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Novel 2-amino-substituted (thio)morpholine-3,5-diones: synthesis and cytotoxicity studies

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Contents

1. Experimental procedures and characterization data

General considerations. All commercial reagents and solvents were used without further purification, unless otherwise noted. Methanol was distilled over suitable drying agents. Mass spectra were recorded with a Bruker Maxis HRMS-ESI-qTOF spectrometer (electrospray ionization mode). NMR spectroscopic data were recorded with Bruker Avance III spectrometer in $CDCl_3$, DMSO-d_6 or acetone-d_6 (^{1}H: 400.13 MHz; ^{13}C: 100.61 MHz); chemical shifts are reported as parts per million (δ, ppm); the residual solvent peaks were used as internal standard: 7.26, 2.50 or 2.05 for ^{1}H and 77.16, 77.02 or 39.9 ppm for ^{13}C in $CDCl_3$, DMSO-d_6 or acetone-d_6, respectively; multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet/doublets of doublets; coupling constants, *J*, are reported in Hz. Mass spectra were recorded using Bruker microTOF spectrometer (ionization by electrospray, positive ions detection). Melting points were determined in open capillary tubes on Stuart SMP50 Automatic Melting Point Apparatus. Analytical thin-layer chromatography was carried out on UV-254 silica gel plates using appropriate eluents. Compounds were visualized with short-wavelength UV light. Column chromatography was performed using silica gel Merck grade 60 (0.040−0.063 mm) 230−400 mesh.

Thiomorpholine-3,5-dione **2a** and morpholine-3,5-dione **2b** were synthesized according to known procedures [C. Barkenbus, P.S. Landis. *J. Am. Chem. Soc*., 1948, **70**, 684].

Thiomorpholine-3,5-dione (2a). Yield 80%. White solid; m.p. 127–130 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 – 10.98 (br. s, 1H), 3.55 (s, 4H) ppm. HRMS (ESI) m/z calcd for $[M+H]^+$ $C_4H_6NO_2S$, 132.0114; Found 132.0117.

Morpholine-3,5-dione (2b). Yield 83%; m.p. 142–144 °C. White solid. ^{1}H NMR (400 MHz, Acetone-d_6) δ 10.33 – 9.9 (br. s, 1H), 4.32 (s, 4H) ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_4H_6NO_3$, 116.0342; Found 116.0345.

Preparation of 2-chlorothiomorpholine-3,5-dione (3a). To a vigorously stirred solution of thiomorpholine-3,5-dione **2a** (1.000 g, 7.6 mmol) in CH_2Cl_2 (20 mL) was added a solution of SO_2Cl_2 (1.079 mg, 8.0 mmol) in CH_2Cl_2 (10 mL) at room temperature for 6 h. After addition, the reaction mixture was stirred at room temperature for 2 h. Then the organic solution was washed with water (3x10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a pure product. Yield 67%, 847 mg. Slightly yellow amorphous solid. ^{1}H NMR (400 MHz, Acetone-d_6) δ 10.27 – 9.98 (br. s, 1H), 5.99 (d, *J* = 1.8 Hz, 1H), 4.07 (d, *J* = 17.2 Hz, 1H), 3.65 (dd, *J* =

17.2, 1.8 Hz, 1H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, Acetone-d_6) δ 167.5, 164.4, 97.5, 65.4 ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_4H_5ClNO_2S$, 165.9724; Found 165.9728.

Preparation of 2-bromomorpholine-3,5-dione (3b). In a screw glass vial with PTFE cap, a solution of morpholine-3,5-dione **2b** (750 mg, 6.5 mmol) in $CHCl_3$ (15 ml) and Br_2 (1.092 g, 6.82 mmol) were placed. The reaction mixture was stirred at 100 °C and irradiated with a 250 W halogen lamp (Philips 127720) for 4 h. The mixture was cooled to room temperature, the organic solution was diluted with $CHCl_3$ (15 mL), washed with water (4x10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The product was isolated by a column chromatography on SiO_2 using 2% acetone in CH_2Cl_2 as eluent. Yield 41%, 511 mg. White amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.46 – 11.23 (br. s, 1H), 5.20 (s, 1H), 4.42 (d, *J* = 17.1 Hz, 1H), 4.27 (d, *J* = 17.0 Hz, 1H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 167.8, 163.4, 63.2, 36.0 ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_4H_5BrNO_3$, 193.9447; Found 165.9728.

General procedure of preparation of compounds 4 and **5.** To stirred solution of amine (0.44 mmol) and DIPEA (78 μL, 0.44 mmol) in anhydrous MeCN (1.5 mL) halo derivative **3a,b** (0.4 mmol) was added at 5-10 °C. The reaction mixture was stirred at room temperature for 12 h. The mixture was diluted with CH_2Cl_2 (10 mL), washed with water (3x10 mL), dried over anhydrous $Na2SO4$, filtered and concentrated *in vacuo*. The product was isolated by a column chromatography on SiO_2 using 4% acetone in CH_2Cl_2 as eluent.

