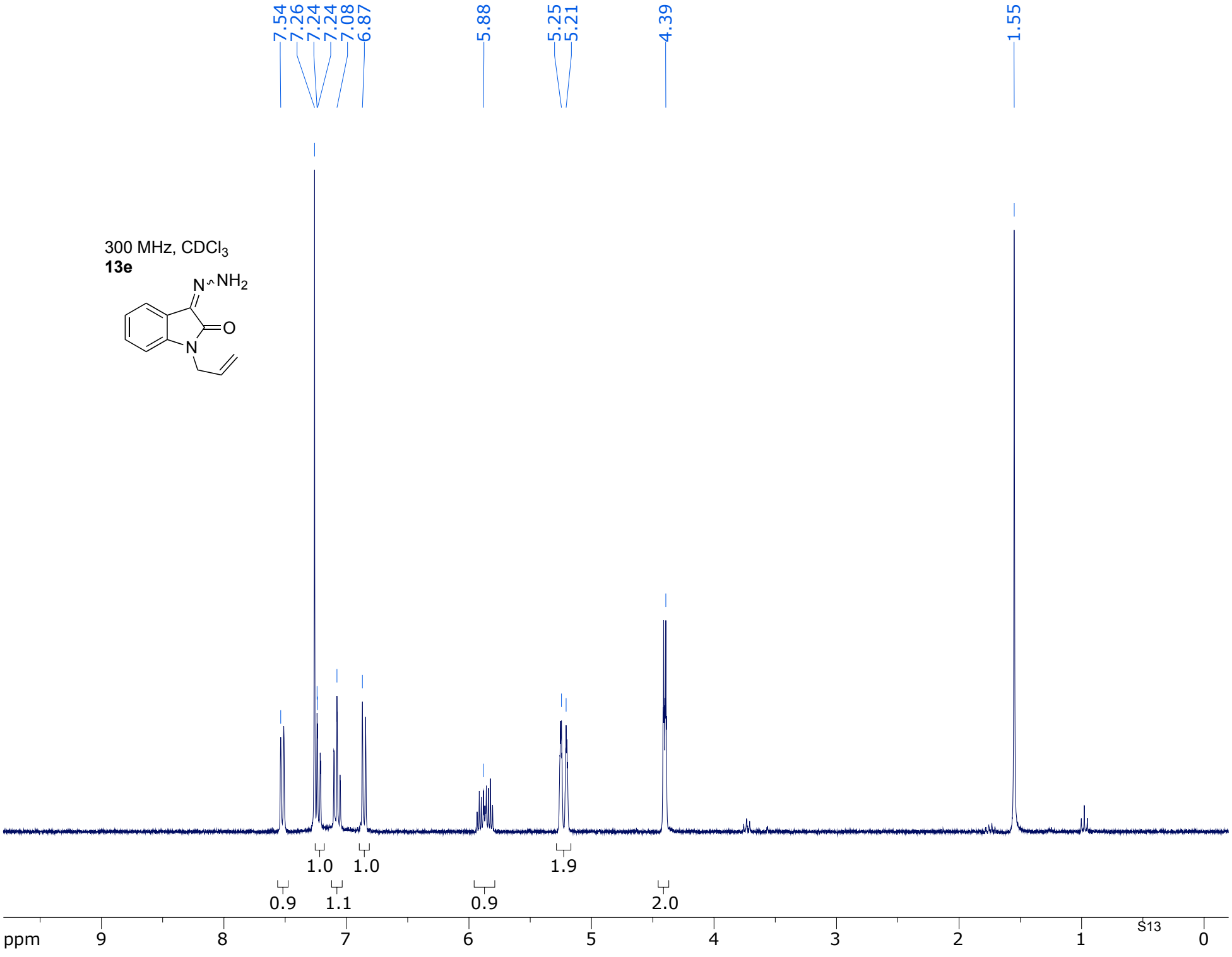
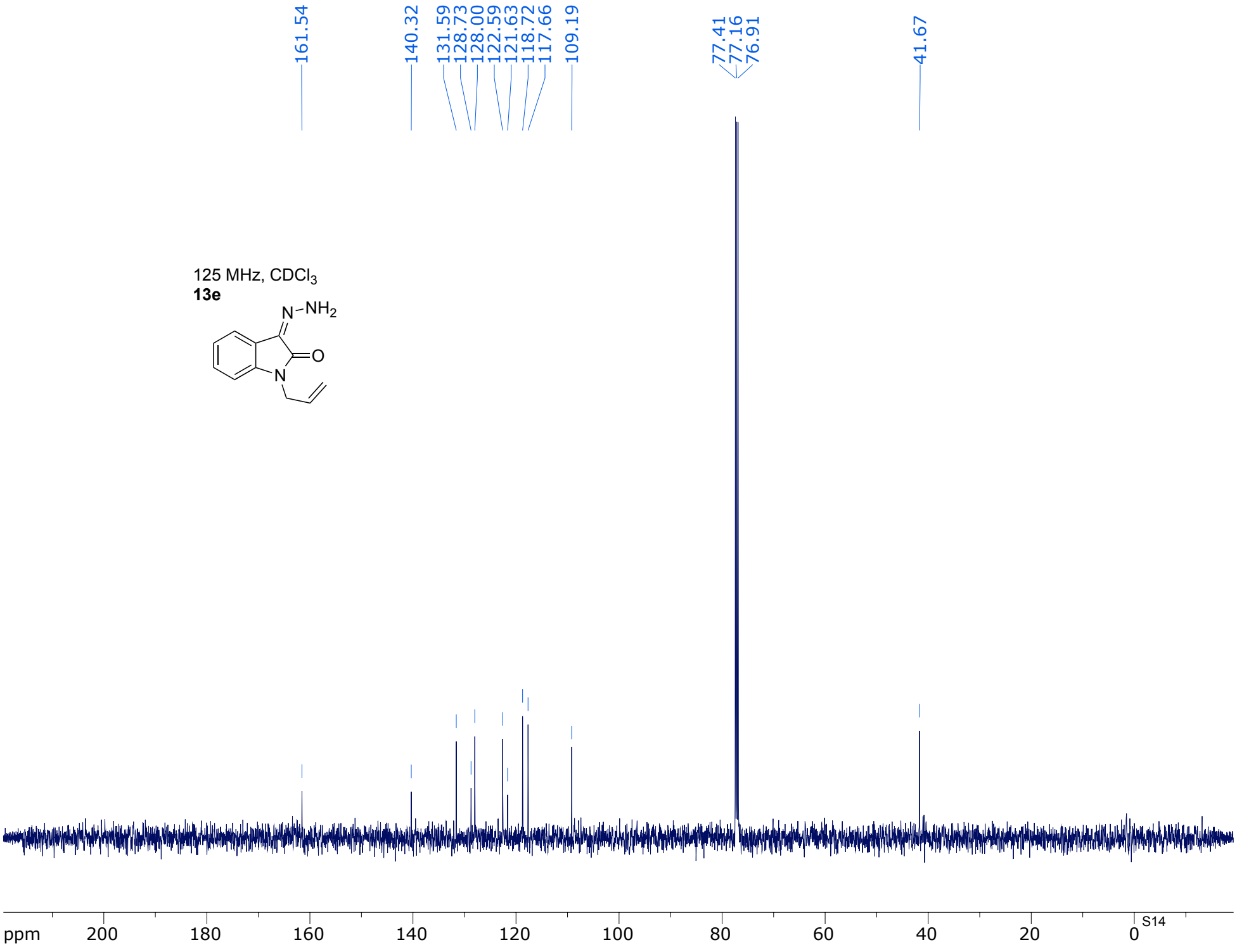
142.34
131.55
129.68
123.04
122.11
116.55
108.72
77.41
77.16
76.91
39.88
31.51
27.66
26.63
22.53
14.02
125 MHz, CDCl3
13d
N–NH2
O
N
C6H13
ppm
150
100
50
0


7.54
7.26
7.24
7.24
7.08
6.87
5.88
5.25
5.21
4.39
1.55
300 MHz, CDCl3
13e
N
NH2
O
N
1.0
1.0
1.9
0.9
1.1
0.9
2.0
ppm
9
8
7
6
5
4
3
2
1
0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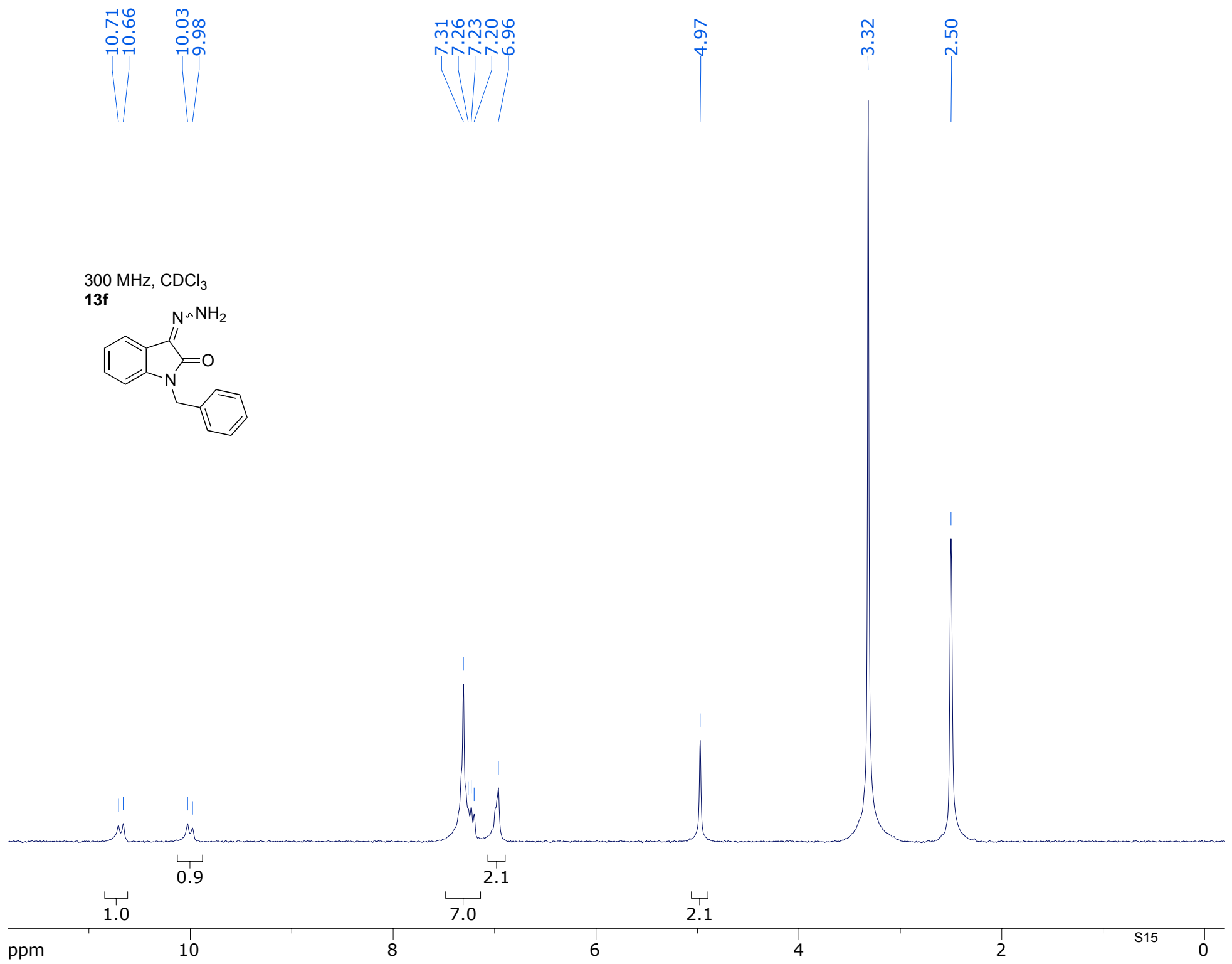
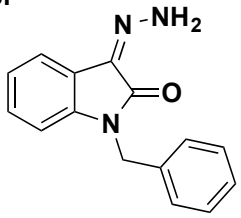
140.32
131.59
128.73
128.00
122.59
121.63
118.72
117.66
109.19
77.41
77.16
76.91
41.67
125 MHz, CDCl3
13e
N–NH2
O
N
ppm
200
180
160
140
120
100
80
60
40
20
0

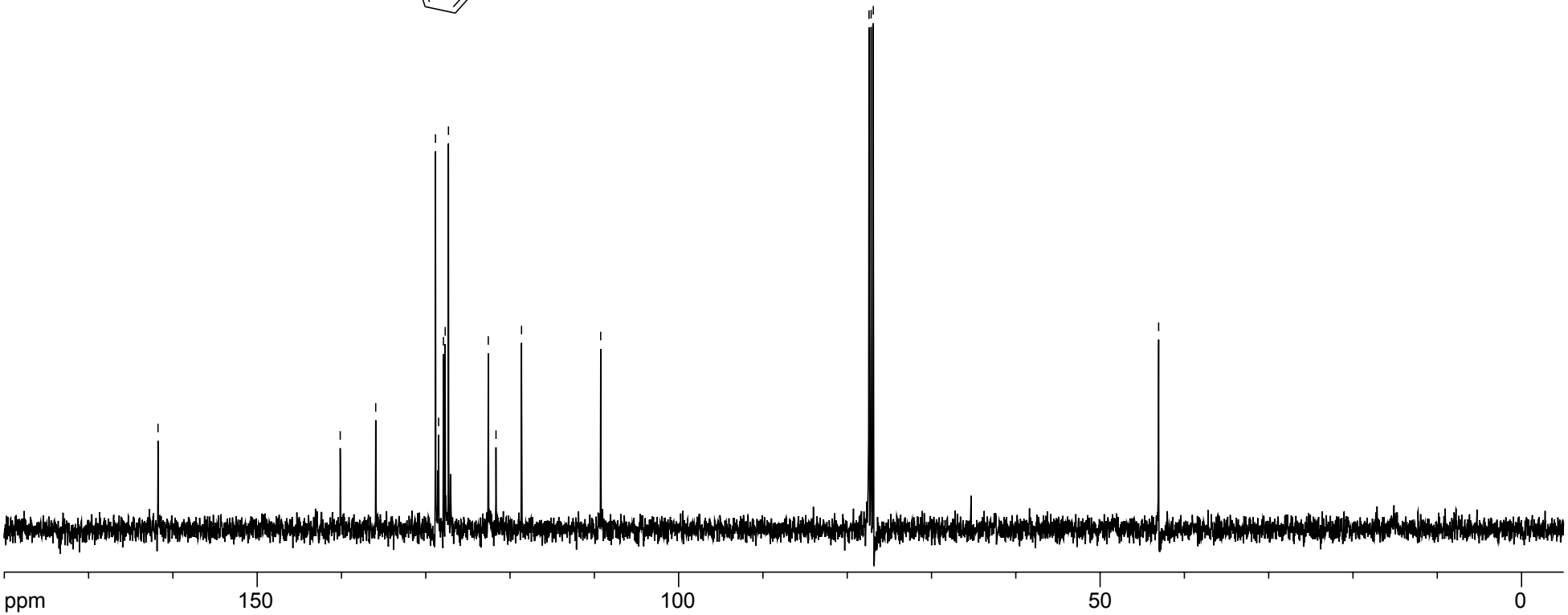

10.71
10.66
10.03
9.98
7.31
7.26
7.23
7.20
6.96
4.97
3.32
2.50
300 MHz, CDCl3
13f
N
NH2
O
N
1.0
0.9
7.0
2.1
2.1
ppm
10
8
6
4
2
0
S15

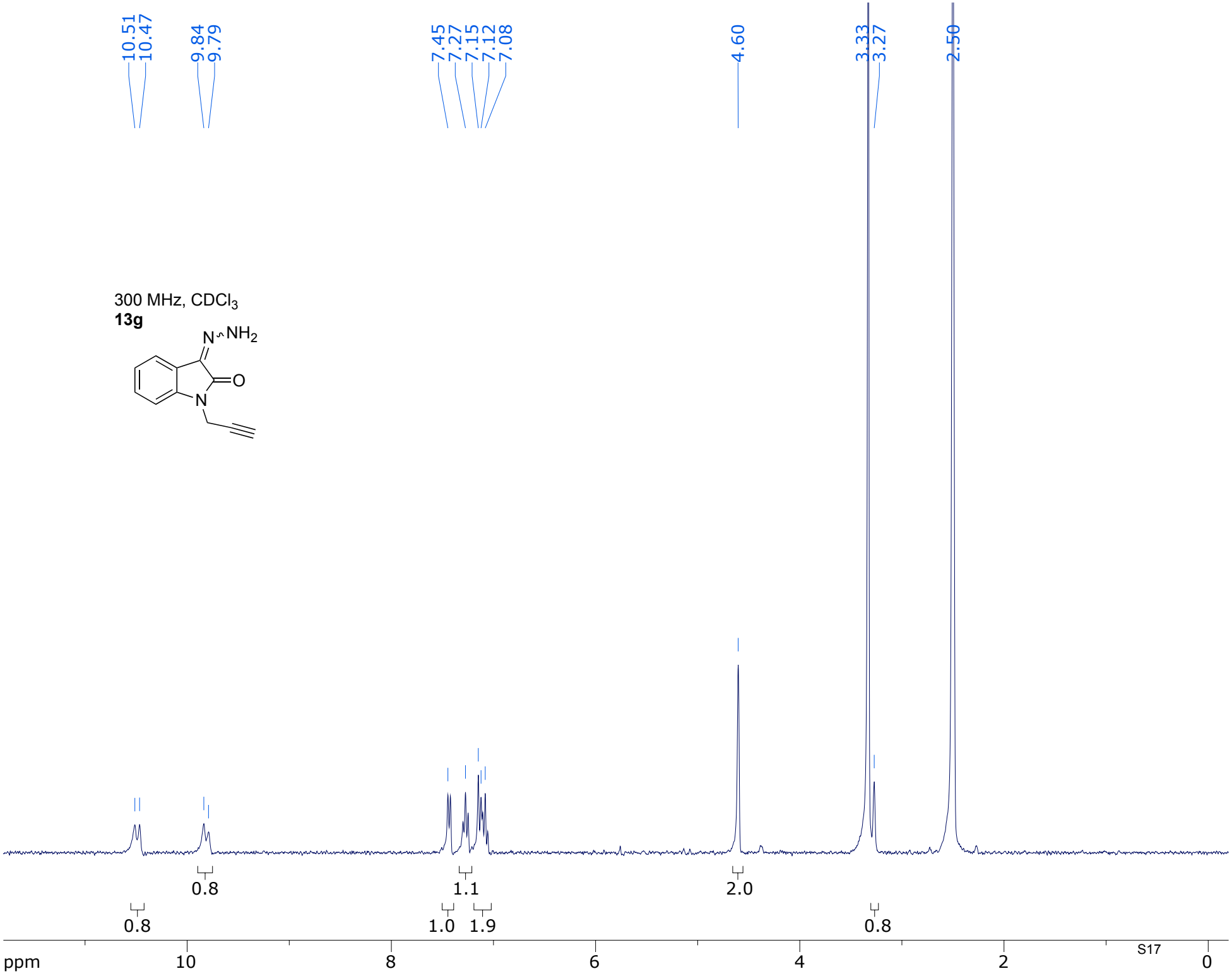
161.76
140.15
135.93
128.84
128.47
127.90
127.69
127.31
122.58
121.67
118.64
109.25
77.41
77.16
76.91
43.05

