SUPPORTING INFORMATION

Synthesis and Selective Functionalization of Thiadiazine 1,1-Dioxides with Efficacy in a Model of Huntington's Disease[§]

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Contents

I. General Information

All glassware was flame dried or oven-dried and cooled under dry N_2 or Ar prior to use. All moisture sensitive reactions were performed under dry N_2 or Ar. Reactions carried out below 0 °C employed an acetone/dry ice bath or a cyrocool and an isopropanol/ethanol bath. Reagents obtained from commercial sources were used as received unless otherwise specified. THF, Et_2O, and 1,4-dioxane were distilled from sodium/benzophenone ketyl; DIPEA and TEA were distilled from CaH_2 and stored over KOH; *t*-BuOH was distilled over CaH_2; and CH_2Cl_2 and toluene were purified by passage through an activated alumina filtration system. HFIP was distilled from 4Å MS and stored over 4Å MS. Benzaldehyde was distilled under vacuum (~30 mmHg) immediately prior to use. Concentrating under reduced pressure refers to the use of a rotary evaporator connected to a membrane vacuum pump to remove solvent.

Melting points were determined using a Laboratory Devices Mel-Temp II in open capillary tubes and are uncorrected. Infrared spectra were determined as neat solids or oils (unless otherwise

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[§]Dedicated to Prof. Maurizio Botta (University of Siena) in gratitude for his friendship and in appreciation of his scholarship.

[^]L. Terrab, C.J. Rosenker, and L. Johnstone contributed equally to this work and should be considered co-first authors.

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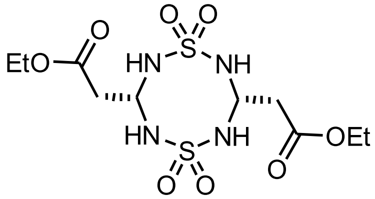
specified) on a Smiths Detection IdentifyIR FT-IR spectrometer or Perkin Elmer Spectrum 100; or as KBr pellets or thin films on a Nicolet Avatar 360 FT-IR. Low-resolution mass spectra were obtained on a Shimadzu 2020-LCMS or Agilent Technologies 1260 Infinity II LCMS. High-resolution mass spectra were obtained on a Micromass UK Limited, Q-TOF Ultima API or a Thermo Scientific Exactive Orbitrap LCMS. Purity of compounds tested in biological assays was assessed using an Agilent Technologies 1260 Infinity II LC at 220 nm UV absorption (Waters XBridge BEH C_{18} 2.1 x 50 mm, 2.5 µm) or an Agilent Technologies 385-ELSD (Microsolv Cogent 2.0 Bidentate C_{18} 2.1 x 50 mm, 2.2 µm; ELSD conditions: evaporator and nebulizer set at 45 °C; gas flow set at 1.80 standard liter/min).

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 300MHz, 400 MHz, 500 MHz, and a cryoprobe equipped 600MHz instruments. $CDCl_3$ was filtered though basic Al_2O_3 immediately prior to sample preparation. Chemical shifts (δ) were reported in parts per million with the residual solvent peak used as an internal standard δ ^{1}H / ^{13}C (Solvent); 7.26 / 77.16 ($CDCl_3$); 2.50 / 39.52 (DMSO-d_6); 2.05 / 29.84 (acetone-d_6) and are tabulated as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s). ^{13}C NMR spectra were obtained at 75 MHz, 100 MHz, and 125 MHz using a proton-decoupled pulse sequence and are tabulated by observed peak. Thin-layer chromatography was performed using pre-coated silica gel 60 F_{254} plates (EMD, 250 µm thickness) and visualization was accomplished with a 254 nm UV light and by staining with a phosphomolybdic acid solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH), a *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution), or Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}$•4 H_2O and 0.2 g of $Ce(SO_4)_2$

in 100 mL of a 3.5 N H_2SO_4 solution). Flash chromatography on SiO_2 (Silicycle, Silia-P Flash Silica Gel or SiliaFlash® P60, 40-63 µm) was used to purify crude reaction mixtures.

II. Experimental Procedures



3

Diethyl 2,2'-((3*SR*,7*SR*)-1,1,5,5-tetraoxido-1,5,2,4,6,8-dithiatetrazocane-3,7-diyl)diacetate (3).[1] To a suspension of sulfamide **2** (11.0 g, 113 mmol) in CH_2Cl_2 (217 mL) and TFA (44.0 mL, 586 mmol) was added diethoxypropionate **1** (25.5 mL, 125 mmol) over 5 min. The solution was stirred for 4 h at rt, filtered through a medium glass fritted funnel, washed with CH_2Cl_2 (~60 mL), MeOH (~50 mL), and Et_2O (~50 mL), and dried under high vacuum to give **3** (21.2 g, 96%) as a colorless solid: Mp 183-183°C (CH_2Cl_2); IR (ATR) 3318, 2990, 1717, 1348, 1335, 1048 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.52 (d, 4 H, $J = 9.4$ Hz), 5.18 (ddt, 2 H, $J = 9.2, 9.2, 7.3$ Hz), 4.06 (q, 4 H, $J = 7.1$ Hz), 2.64 (d, 4 H, $J = 7.2$ Hz), 1.18 (t, 6 H, $J = 7.1$ Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 168.5, 62.1, 60.2, 41.1, 14.0; HRMS (ESI$^+$) m/z calcd for $C_{10}H_{19}O_8N_4S_2$ [M-H]$^-$ 387.0639, found 387.0643.

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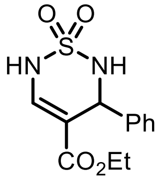
[1] Goya, P.; Stud, M. *J. Heterocycl. Chem.* **1978**, *15*, 253.



4a

Ethyl 3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (4a).[2] To a suspension of sulfamide **3** (9.76 g, 25.1 mmol) and benzaldehyde (5.20 mL, 51.2 mmol) in HFIP (100 mL) was added dropwise TFA (9.65 mL, 126 mmol). The solution was stirred at 35-40 °C in a round bottom flask capped with a glass stopper for 17 h. The solvent was evaporated under reduced pressure to give a yellow oil that was purified by chromatography on SiO_2 (2:8 to 4:6; EtOAc:hexanes) to give the thiadiazine **4a** (9.33 g, 66%) as a colorless solid: Mp 144-145°C ($CHCl_3$); IR (ATR) 3269, 3176, 2980, 1655, 1150, 1100 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.82 (s, 1 H), 7.93 (d, 1 H, *J* = 7.2 Hz), 7.49 (s, 1 H), 7.31-7.21 (m, 5 H), 5.33 (d, 1 H, *J* = 7.2 Hz), 4.01, 3.96 (dq, 2 H, *J* = 10.9, 7.1 Hz), 1.04 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.2, 139.0, 138.8, 127.9, 127.8, 127.3, 102.8, 59.6, 57.5, 14.0; HRMS (ESI$^+$) *m/z* calcd for $C_{12}H_{15}N_2O_4S$ [M+H] 283.0753, found 283.0786.

SFC Separation: Chiral IA, run time 6.08 min; Peak A: 2.57 min, $[\alpha]_D$ -8.1 (*c* 0.16, CH_2Cl_2); Peak B: 3.08 min, $[\alpha]_D$ +9.0 (*c* 0.13, CH_2Cl_2).

General Procedure A: Ethyl 3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide. To a stirred suspension of sulfamide dimer **3** (50 mg, 0.13 mmol) and aldehyde (0.26 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (0.190 mL, 2.56 mmol) dropwise at rt. The suspension was stirred for 16 to 48 h while the solution turned clear. The reaction mixture was concentrated under reduced

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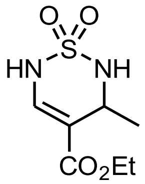
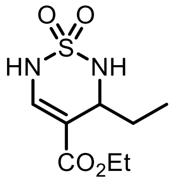
[2] Lee, C.-H.; Lee, Y. H.; Choi, W. S.; Chung, B. Y. *Bull. Korean Chem. Soc.* **1992**, *13*, 462.

pressure and the residue was purified by chromatography on SiO_2 (EtOAc:hexanes) to give the desired ethyl 3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide.



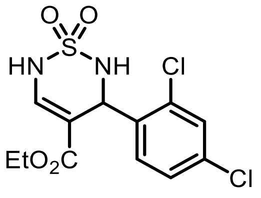
4b

Ethyl 3-methyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (4b). According to General Procedure A, sulfamide **3** (2.00 g, 5.15 mmol), acetaldehyde (0.580 mL, 10.3 mmol), and TFA (7.73 mL, 101 mmol) were stirred at rt for 26 h and provided a crude residue that was purified by chromatography on SiO_2 (15:85 to 3:7; EtOAc:hexanes) to give **4b** (1.34 g, 59%) as a colorless oil: IR (KBr) 1693, 1274, 1163 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 10.61 (d, 1 H, $J = 4.2$ Hz), 7.60 (d, 1 H, $J = 6.9$ Hz), 7.20 (d, 1 H, $J = 4.5$ Hz), 4.25-3.95 (m, 3 H), 1.37 (d, 3 H, $J = 7.2$ Hz), 1.19 (t, 3 H, $J = 7.2$ Hz); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 164.9, 135.4, 107.8, 60.0, 51.6, 18.5, 13.5; MS (EI) *m/z* 220 (M^+); HRMS (EI) *m/z* calcd for $C_7H_{12}N_2O_4S$ [M^+] 220.0517, found 220.0518.



4c

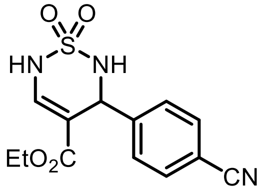
Ethyl 3-ethyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (4c). According to General Procedure A, sulfamide **3** (2.00 g, 5.15 mmol), propanal (0.900 mL, 12.4 mmol), and TFA (7.65 mL, 103 mmol) were stirred at rt for 24 h and provided a crude residue that was purified by chromatography on SiO_2 (100% hexanes to 35:65; EtOAc:hexanes) to give **4c** (1.34 g, 56%) as a colorless solid: Mp 128-130 ºC; IR (ATR) 3288, 3148, 1657, 1638, 1299, 1156 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d$_6$*) δ 10.60 (d, 1 H, *J* = 5.6 Hz), 7.52 (d, 1 H, *J* = 6.6 Hz), 7.21 (d, 1 H, *J* = 5.8 Hz), 4.11 (dq, 1 H, *J* = 7.1, 3.7 Hz), 4.07 (dq, 1 H, *J* = 7.1, 3.8 Hz), 3.92 (ddd, 1 H, *J* = 10.8, 6.6, 3.8 Hz), 1.90-1.78 (m, 1 H), 1.72-1.62 (m, 1 H), 1.94 (t, 3 H, *J* = 7.1 Hz), 0.92 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-*d$_6$*) δ 165.3, 137.1, 104.9, 59.6, 56.7, 24.7, 14.2, 10.7; HRMS (ESI-ASAP) m/z calcd for $C_8H_{13}N_2O_4S$ [M-H]$^-$ 233.0596, found 233.0592.



4d

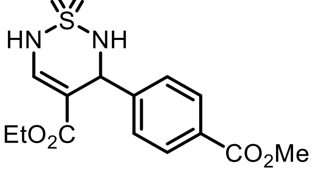
Ethyl 3-(2,4-dichlorophenyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (4d). To a suspension of **3** (1.85 g, 4.69 mmol) in HFIP (18.5 mL) was added 2,4-dichlorobenzaldehyde (1.68 g, 9.38 mmol) and TFA (1.81 mL, 23.5 mmol) dropwise. The reaction mixture was stirred for 19 h at 35-40 °C. The yellow solution was diluted with CH_2Cl_2, quenched with $NaHCO_3$ (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine (40 mL) and concentrated to afford **4d** (1.23 g, 73%) as an off-white solid: Mp 191-202 °C; IR (ATR) 3270, 3174, 2833, 1666, 1636 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d$_6$*) δ 11.0 (bs, 1 H) 8.17 (d, 1 H, *J* = 7.2 Hz) 7.62 (d, 1 H, *J* = 2 Hz), 7.59 (bs, 1 H) 7.36 (dd, 1 H, *J* = 8.4, 2.0 Hz) 7.21 (d, 1 H, *J* = 8.4 Hz), 5.60 (d, 1 H, *J* = 7.2 Hz), 3.98 (dq, 2 H, *J* = 11.2, 7.3 Hz), 1.05 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-*d$_6$*) δ 164.8, 139.8, 135.1, 134.0 133.1, 131.4, 128.7, 126.7, 101.2, 59.8, 54.0,14.0); HRMS

(ESI$^+$) m/z calcd for $C_{12}H_{11}Cl_2N_2O_4S$ [M-H]$^-$ 348.9811, found 348.98920.



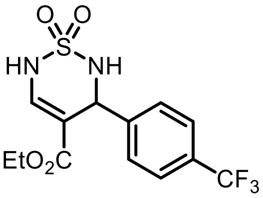
4e

Ethyl 3-(4-cyanophenyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (4e). According to General Procedure A, sulfamide **3** (0.050 g, 0.13 mmol), 4-formylbenzenecarbonitrile (0.0360 mL, 0.261 mmol), and TFA (0.100 mL, 1.31 mmol) were stirred at rt for 22 h. The reaction was incomplete, and TFA (0.100 mL, 1.31 mmol) was added. The reaction mixture was stirred for another 24 h and provided a crude residue that was purified by chromatography on SiO_2 (1:3 to 35:65; EtOAc:hexanes) to give **4e** (0.0320 g, 41%) as a colorless solid: Mp 185-186 ºC; IR (KBr) 1698, 1268, 1156 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.02 (s, 1 H), 8.15 (d, 1 H, J = 7.2 Hz), 7.76 (d, 2 H, J = 8.4 Hz), 7.56 (s, 1 H), 7.43 (d, 2 H, J = 8.4 Hz), 5.41 (d, 1 H, J = 7.2 Hz), 4.07-3.99 (m, 2 H), 1.07 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 165.0, 144.8, 139.5, 131.7, 128.9, 118.8, 110.0, 101.4, 59.7, 56.6, 14.0; MS (EI) *m/z* 307 (M$^+$, 60), 242 ([M-SO$_2$]$^+$, 90); HRMS (EI) *m/z* calcd for $C_{13}H_{13}N_3O_4S$ [M$^+$] 307.0627 found 307.0623.



4f

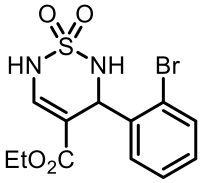
Ethyl 3-(4-(methoxycarbonyl)phenyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (4f). According to General Procedure A, sulfamide **3** (0.050 g, 0.13 mmol), methyl 4-formylbenzoate (0.047 g, 0.26 mmol), and TFA (0.190 mL, 2.48 mmol) were stirred at rt for 20 h and provided a crude residue that was purified by chromatography on SiO_2 (100% hexanes to 35:65; EtOAc:hexanes) to give **4f** (49.4 mg, 57%) as a colorless solid: Mp 176-178 °C; IR (KBr) 1700, 1286, 1159 cm^{-1}; ^{1}H NMR (DMSO-d_6, 600 MHz) δ 10.98 (s, 1 H), 8.12 (d, 1 H, J = 7.2 Hz), 7.93 (d, 2 H, J = 8.2 Hz), 7.59 (s, 1 H), 7.43 (d, 2 H, J = 8.4 Hz), 5.44 (d,1 H, J = 6.6 Hz), 4.09-4.01 (m, 2 H), 3.88 (s, 3 H), 1.11 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 166.1, 165.0, 144.5, 139.3, 128.7, 128.6, 128.2, 101.9, 59.7, 56.8, 52.1, 14.0; MS (EI) *m/z* 340 (M^+, 15), 275 ($[M-SO_2]^+$, 100); HRMS (EI) *m/z* calcd for $C_{14}H_{16}N_2O_6S$ [M^+] 340.0729, found 340.0727.



4g

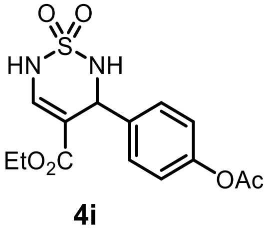
Ethyl 3-(4-(trifluoromethyl)phenyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (4g). According to General Procedure A, sulfamide **3** (1.00 g, 2.57 mmol), 4-(trifluoromethyl)benzaldehyde (0.850 mL, 6.20 mmol), and TFA (3.80 mL, 49.6 mmol) were stirred at rt for 36 h and provided a crude residue that was purified by chromatography on SiO_2 (100% hexanes to 35:65; EtOAc:hexanes) to give **4g** (1.17 g, 65%) as a colorless solid: Mp 179-181 °C; IR (KBr) 1696, 1280, 1163 cm^{-1}; ^{1}H NMR (DMSO-d_6, 600 MHz) δ 10.98 (s, 1 H), 8.14 (d, 1 H, J = 6.6 Hz), 7.68 (d, 2 H, J = 7.8 Hz), 7.57 (s, 1 H), 7.48 (d, 2 H, J = 7.8 Hz), 5.44 (d, 1

H, *J* = 7.6 Hz), 4.12-3.99 (m, 2 H), 1.08 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (MeOD-*d*$_4$, 150 MHz) δ 166.0, 143.5, 139.4, 129.2 (q, $J_{C\text{-}F}$ = 30 Hz), 128.4, 124.5, 124.3 (q, $J_{C\text{-}F}$ = 269 Hz) 102.7, 60.1, 57.5, 13.0; MS (EI) m/z 350 (M$^+$); HRMS (EI) m/z calcd for $C_{13}H_{13}F_3N_2O_4S$ [M$^+$] 350.0548, found 350.0546.



4h

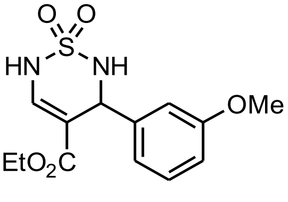
Ethyl 3-(2-bromophenyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (4h). According to General Procedure A, sulfamide **3** (0.050 g, 0.13 mmol), 2-bromobenzaldehyde (0.031 mL, 0.26 mmol), and TFA (0.193 mL, 2.52 mmol) were stirred at rt for 16 h and provided a crude residue that was purified by chromatography on SiO_2 (1:3 to 3:7; EtOAc:hexanes) to give **4h** (0.042 g, 45%) as a colorless solid: Mp 172-174 °C; IR (KBr) 1682, 1275, 1150 cm^{-1}; ^{1}H NMR (DMSO-*d*$_6$, 600 MHz) δ 10.94 (s, 1 H), 8.11 (d, 1 H, *J* = 7.2 Hz), 7.62 (d, 1 H, *J* = 7.2 Hz), 7.57 (s, 1 H), 7.31-7.22 (m, 3 H), 5.64 (d, 1 H, *J* = 7.2 Hz), 4.01-3.94 (m, 2 H), 1.03 (t, 3 H, *J* = 6.8 Hz); ^{13}C NMR (MeOD-*d*$_4$, 150 MHz) δ 165.8, 139.4, 137.4, 132.5, 129.9, 129.2, 126.6, 124.1, 103.2, 60.0, 57.6, 13.0; MS (EI) 360/362 (M$^+$); HRMS (EI) *m/z* calcd for $C_{12}H_{13}N_2O_4SBr$ [M$^+$] 360.9858, found 360.9861.



4i

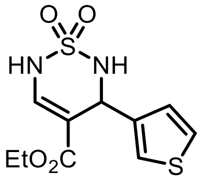
Ethyl 3-(4-acetoxyphenyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (4i). According to General Procedure A, sulfamide **3** (0.050 g, 0.13 mmol), 4-formylphenyl acetate

(0.0370 mL, 0.260 mmol), and TFA (0.190 mL, 2.48 mmol) were stirred at rt for 16 h and provided a crude residue that was purified by chromatography on SiO_2 (15:85 to 35:65; EtOAc:hexanes) to give **4i** (0.042 g, 48%) as a colorless solid: Mp 126-127 ºC; IR (KBr) 1724, 1704, 1276, 1158 cm^{-1}; ^{1}H NMR (DMSO-*d*$_6$, 600 MHz) δ 10.86 (s, 1 H), 7.98 (d, 1 H, *J* = 7.2 Hz), 7.51 (s, 1 H), 7.28 (d, 2 H, *J* = 8.4 Hz), 7.05 (d, 2 H, *J* = 7.8 Hz), 5.35 (d, 1 H, *J* = 7.2 Hz), 4.06-3.97 (m, 2 H), 2.26 (s, 3 H), 1.07 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (DMSO-*d*$_6$, 150 MHz) δ 169.1, 165.1, 149.6, 138.9, 136.5, 128.9, 122.0, 102.6, 59.6, 56.9, 20.8, 14.0; MS (EI) *m/z* 340 (M$^+$); HRMS (EI) *m/z* calcd for $C_{14}H_{16}N_2O_6S$ [M$^+$] 340.0729, found 340.0735.



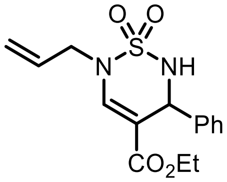
4j

Ethyl 3-(3-methoxyphenyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (4j). According to General Procedure A, sulfamide **3** (2.00 g, 5.15 mmol), 3-methoxybenzaldehyde (1.38 mL, 11.3 mmol), and TFA (7.65 mL, 99.9 mmol) were stirred at rt for 48 h and provided a crude residue that was purified by chromatography on SiO_2 (100% hexanes to 35:65; EtOAc:hexanes) to give **4j** (2.00 g, 62%) as a colorless solid: Mp 74-77 ºC; IR (KBr) 1701, 1265, 1156 cm^{-1}; ^{1}H NMR (DMSO-*d*$_6$, 300 MHz) δ 10.80 (s, 1 H), 7.89 (d, 1 H, *J* = 7.5 Hz), 7.48 (s, 1 H), 7.21 (t, 1 H, *J* = 7.8 Hz), 6.85-6.79 (m, 3 H), 5.30 (d, 1 H, *J* = 7.5 Hz), 4.04-3.95 (m, 2 H), 3.73 (s, 3 H), 1.06 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (MeOD-*d*$_4$, 150 MHz) δ 166.1, 157.2, 138.6, 128.9, 128.6, 126.6, 119.5, 110.4, 104.5, 59.8, 54.7, 52.5, 12.9; MS (EI) *m/z* 312 (M$^+$, 10), 247 ([M-SO$_2$]$^+$, 60); HRMS (EI) *m/z* calcd for $C_{13}H_{16}N_2O_5S$ [M$^+$] 312.0780, found 312.0769.



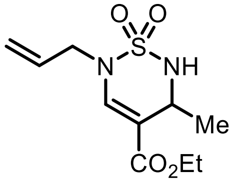
4k

Ethyl 3-(thiophen-3-yl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (4k). According to General Procedure A, sulfamide **3** (0.101 g, 0.260 mmol), thiophene-3-carbaldehyde (0.0455 mL, 0.519 mmol), and TFA (0.385 mL, 5.18 mmol) were stirred at rt for 23 h and provided a crude residue that was purified by chromatography on SiO_2 (2:8 to 4:6; EtOAc:hexanes) to give **4k** (0.0455 g, 30%) as a colorless solid: Mp 147-148 °C ($CHCl_3$); IR (ATR) 3241, 3129, 1663, 1281, 1150 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.78 (bs, 1 H), 7.90 (d, 1 H, $J = 7.0$ Hz), 7.43-7.38 (m, 2 H), 7.21-7.16 (m, 1 H), 7.03 (dd, 1 H, $J = 5.0, 1.1$ Hz), 5.36 (d, 1 H, $J = 6.9$ Hz), 4.03 (dq, 2 H, $J = 10.8, 7.1$ Hz), 1.09 (t, 3 H, $J = 7.1$ Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.2, 140.2, 138.2, 127.7, 125.1, 123.1, 103.6, 59.6, 53.3, 14.1; HRMS (ESI$^+$) *m/z* calcd for $C_{10}H_{12}N_2O_4S_2Na$ $[M+Na]^+$ 311.0136, found 311.0116 (note: error >5 ppm).



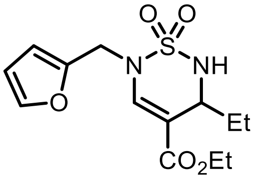
5a

General Procedure B: Preparation of monoalkylated thiadiazines. Ethyl 3-(thiophen-3-yl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (5a). To a solution of thiadiazine **4a** (0.130 g, 0.460 mmol) and allyl alcohol (0.0380 mL, 0.550 mmol) in THF (4 mL) was added PPh_3 (0.144 g, 0.550 mmol) and DBAD (0.127 g, 0.550 mmol). The reaction mixture was stirred at rt for 1 h, concentrated under reduced pressure, and purified by chromatography on SiO_2 (1:6 to 1:2; EtOAc:hexanes) to give **5a** (0.144 g, 77%) as a colorless oil: IR (KBr) 1701, 1266, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.41 (s, 1 H), 7.35-7.30 (m, 5 H), 5.94-5.88 (m, 1 H), 5.56 (d, 1 H, *J* = 8.4 Hz), 5.40 (d, 1 H, *J* = 16.8 Hz), 5.36 (d, 1 H, *J* = 10.2 Hz), 4.74 (d, 1 H, *J* = 8.4 Hz), 4.18-4.12 (m, 2 H), 4.03-3.99 (m, 1 H), 3.98-3.93 (m, 1 H), 0.98 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 164.5, 140.5, 137.6, 131.1, 127.9, 126.9, 119.8, 106.7, 59.8, 59.0, 50.8, 27.5, 13.3; MS (EI) m/z 323 (M^+); HRMS (ESI$^+$) m/z calcd for $C_{15}H_{19}N_2O_4S$ [M^+] 323.1066, found 323.1062.



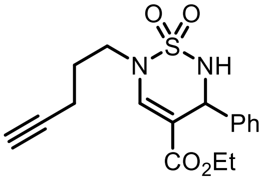
5b

Ethyl 6-allyl-3-methyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (5b). According to General Procedure B, **4b** (0.120 g, 0.545 mmol), allyl alcohol (0.0440 mL, 0.645 mmol), PPh_3 (0.171 g, 0.652 mmol), and DBAD (0.150 g, 0.651 mmol) in THF (4 mL) were stirred at rt for 30 min and provided a crude residue that was purified by chromatography on SiO_2 (1:2; EtOAc:hexanes) to give **5b** (0.102 g, 72%) as a colorless oil: IR (KBr) 1700, 1265, 1179 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.18 (s, 1 H), 5.91-5.85 (m, 1 H), 5.38-5.33 (m, 2 H), 4.68 (d, 2 H, *J* = 7.8 Hz), 4.50 (quint., 1 H, *J* = 7.2 Hz), 4.23-4.17 (m, 2 H), 4.13 (dd, 2 H, *J* = 11.2, 6.0 Hz), 1.59 (d, 3 H, *J* = 7.2 Hz), 1.29 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.3, 139.3, 131.8, 120.2, 108.6, 60.5, 52.2, 51.3, 19.4, 14.3; MS (ESI$^+$) m/z 260 (M^+); HRMS (ESI$^+$) m/z calcd for $C_{10}H_{16}N_2O_4S$ (M^+) 260.0831, found 260.0837.



5c

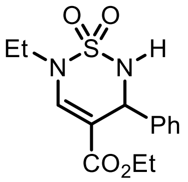
Ethyl 3-ethyl-6-(furan-2-ylmethyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (5c). According to General Procedure B, **4c** (0.211 g, 0.900 mmol), 2-furylmethan-1-ol (0.0650 mL, 0.747 mmol), PPh_3 (0.236 g, 0.900 mmol), and DEAD (0.142 mL, 0.900 mmol) in THF (6 mL) were stirred at 0 °C for 10 min and provided a crude residue that was purified by chromatography on SiO_2 (1:10 to 1:4; EtOAc:hexanes) to give **5c** (0.088 g, 37%) as a colorless oil: IR (ATR) 3263, 1690, 1625, 1353, 1236, 1176 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (d, 1 H, *J* = 1.8 Hz), 7.26 (s, 1 H), 6.41 (d, 1 H, *J* = 2.1 Hz), 6.37-6.35 (m, 1 H), 4.67, 4.62 (d, 2 H, *J* = 15.8 Hz), 4.46 (d, 1 H, *J* = 7.2 Hz), 4.25-4.12 (m, 3 H), 2.06-1.83 (m, 2 H), 1.27 (t, 3 H, *J* = 7.2 Hz), 1.02 (t, 3 H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.3, 148.3, 143.5, 139.3, 110.8, 110.3, 108.4, 60.5, 58.3, 44.9, 25.2, 14.3, 10.4; HRMS (EI) *m/z* calcd for $C_{13}H_{18}N_2O_5S$ (M^+) 314.0936, found 314.0937.



5d

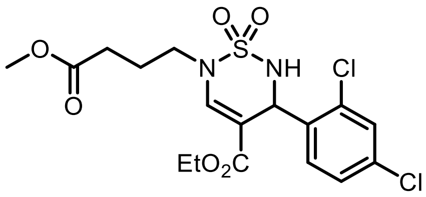
Ethyl 6-(pent-4-yn-1-yl)-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (5d). According to General Procedure B, **4a** (1.45 g, 5.12 mmol), 4-pentyn-1-ol (0.572 mL, 6.15 mmol), PPh_3 (1.46 g, 5.52 mmol), and DBAD (1.30 g, 5.55 mmol) in THF (30 mL) were stirred at rt for 5 h and provided a crude residue that was purified by chromatography on

SiO_2 (1:9 to 1:1; EtOAc:hexanes) to give **5d** (1.033 g, 58%) as a colorless oil: IR (ATR) 3439, 3282, 1685, 1618, 1165, 1034 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50 (d, 1 H, *J* = 0.9 Hz), 7.38-7.30 (m, 5 H), 5.55 (d, 1 H, *J* = 8.5 Hz), 4.55 (d, 1 H, *J* = 8.5 Hz), 4.03, 3.96 (dq, 2 H, *J* = 10.9, 7.2 Hz), 3.73 (dt, 2 H, *J* = 14.5, 7.1 Hz), 2.34 (td, 2 H, *J* = 6.8, 2.7 Hz), 2.06 (t, 1 H, *J* = 2.7 Hz), 1.97 (quint., 2 H, *J* = 6.9 Hz), 1.00 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.2, 142.3, 138.3, 128.9, 128.7, 127.6, 106.7, 82.6, 70.2, 60.5, 59.8, 49.2, 28.1, 15.6, 14.0; HRMS (ESI$^+$) *m/z* calcd for $C_{17}H_{21}N_2O_4S$ [M+H] 349.1222, found 349.1243 (note: error >5 ppm).



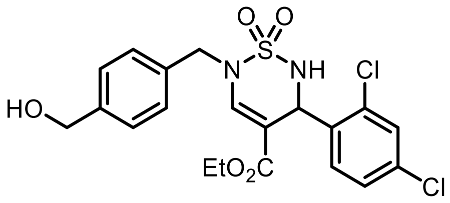
5e

Ethyl 6-ethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (5e). According to General Procedure B, **4a** (0.871 g, 3.09 mmol), ethanol (0.213 mL, 3.70 mmol), PPh_3 (0.984 g, 3.72 mmol), and DBAD (0.853 g, 3.63 mmol) in THF (20 mL) were stirred at rt for 4.5 h and provided a crude residue that was purified by chromatography on SiO_2 (15:85 to 3:7; EtOAc:hexanes) to give **5e** (0.723 g, 75%) as a colorless solid: Mp 99-101°C (CH_2Cl_2); IR (ATR) 3197, 1661, 1609, 1171 cm^{-1}; ^{1}H NMR (acetone-*d6*, 400 MHz) δ 7.63 (s, 1 H), 7.39-7.35 (m, 2 H), 7.34-7.23 (m, 3 H), 6.95 (d, 1 H, *J* = 7.6 Hz), 5.55 (d, 1 H, *J* = 7.7 Hz), 4.03, 3.97 (dq, 2 H, *J* = 10.8, 7.1 Hz), 3.73, 3.68 (dq, 2 H, *J* = 14.5, 7.2 Hz), 1.32 (t, 3 H, *J* = 7.2 Hz), 1.03 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR (acetone-*d6*, 100 MHz) δ 165.8, 142.6, 139.9, 129.0, 128.8, 128.4, 106.3, 60.4, 59.5, 45.6, 15.6, 14.4; HRMS (ESI$^+$) *m/z* calcd for $C_{14}H_{19}N_2O_4S$ [M+H]$^+$ 311.1066, found 311.1069.



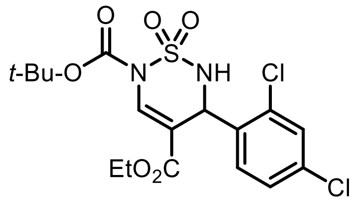
5g

Ethyl 3-(2,4-dichlorophenyl)-6-(4-methoxy-4-oxobutyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (5g). To a solution of **4d** (3.15 g, 8.96 mmol) in THF (55 mL) was added methyl 4-hydroxybutanoate (1.00 mL, 8.96 mmol). PPh_3 (2.37 g, 8.96 mmol) and DBAD (2.08 g, 8.96 mmol) were sequentially added at 0 °C. The reaction mixture was warmed to rt, stirred for 15 h, and quenched with H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (150 mL), concentrated, and purified by column chromatography on SiO_2 (2:3, EtOAc:hexanes, followed by 3:7, acetone:hexanes) to afford **5g** (4.04 g, 53%) as a sticky clear foam: IR (ATR) 3197, 3064, 2953, 1725, 1664, 1626, 1589, 759 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (bs, 1 H), 7.43 (d, 1 H, *J* = 2 Hz), 7.28 (d, 1 H), 7.2 (dd, 1 H, *J* = 2, 9 Hz), 5.9 (d, 1 H, *J* = 8 Hz), 4.91 (d, 1 H, *J* = 8 Hz), 4.07 (dq, 2 H, *J* = 4.0, 7.2 Hz), 3.70 (app bs, 3 H), 3.68 (dt, 2 H, *J* = 3, 6.8 Hz), 2.46 (t, 2 H, *J* = 7 Hz), 2.09 (dquint, 2 H, *J* = 6.8, 7.0 Hz), 1.09 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 164.9, 142.4, 134.9, 134.6, 133.8, 130.6, 129.7, 127.0, 104.6, 60.1, 55.6, 52.0, 49.5, 30.7, 24.8, 14.1; HRMS (ESI$^+$) *m/z* calcd for $C_{17}H_{21}O_6N_2Cl_2S$ [M+H]$^+$ 451.0492, found 451.0493. LCMS-ELSD purity 100%.



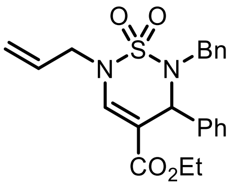
5h

Ethyl 3-(2,4-dichlorophenyl)-6-(4-(hydroxymethyl)benzyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (5h). In a 500-mL 3-neck flask equipped with a N_2 inlet, septum, and a N_2-sparge needle, thiadiazine **4d** (1.02 g, 2.90 mmol), THF (16.0 mL), and 1,4-benzenedimethanol (0.398 g, 2.88 mmol) were added. The reaction mixture was sparged with N_2 and cooled to 0 °C. After 5 min, PPh_3 (0.748 g, 2.85 mmol) was added, followed by a portionwise addition of DBAD (0.671 g, 2.91 mmol). After 30 min, the reaction was warmed to rt, and the N_2-sparge line was removed. The reaction mixture was stirred for 20 h and was treated with water (40 mL), transferred to a separatory funnel, and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (100% hexanes to 1:1; EtOAc:hexanes) afforded a mixture of the alkylated product and 1,4-benzenedimethanol. The mixture was dissolved in acetone (4 mL) and triturated with hexanes (20 mL), and the white precipitate was filtered under vacuum to afford **5h** (0.714 g, 52%) as a white solid: Mp 75-77 °C; IR (ATR, CH_2Cl_2) 3467, 3074, 1686, 1625, 1270, 1174 cm^{-1}; ^1H NMR (500 MHz; DMSO-d_6) δ 8.70 (d, 1 H, *J* = 7.2 Hz) 7.73 (s, 1 H), 7.64 (d, 1 H, *J* = 2.15 Hz), 7.38 (dd, 1 H, *J* = 8.4, 2.1 Hz) 7.36-7.33 (m, 4 H), 7.21 (d, 1 H, *J* = 8.4 Hz), 5.62 (d, 1 H, *J* = 7.2 Hz), 5.20 (t, 1 H, *J* = 5.7 Hz), 4.86 (d, 1 H, *J* = 15.7 Hz), 4.78 (d, 1 H, *J* = 15.7 Hz), 4.50 (d, 2 H, *J* = 5.7 Hz), 4.02-3.91 (m, 2 H), 1.01 (t, 3 H, *J* = 7.05 Hz); ^{13}C NMR (126 MHz; DMSO-d_6) δ 164.4, 142.9, 142.3, 134.7, 134.6, 133.9, 133.2, 131.3, 128.8, 127.7, 126.75, 126.71, 102.5, 62.6, 59.9, 53.9, 51.4, 14.0; HRMS (ESI$^+$) m/z calcd for $C_{20}H_{21}O_5N_2Cl_2S$ [M+H]$^+$ 471.0543, found 471.0547; LCMS-220 nm purity 100%.



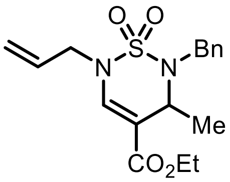
5i

2-(*tert*-Butyl) 4-ethyl 5-(2,4-dichlorophenyl)-5,6-dihydro-2*H*-1,2,6-thiadiazine-2,4-dicarboxylate 1,1-dioxide (5i). A solution of compound **4d** (5.06 g, 14.4 mmol) in acetonitrile (120 mL) was treated with K_2CO_3 (4.45 g, 13.2 mmol). After stirring at rt for 25 min, Boc_2O (2.8 g, 13.0 mmol) was added and the reaction mixture was stirred for 7 h. The mixture was treated with water (300 mL), transferred to a separatory funnel, and extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography on SiO_2 (100% hexanes to 1:1; EtOAc:hexanes) to afford **5i** (5.08 g, 86%) as a white solid: Mp 56-58 °C (dec); IR (ATR, CH_2Cl_2) 3246, 2985, 1745, 1709, 1372, 1254, 1141 cm^{-1}; ^{1}H NMR (500 MHz; DMSO-d_6) δ 9.36 (d, 1 H, J = 5.5 Hz), 8.07 (d, 1 H, J = 0.6 Hz), 7.69 (d, 1 H, J = 2.2 Hz), 7.38 (dd, 1 H, J = 8.4, 2.2 Hz), 7.27 (d, 1 H, J = 8.4 Hz), 5.59 (d, 1 H, J = 5.2 Hz), 4.12-4.01 (m, 2 H), 1.52 (m, 9 H), 1.09 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (126 MHz; DMSO-d_6) δ 163.7, 147.5, 135.9, 133.9, 133.7, 133.3, 131.4, 128.9, 127.0, 108.2, 86.1, 60.7, 53.1, 27.4, 13.8; HRMS (ESI$^-$) m/z calcd for $C_{17}H_{19}O_6N_2Cl_2S$ [M-H]$^-$ 449.0335, found 449.0333.



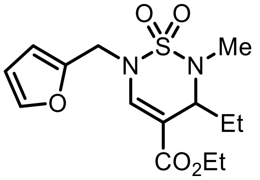
6a

Ethyl 6-allyl-2-benzyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (6a). To a suspension of NaH (0.022 g, 0.92 mmol) in THF (4.0 mL) cooled to 0 °C was added thiadiazine **5a** (0.071 g, 0.22 mmol). The reaction mixture was stirred for 30 min at 0 °C, treated with benzyl bromide (0.0560 g, 0.330 mmol), warmed to rt, stirred for 30 min, and treated with TBAI (0.0053 g, 0.022 mmol). The reaction mixture was stirred for an additional 10 min, quenched with sat. aq. NH_4Cl (3 mL), and diluted with EtOAc (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 7 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (1:9 to 4:6; EtOAc:hexanes) to give **6a** (0.061 g, 68%) as a colorless oil: IR (KBr) 1701, 1263, 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.55 (s, 1 H), 7.50-7.44 (m, 4 H), 7.43-7.41 (m, 1 H), 7.23-7.20 (m, 3 H), 7.04-7.02 (m, 2 H), 5.96-5.91 (m, 1 H), 5.45-5.37 (m, 3 H), 4.83 (d, 1 H, *J* = 13.2 Hz), 4.26-4.12 (m, 4 H), 3.73 (d, 1 H, *J* = 13 Hz), 1.14 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.9, 140.6, 138.0, 134.6, 132.0, 129.7, 129.0, 128.7, 127.8, 127.6, 127.5, 120.4, 102.4, 61.8, 60.6, 55.4, 51.9, 14.2; MS (ESI$^+$) *m/z* 435 [M+Na]$^+$; HRMS (ESI$^+$) *m/z* calcd for $C_{22}H_{24}N_2O_4NaS$ [M+Na]$^+$ 435.1354, found 435.1352.



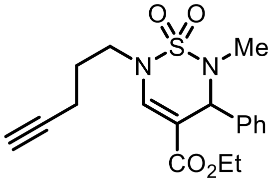
6b

Ethyl 6-allyl-2-benzyl-3-methyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (6b). To a suspension of NaH (0.023 g, 0.96 mmol) in THF (4.0 mL) cooled to 0 °C was added thiadiazine **5b** (0.061 g, 0.24 mmol). The reaction mixture was stirred for 30 min at 0 °C, treated with benzyl bromide (0.060 g, 0.35 mmol), warmed to rt, stirred for 30 min, and treated with NH_4I (0.0035 g, 0.024 mmol). The reaction mixture was stirred for an additional 10 min, quenched with sat. aq. NH_4Cl (3 mL), and diluted with EtOAc (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 7 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (1:9 to 4:6; EtOAc:hexanes) to give **6b** (0.058 g, 71%) as a colorless oil: IR (KBr) 1698, 1265, 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.39-7.32 (m, 5 H), 7.20 (s, 1 H), 5.92-5.88 (m, 1 H), 5.41 (d, 1 H, *J* = 17.4 Hz), 5.36 (d, 1 H, *J* = 10.2 Hz), 4.70 (d, 1 H, *J* = 14.4 H), 4.25 (q, 1 H, *J* = 7.2 Hz), 4.22-4.13 (m, 4 H), 3.69 (d, 1 H, *J* = 14.4 Hz), 1.53 (d, 3 H, *J* = 7.2 Hz), 1.26 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.6, 138.6, 134.9, 132.1, 128.8, 128.5, 128.2, 120.2, 106.3, 60.5, 56.9, 55.3, 51.6, 20.2, 14.3; MS (ESI$^+$) m/z 350 (M$^+$); HRMS (EI$^+$) *m/z* calcd for $C_{17}H_{22}N_2O_4S$ [M$^+$] 350.1300, found 350.1308.



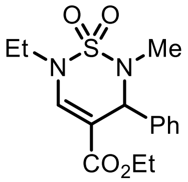
6c

Ethyl 3-ethyl-6-(furan-2-ylmethyl)-2-methyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (6c). To a suspension of thiadiazine **5c** (0.029 g, 0.090 mmol) and K_2CO_3 (0.037 g, 0.27 mmol) in CH_3CN (2 ml) was added iodomethane (0.015 ml, 0.23 mmol). The reaction mixture was stirred at rt for 16 h and diluted with EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give **6c** (0.027 g 91%) as a colorless oil: IR (ATR) 2976, 1694, 1623, 1366, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (dd, 1 H, *J* = 1.8, 0.6 Hz), 7.29 (s, 1 H), 6.42 (dd, 1 H, *J* = 3.0, 0.6 Hz), 6.37 (dd, 1 H, *J* = 3.3, 1.8 Hz), 4.74 (d, 1 H, *J* = 15.9 Hz), 4.59 (d, 1 H, *J* = 15.9 Hz), 4.19 (q, 2 H, *J* = 6.9 Hz), 3.95 (dd, 1 H, 11.4, 4.2 Hz), 2.71 (s, 3 H), 2.17-2.06 (m, 1 H), 1.90-1.81 (m, 1 H), 1.29 (t, 3 H, *J* = 7.2 Hz), 1.04 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.8, 148.7, 143.3, 138.1, 110.7, 110.0, 105.6, 67.1, 60.4, 45.3, 40.4, 25.9, 14.2, 10.6; HRMS (EI) *m/z* calcd for $C_{14}H_{20}N_2O_5S$ [M$^+$] 328.1093, found 328.1090.



6d

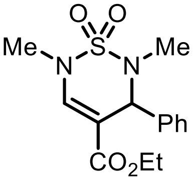
Ethyl 2-methyl-6-(pent-4-yn-1-yl)-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (6d). To a suspension of thiadiazine **5d** (1.01 g, 2.90 mmol) and K_2CO_3 (1.21 g, 8.74 mmol) in MeCN (14 mL) was added iodomethane (0.450 mL, 7.23 mmol) over 5 min. The solution was stirred at rt for 3.5 h. The reaction mixture was diluted with water (25 mL) and EtOAc (25 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with sat. aq. Na_2SO_3 (1 x 20 mL), sat. aq. $NaHCO_3$ (1 x 20 mL), and brine (1 x 20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by chromatography on SiO_2 (1:9 to 2:8; EtOAc:hexanes) to give **6d** (1.03 g, 98%) as a colorless oil: IR (ATR) 3286, 1692, 1622, 1366, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.57 (s, 1 H), 7.33-7.26 (m, 5 H), 5.46 (s, 1 H), 4.16, 4.10 (dq, 2 H, *J* = 10.9, 7.2 Hz), 3.77, 3.70 (dt, 2 H, = 14.7, 6.3 Hz), 2.90 (s, 3 H), 2.32 (dt, 2 H, *J* = 6.7, 2.6 Hz), 2.07 (t, 1 H, *J* = 2.4 Hz), 2.01-1.88 (m, 2 H), 1.15 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.0, 141.3, 138.0, 128.1, 128.0, 127.8, 102.2, 82.4, 70.2, 66.4, 60.7, 49.5, 39.6, 28.5, 15.5, 14.3; HRMS (ESI^+) *m/z* calcd for $C_{18}H_{23}N_2O_4S$ $[M+H]^+$ 363.1379, found 363.1400 (note: error >5 ppm).



6e

Ethyl 6-ethyl-2-methyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (6e). To a suspension of thiadiazine **5e** (0.741 g, 2.39 mmol) and K_2CO_3 (1.01 g, 7.27 mmol) in MeCN (24 mL) was added iodomethane (0.372 mL, 5.98 mmol). The reaction mixture was stirred at rt for 2.5 h, then diluted with water (20 mL) and EtOAc (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with sat. aq. Na_2SO_3 (1 x 15 mL) and brine (1 x 15 mL), dried

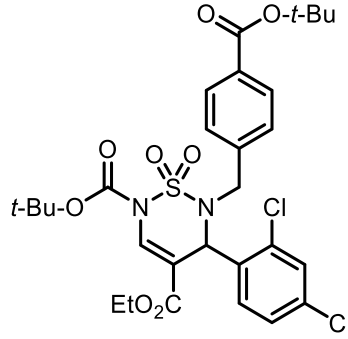
(Na_2SO_4), decanted, and concentrated under reduced pressure to give a yellow crude oil. The crude oil was purified by chromatography on SiO_2 (15:85 to 2:8; EtOAc:hexanes) to give the dialkylated thiadiazine **6e** (0.782 g, 100%) as a light yellow viscous oil: IR (ATR) 2977, 1692, 1141, 1038 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 7.70 (s, 1 H), 7.34-7.17 (m, 5 H), 5.52 (s, 1 H), 4.10, 4.06 (dq, 2 H, *J* = 10.8, 7.1 Hz), 3.73 (q, 2 H, *J* = 7.2 Hz), 2.95 (s, 3 H), 1.32 (t, 3 H, *J* = 7.2 Hz), 1.12 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR (acetone-d_6, 100 MHz) δ 166.3, 141.6, 140.0, 128.8, 128.4, 128.1, 102.7, 67.0, 60.7, 46.0, 40.1, 15.8, 14.5; HRMS (ESI$^+$) *m/z* calcd for $C_{15}H_{21}N_2O_4S$ $[M+H]^+$ 325.1222, found 325.1236.



6f

Ethyl 2,6-dimethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (6f). To a suspension of thiadiazine **4a** (2.39 g, 8.47 mmol) and K_2CO_3 (7.00 g, 50.7 mmol) in MeCN (40 mL) was added iodomethane (2.65 mL, 42.6 mmol). The reaction mixture was stirred at rt for 2.25 h, then diluted with water (50 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with sat. aq. Na_2SO_3 (1 x 25 mL), sat. aq. $NaHCO_3$ (1 x 25 mL), and brine (1 x 25 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light yellow sticky oil. The crude oil was purified by chromatography on SiO_2 (1:9 to 2:8; EtOAc:hexanes) to give **6f** (2.620 g, 100%) as a light yellow oil: IR (ATR) 2977, 2932, 1691, 1366 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.45 (s, 1 H), 7.34-7.25 (m, 5 H), 5.46 (s, 1 H), 4.15, 4.11 (dq, 2 H, *J* = 10.9, 7.1 Hz), 3.28 (s, 3 H), 2.93 (s, 3 H), 1.15 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR

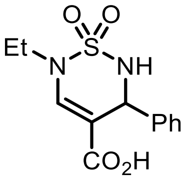
($CDCl_3$, 100 MHz) δ 166.0, 142.1, 138.0, 128.1, 128.0, 127.8, 102.4, 66.4, 60.7, 39.8, 36.8, 14.3; HRMS (ESI$^+$) *m/z* calcd for $C_{14}H_{19}N_2O_4S$ $[M+H]^+$ 311.1060, found 311.1050.



6i

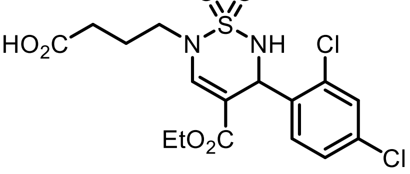
2-(*tert*-Butyl) 4-ethyl 6-(4-(*tert*-butoxycarbonyl)benzyl)-5-(2,4-dichlorophenyl)-5,6-dihydro-2*H*-1,2,6-thiadiazine-2,4-dicarboxylate 1,1-dioxide (6i). To a suspension of **5i** (4.43 g, 9.81 mmol) and K_2CO_3 (7.49 g, 54.2 mmol) in MeCN (125 mL) was added the bromide (2.80 g, 10.3 mmol). The reaction mixture was stirred at rt for 2 h, diluted with water (150 mL)/brine (150 mL) and EtOAc (200 mL). The layers were transferred to a separatory funnel and separated. The aqueous layer was extracted with EtOAc (2 x 300 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (100% hexanes to 1:5; EtOAc:hexanes) afforded **6i** (5.00 g, 79%) as a white solid: Mp 99-102 °C; IR (ATR, CH_2Cl_2) 2981, 1746, 1709, 1396, 1242, 1142 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.933 (d, 2 H, *J* = 8.2 Hz), 7.927 (s, 1 H), 7.45 (d, 2 H, *J* = 8.2 Hz), 7.37 (s, 1 H), 7.16-7.14 (m, 2 H), 5.77 (s, 1 H), 4.75 (d, 1 H, *J* = 14.8 Hz), 4.61 (d, 1 H, *J* = 14.8 H), 4.20-4.01 (m, 2 H), 1.60 (s, 9 H), 1.59 (s, 9 H), 1.16 (t,3 H, *J* = 7.1 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 165.3, 164.2, 148.0, 138.1, 136.1, 135.3, 134.9, 133.0, 132.5, 131.4, 129.7, 129.65, 129.61, 126.8, 107.3, 87.1, 81.5, 61.3, 60.2, 57.4, 28.3, 28.0, 14.3;

HRMS (ESI$^+$) m/z calcd for $C_{29}H_{35}O_8N_2Cl_2S$ [M+H]$^+$ 641.1486, found 641.1513; LCMS-220 nm purity 100%.



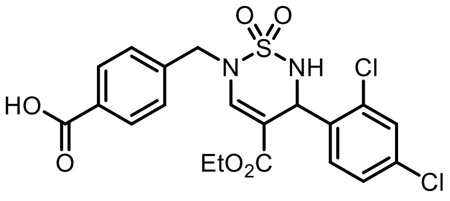
7e

6-Ethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylic acid 1,1-dioxide (7e). To a suspension of ester **5e** (0.250 g, 0.805 mmol) in EtOH (1.0 mL) was added in one portion 2 M KOH (4.0 mL, 8.0 mmol). The reaction mixture was stirred at 80 °C for 4 h then cooled to rt, diluted with EtOAc (5 mL), and acidified with 5 M HCl (~ 2 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried (Na_2SO_4), decanted, and concentrated under reduced pressure to give acid **7e** (0.222 g, 98%) as a yellow-orange solid: Mp 170-175 °C (dec, CH_2Cl_2); IR (ATR) 3245, 2922, 1661, 1152 cm^{-1}; ^{1}H NMR (acetone-d$_6$, 400 MHz) δ 10.53 (bs, 1 H), 7.66 (s, 1 H), 7.40-7.37 (m, 2 H), 7.32-7.22 (m, 3 H), 7.01 (d, 1 H, *J* = 7.5 Hz), 5.56 (d, 1 H, *J* = 7.5 Hz), 3.74, 3.69 (dq, 2 H, *J* = 14.4, 7.1 Hz), 1.33 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (acetone-d$_6$, 100 MHz) δ 167.0, 143.1, 139.9, 129.0, 128.7, 128.3, 105.6, 59.2, 45.6, 15.6; HRMS (ESI$^-$) *m/z* calcd for $C_{12}H_{13}N_2O_4S$ [M-H]$^-$ 281.0596, found 281.0609.



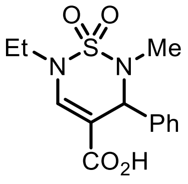
7g

4-(5-(2,4-Dichlorophenyl)-4-(ethoxycarbonyl)-1,1-dioxido-5,6-dihydro-2*H*-1,2,6-thiadiazin-2-yl)butanoic acid (7g). A solution of 5g (0.100 g, 0.222 mmol) in THF/MeOH (2 mL/2 mL) was treated with 6M NaOH (0.370 mL, 2.22 mmol). After stirring at room temperature for 2 h, the mixture was cooled to 0 oC and treated with sat. aq. KHSO4 (15 mL), pH ~2-3. The aqueous solution was transferred to a separatory funnel and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na2SO4), filtered, and concentrated, yielding **7g** (0.0977 g, quant.) as a white solid.: Mp 61 °C (dec.); IR (ATR, CH_2Cl_2) 3220, 2928, 1705, 1+626, 1354, 1173cm^{-1}; ^{1}H NMR (400 MHz; DMSO-d_6) δ 12.19 (s, 1 H), 8.61 (d, 1 H, J = 7.2 Hz), 7.74 (s, 1 H), 7.64 (d, 1 H, J = 2.1 Hz), 7.38 (dd, 1 H, J = 8.4, 2.1 Hz), 7.23 (d, 1 H, J = 8.4 Hz), 5.60 (d, 1 H, J = 7.2 Hz), 4.06-3.93 (m, 2 H), 3.65 (t, 2 H, J = 7.3 Hz), 2.31 (t, 2 H, J = 7.4 Hz), 1.89-1.82 (m, 2 H), 1.05 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (100 MHz; DMSO-d_6) δ 173.8, 164.5, 143.3, 134.7, 133.9, 133.2, 131.3, 128.7, 126.7, 102.1, 59.8, 53.8, 48.6, 30.2, 24.9, 14.1; HRMS (ESI$^+$) m/z calcd for $C_{16}H_{19}O_6N_2Cl_2S$ [M+H]$^+$ 437.0335, found 437.0315.



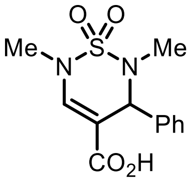
7h

4-((5-(2,4-Dichlorophenyl)-4-(ethoxycarbonyl)-1,1-dioxido-5,6-dihydro-2*H*-1,2,6-thiadiazin-2-yl)methyl)benzoic acid (7h). A 0 °C solution of **5h** (2.39 g, 5.07 mmol) in acetone (18 mL) was treated with dropwise addition of the Jones Reagent (2.5 M, 5.00 mL, 12.5 mmol). The reaction mixture was stirred at 0 °C for 1.5 h. The dark/brown solution was quenched with a small amount of iPrOH (6 mL) and the reaction mixture was stirred for 5 min. The blue mixture was treated with water (60 mL) and extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4), filtered, and concentrated to yield **7h**(2.32 g, 94%) as a white solid: Mp 101-104 °C; IR (ATR, CH_2Cl_2) 3183, 2983, 1687, 1614, 1270, 1175 cm^{-1}; ^1H NMR (300 MHz; DMSO-*d*$_6$) δ 12.99 (s, 1 H), 8.76 (d, 1 H, *J* = 7.2 Hz), 7.97 (d, 2 H, *J* = 8.3 Hz), 7.81 (s, 1 H), 7.65 (d, 1 H, *J* = 2.2 Hz), 7.51 (d, 2 H, *J* = 8.3 Hz), 7.40 (dd, 1 H, *J* = 8.4, 2.2 Hz), 7.25 (d, 1 H, *J* = 8.4 Hz), 5.64 (d, 1 H, *J* = 7.1 Hz), 4.99 (d, 1 H, *J* = 16.4 Hz), 4.91 (d, 1 H, *J* = 16.5 Hz), 4.06-3.90 (m, 2 H), 1.02 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR (75 MHz; DMSO-*d*$_6$) δ 167.1, 164.3, 143.2, 141.5, 134.6, 133.9, 133.3, 131.3, 130.3, 129.6, 128.8, 127.8, 126.8, 102.8, 60.0, 53.9, 51.4, 14.0; HRMS (ESI^+) m/z calcd for $C_{20}H_{19}O_6N_2Cl_2S$ $[M+H]^+$ 485.0335, found 485.0360; LCMS-220 nm purity 100%.



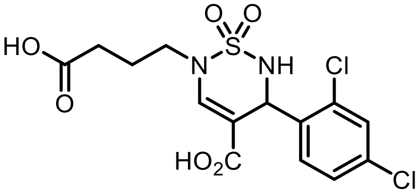
8e

6-Ethyl-2-methyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylic acid 1,1-dioxide (8e). To a solution of dialkylated thiadiazine **6e** (2.69 g, 8.29 mmol) in EtOH (10 mL) was added in one portion 2 M KOH (43 mL, 85 mmol). The reaction mixture was warmed to 90 °C and stirred for 5 h, cooled to rt, diluted with EtOAc (50 mL), cooled to 0 °C, and acidified with 5 M HCl (~ 17 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (1 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), decanted, and concentrated under reduced pressure. The crude product contained AcOH that was removed by evaporating with hexanes and $CHCl_3$ to give the acid **8e** (2.06 g, 84%) as a light yellow powder: Mp 157-159 °C (dec, CH_2Cl_2); IR (ATR) 2969, 2563, 1668, 1655, 1169, 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 10.96 (bs, 1 H), 7.63 (s, 1 H), 7.37-7.26 (m, 5 H), 5.41 (s, 1 H), 3.62 (q, 2 H, *J* = 7.2 Hz), 2.91 (s, 3 H), 1.33 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 142.9, 137.8, 128.1, 128.0, 127.7, 100.1, 66.1, 45.9, 40.1, 15.5; MS (ESI$^-$) *m/z* 295 ([M-1]$^-$, 100), 231 (-SO_2, 85); HRMS (ESI$^-$) *m/z* calcd for $C_{13}H_{15}N_2O_4S$ [M-H]$^-$ 295.0753, found 295.0795 (note: error >5 ppm).



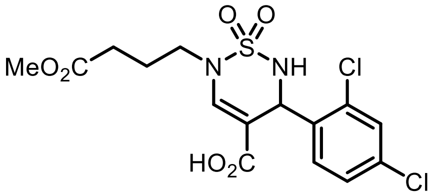
8f

2,6-Dimethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylic acid 1,1-dioxide (8f). To a solution of thiadiazine **6f** (2.59 g, 8.34 mmol) in EtOH (10 mL) was added in one portion 2 M KOH (41.5 mL, 83.0 mmol). The reaction mixture was heated to 75 °C and stirred for 3.5 h. The reaction mixture was cooled to rt, diluted with water (10 mL), and acidified with conc. aq. HCl (~5 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude oil was placed under high vacuum for 6 h to give the desired acid **8f** (2.06 g, 88%) as a light yellow solid: Mp 158-161 °C (dec, Et_2O); IR (ATR) 3062, 2951, 2626, 2561, 1663, 1279, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.70 (bs, 1 H), 7.56 (s, 1 H), 7.37-7.27 (m, 5 H), 5.42 (s, 1 H), 3.26 (s, 1 H), 2.95 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6, 144.4, 137.7, 128.2, 127.7, 100.2, 66.1, 40.3, 37.0; HRMS (ESI$^-$) *m/z* calcd for $C_{12}H_{13}N_2O_4S$ [M-H]$^-$ 281.0596, found 281.0632.



9g

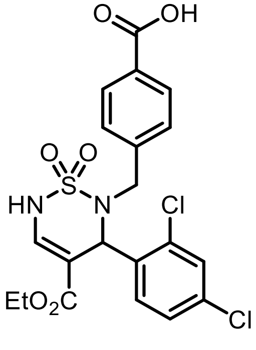
6-(3-Carboxypropyl)-3-(2,4-dichlorophenyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylic acid 1,1-dioxide (9g). To a solution of **5g** (0.231 g, 0.514 mmol) in EtOH (2.6mL) was added 2M KOH (3.6 mL, 7.2 mmol) in one portion. The solution was stirred at 80-85 °C for 5 h. Upon completion, the solution was cooled to rt, diluted with EtOAc, and acidified with 5M HCl. The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (15), dried (Na_2SO_4), and concentrated to afford **9g** (0.110 g, 52%) as an off-white solid: Mp 193-196 °C; IR (ATR) 3168 1718 1660 1631 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-*d₆*) δ 12.2 (bs, 2 H), 8.55 (bs, 1 H), 7.69 (s, 1 H), 7.62 (d, 1 H, *J* = 2.5 Hz), 7.38 (dd, 1 H, *J* = 8.5, 2.5 Hz), 7.24 (d, 1 H, *J* = 8.5 Hz), 5.55 (s, 1 H), 3.63 (t, 2 H, *J* = 7.5 Hz), 2.40 (t, 2 H, *J* = 7.5 Hz), 1.85 (dquint, 2 H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-*d₆*) δ 173.8, 166.1, 143.0, 135.0, 133.9, 133.1, 131.4, 128.7, 126.7, 102.7, 53.8, 48.5, 30.2, 24.8; HRMS (ESI$^+$) m/z calcd for $C_{14}H_{15}Cl_2N_2O_6S$ $[M+H]^+$ 409.0023, found 409.0020. LCMS-ELSD purity 100%.