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)thiomorpholine-3,5-dione (4a). Yield 59%, 62 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 – 8.28 (br. s, 1H), 7.22 – 7.10 (m, 3H), 7.10 – 7.00 (m, 1H), 4.45 (s, 1H), 4.15 (d, *J* = 14.8 Hz, 1H), 3.90 – 3.71 (m, 2H), 3.40 (d, *J* = 17.1 Hz, 1H), 3.27 (dt, *J* = 10.9, 5.6 Hz, 1H), 3.12 – 2.86 (m, 2H), 2.87 – 2.75 (m, 1H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.1, 168.1, 133.6, 133.2, 128.7, 126.7, 126.6, 125.9, 67.4, 52.6, 47.6, 28.7 (2C) ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_{13}H_{15}N_2O_2S$, 263.0849; Found 263.0853.

2-(Benzyl(methyl)amino)thiomorpholine-3,5-dione (4b). Yield 45%, 45 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.13 (br. s, 1H), 7.45 – 7.26 (m, 5H), 4.53 (s, 1H), 3.99 (d, *J* = 13.2 Hz, 1H), 3.73 (d, *J* = 17.1 Hz, 1H), 3.63 (d, *J* = 13.2 Hz, 1H), 3.44 (d, *J* = 17.1 Hz, 1H), 2.43 (s, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 168.8, 168.3, 137.0, 128.9 (2C), 128.6 (2C), 127.7, 67.7, 58.5, 39.0, 29.9 ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_{12}H_{15}N_2O_2S$, 251.0849; Found 251.0845.

2-(4-Phenylpiperidin-1-yl)thiomorpholine-3,5-dione (4c). Yield 58%, 67 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 – 8.31 (br. s, 1H), 7.44 – 7.29 (m, 2H), 7.29 – 7.14 (m,

3H), 4.46 (s, 1H), 3.81 (d, *J* = 17.1 Hz, 1H), 3.53 – 3.39 (m, 2H), 3.09 – 2.95 (m, 1H), 2.72 (td, *J* = 11.0, 4.2 Hz, 1H), 2.57 (tt, *J* = 10.4, 4.9 Hz, 1H), 2.31 (td, *J* = 11.0, 3.3 Hz, 1H), 1.98 – 1.82 (m, 4H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.1, 168.1, 145.5, 128.5 (2C), 126.8 (2C), 126.3, 68.7, 52.5, 49.7, 42.1, 33.1, 32.9, 29.4 ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_{15}H_{19}N_2O_2S$, 291.1162; Found 291.1167.

2-(Morpholino)thiomorpholine-3,5-dione (4d). Yield 58%, 50 mg. White amorphous solid. ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.91 – 9.30 (br. s, 1H), 4.44 (s, 1H), 3.78 (d, *J* = 17.1 Hz, 1H), 3.72 – 3.66 (m, 3H), 3.54 (d, *J* = 17.1, 1H), 2.93 (dt, *J* = 11.9, 4.7 Hz, 2H), 2.54 – 2.42 (m, 2H) ppm. ^{13}C NMR$\{^{1}H\}$ (126 MHz, Acetone-d_6) δ 168.9, 167.9, 67.6, 66.2 (2C), 50.2 (2C), 28.2 ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_8H_{13}N_2O_3S$, 217.0641; Found 217.0645.

Ethyl 1-(3,5-dioxothiomorpholin-2-yl)piperidine-4-carboxylate (4e). Yield 52%, 57 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 – 8.13 (br. s, 1H), 4.34 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.77 (d, *J* = 17.0 Hz, 1H), 3.40 (d, *J* = 17.0 Hz, 1H), 3.35 – 3.25 (m, 1H), 2.88 – 2.78 (m, 1H), 2.64 (td, *J* = 10.9, 2.9 Hz, 1H), 2.35 (tt, *J* = 10.9, 4.0 Hz, 1H), 2.27 – 2.17 (m, 1H), 2.04 – 1.91 (m, 2H), 1.92 – 1.72 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 4H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 174.4, 168.9, 167.8, 68.2, 60.5, 50.6, 48.8, 40.4, 29.1, 27.8 (2C), 14.2 ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_{12}H_{19}N_2O_4S$, 287.1060; Found 278.1063.