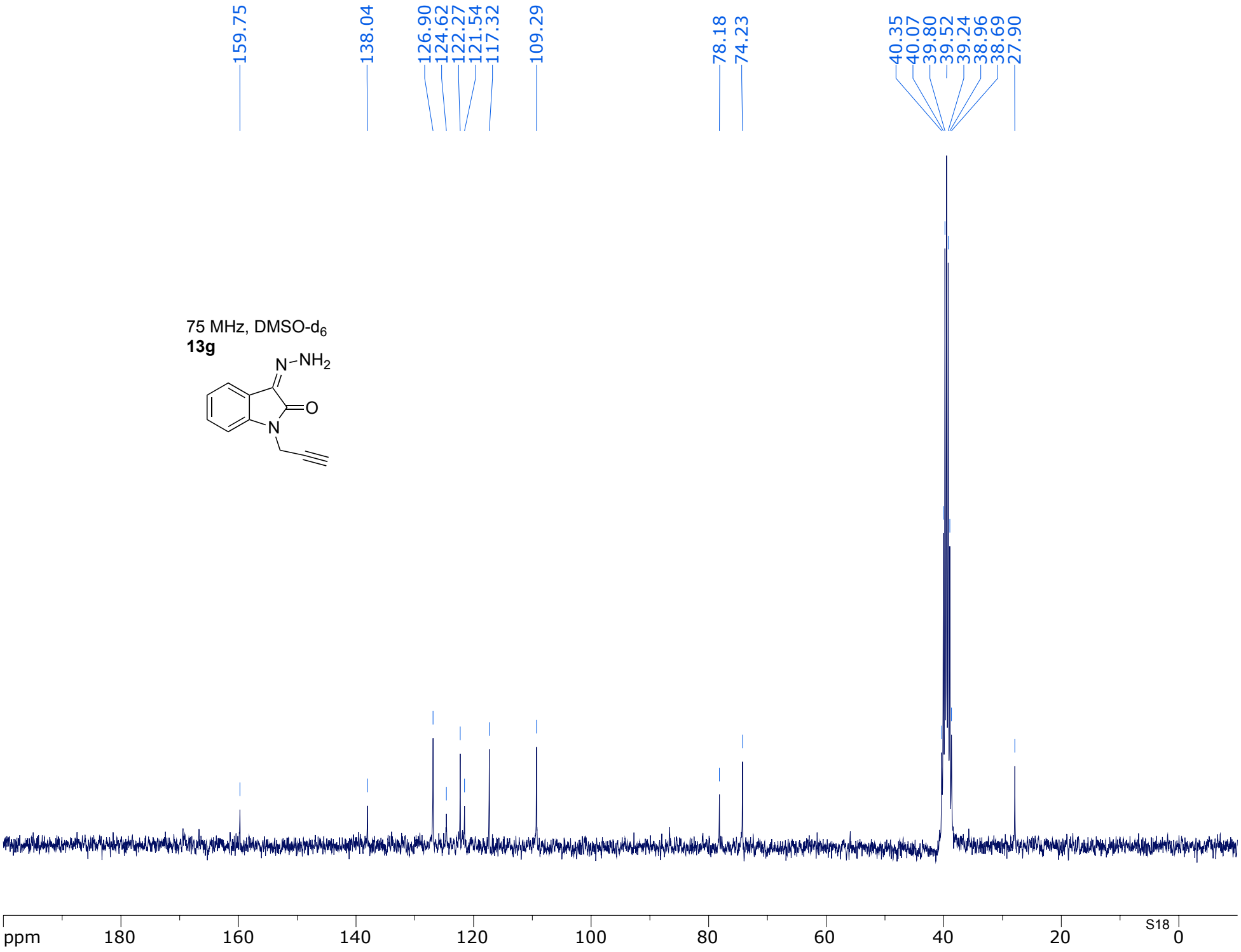
C13 Set-up for TXI AVANCE 500

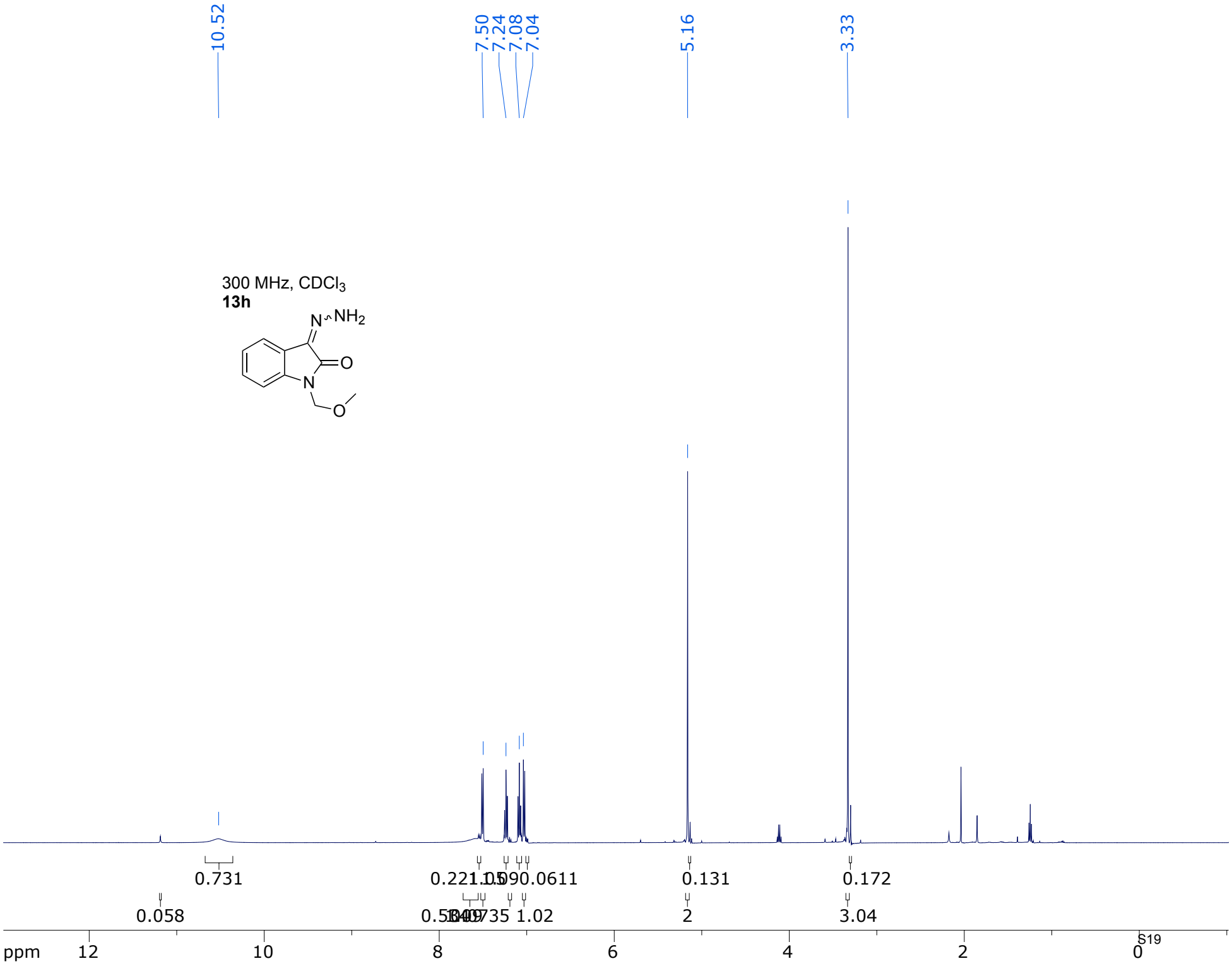
125 MHz, $CDCl_3$
13f






10.51
10.47
9.84
9.79
7.45
7.27
7.15
7.12
7.08
4.60
3.33
3.27
2.50
300 MHz, CDCl3
13g
N
NH2
O
N
0.8
1.1
2.0
0.8
1.0
1.9
0.8
ppm
10
8
6
4
2
0


159.75
138.04
126.90
124.62
122.27
121.54
117.32
109.29
78.18
74.23
40.35
40.07
39.80
39.52
39.24
38.96
38.69
27.90
75 MHz, DMSO-d6
13g
N
NH2
O
N
ppm
180
160
140
120
100
80
60
40
20
0

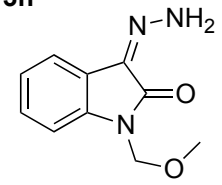

10.52
7.50
7.24
7.08
7.04
5.16
3.33
300 MHz, CDCl3
13h
N
NH2
O
N
O
0.731
0.221
1.05
0.90
0.0611
0.131
0.172
0.058
2
3.04
1.02
ppm
12
10
8
6
4
2
0

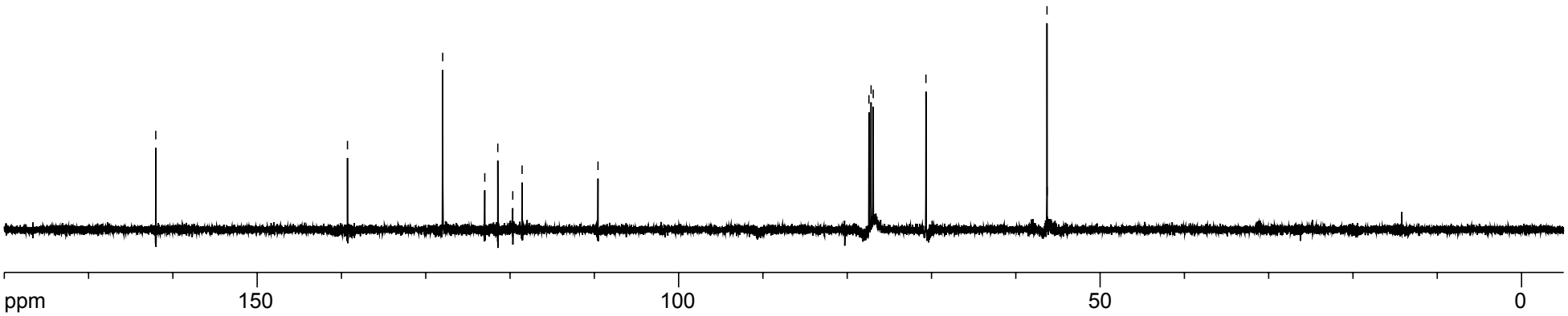
162.03
139.28
127.99
123.00
121.45
119.68
118.57
109.57
77.42
77.17
76.91
70.66
56.30
56.28