10g

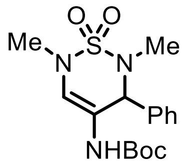
3-(2,4-Dichlorophenyl)-6-(4-methoxy-4-oxobutyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylic acid 1,1-dioxide (10g). A solution of compound **9g** (0.102 g, 0.249 mmol) in MeOH

(3.5 mL) was treated with 0.2 mL of a H_2SO_4/MeOH (0.1 mL/25 mL) solution. The reaction mixture was stirred for 6 h at 50 °C. Analysis by LCMS indicated >95 % conversion to the methyl ester. The mixture was treated with brine (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated to give **10g** (0.0981 g, 93%) as an off-white solid: Mp 188-191 °C; IR (ATR, CH_2Cl_2) 3162, 3129, 1720, 1674, 1609, 1354, 1169 cm^{-1}; ^{1}H NMR (500 MHz; DMSO-*d*$_6$) δ 12.27 (bs, 1 H), 8.55 (d, 1 H, *J* = 6.9 Hz), 7.70 (s, 1 H), 7.62 (d, 1 H, *J* = 2.1 Hz), 7.38 (dd, 1 H, *J* = 8.4, 2.1 Hz), 7.23 (d, 1 H, *J* = 8.4 Hz), 5.55 (d, 1 H, *J* = 6.4 Hz), 3.63 (t, 2 H, *J* = 7.5 Hz), 3.61 (s, 3 H), 2.40 (t, 2 H, *J* = 7.6 Hz), 1.93-1.84 (m, 2 H); ^{13}C NMR (126 MHz; DMSO-*d*$_6$) δ 172.7, 166.1, 143.0, 134.9, 133.9, 133.1, 131.4, 128.7, 126.6, 102.7, 53.8, 51.4, 48.4, 29.9, 24.7; HRMS (ESI$^+$) *m/z* calcd for $C_{15}H_{17}O_6N_2Cl_2S$ [M+H]$^+$ 423.0179, found 423.0177; LCMS-ELSD purity 100%.



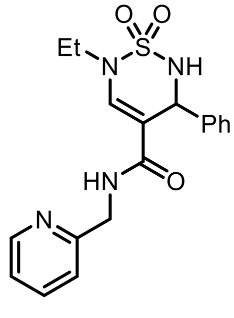
10i

4-((3-(2,4-Dichlorophenyl)-4-(ethoxycarbonyl)-1,1-dioxido-3,6-dihydro-2*H*-1,2,6-thiadiazin-2-yl)methyl)benzoic acid (10i). A solution of compound **6i** (4.80 g, 7.48 mmol) in CH_2Cl_2 (25 mL) was treated with TFA (11.1 mL, 150 mmol), and the reaction mixture was stirred at rt under N_2. After 1.5 h, TLC (2:1; CH_2Cl_2:EtOAc) indicated reaction completion. The reaction mixture was treated with water (~80 mL), and the precipitate was filtered in vacuo to give **10i** (3.56 g, 98%) as a white solid: Mp 213-215 °C; IR (ATR, CH_2Cl_2) 3185, 1287, 1662, 1634, 1286, 1166 cm-1; ^1H NMR (500 MHz; DMSO-d_6) δ 12.99 (s, 1 H), 11.42 (s, 1 H), 7.91 (d, 2 H, *J* = 8.1 Hz), 7.54-7.51(m, 4 H), 7.33 (dd, 1 H, *J* = 8.5, 2.1 Hz), 7.20 (d, 1 H, *J* = 8.5 Hz), 5.64 (s, 1 H), 4.55 (d, 1 H, *J* = 15.1 Hz), 4.37 (d, 1 H, *J* = 15.1 Hz), 4.06-3.94 (m, 2 H), 1.07 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR (126MHz; DMSO-d_6) δ 167.1, 164.5, 140.3, 139.1, 134.8, 133.9, 133.2, 132.3, 130.2, 129.5, 129.0, 128.5, 126.4, 99.9, 61.3, 59.9, 55.5, 14.0; HRMS (ESI$^+$) m/z calcd for $C_{20}H_{19}O_6N_2Cl_2S$ $[M+H]^+$ 485.0335, found 485.0357; LCMS-220 nm purity 100%.



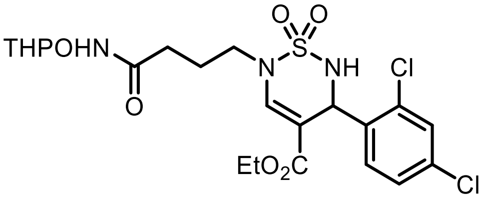
11f

tert-Butyl (2,6-dimethyl-1,1-dioxido-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazin-4-yl)carbamate (11f). To a suspension of dimethyl thiadiazine carboxylate **8f** (0.0770 g, 0.273 mmol) in toluene (0.6 mL) was added TEA (0.0840 mL, 0.598 mmol). The reaction mixture was degassed by FPT (3 x), backfilled with Ar, and treated with DPPA (0.0640 mL, 0.297 mmol). The reaction mixture was stirred at rt for 2 h, and heated to 95 °C for 1 h (during which time bubbling occurred for 30 min then stopped). The mixture was then cooled to rt, treated with *t*-BuOH (0.200 mL, 2.10 mmol) and heated to 100 °C for 3 h. The reaction mixture was cooled to rt, diluted with EtOAc (5 mL) and washed with 1 M NaOH (1 x 5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified by chromatography on SiO_2 (1:9 to 2:8; EtOAc:hexanes), dissolved in $CHCl_3$ and concentrated under reduced pressure (3 x) to remove trace EtOAc to give *N*-Boc amine **11f** (21.5 mg, 22%) as a colorless solid: Mp 125-127 °C ($CHCl_3$); IR (ATR) 3336, 2973, 1722 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.45-7.37 (m, 5 H), 6.69 (bs, 1 H), 5.08 (s, 1 H), 4.77 (s, 1 H), 3.10 (s, 3 H), 2.56 (s, 3 H), 1.36 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.9, 135.2, 129.6, 129.5, 129.3, 122.2, 119.3, 81.0, 68.7, 38.7, 34.8, 28.3; HRMS (ESI^+) *m/z* calcd for $C_{16}H_{23}N_3O_4SNa$ $[M+Na]^+$ 376.1307, found 376.1346 (note: error >5 ppm).



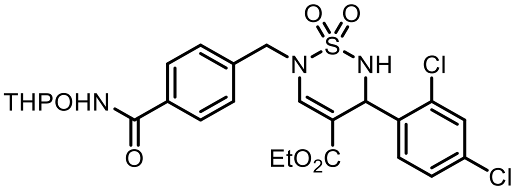
11e

6-Ethyl-3-phenyl-*N*-(pyridin-2-ylmethyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxamide 1,1-dioxide (11e). To a solution of monoalkylated thiadiazine **7e** (0.101 g, 0.357 mmol), 2-pyridylmethylamine (0.445 mL, 0.428 mmol), EDCI (0.0756 g, 0.394 mmol), and DMAP (0.0267 g, 0.219 mmol) in CH_2Cl_2 (0.5 mL) was added DIPEA (0.0445 mL, 0.432 mmol). The reaction mixture was sealed under Ar in a screw cap vial, stirred at rt for 15 h, quenched with sat. aq. NH_4Cl (2 mL), diluted with EtOAc (5 mL), and separated. The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 x 5 mL), water (1 x 5 mL), and brine (1 x 5 mL), dried (Na_2SO_4), decanted, and concentrated under reduced. The crude solid was purified by chromatography on SiO_2 (6:94; MeOH:CH_2Cl_2) to give amide **11e** (0.0950 g, 72%) as a colorless solid: Mp 157-158 °C ($CHCl_3$); IR (ATR) 3333, 3314, 3066, 1644, 1171 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 8.41 (ddd, 1 H, *J* = 4.8, 1.8, 0.9 Hz), 7.57 (td, 1 H, *J* = 7.6, 1.8 Hz), 7.53-7.48 (m, 1 H), 7.48-7.44 (m, 2 H), 7.41-7.40 (m, 1 H), 7.34-7.26 (m, 3 H), 7.15 (ddd, 1 H, *J* = 7.4, 4.8, 0.8 Hz), 6.98 (d, 1 H, *J* = 7.6 Hz), 6.92 (d, 1 H, *J* = 7.8 Hz), 5.77 (d, 1 H, *J* = 7.4 Hz), 4.45, 4.36 (dd, 2 H, *J* = 16.2, 5.7 Hz), 3.64, 3.59 (dq, 2 H, *J* = 10.9, 7.2 Hz), 1.30 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (acetone-d_6, 100 MHz) δ 166.5, 159.5, 149.6, 139.5, 137.8, 137.2, 129.4, 128.9, 128.7, 122.7, 121.7, 111.6, 59.7, 45.3, 45.2, 15.3; HRMS (ESI$^+$) *m/z* calcd for $C_{18}H_{21}N_4O_3S$ [M+H]$^+$ 373.1334, found 373.1348.



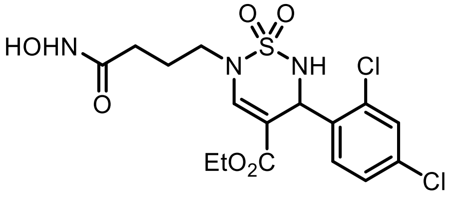
11g

Ethyl 3-(2,4-dichlorophenyl)-6-(4-oxo-4-(((tetrahydro-2*H*-pyran-2-yl)oxy)amino)butyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (11g). A solution of compound **7g** (0.500 g, 1.143 mmol) in CH_2Cl_2 (3 mL) was treated with O-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (0.411 g, 3.51 mmol). The reaction mixture was cooled to 0 °C and treated with T_3P (50% in EtOAc, 1.00 mL, 1.68 mmol) and TEA (0.480 mL, 3.44 mmol). The reaction mixture was warmed to rt, and stirred under N_2. After 14 h, the mixture was diluted with CH_2Cl_2 (10 mL), washed with 0.25 M HCl (10 mL), brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (100% hexanes to 100% EtOAc), afforded **11g** (0.470 g, 77%, dr ~ 1:1 based on ^{1}H NMR) as a white solid: ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.47 (s, 1 H), 8.40 (s, 1 H), 7.45-7.6 (m, 4 H), 7.37 (d, 1 H, *J* = 8.2 Hz), 7.29-7.26 (m, 1 H), 7.21-7.18 (m, 2 H), 6.30 (d, 1 H, *J* = 6.1 Hz), 5.89 (d, 1 H, *J* = 6.8 Hz), 5.85 (d, 1 H, *J* = 7.9 Hz), 5.82 (bs, 1 H), 5.00 (s, 2 H), 4.10-4.00 (m, 4 H), 4.00-3.95 (m, 1 H), 3.75-3.63 (m, 4 H), 3.63-3.54 (m, 2 H), 2.28-2.18 (m, 6 H), 2.14-2.04 (m, 2 H), 1.90-1.72 (m, 6 H), 1.52-1.47 (m, 3 H), 1.33-1.25 (m, 2 H), 1.12-1.08 (m, 6 H); HRMS (ESI$^-$) m/z calcd for $C_{21}H_{26}O_7N_3Cl_2S$ [M-H]$^-$ 534.0863, found 534.0859.



11h

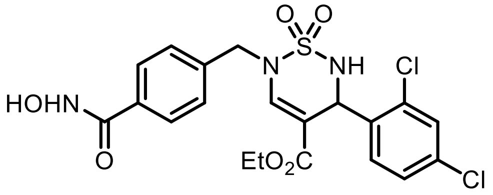
Ethyl 3-(2,4-dichlorophenyl)-6-(4-(((tetrahydro-2*H*-pyran-2-yl)oxy)carbamoyl)benzyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (11h). A solution of compound **7h** (1.80 g, 3.71 mmol) in CH_2Cl_2 (12 mL) was treated with O-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (1.24 g, 10.6 mmol). The mixture was cooled to 0 °C, and treated with T_3P (50%, 3.30 mL, 5.54 mmol) and TEA (1.60 mL, 11.5 mmol). The reaction mixture was warmed to rt, and stirred under N_2. After 4 h, the mixture was diluted with CH_2Cl_2 (150 mL), washed with 0.25 M HCl (100 mL), brine (100 mL), dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2(100% hexanes to 100% EtOAc), afforded **11h** (1.76 g, 81%, dr ~ 1:1 based on ^{1}H NMR) as a white solid: Mp 115-117°C (dec, hexanes); IR (ATR, CH_2Cl_2) 3183, 2949, 2871, 1627, 1269, 1176 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 9.35 (s, 1 H), 7.64 (app d, 2 H, *J* = 8.0 Hz), 7.63 (app d, 2 H, *J* = 7.9 Hz), 7.43 (app d, 2 H, *J* = 5.5 Hz), 7.41 (app d, 2 H, *J* = 2.1 Hz), 7.36 (app dd, 4 H, *J* = 8.2, 2.1 Hz), 7.24 (app dd, 2 H, *J* = 8.4, 1.5 Hz), 7.17 (app dd, 2 H, *J* = 8.4, 2.0 Hz), 6.24-6.20 (m, 2 H), 5.91 (app d, 2 H, *J* = 7.7 Hz), 5.02 (s, 2 H), 4.80 (d, 1 H, *J* = 15.9 Hz), 4.78 (d, 1 H, *J* = 15.8 Hz), 4.63 (d, 1 H, *J* = 15.8 Hz), 4.62 (d, 1 H, *J* = 15.9 H), 4.03-3.93 (m, 6 H), 3.65-3.63 (m, 2 H), 1.88-1.81 (m, 8 H), 1.66-1.57 (m, 2 H), 1.016 (t, 3 H, *J* = 7.1 Hz), 1.014 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR (500 MHz; $CDCl_3$) δ 165.7, 164.9, 141.96, 141.93, 139.47, 139.46, 135.0, 134.7, 133.8, 131.98, 131.97, 130.7, 129.7, 128.37, 128.35, 128.1, 127.0, 105.59, 105.56, 102.9, 62.95, 62.91, 55.5, 52.2, 52.1, 28.2, 25.1, 18.7, 14.1; HRMS (ESI$^-$) m/z calcd for $C_{25}H_{26}O_7N_3Cl_2S$ [M-H]$^-$ 582.0863, found 582.0860.



12g

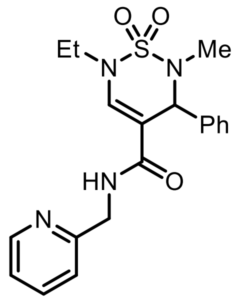
Ethyl 3-(2,4-dichlorophenyl)-6-(4-(hydroxyamino)-4-oxobutyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (12g). To a solution of **11g** (0.465 g, 0.867 mmol) in MeOH (5.0 mL) was added Amberlyst-15 (0.174 g, 818 mmol) at rt under N_2. After 21 h of stirring, the reaction mixture was filtered through Celite®. , rinsed with MeOH, and concentrated. Purification by chromatography on SiO_2* (100% EtOAc) afforded **12g** (0.206 g, 53%) as a white solid: Mp 76-78 °C; IR (ATR, CH_2Cl_2) 3190, 2985, 1622, 1349, 1167 cm-1; ^{1}H NMR (400 MHz; DMSO-*d*$_6$) δ 10.43 (s, 1 H), 8.74 (s, 1 H), 8.60 (d, 1 H, *J* = 6.4 Hz), 7.75 (s, 1 H), 7.64 (s, 1 H), 7.37 (d, 1 H, *J* = 8.4 Hz), 7.24 (d, 1 H, *J* = 8.4 Hz), 5.59 (d, 1 H, *J* = 5.9 Hz), 4.06-3.93 (m, 2 H), 3.70-3.57 (m, 2 H), 2.03 (t, 2 H, *J* = 7.6 Hz), 1.90-1.81 (m, 2 H), 1.05 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR (101 MHz; DMSO-*d*$_6$) δ 168.3, 164.5, 143.4, 134.8, 133.9, 133.2, 131.4, 128.7, 126.7, 102.1, 59.9, 53.8, 49.0, 28.9, 25.6, 14.1; HRMS (ESI$^+$) m/z calcd for $C_{16}H_{20}O_6N_3Cl_2S$ [M+H]$^+$ 452.0444, found 452.046; LCMS-220 nm purity 100%.

*The SiO_2 was washed with aqueous 6 M HCl until colorless, neutralized with distilled water, and dried in an oven at 80-100 °C prior to use.



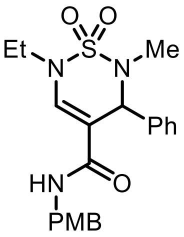
12h

Ethyl 3-(2,4-dichlorophenyl)-6-(4-(hydroxycarbamoyl)benzyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (12h). To a solution of **11h** (0.190 g, 0.325 mmol) in MeOH (5.0 mL) and CH_2Cl_2 (1.0 mL) was added Amberlyst-15 (0.0517 g, 253 mmol) at room temperature under N_2. After 17 h of stirring, the reaction mixture was filtered through Celite®, rinsed with MeOH, and concentrated. The residue was purified by trituration (4:1; hexanes:EtOAc) to afford **12h** (0.133 g, 82%) as a white solid: Mp 97 °C (dec); IR (ATR, CH_2Cl_2) 3188, 2862, 1627, 1265, 1175 cm^{-1}; ^1H NMR (500 MHz; DMSO-d_6) δ 11.24 (s, 1 H), 9.06 (s, 1 H), 8.76 (d, 1 H, J = 7.3 Hz), 7.79 (s, 1 H), 7.77 (d, 2 H, J = 8.2 Hz), 7.65 (d, 1 H, J = 2.2 Hz), 7.46 (d, 2 H, J = 8.3 Hz), 7.39 (dd, 1 H, J = 8.5, 2.1 Hz), 7.24 (d, 1 H, J = 8.5 Hz), 5.64 (d, 1 H, J = 7.2 Hz), 4.95 (d, 1 H, J = 16.3 Hz), 4.88 (d, 1 H, J = 16.3 Hz), 4.03-3.92 (m, 2 H), 1.02 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (126 MHz; DMSO-d_6) δ 164.4, 164.0, 143.2, 139.7, 134.7, 133.9, 133.3, 132.3, 131.3, 128.8, 127.7, 127.2, 126.8, 102.8, 60.0, 54.0, 51.4, 14.0; HRMS (ESI$^+$) m/z calcd for $C_{20}H_{20}O_6N_3Cl_2S$ [M+H]$^+$ 500.0444, found 500.0469; LCMS-220 nm purity 100%.



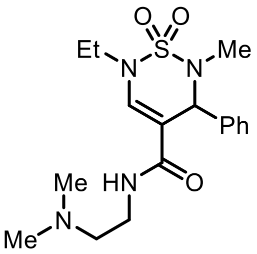
13e

6-Ethyl-2-methyl-3-phenyl-N-(pyridin-2-ylmethyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxamide 1,1-dioxide (13e). To a vial containing acid **8e** (0.0900 g, 0.304 mmol) in CH_2Cl_2 (0.85 mL) was added PyBOP (0.173 g, 0.333 mmol), 2-pyrididylmethylamine (34.0 µL, 0.330 mmol), and DIPEA (0.110 mL, 0.632 mmol). The reaction mixture was sealed under Ar and stirred for 23 h at rt. The reaction mixture was diluted with EtOAc (15 mL) and washed with sat. aq. NH_4Cl (1 x 10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by chromatography on SiO_2 (6:4; EtOAc:hexanes to 100% EtOAc) to give the amide **13e** (0.100 g, 85%) as a colorless foam: IR (ATR) 3307, 1638, 1357, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.34 (d, 1 H, *J* = 4.8 Hz), 7.59 (dt, 1 H, *J* = 7.7, 1.8 Hz), 7.42-7.40 (m, 3 H), 7.34-7.26 (m, 3 H), 7.15-7.09 (m, 2 H), 6.62 (bs, 1 H), 5.52 (s, 1 H), 4.51, 4.46 (dd, 2 H, *J* = 16.5, 4.7 Hz), 3.64 (dq, 2 H, *J* = 7.3, 1.8 Hz), 2.84 (s, 3 H), 1.35 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.9, 156.0, 148.9, 137.5, 136.8, 136.7, 128.9, 128.7, 128.5, 122.3, 122.0, 106.0, 66.5, 45.3, 44.6, 39.0, 15.5; HRMS (ESI$^+$) *m/z* calcd for $C_{19}H_{23}N_4O_3S$ $[M+H]^+$ 387.1491, found 387.1474..



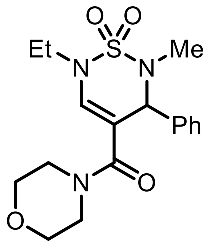
14e

6-Ethyl-*N*-(4-methoxybenzyl)-2-methyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxamide 1,1-dioxide (14e). To a solution of acid **8e** (0.0974 g, 0.329 mmol), PyBOP (0.2052 g, 0.3944 mmol), and *p*-methoxybenzylamine (0.0520 mL, 0.398 mmol) in CH_2Cl_2 (0.9 mL) was added DIPEA (0.125 mL, 0.718 mmol). The reaction mixture was sealed under and atmosphere of Ar, stirred at rt for 23 h, concentrated under reduced pressure, and partitioned between EtOAc (10 mL) and water (10 mL). The organic layer was washed with 1 M $NaHSO_4$ (2 x 5 mL), sat. aq. $NaHCO_3$ (1 x 5 mL), and brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (2:8 to 1:1; EtOAc:hexanes) to give a light yellow oil that was dissolved in $CHCl_3$ (3 x 10 mL) and concentrated under reduced pressure to remove trace EtOAc to give amide **14e** (0.114 g, 83%) as a light yellow sticky foam: IR (ATR) 3405, 3297, 2973, 2931, 1637, 1357, 1338 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (d, 1 H, *J* = 0.7 Hz), 7.39-7.32 (m, 5 H), 6.90 (d, 2 H, *J* = 8.7 Hz), 6.76-6.74 (m, 2 H), 5.41 (s, 1 H), 5.30 (t, 1 H, *J* = 5.1 Hz), 4.32, 4.23 (dd, 2 H, *J* = 14.7, 5.8 Hz), 3.77 (s, 3 H), 3.62 (q, 2 H, *J* = 7.2 Hz), 2.77 (s, 3 H), 1.34 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.6, 159.1, 137.9, 136.4, 130.1, 128.98, 128.96, 128.9, 128.7, 114.1, 105.8, 66.2, 55.4, 45.4, 43.4, 38.4, 15.5; HRMS (ESI$^+$) *m/z* calcd for $C_{21}H_{26}N_3O_4S$ [M+H]$^+$ 416.1644, found 416.1648.



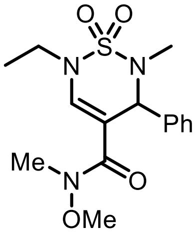
15e

***N*-(2-(Dimethylamino)ethyl)-6-ethyl-2-methyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxamide 1,1-dioxide (15e)**. To a vial containing acid **8e** (0.0900 g, 0.304 mmol) in CH_2Cl_2 (0.85 mL) was added PyBOP (0.173 g, 0.333 mmol), *N*,*N*-dimethylethylene diamine (36.0 µL, 0.330 mmol), and DIPEA (0.110 mL, 0.632 mmol). The reaction mixture was sealed under Ar and stirred for 23 h at rt. The reaction mixture was diluted with EtOAc (15 mL) and washed with sat. aq. NH_4Cl (1 x 10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified by chromatography on SiO_2 (1:99 to 1:9; MeOH:$CHCl_3$) to give amide **15e** (0.0847 g, 76%) as a light yellow foam: IR (ATR) 3420, 3307, 2975, 1638, 1357, 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41-7.29 (m, 5 H), 7.37 (s, 1 H), 6.04 (bs, 1 H), 5.45 (s, 1 H), 3.64 (q, 2 H, *J* = 7.3 Hz), 3.27-3.18 (m, 2 H), 2.79 (s, 3 H), 2.39, 2.52 (ddd, 2 H, *J* = 12.1, 6.6, 4.9 Hz), 2.06 (s, 6 H), 1.35 (3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.5, 137.7, 136.8, 128.9, 128.7, 128.5, 105.9, 66.3, 57.7, 45.4, 44.7, 38.5, 37.0, 15.5; HRMS (ESI$^+$) *m/z* calcd for $C_{17}H_{27}N_4O_3S$ [M+H]$^+$ 367.1804, found 367.1797.



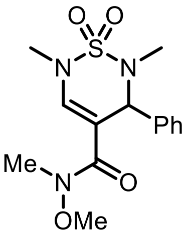
16e

(6-Ethyl-2-methyl-1,1-dioxido-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazin-4-yl)(morpholino)methanone (16e). To a vial containing acid **8e** (0.0900 g, 0.304 mmol) in CH_2Cl_2 (0.85 mL) was added PyBOP (0.173 g, 0.333 mmol), morpholine (29.0 uL, 0.332 mmol), and DIPEA (0.110 mL, 0.632 mmol). The reaction mixture was sealed under and atmosphere of Ar and stirred for 23 h at rt. The reaction mixture was diluted with EtOAc (15 mL) and washed with sat. aq. NH_4Cl (1 x 10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by chromatography on SiO_2 (3:7 to 1:1; EtOAc:hexanes) to give amide **16e** (0.0933 g, 84%) as a colorless white powder: Mp 116-117 °C ($CHCl_3$); IR (ATR) 2969, 2923, 2852, 1623, 1610, 1357 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.37-7.32 (m, 5 H), 6.56 (d, 1 H, J = 1.6 Hz), 5.68 (d, 1 H, J = 1.5 Hz), 3.62, 3.58 (dq, 2 H, J = 14.5, 7.2 Hz), 3.54-3.47 (m, 2 H), 3.43-3.34 (m, 4 H), 3.34-3.27 (m, 2 H), 2.54 (s, 3 H), 1.34 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6, 135.4, 134.2, 129.2, 129.1, 128.7, 109.8, 66.6, 66.5, 45.2, 34.5, 15.3; HRMS (ESI^+) *m/z* calcd for $C_{17}H_{23}N_3O_4SNa$ [M+Na] 388.1307, found 388.1314.



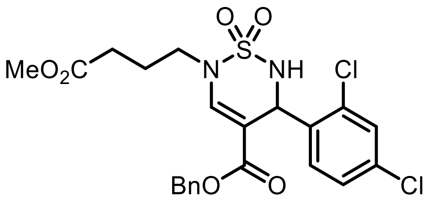
17e

6-Ethyl-*N*-methoxy-N,2-dimethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxamide 1,1-dioxide (17e). To a round bottom flask containing acid **8e** (0.999 g, 3.37 mmol), dimethylhydroxylamine hydrochloride (0.441 g, 4.52 mmol), and PyBOP (2.07 g, 3.98 mmol) was added CH_2Cl_2 (9.9 mL). The solution was cooled to 0 °C and treated with DIPEA (2.05 mL, 11.8 mmol), slowly warmed to rt, and stirred for 23 h. The reaction mixture was concentrated under reduced pressure and partitioned between EtOAc (40 mL) and water (20 mL). The organic layer was washed with 1 M $NaHSO_4$ (2 x 20 mL), sat. aq. $NaHCO_3$ (1 x 20 mL), and brine (1 x 20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (2:8 to 1:1; EtOAc:hexanes) to give a light yellow oil. The oil was dissolved in $CHCl_3$ (3 x 10 mL) and concentrated under reduced pressure to remove trace EtOAc to give **17e** (1.03 g, 90%) as a light yellow sticky oil: IR (ATR) 2977, 2936, 1627, 1163 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36-7.31 (m, 5 H), 7.05 (d, 1 H, *J* = 1.8 Hz), 5.92 (d, 1 H, *J* = 1.8 Hz), 3.65, 3.61 (dq, 2 H, *J* = 14.4, 7.2 Hz), 3.54 (s, 3 H), 2.99 (s, 3 H), 2.43 (s, 3 H), 1.36 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 137.7, 136.1, 129.2, 128.7, 128.6, 108.4, 65.7, 61.1, 45.1, 34.0, 33.2, 15.5; HRMS (ESI$^+$) *m/z* calcd for $C_{15}H_{22}N_3O_4S$ $[M+H]^+$ 340.1331, found 340.1330.



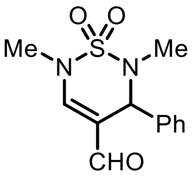
17f

***N*-Methoxy-N,2,6-trimethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxamide 1,1-dioxide (17f)**. To a solution of acid **8f** (5.0772 g, 17.984 mmol), dimethylhydroxylamine hydrochloride (2.330 g, 23.89 mmol), PyBOP (11.306 g, 21.730 mmol) was added CH_2Cl_2 (51 mL) and stirred at rt for 5 min then cooled to 0 °C for 10 min. The cooled solution was treated dropwise over 5 min with DIPEA (10.95 mL, 62.92 mmol) and slowly warmed to rt and stirred for 24.25 h. The reaction mixture was diluted with EtOAc (150 mL) and water (100 mL). The organic layer was separated and washed with 1 M $NaHSO_4$ (2 x 50 mL), sat. aq. $NaHCO_3$ (1 x 50 mL), and brine (1 x 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified by chromatography on SiO_2 (2:8 to 1:1; EtOAc:hexanes) to give a light yellow oil that was dissolved in $CHCl_3$ (100 mL) and washed with 1 M $NaHSO_4$ (2 x 50 mL), $NaHCO_3$ (1 x 50 mL), and brine (1 x 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the amide **17f** (5.50 g, 94%) a light yellow oil: IR (ATR) 2936, 1629, 1163 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.29 (m, 5 H), 6.96 (d, 1 H, J = 1.8 Hz), 5.91 (d, 1 H, J = 1.8 Hz), 3.53 (s, 3 H), 3.25 (s, 3 H), 2.97 (s, 3 H), 2.46 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.6, 139.2, 135.9, 129.2, 128.7, 128.6, 108.7, 65.7, 61.1, 36.4, 34.0, 33.2; HRMS (ESI$^+$) *m/z* calcd for $C_{14}H_{20}N_3O_4S$ [M+H]$^+$ 326.1175, found 326.1186.



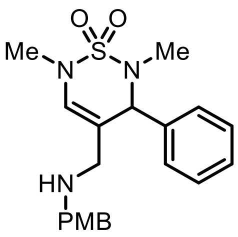
18g

Benzyl 3-(2,4-dichlorophenyl)-6-(4-methoxy-4-oxobutyl)-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carboxylate 1,1-dioxide (18g). To a solution of **10g** (0.150 g, 0.35 mmol, 1 eq) in CH_2Cl_2 (1.7 mL) was sequentially added benzyl alcohol (0.11 mL, 1.063 mmol, 3 eq), EDCI (0.170 g, 0.886 mmol, 2.5 eq), DMAP (0.022 g, 0.180 mmol, 0.5 eq), and TEA (125 µL, 0.886 mmol, 2.5 eq). Reaction progress was monitored by TLC (3:7; EtOAc:hexanes). After stirring at rt for 25 h, the reaction mixture was quenched with $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (3:7, EtOAc:hexanes) afforded **18g** (0.109 g, 60%) as a clear foam: Mp 47- 49 °C; IR (ATR) 3210 3033, 2953, 2852, 1731, 1697, 1623, 1588, 1561 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (s, 1 H), 7.38 (d, 1 H, *J* = 2 Hz), 7.28 (m, 3 H), 7.22 (d, 1 H *J* = 8.5 Hz), 7.13 (dd, 1 H, *J* = 2, 8.3 Hz), 7.05 (dd, 2 H, *J* = 7.5, 2.0 Hz), 5.91 (s, 1 H), 5.13 (d, 1 H, *J* = 12 Hz), 4.95 (d, 1 H, *J* = 12 Hz), 4.90 (brs, 1 H), 3.69 (t, 2 H, *J* = 7.0 Hz), 3.68 (s, 3 H), 2.45 (t, 2 H, *J* = 7 Hz), 2.08 (dquint, 2 H, *J* = 10.0, 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 164.6, 142.9, 135.6, 135.2, 134.7, 133.7, 130.6, 129.8, 128.6, 128.4, 128.2, 127,2, 104.5, 66.5, 55.8, 52.0, 49.7, 30.7, 24.8); HRMS (ESI$^+$) m/z calcd for $C_{22}H_{23}O_6N_2Cl_2S$ $[M+H]^+$ 513.0648, found 513.0663; LCMS-220 nm purity 100%.



19f

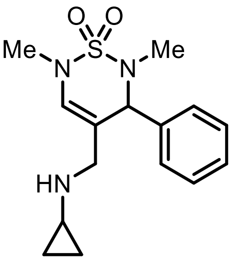
2,6-Dimethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine-4-carbaldehyde 1,1-dioxide (19f). To a solution of Weinreb amide **17f** (1.2654 g, 3.8890 mmol) in THF (26 mL) cooled to -78 °C was added dropwise $LiAlH_4$ (1 M in Et_2O, 7.80 mL, 7.80 mmol) over 5 min. The reaction mixture was stirred for 2 h at -78 °C, warmed to 0 °C, stirred for 15 min, diluted with Et_2O (80 mL), and quenched with water (100 mL). 1 M HCl (40 mL) was added, the phases were separated, and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with brine (1 x 50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light yellow oil. The crude material was purified by chromatography on SiO_2 (4:6 to 6:4; EtOAc:hexanes) to give the aldehyde **19f** (0.7267 g, 70%) as a colorless foam: IR (ATR) 1659, 1610, 1363, 1307, 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.38 (s, 1 H), 7.34-7.26 (m, 5 H), 7.13 (s, 1 H), 5.51 (s, 1 H), 3.35 (s, 3 H), 2.93 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.7, 150.3, 136.4, 128.3, 127.7, 113.9, 64.8, 39.9, 37.2; HRMS (ESI^+) *m/z* calcd for $C_{12}H_{14}N_2O_3S$ $[M+H]^+$ 267.0803, found 267.0815.



20f

4-(((4-Methoxybenzyl)amino)methyl)-2,6-dimethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxide (20f). To a solution of aldehyde **19f** (0.0603 g, 0.226 mmol) in CH_2Cl_2 (0.28 mL) was added 4-methoxybenzylamine (0.0320 mL, 0.245 mmol) and Ti(*i*-PrO)$_4$ (0.205 mL, 0.676 mmol). The reaction mixture was sealed under Ar and stirred at rt for 24 h. The reaction mixture was diluted with EtOAc (10 mL), quenched with water (10 mL), stirred at rt for 5 min, and filtered through a pad of Celite®. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, concentrated under reduced pressure to give a light yellow oil that was dried under high vacuum for several hours to give the imine that was taken on without further purification.

To a solution of imine in MeOH (0.9 mL) cooled to 0 °C was slowly added $NaBH_4$ (0.0261 g, 0.690 mmol). The reaction mixture was stirred at 0 °C for 30 min and warmed to rt and stirred for 3.5 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with 5% aq. K_2CO_3 (2 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by chromatography through a short plug of SiO_2 (4:6 to 1:1; EtOAc:hexanes w/ 2% TEA) to give the amine **20f** (0.0604 g, 69%) as a light yellow oil: IR (ATR) 3329, 2900, 2831, 1510, 1241, 1158 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.30 (m, 5 H), 7.12 (d, 2 H, *J* = 8.2 Hz), 6.82 (d, 2 H, *J* = 8.2 Hz), 6.04 (s, 1 H), 4.80 (s, 1 H), 3.79 (s, 3 H), 3.61, 3.51 (d, 2 H, *J* = 13.0 Hz), 3.09 (s, 3 H), 2.89, 2.85 (d, 2 H, *J* = 14.6 Hz), 2.58 (s, 3 H), 1.42 (bs, 1 H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.8, 137.1, 132.2, 129.4, 129.1, 128.82, 128.77, 128.3, 121.8, 113.9, 69.1, 55.4, 52.2, 49.8, 38.0, 34.7; HRMS (ESI$^+$) *m/z* calcd for $C_{20}H_{26}N_3O_3S$ $[M+H]^+$ 388.1695, found 388.1707.



21f

4-((Cyclopropylamino)methyl)-2,6-dimethyl-3-phenyl-3,6-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxide (21f). To a solution of aldehyde **19f** (0.0603 g, 0.226 mmol) in CH_2Cl_2 (0.28 mL) was added cyclopropylamine (0.0170 mL, 0.245 mmol) and Ti(*i*-PrO)$_4$ (0.200 mL, 0.676 mmol). The reaction mixture was sealed under Ar and stirred at rt for 21 h. The reaction mixture was diluted with EtOAc (10 mL), quenched with brine (10 mL), and filtered through a pad of Celite®. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The oil was dried under high vacuum overnight to give the imine as a colorless foam that was taken on without purification.

To a solution of imine (0.0691 g, 0.226 mmol) in MeOH (0.4 mL) and THF (0.4 mL) cooled to 0 °C was slowly added $NaBH_4$ (0.0261 g, 0.690 mmol). The reaction mixture was stirred at 0 °C for 15 min then warmed to rt. After 1.5 h the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with 5% aq. K_2CO_3 (2 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by chromatography through a short plug of SiO_2 (2:8 to 1:1; EtOAc:hexanes w/ 2% TEA) to give the amine **21f** (0.0455 g, 65%) as a colorless solid: Mp 87-88 °C ($CHCl_3$); IR (ATR) 3308, 2839, 1338, 1158, 755, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.30 (m, 5 H), 6.03 (s, 1 H), 4.74 (s, 1 H), 3.08 (s, 3 H), 2.94, 2.86 (d, 2 H, *J* = 13.7 Hz), 2.55 (s, 3 H), 2.00 (m, 1 H), 1.41 (bs, 1 H), 0.41-0.32 (m, 1 H), 0.32-0.24 (m, 2 H), 0.12-0.02 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.0, 129.1, 128.8, 128.1, 122.1, 69.1, 50.4, 38.0, 34.5, 29.8, 6.7, 6.0; HRMS (ESI$^+$) *m/z* calcd for $C_{12}H_{15}N_2O_2S$ $[M{-}C_3H_6N]^+$ 251.0849, found 251.0841.

III. Biological Assays

For HD assays, HEK293H cells were grown in DMEM (Sigma-Aldrich, Saint Louis, MO) supplemented with 10% fetal bovine serum (GE Healthcare Hyclone) and 1% penicillin/streptomycin (Thermo Fisher Scientific, Waltham, MA) at 37 °C and at a 5% CO_2 atmosphere. Cells were seeded at 250,000 cells/plate in Poly-D-Lysine Coated 35 mm MatTek dishes (P35GC-1.5-10-C, MatTek Corporation, Ashland, MA). After 24 h growth, a total of 4 µg of mCherry tagged-polyglutamine-expanded (17-polyQ-expanded) huntingtin (HTT) was introduced using Lipofectamine 2000 (Invitrogen, Thermo Fisher Scientific) according to the manufacturer’s instructions. HTT-17polyQ (PMID: 24584051) was fused to mCherry and the HTT-17polyQ-mcherry was cloned between KpnI and BamHI sites in the pcDNA3.1 vector. The following day, cells were treated with vehicle (DMSO) as control or with 10 µM of the examined compounds for 6 h. The cells were then washed with PBS and fixed in 4% formaldehyde for 15 min at room temperature. Finally, cells were stained with DAPI (1:250 in PBS) for 4 h and maintained in PBS for confocal microscope imaging.

Samples were imaged using a Nikon A1 point scanning confocal with a 60x objective and a 1.68 numerical aperture. Complete volumes of cells were acquired at 0.5-µm steps, and volumes were reconstructed and analyzed using Nikon’s NIS-Elements software (Nikon Instrument, Melville, NY). Bright spot detection tool was used to identify and quantify the number of protein aggregates (“dots”) per cell. A non-parametric Kruskal-Wallis test analysis was performed using Prism software (GraphPad, La Jolla, CA). Statistically significant differences between control

(DMSO) and compound treated samples are indicated by asterisks in figure. To obtain representative images from this experiment, maximum intensity projections of 0.5-μm steps though the entire cell were generated using Nikon's NIS-Elements software.

For HDAC 1-3 assays, kits from BioVision Incorporated (https://www.biovision.com/) were used and their recommended protocols followed. For HDAC 4-8 assays, kits from BPS Bioscience (https://bpsbioscience.com/) were used and their recommended protocols followed. For a summary of results, see Table 1. Each compound was dissolved in DMSO to generate a 100 μM stock solution, then diluted using HPLC-grade water to prepare 10 μM, 2 μM, and 1 μM solutions. These solutions were used for the assays. For the HDAC 1-3 assay, samples were subjected to an additional 2x dilution and for HDAC 4, 5, 6, 7, and 8 assays the additional dilution was 10x. The standards Trichostatin A (TSA) and Vorinostat (SAHA) were measured each time an HDAC assay was performed (Table 2). Assays utilized a BioTek Synergy H1 microplate reader and black Nunc MicroWell 96-well optical-bottom plates with polymer base.

HDAC 1-3: 10 μL of each diluted compound (10 μM) and 40 μL of HPLC-grade water were mixed and added into a well on the plate. Different concentrations of TSA and SAHA (for standard curves) were added to their respective wells. 50 μL of HPLC-grade water was added to each positive control well. Then, 50 μL of the reaction mixture was added to each well and the the solution was mixed thoroughly. The reaction mixture consisted of 500 μL of 10x HDAC Assay buffer, 100 μL of HeLa nuclear extract, 250 μL of HDAC substrate, and 1.65 mL of HPLC-grade water. The plate was then warmed in an incubator at 37 °C with a rocker platform and was incubated for 30 min. After the incubation, 10 μL of Lysine Developer solution was added to each well. The plate was kept in the incubator for an additional 30 min. Afterwards, the plate was analyzed using a BioTek Synergy H1 microplate reader, taking two independent readings per well that were subsequently averaged.

HDAC 4 (and, by analogy, HDAC 5, 6, 7, and 8): 40 μL of the parent solution was added to each well on the plate. The parent solution was prepared from a fluorogenic HDAC substrate, a 1 mg/mL solution of bovine serum albumin (BSA) in water, and HDAC assay buffer. 5 μL of the inhibitor buffer (10% DMSO in water) was added to the wells designated as "Blank" and "Positive Control" (no inhibitor). 5 μL of the test compound was added to each well designated as "Test Inhibitor". Different concentrations of TSA (for a standard curve) was added to each well designated as "Standard." 5 μL of HDAC assay buffer was added to the "Blank" wells. Then, 5 μL of HDAC 4 human recombinant enzyme was added to the wells designated as "Positive Control", "Test Inhibitor", and "Standard." The plate was then warmed in an incubator at 37 °C with a rocker platform for 30 min. After the incubation, 50 μL of 2x HDAC Developer solution was added to each well. The plate was returned to the incubator and was shaken on the rocker for an additional 15 min. at room temperature. Afterwards, the plate was analyzed using a BioTek Synergy H1 microplate reader, taking two independent readings per well that were subsequently averaged.

For HDAC 1-3, HDAC 4, and HDAC 8, samples were tested at 1 uM; for HDAC 5, HDAC 6, samples were tested at 200 nM, and for HDAC 6, HDAC 7, and HDAC 8, samples were also tested at 100 nM. These specific concentrations were selected based on the preliminary tests with the positive controls, TSA and SAHA; i.e. the positive standards TSA and SAHA were used as a guide to determine suitable test concentrations for different HDACs.

Table 1. Percent inhibition of **10g**, **10i**, **12g**, and **12h** in HDAC 1-8 assays

Entry	Compound	HDAC 1-3[a]	HDAC 4[a]	HDAC 5[b]	HDAC 6[b,c]	HDAC 7[c]	HDAC 8[a,c]
1	**10g**	NIA	NIA	NIA	NIA	1%	60%[e]
7	**10i**	NIA	NIA	9%	40%[d]	NIA	37%[e]
8	**12g**	1%	5%	NIA	10%[d]	NIA	46%[e]
9	**12h**	22%	23%	19%	20%[d]	40%	58%[e]

[a]Compound tested at 1 uM; [b]Compound tested at 200 nM; [c]Compound tested at 100 nM. [d]Activity was variable, data shown is the average of 2 independent measurements; [e]Data shown is the average of 2 independent measurements. NIA = no inhibitory activity noted.

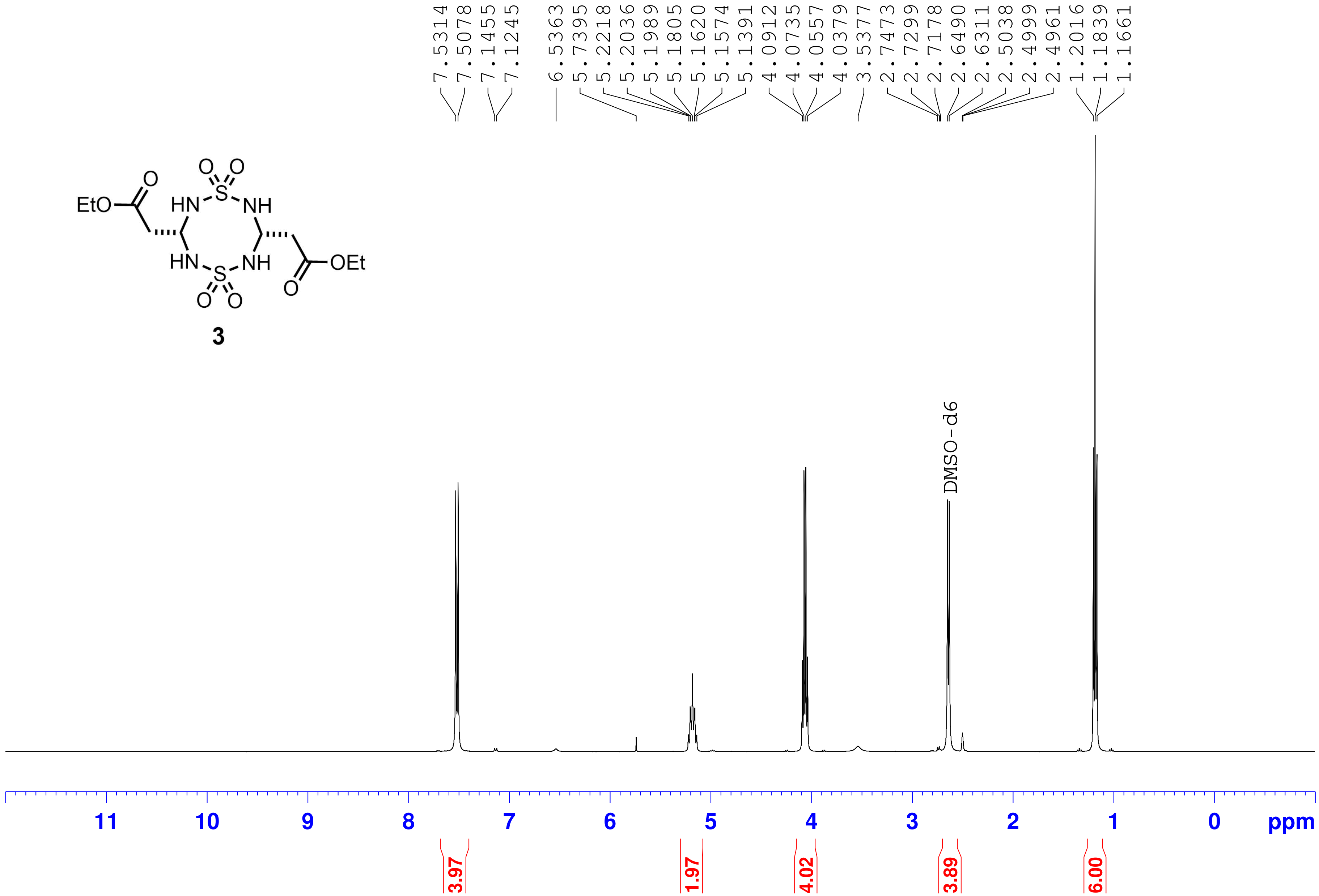
Table 2. Percent HDAC inhibition of Trichostatin A (**TSA**) and Vorinostat (**SAHA**) positive controls. NIA = no inhibitory activity noted.

Entry	HDAC	Standard	Concentration (uM)	Percent Inhibition
1	1-3	TSA	1	68%
			0.1	49%
			0.05	33%
			0.005	NIA
			0.0025	NIA
		SAHA	1	29%
			0.1	3%
			0.05	NIA
			0.005	NIA
			0.0025	NIA
2	4	TSA	10	77%
			7	67%
			3	35%
			1	17%
			0.5	NIA
3	5	TSA	10	85%
			5	73%
			2	63%
			1	41%
			0.5	20%
			0.2	NIA
4	6	SAHA	0.5	94%
			0.1	82%
			0.01	47%
			0.005	25%
			0.001	6%
			5	83%

5	7	TSA	1	37%
			0.5	NIA
			0.1	NIA
			0.01	9%
6	8	TSA	10	97%
			5	87%
			1	80%
			0.1	67%
			0.01	51%
		SAHA	5	96%
			2	86%
			1	70%
			0.2	67%
			0.05	54%

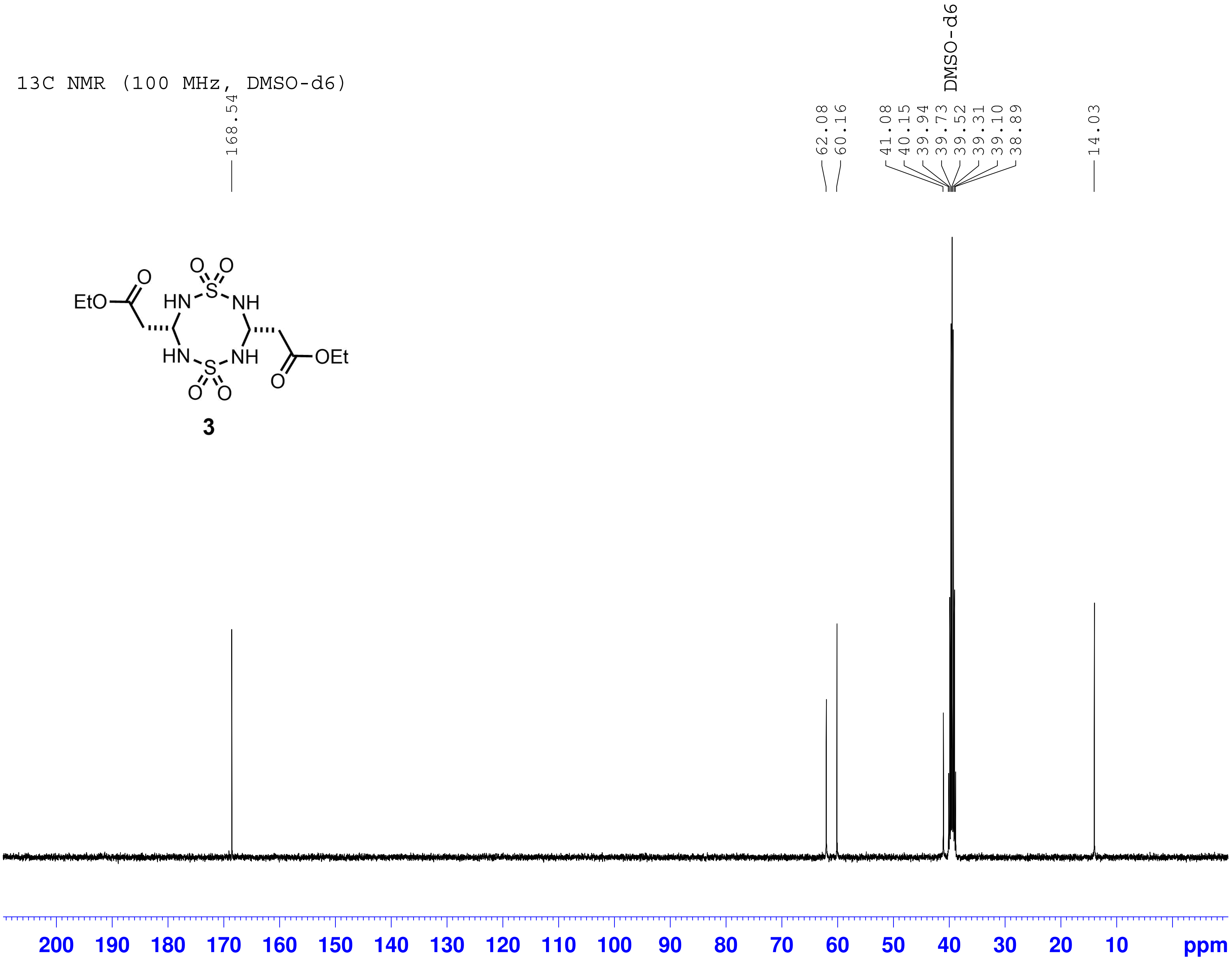
IV. ^{1}H NMR and ^{13}C NMR Spectra

1H NMR (400 MHz, DMSO-d6)



3

13C NMR (100 MHz, DMSO-d6)



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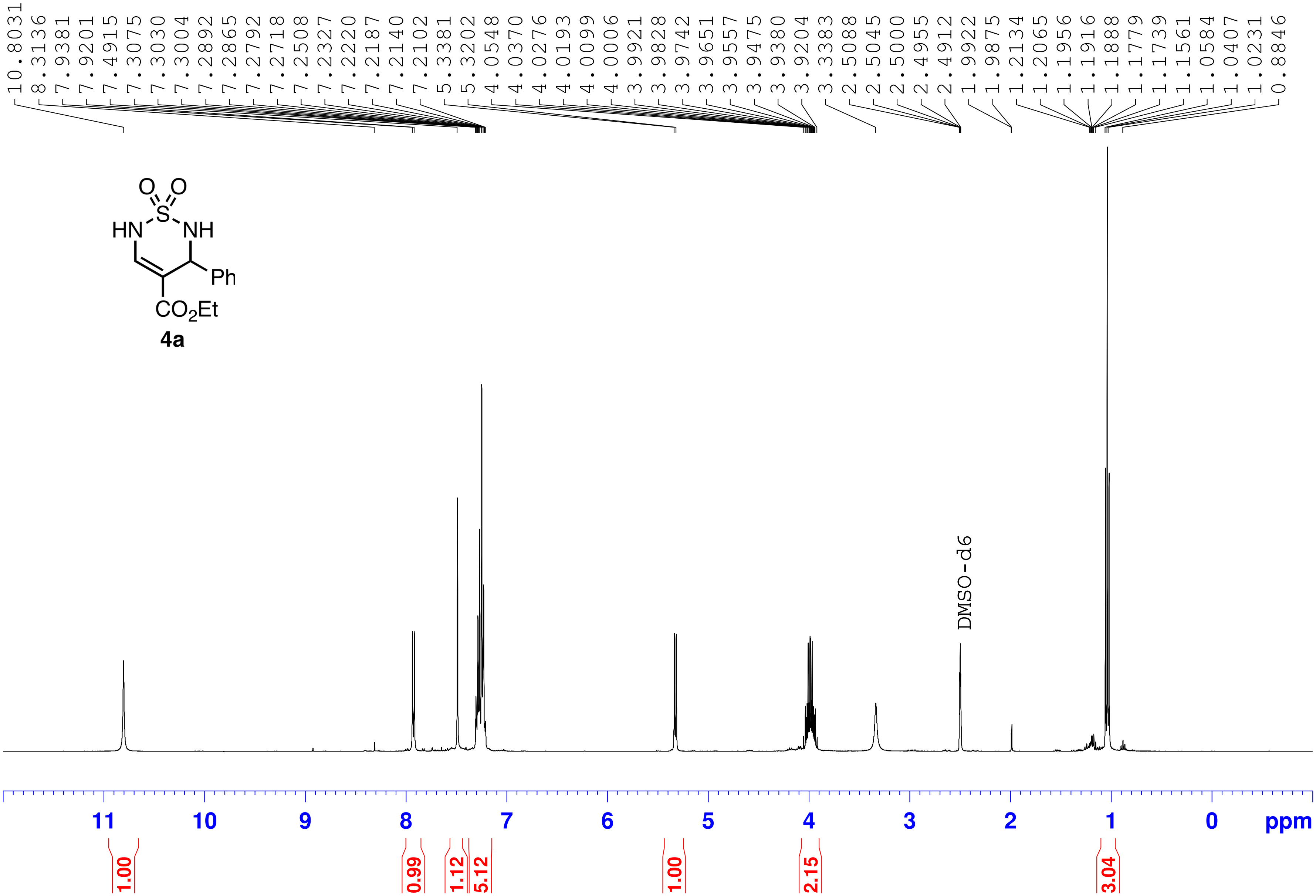
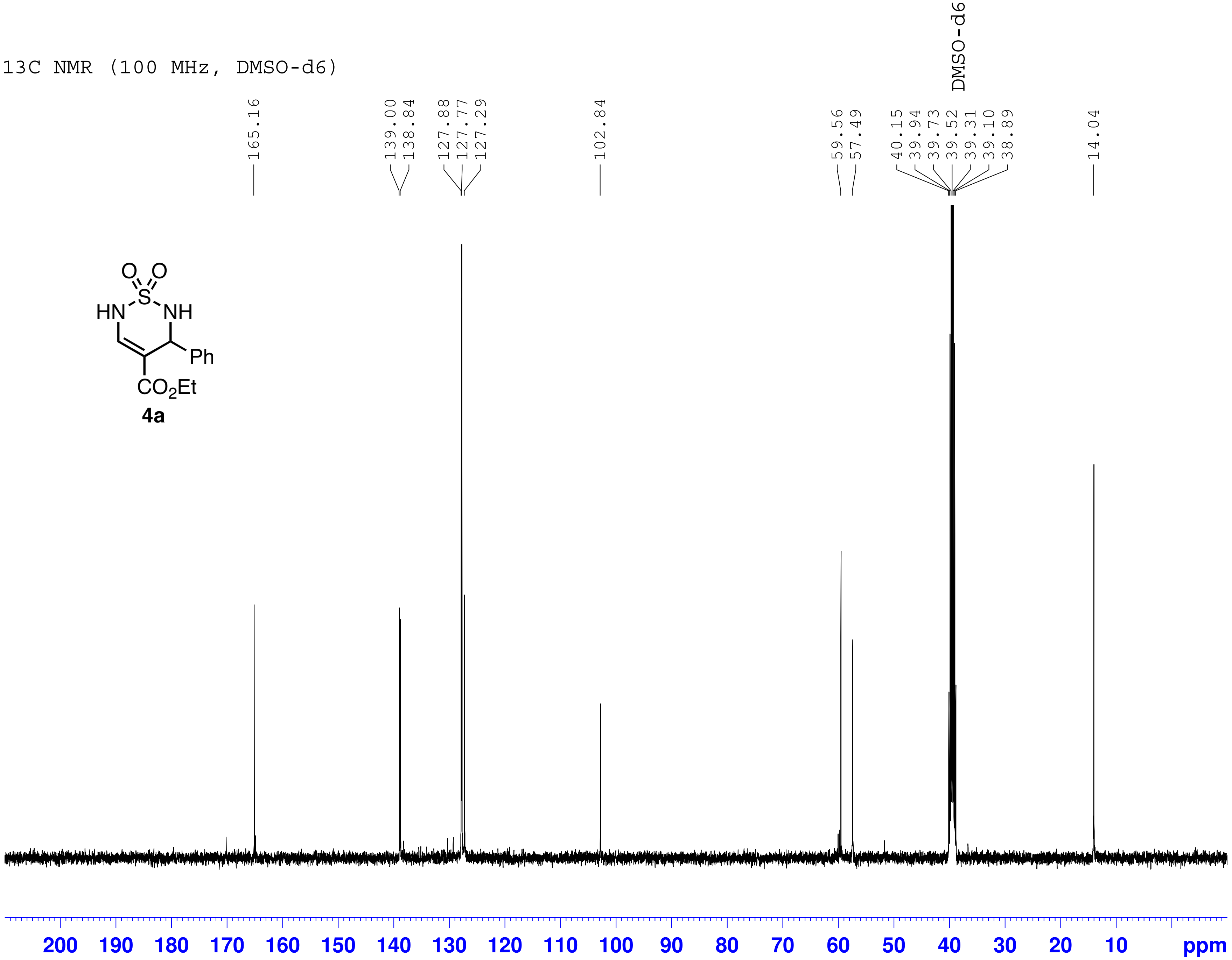
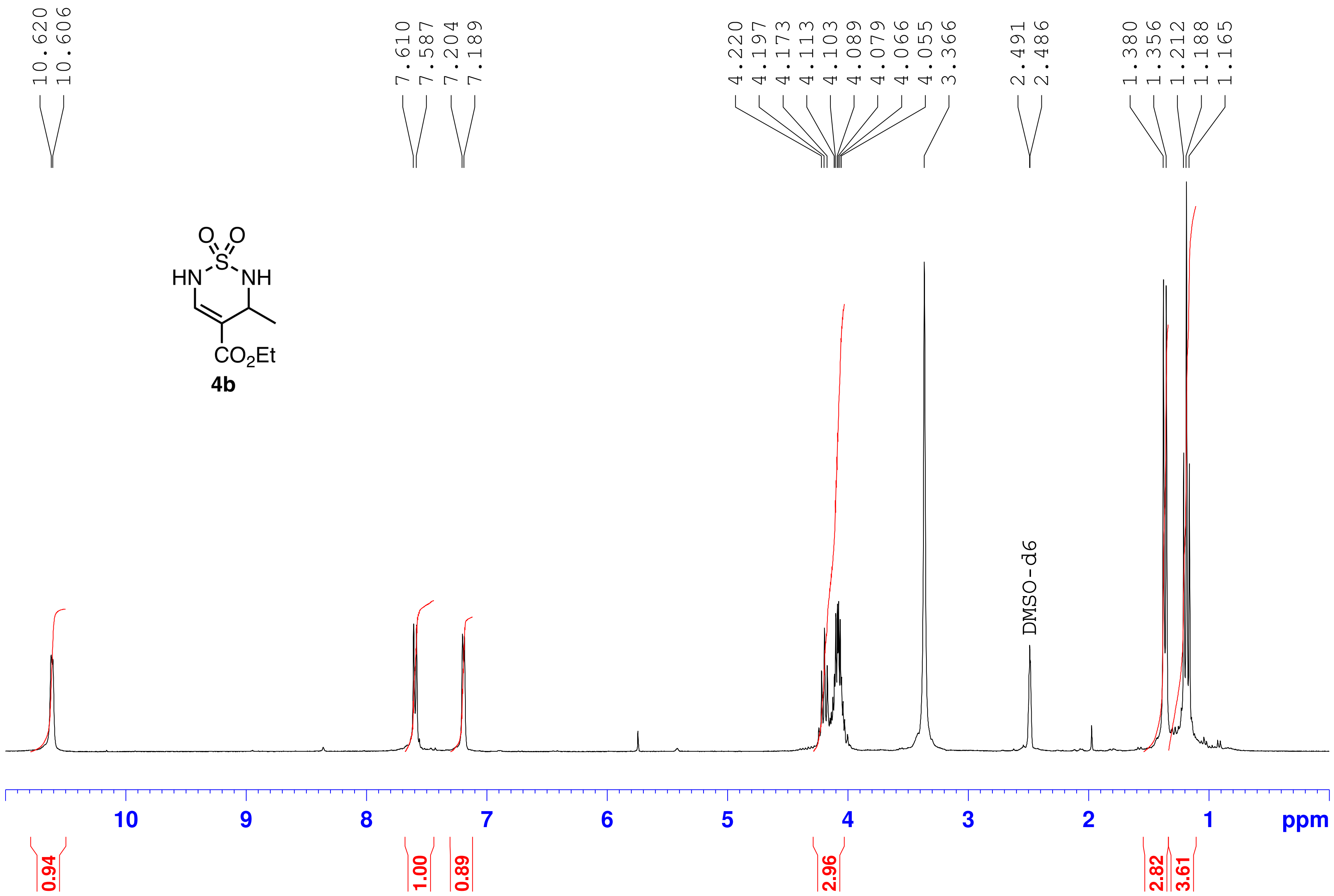
1H NMR (400 MHz, DMSO-d6)