***tert*-Butyl 4-(3,5-dioxothiomorpholin-2-yl)piperazine-1-carboxylate (4f).** Yield 60%, 76 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.75 (br. s, 1H), 4.28 (s, 1H), 3.77 (d, *J* = 17.1 Hz, 1H), 3.59 – 3.46 (m, 4H), 3.40 (d, *J* = 17.1 Hz, 1H), 3.03 – 2.86 (m, 2H), 2.46 (dt, *J* = 10.8, 5.1 Hz, 2H), 1.48 (s, 9H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 168.5, 167.4, 154.5, 80.1, 77.2, 67.9 (2C), 49.9 (2C), 28.9, 28.3 (3C) ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_{13}H_{22}N_3O_4S$, 316.1326; Found 316.1321.

2-(4-Benzylpiperazin-1-yl)thiomorpholine-3,5-dione (4g). Yield 54%, 66 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 – 8.32 (br. s, 1H), 7.44 – 7.19 (m, 5H), 4.26 (s, 1H), 3.77 (d, *J* = 17.1 Hz, 1H), 3.56 (s, 2H), 3.36 (d, *J* = 17.1 Hz, 1H), 3.07 – 2.90 (m, 2H), 2.66 – 2.40 (m, 4H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.1, 168.0, 137.4, 129.2 (2C), 128.3 (2C), 127.2, 67.8, 62.6 (2C), 52.4 (2C), 49.9, 28.8 ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_{15}H_{20}N_3O_2S$ 306.1271; Found 306.1275.

2-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]thiomorpholine-3,5-dione (4h). Yield 80%, 115 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.73 (br. s, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.22 – 7.06 (m, 3H), 4.33 (s, 1H), 3.82 (d, *J* = 17.1 Hz, 1H), 3.42 (d, *J* = 17.1 Hz,

1H), 3.36 – 3.28 (m, 4H), 3.19 (dt, *J* = 10.7, 4.9 Hz, 2H), 2.77 – 2.66 (m, 2H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 168.65, 167.52, 150.90, 131.4 (q, *J* = 31.8 Hz), 129.68, 124.3 (q, *J* = 272.9 Hz), 119.15, 112.61 (q, *J* = 3.9 Hz), 112.57 (q, *J* = 3.9 Hz), 67.64, 49.89 (2C), 48.69 (2C), 28.74 ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_{15}H_{17}F_3N_3O_2S$ 360.0988; Found 360.0985.

2-(4-Phenylsulfonylpiperazin-1-yl)thiomorpholine-3,5-dione (4i). Yield 45%, 64 mg. White amorphous solid. ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.75 – 9.58 (br. s, 1H), 7.88 – 7.77 (m, 2H), 7.76 – 7.65 (m, 3H), 4.59 (s, 1H), 3.67 (d, *J* = 17.0 Hz, 1H), 3.55 (d, *J* = 17.0 Hz, 1H), 3.13 – 2.99 (m, 6H), 2.64 (dt, *J* = 11.6, 4.7 Hz, 2H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, Acetone-d_6) δ 168.8, 167.9, 135.8, 133.0, 129.2 (2C), 127.7 (2C), 67.0, 59.6, 48.9 (2C), 46.0 (2C) ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_{14}H_8N_3O_4S_2$ 356.0733; Found 356.0735.

2-[*N*-(3,4-Dimethoxyphenethyl)-*N*-methylamino]morpholine-3,5-dione (5a). Yield 47%, 58 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 – 8.57 (br.s, 1H), 6.89 – 6.67 (m, 3H), 4.76 (s, 1H), 4.48 (d, *J* = 17.0 Hz, 1H), 4.20 (d, *J* = 17.0 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.07 – 2.88 (m, 2H), 2.87 – 2.72 (m, 2H), 2.54 (s, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.0, 167.9, 148.8, 147.5, 132.2, 120.5, 112.0, 111.3, 90.8, 65.1, 55.9, 55.8, 55.2, 36.9, 33.9 ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_{15}H_{21}N_2O_5$ 309.1445; Found 309.1448.

2-[*N*-Methyl(3-phenyl-1,2,4-oxadiazol-5-yl-*N*-methylamino]morpholine-3,5-dione (5b). Yield 69%, 83 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 – 8.31 (br. s, 1H), 8.15 – 8.06 (m, 2H), 7.61 – 7.44 (m, 3H), 4.98 (s, 1H), 4.57 (d, *J* = 17.0 Hz, 1H), 4.30 (d, *J* = 17.0 Hz, 1H), 4.22 (s, 2H), 2.71 (s, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 176.1, 169.4, 168.4, 167.0, 131.3, 128.8 (2C), 127.5 (2C), 126.5, 89.5, 65.1, 48.1, 37.8 ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_{14}H_{15}N_4O_4$ 303.1088; Found 303.1085.