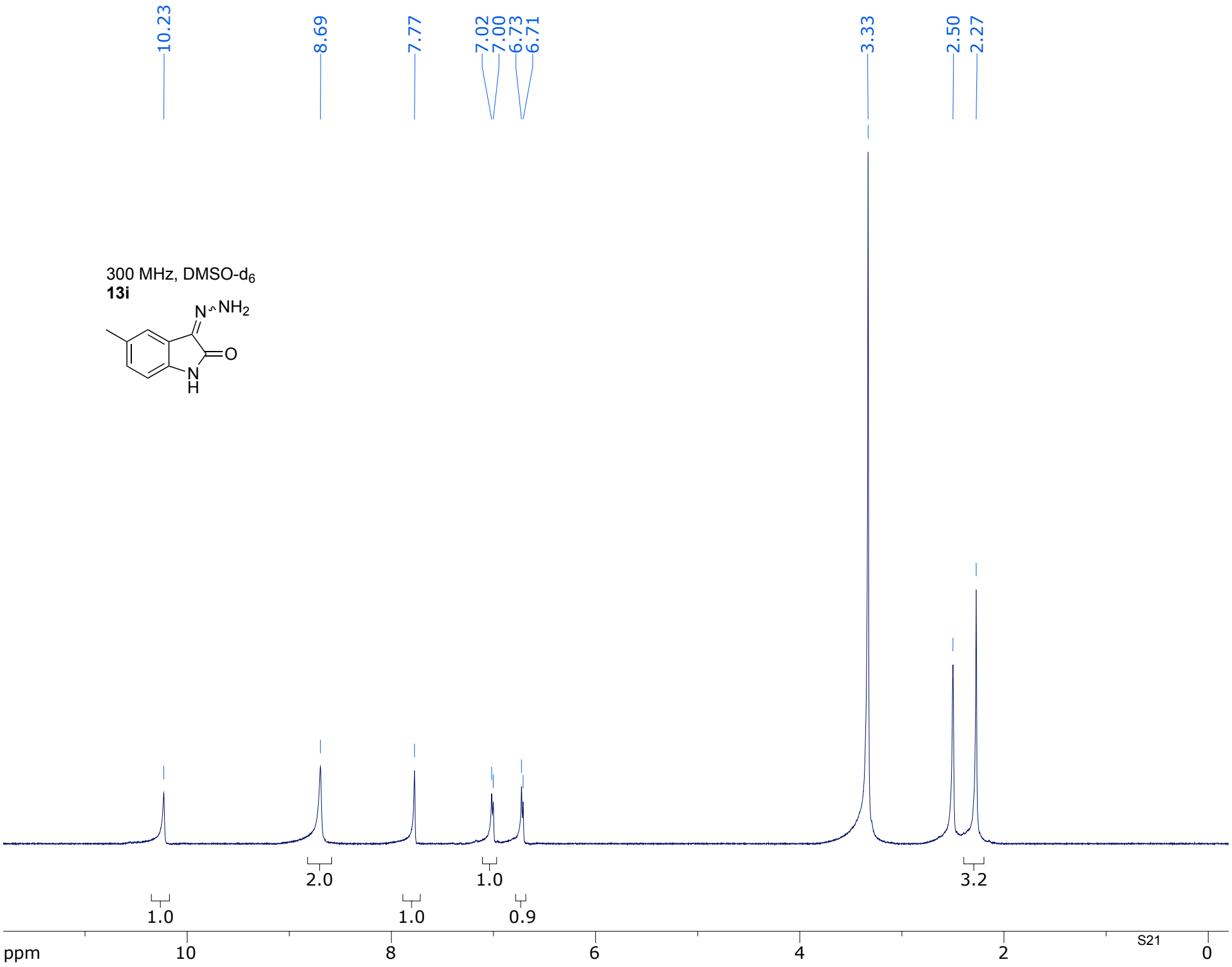
C13 Set-up for TXI AVANCE 500

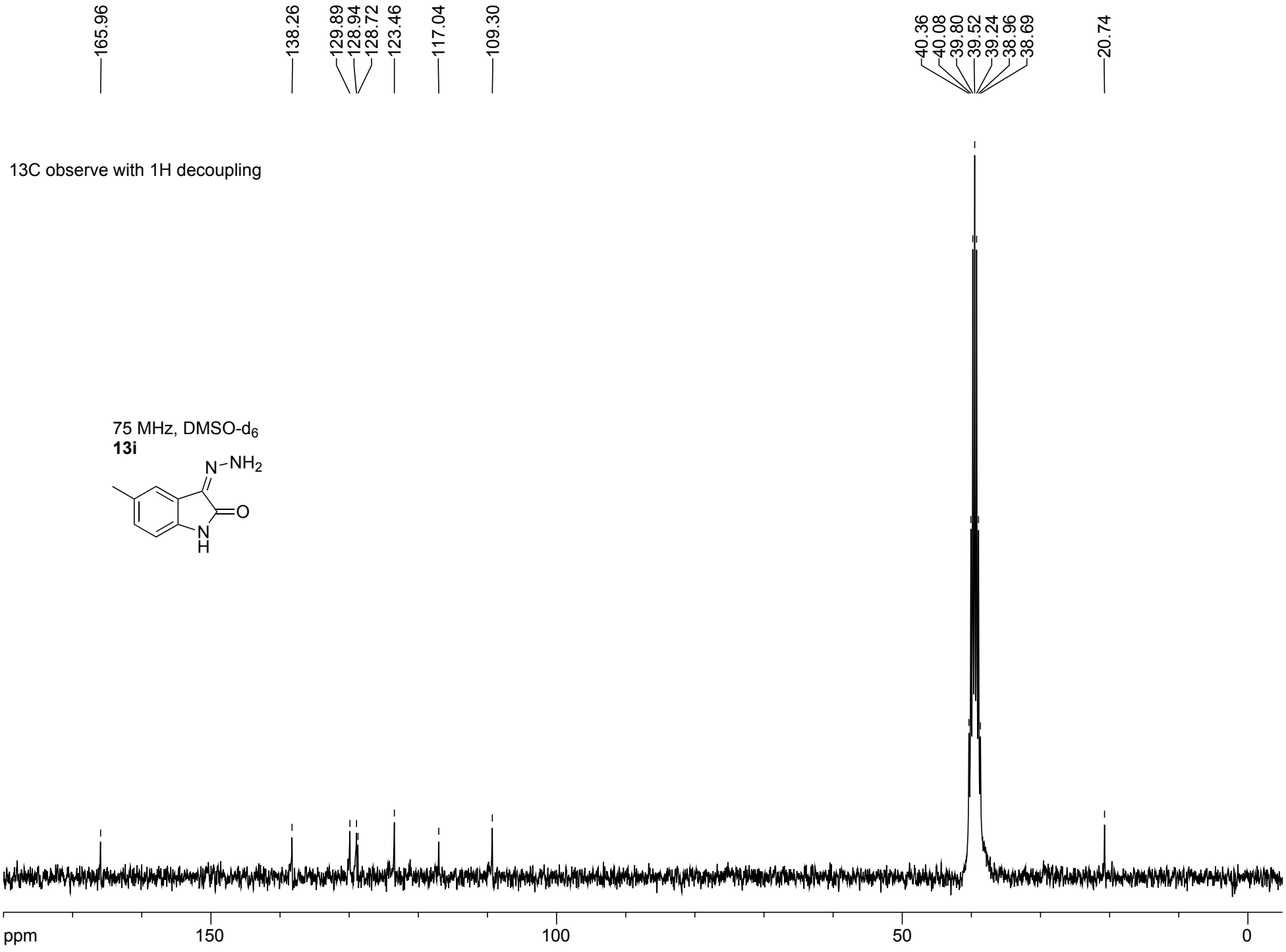
75 MHz, $CDCl_3$

13h






10.23
8.69
7.77
7.02
7.00
6.73
6.71
3.33
2.50
2.27
300 MHz, DMSO-d6
13i
N
NH2
O
N
H
2.0
1.0
3.2
1.0
1.0
0.9
ppm
10
8
6
4
2
0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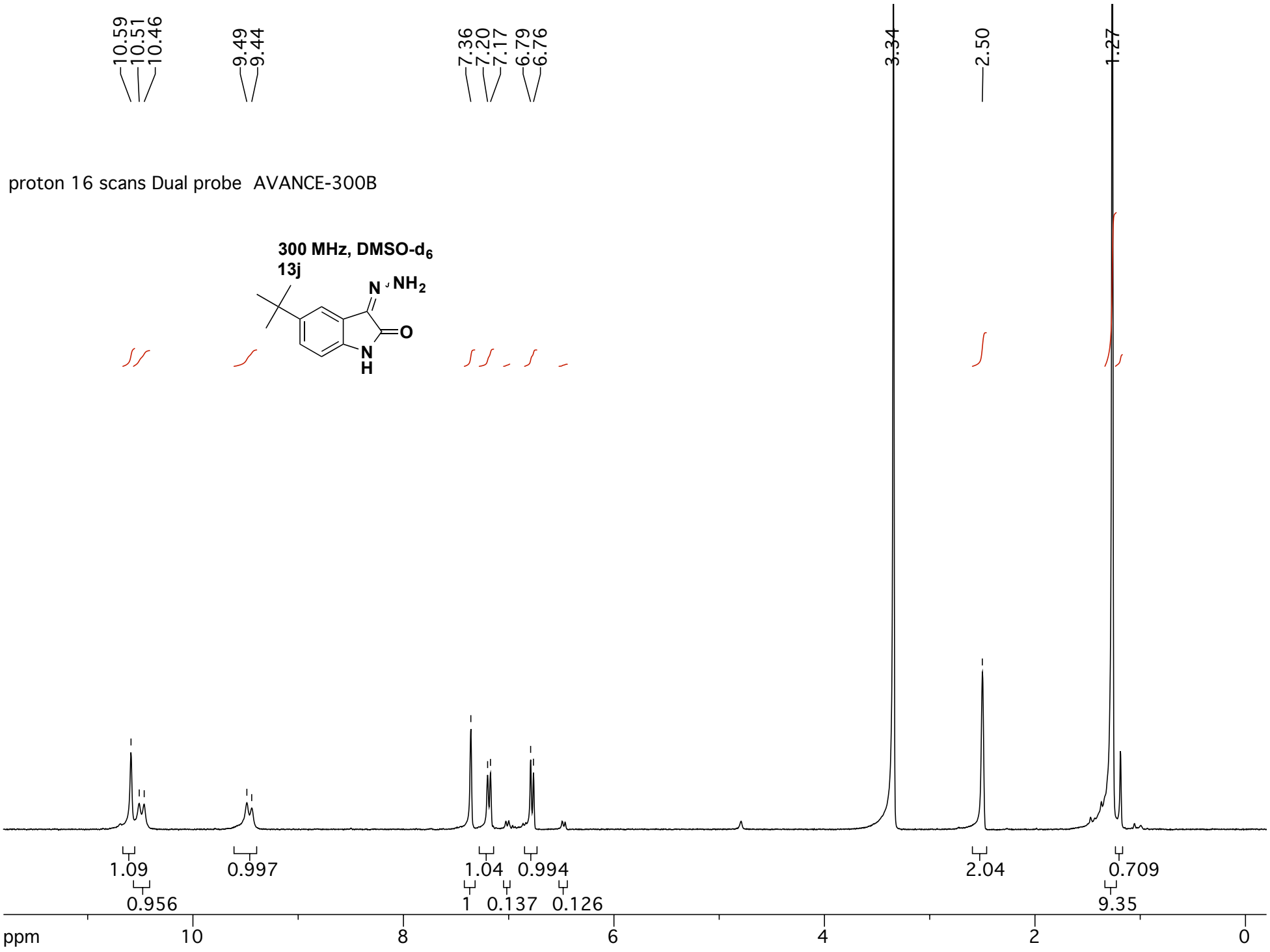
138.26
129.89
128.94
128.72
123.46
117.04
109.30
40.36
40.08
39.80
39.52
39.24
38.96
38.69
20.74
13C observe with 1H decoupling
75 MHz, DMSO-d6
13i
N–NH2
O
N
H
ppm
150
100
50
0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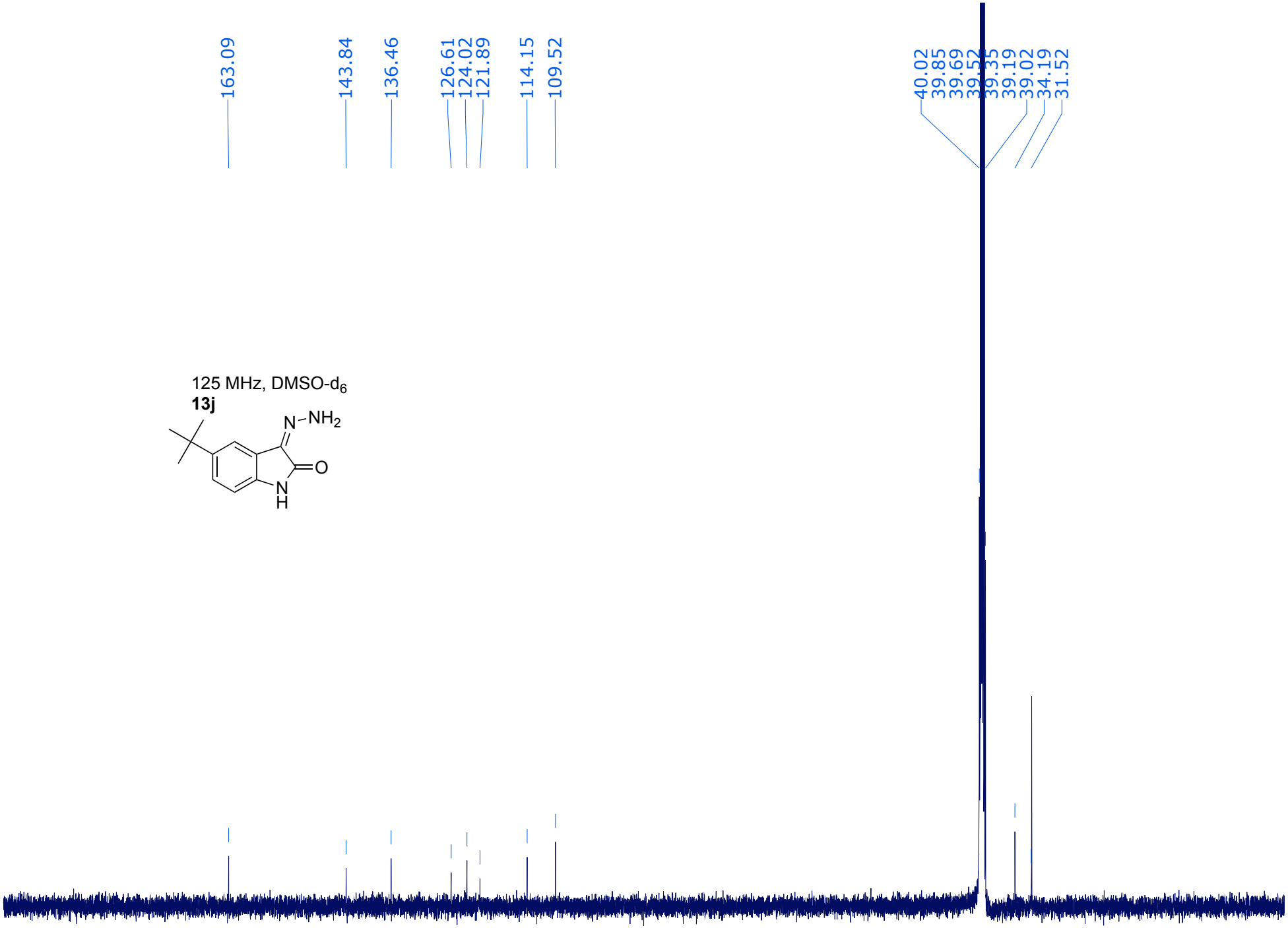
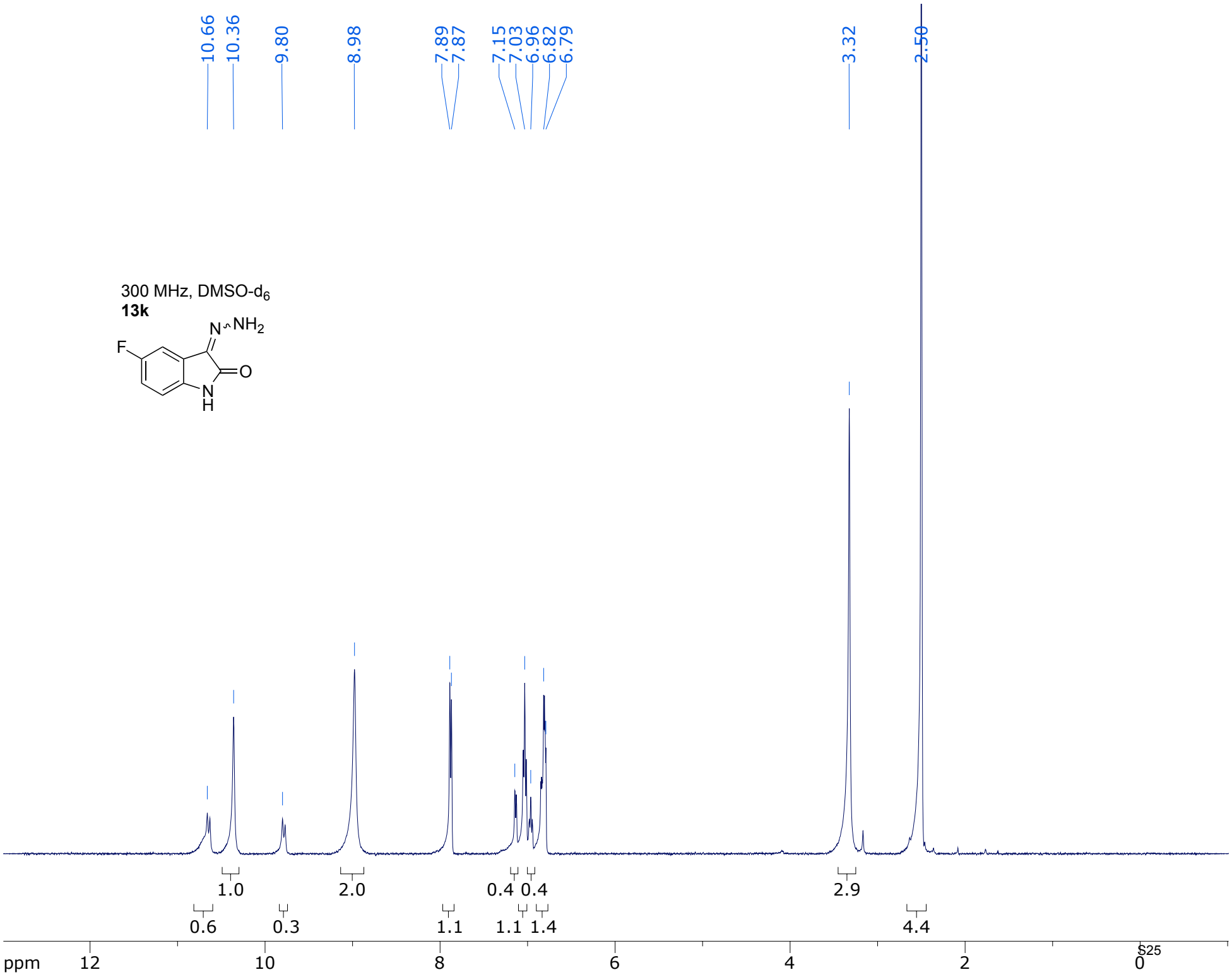
10.46
9.49
9.44
7.36
7.20
7.17
6.79
6.76
3.34
2.50
1.27
proton 16 scans Dual probe AVANCE-300B
300 MHz, DMSO-d6
13j
N
NH2
O
N
H
1.09
0.956
0.997
1.04
1
0.994
0.137
0.126
2.04
0.709
9.35
ppm
10
8
6
4
2
0


163.09
143.84
136.46
126.61
124.02
121.89
114.15
109.52
40.02
39.85
39.69
39.52
39.35
39.19
39.02
34.19
31.52
125 MHz, DMSO-d6
13j
N–NH2
O
N
H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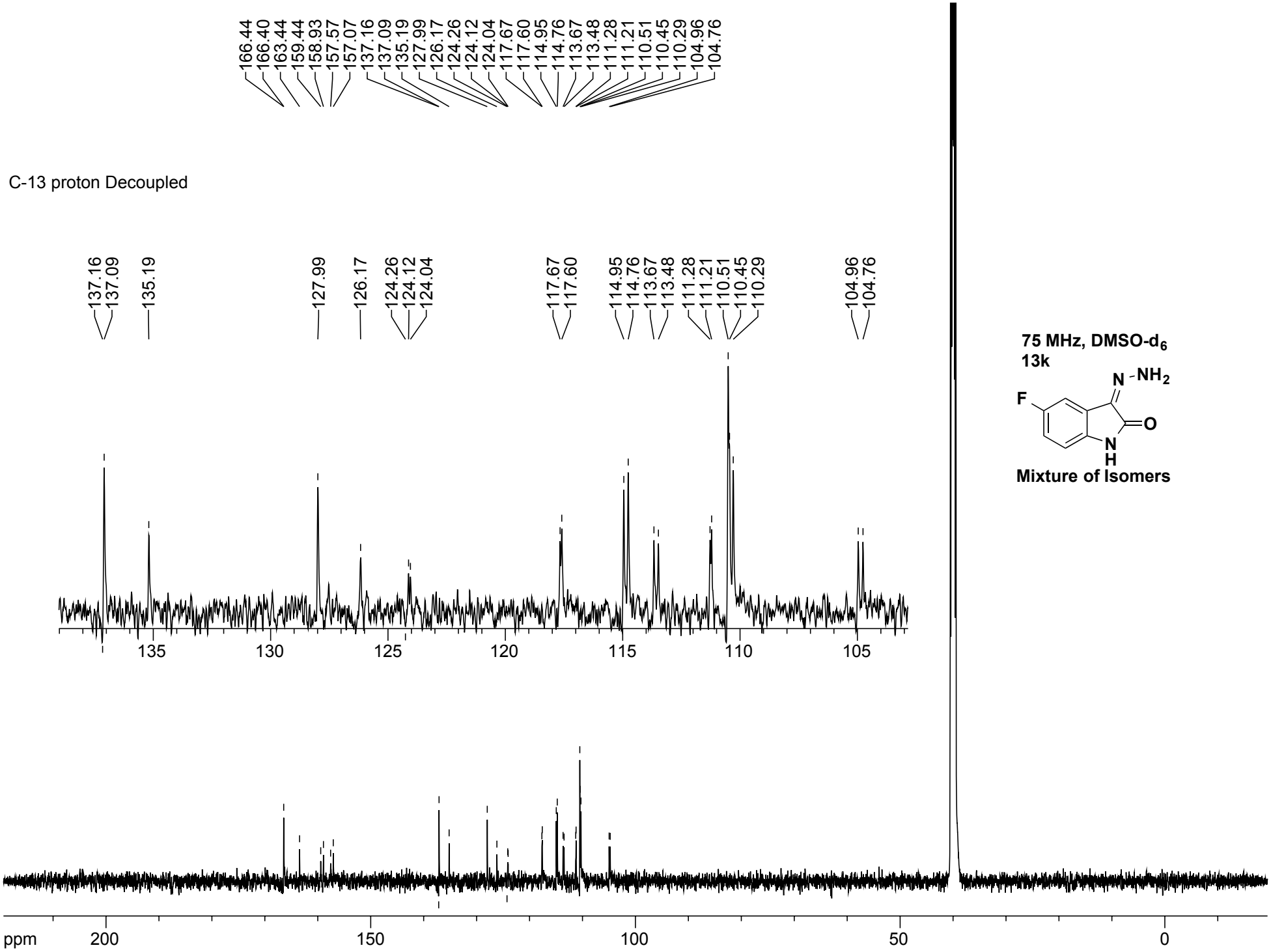
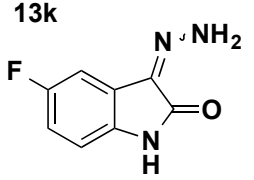
10.36
9.80
8.98
7.89
7.87
7.15
7.03
6.96
6.82
6.79
3.32
2.50
300 MHz, DMSO-d6
13k
F
N
NH2
O
N
H
1.0
2.0
0.4
0.4
2.9
0.6
0.3
1.1
1.1
1.4
4.4
ppm
12
10
8
6
4
2
0

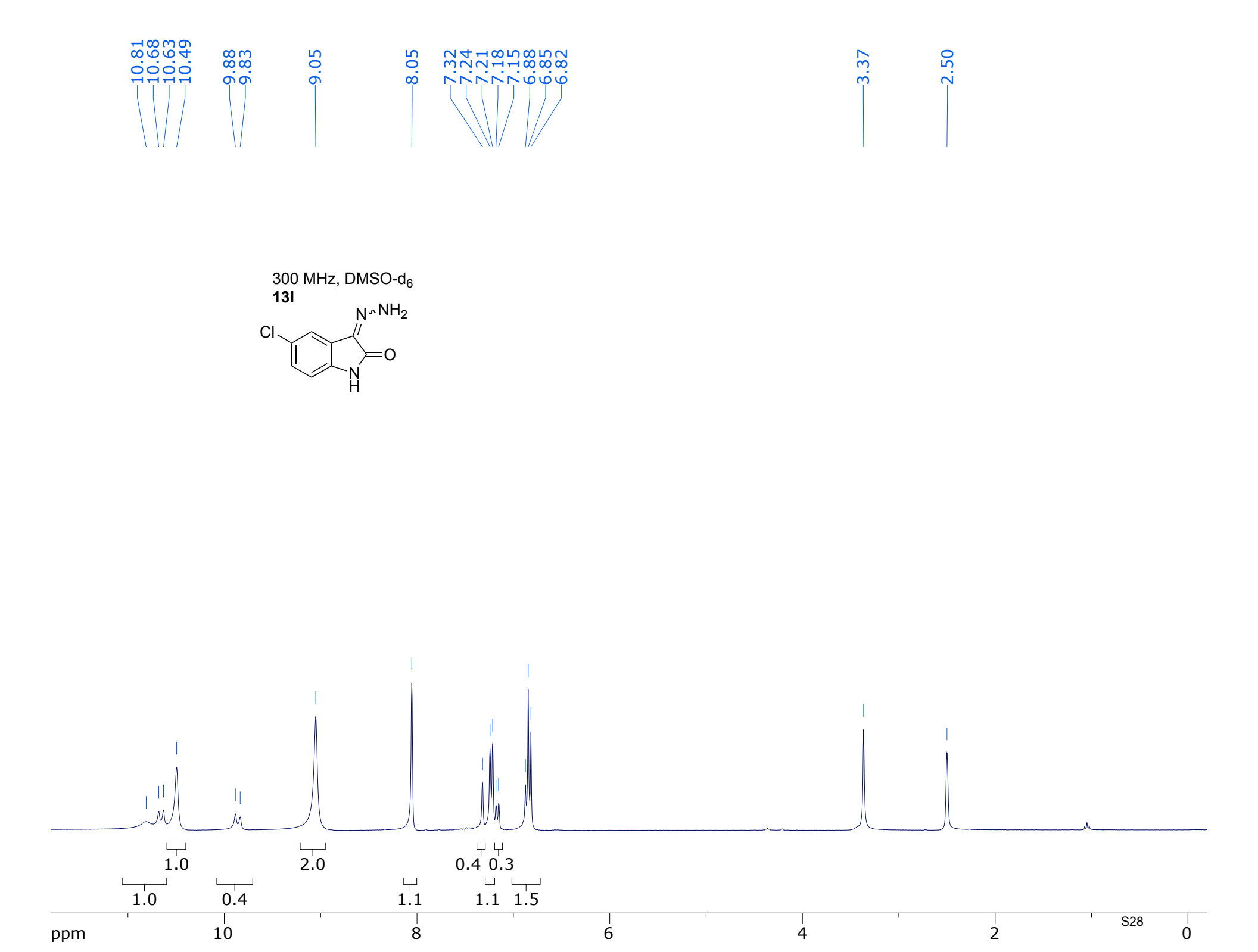

166.44
166.40
163.44
159.44
158.93
157.57
157.07
137.16
137.09
135.19
127.99
126.17
124.26
124.12
124.04
117.67
117.60
114.95
114.76
113.67
113.48
111.28
111.21
110.51
110.45
110.29
104.96
104.76
C-13 proton Decoupled
75 MHz, DMSO-d6
13k
Mixture of Isomers
135
130
125
120
115
110
105
ppm
200
150
100
50
0