13C NMR (100 MHz, DMSO-d6)

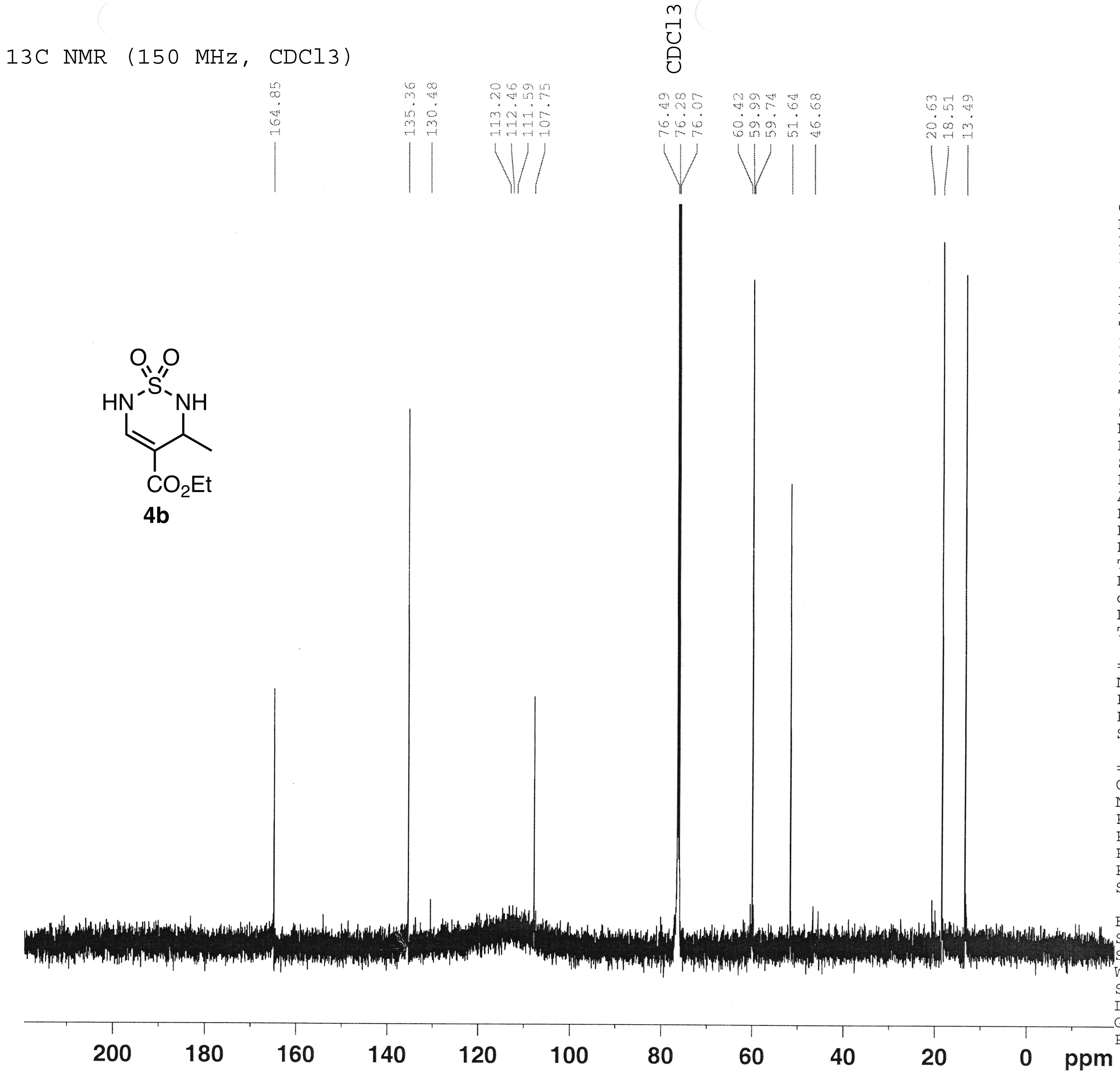


1H NMR (300 MHz, DMSO-d6)



4b

13C NMR (150 MHz, CDCl3)



4b

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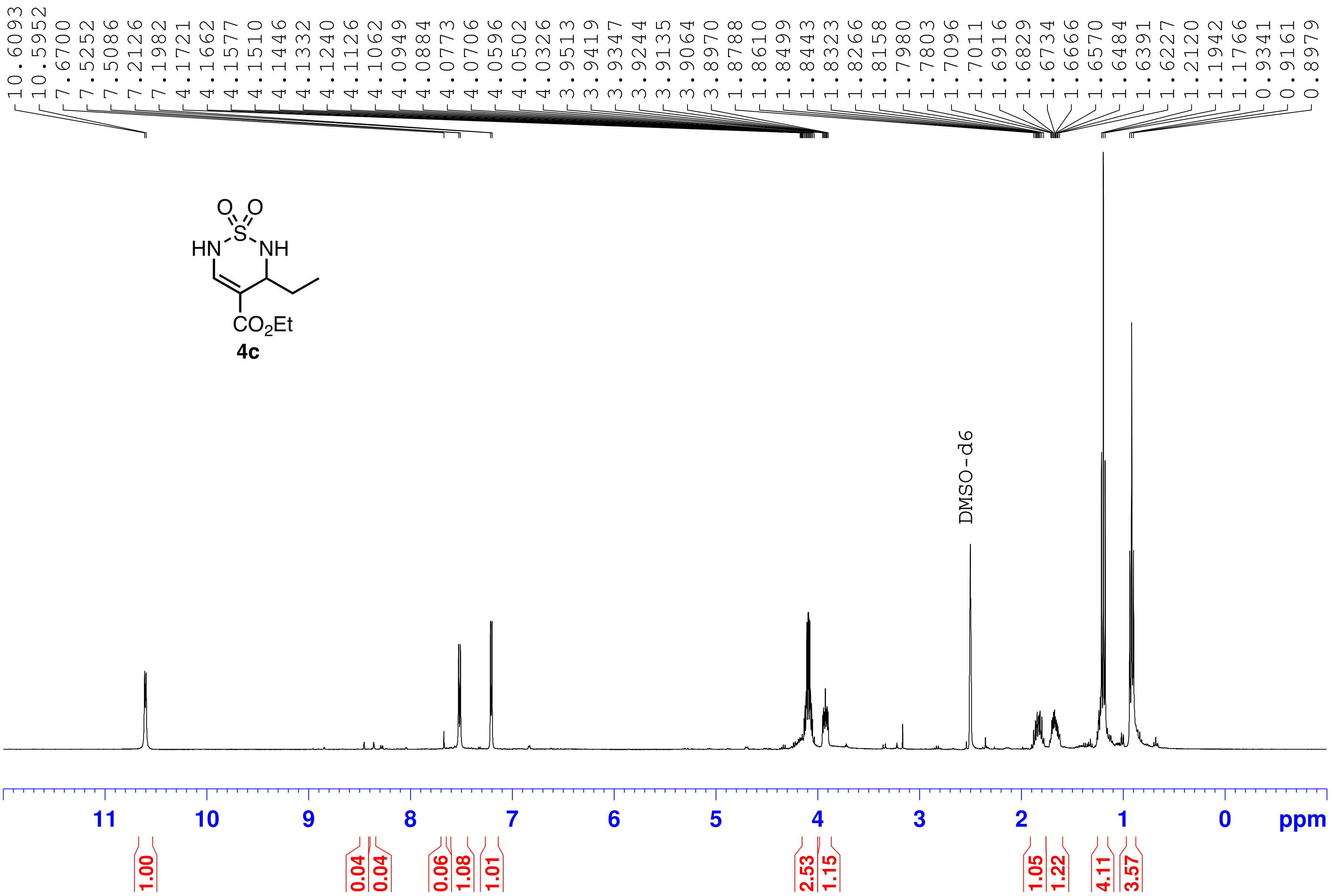
Date_                20070309
Time                     0.45
INSTRUM                 spect
PROBHD       5 mm PABBI 1H/
PULPROG               zgpg30
TD                      65536
SOLVENT                 CDCl3
NS                       1024
DS                          4
SWH              35971.223 Hz
FIDRES            0.548877 Hz
AQ               0.9110143 sec
RG                       8192
DW                 13.900 usec
DE                   6.00 usec
TE                    299.9 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                 15.00 usec
PL1                   0.33 dB
SFO1           150.9178988 MHz

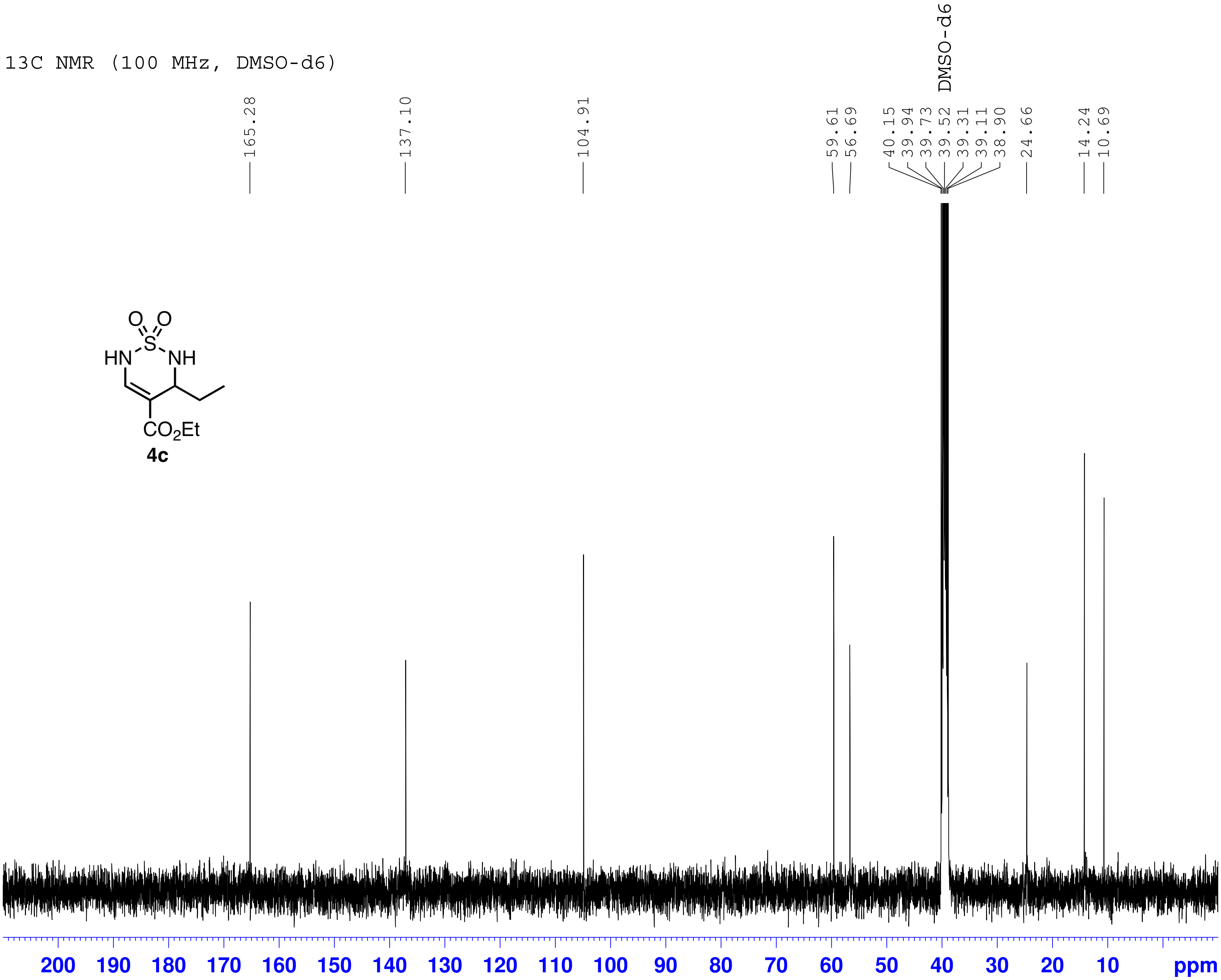
======== CHANNEL f2 ========
CPDPRG2               waltz16
NUC2                       1H
PCPD2              70.00 usec
PL2                   4.00 dB
PL12                 23.22 dB
PL13                 24.00 dB
SFO2           600.1324005 MHz

F2 - Processing parameters
SI                      32768
SF             150.9028090 MHz
WDW                        EM
SSB                         0
LB                    1.00 Hz
GB                          0
PC                       1.40
```

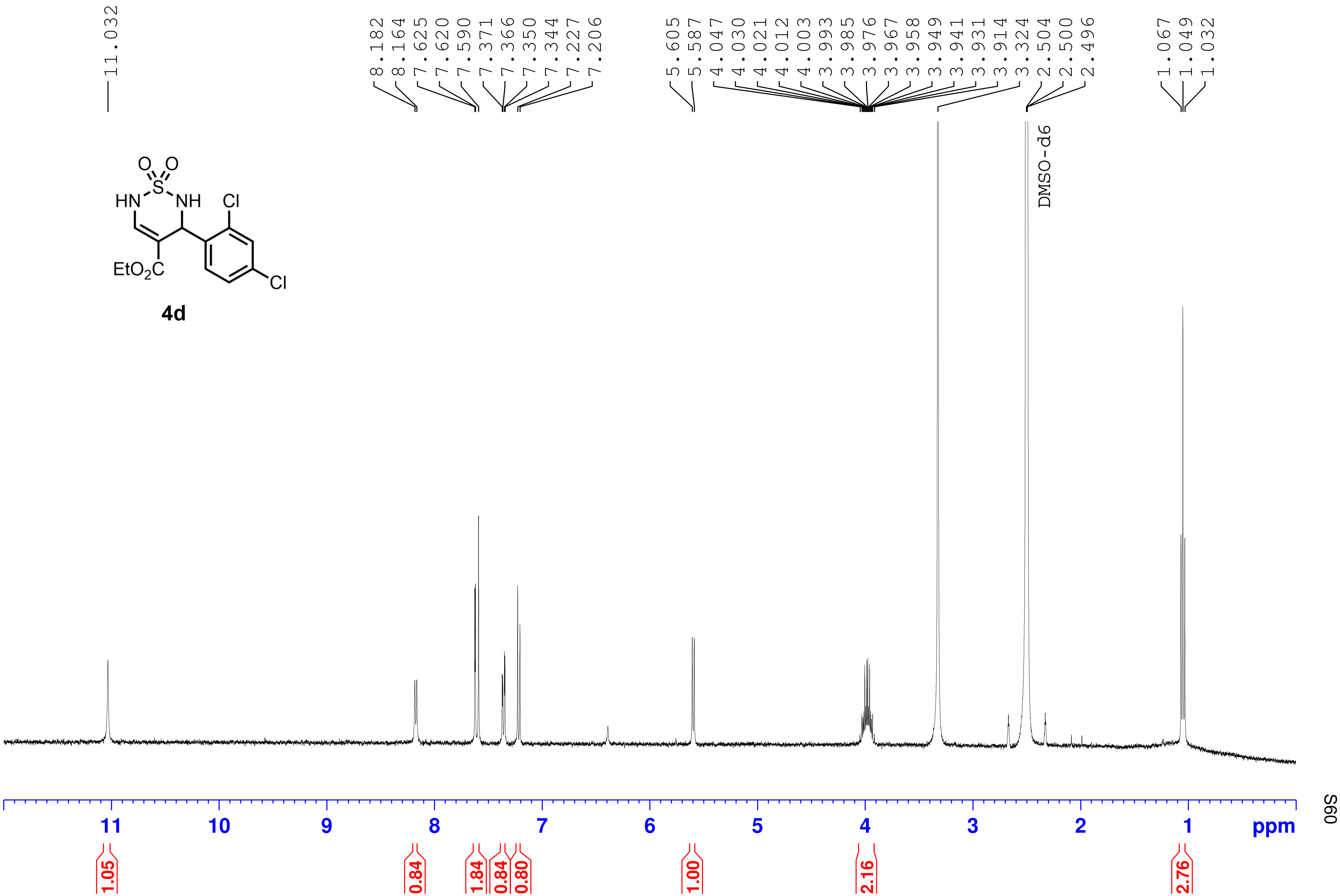
1H NMR (400 MHz, DMSO-d6)



13C NMR (100 MHz, DMSO-d6)

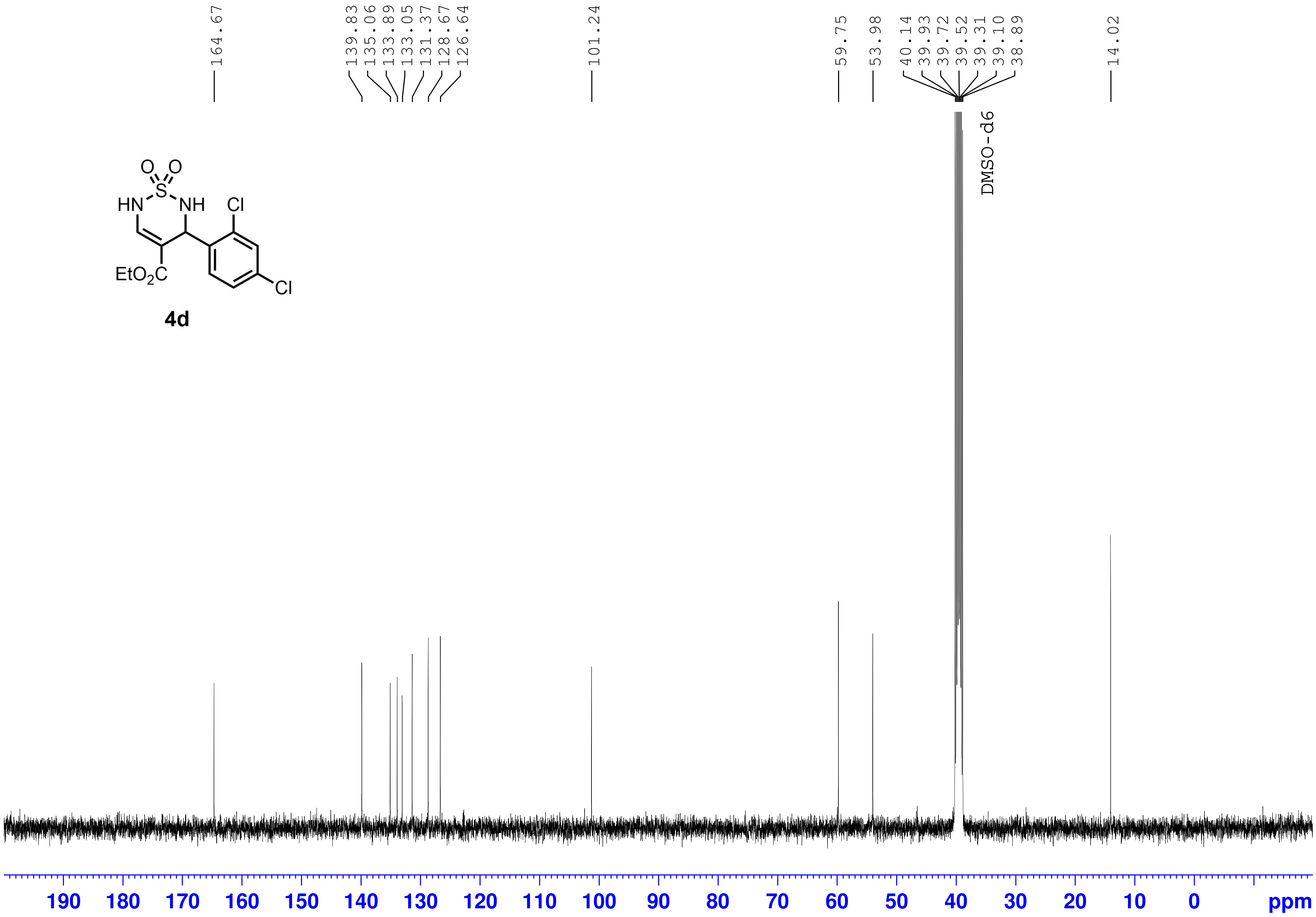


1H NMR (400 MHz, DMSO-d6)



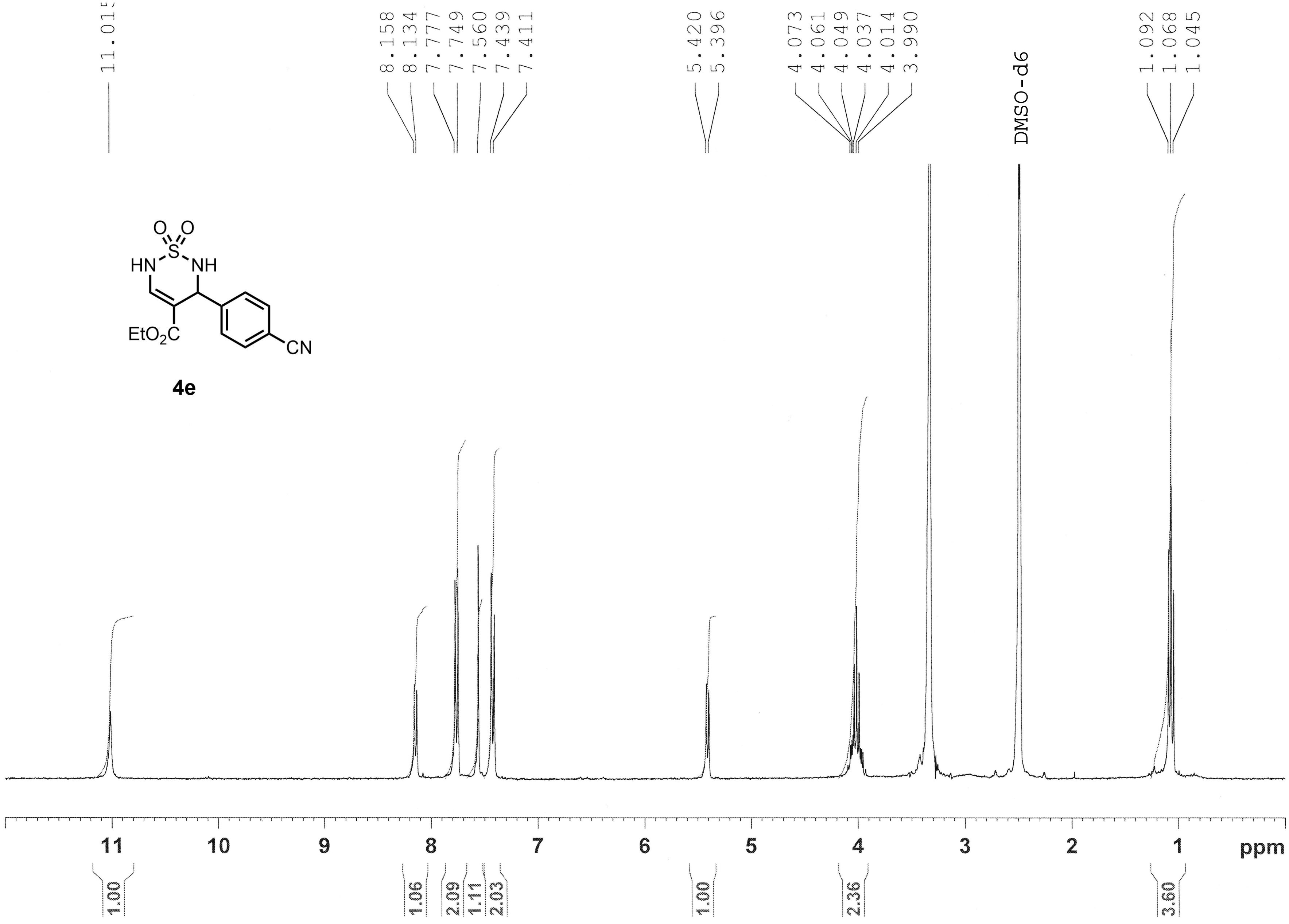
4d

1H NMR (100 MHz, DMSO-d6)



4d

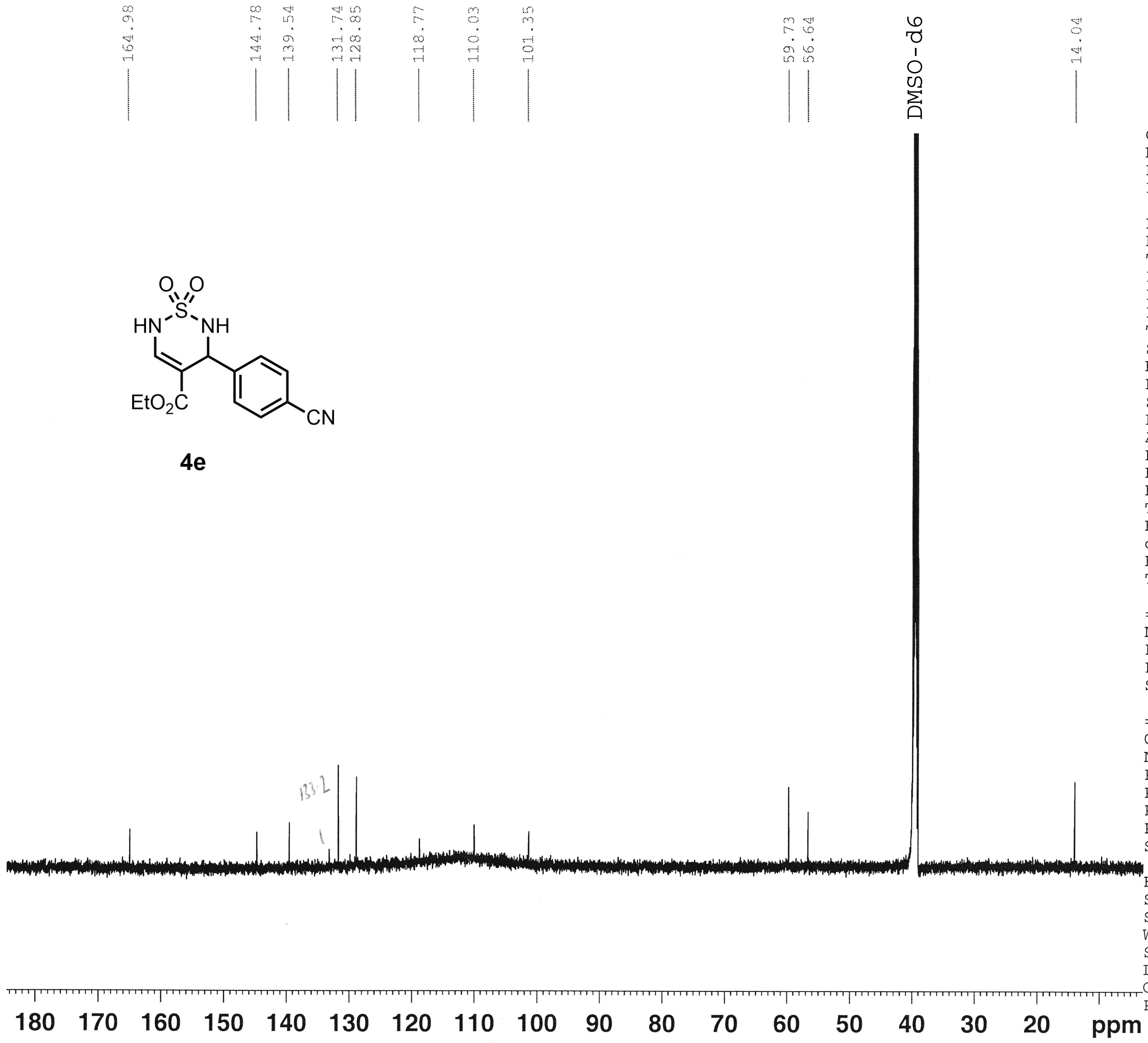
1H NMR (300 MHz, DMSO-d6)



4e

13C NMR (150 MHz, DMSO-d6)

4e



```
Current Data Parameters
NAME          lj 104 13 c
EXPNO                  11
PROCNO                  1

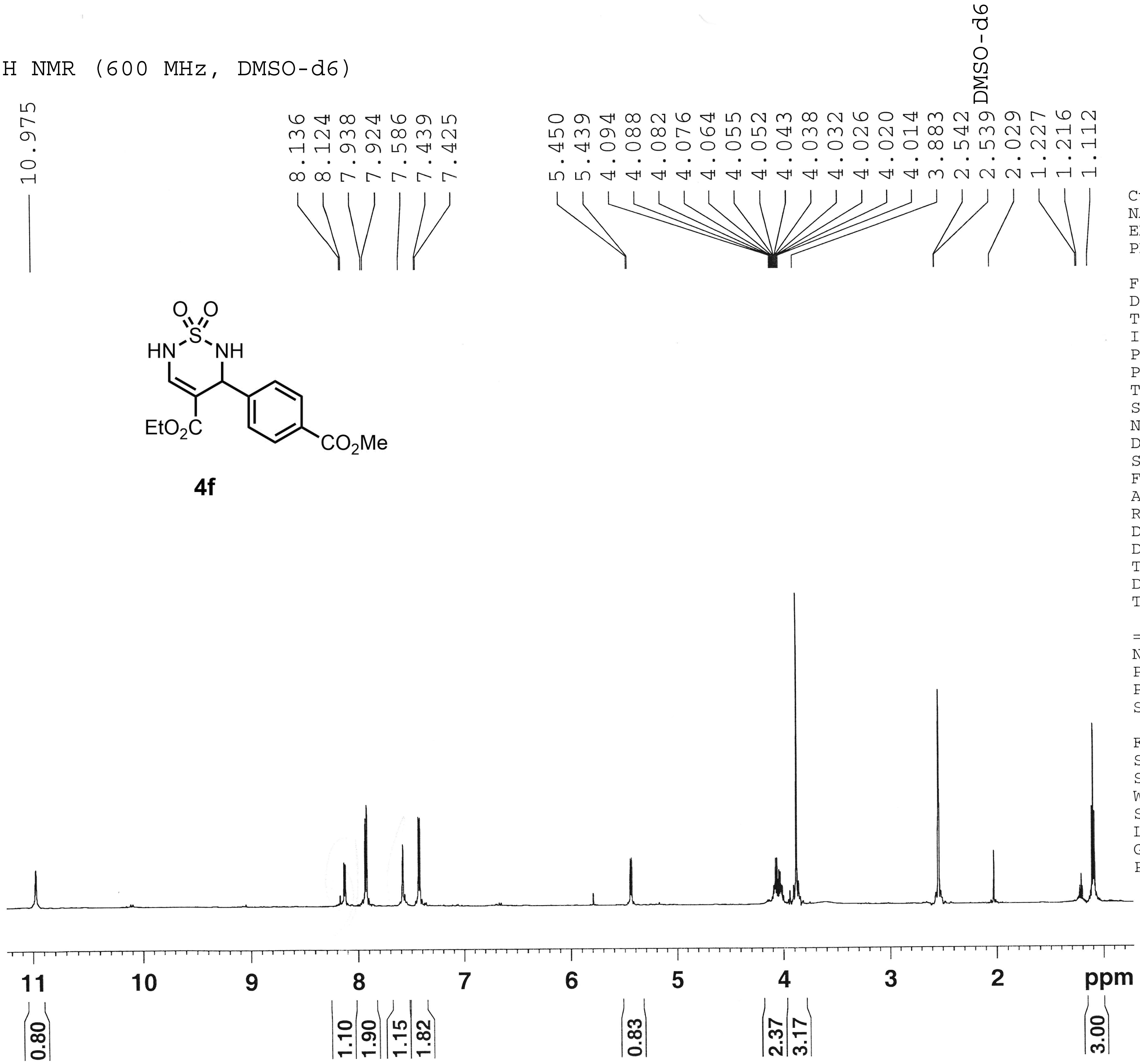
F2 - Acquisition Parameters
Date_            20070308
Time                22.52
INSTRUM             spect
PROBHD   5 mm PABBI 1H/
PULPROG           zgpg30
TD                 65536
SOLVENT             DMSO
NS                  2048
DS                     4
SWH            35971.223 Hz
FIDRES          0.548877 Hz
AQ             0.9110143 sec
RG               14596.5
DW                13.900 usec
DE                  6.00 usec
TE                 299.9 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 15.00 usec
PL1                 0.33 dB
SFO1         150.9178988 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              70.00 usec
PL2                 4.00 dB
PL12               23.22 dB
PL13               24.00 dB
SFO2         600.1324005 MHz

F2 - Processing parameters
SI                 32768
SF           150.9028845 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

1H NMR (600 MHz, DMSO-d6)



4f

```
Current Data Parameters
NAME                 1j 101
EXPNO                    10
PROCNO                    1

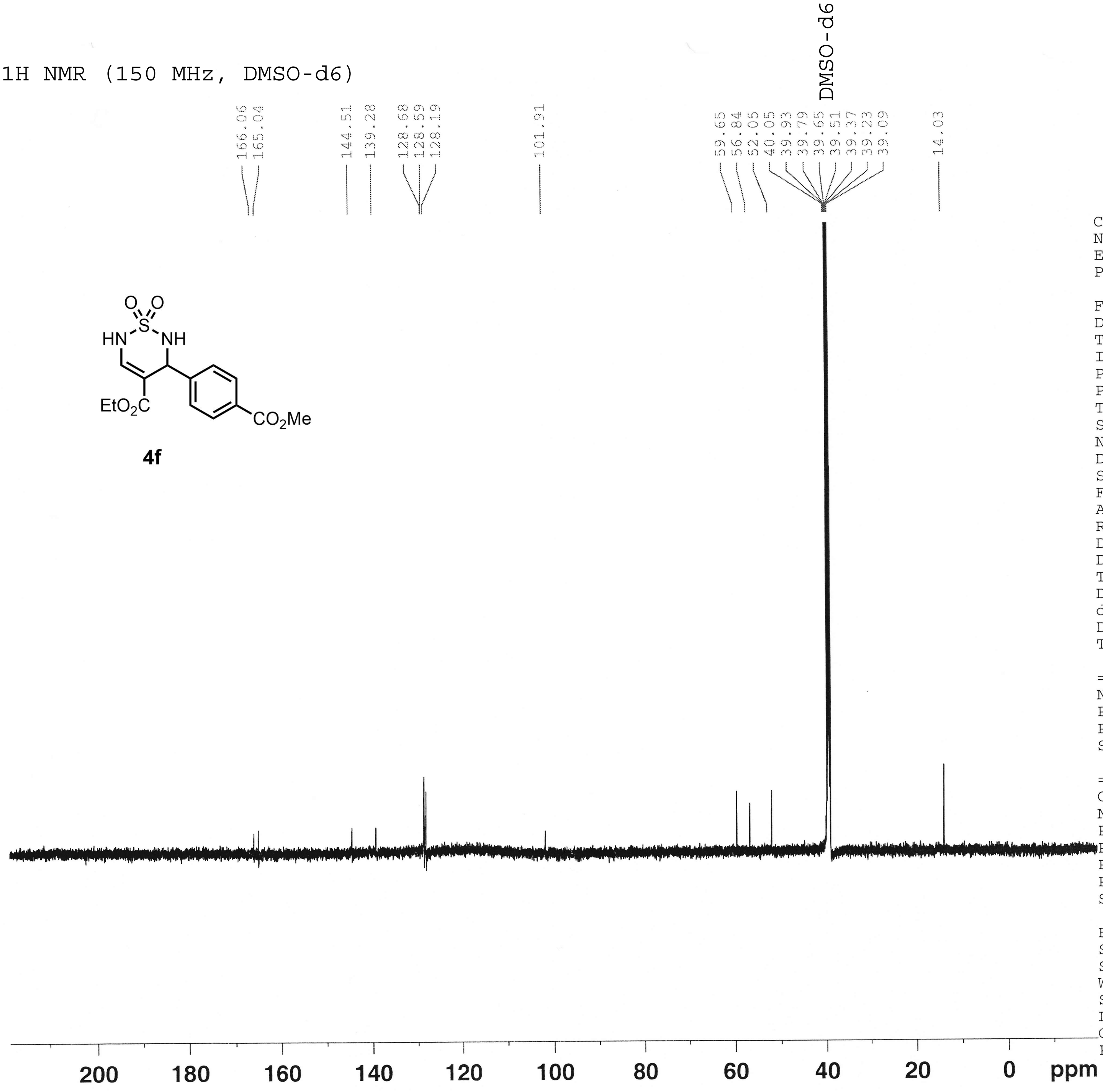
F2 - Acquisition Parameters
Date_              20070307
Time                  16.31
INSTRUM               spect
PROBHD   5 mm PABBI 1H/
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH               12376.237 Hz
FIDRES             0.188846 Hz
AQ                2.6477449 sec
RG                      181
DW                   40.400 usec
DE                     6.00 usec
TE                    298.8 K
D1               1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     1H
P1                     7.66 usec
PL1                    4.00 dB
SFO1         600.1337060 MHz

F2 - Processing parameters
SI                    32768
SF           600.1299817 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```

1H NMR (150 MHz, DMSO-d6)

4f



```
Current Data Parameters
NAME             1j 101 13 C
EXPNO                     10
PROCNO                     1

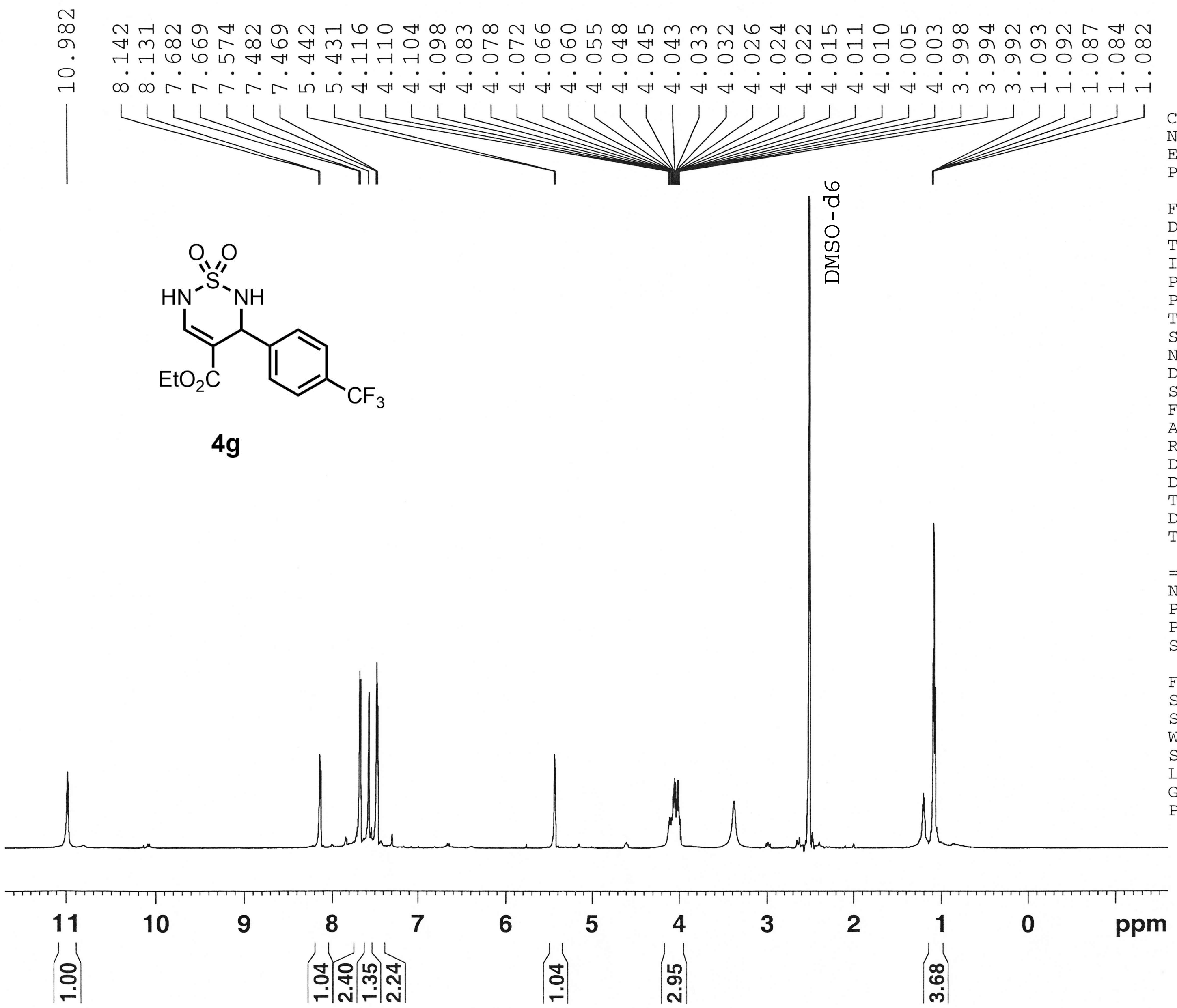
F2 - Acquisition Parameters
Date_               20070307
Time                   21.22
INSTRUM                spect
PROBHD      5 mm PABBI 1H/
PULPROG              zgpg30
TD                     65536
SOLVENT                 DMSO
NS                      2048
DS                         4
SWH               35971.223 Hz
FIDRES             0.548877 Hz
AQ                0.9110143 sec
RG                     16384
DW                    13.900 usec
DE                      6.00 usec
TE                     299.4 K
D1                2.00000000 sec
d11               0.03000000 sec
DELTA             1.89999998 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                     15.00 usec
PL1                     0.33 dB
SFO1             150.9178988 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                      1H
PCPD2                  70.00 usec
PL2                     4.00 dB
PL12                   23.22 dB
PL13                   24.00 dB
SFO2             600.1324005 MHz

F2 - Processing parameters
SI                     32768
SF               150.9028845 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

1H NMR (600 MHz, DMSO-d6)



4g

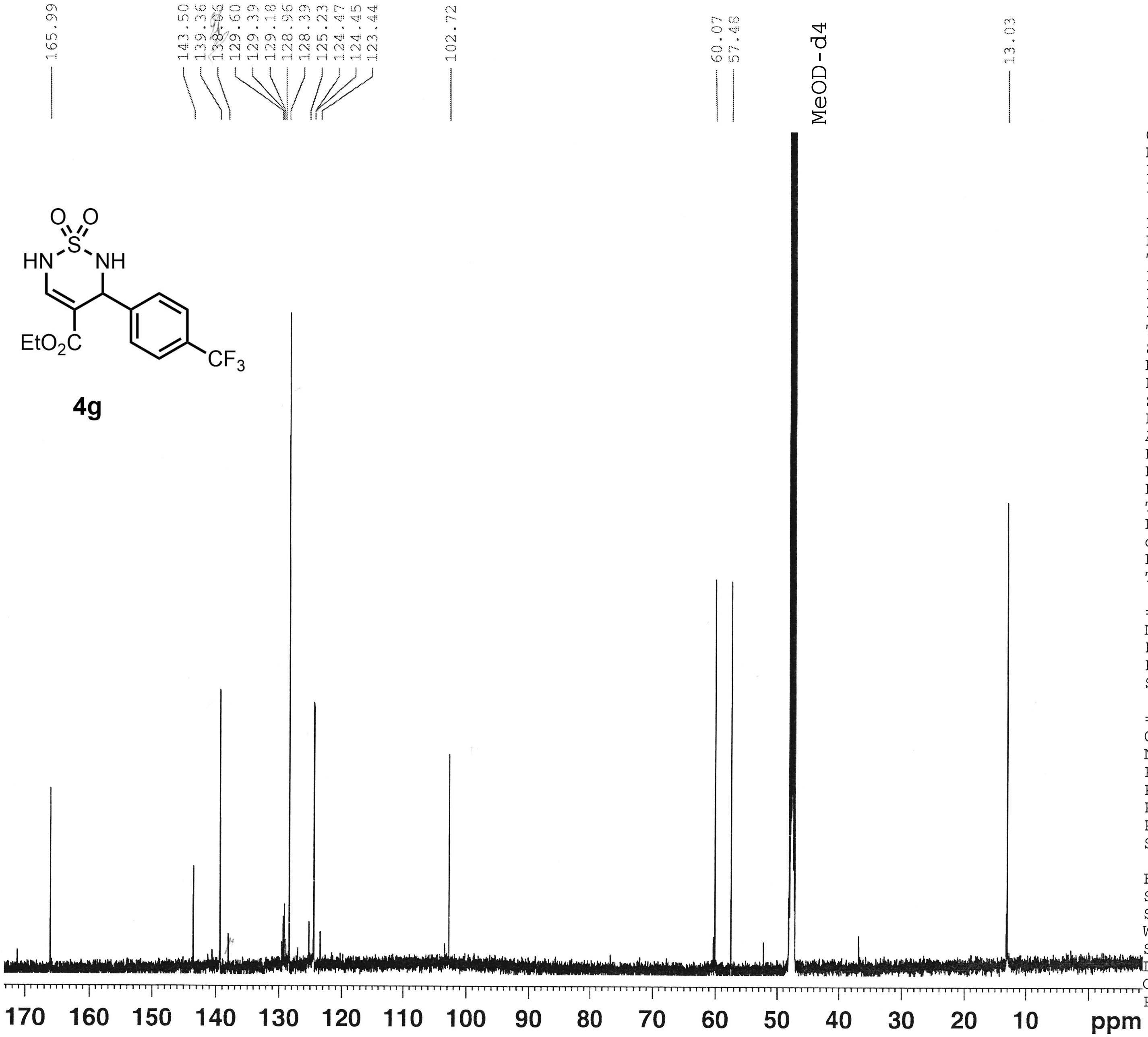
```
Current Data Parameters
NAME          lj 125 13 c
EXPNO                  10
PROCNO                  1

F2 - Acquisition Parameters
Date_            20070320
Time                17.47
INSTRUM             spect
PROBHD   5 mm PABBI 1H/
PULPROG              zg30
TD                  65536
SOLVENT              DMSO
NS                     16
DS                      2
SWH             12376.237 Hz
FIDRES           0.188846 Hz
AQ              2.6477449 sec
RG                  287.4
DW                 40.400 usec
DE                   6.00 usec
TE                  298.8 K
D1             1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                   7.66 usec
PL1                  4.00 dB
SFO1          600.1337060 MHz

F2 - Processing parameters
SI                  32768
SF            600.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

13C NMR (150 MHz, MeOD-d4)



4g

```
Current Data Parameters
NAME              1j 125
EXPNO                  2
PROCNO                 1

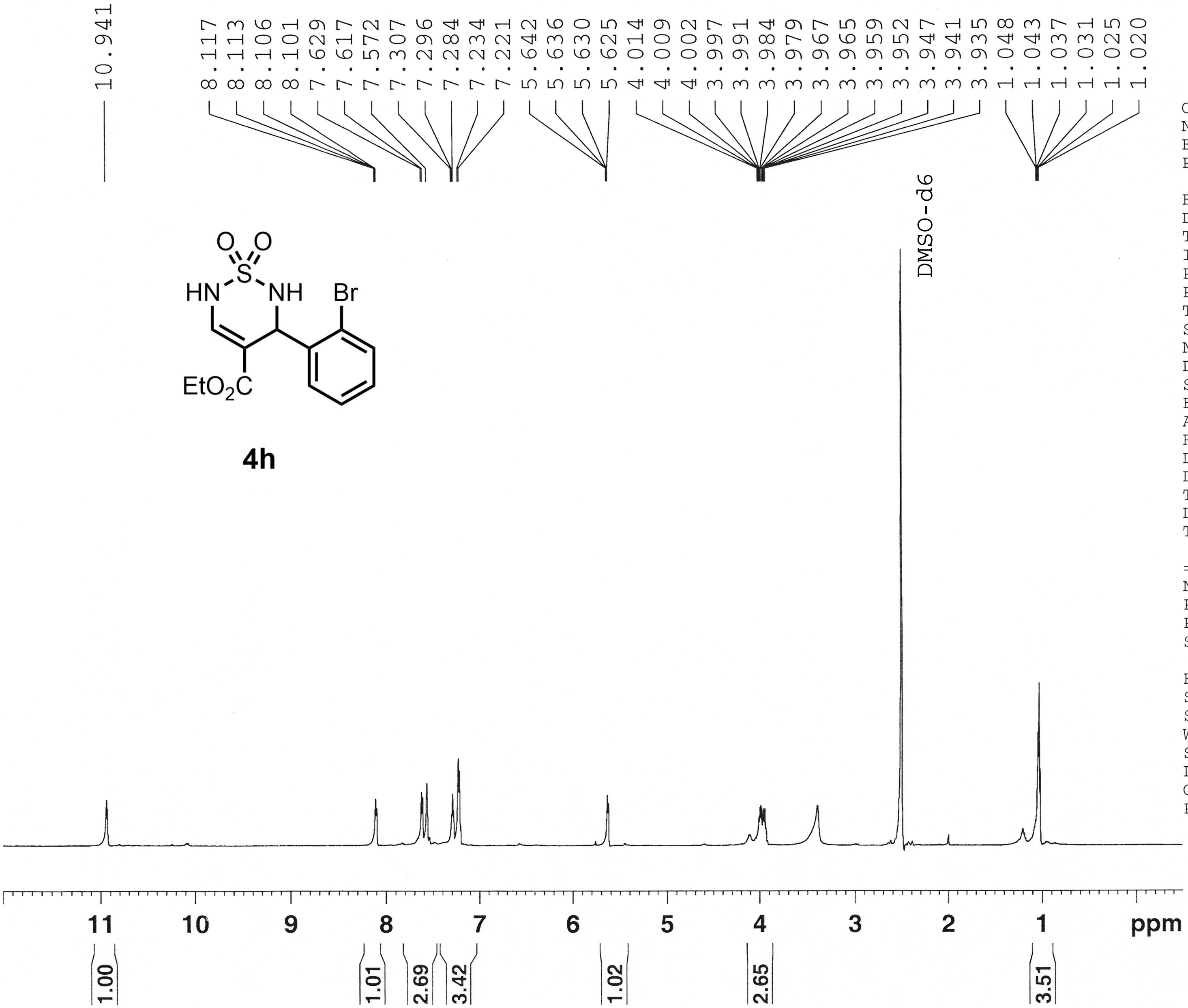
F2 - Acquisition Parameters
Date_           20070712
Time                9.11
INSTRUM            spect
PROBHD   5 mm CPTCI 1H-
PULPROG          zgpg30
TD                 65536
SOLVENT             MeOD
NS                   423
DS                     4
SWH           35971.223 Hz
FIDRES         0.548877 Hz
AQ            0.9110143 sec
RG                 13004
DW                13.900 usec
DE                  6.00 usec
TE                 298.0 K
D1          2.00000000 sec
d11         0.03000000 sec
DELTA       1.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 12.00 usec
PL1                 0.00 dB
SFO1         150.9178988 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 3.90 dB
PL12               23.90 dB
PL13               23.90 dB
SFO2         600.1324005 MHz

F2 - Processing parameters
SI                 32768
SF           150.9028090 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

1H NMR (600 MHz, DMSO-d6)



4h

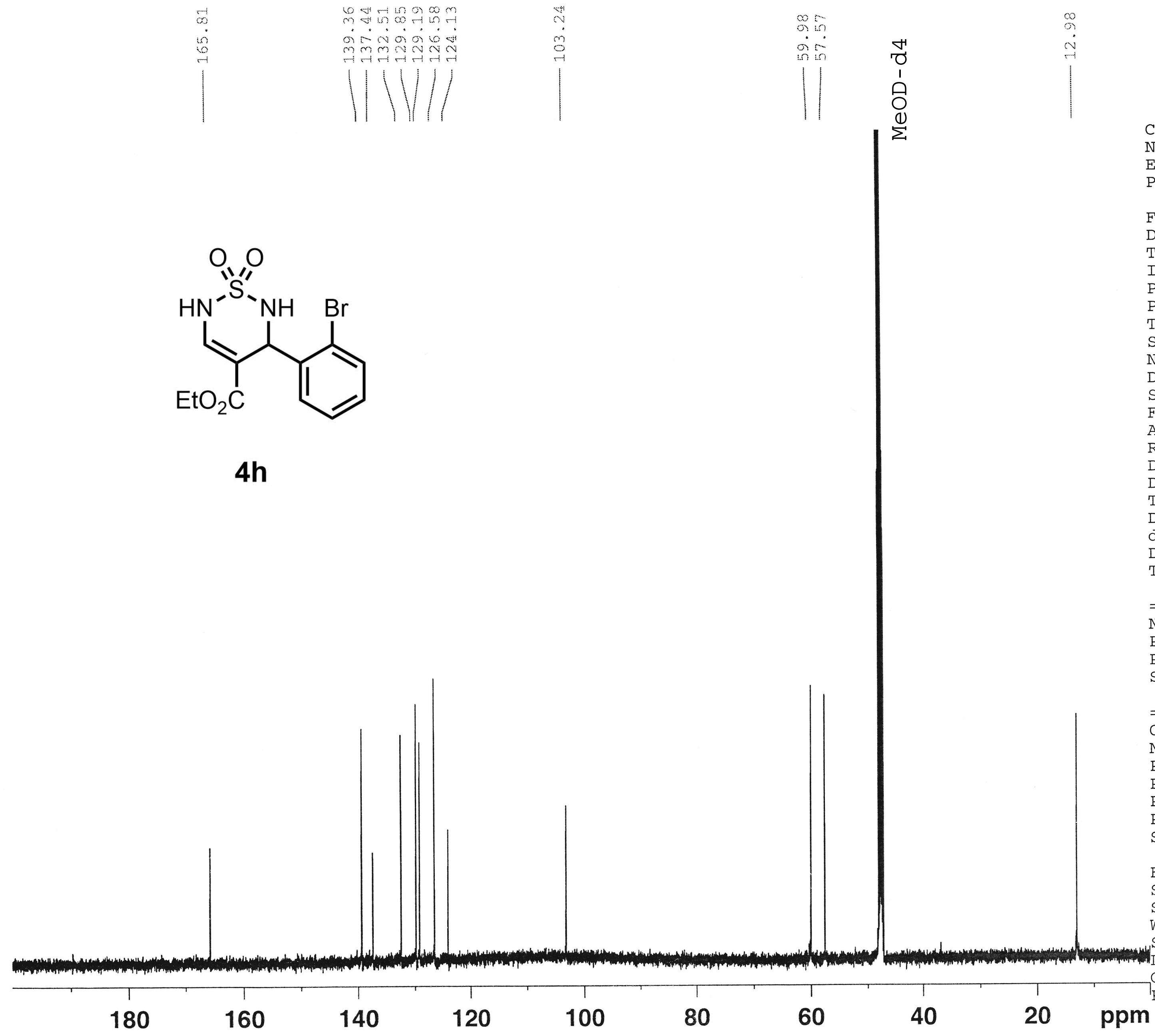
```
Current Data Parameters
NAME        lj 117 b13 c
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20070320
Time               19.38
INSTRUM            spect
PROBHD    5 mm PABBI 1H/
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    16
DS                     2
SWH            12376.237 Hz
FIDRES          0.188846 Hz
AQ             2.6477449 sec
RG                 287.4
DW                40.400 usec
DE                  6.00 usec
TE                 299.2 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                  7.66 usec
PL1                 4.00 dB
SFO1        600.1337060 MHz

F2 - Processing parameters
SI                 32768
SF          600.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

13C NMR (150 MHz, MeOD-d4)



4h

```
Current Data Parameters
NAME          lj 127 13 c
EXPNO                   3
PROCNO                  1

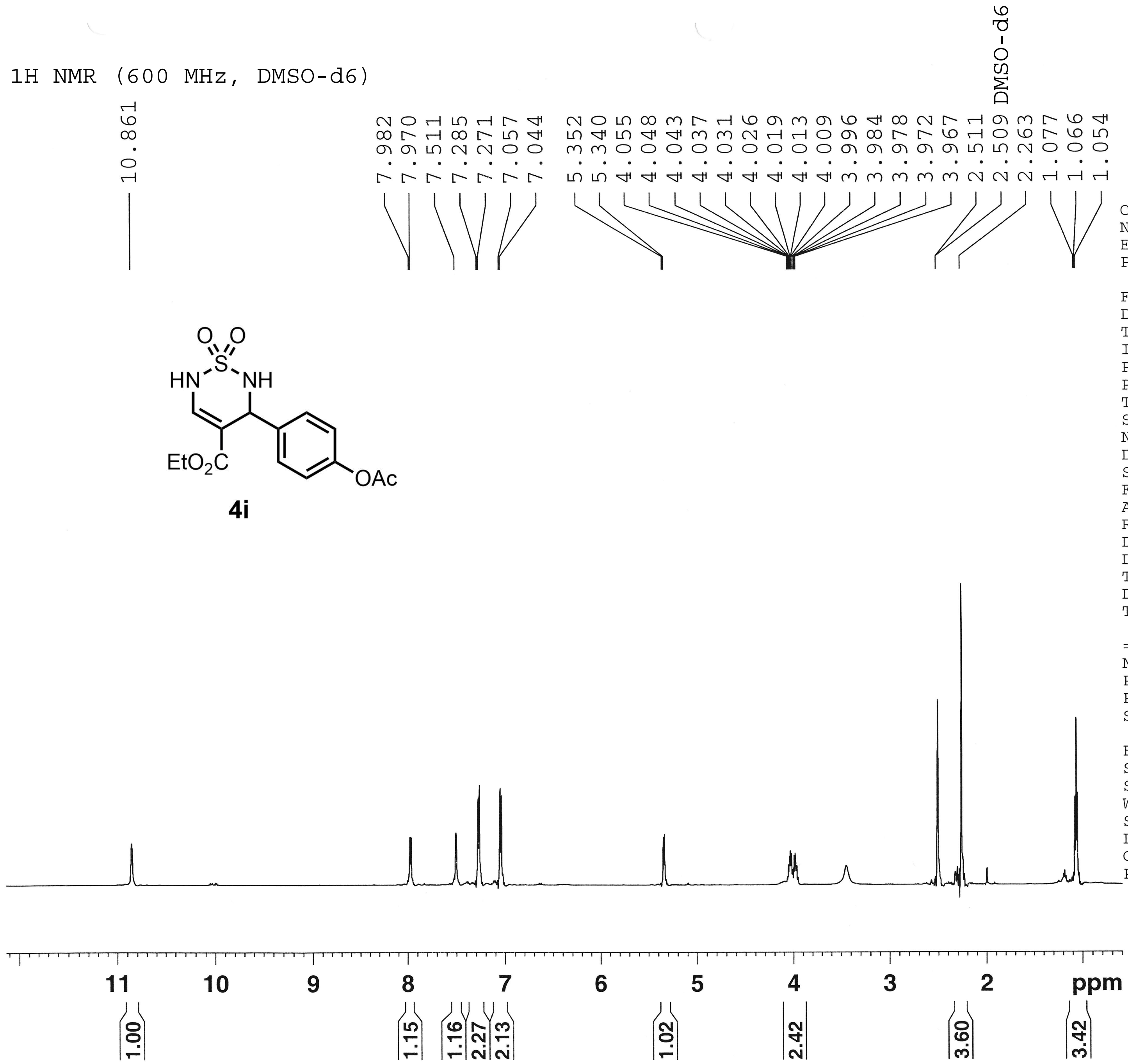
F2 - Acquisition Parameters
Date_            20070710
Time                 7.42
INSTRUM             spect
PROBHD   5 mm CPTCI 1H-
PULPROG           zgpg30
TD                 65536
SOLVENT             MeOD
NS                    45
DS                     4
SWH            35971.223 Hz
FIDRES          0.548877 Hz
AQ             0.9110143 sec
RG               11585.2
DW                13.900 usec
DE                  6.00 usec
TE                 298.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 12.00 usec
PL1                 0.00 dB
SFO1         150.9178988 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 3.90 dB
PL12               23.90 dB
PL13               23.90 dB
SFO2         600.1324005 MHz

F2 - Processing parameters
SI                 32768
SF           150.9028090 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

1H NMR (600 MHz, DMSO-d6)