2-(4-Benzylpiperidin-1-yl)morpholine-3,5-dione (5c). Yield 61%, 70 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 – 8.33 (br. s, 1H), 7.36 – 7.25 (m, 2H), 7.26 – 7.17 (m, 1H), 7.19 – 7.10 (m, 2H), 4.67 (s, 1H), 4.56 (d, *J* = 16.9 Hz, 1H), 4.25 (d, *J* = 16.9 Hz, 1H), 3.03 – 2.82 (m, 2H), 2.70 (td, *J* = 11.7, 2.7 Hz, 1H), 2.57 (d, *J* = 7.0 Hz, 2H), 2.46 (td, *J* = 11.8, 2.7 Hz, 1H), 1.75 – 1.52 (m, 3H), 1.48 – 1.25 (m, 2H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.8, 167.6, 140.3, 129.1 (2C), 128.2 (2C), 125.9, 90.8, 64.9, 49.9, 47.2, 43.0, 37.5, 31.9, 31.7 ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_{16}H_{21}N_2O_3$ 289.1547 Found 289.1541.

***tert*-Butyl [1-(3,5-dioxomorpholin-2-yl)piperidin-4-yl]carbamate (5d).** Yield 50%, 63 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 – 8.46 (br. s, 1H), 4.68 (s, 1H), 4.56 (d, *J* = 17.0 Hz, 1H), 4.53 – 4.44 (m, 1H), 4.26 (d, *J* = 17.0 Hz, 1H), 3.53 (s, 1H), 3.02 – 2.77 (m,

3H), 2.60 (td, *J* = 11.5, 2.7 Hz, 1H), 2.03 – 1.91 (m, 2H), 1.61 – 1.49 (m, 1H), 1.46 (s, 9H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.7, 167.5, 155.1, 90.6, 65.1, 48.4, 47.3, 45.9, 32.4, 28.4 (3C) ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_{14}H_{24}N_3O_5$ 314.1710; Found 314.1714.

2-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)morpholine-3,5-dione (5e). Yield 44%, 45 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.01 (br. s, 1H), 4.73 (s, 1H), 4.59 (d, *J* = 16.9 Hz, 1H), 4.28 (d, *J* = 16.9 Hz, 1H), 3.98 (s, 4H), 3.00 (dt, *J* = 11.7, 5.8 Hz, 2H), 2.85 (dt, *J* = 11.7, 5.8 Hz, 2H), 1.89 – 1.77 (m, 4H), 1.76 – 1.68 (m, 1H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.4, 167.2, 106.5, 90.3, 64.9, 64.3 (2C), 46.4 (2C), 34.67 (2C) ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_{11}H_{17}N_2O_5$ 257.1132; Found 257.1135.

2-(4-Benzylpiperazin-1-yl)morpholine-3,5-dione (5f). Yield 73%, 85 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 – 8.60 (br. s, 1H), 7.39 – 7.22 (m, 5H), 4.63 (s, 1H), 4.57 (d, *J* = 16.9 Hz, 1H), 4.25 (d, *J* = 16.9 Hz, 1H), 3.57 (s, 2H), 2.92 (dt, *J* = 10.8, 4.9 Hz, 2H), 2.73 (dt, *J* = 10.8, 4.9 Hz, 2H), 2.62 – 2.48 (m, 4H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.8, 167.4, 129.2 (2C), 128.2 (2C), 127.2, 90.1, 64.5 (2C), 62.7, 52.5 (2C), 47.8 ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_{15}H_{20}N_3O_3$ 290.1499; Found 290.1495.