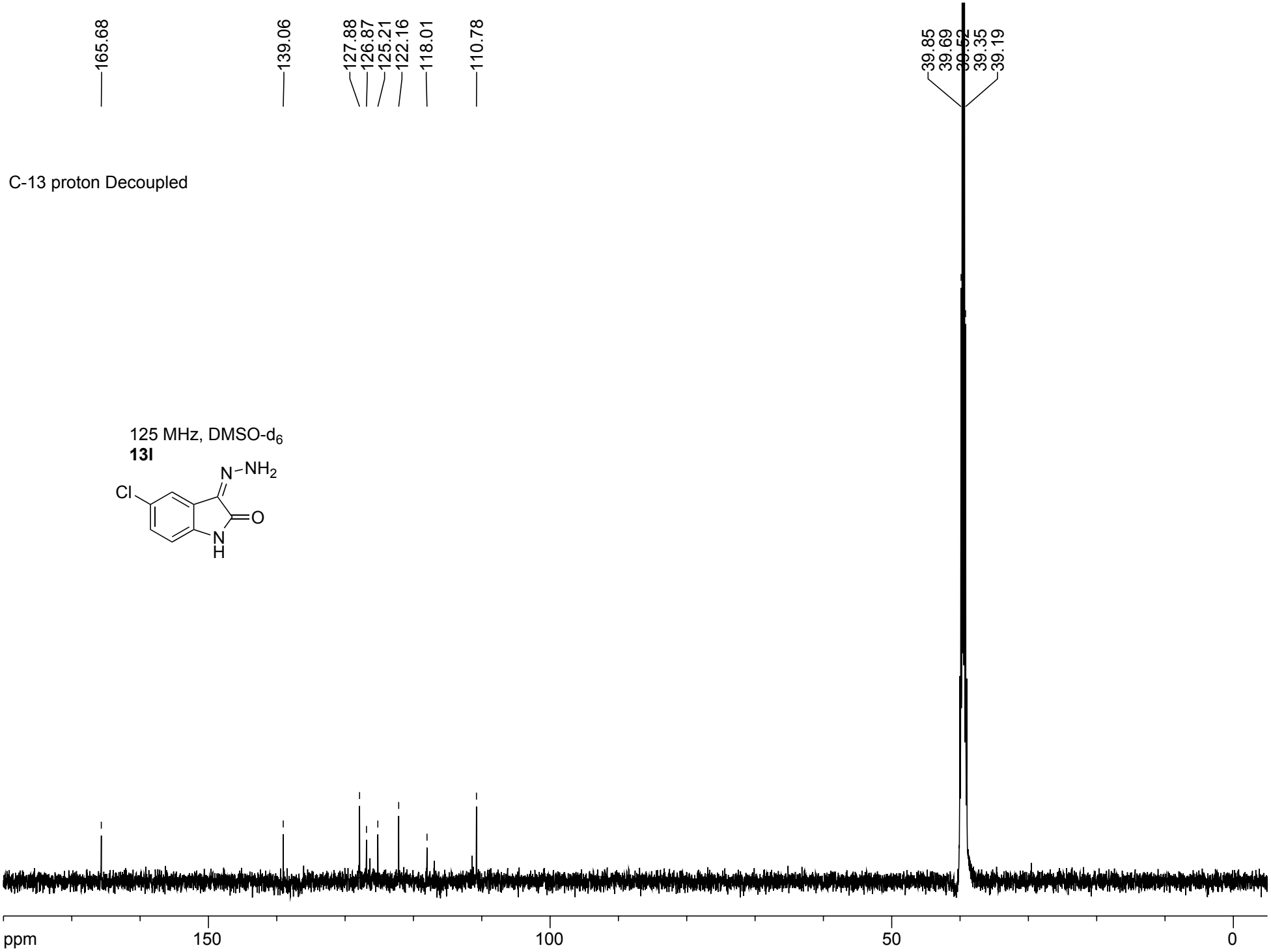
F19CPD- 300 ppm Sweep Width referenced to TFA=-76.53 ppm

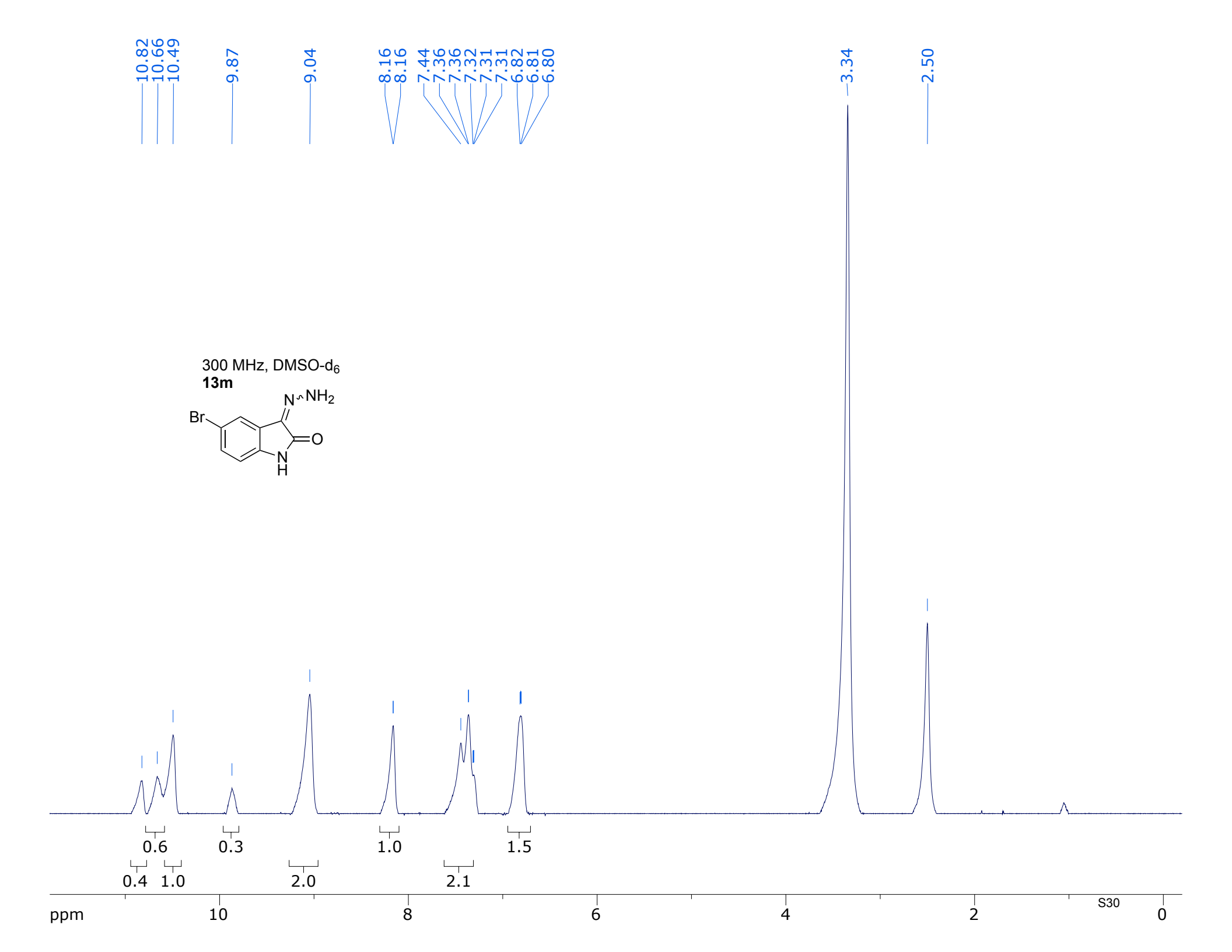
-122.33
-122.84

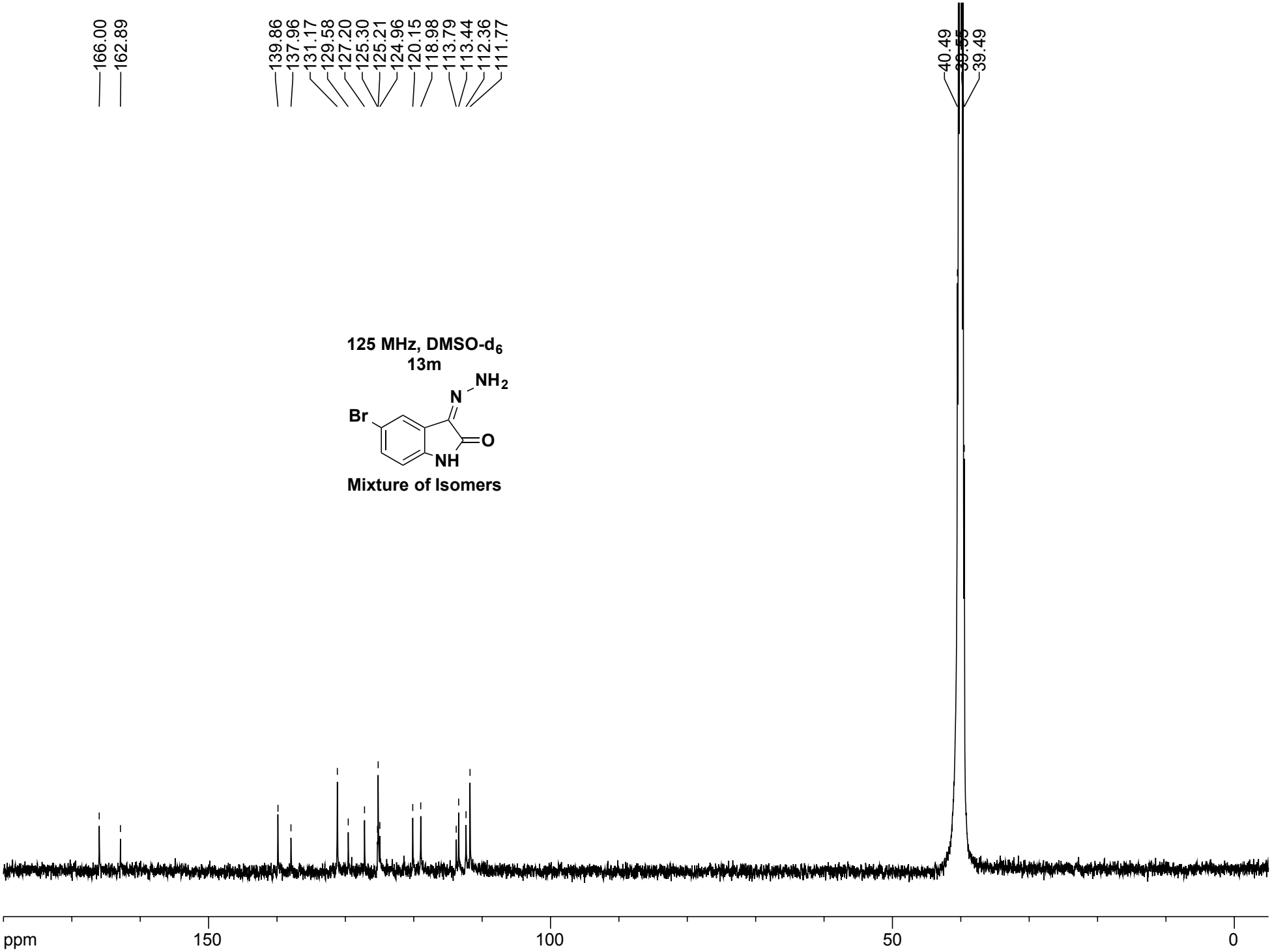
300 MHz, DMSO-d_6
13k

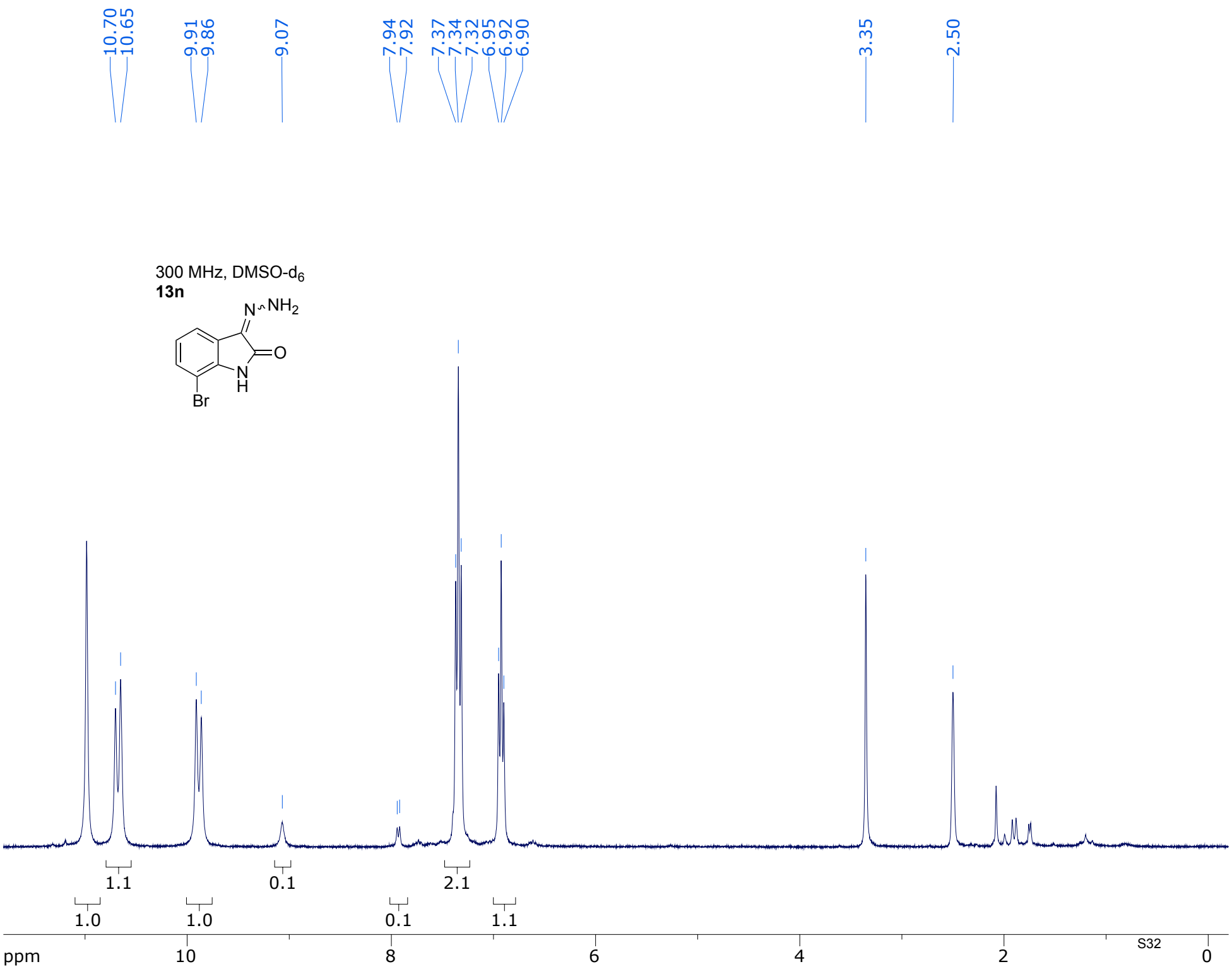


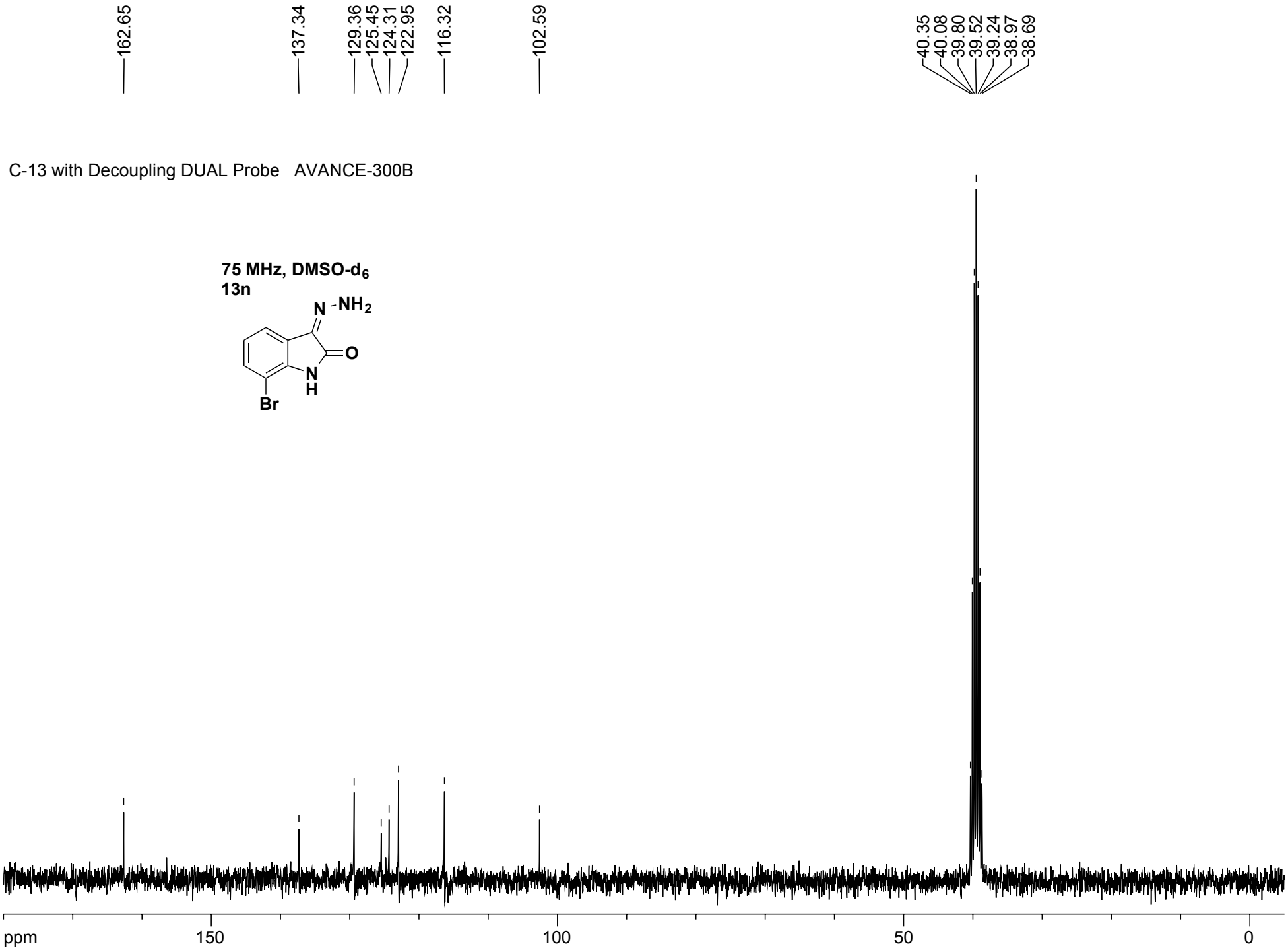

10.81
10.68
10.63
10.49
9.88
9.83
9.05
8.05
7.32
7.24
7.21
7.18
7.15
6.88
6.85
6.82
3.37
2.50
300 MHz, DMSO-d6
13l
N
NH2
Cl
O
N
H
1.0
2.0
0.4
0.3
1.0
0.4
1.1
1.1
1.5
ppm
10
8
6
4
2
0