4i

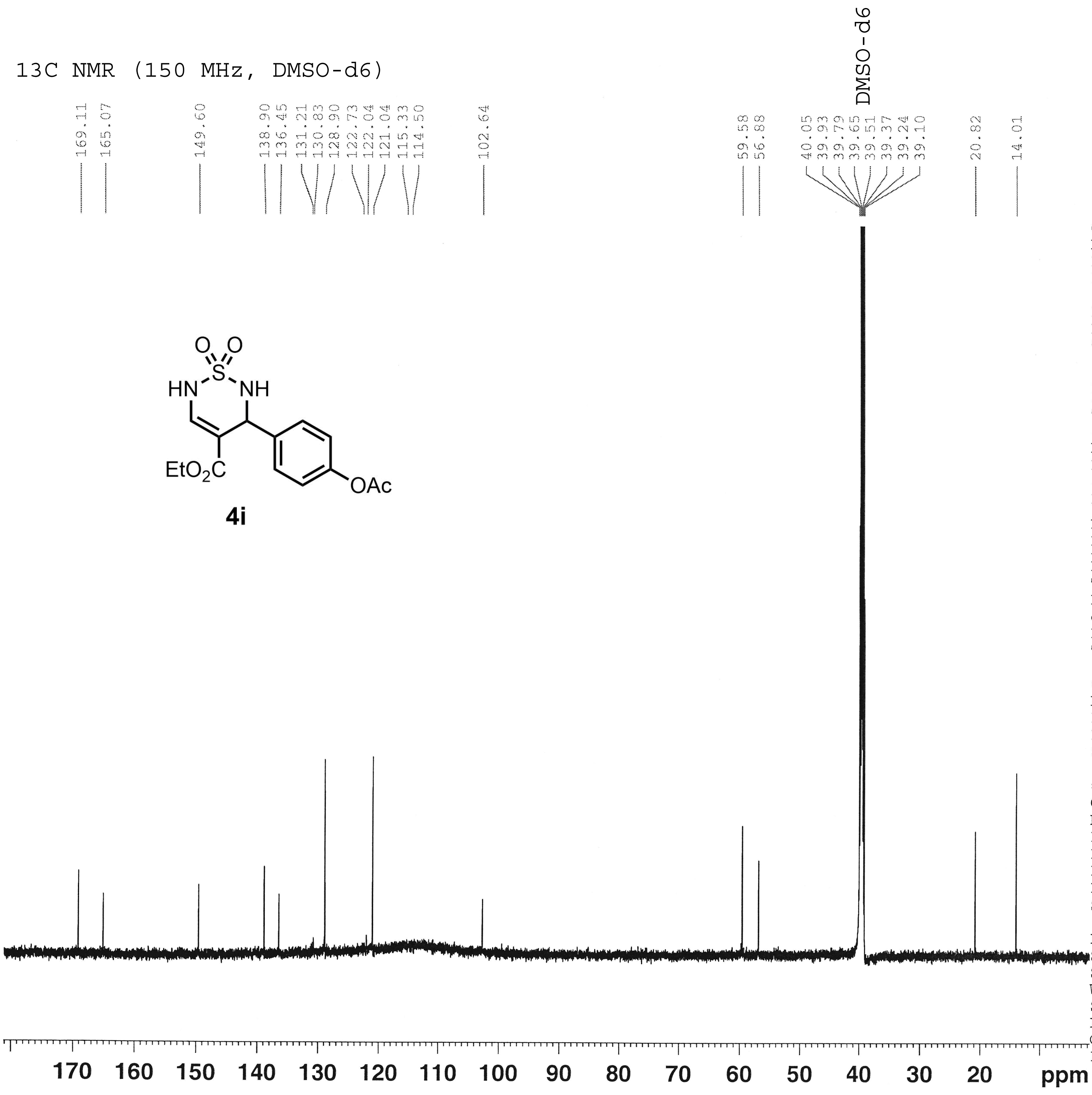
```
Current Data Parameters
NAME          1j 111 13 c
EXPNO                  10
PROCNO                  1

F2 - Acquisition Parameters
Date_            20070314
Time                18.50
INSTRUM             spect
PROBHD   5 mm PABBI 1H/
PULPROG              zg30
TD                  65536
SOLVENT              DMSO
NS                     16
DS                      2
SWH             12376.237 Hz
FIDRES           0.188846 Hz
AQ              2.6477449 sec
RG                  203.2
DW                 40.400 usec
DE                   6.00 usec
TE                  299.2 K
D1             1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                   7.66 usec
PL1                  4.00 dB
SFO1         600.1337060 MHz

F2 - Processing parameters
SI                  32768
SF           600.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

13C NMR (150 MHz, DMSO-d6)



4i

```
Current Data Parameters
NAME          1j 111 13 c
EXPNO                  11
PROCNO                  1

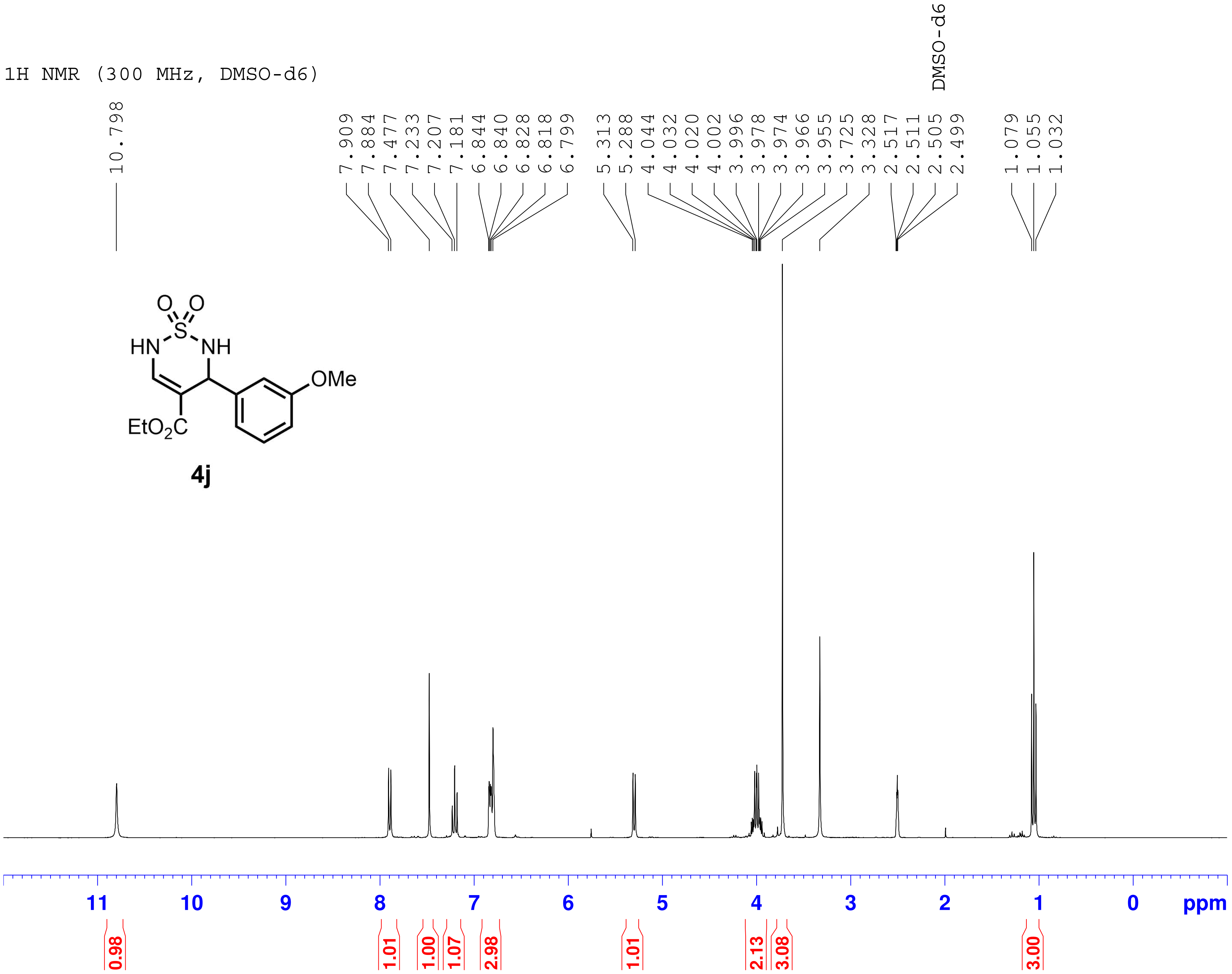
F2 - Acquisition Parameters
Date_            20070314
Time                20.35
INSTRUM             spect
PROBHD   5 mm PABBI 1H/
PULPROG           zgpg30
TD                 65536
SOLVENT             DMSO
NS                  2048
DS                     4
SWH            35971.223 Hz
FIDRES          0.548877 Hz
AQ             0.9110143 sec
RG                  8192
DW                13.900 usec
DE                  6.00 usec
TE                 299.9 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 15.00 usec
PL1                 0.33 dB
SFO1         150.9178988 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              70.00 usec
PL2                 4.00 dB
PL12               23.22 dB
PL13               24.00 dB
SFO2         600.1324005 MHz

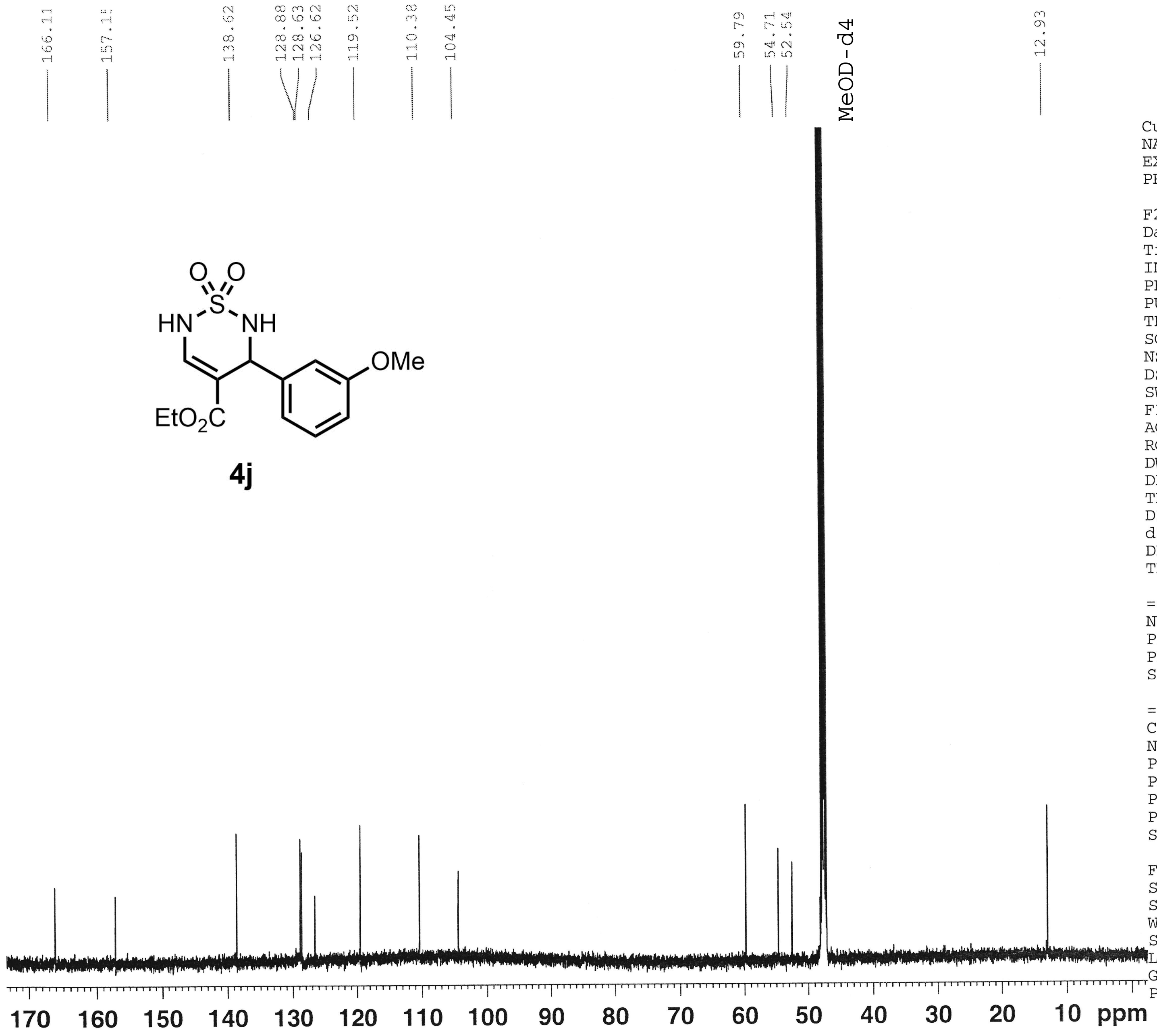
F2 - Processing parameters
SI                 32768
SF           150.9028845 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

1H NMR (300 MHz, DMSO-d6)



4j

1H NMR (150 MHz, MeOD-d4)



4j

```
Current Data Parameters
NAME          1j 094 13 c
EXPNO                   4
PROCNO                  1

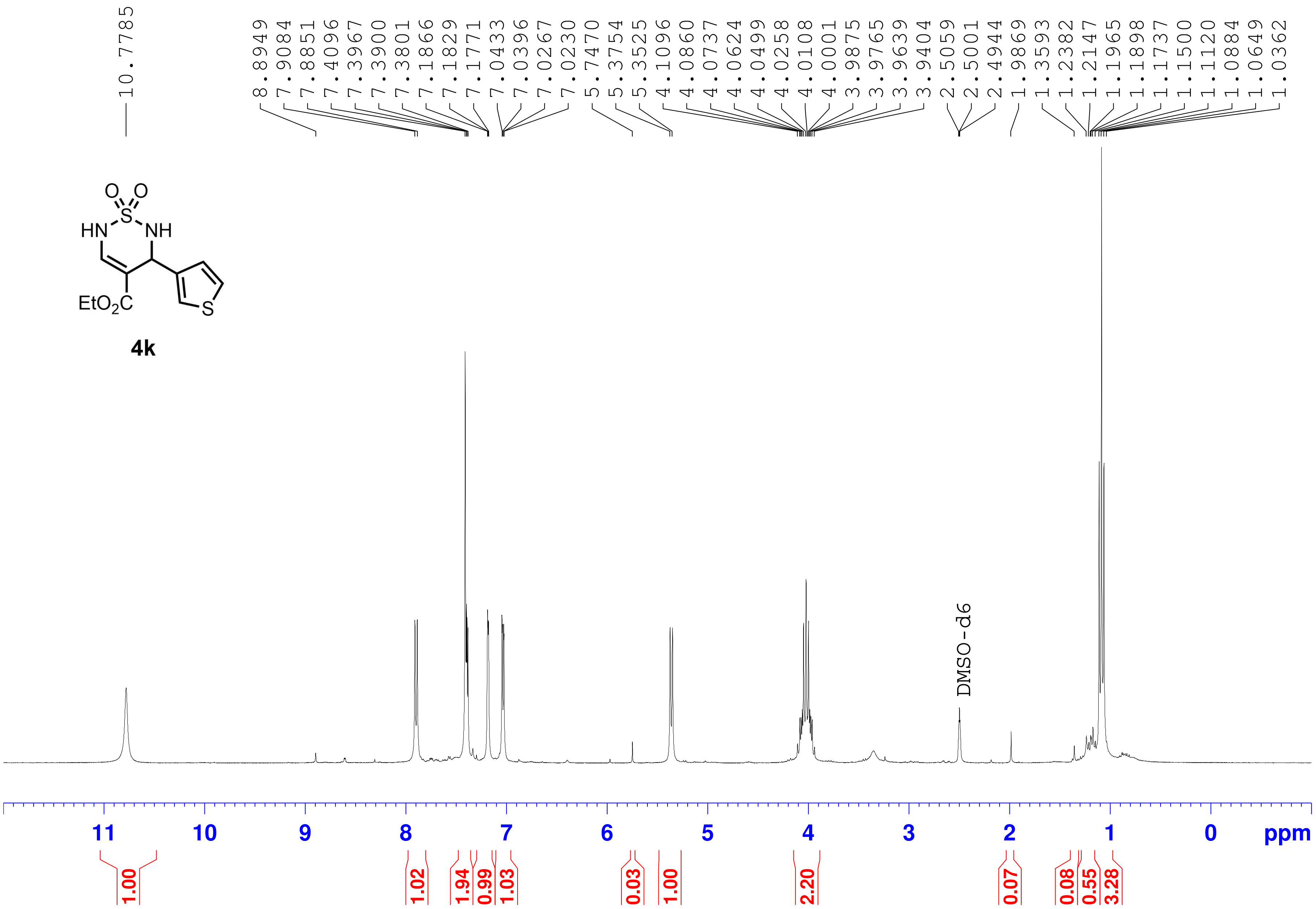
F2 - Acquisition Parameters
Date_            20070710
Time                 7.51
INSTRUM             spect
PROBHD   5 mm CPTCI 1H-
PULPROG           zgpg30
TD                 65536
SOLVENT             MeOD
NS                   301
DS                     4
SWH            35971.223 Hz
FIDRES          0.548877 Hz
AQ             0.9110143 sec
RG                 13004
DW                13.900 usec
DE                  6.00 usec
TE                 298.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 12.00 usec
PL1                 0.00 dB
SFO1         150.9178988 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 3.90 dB
PL12               23.90 dB
PL13               23.90 dB
SFO2         600.1324005 MHz

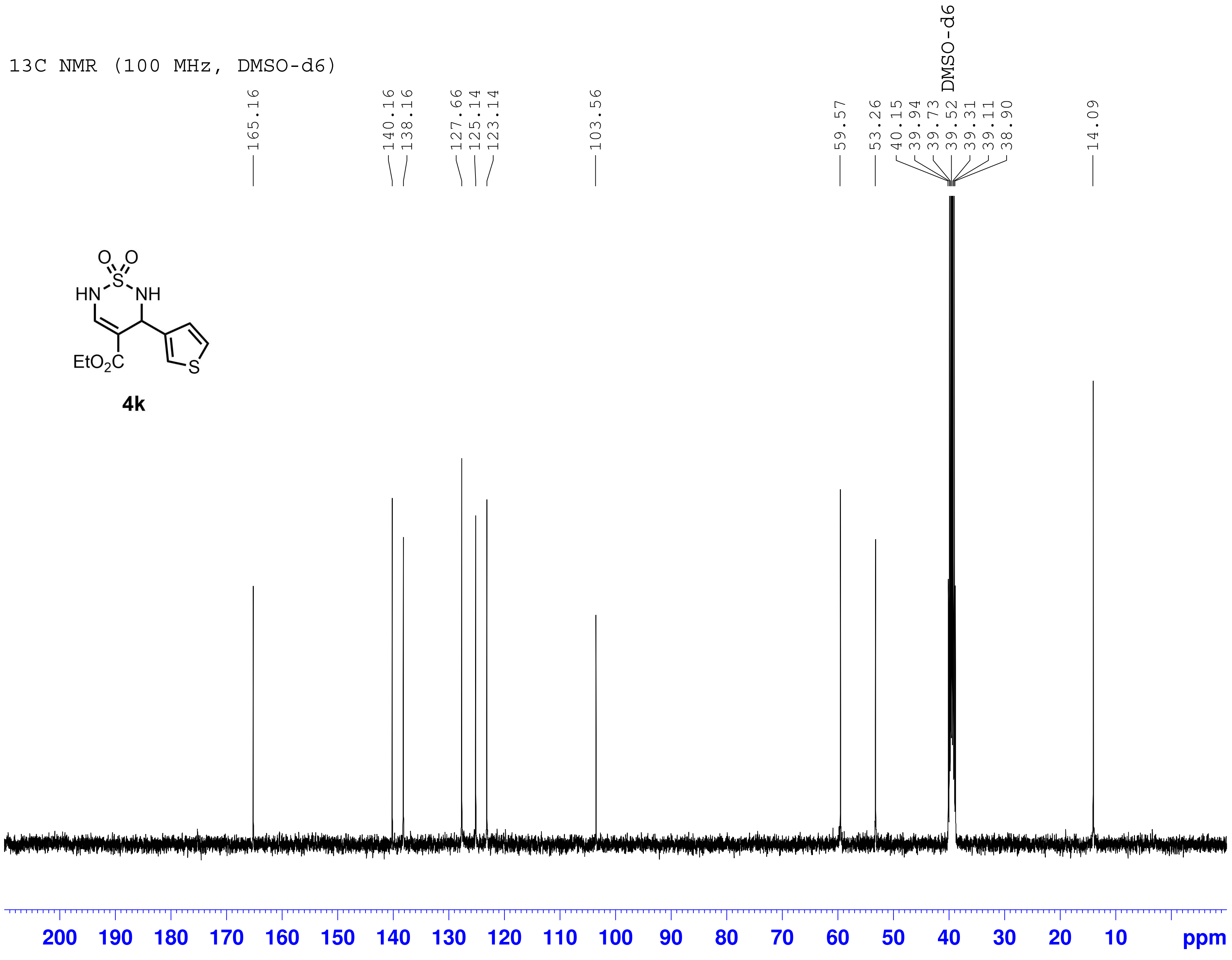
F2 - Processing parameters
SI                 32768
SF           150.9028090 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

1H NMR (400 MHz, DMSO-d6)



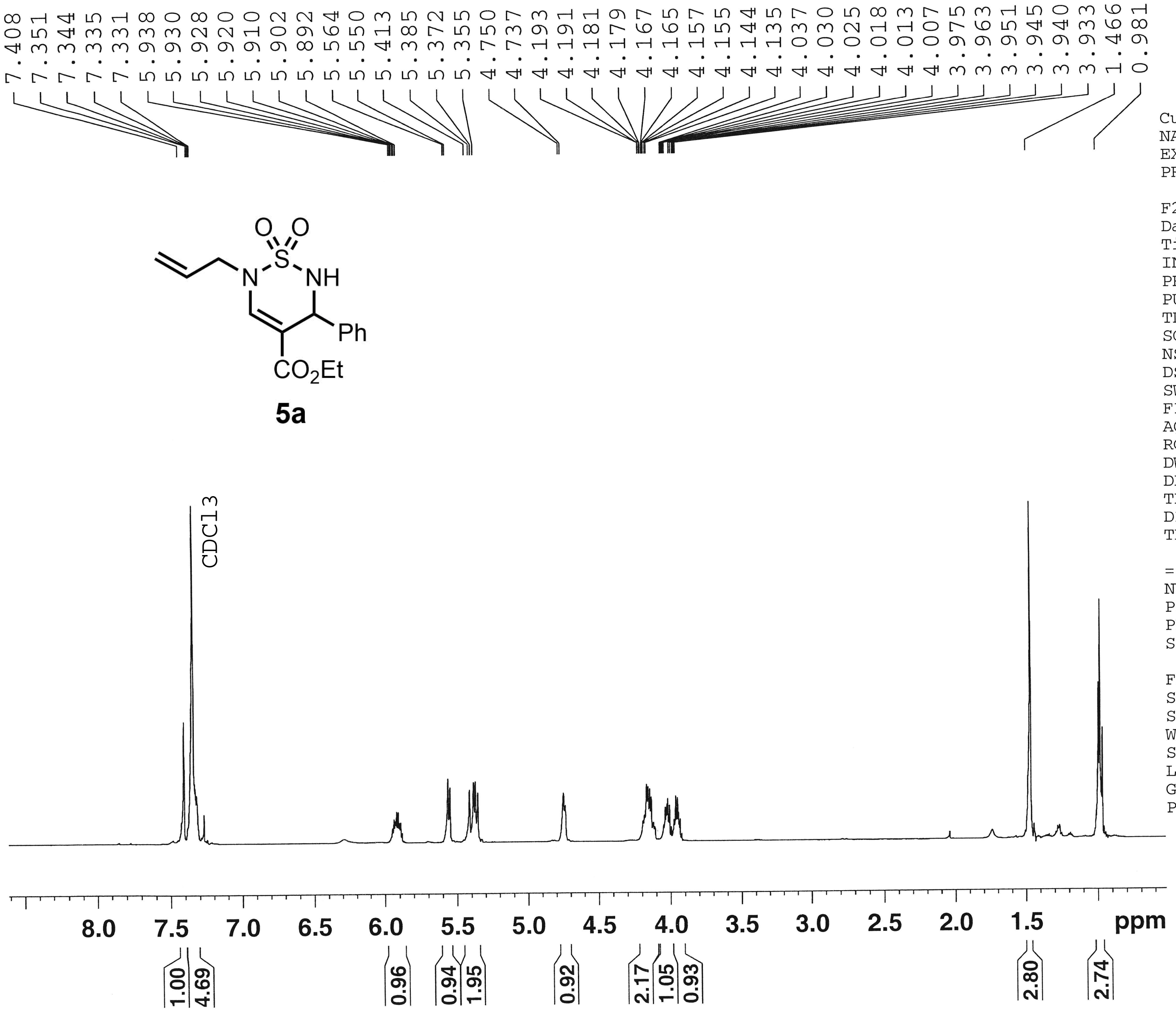
4k

13C NMR (100 MHz, DMSO-d6)



4k

1H NMR (600 MHz, CDCl3)



5a

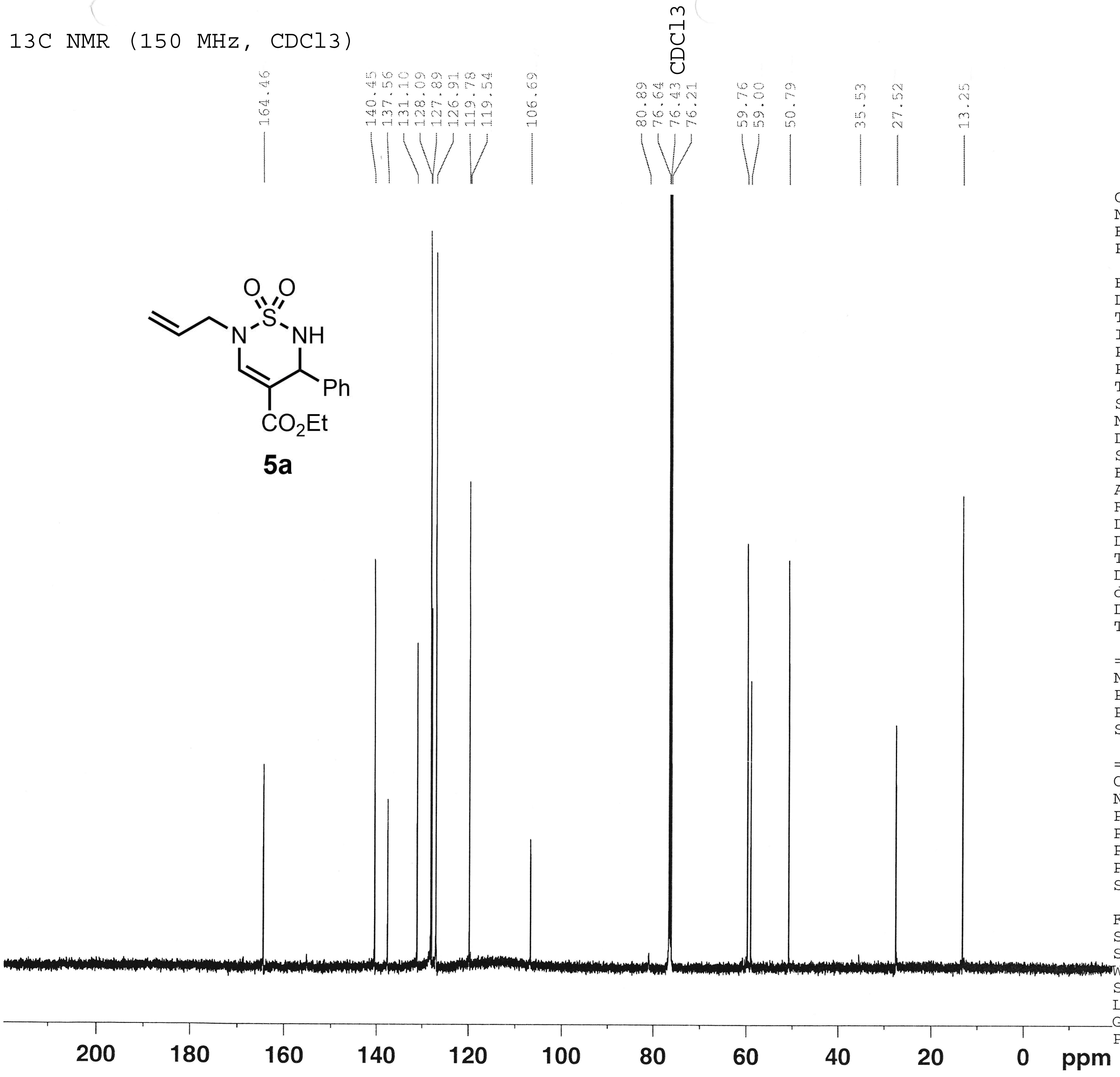
```
Current Data Parameters
NAME          lj 113 check
EXPNO                   10
PROCNO                   1

F2 - Acquisition Parameters
Date_             20070323
Time                  6.51
INSTRUM              spect
PROBHD   5 mm PABBI 1H/
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH              12376.237 Hz
FIDRES            0.188846 Hz
AQ               2.6477449 sec
RG                      64
DW                  40.400 usec
DE                    6.00 usec
TE                   299.0 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                    7.66 usec
PL1                   4.00 dB
SFO1           600.1337060 MHz

F2 - Processing parameters
SI                   32768
SF             600.1295496 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

13C NMR (150 MHz, CDCl3)



5a

```
Current Data Parameters
NAME           lj 113 13 c
EXPNO                   10
PROCNO                   1

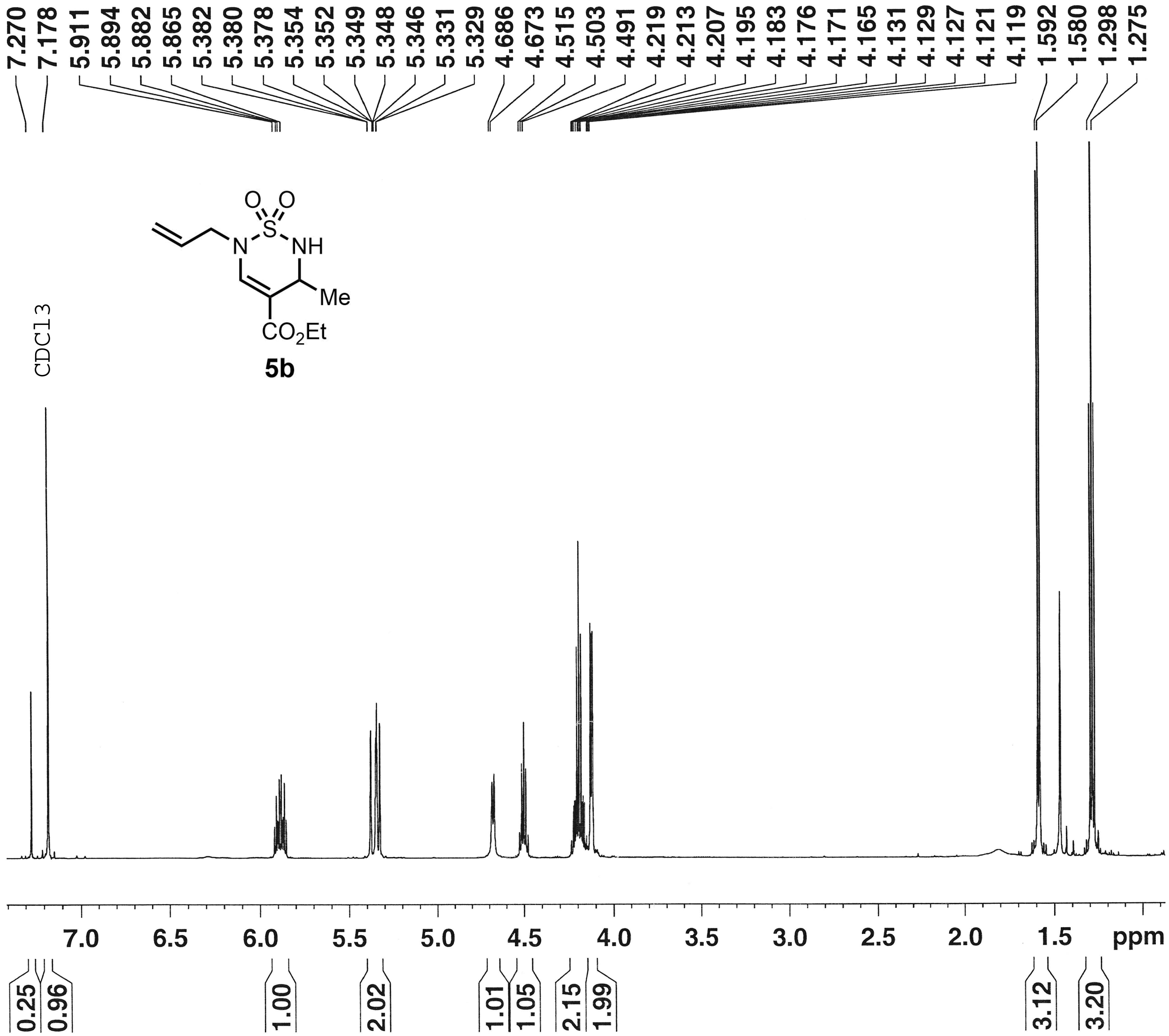
F2 - Acquisition Parameters
Date_             20070315
Time                  7.39
INSTRUM              spect
PROBHD   5 mm PABBI 1H/
PULPROG            zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    1024
DS                       4
SWH              35971.223 Hz
FIDRES            0.548877 Hz
AQ               0.9110143 sec
RG                    8192
DW                  13.900 usec
DE                    6.00 usec
TE                   299.8 K
D1              2.00000000 sec
d11             0.03000000 sec
DELTA           1.89999998 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                   15.00 usec
PL1                   0.33 dB
SFO1           150.9178988 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                70.00 usec
PL2                   4.00 dB
PL12                 23.22 dB
PL13                 24.00 dB
SFO2           600.1324005 MHz

F2 - Processing parameters
SI                   32768
SF             150.9028090 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

1H NMR (600 MHz, CDCl3)



5b

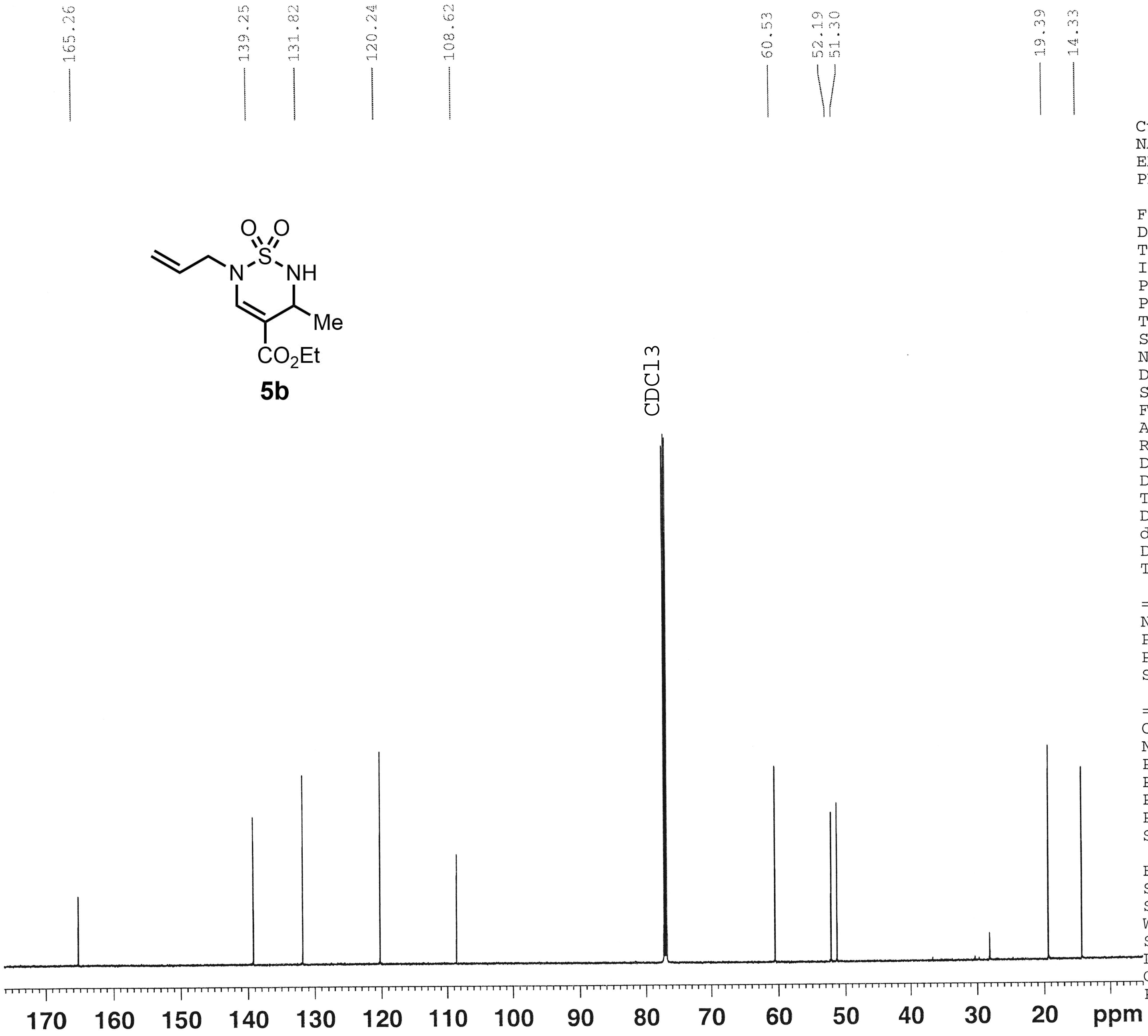
```
Current Data Parameters
NAME      1j methyl allyl ii
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20070704
Time                 10.18
INSTRUM              spect
PROBHD   5 mm CPTCI 1H-
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH             12376.237 Hz
FIDRES           0.188846 Hz
AQ              2.6477449 sec
RG                     6.3
DW                  40.400 usec
DE                    6.00 usec
TE                   298.0 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                    8.00 usec
PL1                   3.90 dB
SFO1        600.1337060 MHz

F2 - Processing parameters
SI                   32768
SF          600.1298475 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```

13C NMR (150 MHz, CDCl3)