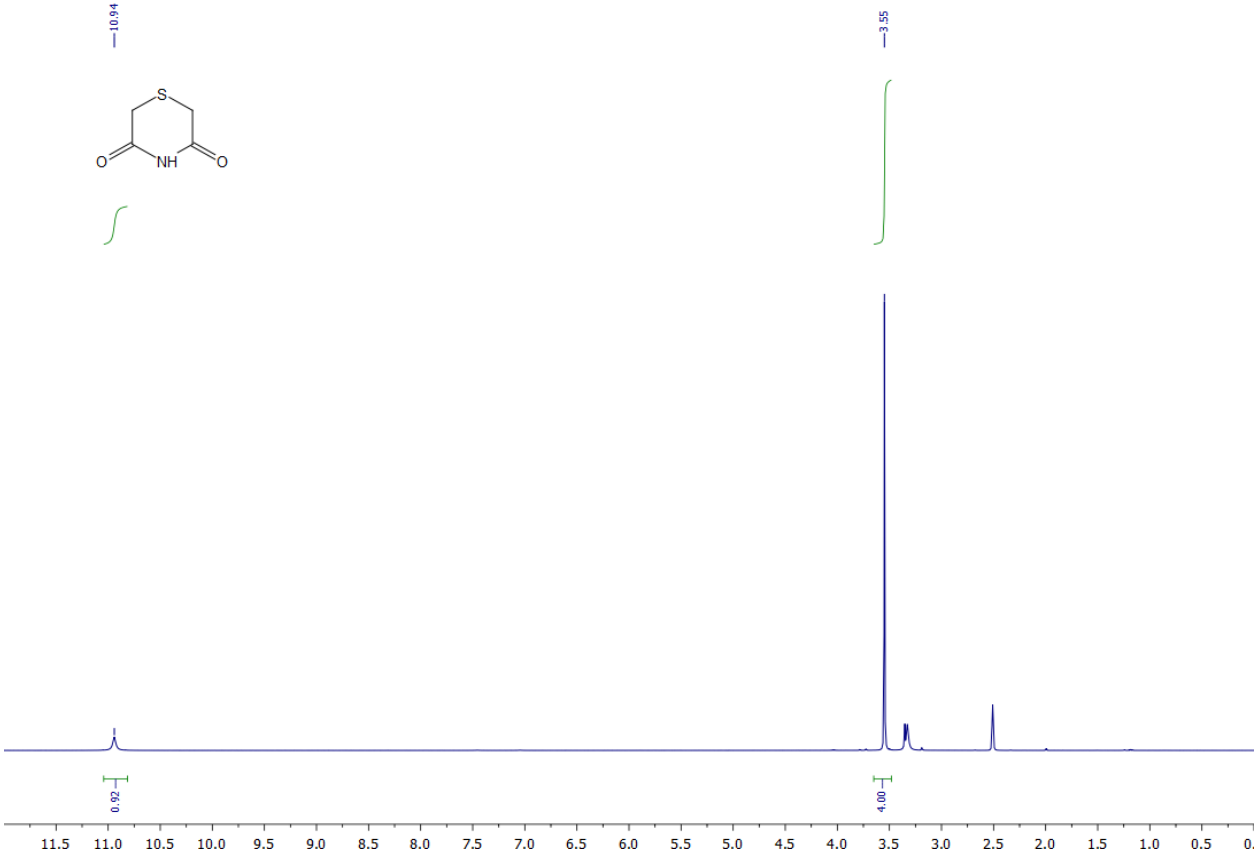
2-[4-(Furan-2-carbonyl)piperazin-1-yl]morpholine-3,5-dione (5g). Yield 48%, 56 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 – 8.71 (s, 1H), 7.49 (d, *J* = 1.8 Hz, 1H), 7.04 (d, *J* = 3.5 Hz, 1H), 6.49 (dd, *J* = 3.5, 1.8 Hz, 1H), 4.72 (s, 1H), 4.57 (d, *J* = 17.0 Hz, 1H), 4.29 (d, *J* = 17.0 Hz, 1H), 4.02 – 3.78 (m, 4H), 2.96 (dt, *J* = 11.0, 5.1 Hz, 2H), 2.80 (dt, *J* = 11.0, 5.1 Hz, 2H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.4, 167.1, 159.0, 147.7, 143.7, 116.8, 111.3, 90.2, 65.1 (2C), 48.1 (2C), 30.9 ppm. HRMS (ESI) m/z calcd for: $[M+H]^+$ $C_{13}H_{16}N_3O_5$ 294.1084; Found 294.1081.

Cell culture. Multiple myeloma cell line KMS-12-PE were purchased from the DSMZ. Human Leukemia T-Lymphoblast cell line MOLT-4 were purchased from the ATCC. Cells were maintained in RPMI-1640 (Gibco, UK) supplemented with 10% fetal bovine serum (FBS, Gibco, UK), penicillin (100 UI mL^{-1}), streptomycin (100 μg mL^{-1}) and GlutaMax (2 mM, Gibco, UK). All cells line cultivation under a humidified atmosphere of 95% air/5% CO_2 at 37 °C. The number of viable cells was determined by trypan blue exclusion.