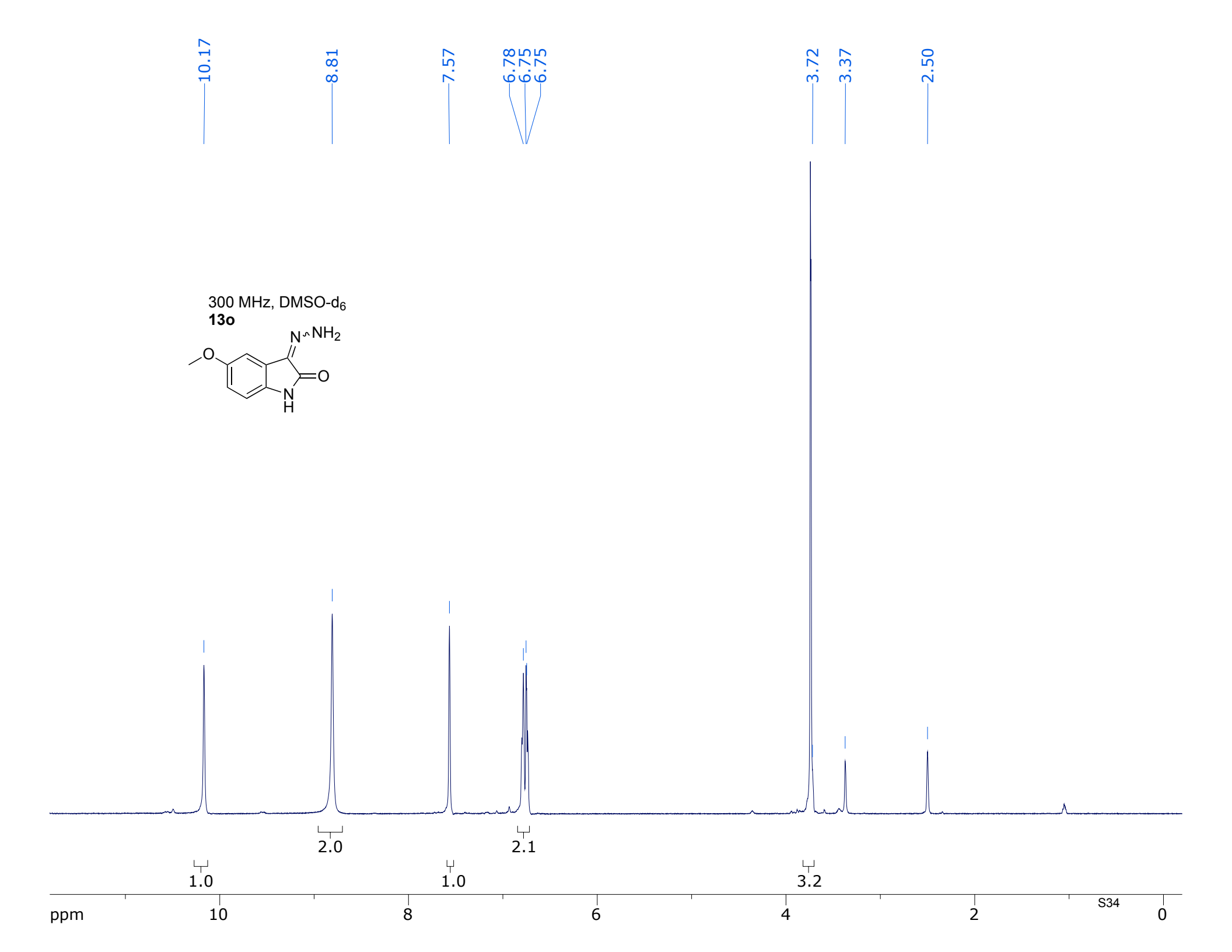

165.68
139.06
127.88
126.87
125.21
122.16
118.01
110.78
39.85
39.69
39.52
39.35
39.19
C-13 proton Decoupled
125 MHz, DMSO-d6
13l
N–NH2
Cl
O
N
H
ppm
150
100
50
0

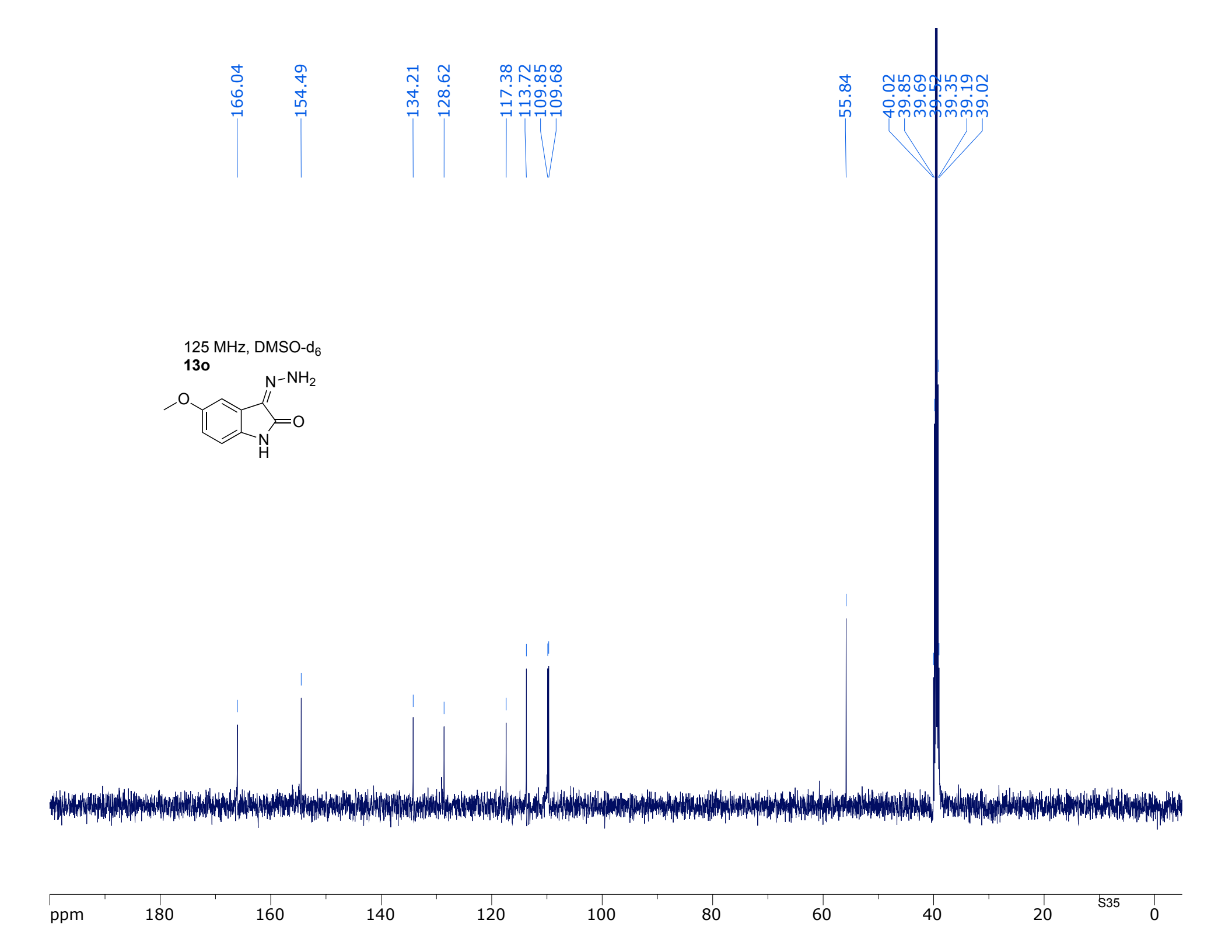

10.82
10.66
10.49
9.87
9.04
8.16
8.16
7.44
7.36
7.36
7.32
7.31
7.31
6.82
6.81
6.80
3.34
2.50
300 MHz, DMSO-d6
13m
Br
N
NH2
O
N
H
0.6
0.3
1.0
1.5
0.4
1.0
2.0
2.1
ppm
10
8
6
4
2
0

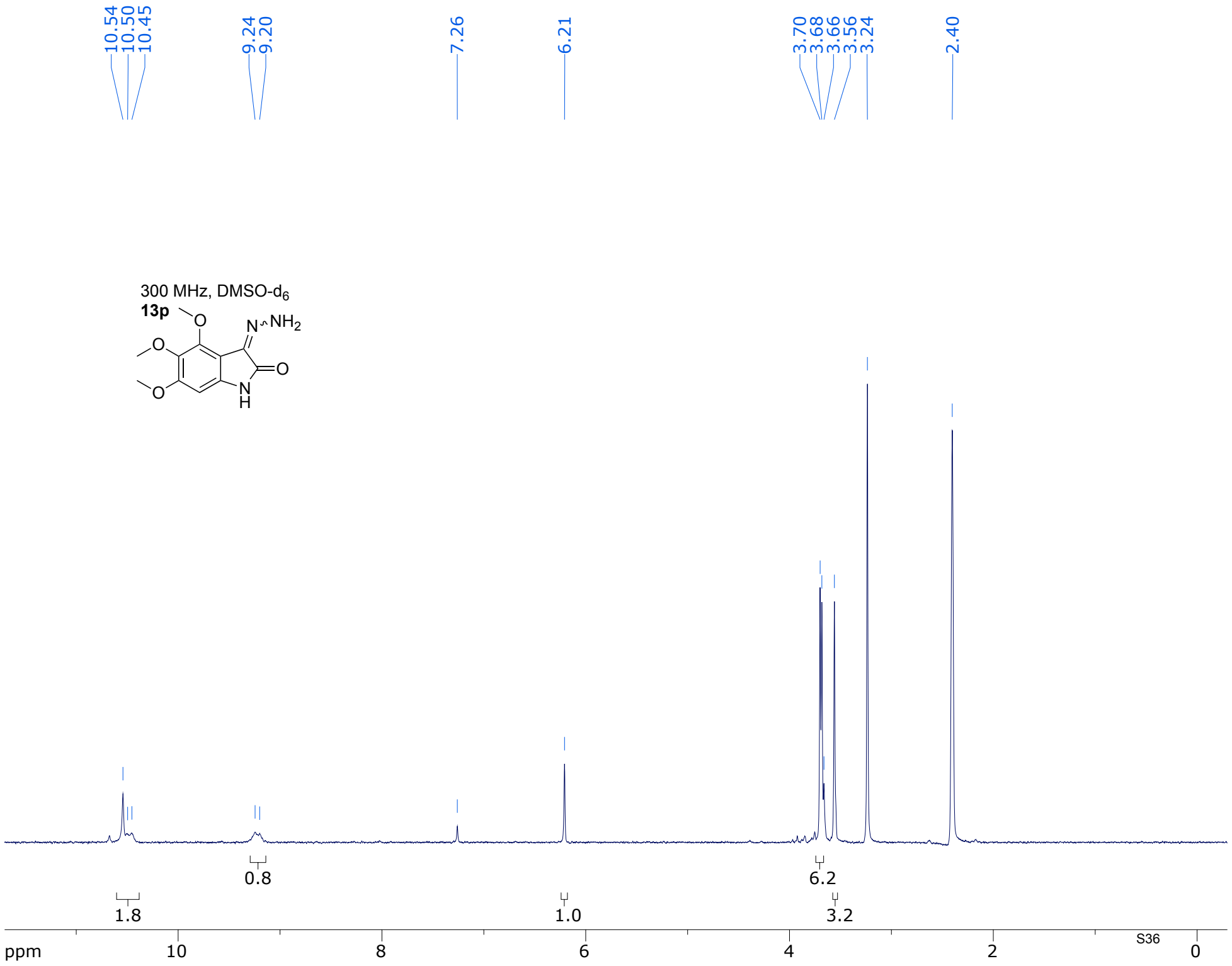

166.00
162.89
139.86
137.96
131.17
129.58
127.20
125.30
125.21
124.96
120.15
118.98
113.79
113.44
112.36
111.77
40.49
39.55
39.49
125 MHz, DMSO-d6
13m
NH2
N
Br
O
NH
Mixture of Isomers
ppm
150
100
50
0

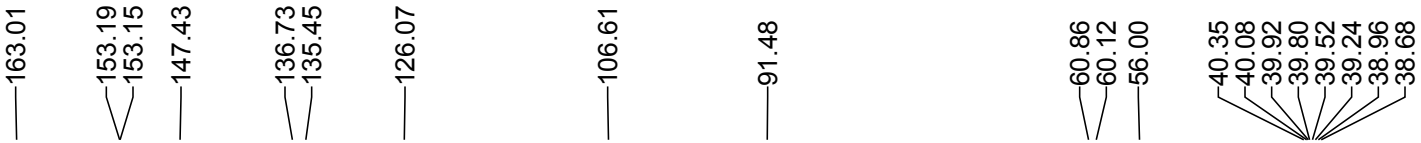

10.70
10.65
9.91
9.86
9.07
7.94
7.92
7.37
7.34
7.32
6.95
6.92
6.90
3.35
2.50
300 MHz, DMSO-d6
13n
N
NH2
O
N
H
Br
1.1
0.1
2.1
1.0
1.0
0.1
1.1
ppm
10
8
6
4
2
0


162.65
137.34
129.36
125.45
124.31
122.95
116.32
102.59
40.35
40.08
39.80
39.52
39.24
38.97
38.69
C-13 with Decoupling DUAL Probe AVANCE-300B
75 MHz, DMSO-d6
13n
N
NH2
O
N
H
Br
ppm
150
100
50
0

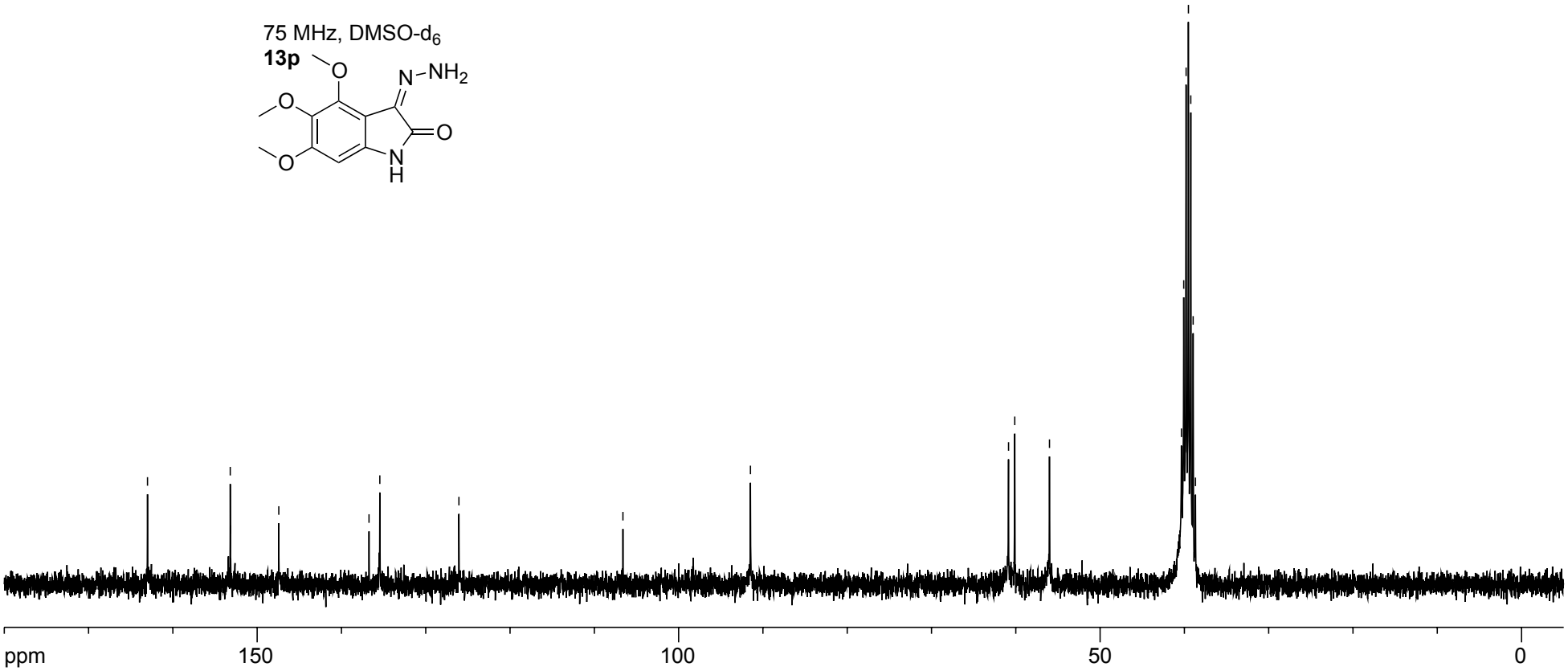

10.17
8.81
7.57
6.78
6.75
6.75
3.72
3.37
2.50
300 MHz, DMSO-d6
13o
N
NH2
O
O
N
H
2.0
2.1
1.0
1.0
3.2
ppm
10
8
6
4
2
0

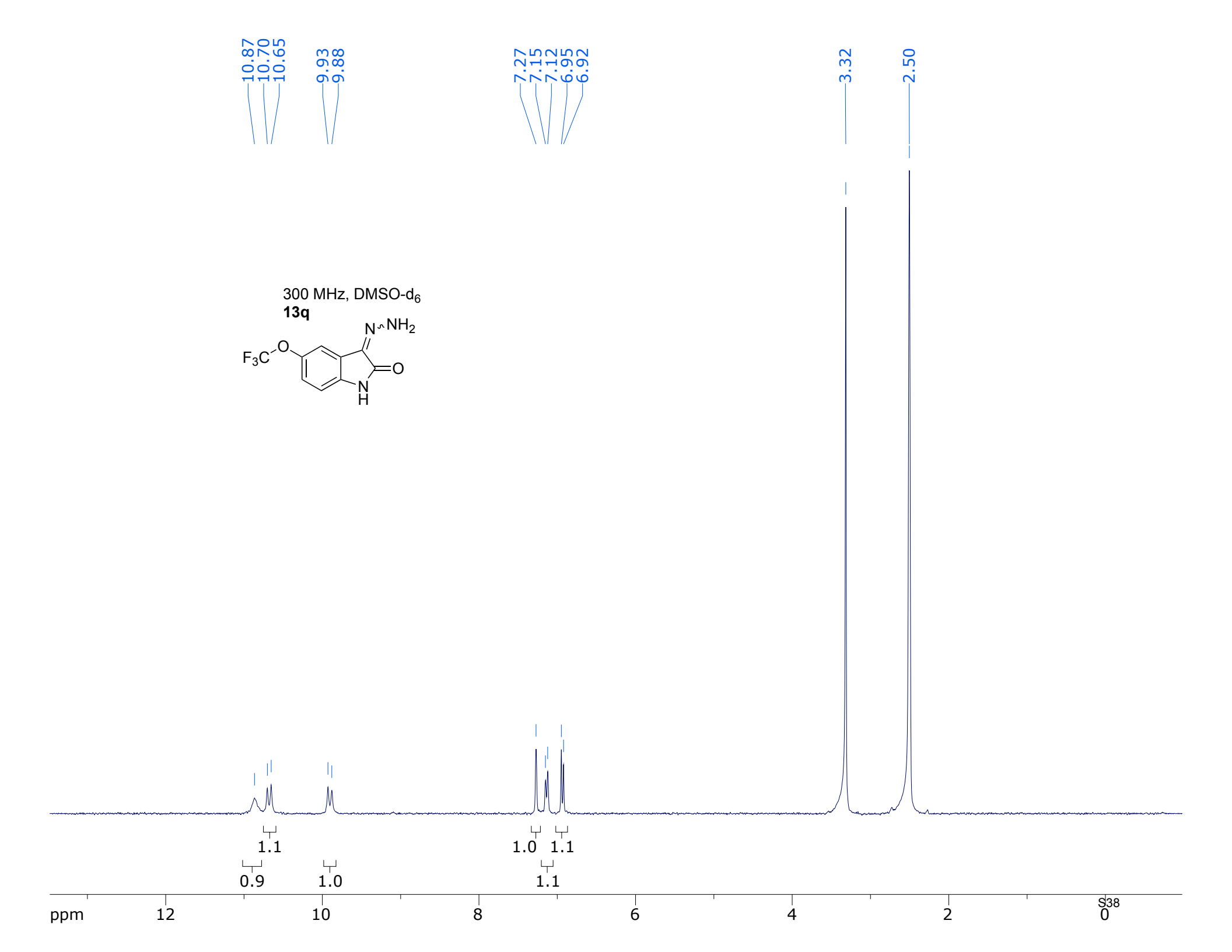

166.04
154.49
134.21
128.62
117.38
113.72
109.85
109.68
55.84
40.02
39.85
39.69
39.52
39.35
39.19
39.02
125 MHz, DMSO-d6
13o
N–NH2
O
O
N
H
ppm
180
160
140
120
100
80
60
40
20
0