5b

```
Current Data Parameters
NAME      1j 2    methylallyl
EXPNO                     2
PROCNO                    1

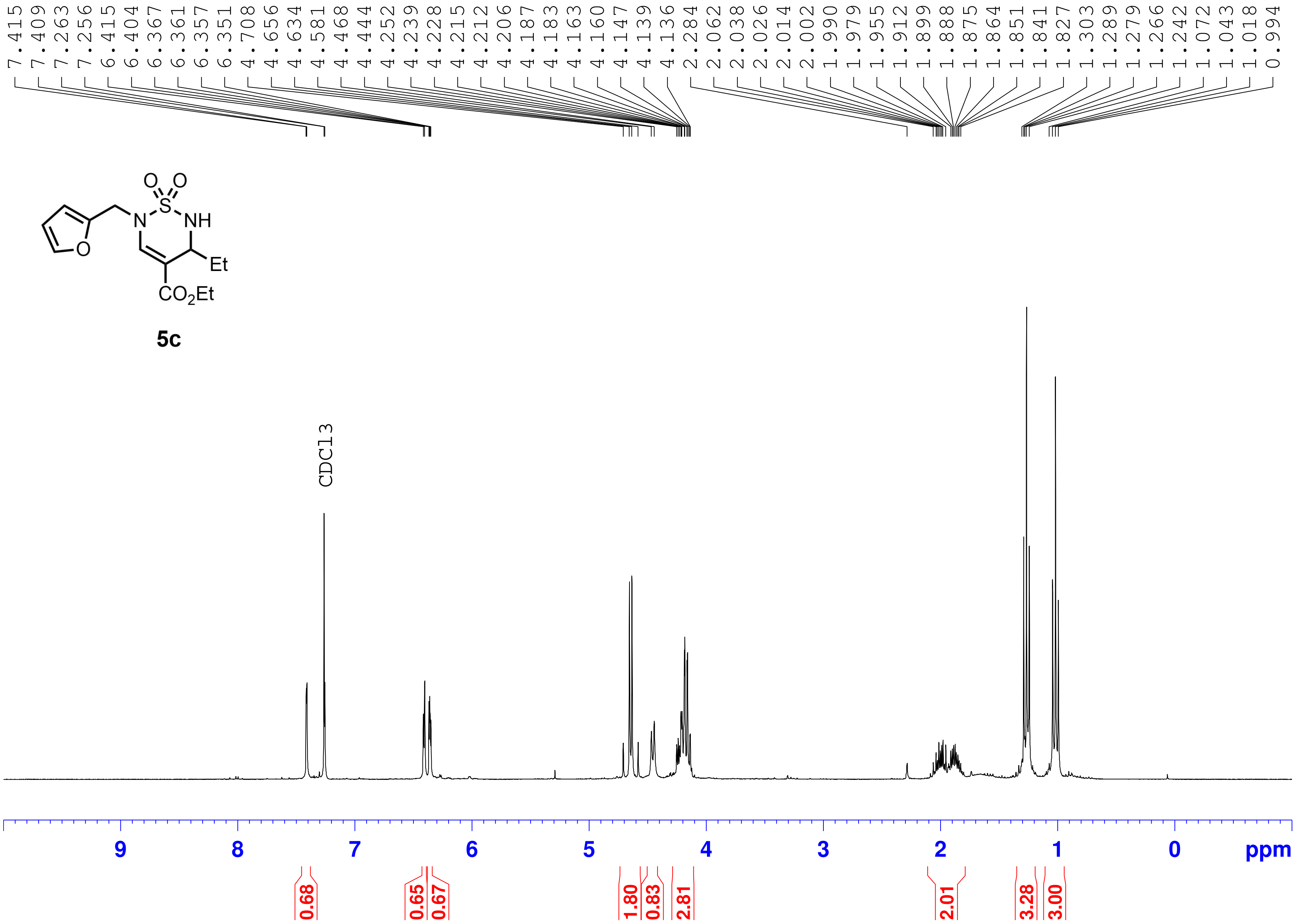
F2 - Acquisition Parameters
Date_              20070704
Time                  10.49
INSTRUM               spect
PROBHD   5 mm CPTCI 1H-
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                      295
DS                        4
SWH             35971.223 Hz
FIDRES           0.548877 Hz
AQ              0.9110143 sec
RG                    16384
DW                 13.900 usec
DE                   6.00 usec
TE                  298.0 K
D1             2.00000000 sec
d11            0.03000000 sec
DELTA          1.89999998 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                    12.00 usec
PL1                    0.00 dB
SFO1           150.9178988 MHz

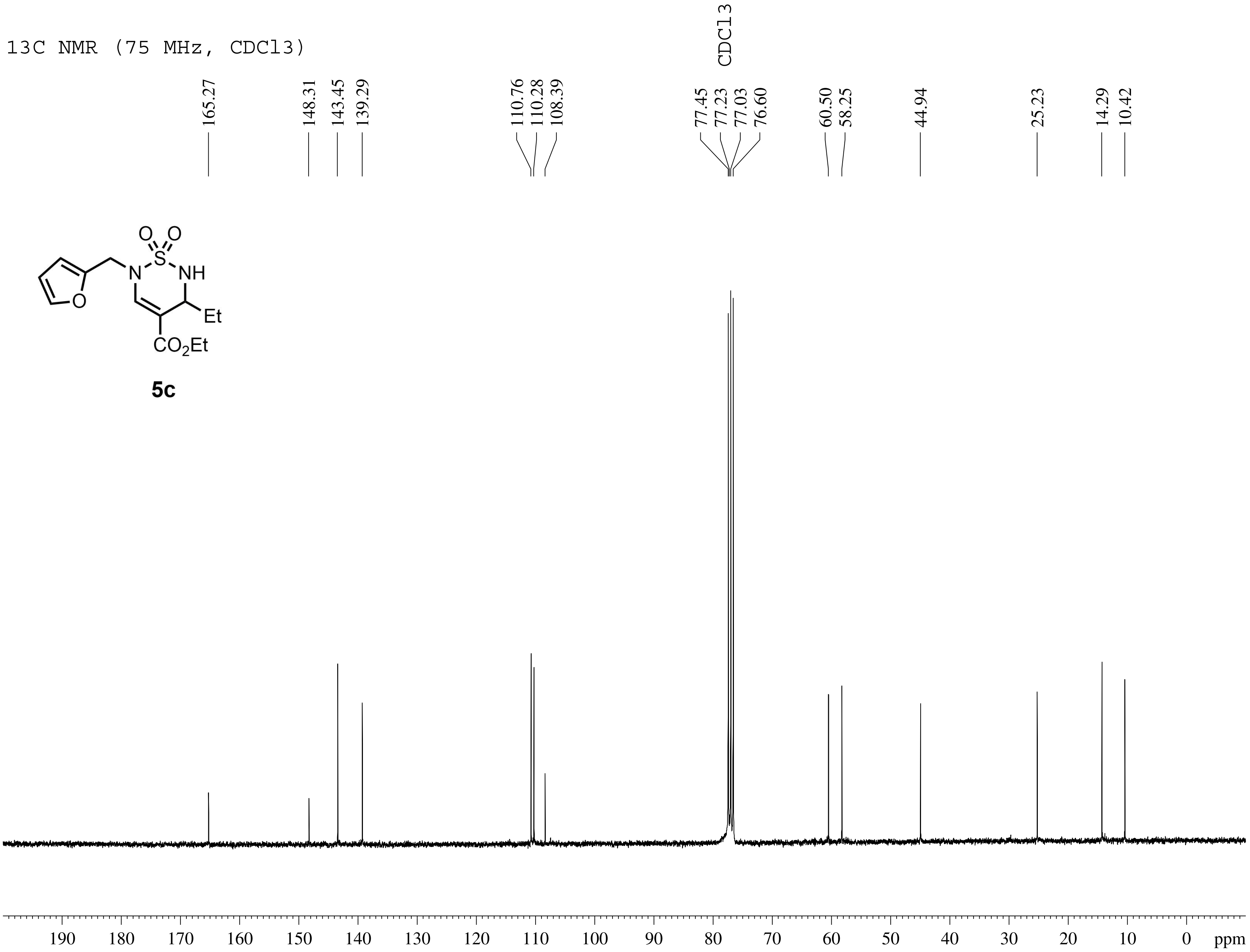
======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                 80.00 usec
PL2                    3.90 dB
PL12                  23.90 dB
PL13                  23.90 dB
SFO2           600.1324005 MHz

F2 - Processing parameters
SI                    32768
SF             150.9028090 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

1H NMR (300 MHz, CDCl3)

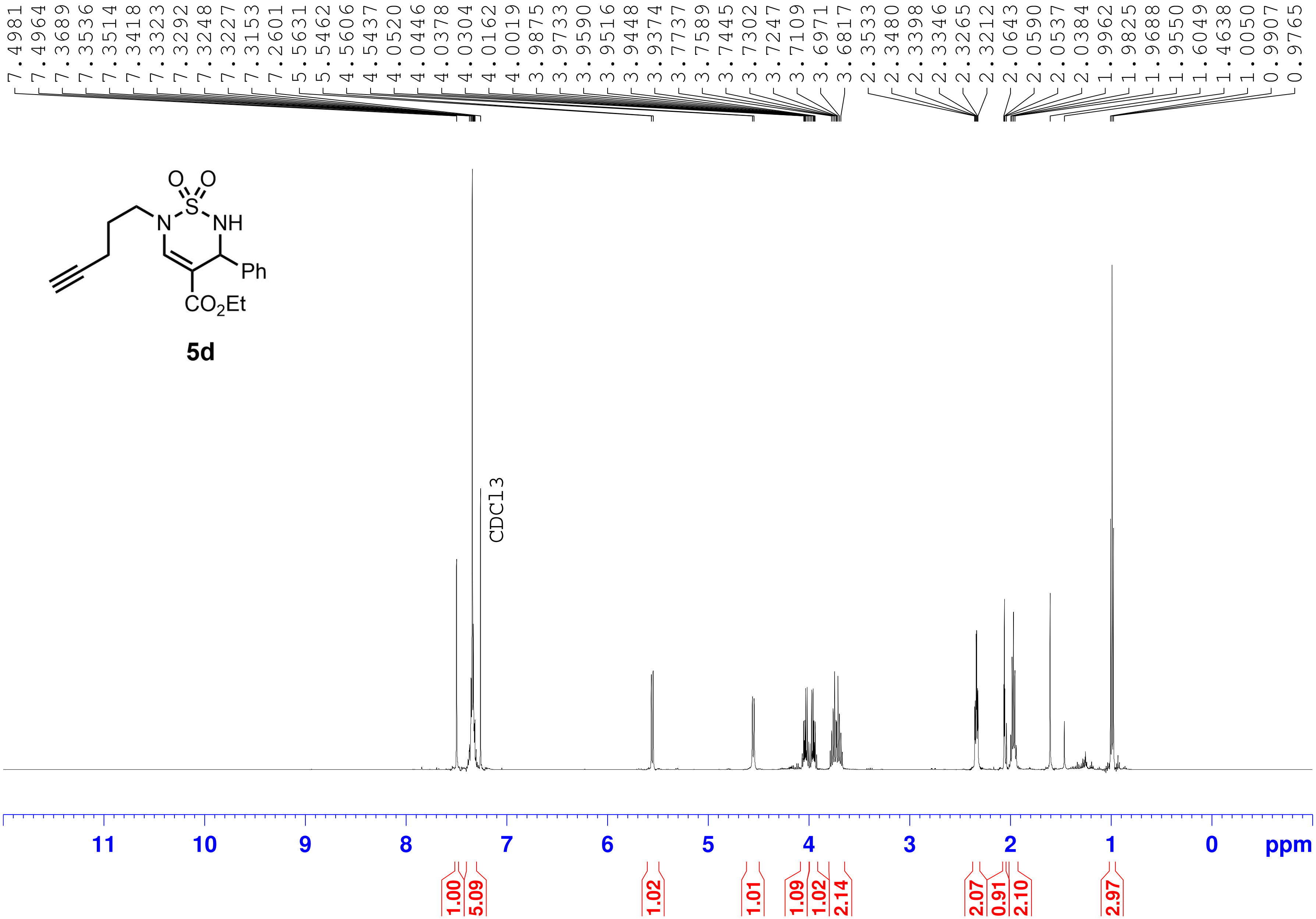


13C NMR (75 MHz, CDCl3)



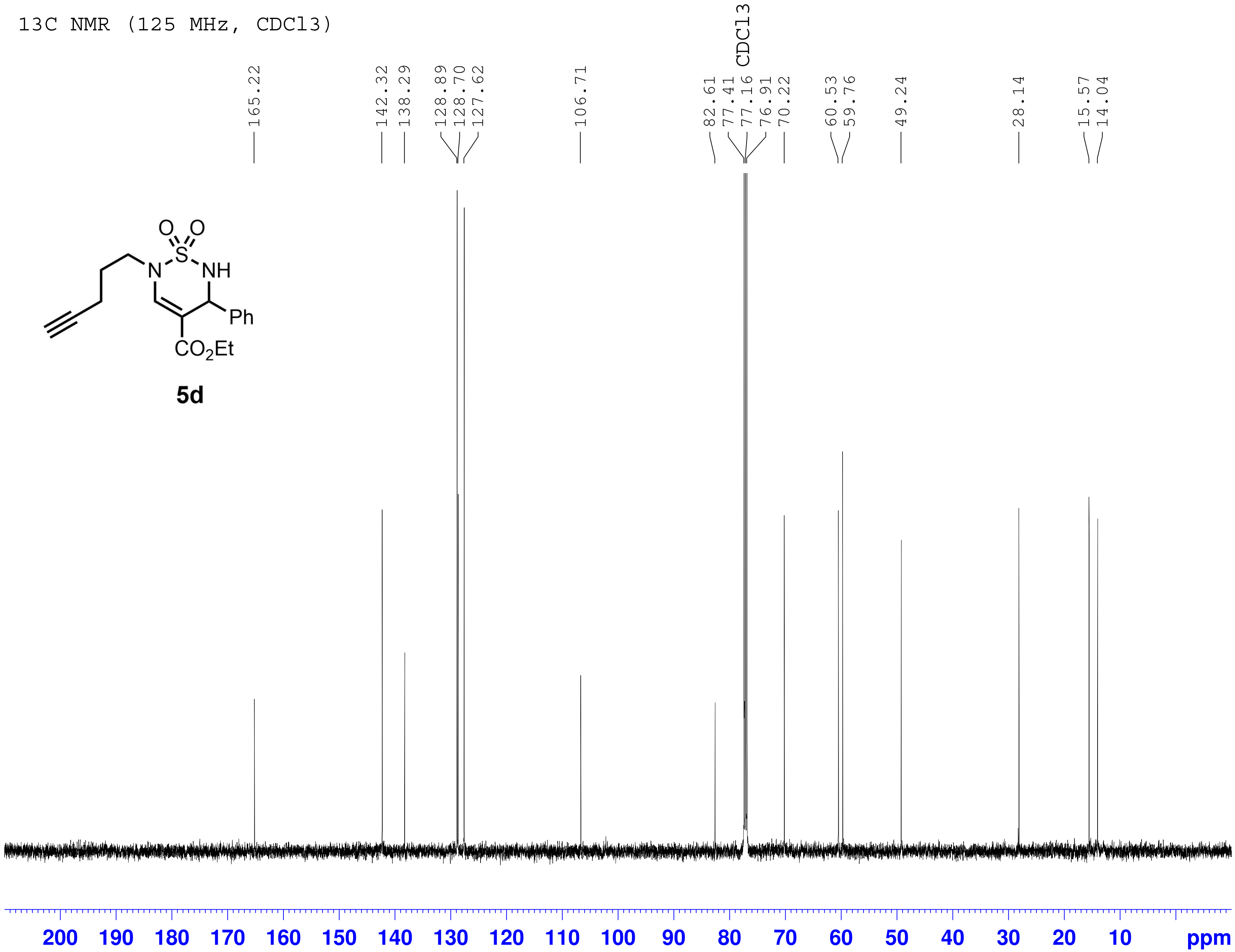
5c

1H NMR (500 MHz, CDCl3)



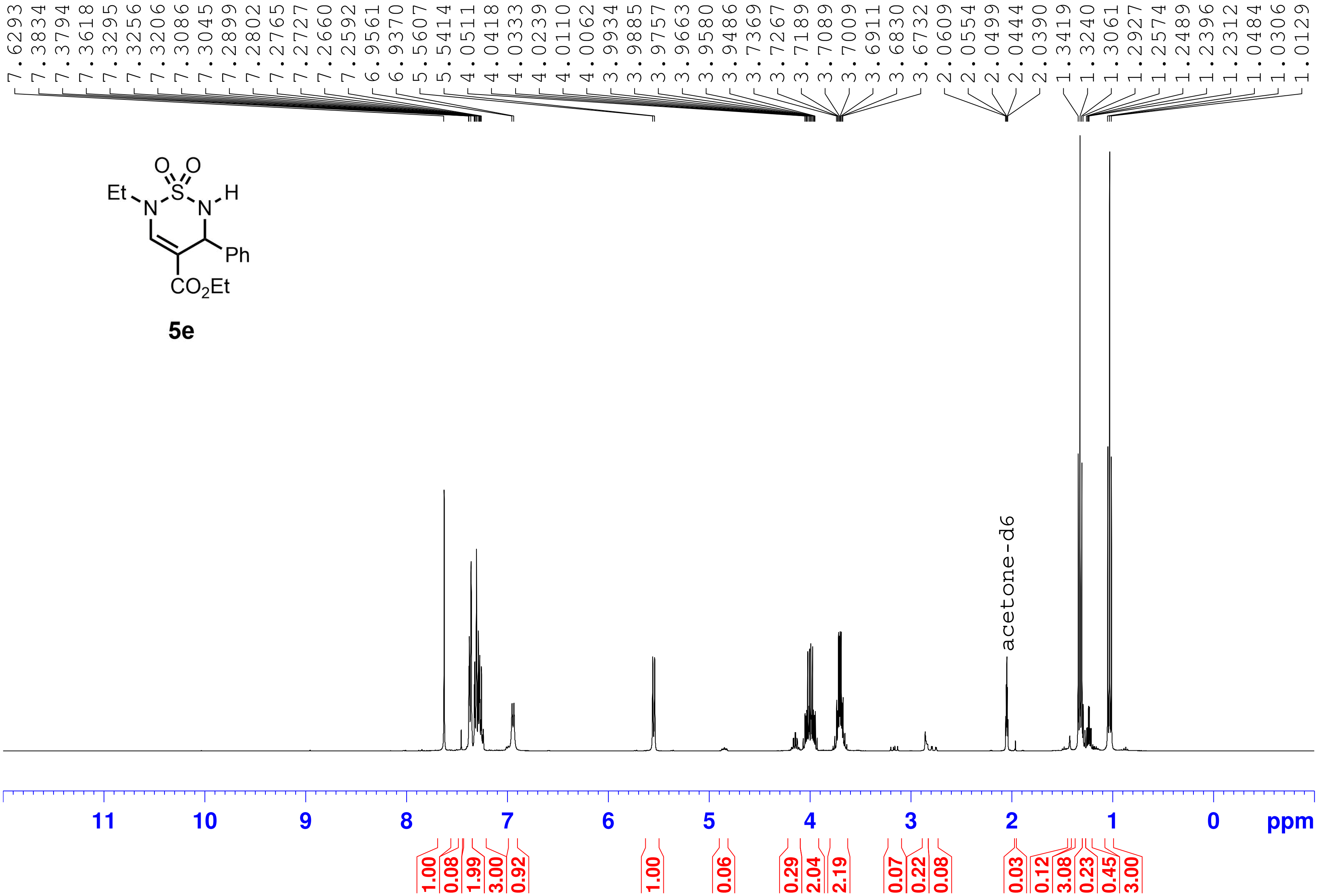
5d

13C NMR (125 MHz, CDCl3)



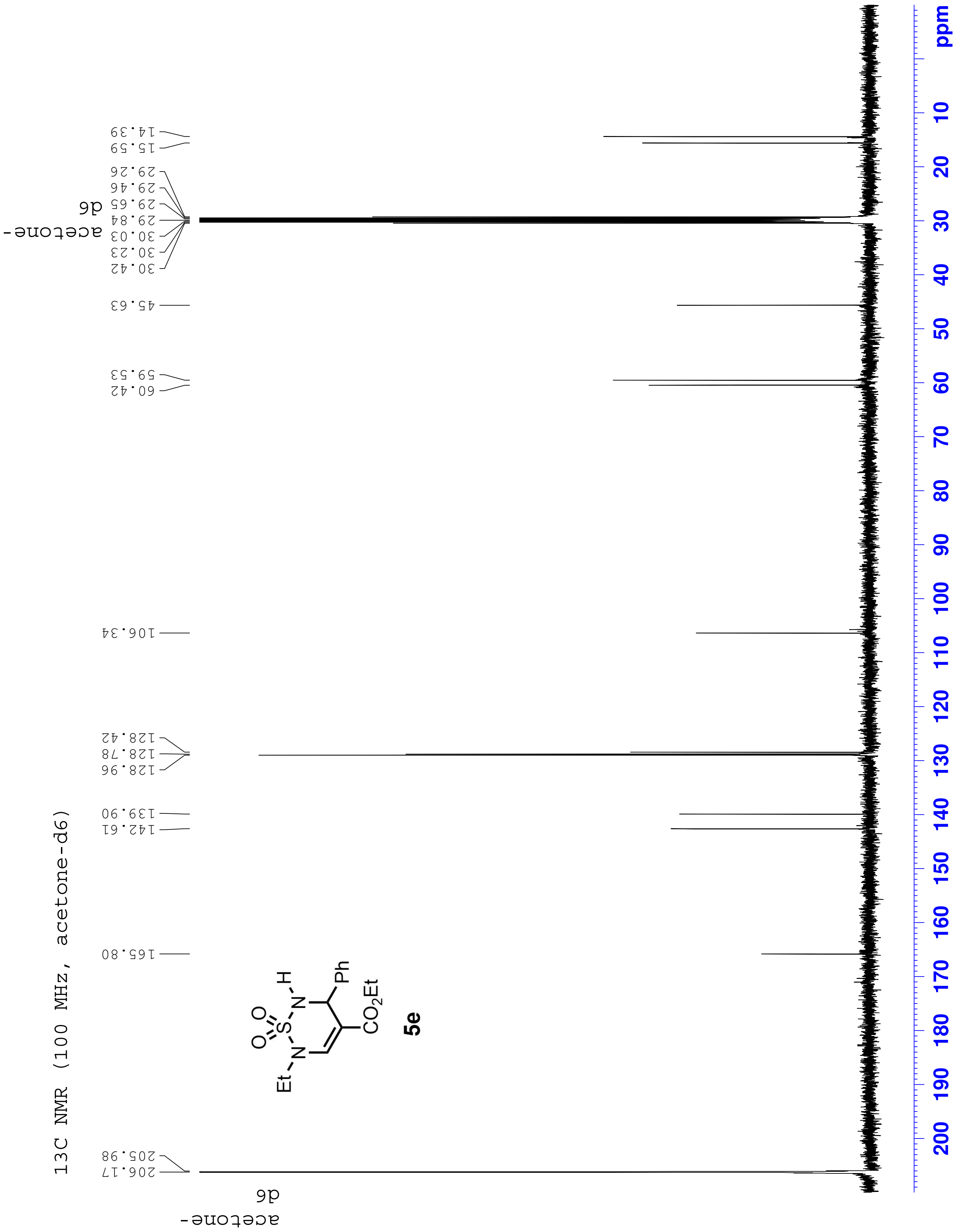
5d

1H NMR (400 MHz, acetone-d6)



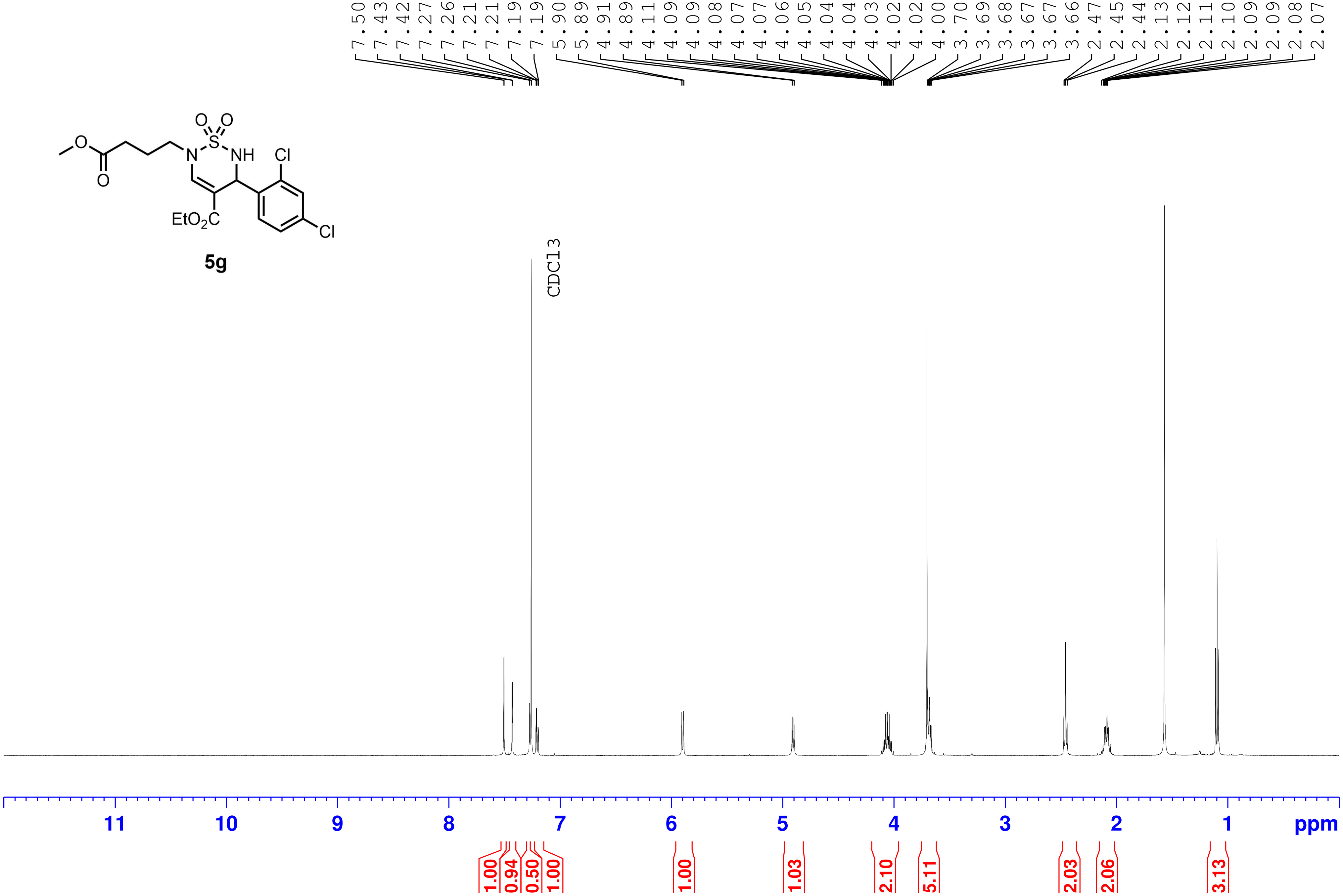
5e

13C NMR (100 MHz, acetone-d6)



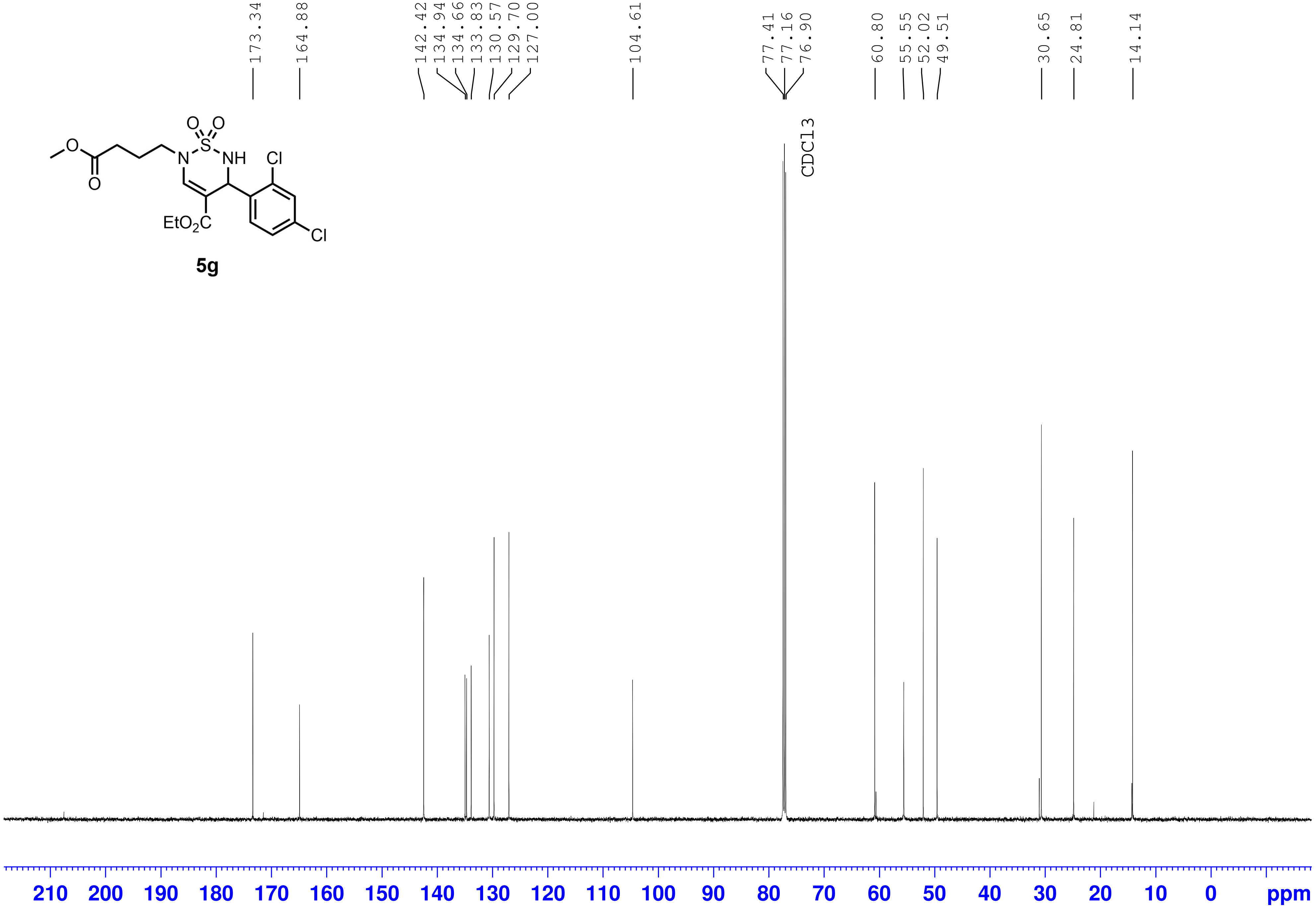
5e

1H NMR (500 MHz, CDCl3)



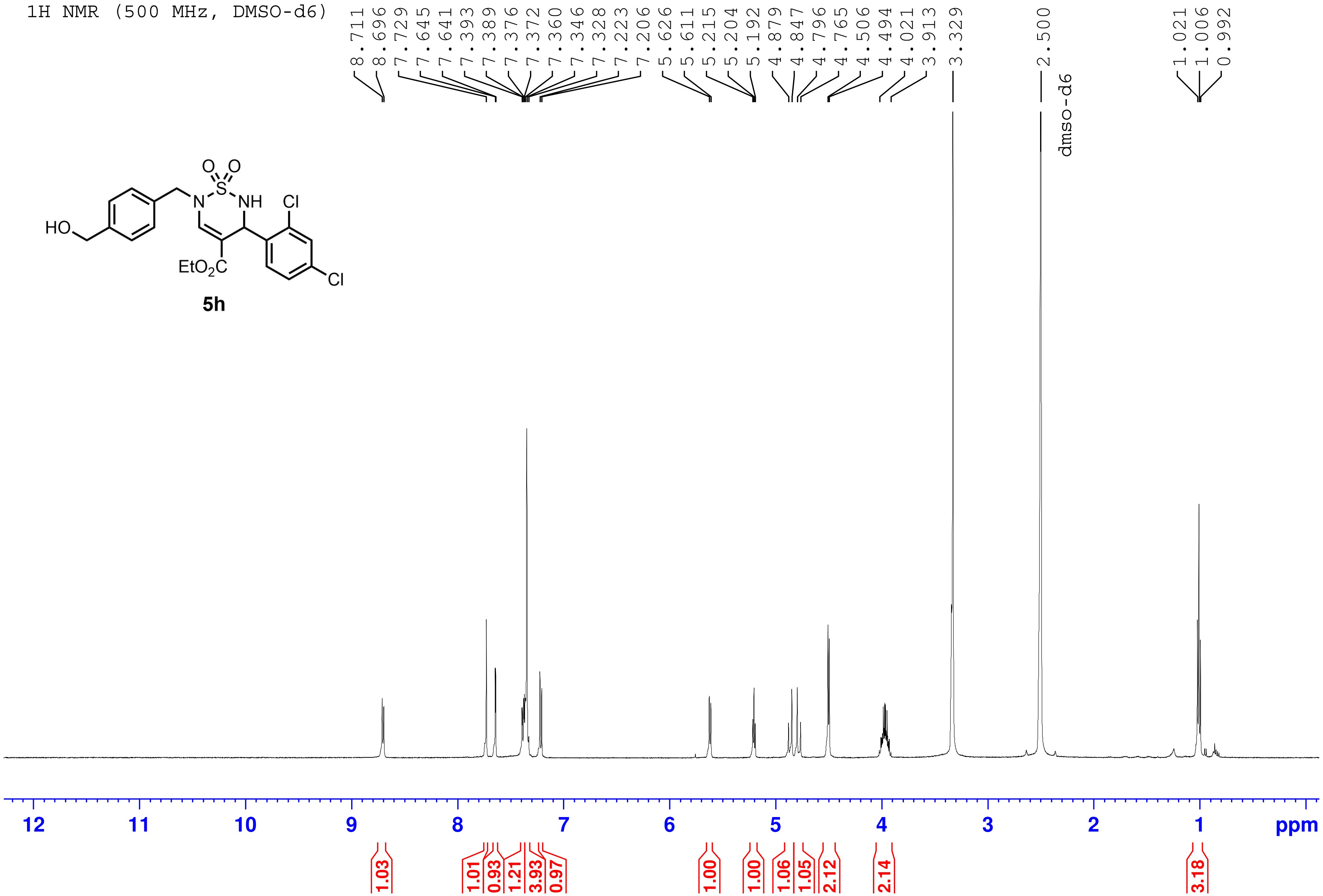
5g

1H NMR (125 MHz, CDCl3)

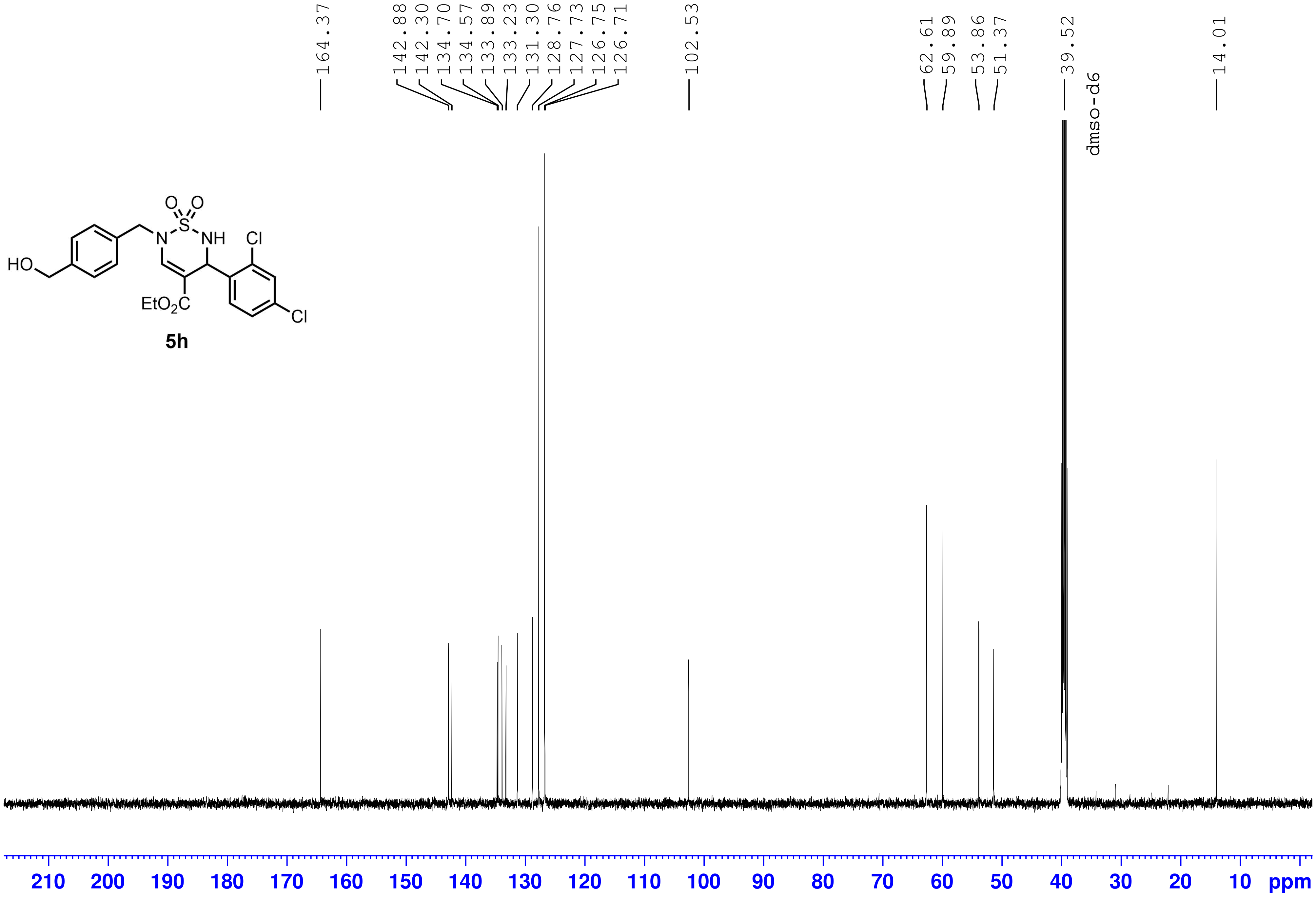


5g

1H NMR (500 MHz, DMSO-d6)

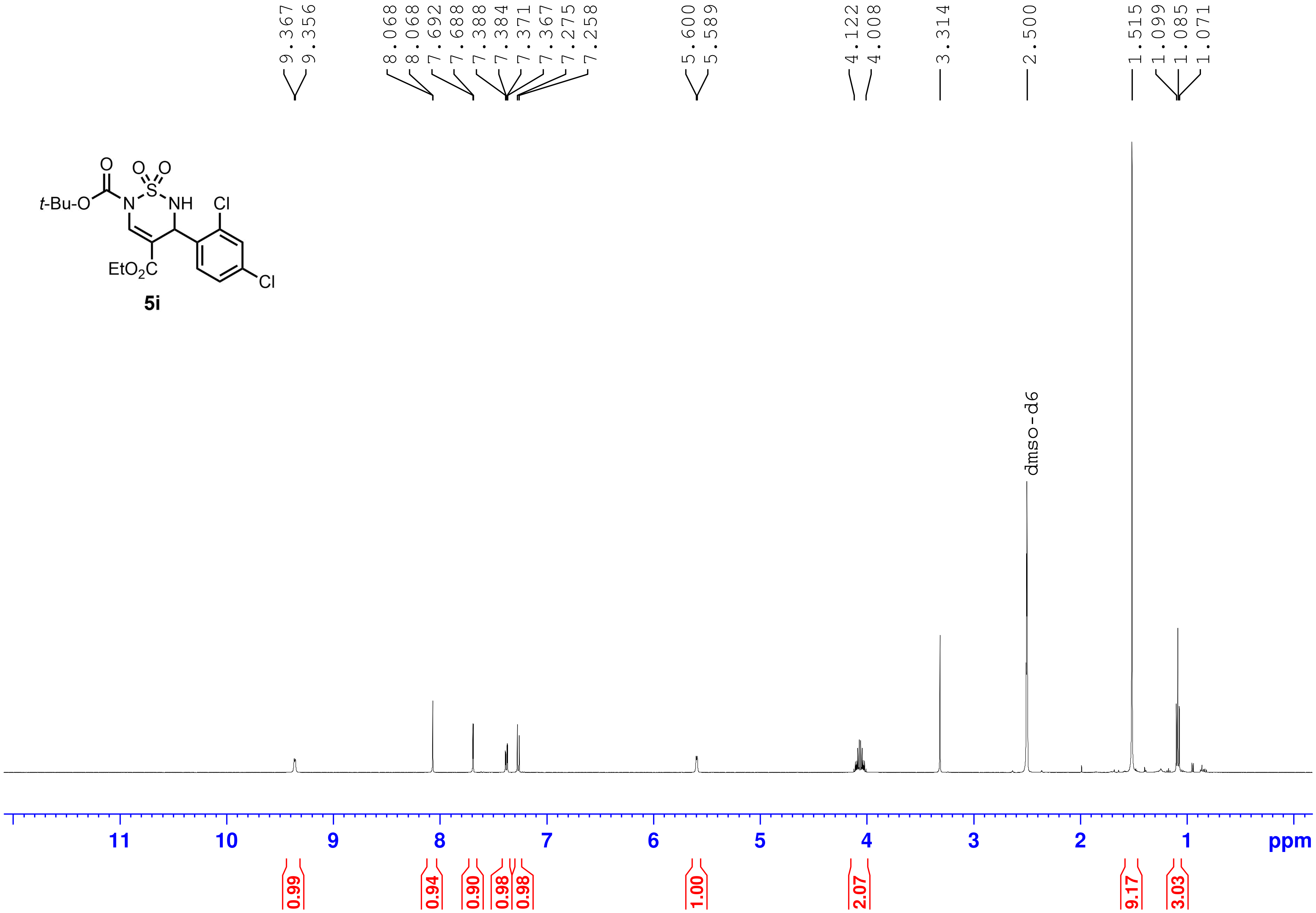


13C NMR (126 MHz, DMSO-d6)

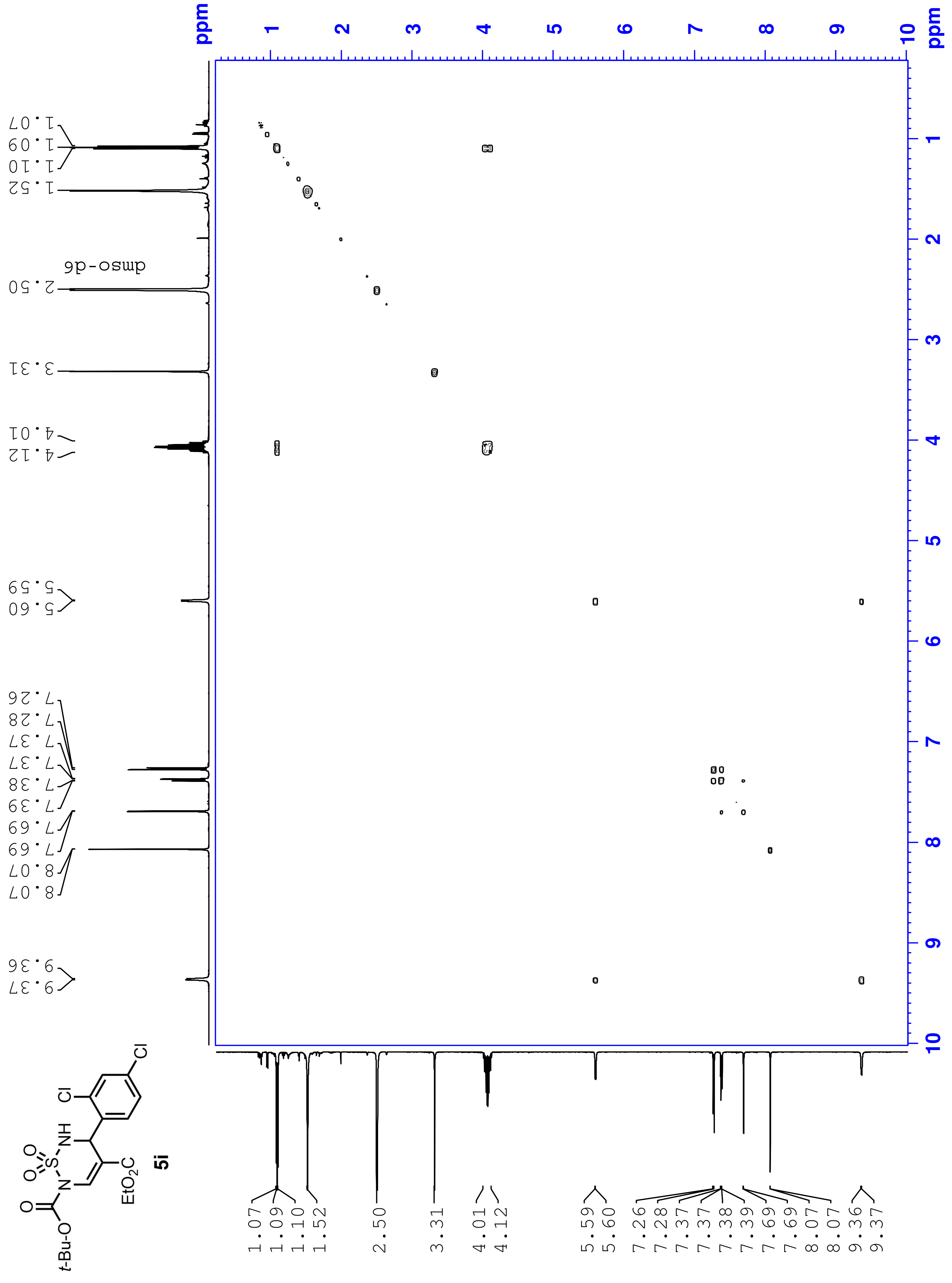


5h

1H NMR (500 MHz, DMSO-d6)



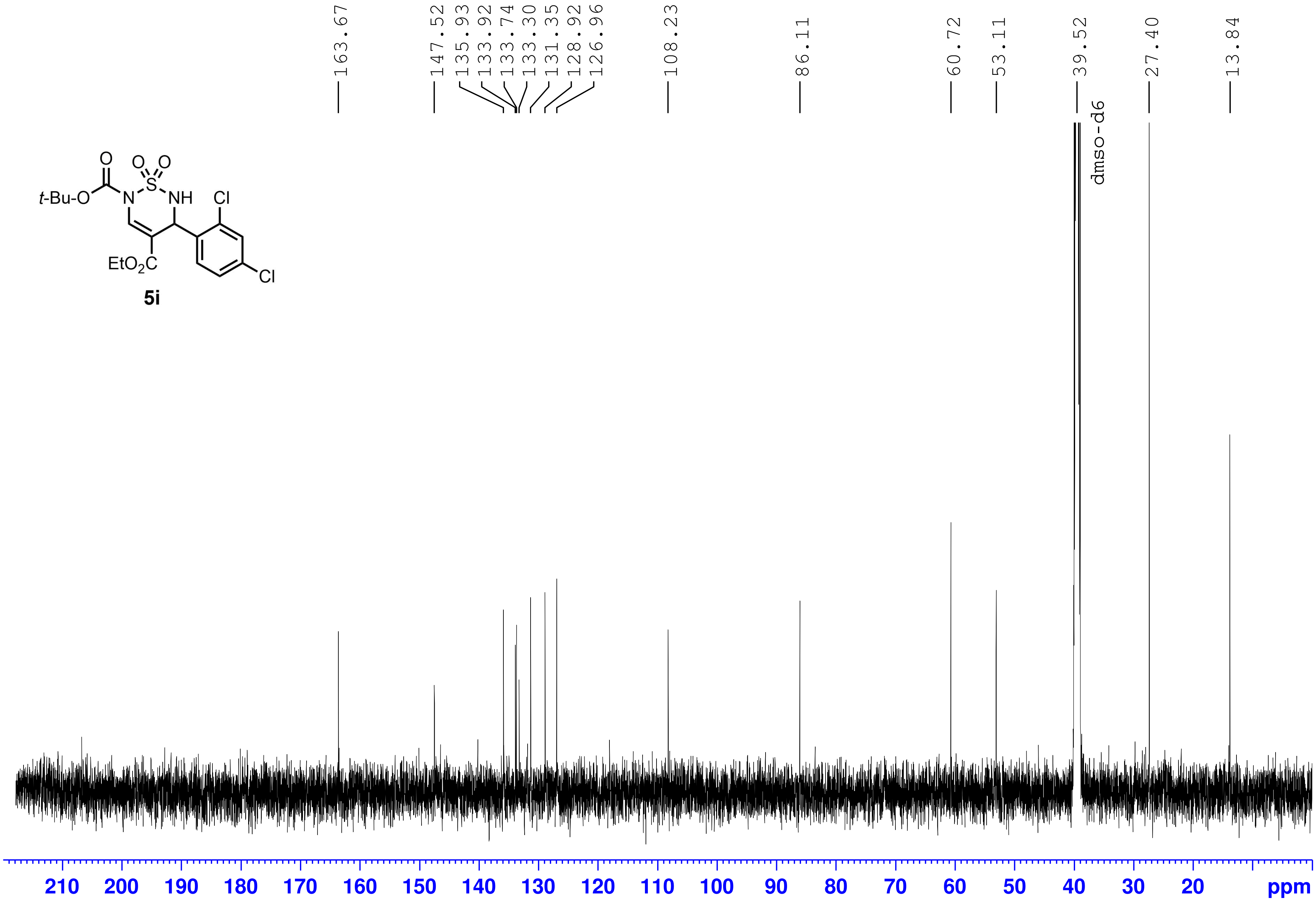
5i



5i

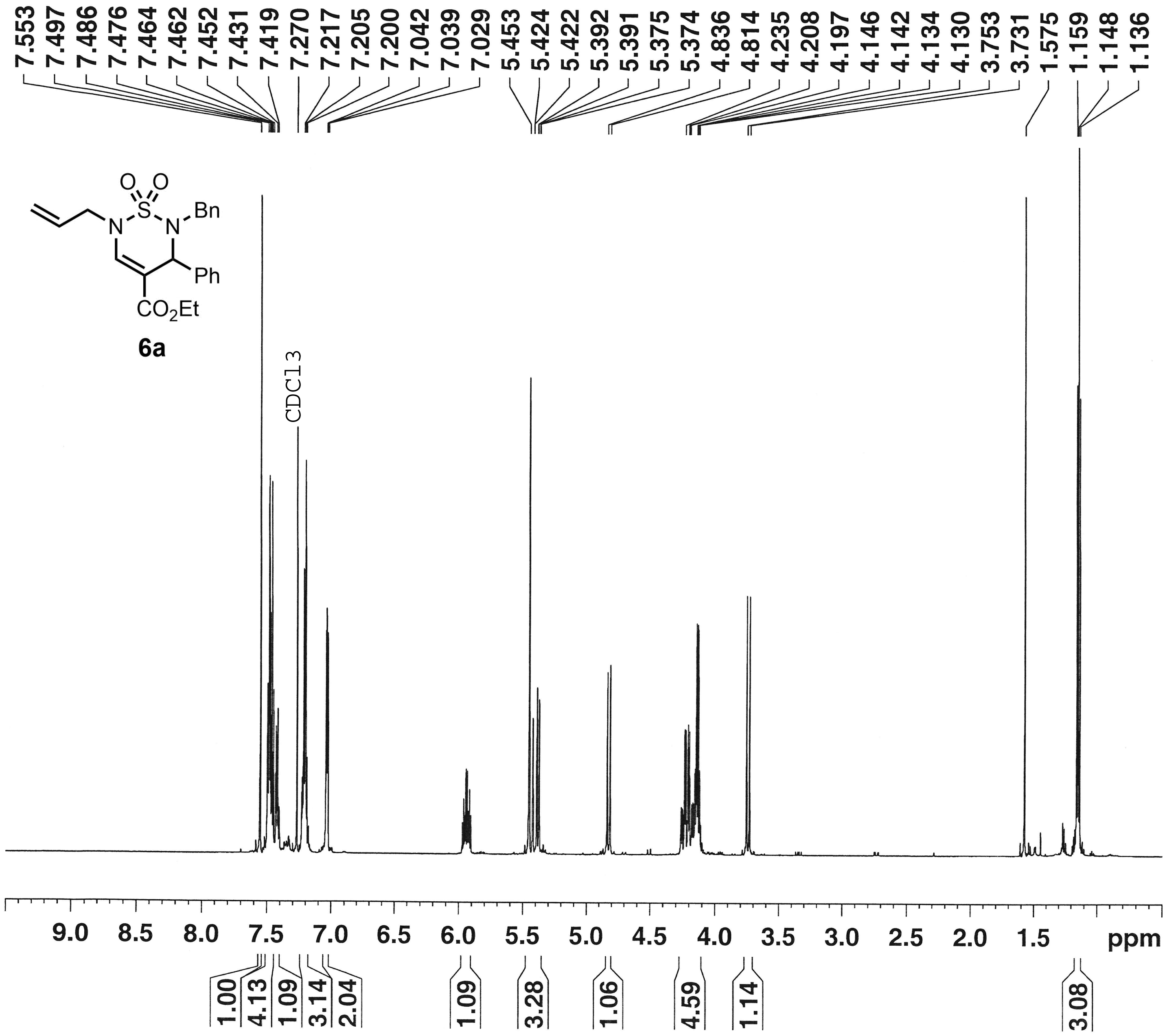
COSY 2D NMR (500 MHz, DMSO-d6)

13C NMR (125 MHz, DMSO-d6)



5i

1H NMR (600 MHz, CDCl3)



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PROCNO                   1

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PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH              12376.237 Hz
FIDRES            0.188846 Hz
AQ               2.6477449 sec
RG                     7.1
DW                  40.400 usec
DE                    6.00 usec
TE                   298.0 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                    8.00 usec
PL1                   3.90 dB
SFO1           600.1337060 MHz

F2 - Processing parameters
SI                   32768
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WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
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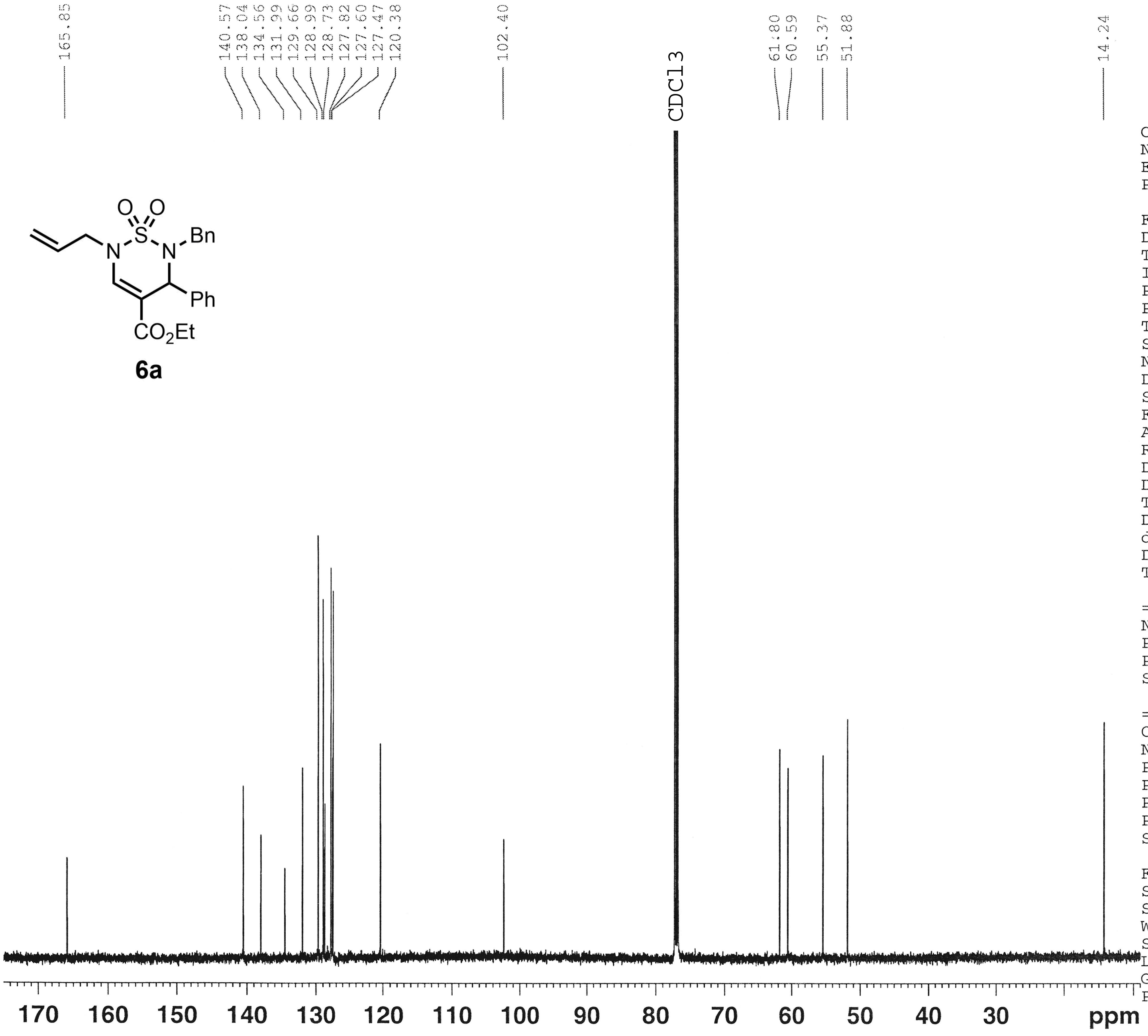
1H NMR (150 MHz, CDCl3)



6a

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EXPNO                   2
PROCNO                  1

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INSTRUM             spect
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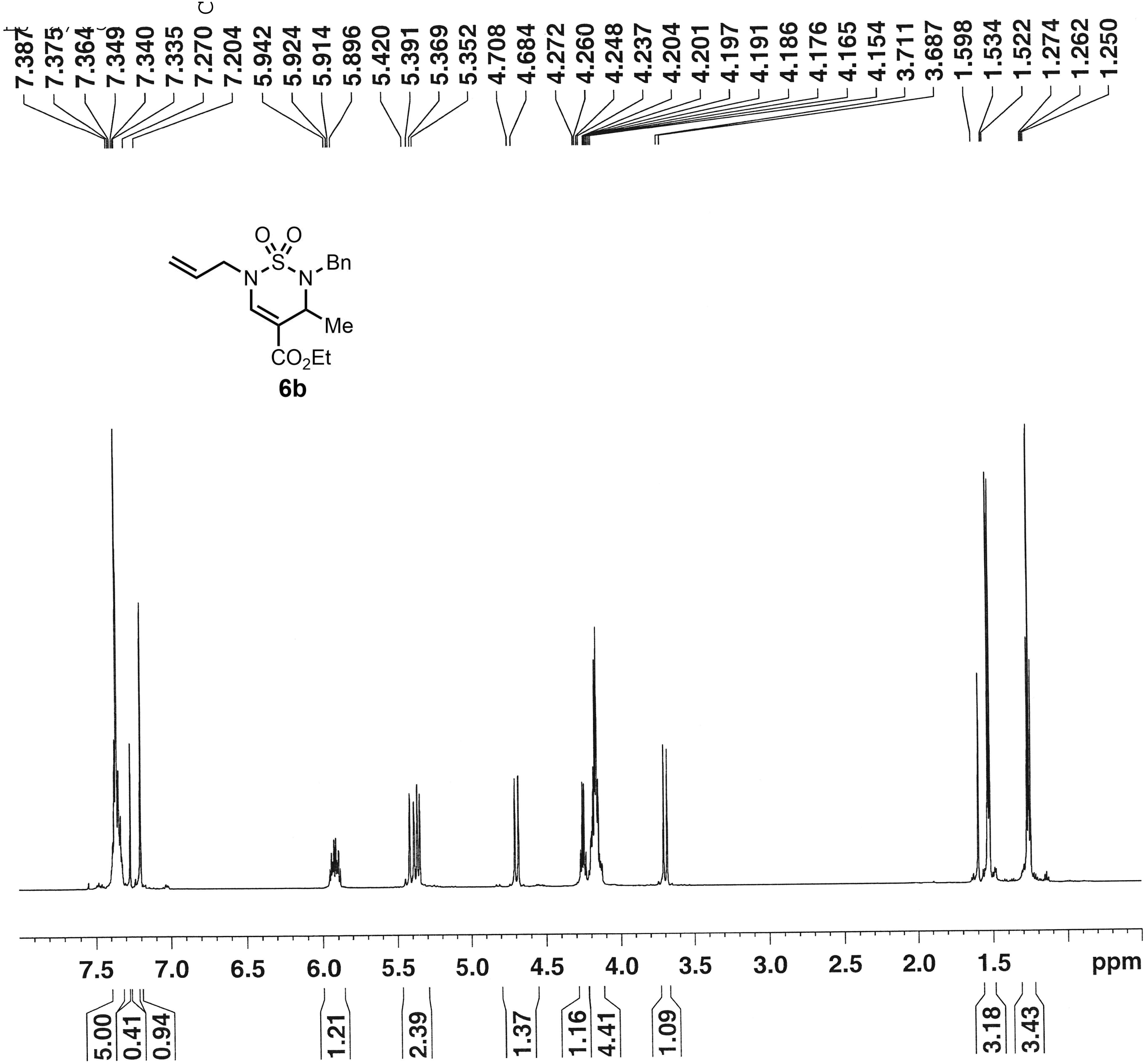
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    58
DS                     4
SWH            35971.223 Hz
FIDRES          0.548877 Hz
AQ             0.9110143 sec
RG               20642.5
DW                13.900 usec
DE                  6.00 usec
TE                 298.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 12.00 usec
PL1                 0.00 dB
SFO1         150.9178988 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 3.90 dB
PL12               23.90 dB
PL13               23.90 dB
SFO2         600.1324005 MHz

F2 - Processing parameters
SI                 32768
SF           150.9028090 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

1H NMR (600 MHz, CDCl3)



6b

```
Current Data Parameters
NAME                LJ 2 059
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
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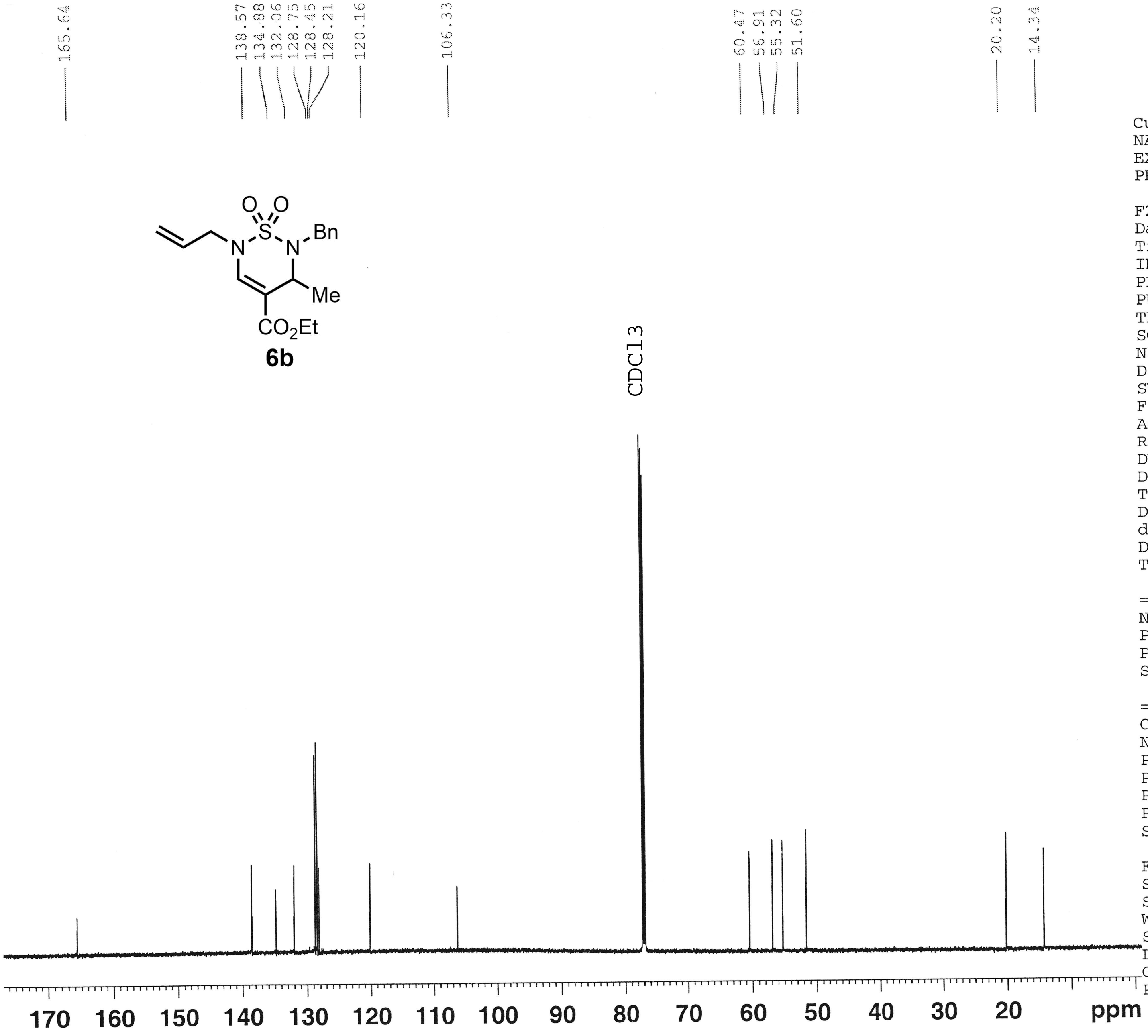
Time                   13.01
INSTRUM                spect
PROBHD   5 mm CPTCI 1H-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH            12376.237 Hz
FIDRES          0.188846 Hz
AQ             2.6477449 sec
RG                       6.3
DW                40.400 usec
DE                  6.00 usec
TE                 298.0 K
D1            1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                  8.00 usec
PL1                 3.90 dB
SFO1         600.1337060 MHz