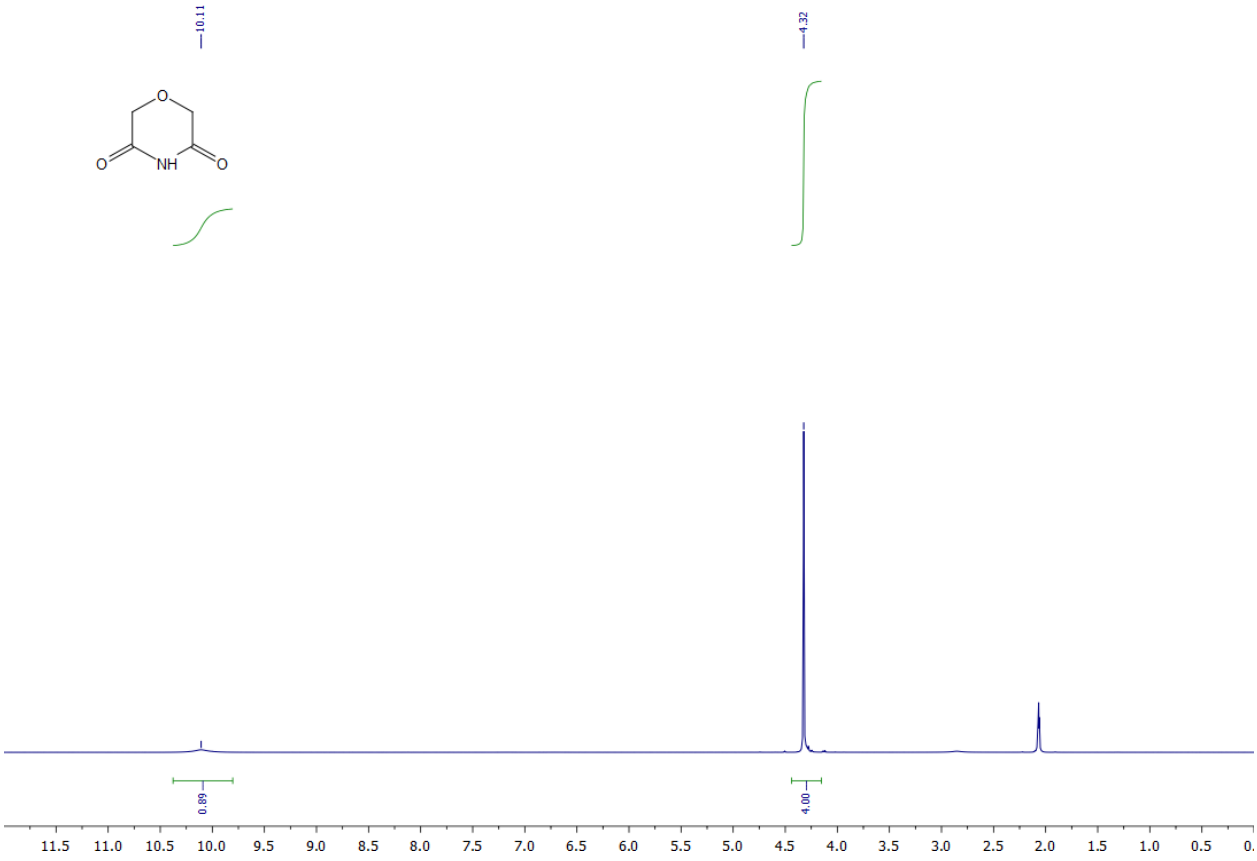
MTT assay. All examined cells were diluted with growth medium to a final concentration of 3.0×10^5 cells per mL. Aliquots of 15×10^3 cells in 50 μL were placed in individual wells of white 96-well multiplates (Nunc, USA). In triplicate wells, test compounds were added, initially starting at a concentration of 60.0 μM, then diluted to achieve a final concentration of 30 μM for testing. Dimethyl sulfoxide (DMSO, Sigma, USA) was used as a control at a final concentration of 0.1%. The plates were incubated for 48 hours at 37 °C in a 5% CO_2 atmosphere. Following incubation, 100 μL of CellTiter-Glo® One Solution (Promega, USA) was added to each well. The plates were then shaken for 10 minutes. Luminescence was measured using a GloMax Multi+ microplate reader (Promega, USA). Cytotoxicity of each compound was evaluated in three separate experiments.