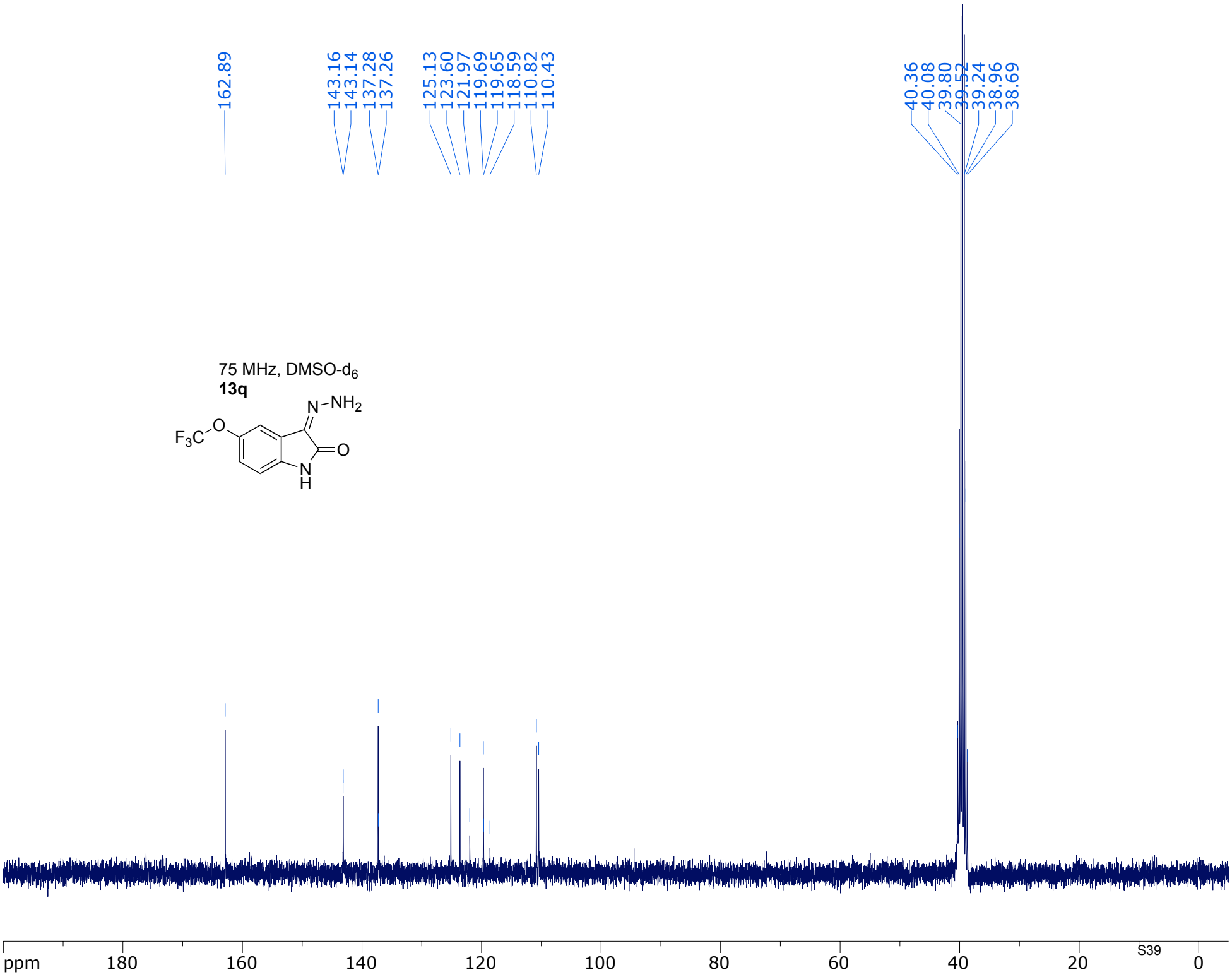

10.54
10.50
10.45
9.24
9.20
7.26
6.21
3.70
3.68
3.66
3.56
3.24
2.40
300 MHz, DMSO-d6
13p
O
N
NH2
O
O
O
N
H
0.8
6.2
1.8
1.0
3.2
ppm
10
8
6
4
2
0



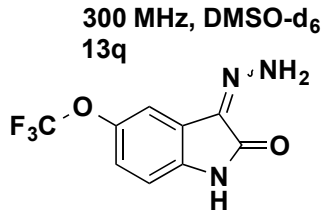
C-13 with Decoupling DUAL Probe AVANCE-300B

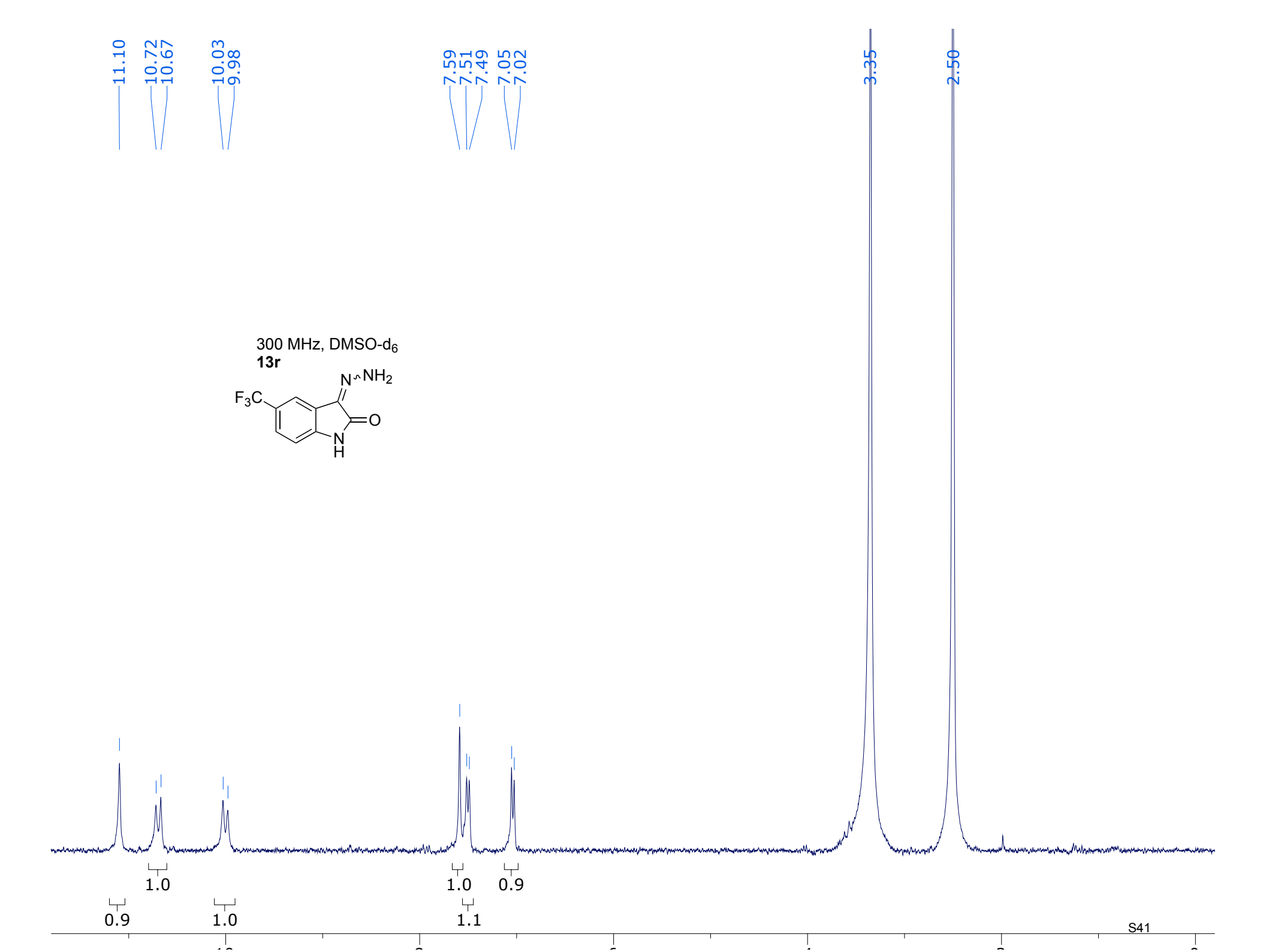


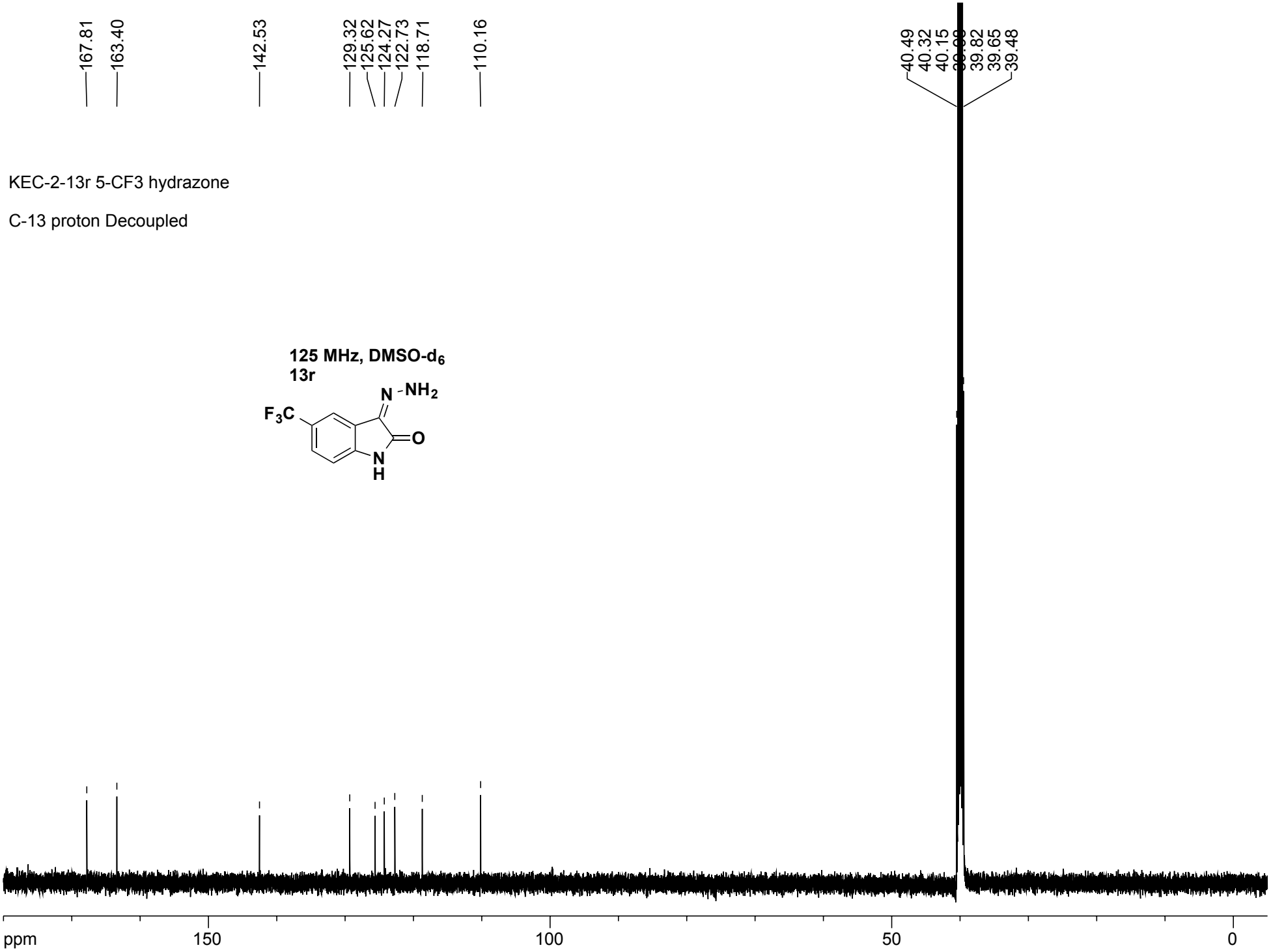

10.87
10.70
10.65
9.93
9.88
7.27
7.15
7.12
6.95
6.92
3.32
2.50
300 MHz, DMSO-d6
13q
N
NH2
F3C
O
O
N
H
1.1
0.9
1.0
1.0
1.1
1.1
ppm
12
10
8
6
4
2
0


162.89
143.16
143.14
137.28
137.26
125.13
123.60
121.97
119.69
119.65
118.59
110.82
110.43
40.36
40.08
39.80
39.52
39.24
38.96
38.69
75 MHz, DMSO-d6
13q
N–NH2
F3C
O
O
N
H
ppm
180
160
140
120
100
80
60
40
20
0

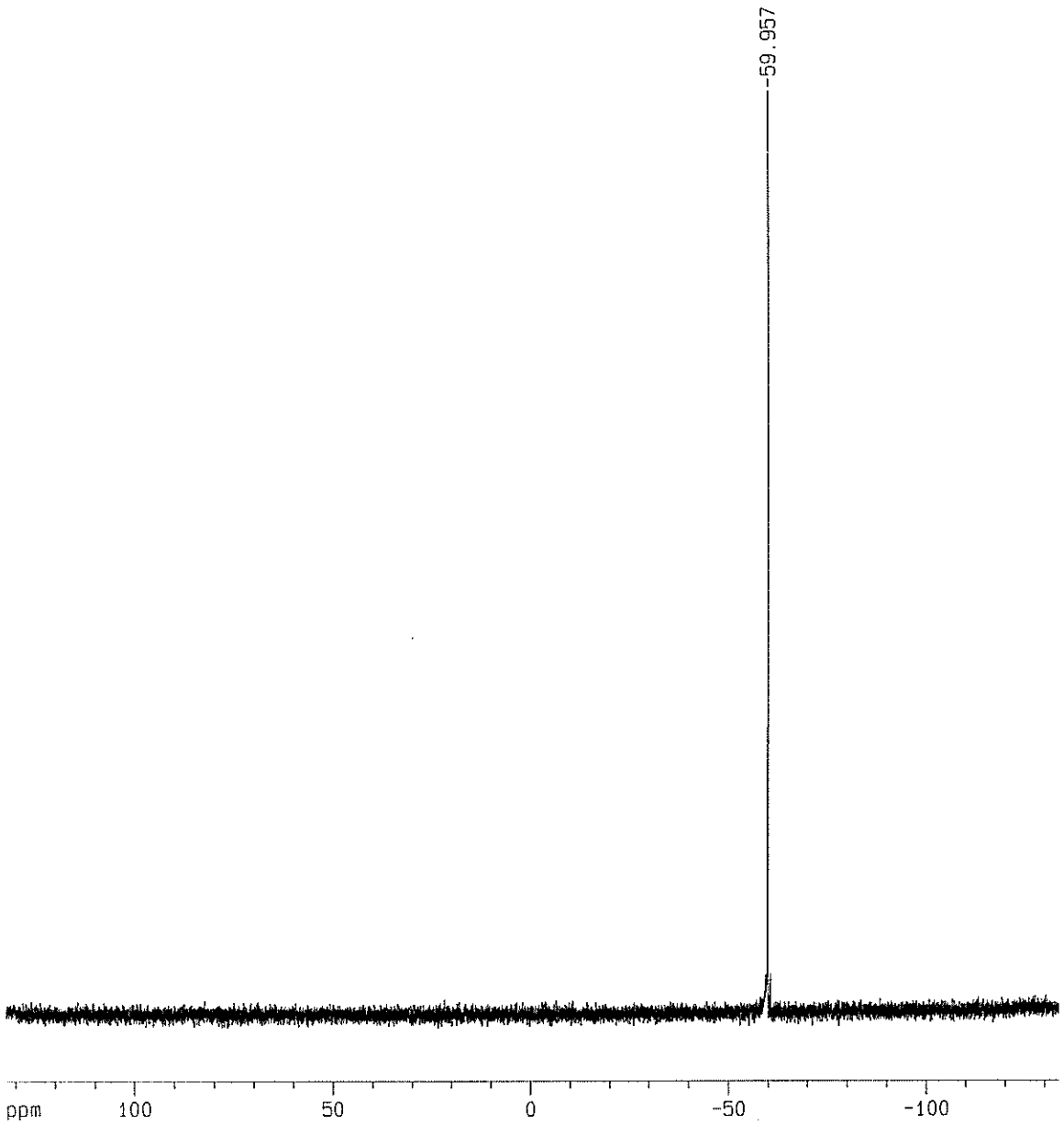
F19CPD- 300 ppm Sweep Width referenced to TFA=-76.53 ppm




11.10
10.72
10.67
10.03
9.98
7.59
7.51
7.49
7.05
7.02
3.35
2.50
300 MHz, DMSO-d6
13r
N
NH2
F3C
O
N
H
1.0
1.0
0.9
0.9
1.0
1.1
S41


167.81
163.40
142.53
129.32
125.62
124.27
122.73
118.71
110.16
40.49
40.32
40.15
39.82
39.65
39.48
KEC-2-13r 5-CF3 hydrazone
C-13 proton Decoupled
125 MHz, DMSO-d6
13r
N
NH2
F3C
O
N
H
ppm
150
100
50
0

F19CPD- 300 ppm Sweep Width referenced to TFA=-76.53 ppm

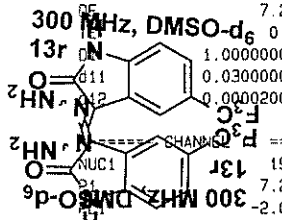


Current Data Parameters (dilute sample)

NAME	KC-2-CF3
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20140711
Time	11.57
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zgfhigqn
TD	131072
SOLVENT	D2O
NS	64
DS	2
SWH	75187.969 Hz
FIDRES	0.573639 Hz
AQ	0.8716788 sec
RG	20642.5
DW	6.650 usec
DE	7.21 usec
TE	0.0 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec



======== CHANNEL f1 ========

NUC1	19F
P1	7.25 usec
PL1	-2.00 dB
SFO1	282.4607319 MHz

======== CHANNEL f2 ========

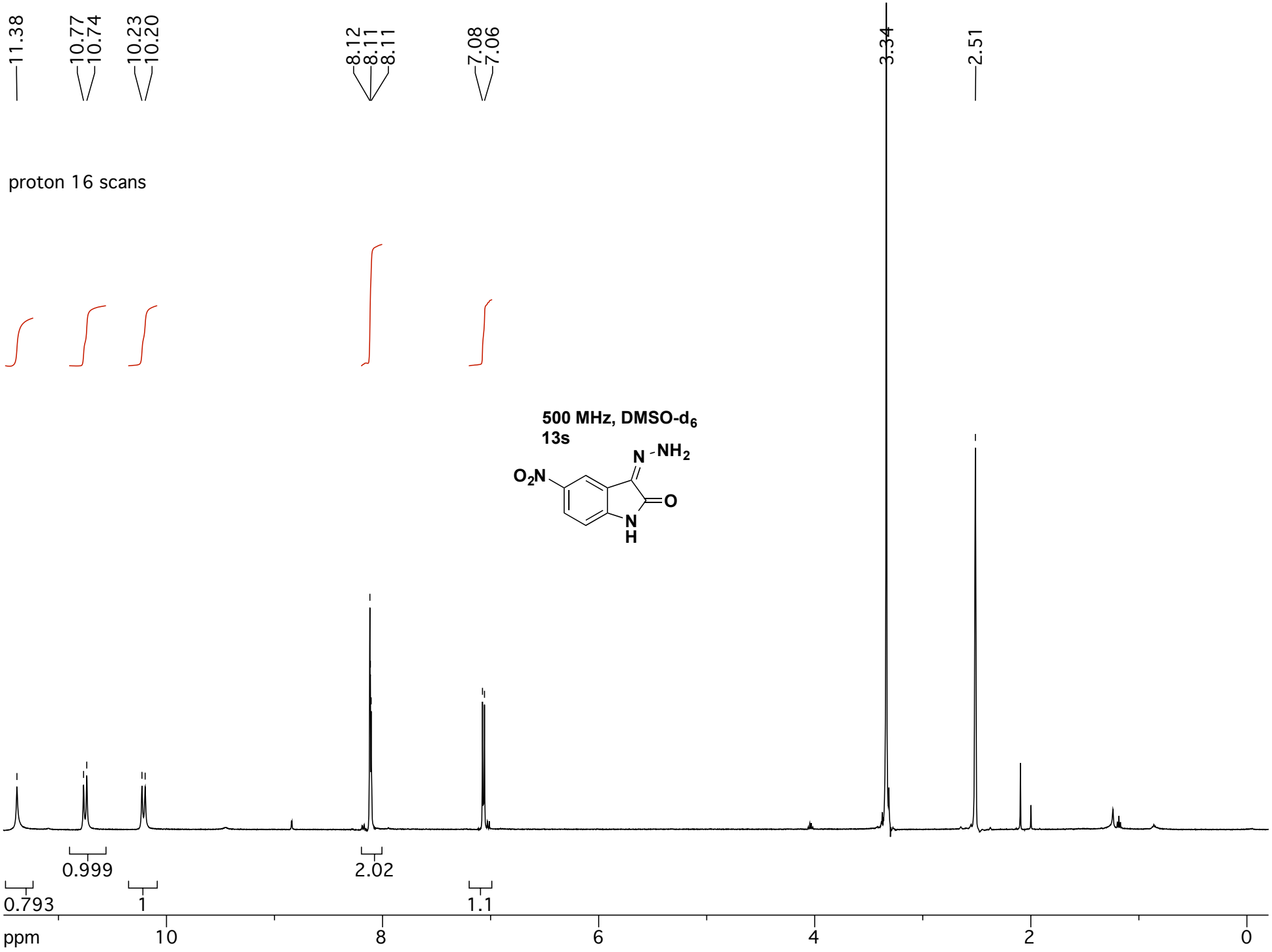
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-4.00 dB
PL12	14.40 dB
SFO2	300.1918534 MHz

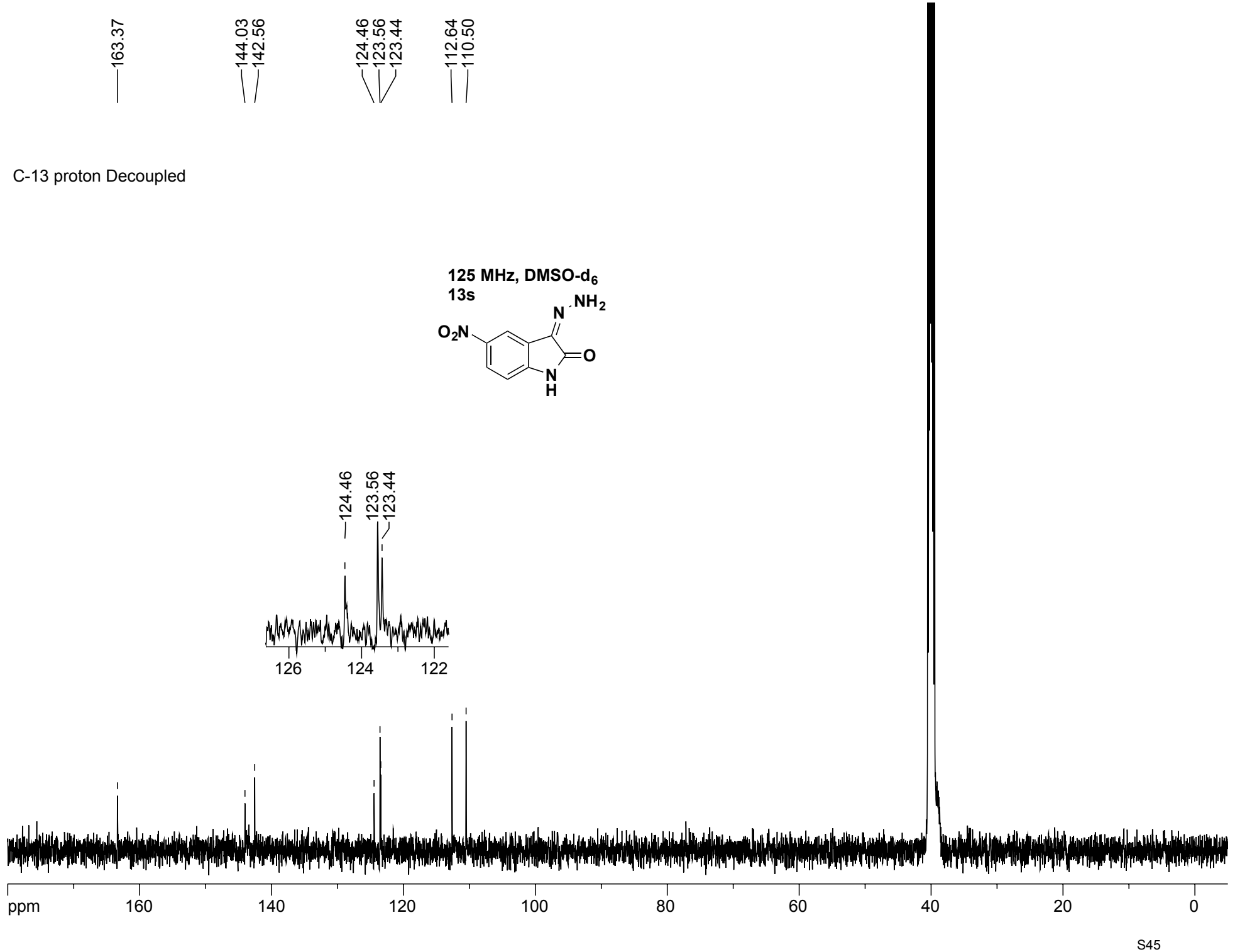
F2 - Processing parameters

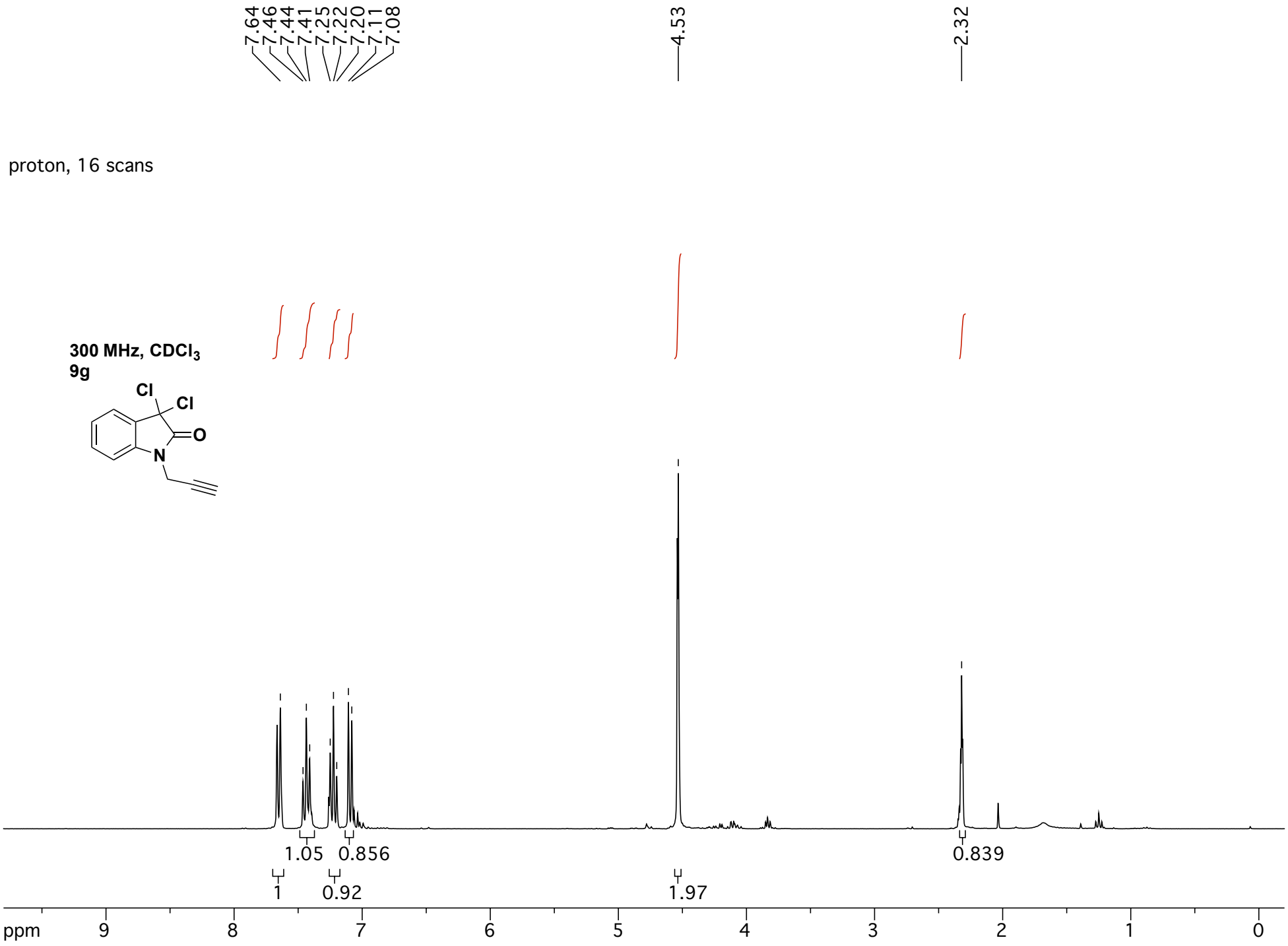
SI	65536
SF	282.4608826 MHz
WDW	EM
SSB	0
LB	3.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	12.50 cm
F1P	175.298 ppm
F1	49514.88 Hz
F2P	-175.298 ppm
F2	-49514.86 Hz
PPMCM	17.52982 ppm/cm
HZCM	4951.48730 Hz/cm


11.38
10.77
10.74
10.23
10.20
8.12
8.11
8.11
7.08
7.06
3.34
2.51
proton 16 scans
500 MHz, DMSO-d6
13s
O2N
N
NH2
O
N
H
0.793
0.999
1
2.02
1.1
ppm
10
8
6
4
2
0

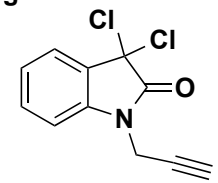

163.37
144.03
142.56
124.46
123.56
123.44
112.64
110.50
C-13 proton Decoupled
125 MHz, DMSO-d6
13s
NH2
N
O2N
O
N
H
124.46
123.56
123.44
126
124
122
ppm
160
140
120
100
80
60
40
20
0

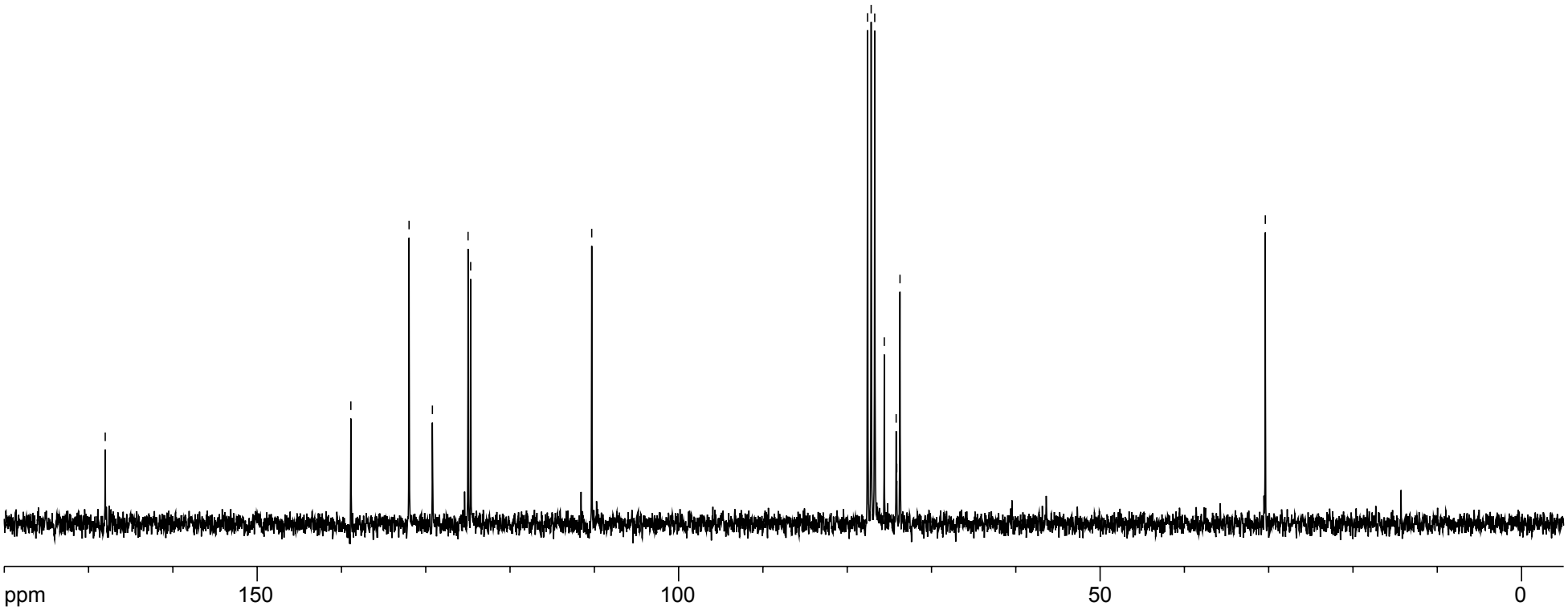

7.64
7.46
7.44
7.41
7.25
7.22
7.20
7.11
7.08
4.53
2.32
proton, 16 scans
300 MHz, CDCl3
9g
Cl
Cl
O
N
1.05
0.856
0.839
1
0.92
1.97
ppm
9
8
7
6
5
4
3
2
1
0

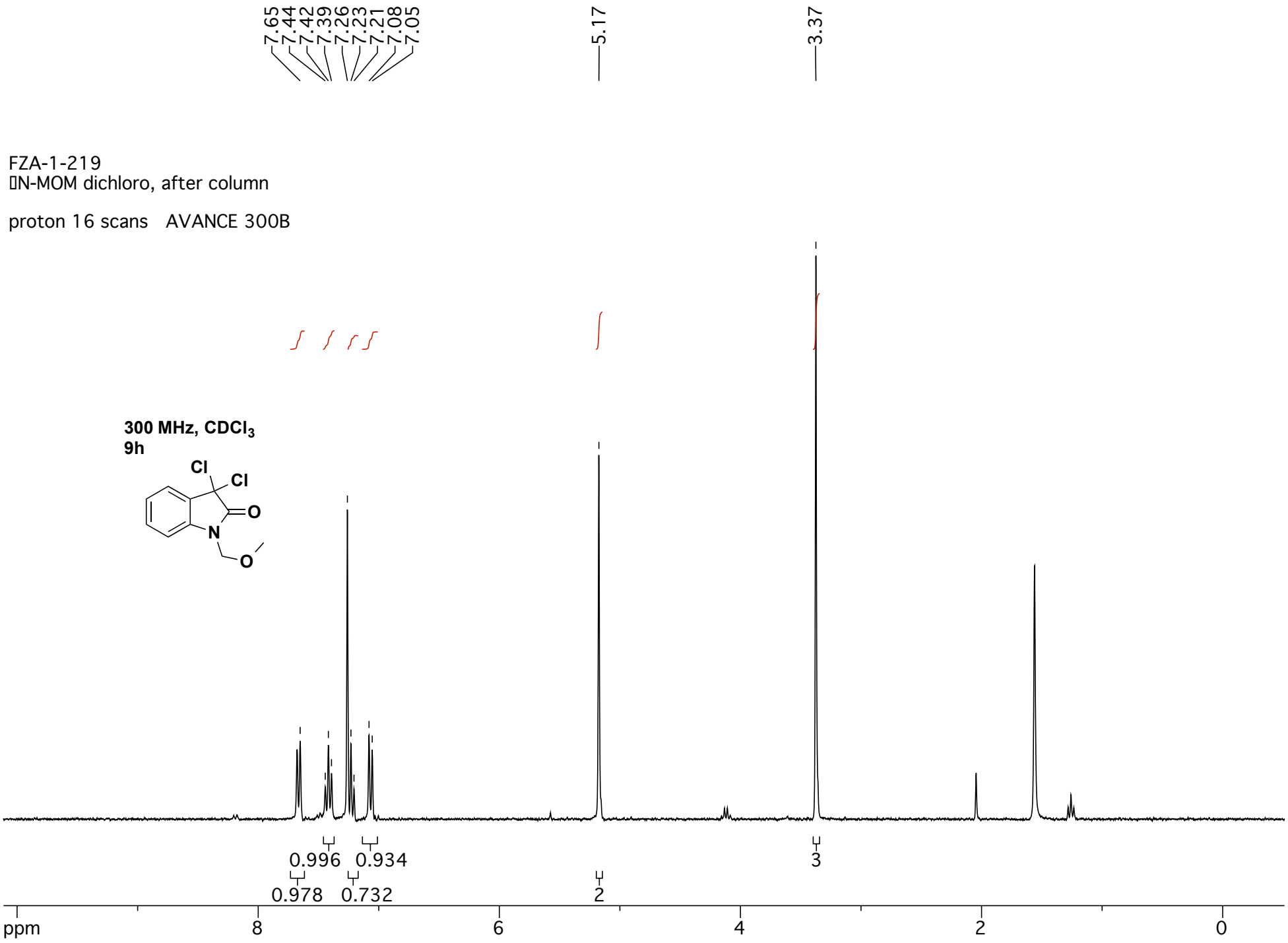
168.02
138.89
131.98
129.21
124.98
124.67
110.31
77.58
77.16
76.74
75.60
74.19
74.12
73.74
30.40