F2 - Processing parameters
SI                     32768
SF           600.1298150 MHz
WDW                       EM
SSB                        0
LB                  0.30 Hz
GB                         0
PC                      1.00
```

13C NMR (150 MHz, CDCl3)



6b

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EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
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Time                  7.40
INSTRUM              spect
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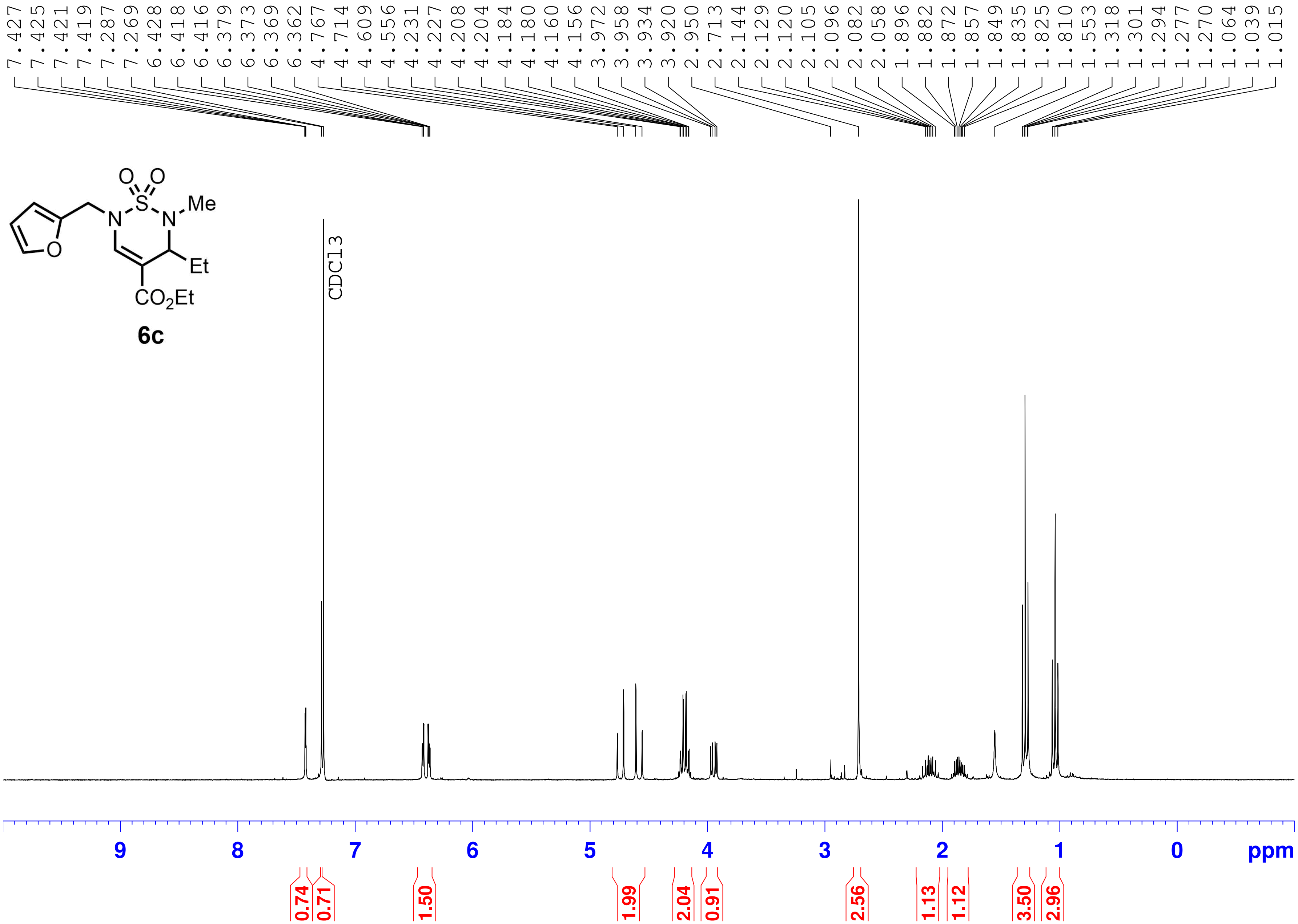
PULPROG            zgpg30
TD                   65536
SOLVENT              CDCl3
NS                      77
DS                       4
SWH             35971.223 Hz
FIDRES           0.548877 Hz
AQ              0.9110143 sec
RG                 18390.4
DW                  13.900 usec
DE                    6.00 usec
TE                   298.0 K
D1              2.00000000 sec
d11             0.03000000 sec
DELTA           1.89999998 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                   12.00 usec
PL1                   0.00 dB
SFO1           150.9178988 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                   3.90 dB
PL12                 23.90 dB
PL13                 23.90 dB
SFO2           600.1324005 MHz

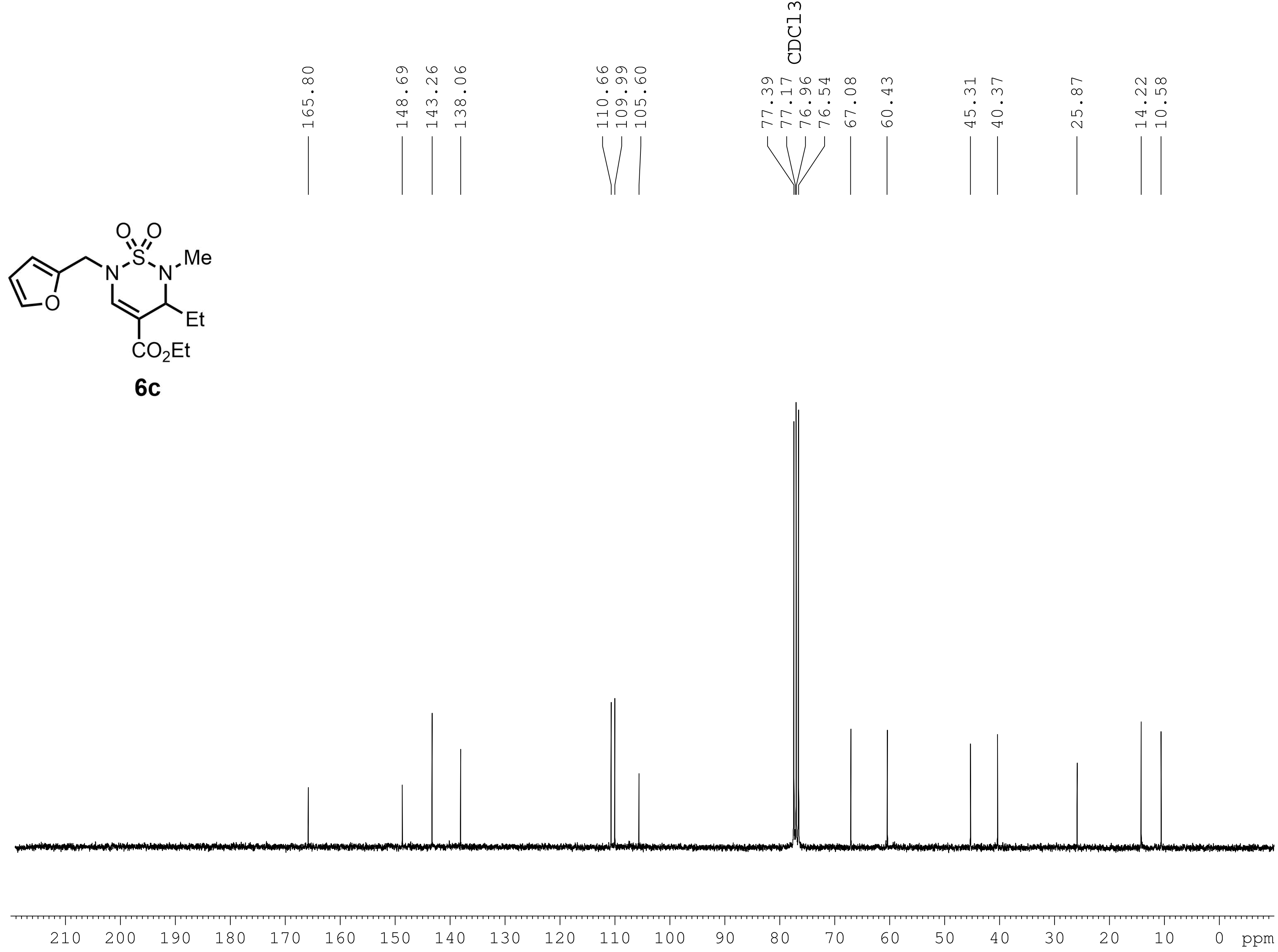
F2 - Processing parameters
SI                   32768
SF             150.9028090 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

1H NMR (300 MHz, CDCl3)

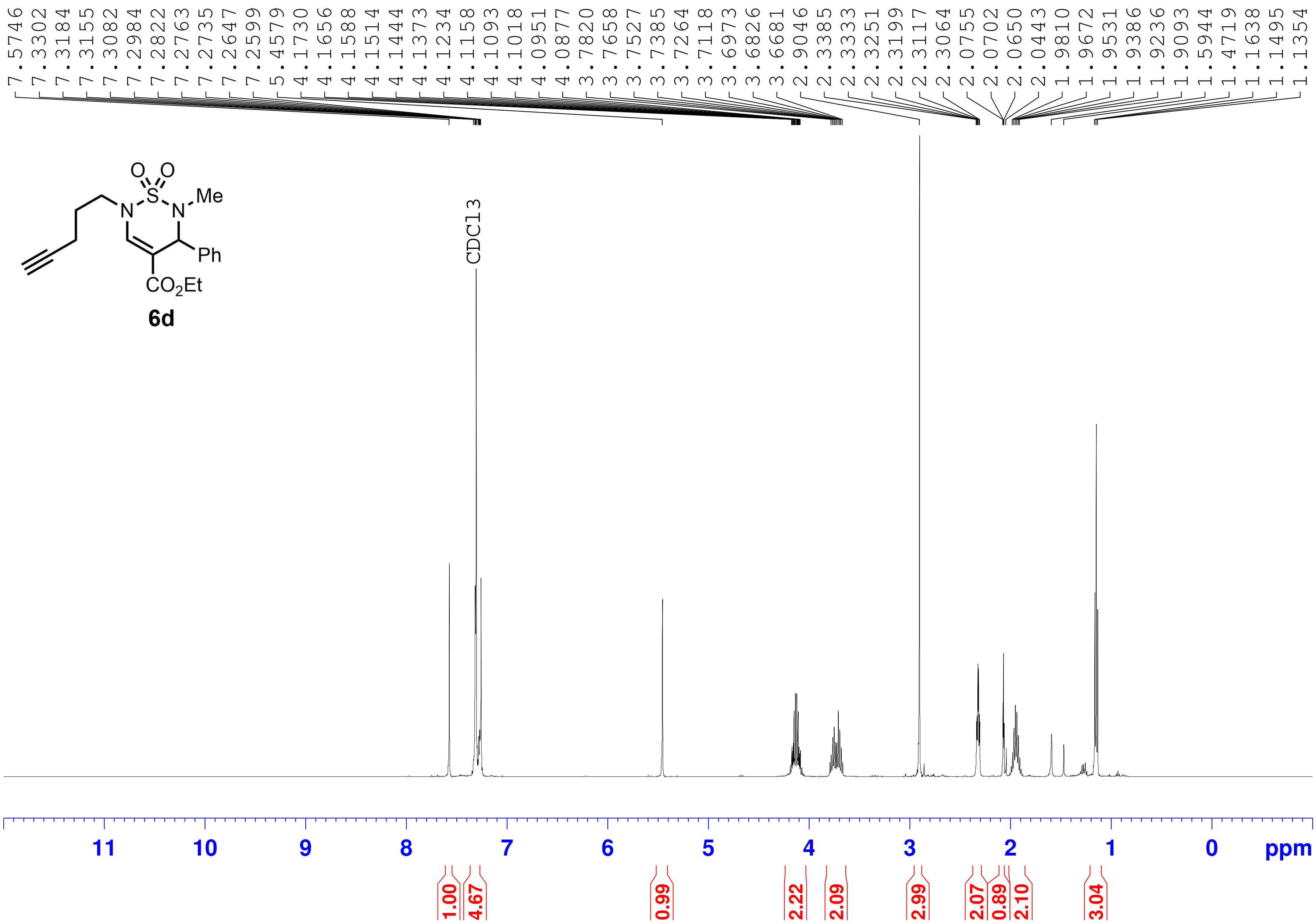


6c

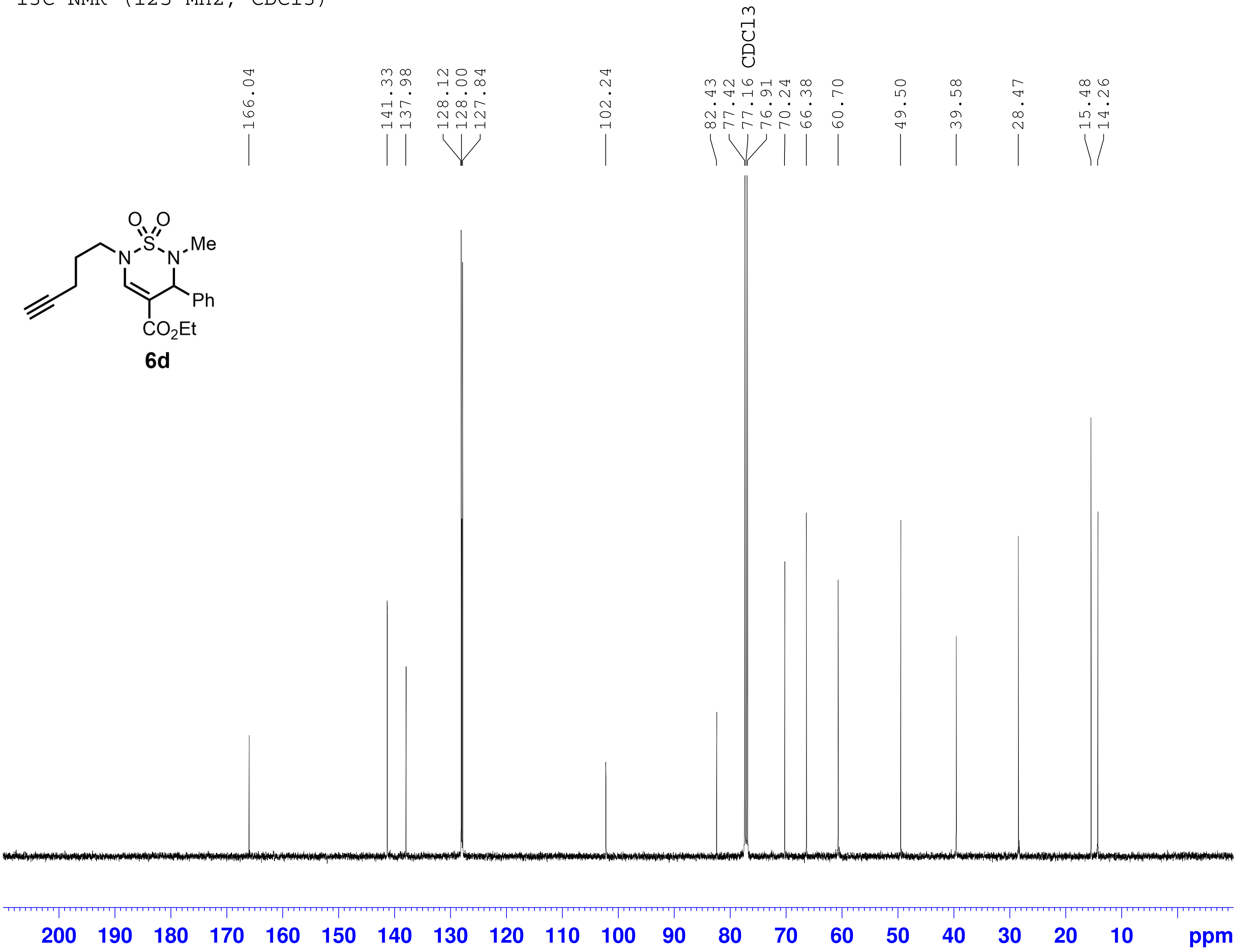
13C NMR (75 MHz, CDCl3)



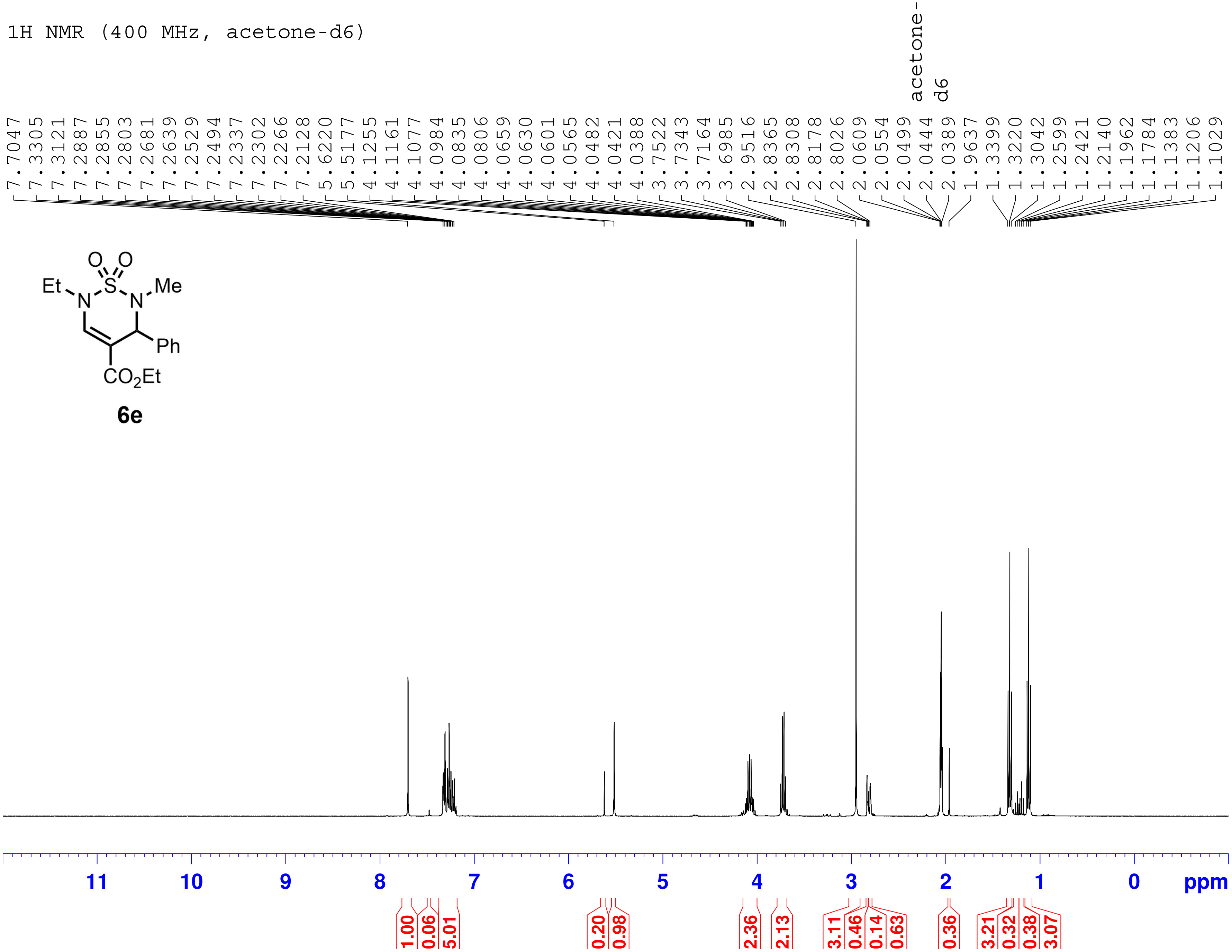
1H NMR (500 MHz, CDCl3)



13C NMR (125 MHz, CDCl3)

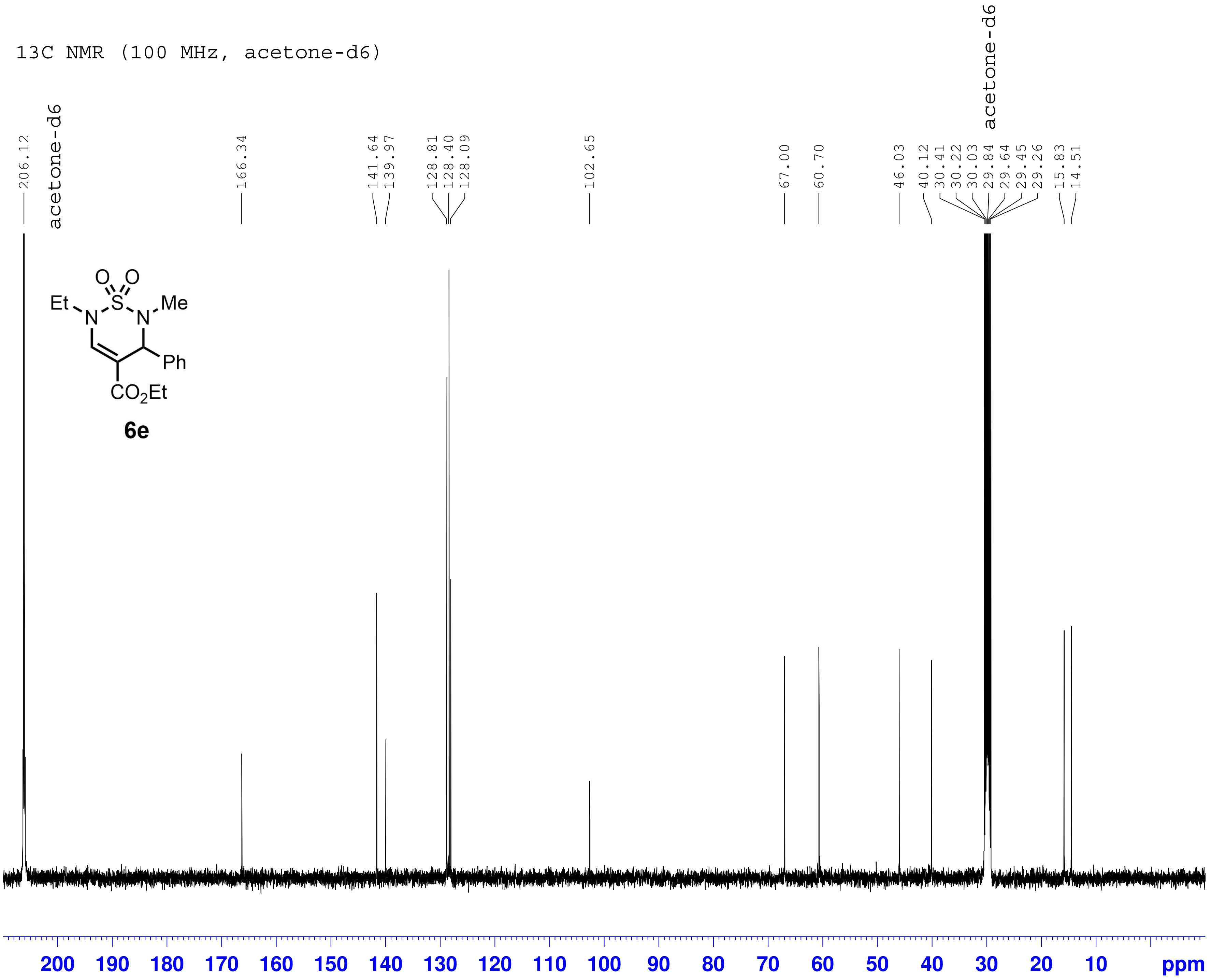


1H NMR (400 MHz, acetone-d6)

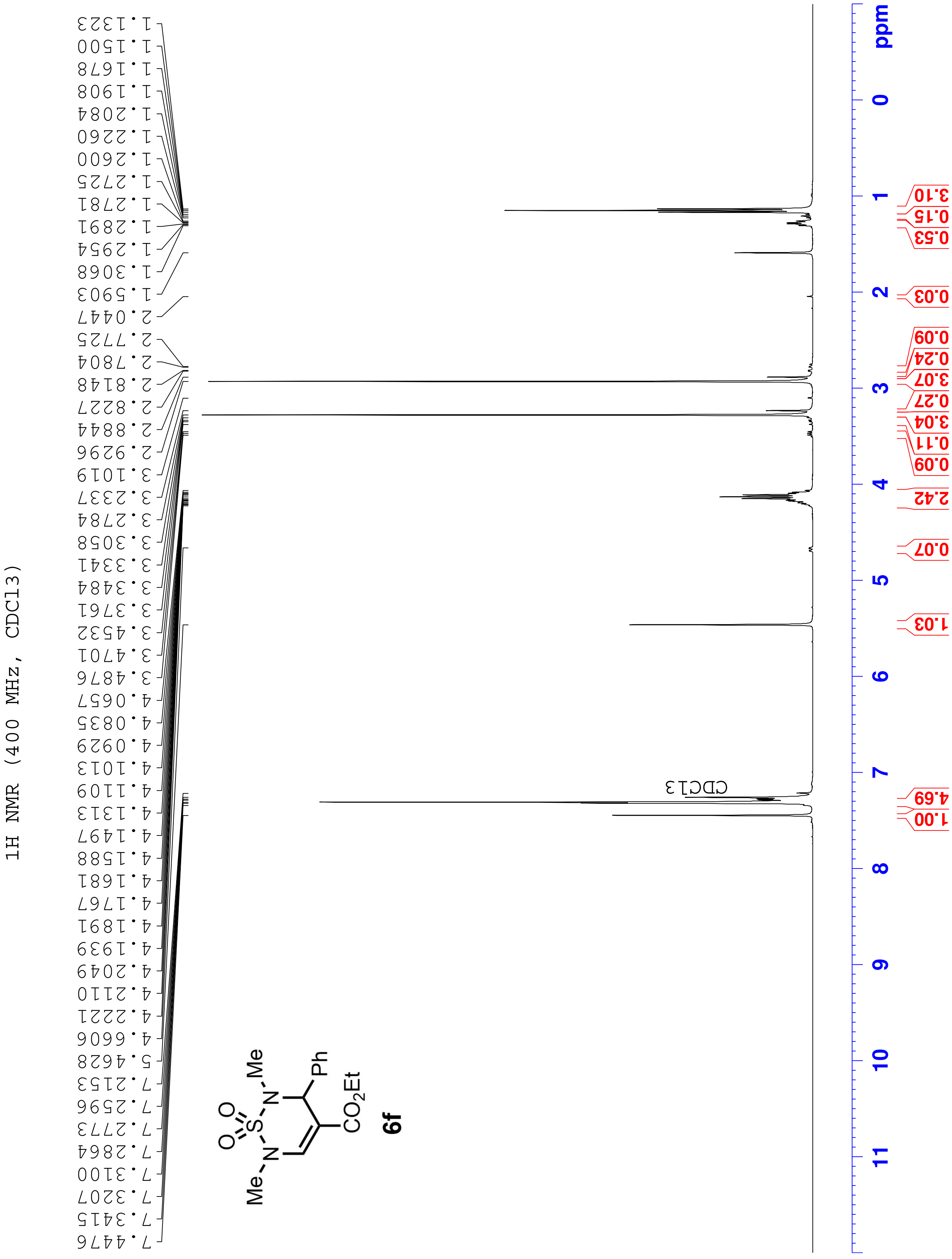


6e

13C NMR (100 MHz, acetone-d6)

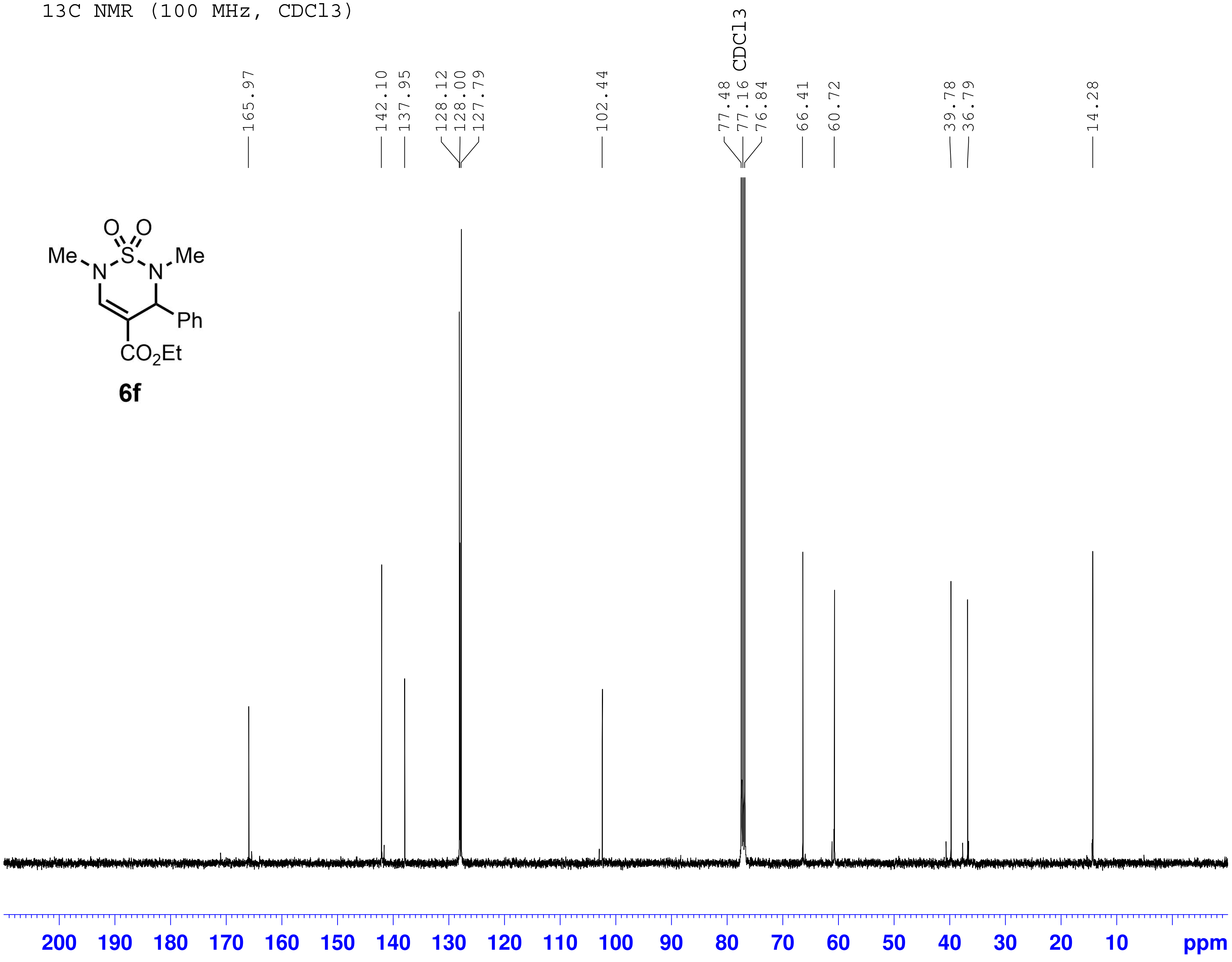


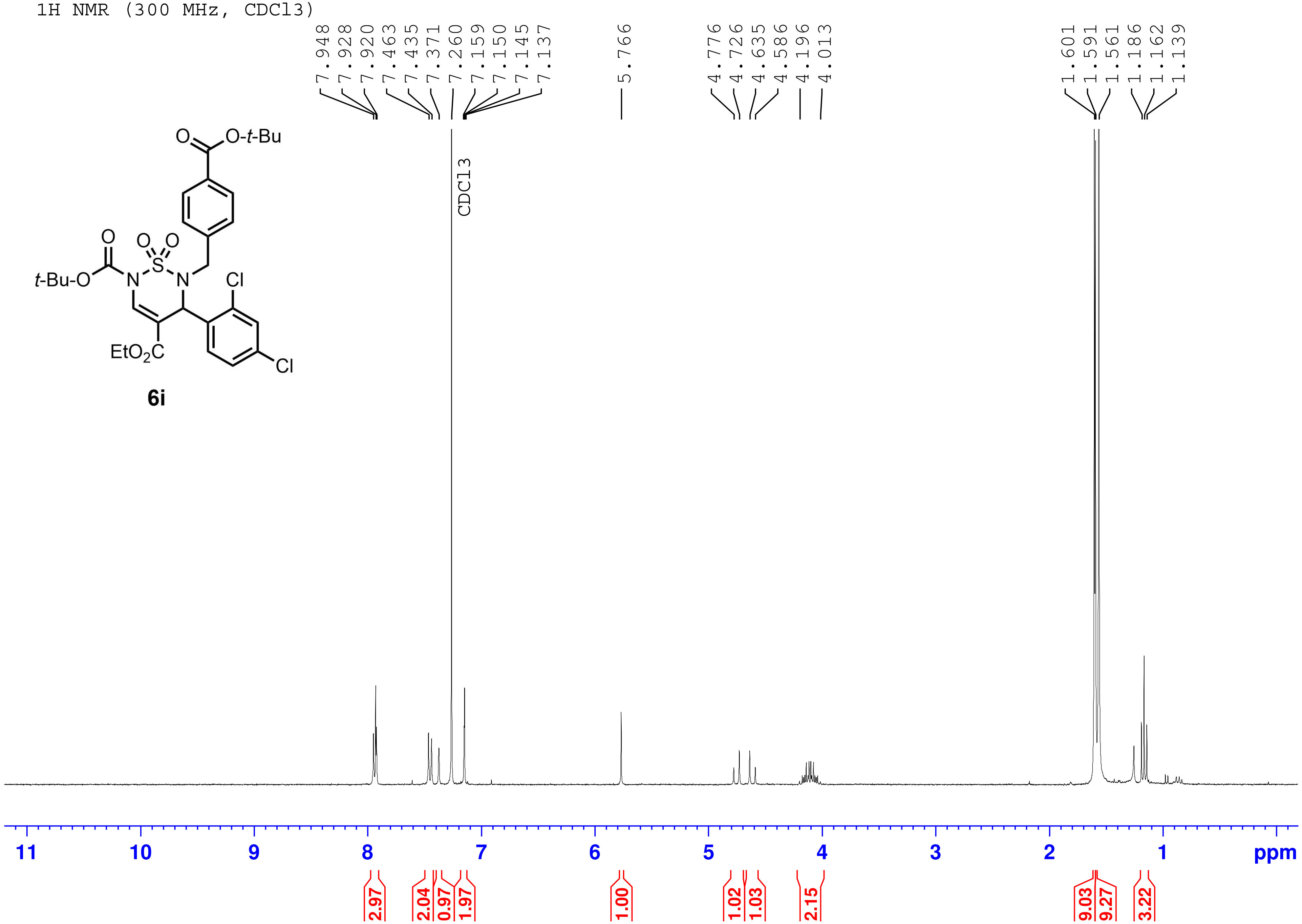
6e


1H NMR (400 MHz, CDCl3)
1.1323
1.1500
1.1678
1.1908
1.2084
1.2260
1.2600
1.2725
1.2781
1.2891
1.2954
1.3068
1.5903
2.0447
2.7725
2.7804
2.8148
2.8227
2.8844
2.9296
3.1019
3.2337
3.2784
3.3058
3.3341
3.3484
3.3761
3.4532
3.4701
3.4876
4.0657
4.0835
4.0929
4.1013
4.1109
4.1313
4.1497
4.1588
4.1681
4.1767
4.1891
4.1939
4.2049
4.2110
4.2221
4.6606
5.4628
7.2153
7.2596
7.2773
7.2864
7.3100
7.3207
7.3415
7.4476
CDCl3
Me
N
S
O
O
N
Me
Ph
CO2Et
ppm
0
1
2
3
4
5
6
7
8
9
10
11
3.10
0.15
0.53
0.03
0.09
0.24
3.07
0.27
3.04
0.11
0.09
2.42
0.07
1.03
4.69
1.00

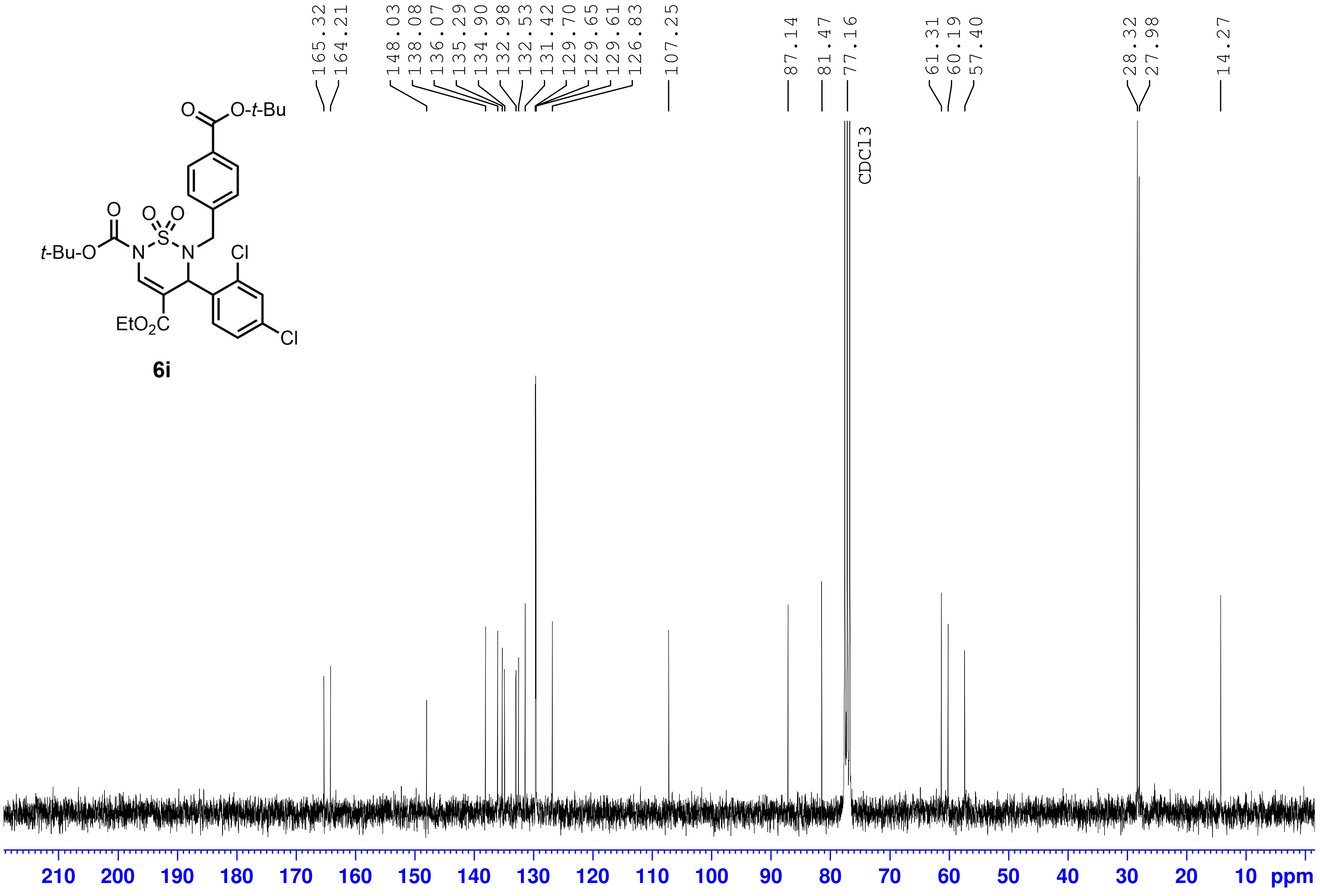
6f

13C NMR (100 MHz, CDCl3)



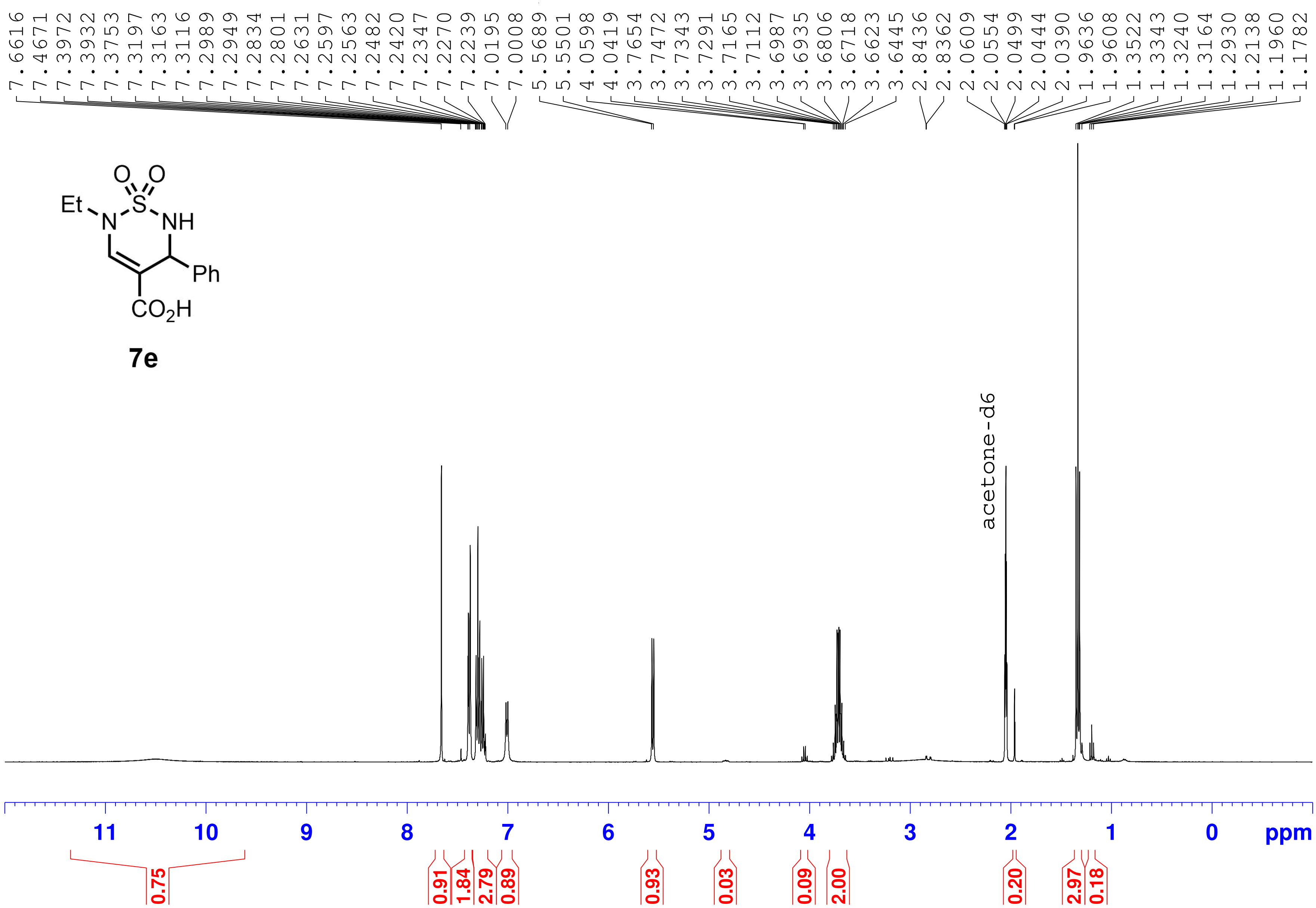

1H NMR (300 MHz, CDCl3)
7.948
7.928
7.920
7.463
7.435
7.371
7.260
7.159
7.150
7.145
7.137
5.766
4.776
4.726