2. Copies of ^{1}H and ^{13}C NMR spectra

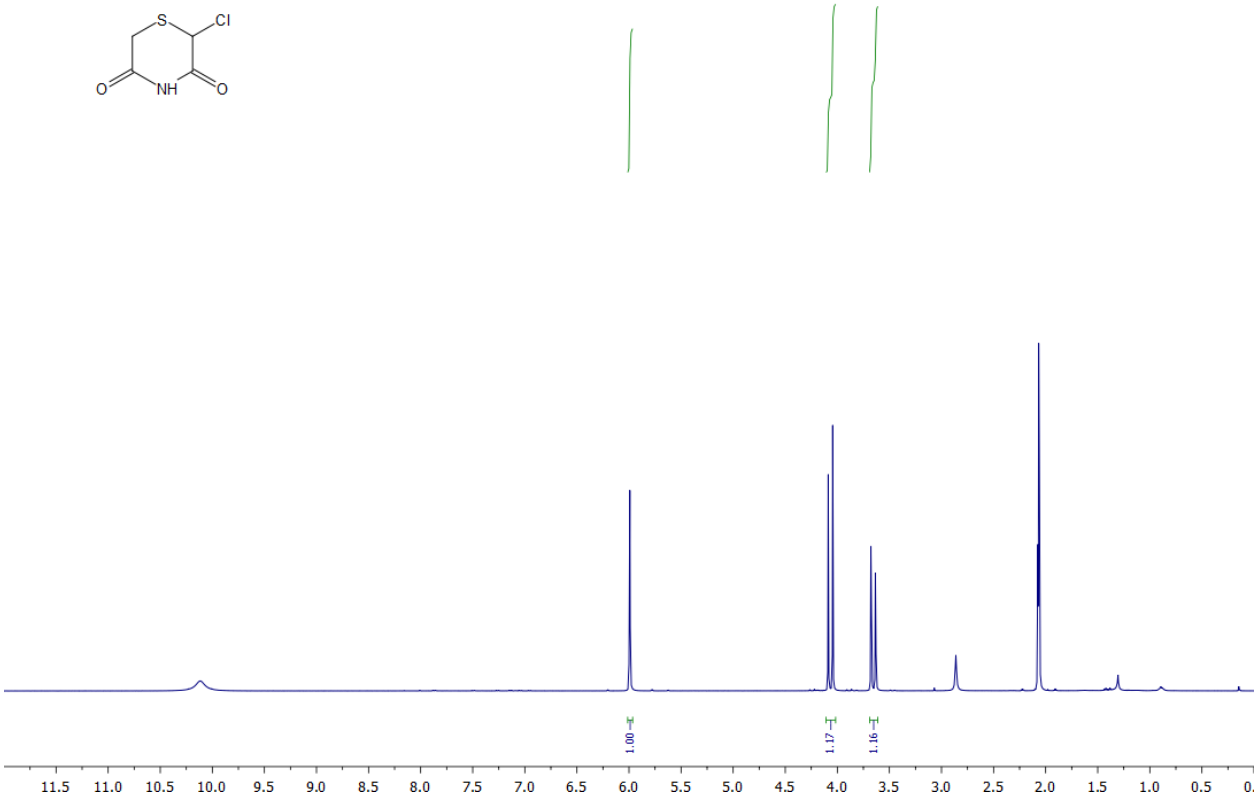
Copy of ^{1}H (400.13 MHz, DMSO-d_6) spectra of **2a**