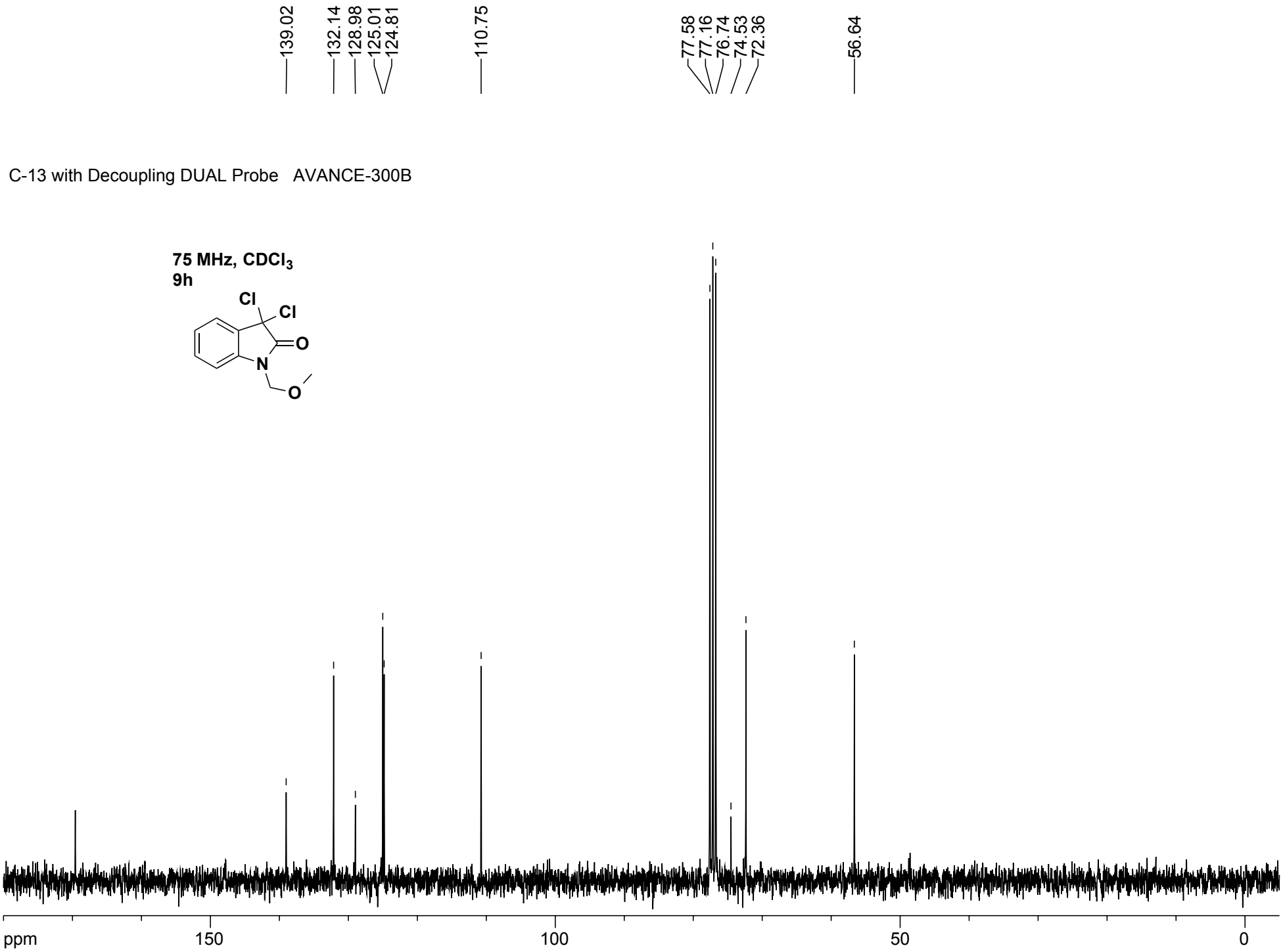
C-13 with Decoupling DUAL Probe AVANCE-300B

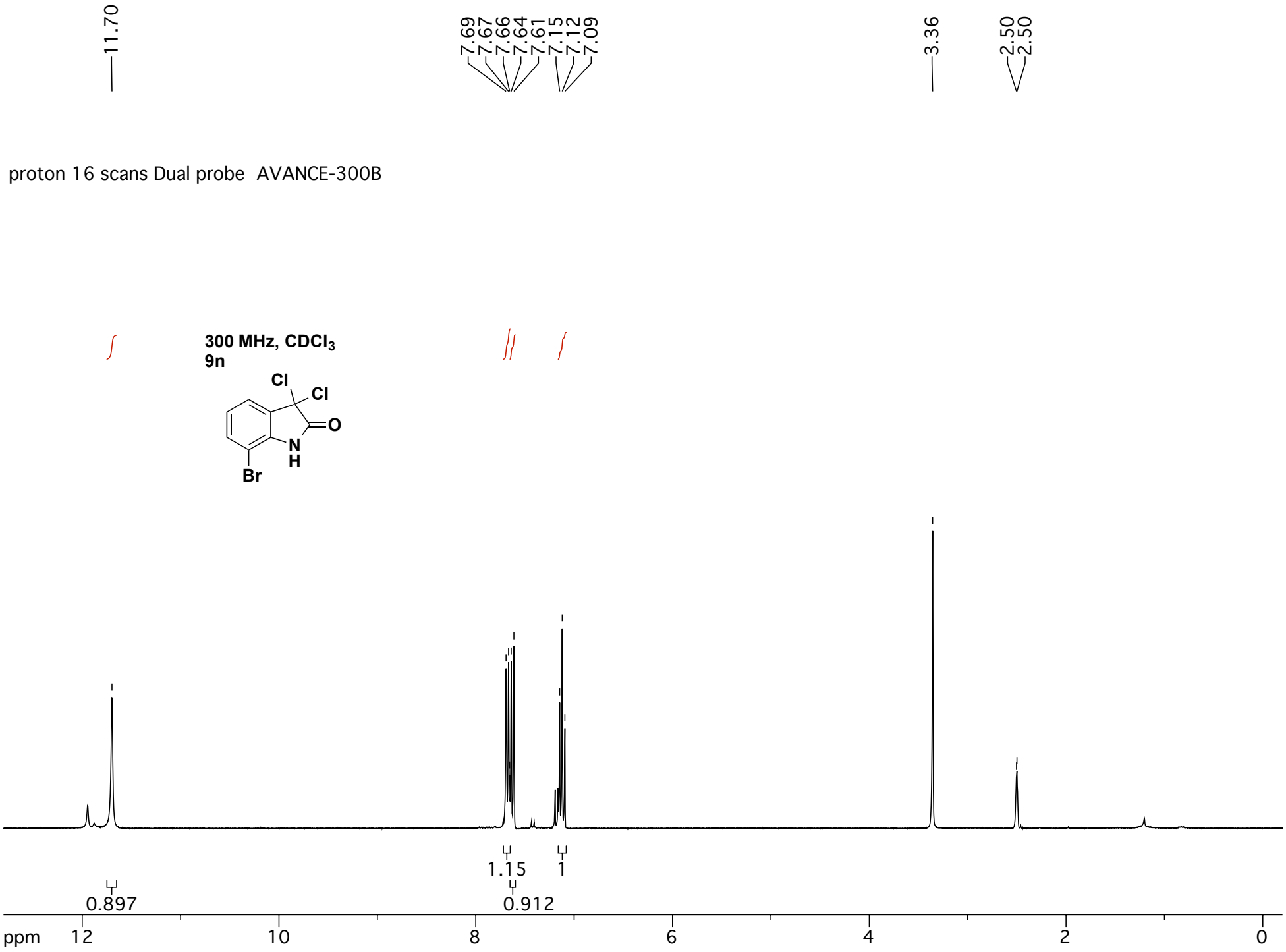
75 MHz, $CDCl_3$
9g



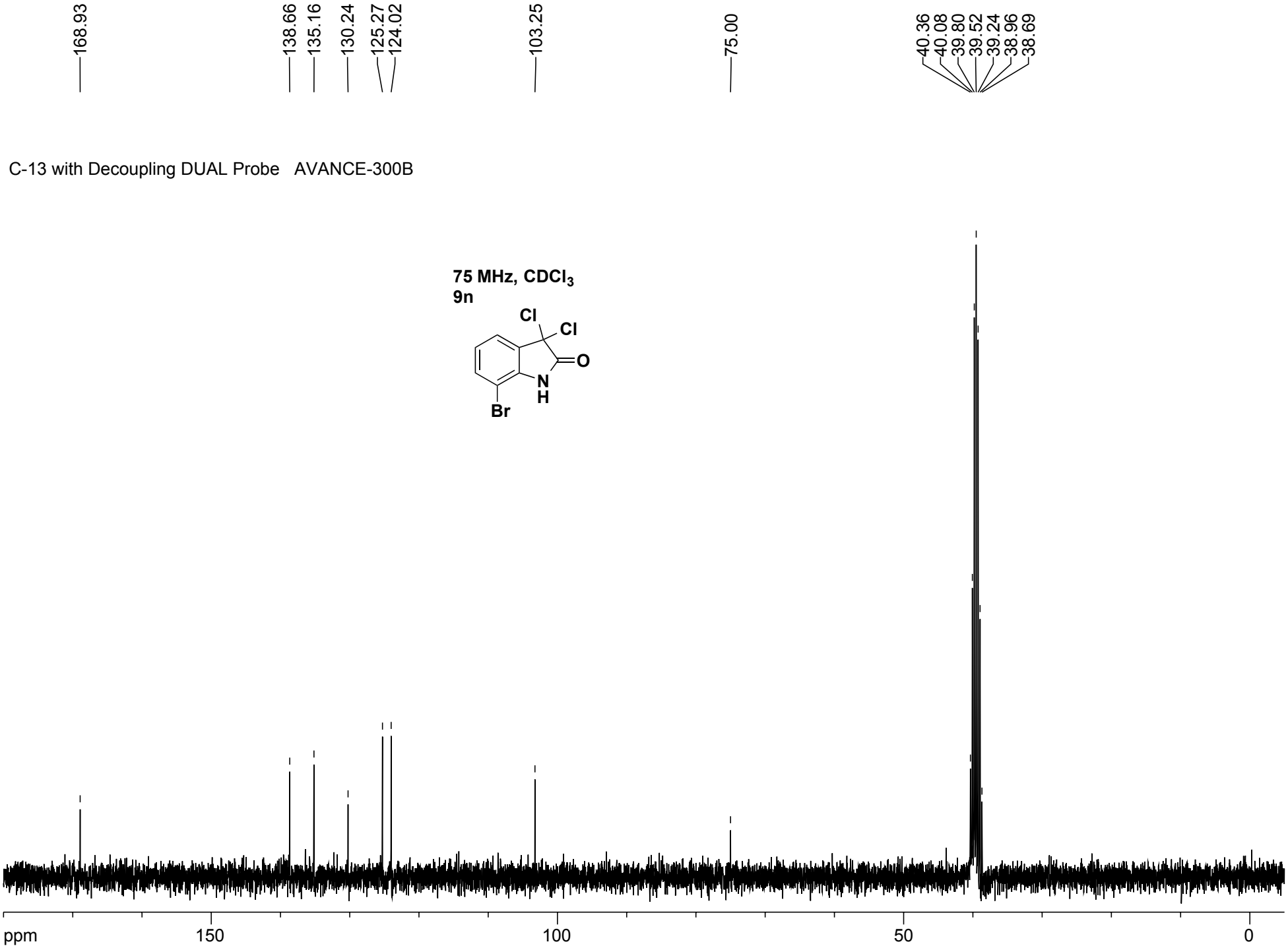


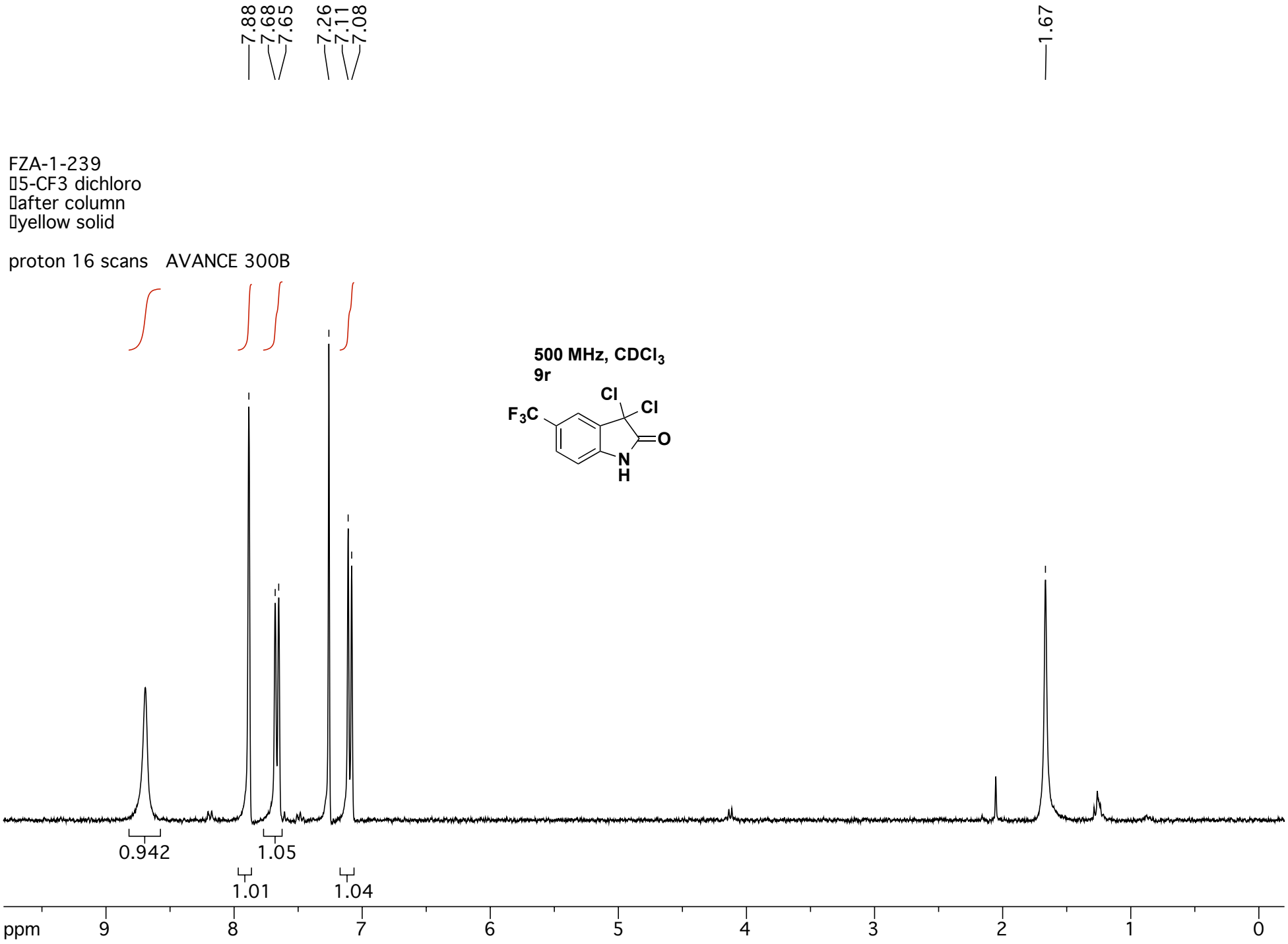

7.65
7.44
7.42
7.39
7.26
7.23
7.21
7.08
7.05
5.17
3.37
FZA-1-219
N-MOM dichloro, after column
proton 16 scans AVANCE 300B
300 MHz, CDCl3
9h
Cl
Cl
O
N
O
0.996
0.934
0.978
0.732
2
3
ppm
8
6
4
2
0

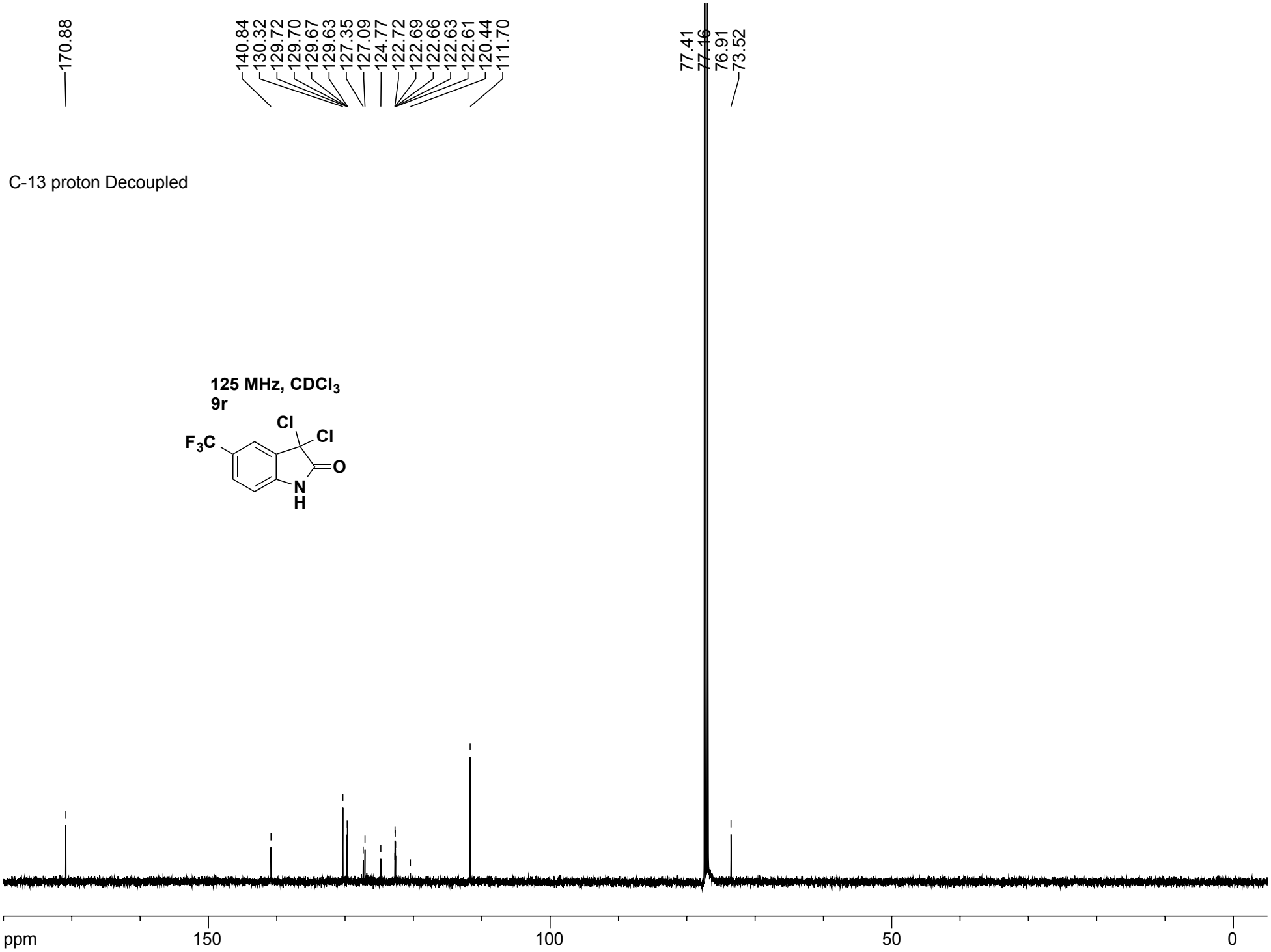

139.02
132.14
128.98
125.01
124.81
110.75
77.58
77.16
76.74
74.53
72.36
56.64
C-13 with Decoupling DUAL Probe AVANCE-300B
75 MHz, CDCl3
9h
Cl
Cl
O
N
O
ppm
150
100
50
0



proton 16 scans Dual probe AVANCE-300B


168.93
138.66
135.16
130.24
125.27
124.02
103.25
75.00
40.36
40.08
39.80
39.52
39.24
38.96
38.69
C-13 with Decoupling DUAL Probe AVANCE-300B
75 MHz, CDCl3
9n
Cl
Cl
O
N
H
Br
ppm
150
100
50
0

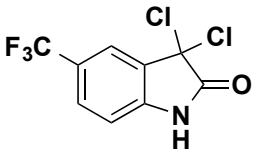

7.88
7.68
7.65
7.26
7.11
7.08
1.67
FZA-1-239
5-CF3 dichloro
after column
yellow solid
proton 16 scans AVANCE 300B
500 MHz, CDCl3
9r
Cl
Cl
F3C
O
N
H
0.942
1.05
1.01
1.04
ppm
9
8
7
6
5
4
3
2
1
0


170.88
140.84
130.32
129.72
129.70
129.67
129.63
127.35
127.09
124.77
122.72
122.69
122.66
122.63
122.61
120.44
111.70
77.41
77.16
76.91
73.52
C-13 proton Decoupled
125 MHz, CDCl3
9r
Cl
Cl
F3C
O
N
H
ppm
150
100
50
0

F19 Decoupled

-62.02

500 MHz, $CDCl_3$
9r



ppm 10 -0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110