4.635
4.586
4.196
4.013
1.601
1.591
1.561
1.186
1.162
1.139
CDCl3
O
O-t-Bu
t-Bu-O
O
O
O
N
S
N
Cl
EtO2C
Cl
6i
11
10
9
8
7
6
5
4
3
2
1
ppm
2.97
2.04
0.97
1.97
1.00
1.02
1.03
2.15
9.03
9.27
3.22

13C NMR (75 MHz, CDCl3)



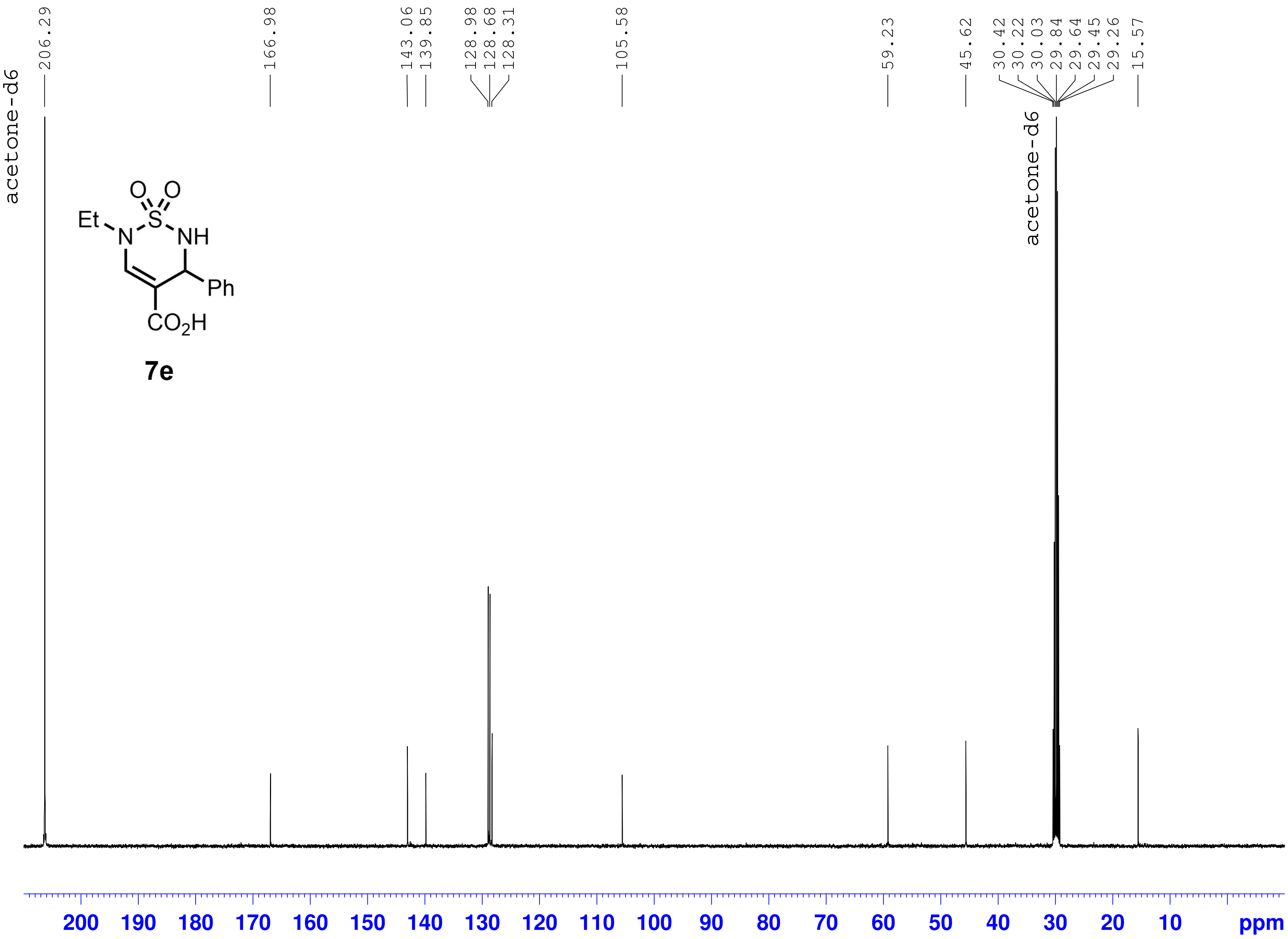
6i

1H NMR (400 MHz, acetone-d6)



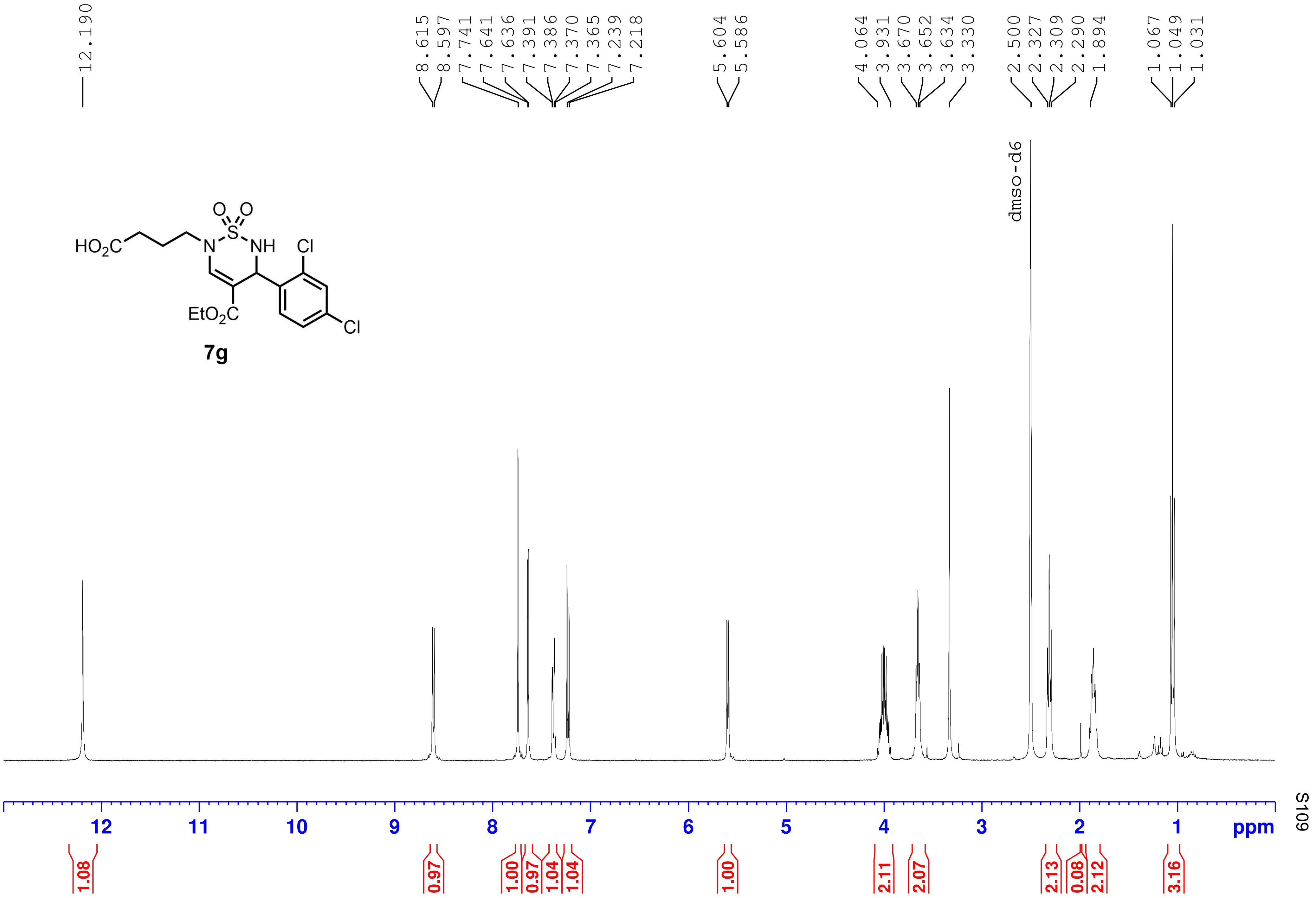
7e

13C NMR (100 MHz, acetone-d6)

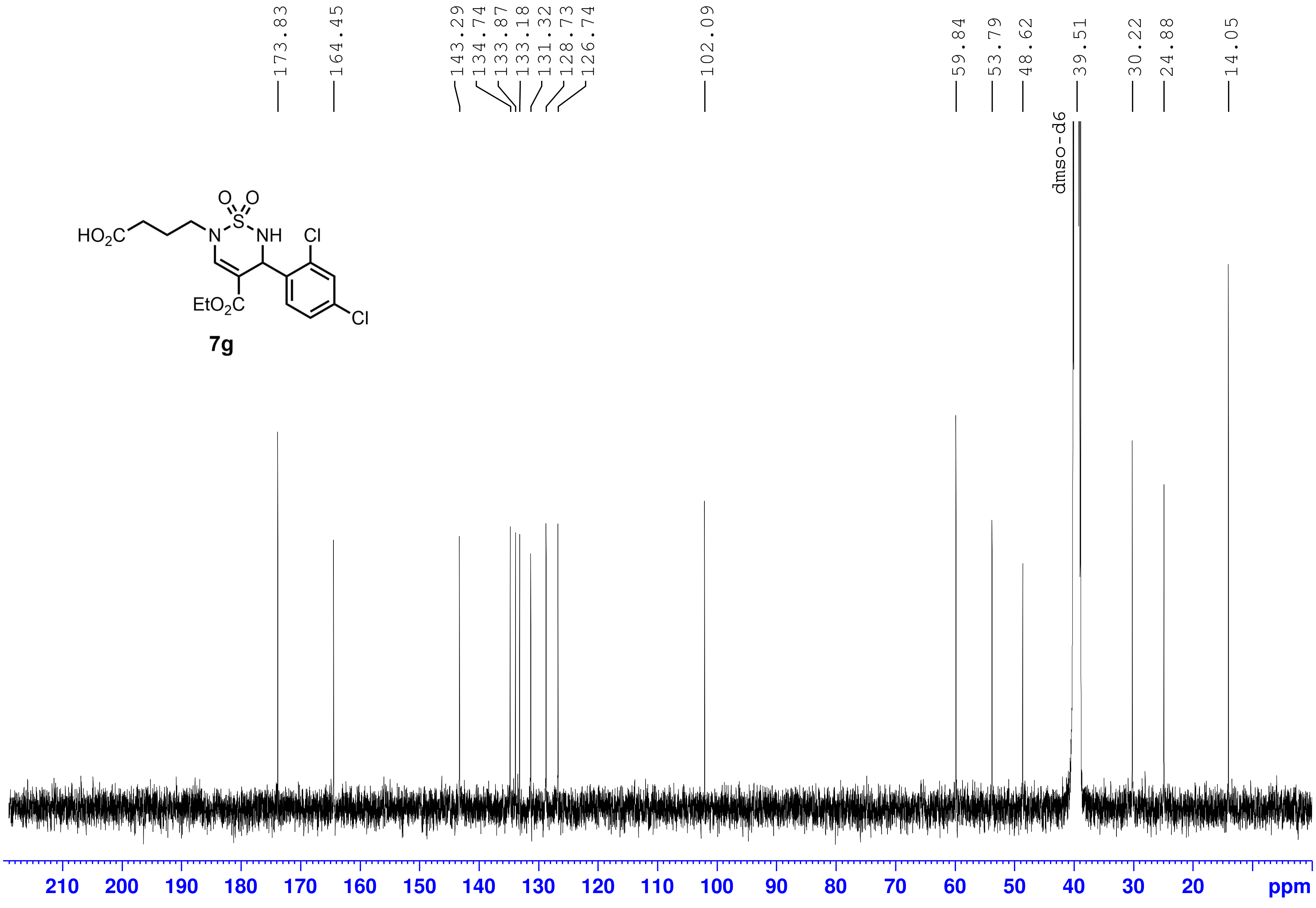


7e

1H NMR (400 MHz, DMSO-d6)

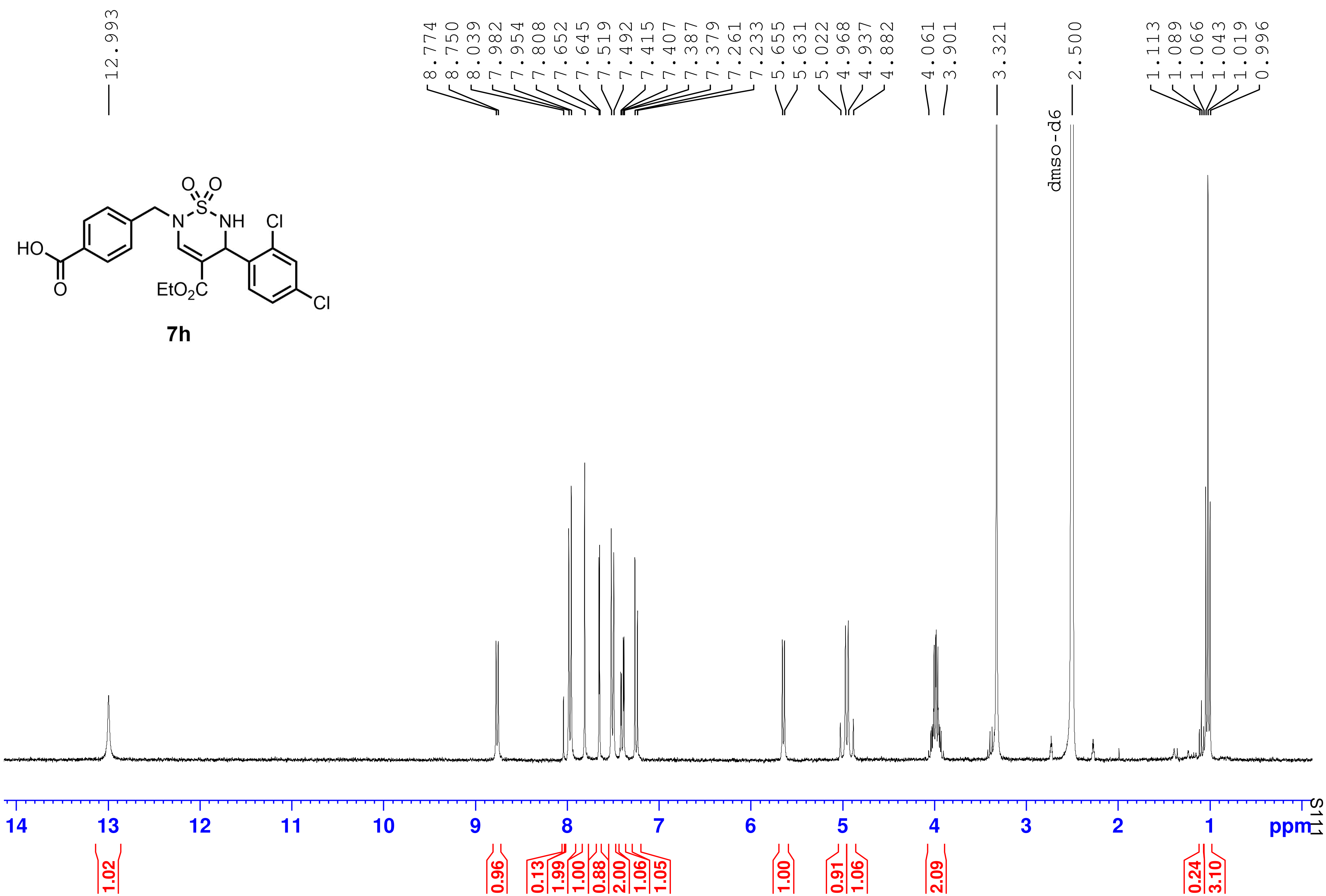


13C NMR (101 MHz, DMSO-d6)



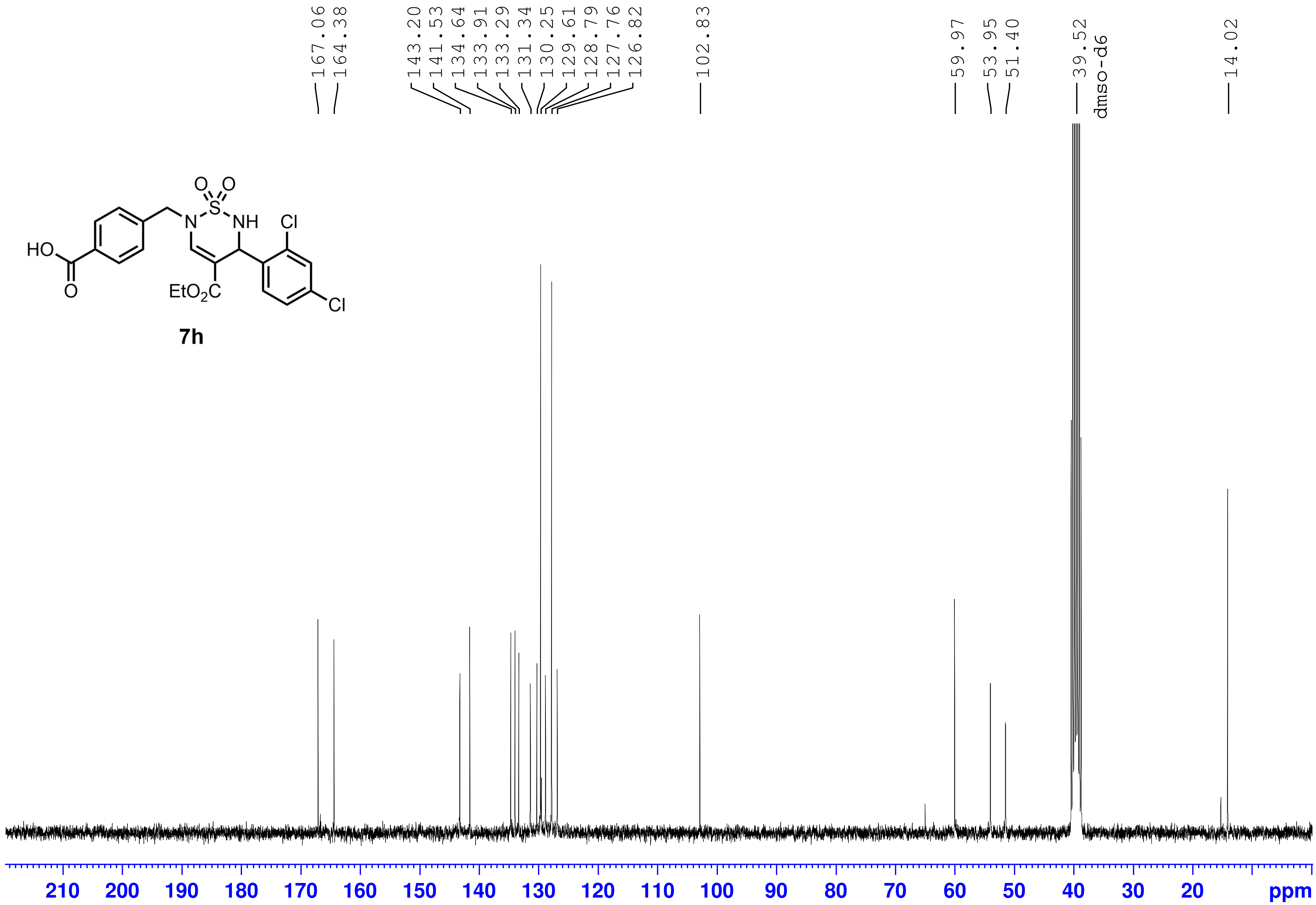
7g

1H NMR (300 MHz, DMSO-d6)



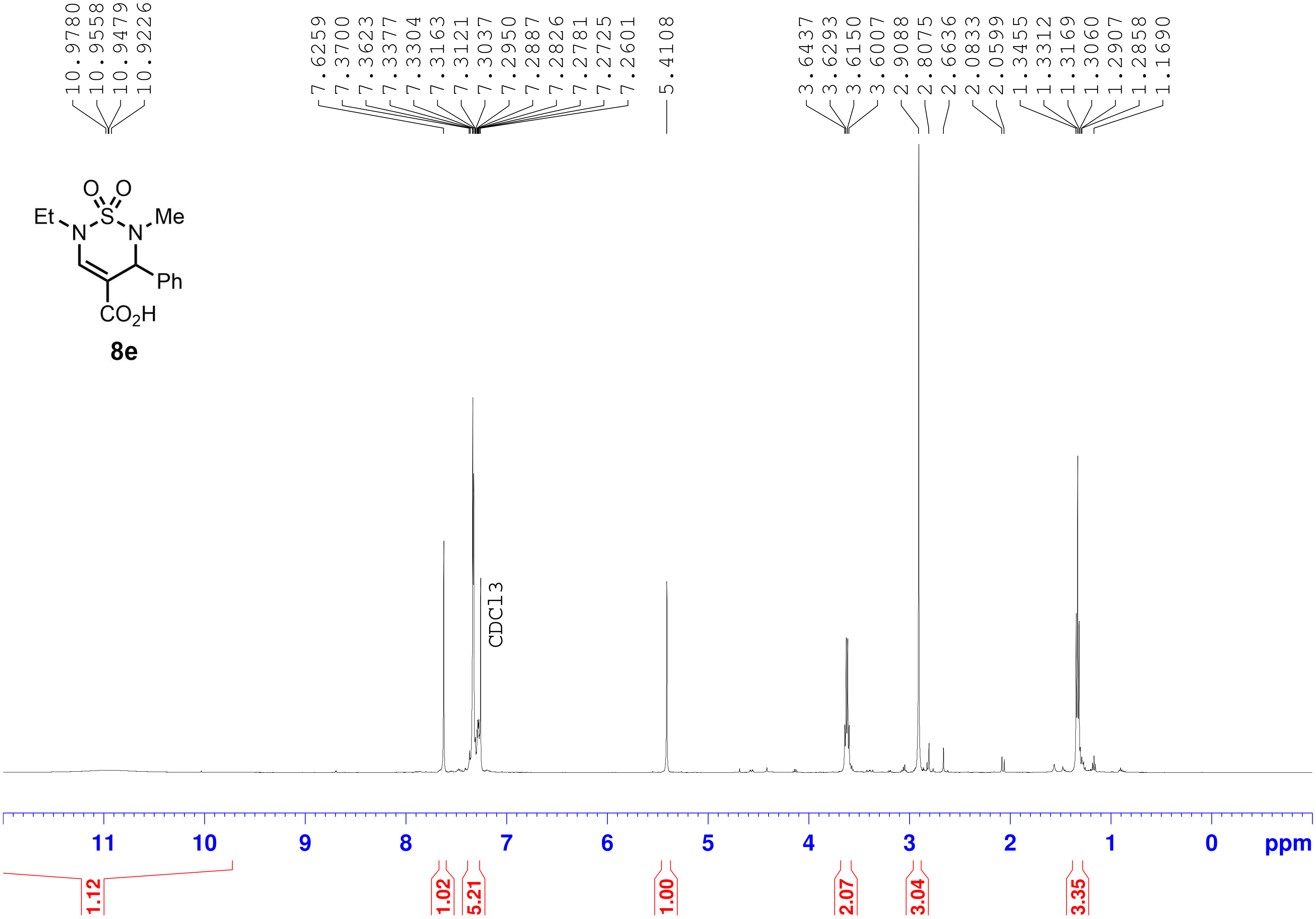
7h

13C NMR (75 MHz, DMSO-d6)

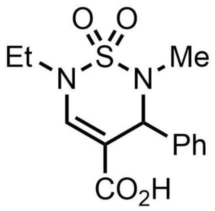


7h

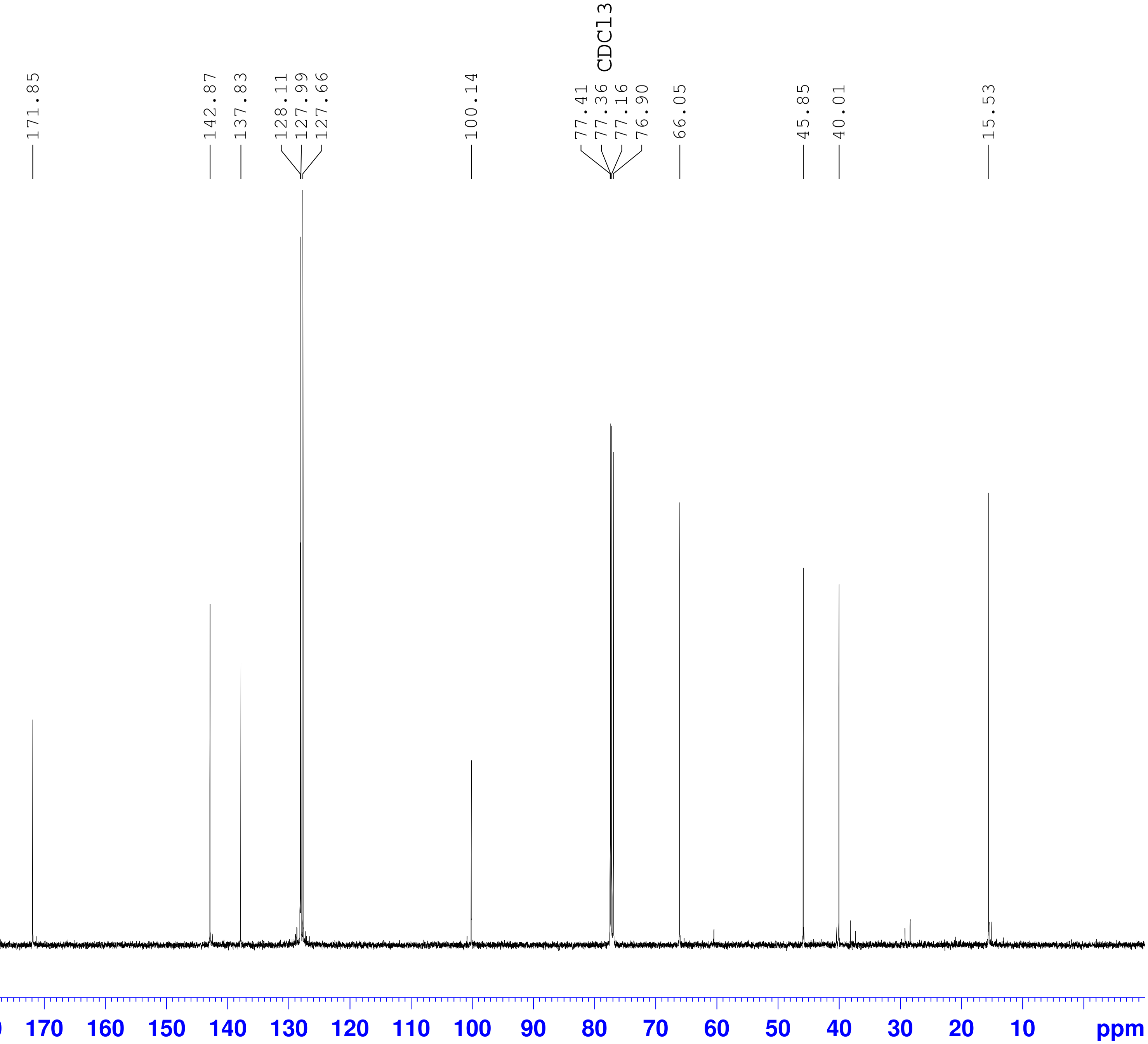
1H NMR (500 MHz, CDCl3)



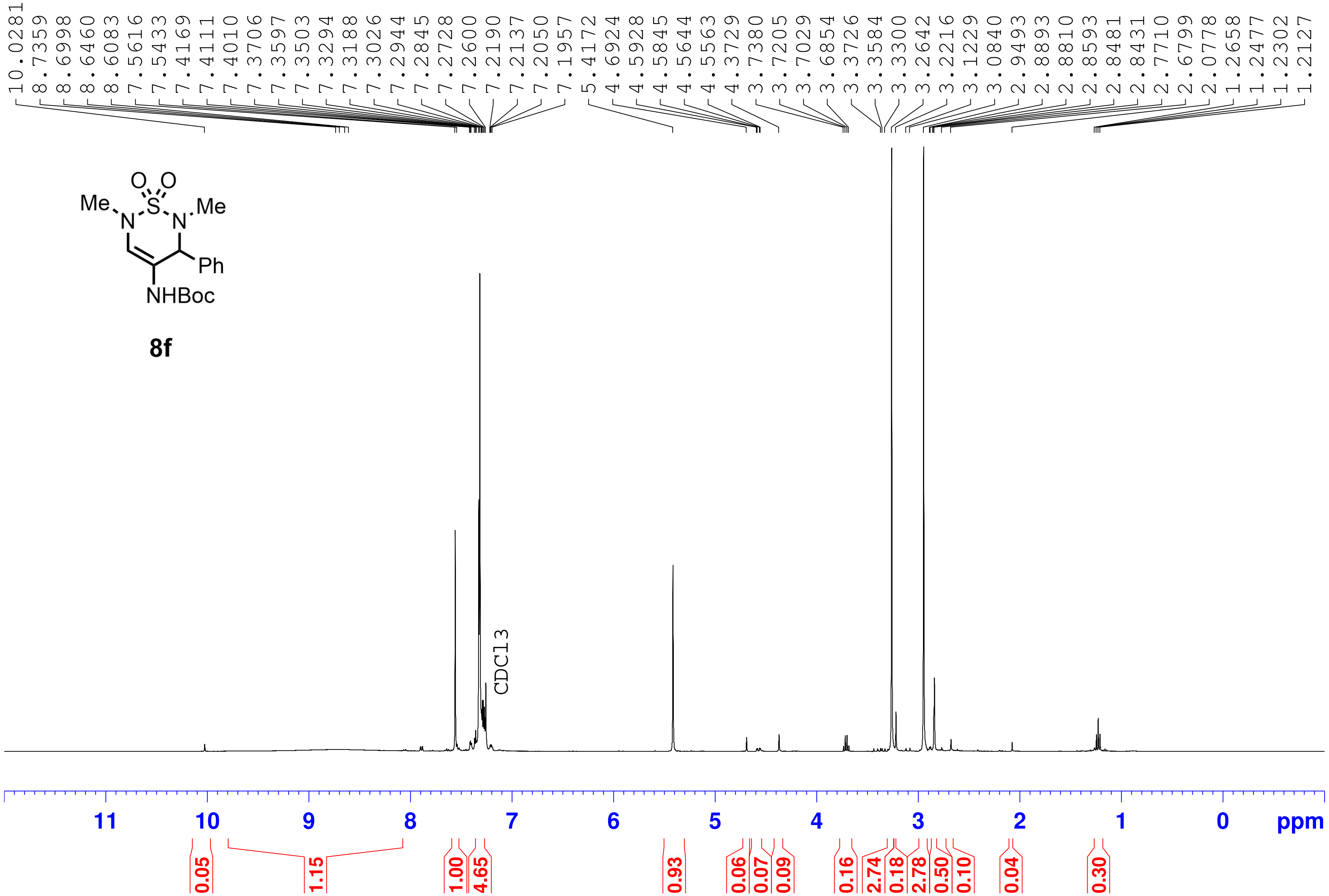
13C NMR (100 MHz, CDCl3)



8e

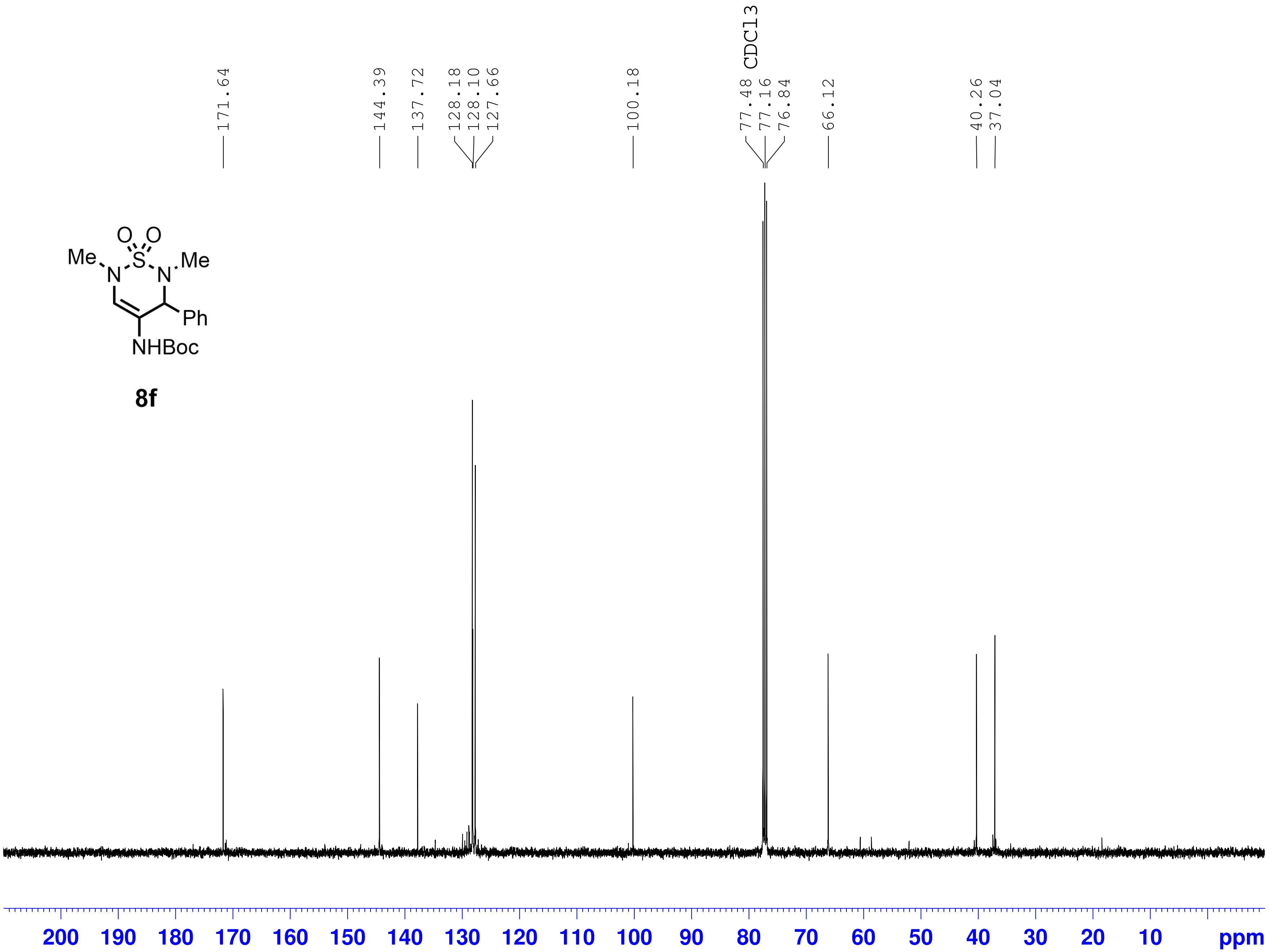


1H NMR (400 MHz, CDCl3)



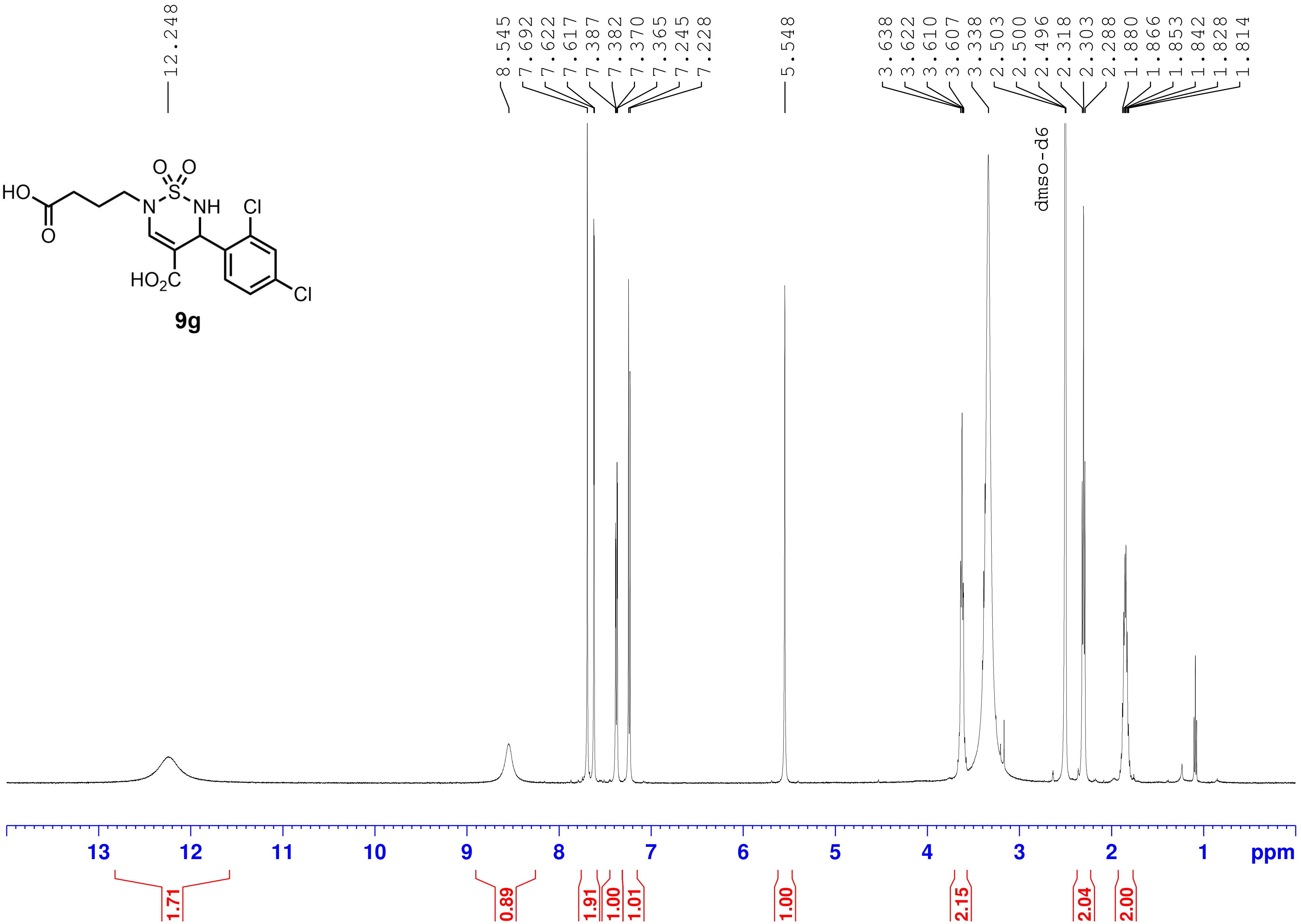
8f

13C NMR (100 MHz, CDCl3)



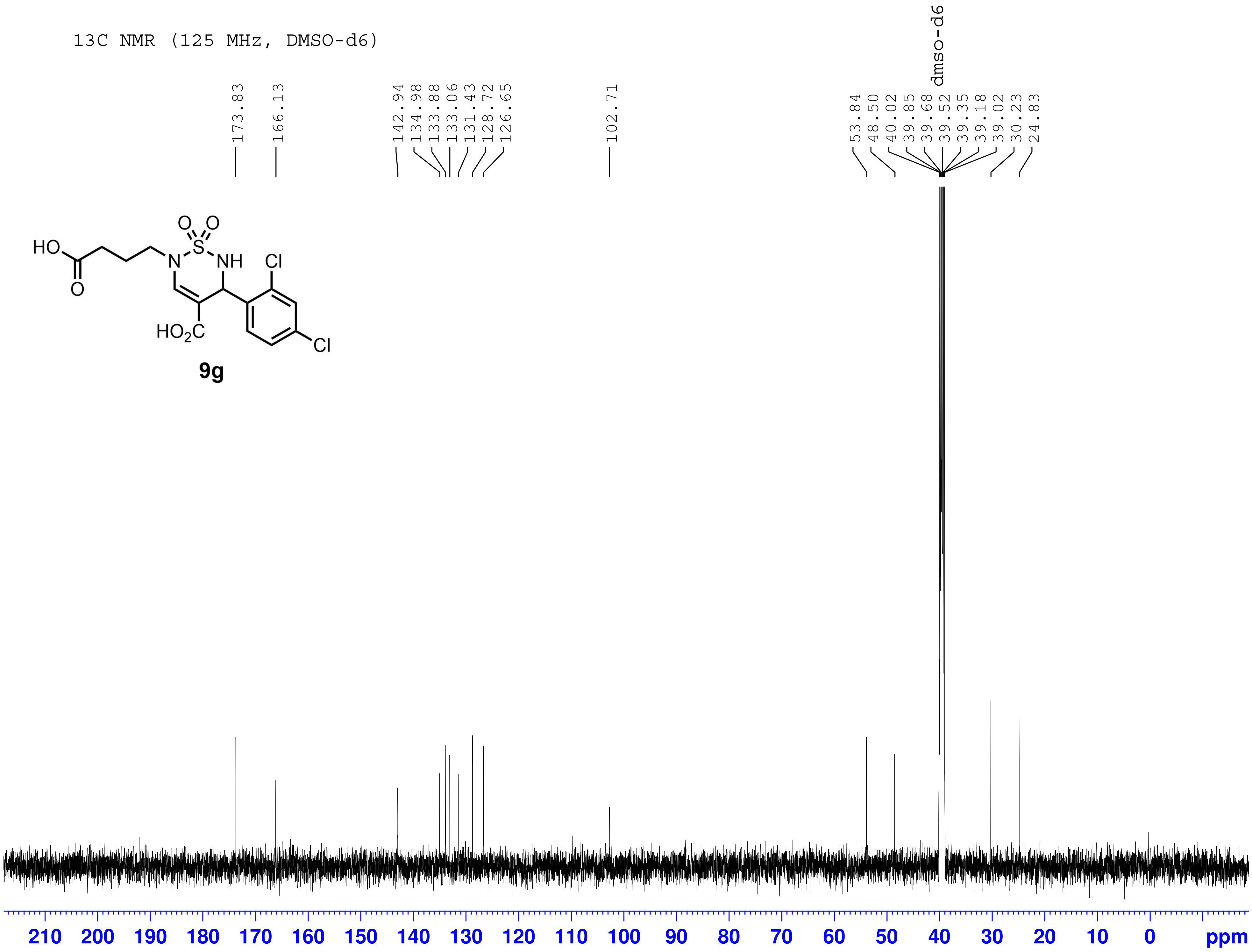
8f

1H NMR (500 MHz, DMSO-d6)



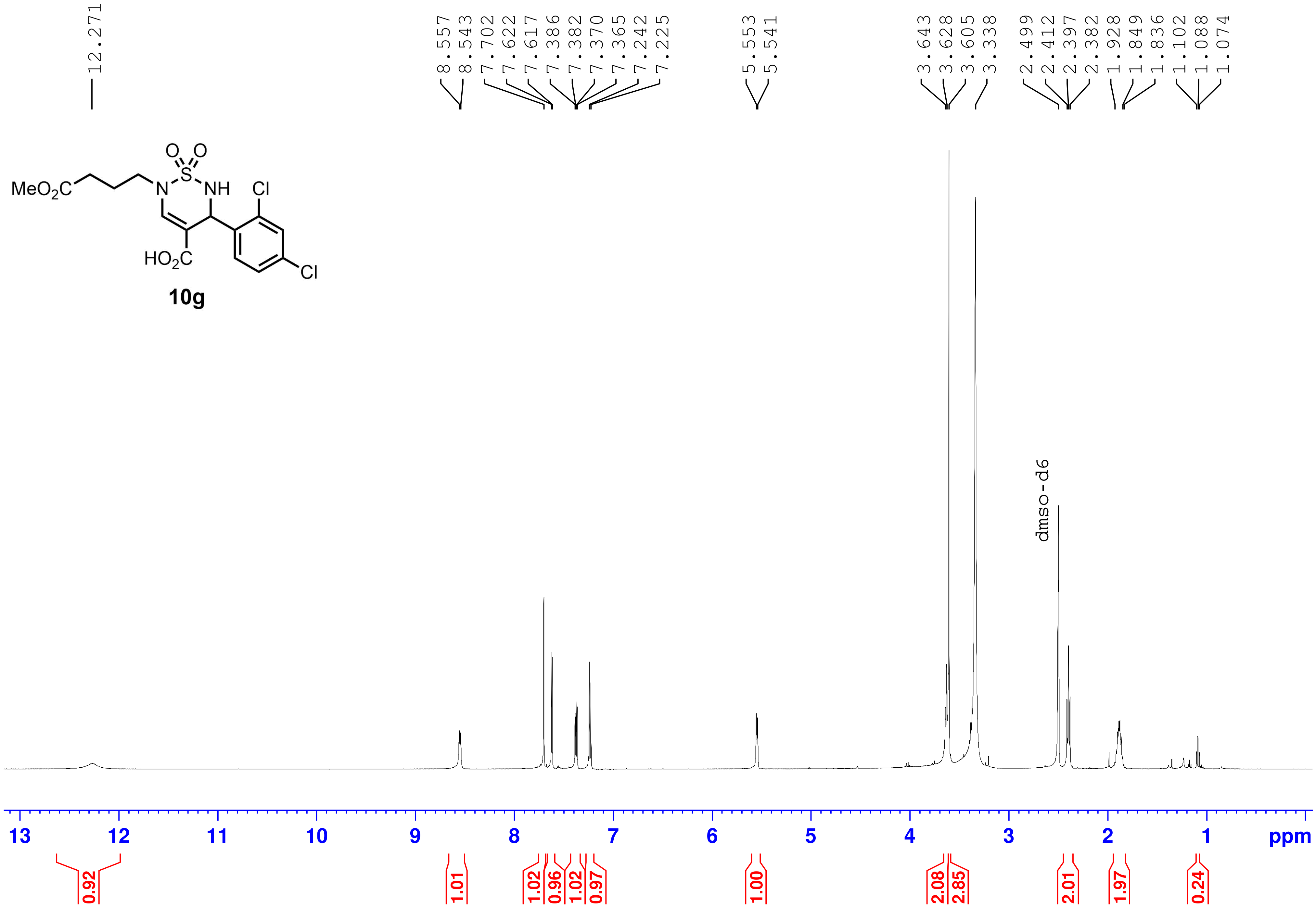
9g

13C NMR (125 MHz, DMSO-d6)



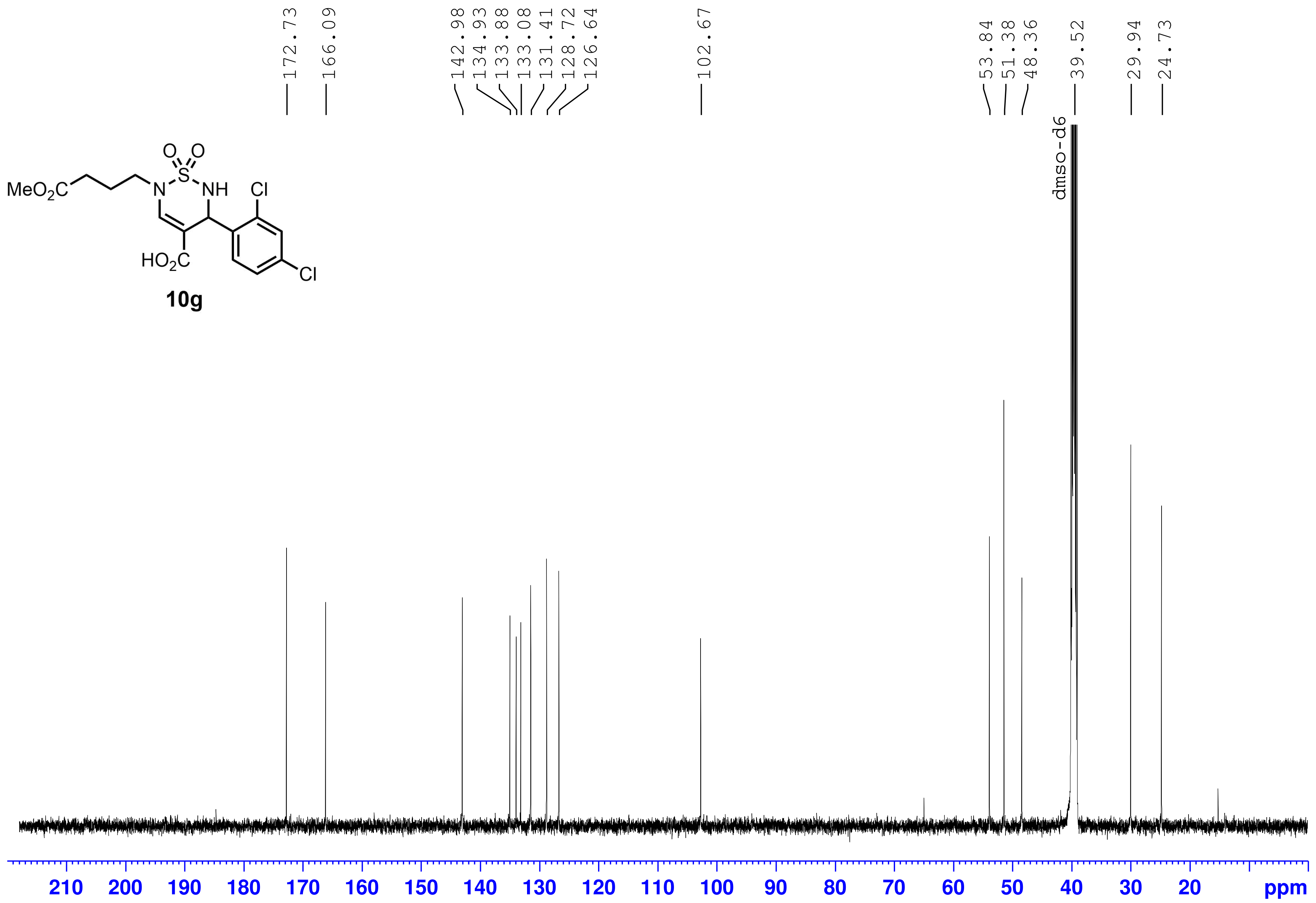
9g

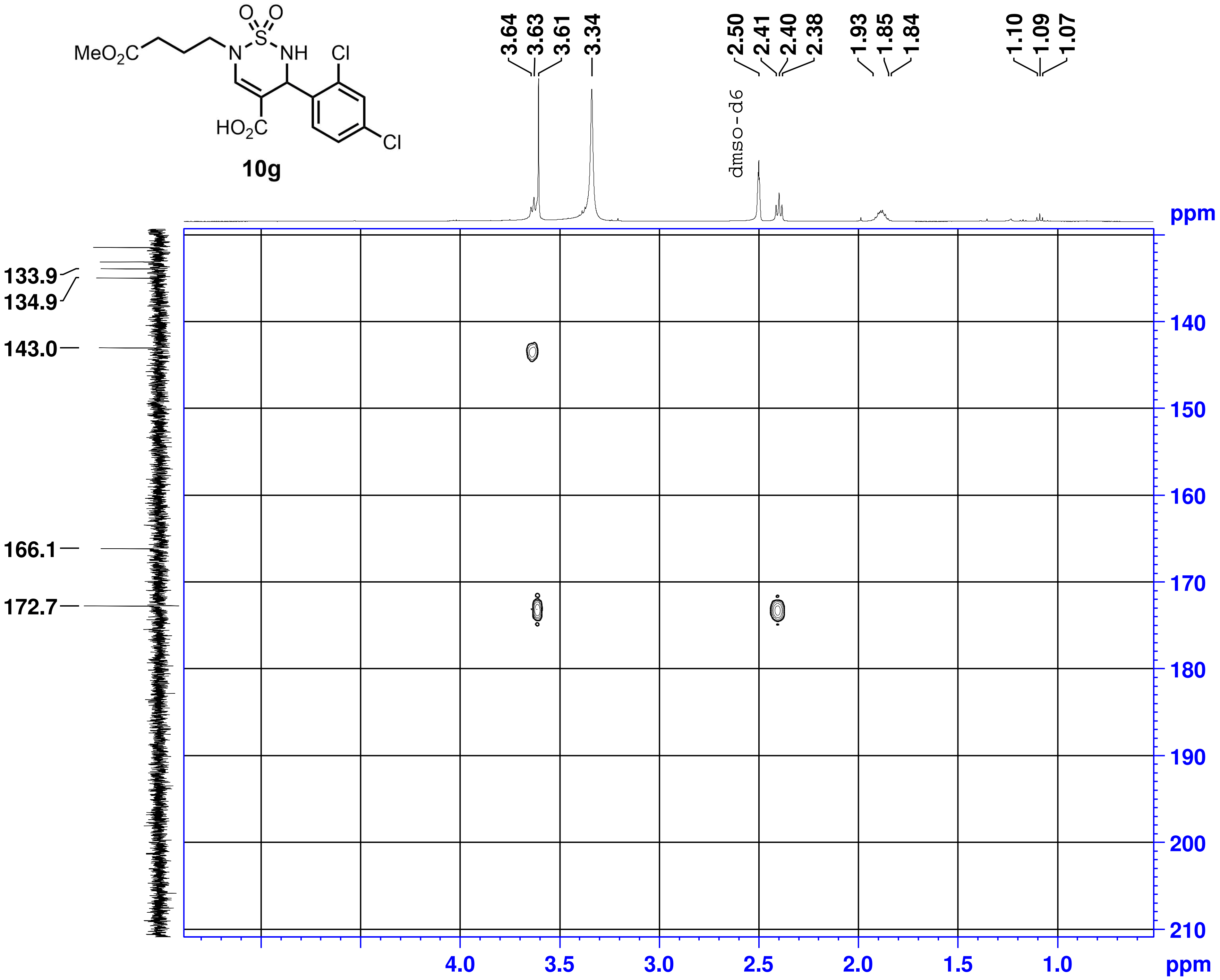
1H NMR (500 MHz, DMSO-d6)



10g

13C NMR (126 MHz, DMSO-d6)





10g

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PROCNO                    1

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PULPROG     hmbcgplpndqf
TD                     2048
SOLVENT                DMSO
NS                        8
DS                       16
SWH                6756.757 Hz
FIDRES             3.299198 Hz
AQ                0.1515520 sec
RG                      203
DW                   74.000 usec
DE                     6.50 usec
TE                    296.3 K
CNST2           145.0000000
CNST13           10.0000000
D0               0.00000300 sec
D1               1.50573397 sec
D2               0.00344828 sec
D6               0.05000000 sec
D16              0.00020000 sec
IN0              0.00001790 sec

======== CHANNEL f1 ========
SFO1            500.1633957 MHz
NUC1                     1H
P1                    11.50 usec
P2                    23.00 usec
PLW1            18.00000000 W

======== CHANNEL f2 ========
SFO2            125.7778879 MHz
NUC2                    13C
P3                    10.50 usec
PLW2           110.00000000 W

====== GRADIENT CHANNEL =====
GPNAM[1]        SMSQ10.100
GPNAM[2]        SMSQ10.100
GPNAM[3]        SMSQ10.100
GPZ1                  50.00 %
GPZ2                  30.00 %
GPZ3                  40.10 %
P16                 1000.00 usec

F1 - Acquisition parameters
TD                      128
SFO1               125.7779 MHz
FIDRES           436.452515 Hz
SW                  222.082 ppm
FnMODE                   QF

F2 - Processing parameters
SI                     2048
SF              500.1600000 MHz
WDW                    SINE
SSB       0
LB        0 Hz
GB        0
PC                     1.40

F1 - Processing parameters
SI                     1024
MC2                      QF
SF              125.7653320 MHz
WDW                    SINE
SSB       0
LB        0 Hz
GB        0
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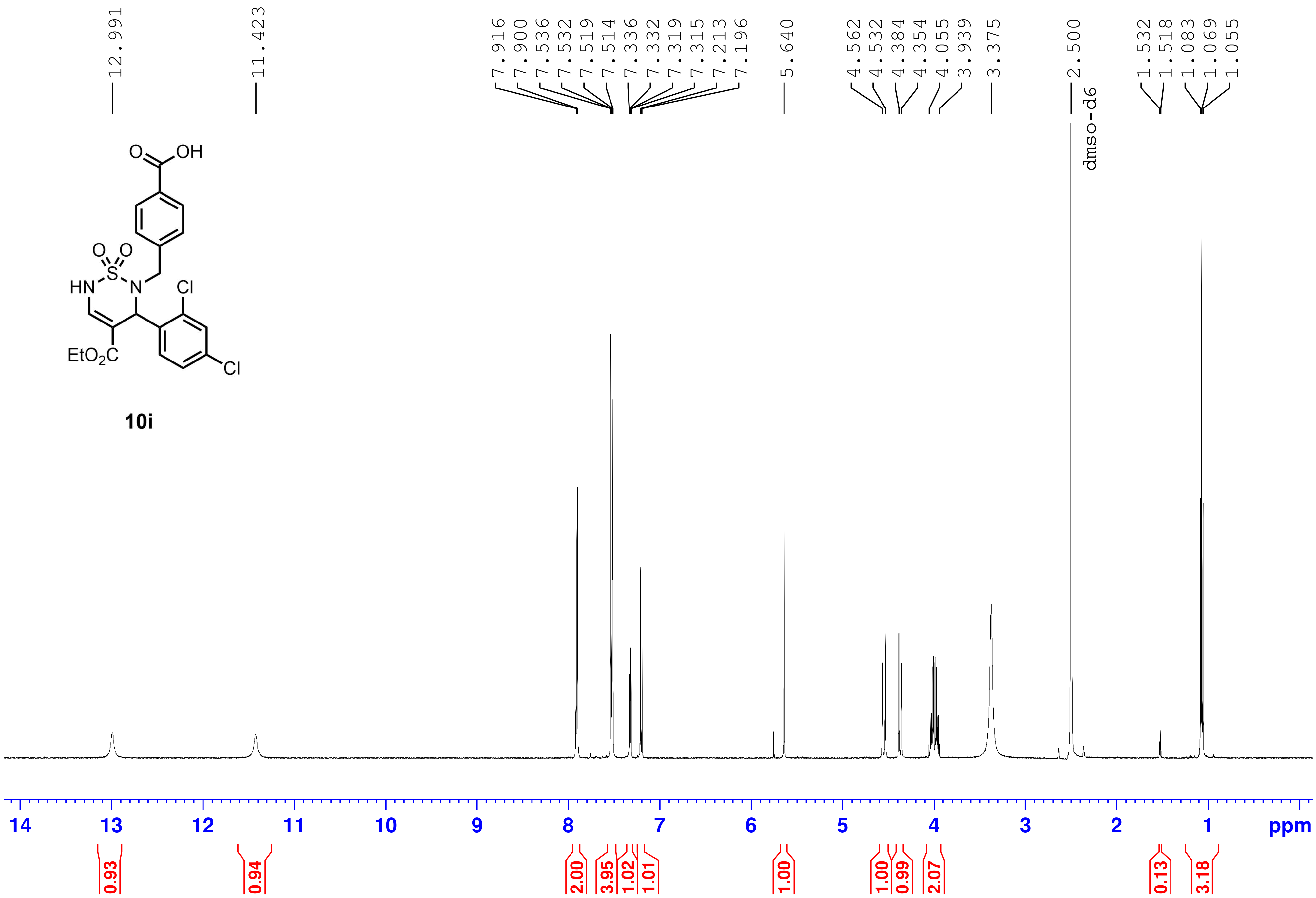
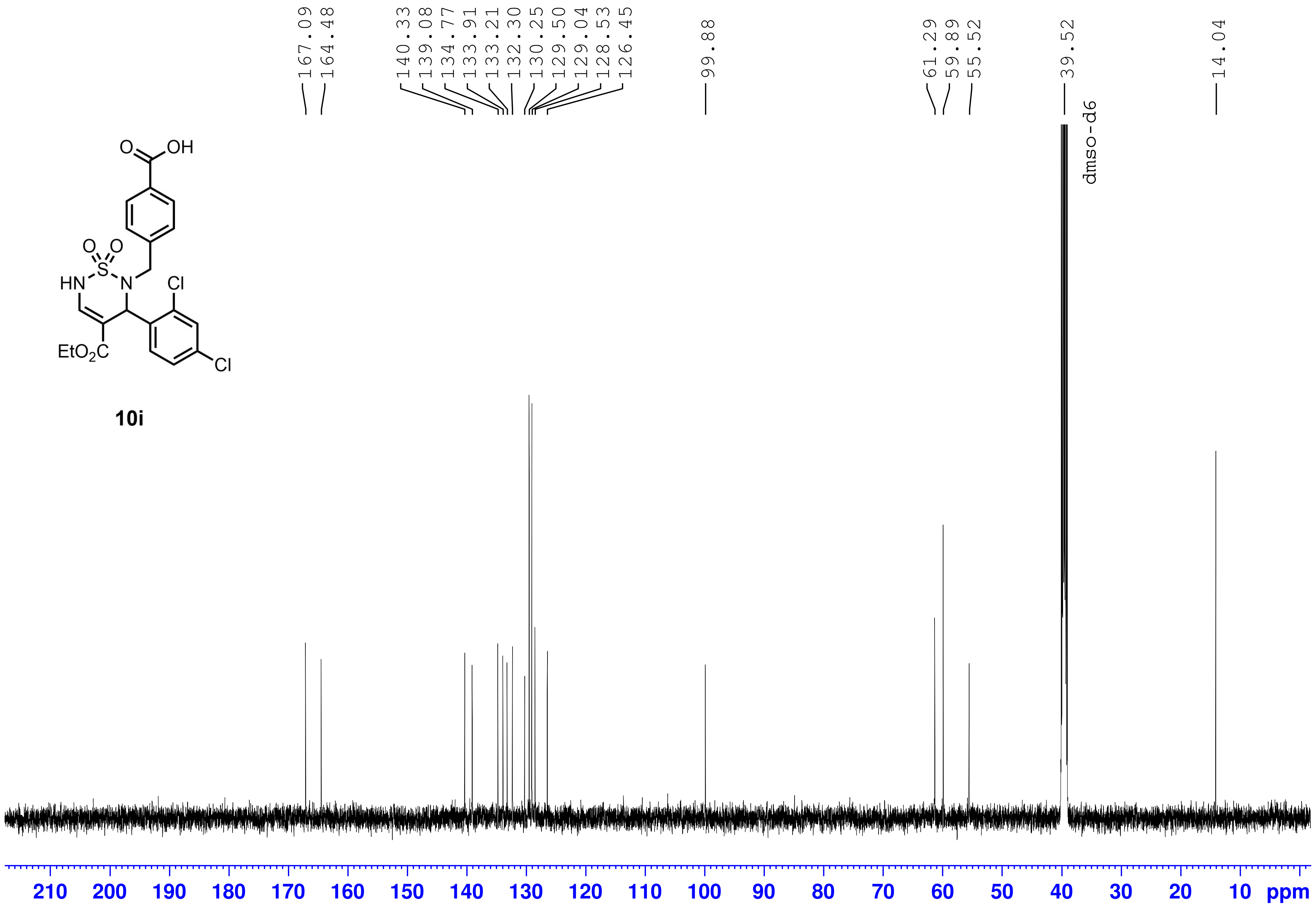
HMBC 2D NMR (500 MHz, DMSO-d6)

1H NMR (500 MHz, DMSO-d6)



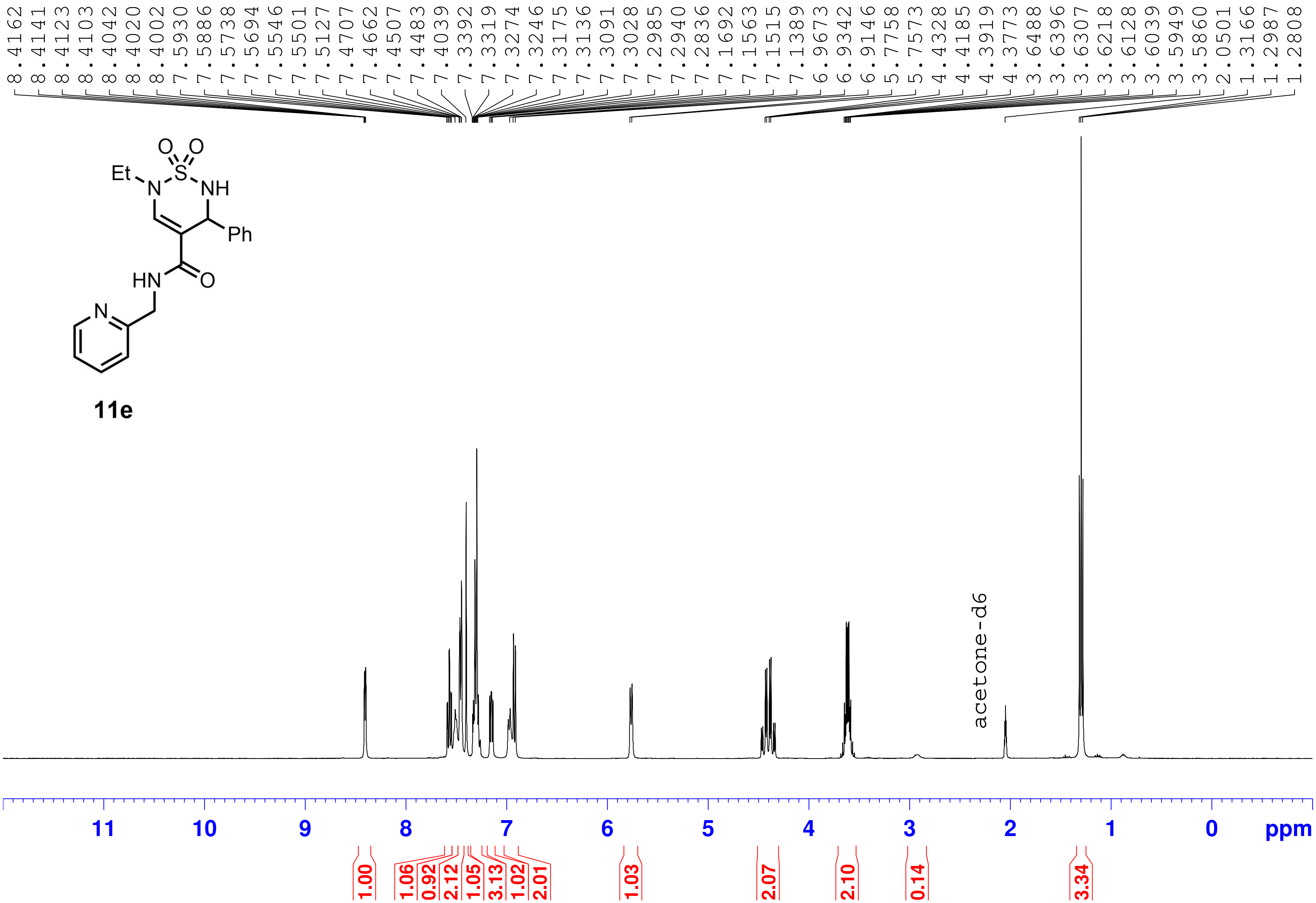
10i

13C NMR (126 MHz, DMSO-d6)



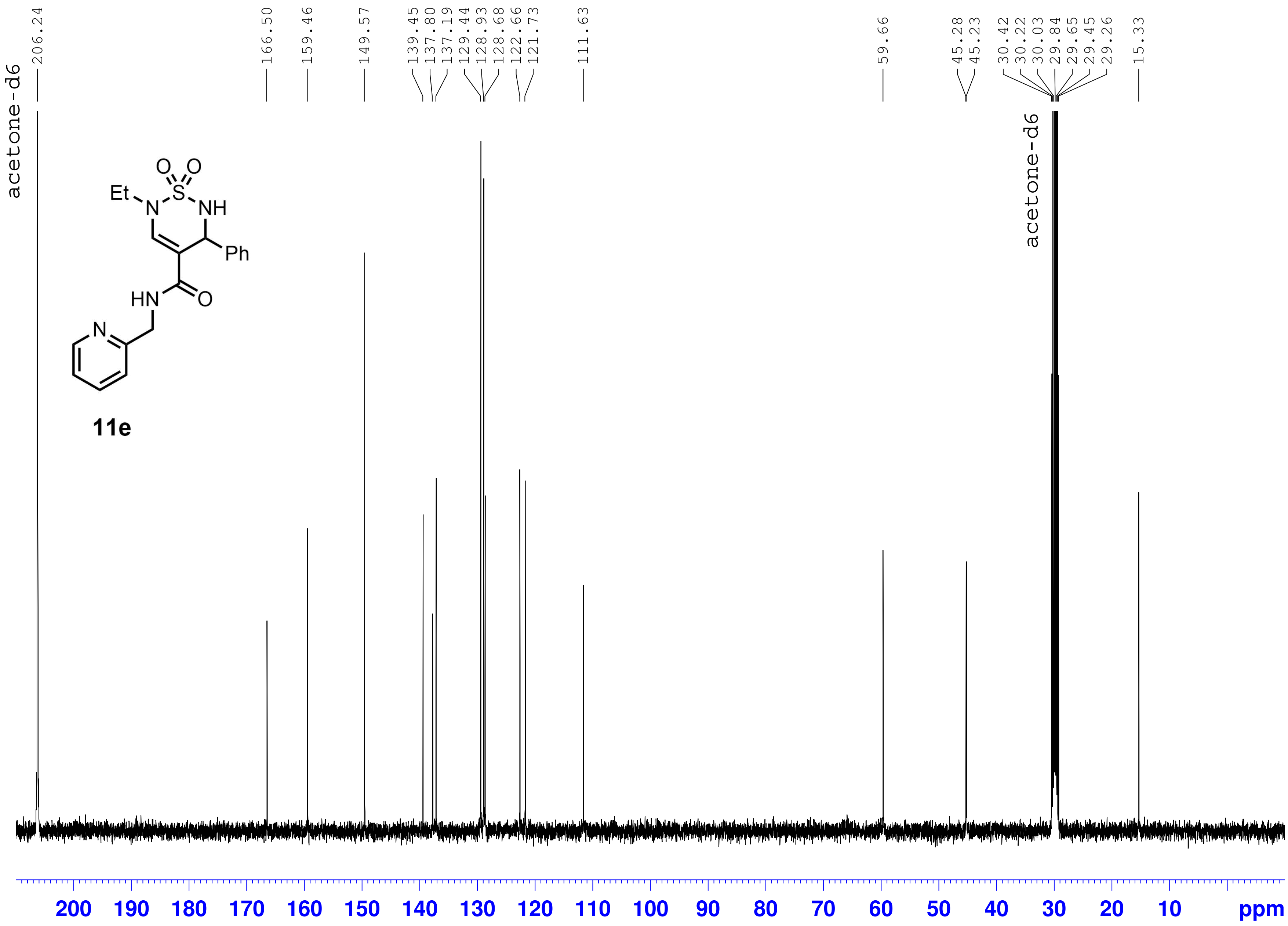
10i

1H NMR (400 MHz, acetone-d6)



11e

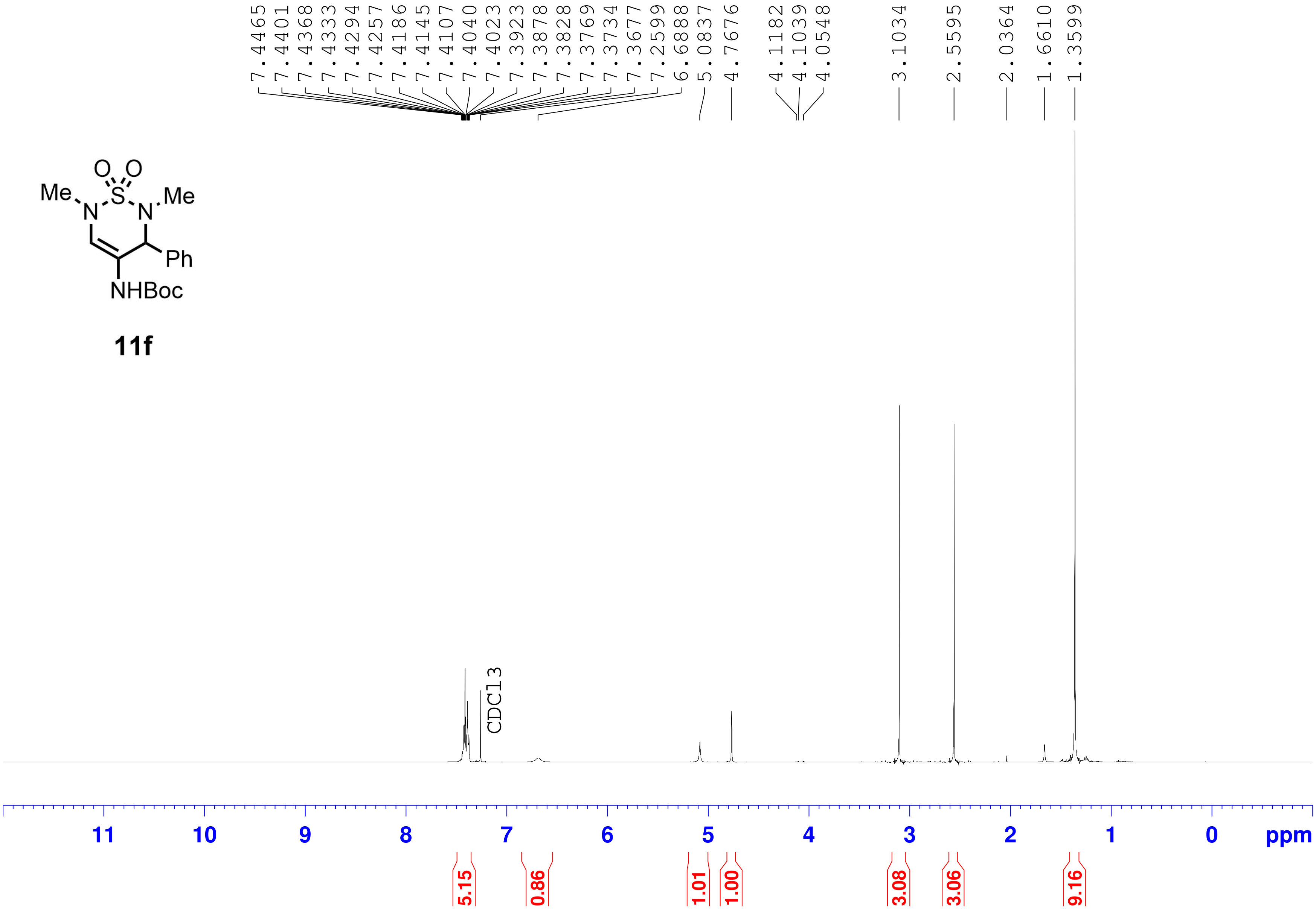
13C NMR (100 MHz, acetone-d6)



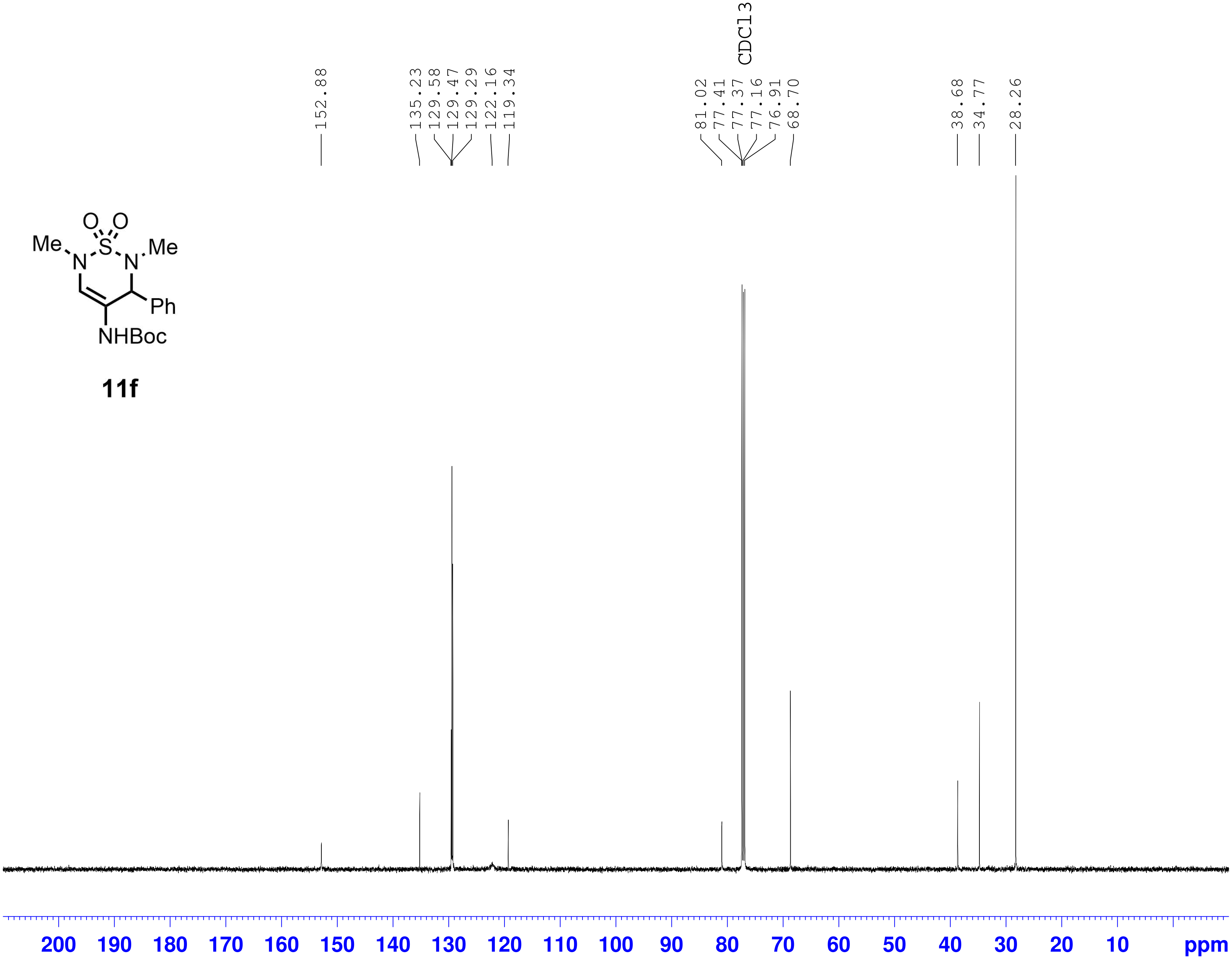
11e

1H NMR (500 MHz, CDCl3)

11f

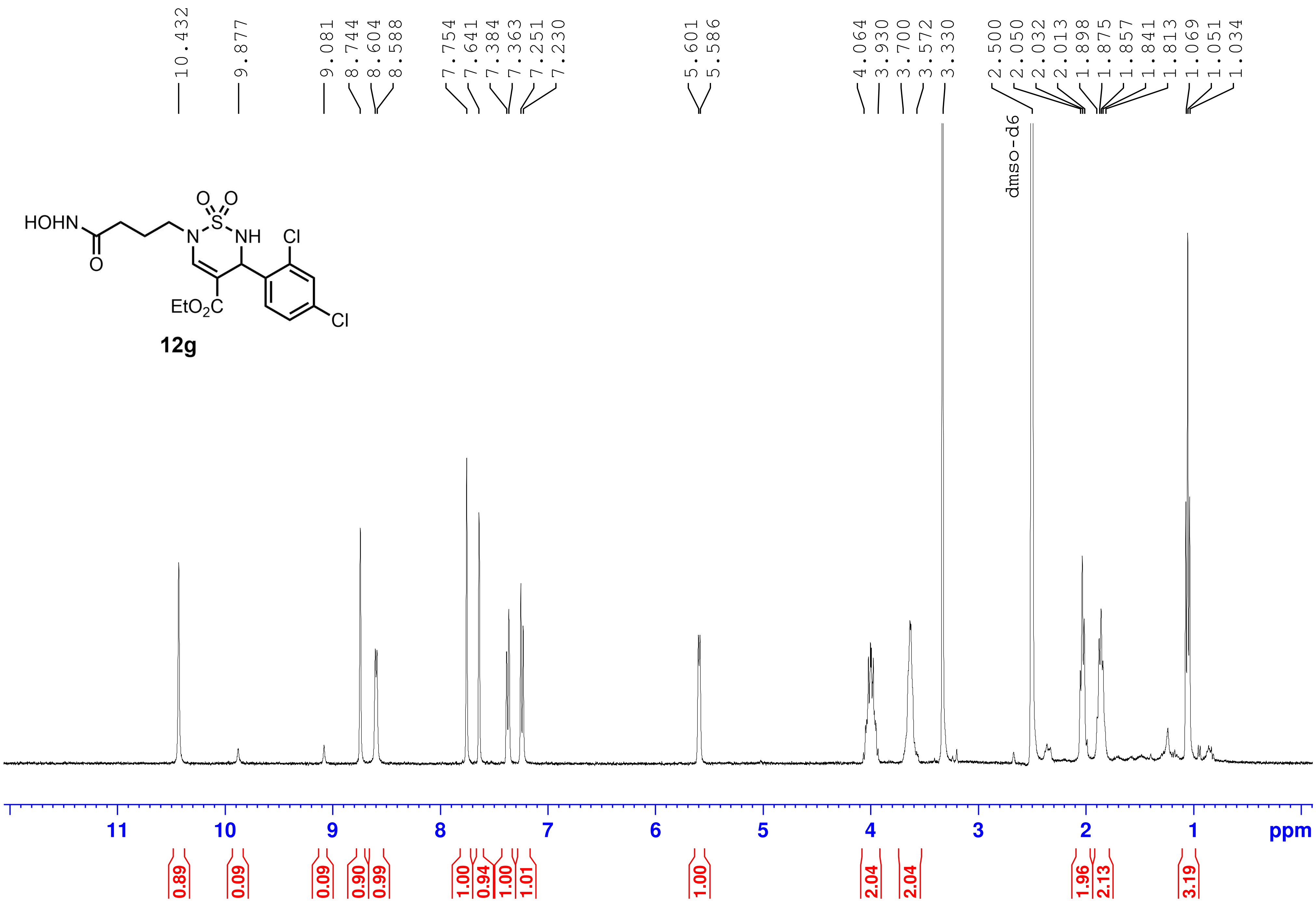


13C NMR (125 MHz, CDCl3)



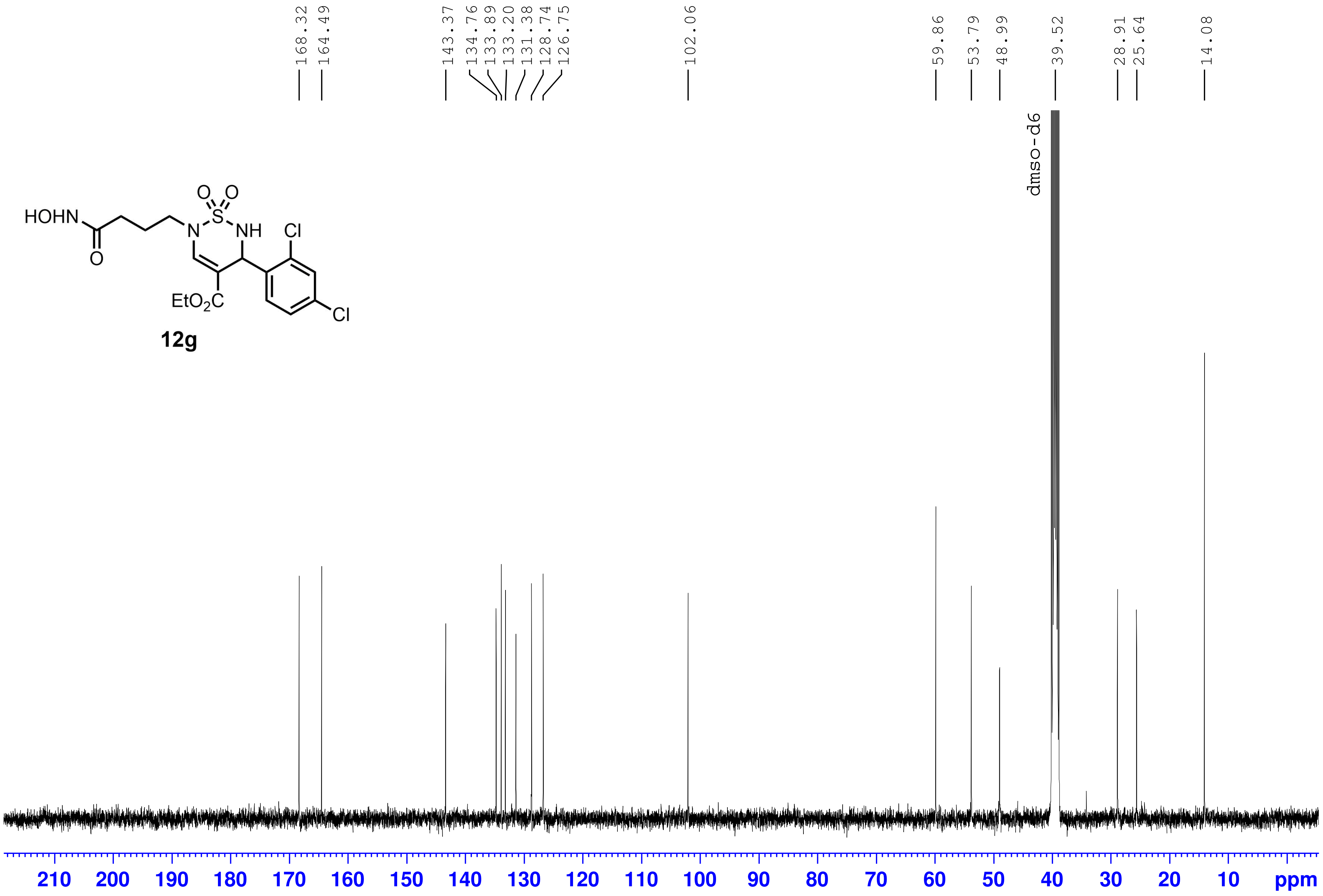
11f

1H NMR (400 MHz, DMSO-d6)



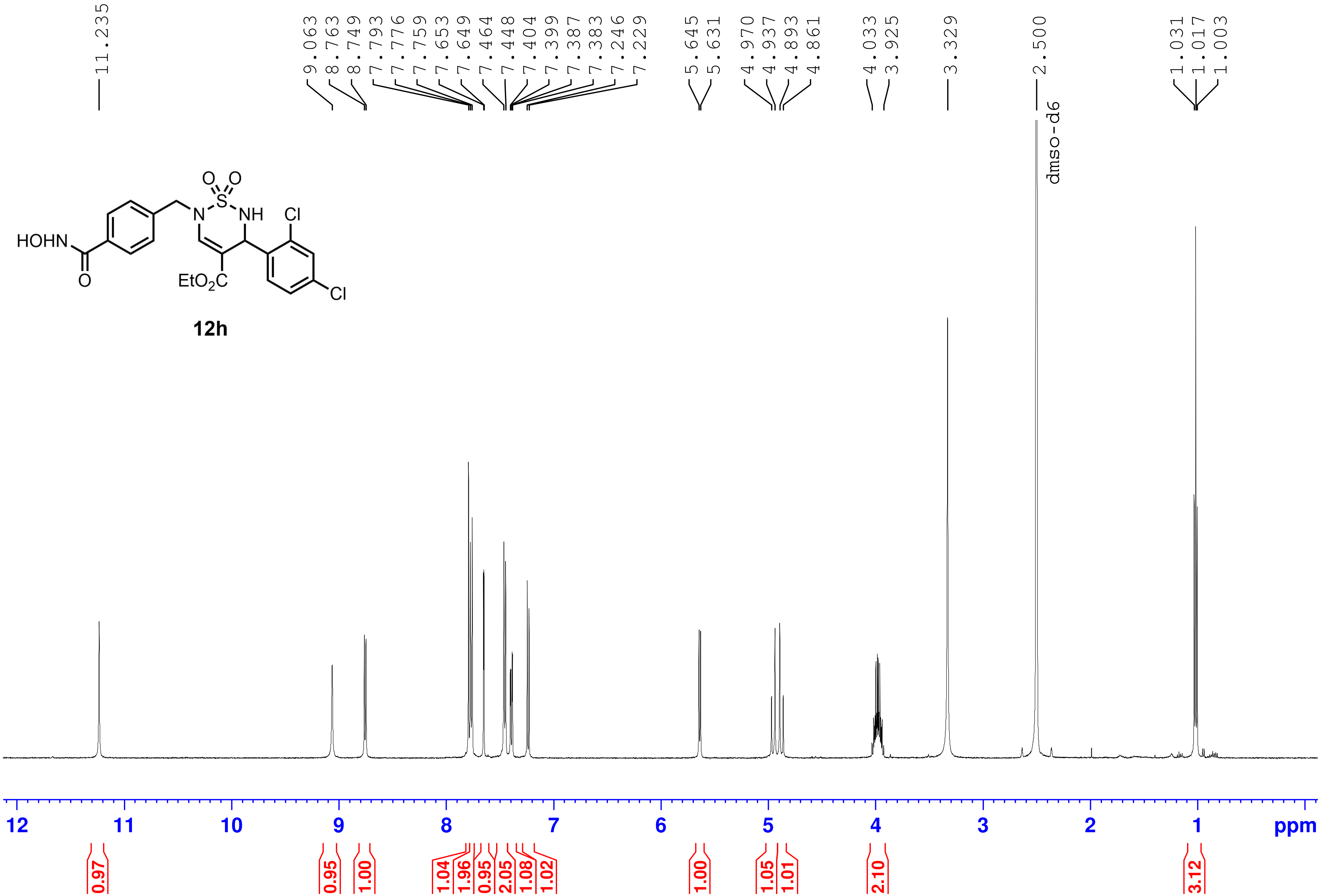
12g

13C NMR (101 MHz, DMSO-d6)



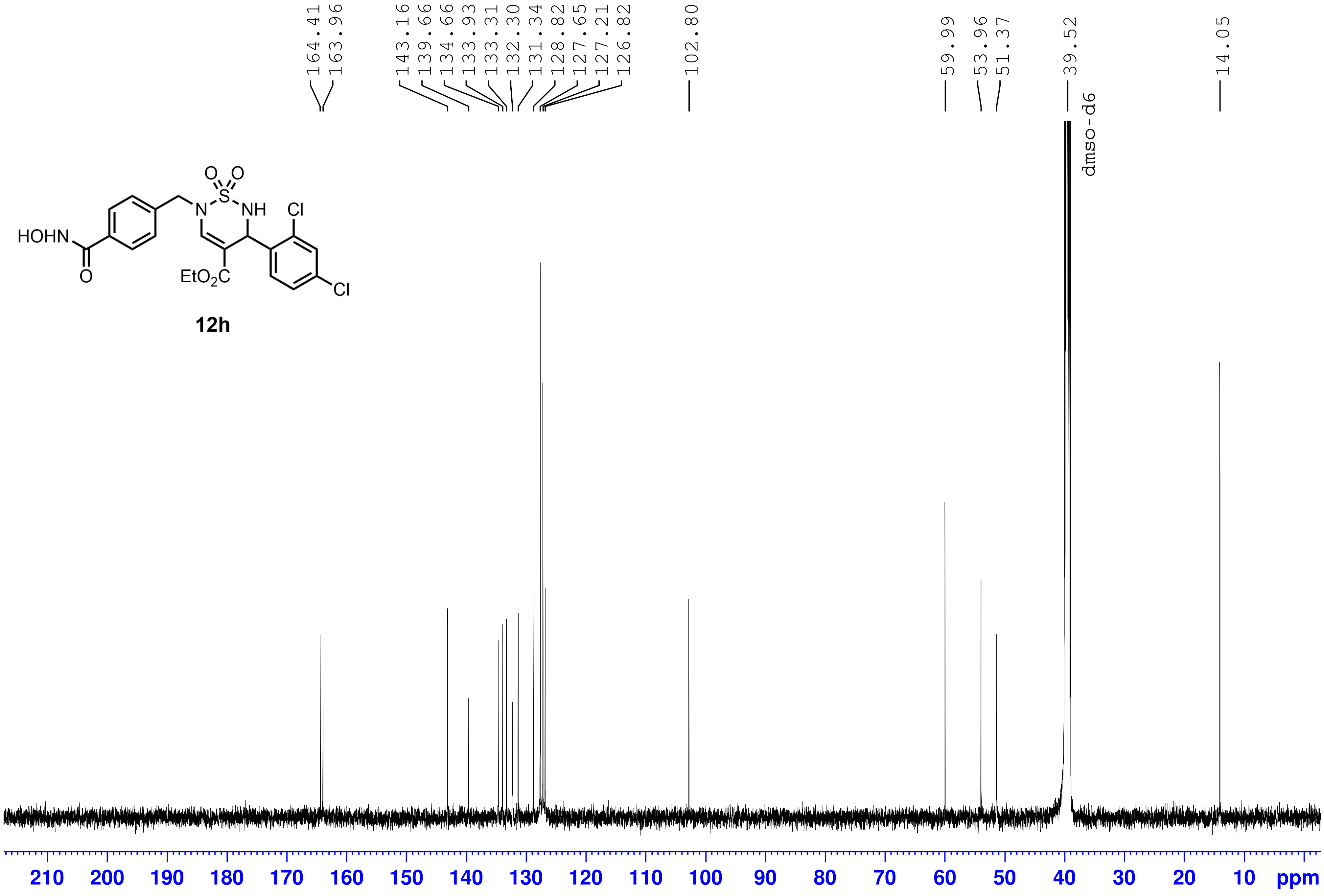
12g

1H NMR (500 MHz, DMSO-d6)



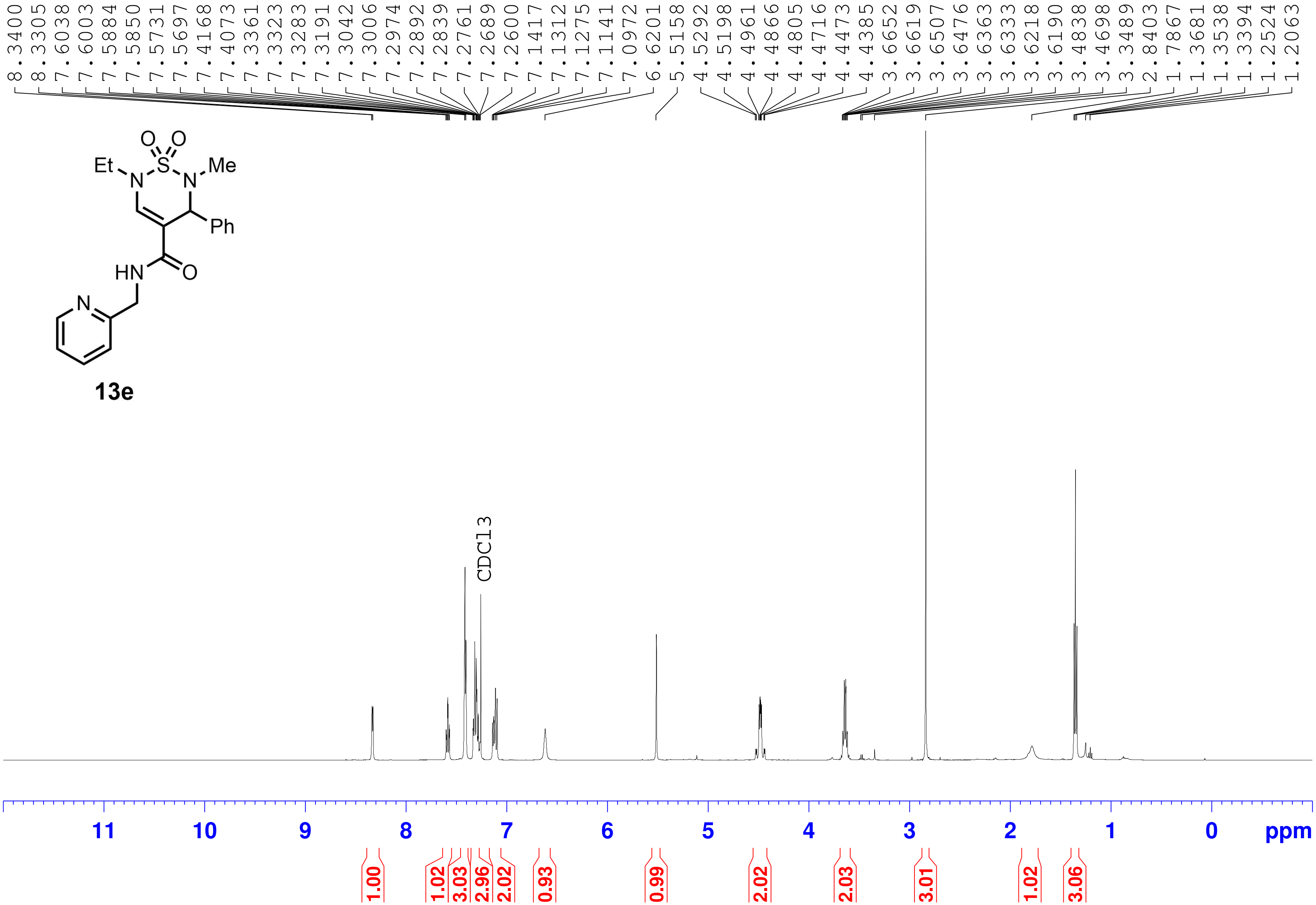
12h

13C NMR (126 MHz, DMSO-d6)



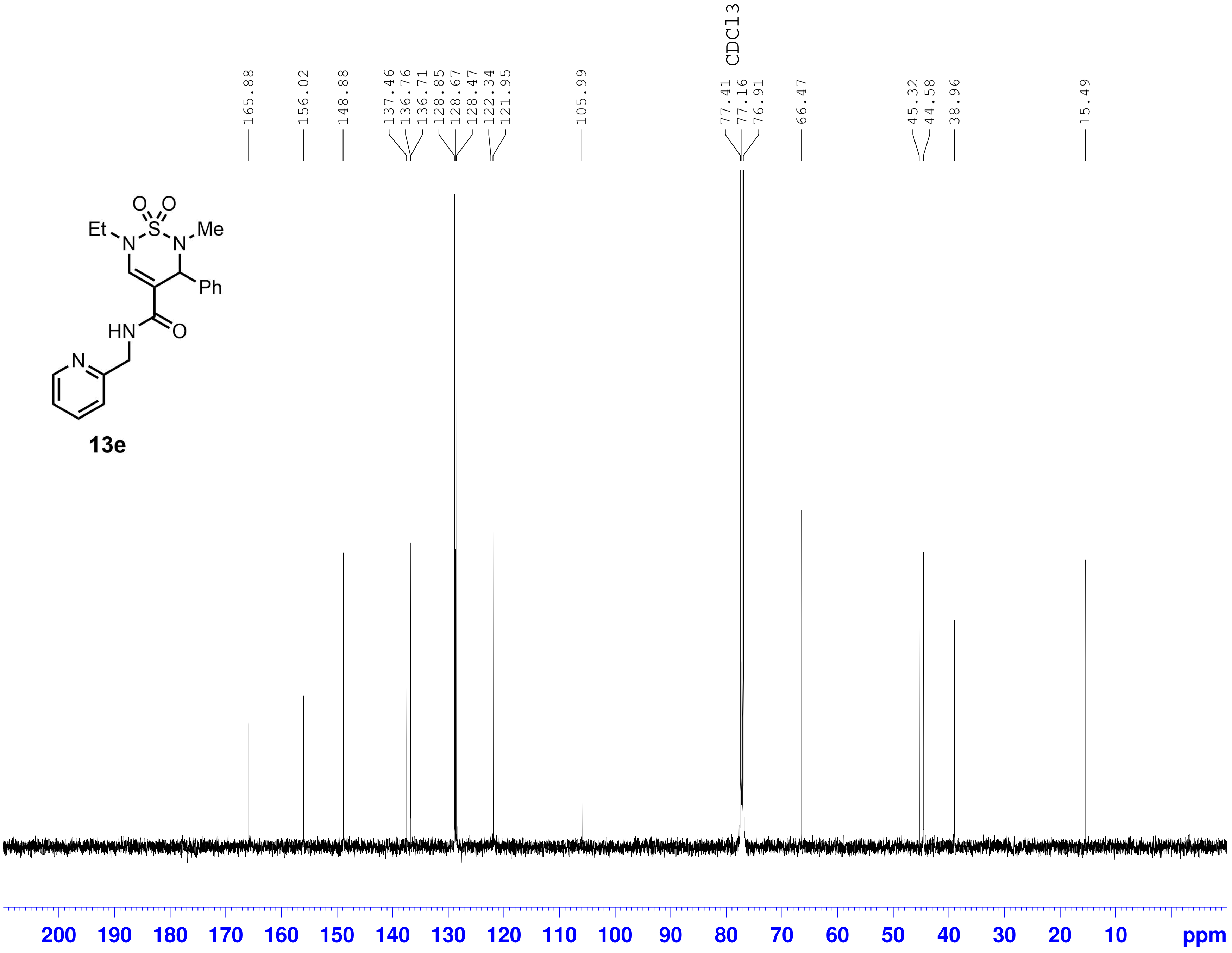
12h

1H NMR (500 MHz, CDCl3)



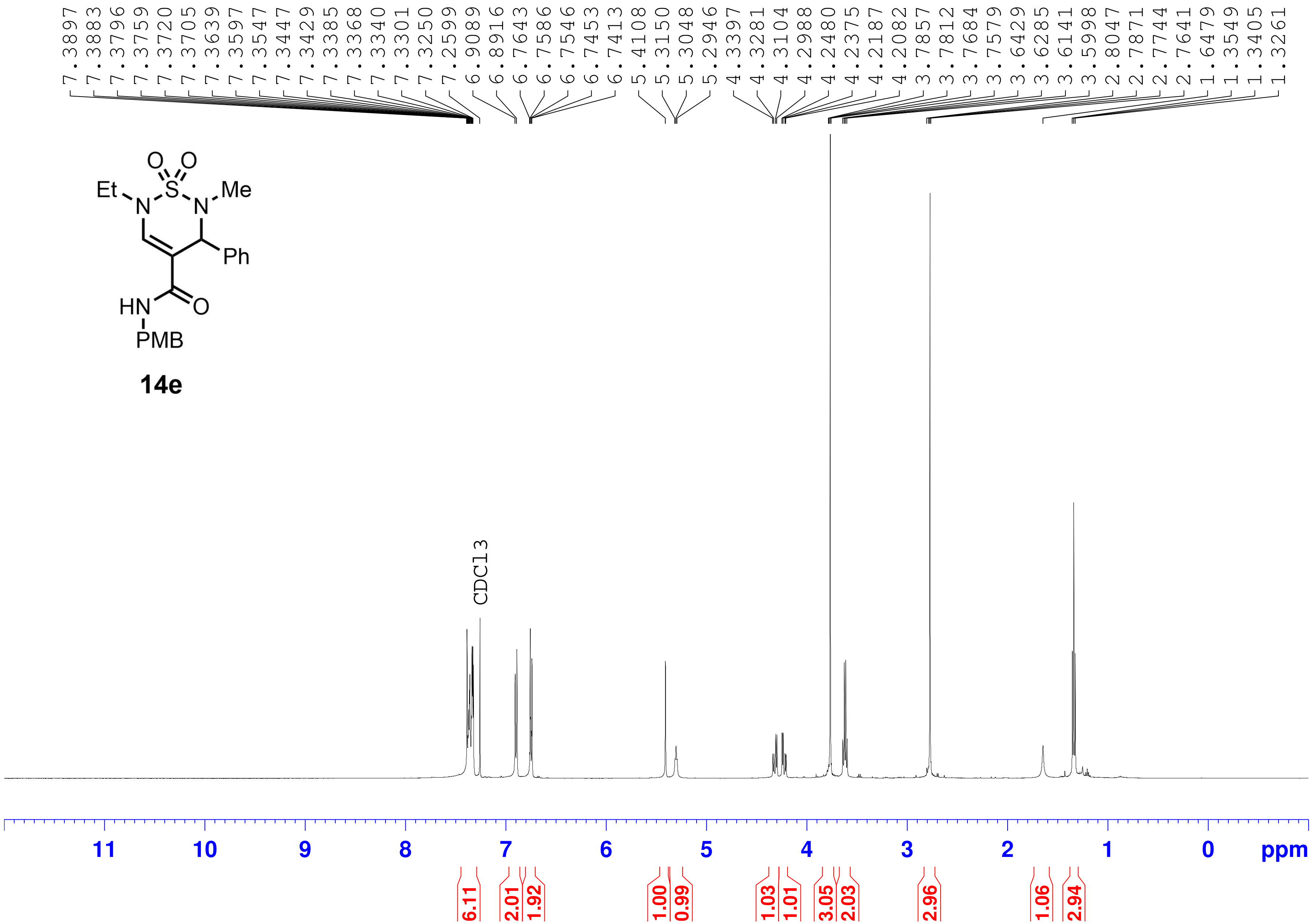
13e

13C NMR (125 MHz, CDCl3)



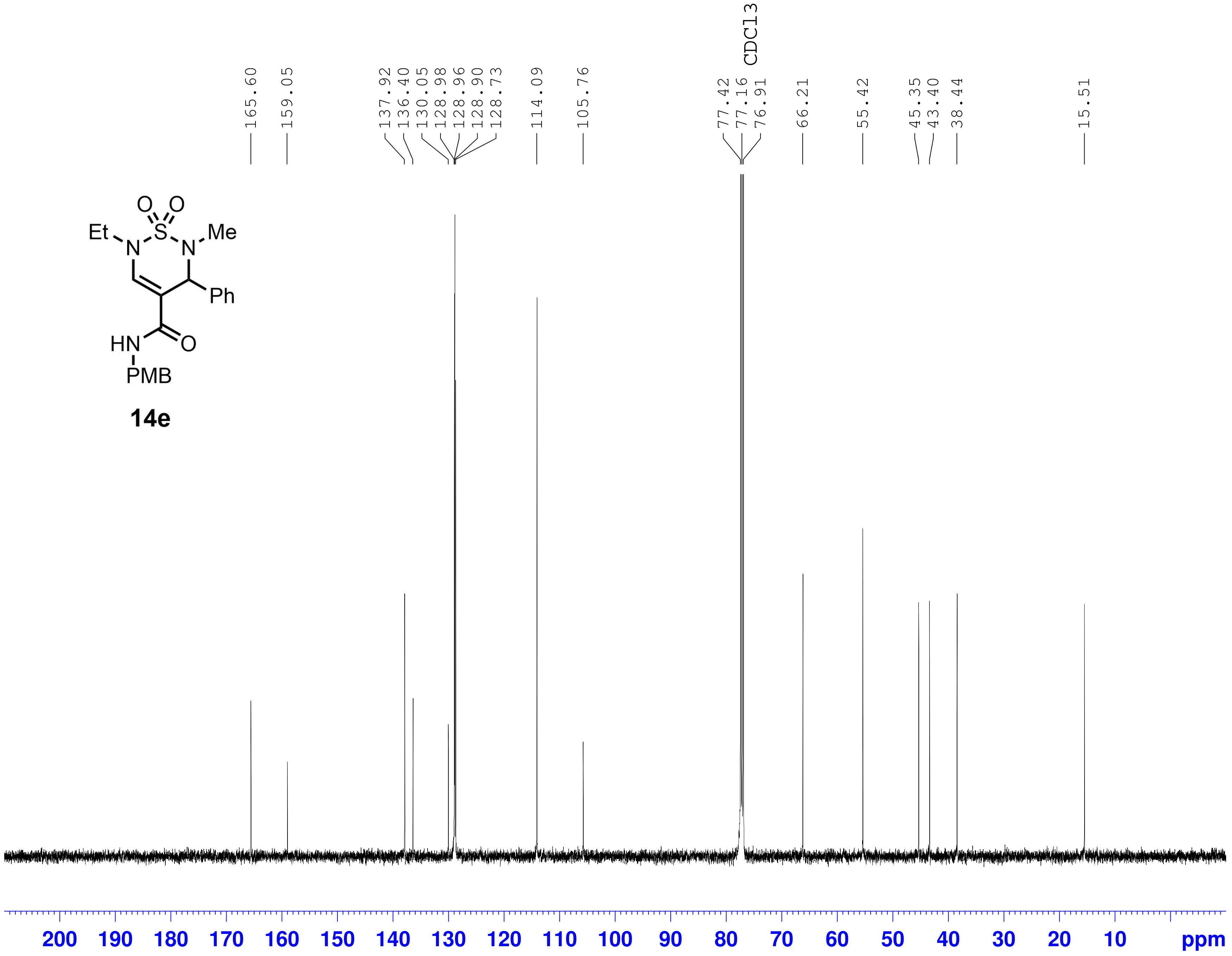
13e

1H NMR (500 MHz, CDCl3)



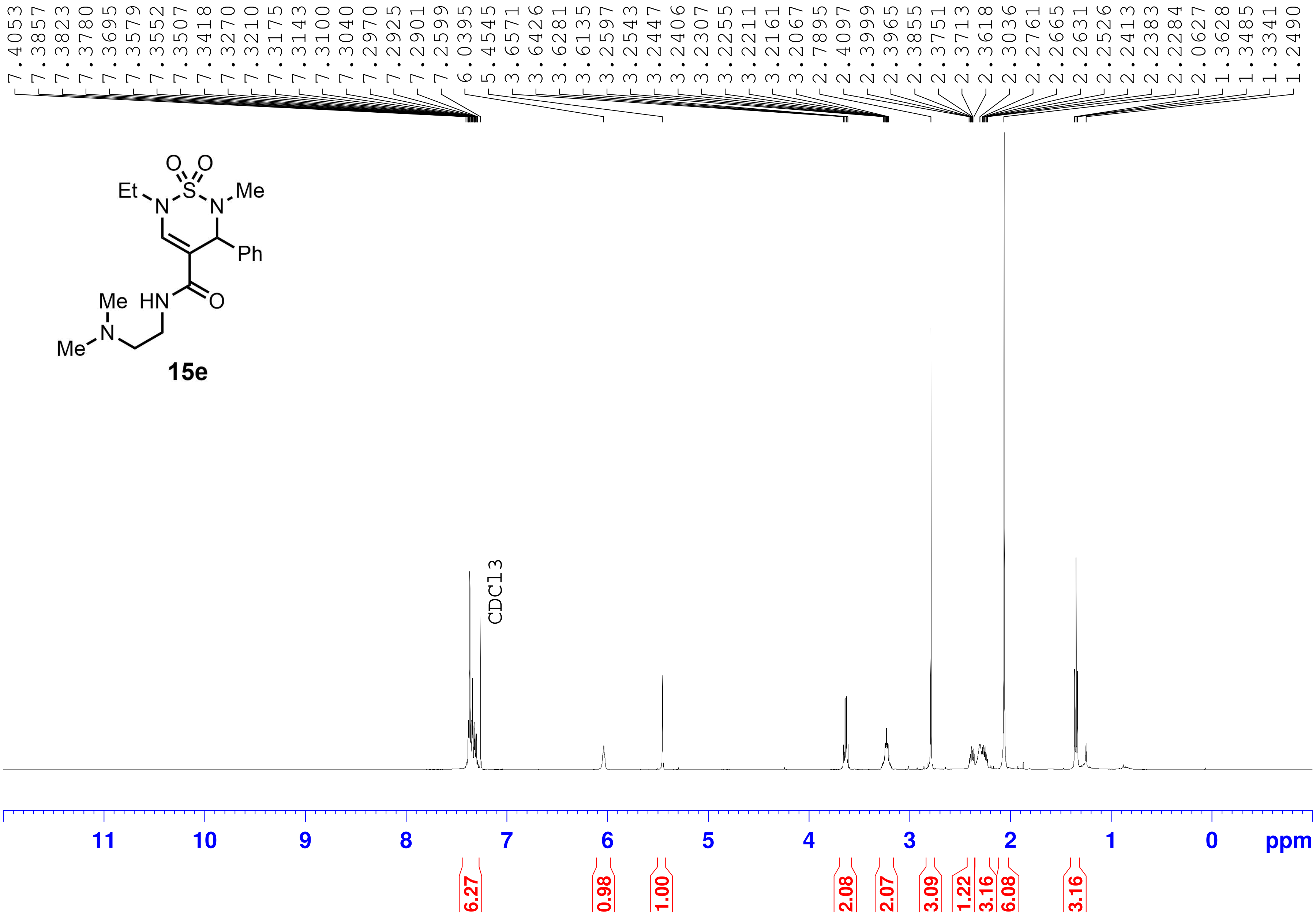
14e

13C NMR (125 MHz, CDCl3)



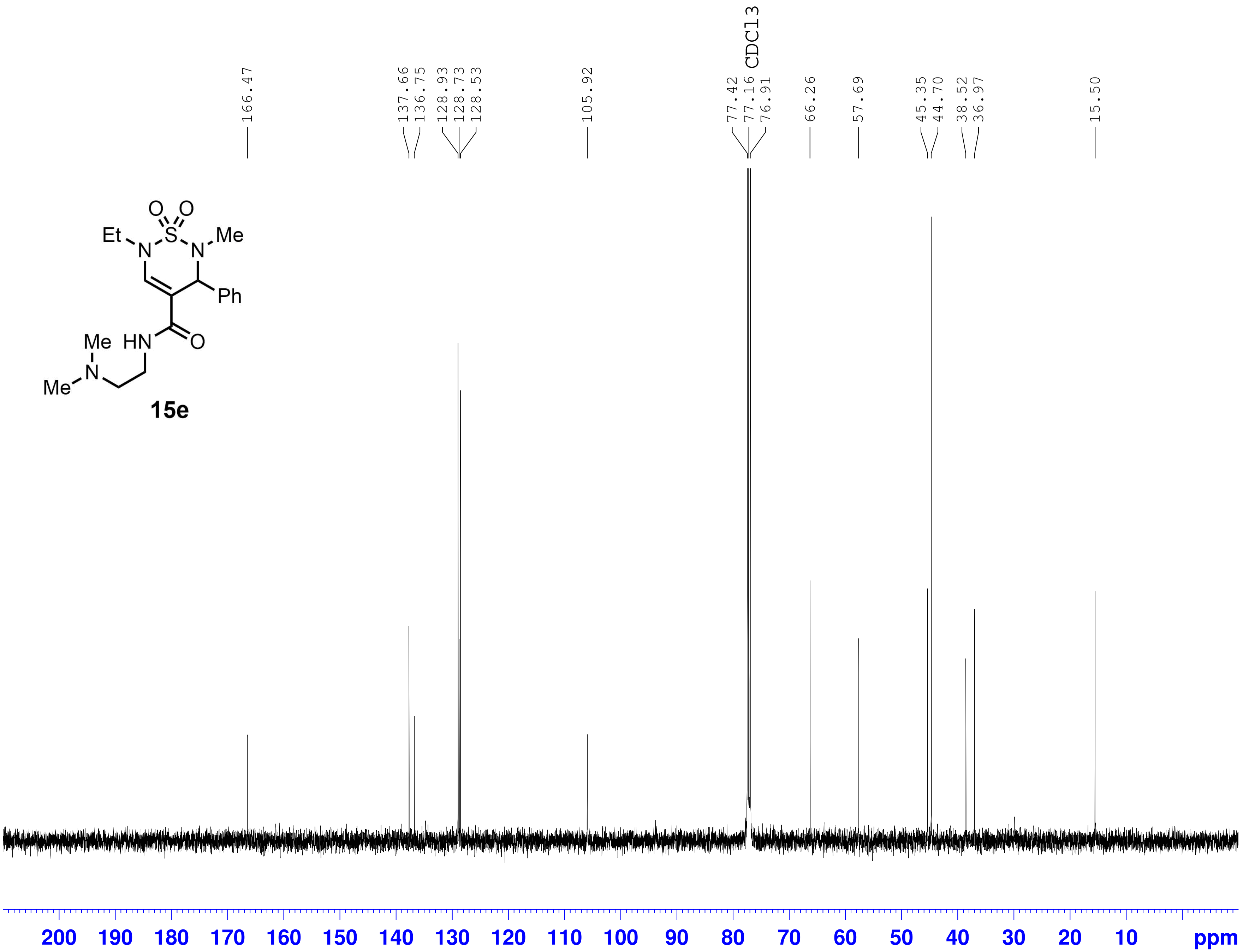
14e

1H NMR (500 MHz, CDCl3)



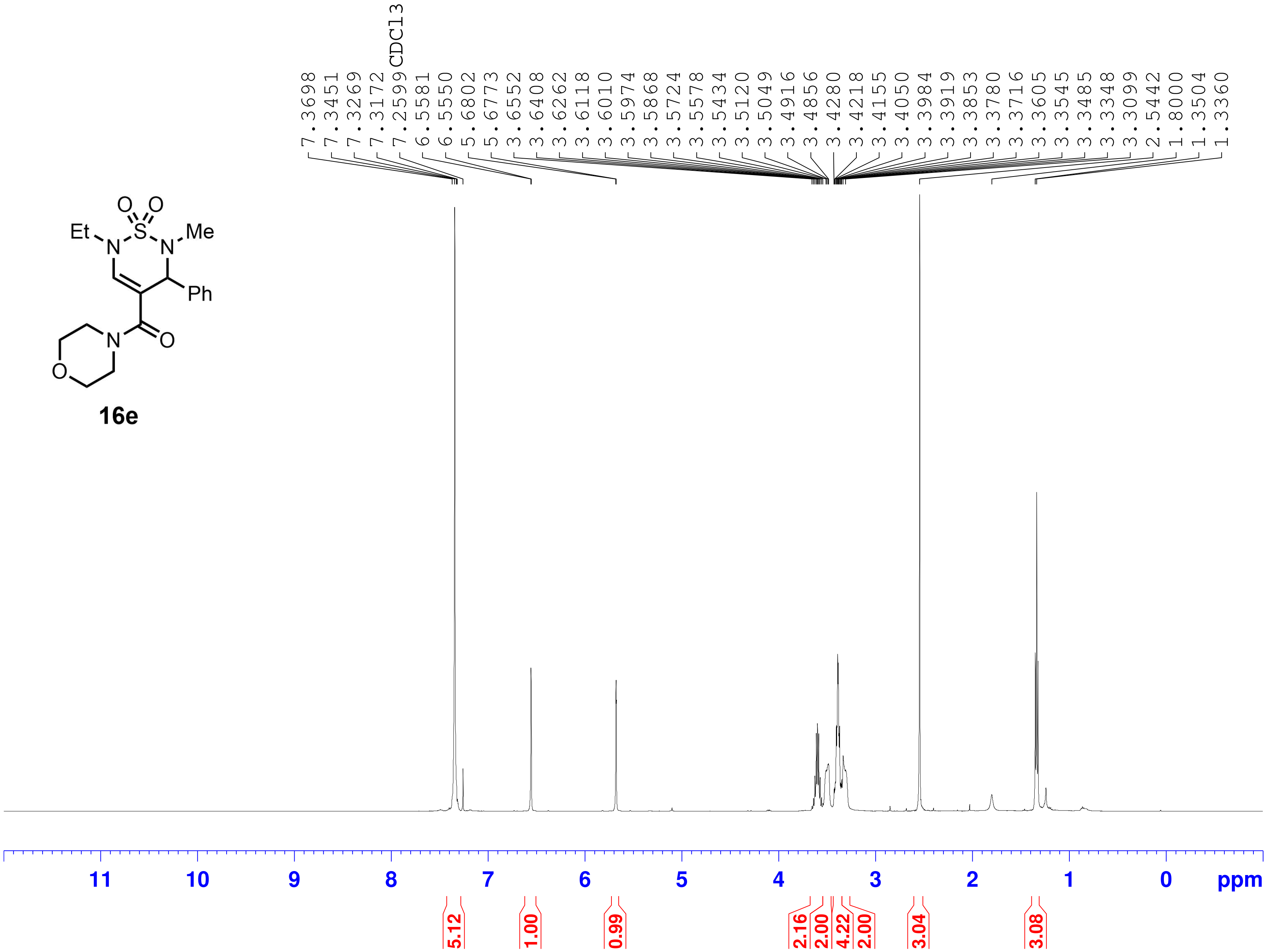
15e

13C NMR (125 MHz, CDCl3)



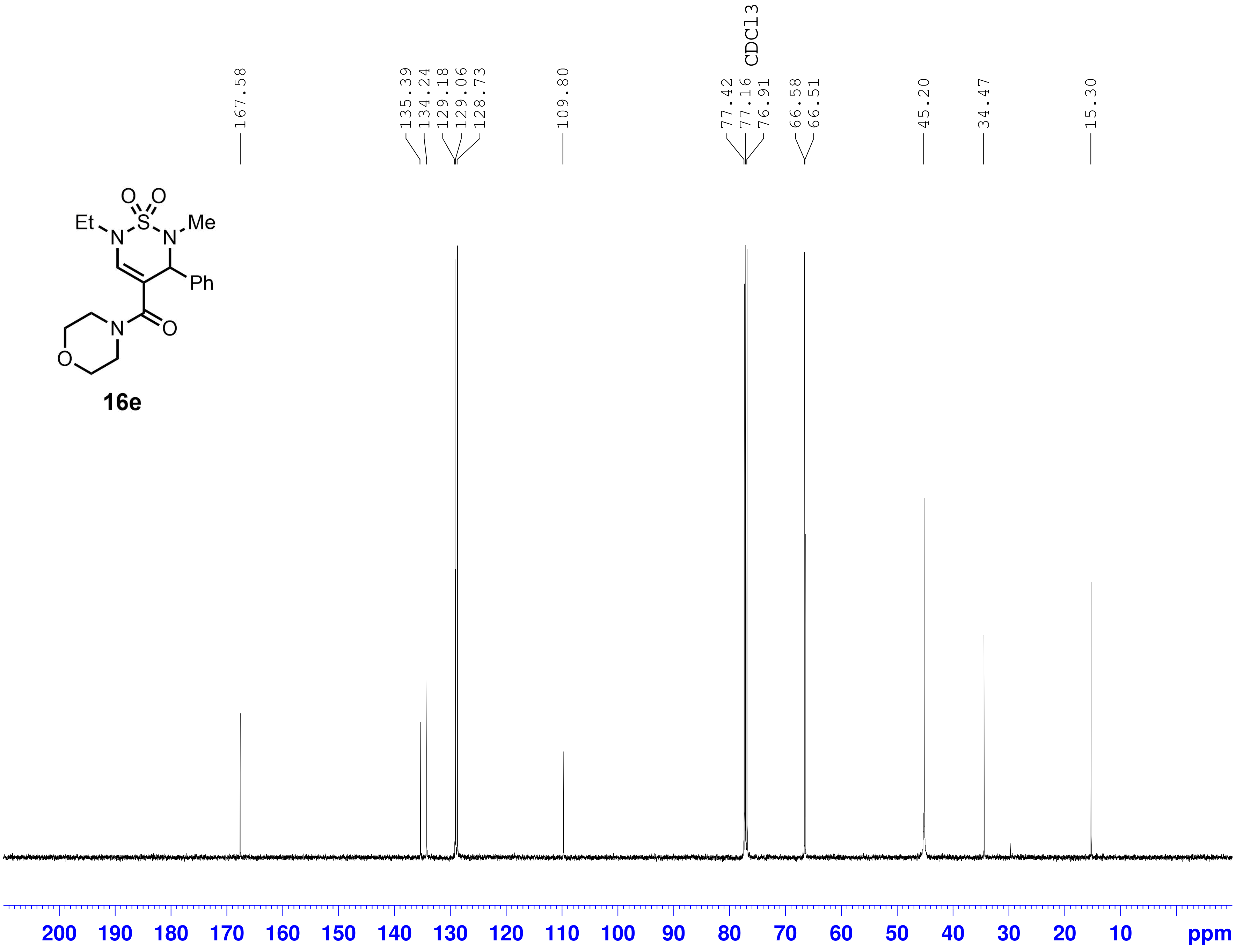
15e

1H NMR (500 MHz, CDCl3)

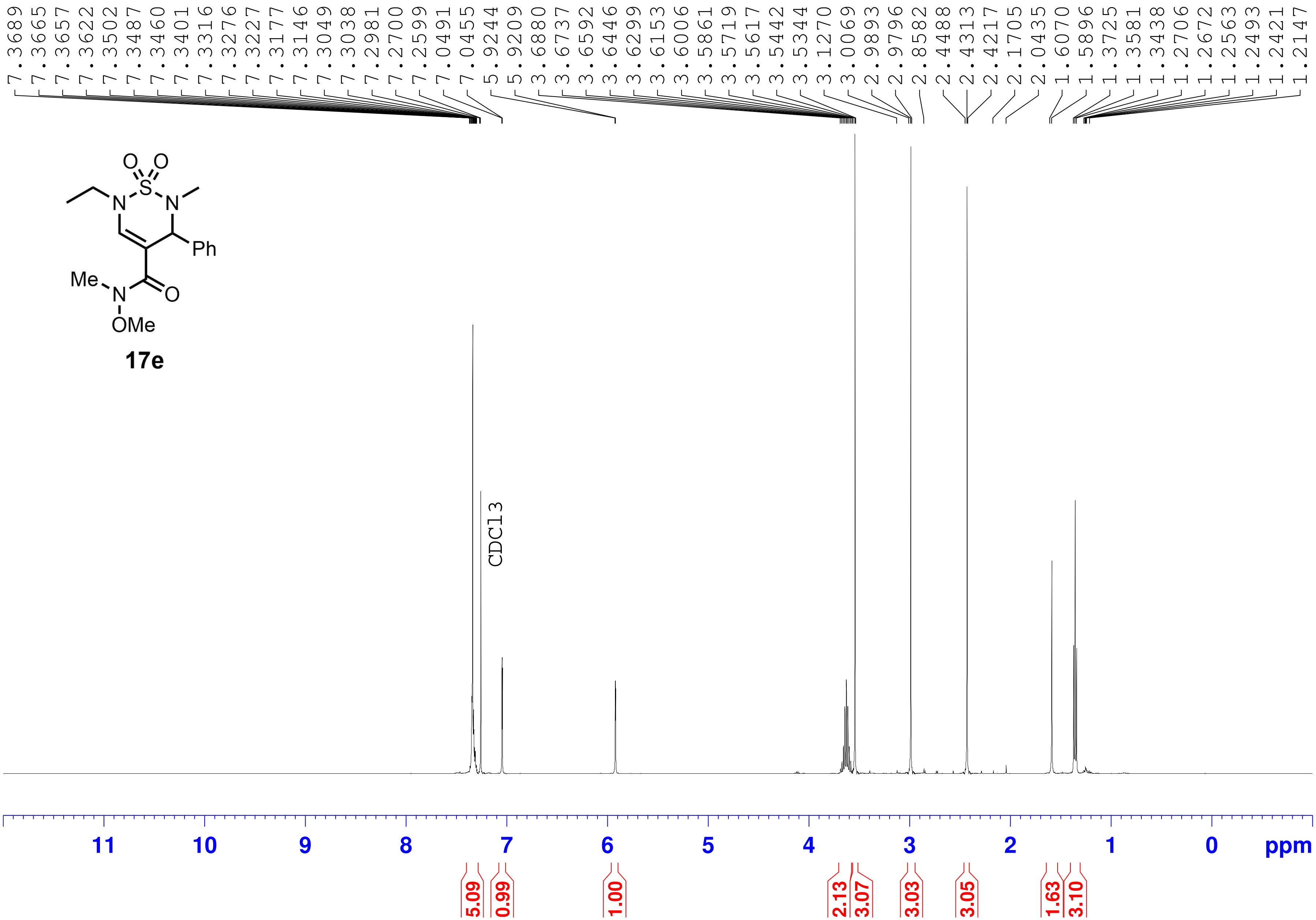


16e

13C NMR (125 MHz, CDCl3)

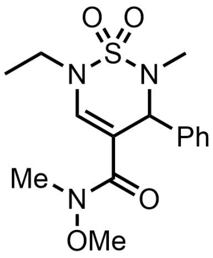


1H NMR (500 MHz, CDCl3)

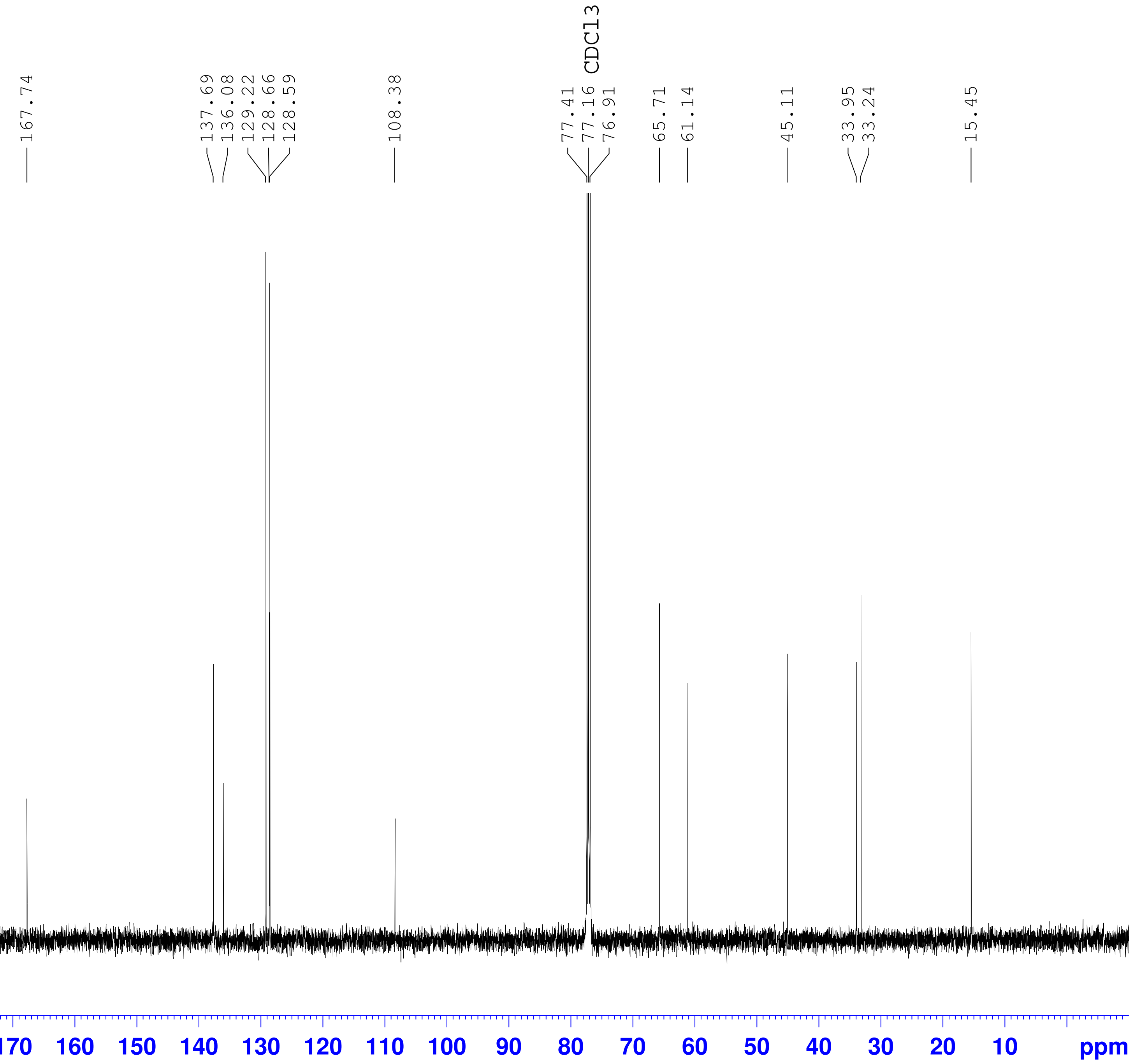


17e

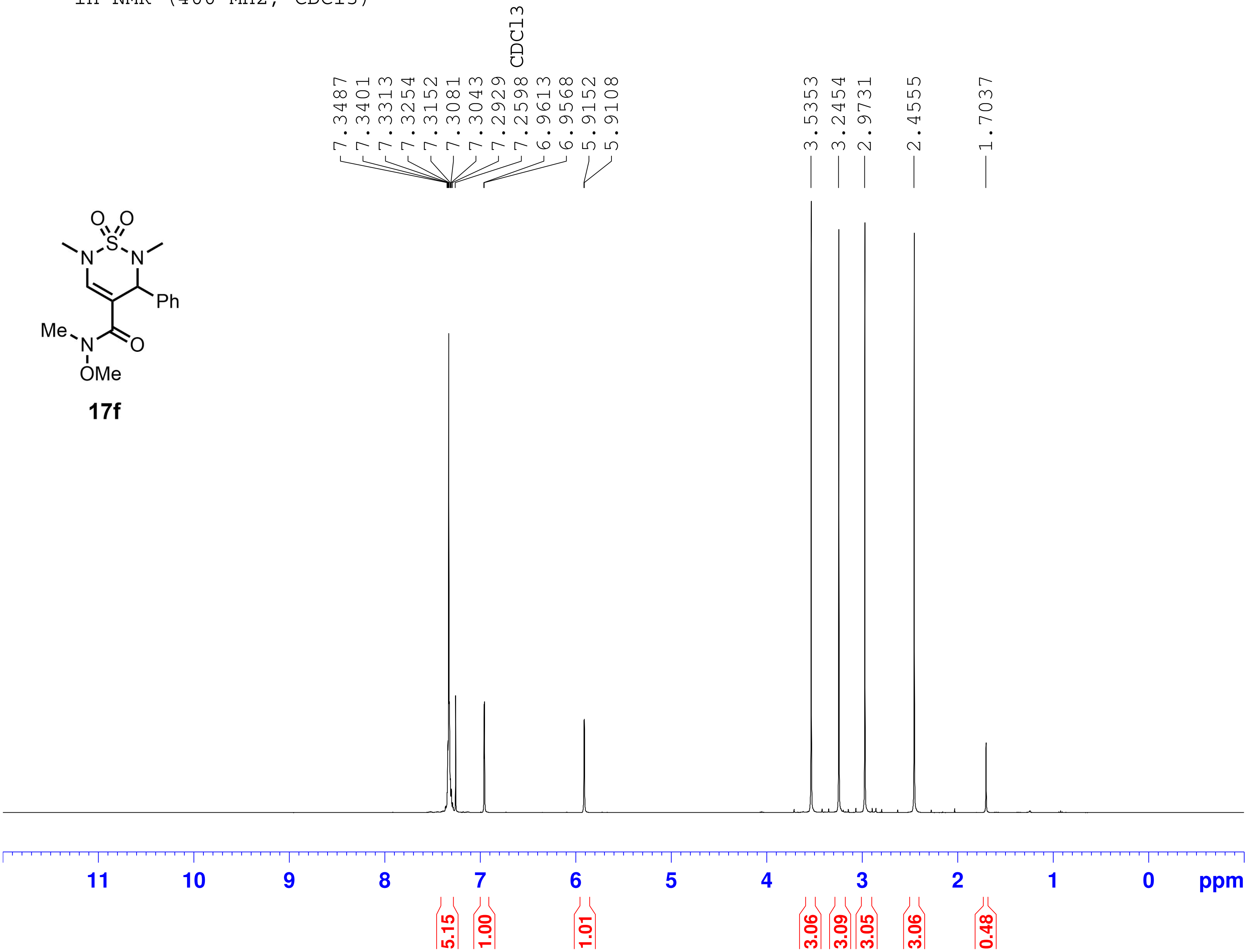
13C NMR (125 MHz, CDCl3)



17e

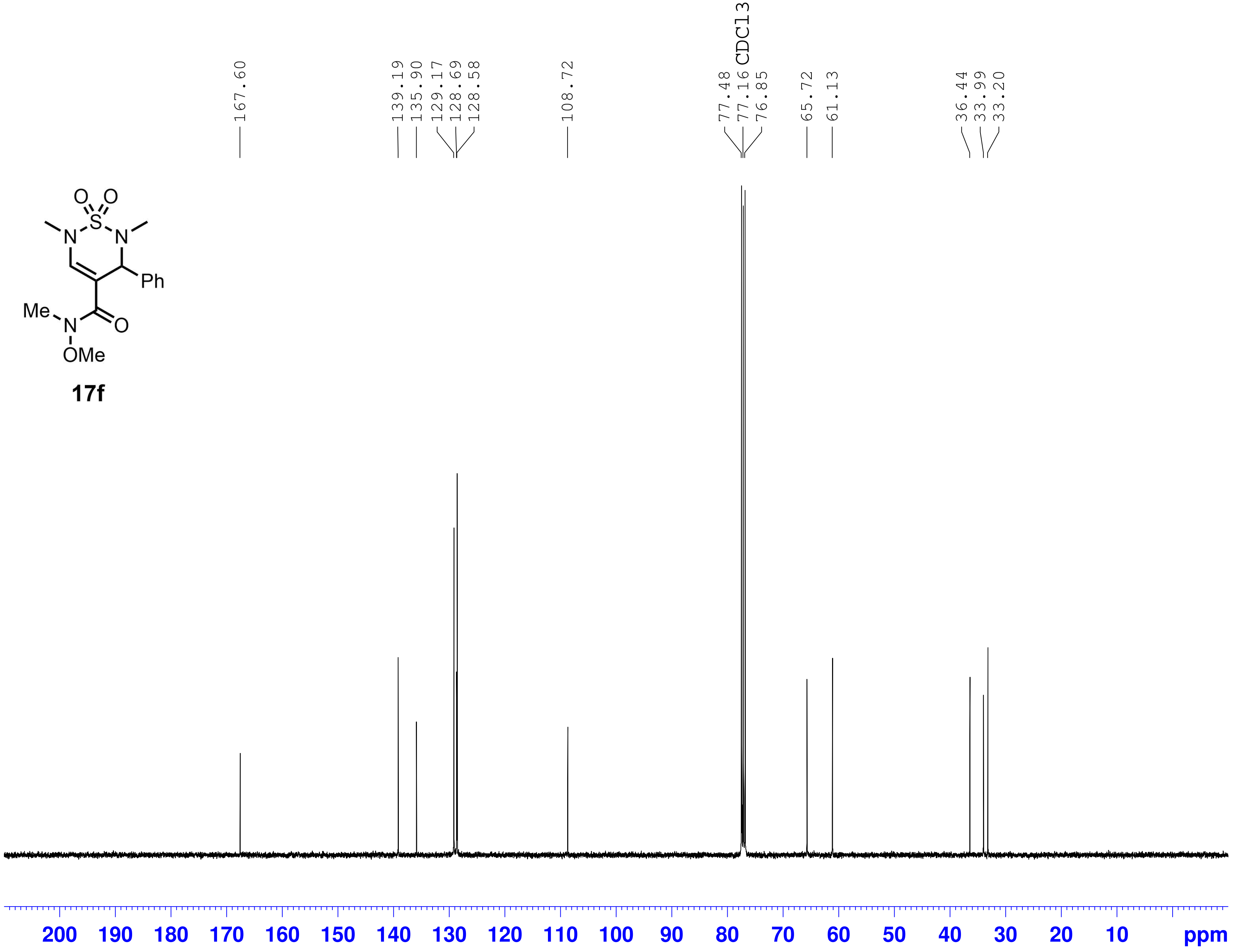


1H NMR (400 MHz, CDCl3)

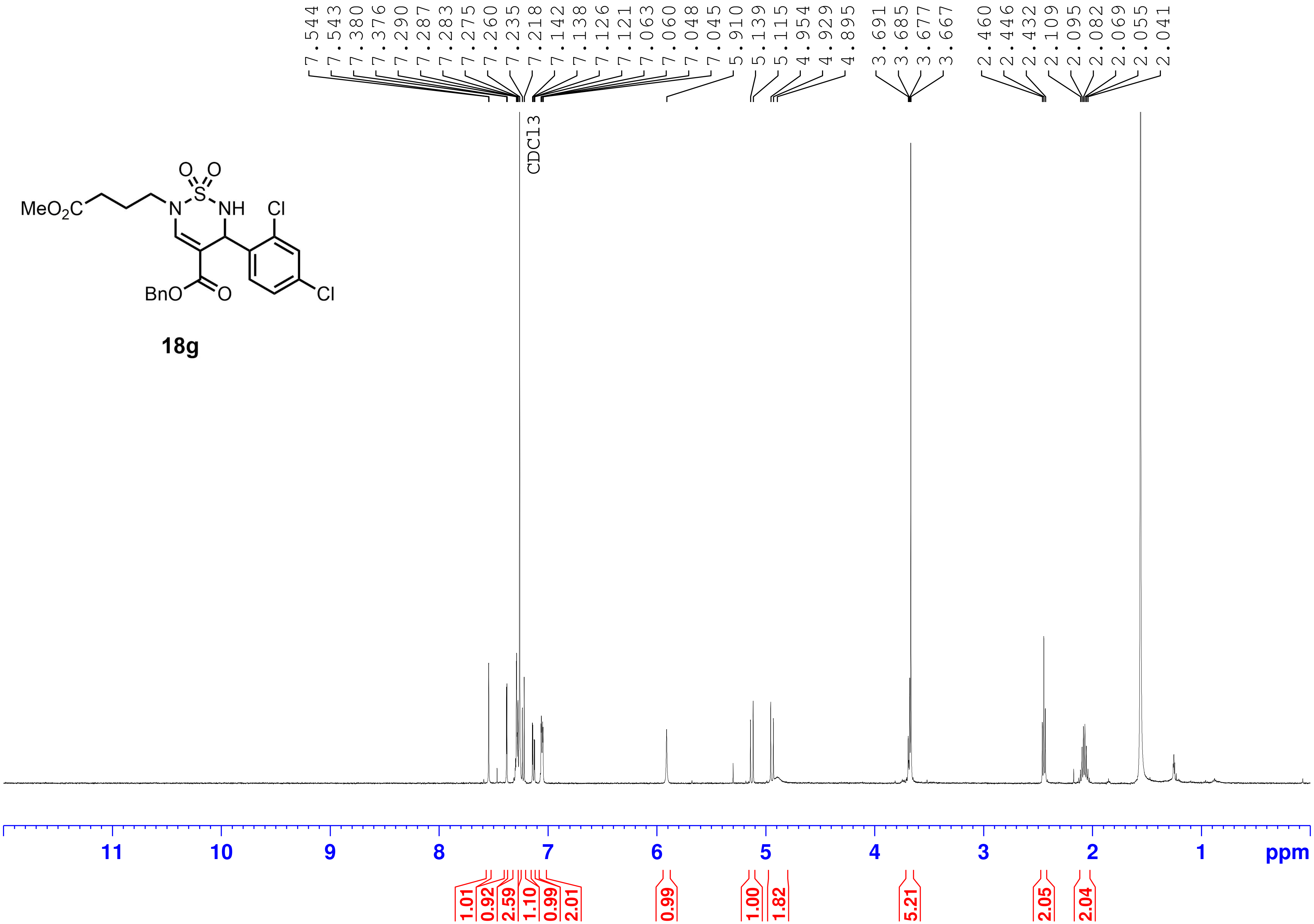


17f

13C NMR (100 MHz, CDCl3)

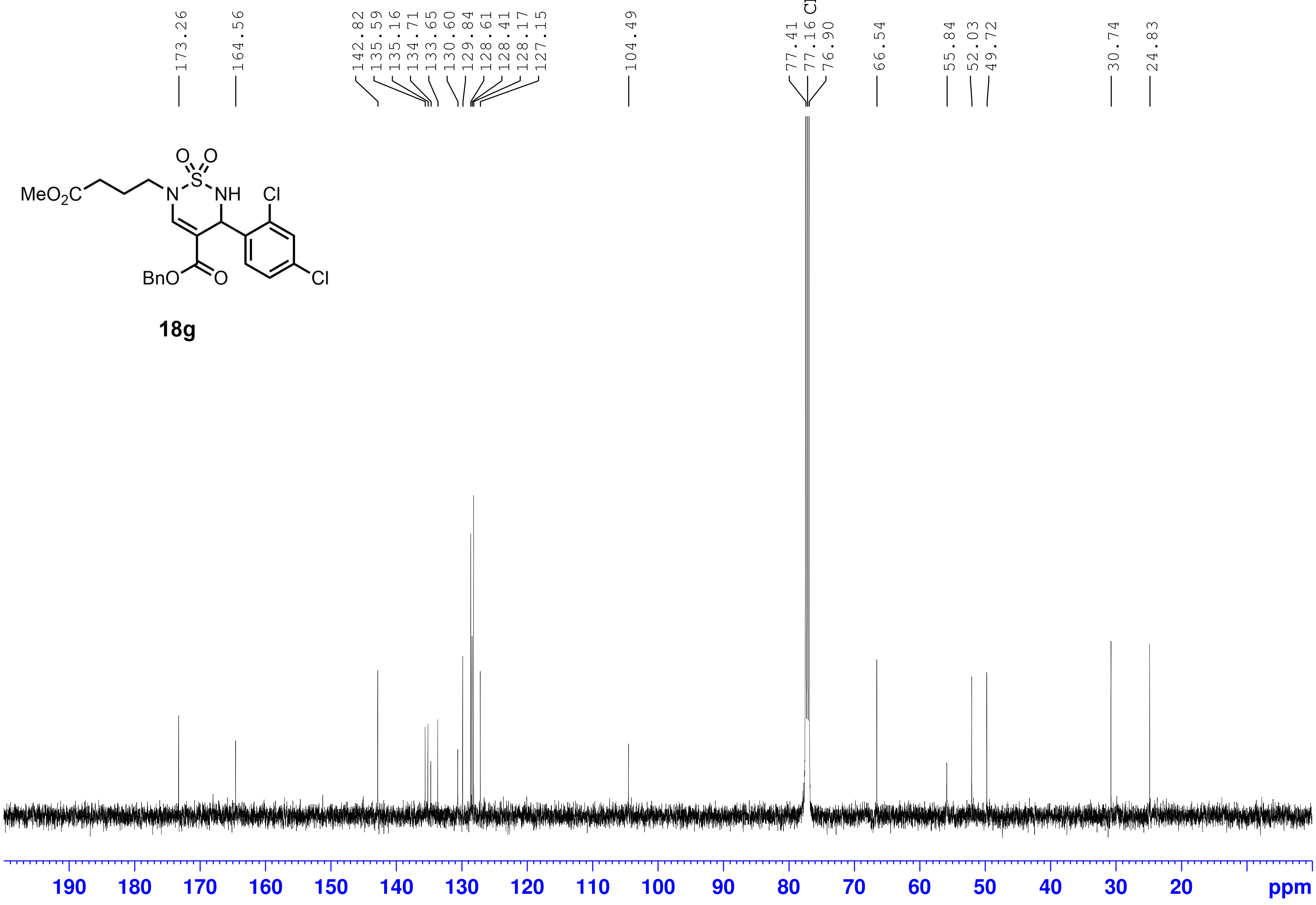


1H NMR (500 MHz, CDCl3)



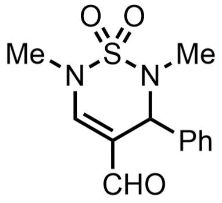
18g

13C NMR (125 MHz, CDCl3)

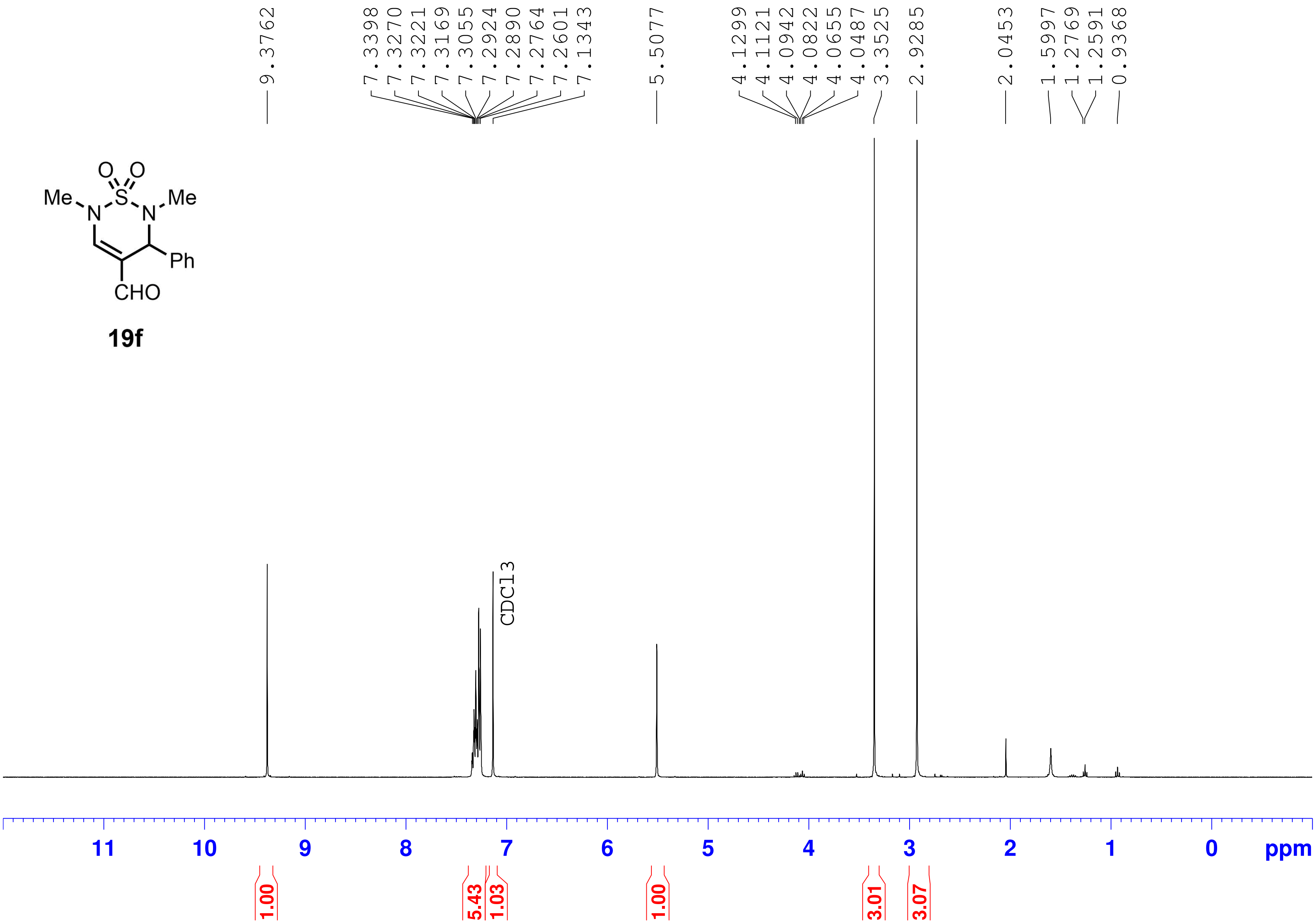


18g

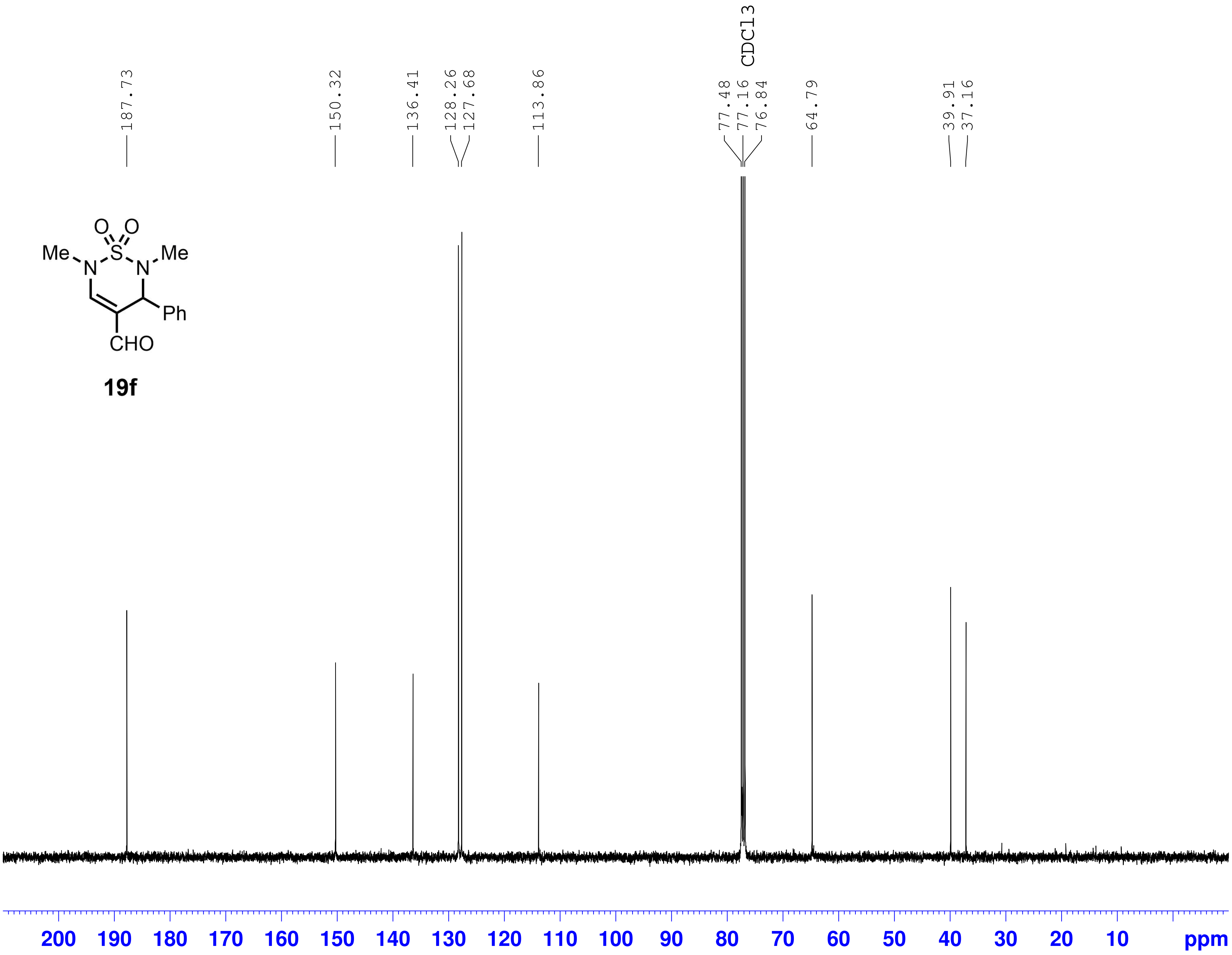
1H NMR (400 MHz, CDCl3)



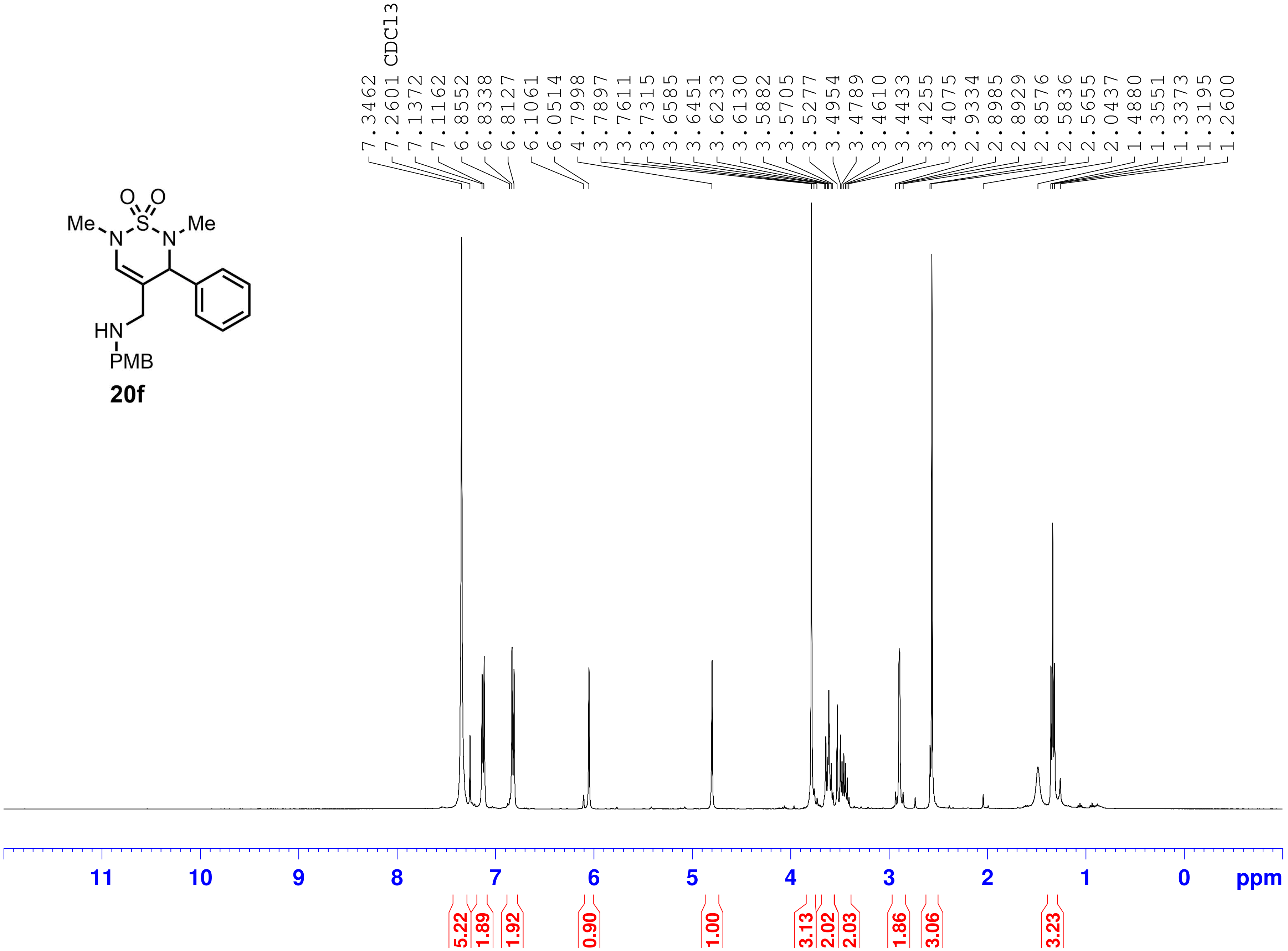
19f



13C NMR (100 MHz, CDCl3)

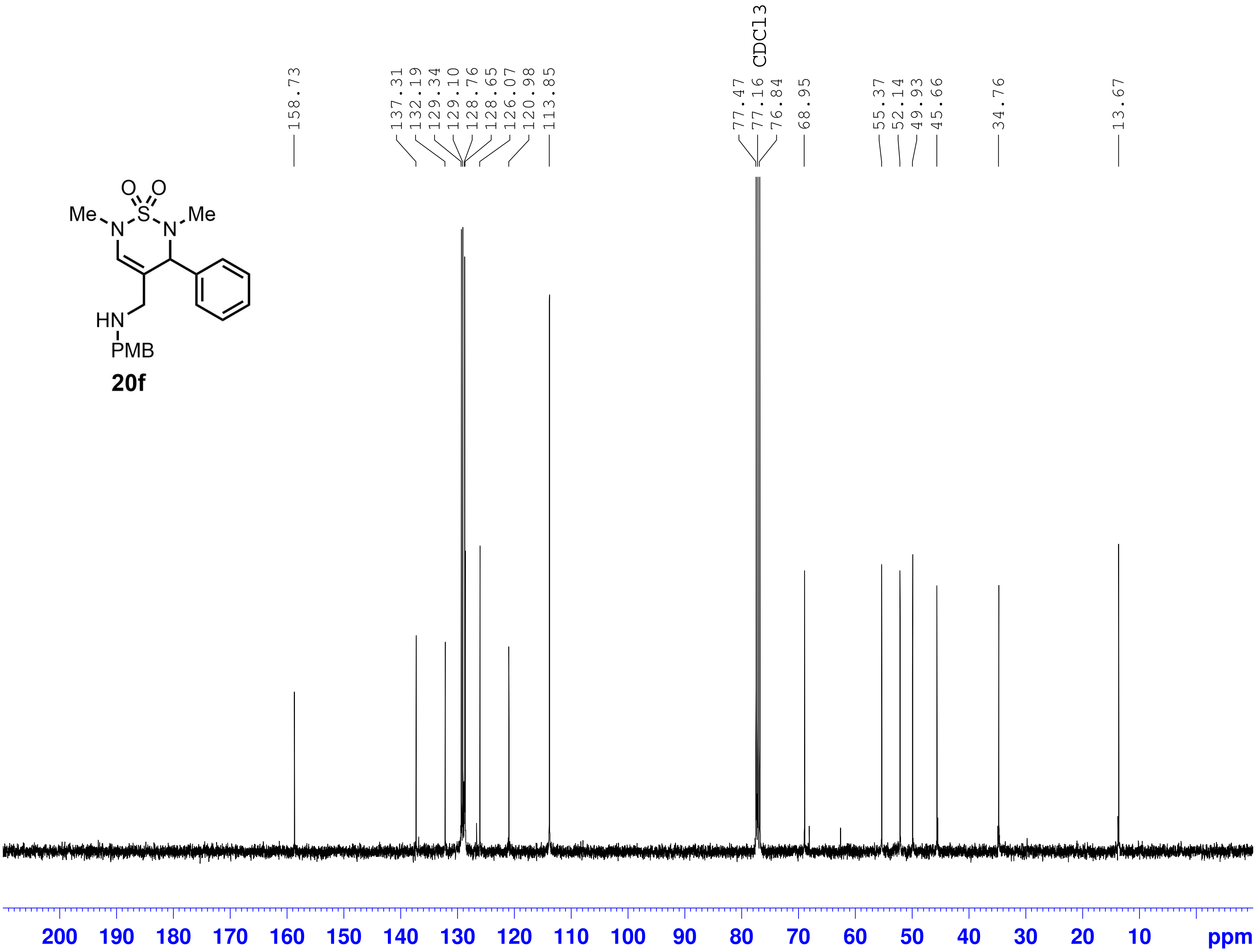


1H NMR (400 MHz, CDCl3)

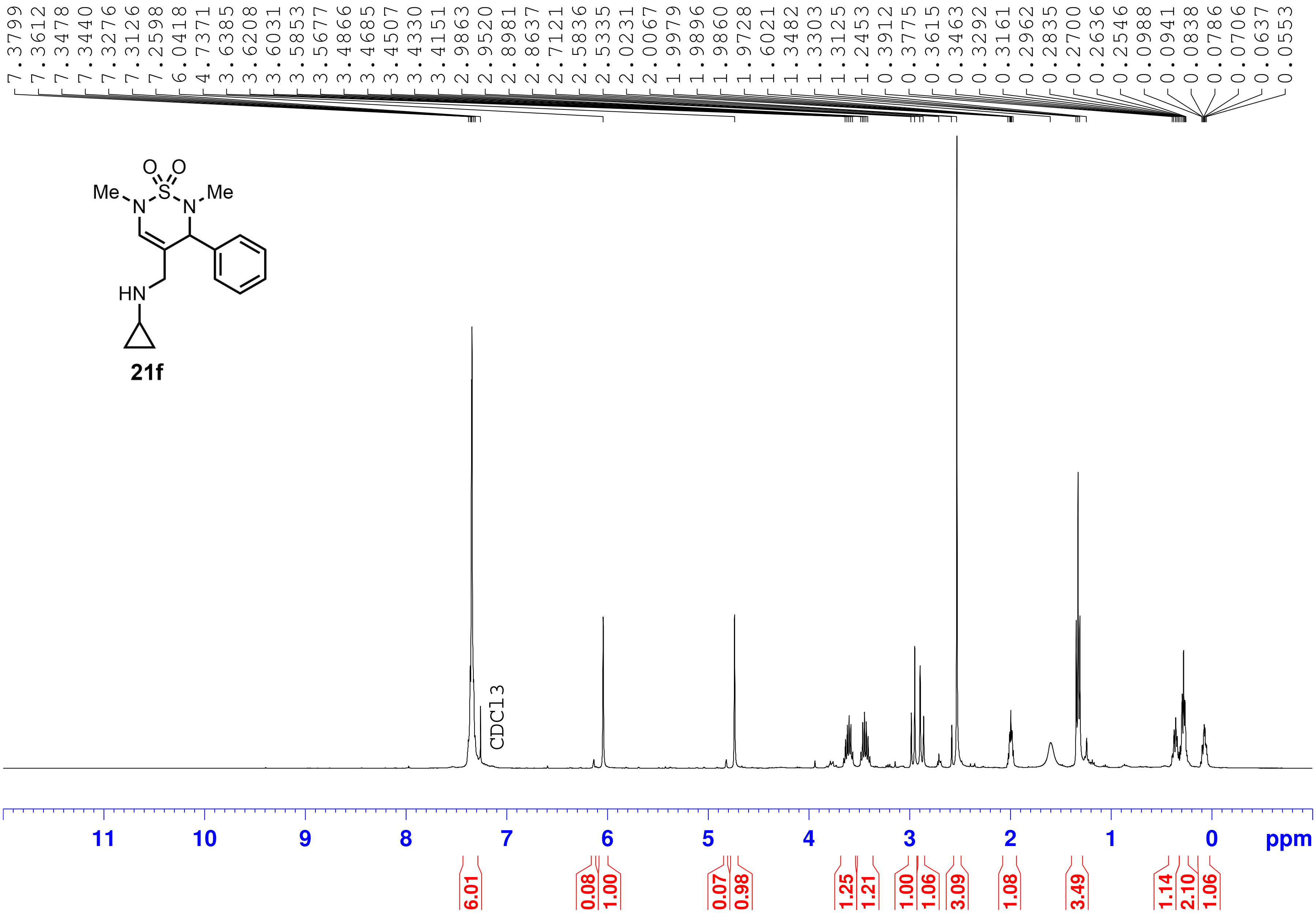


20f

13C NMR (100 MHz, CDCl3)



1H NMR (400 MHz, CDCl3)



21f

13C NMR (100 MHz, CDCl3)