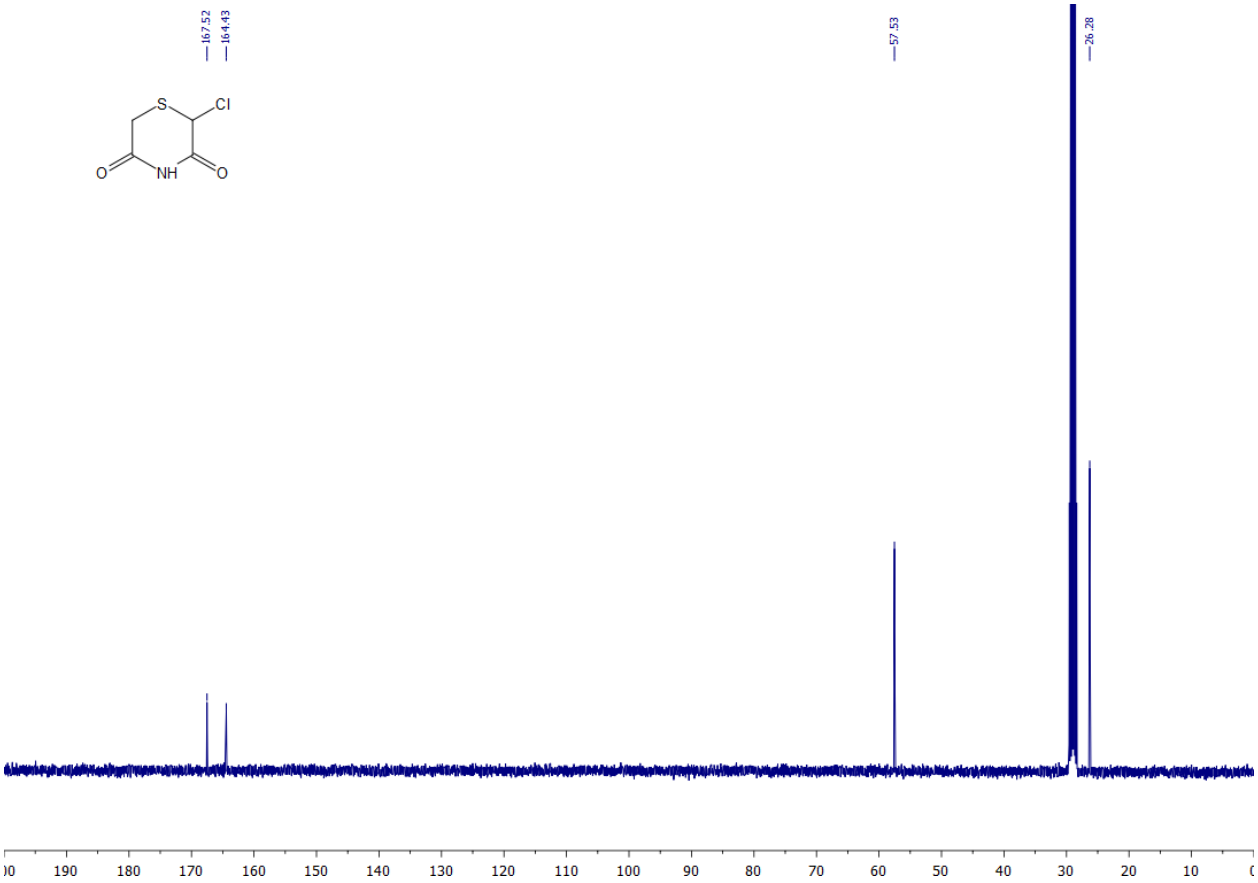


Copy of ^{1}H (400.13 MHz, Acetone-d_6) spectra of **2b**

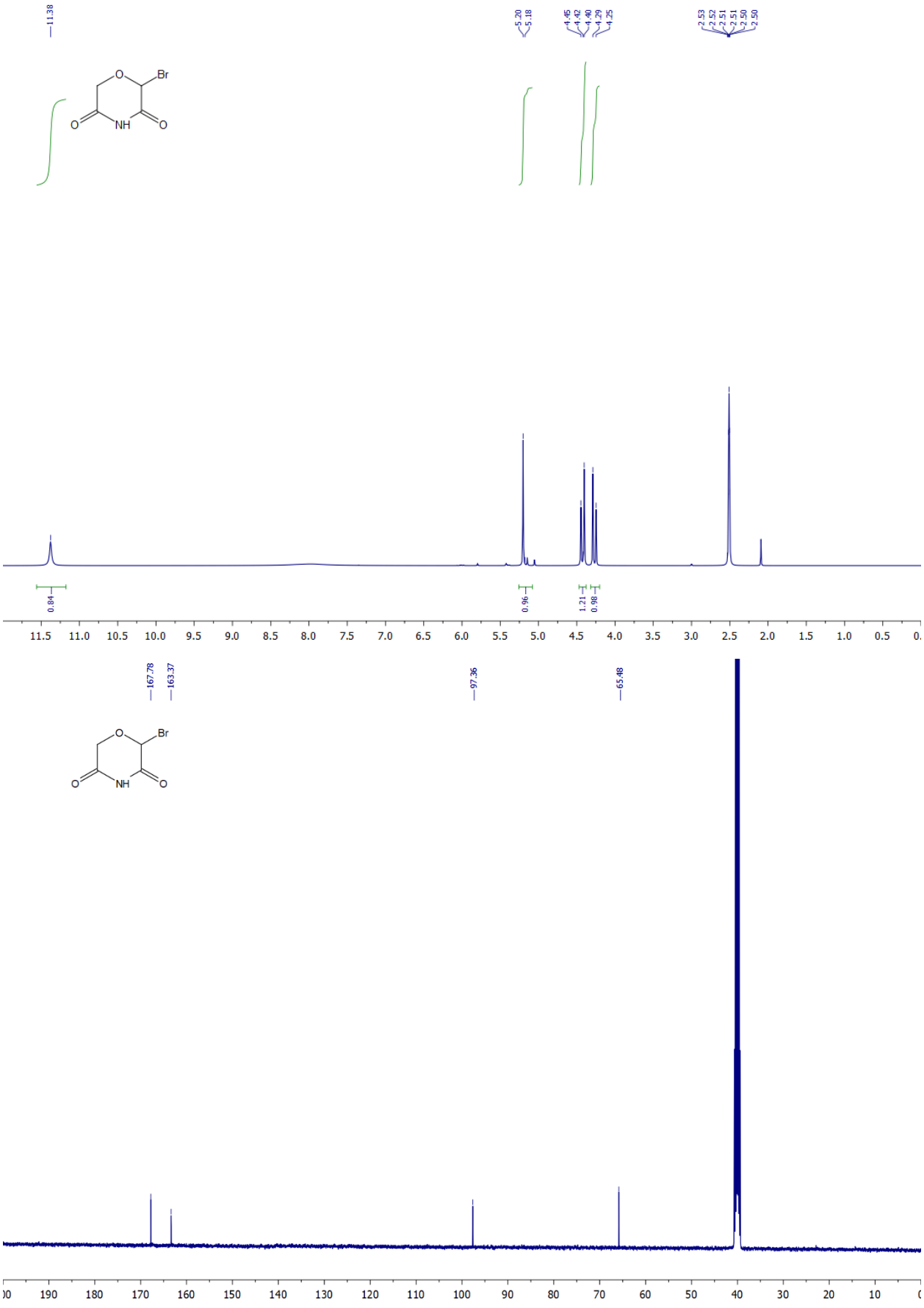


Copies of ^{1}H (400.13 MHz, Acetone-d_6) and $^{13}C\{^{1}H\}$ (100.61 MHz, Acetone-d_6) spectra of **3a**

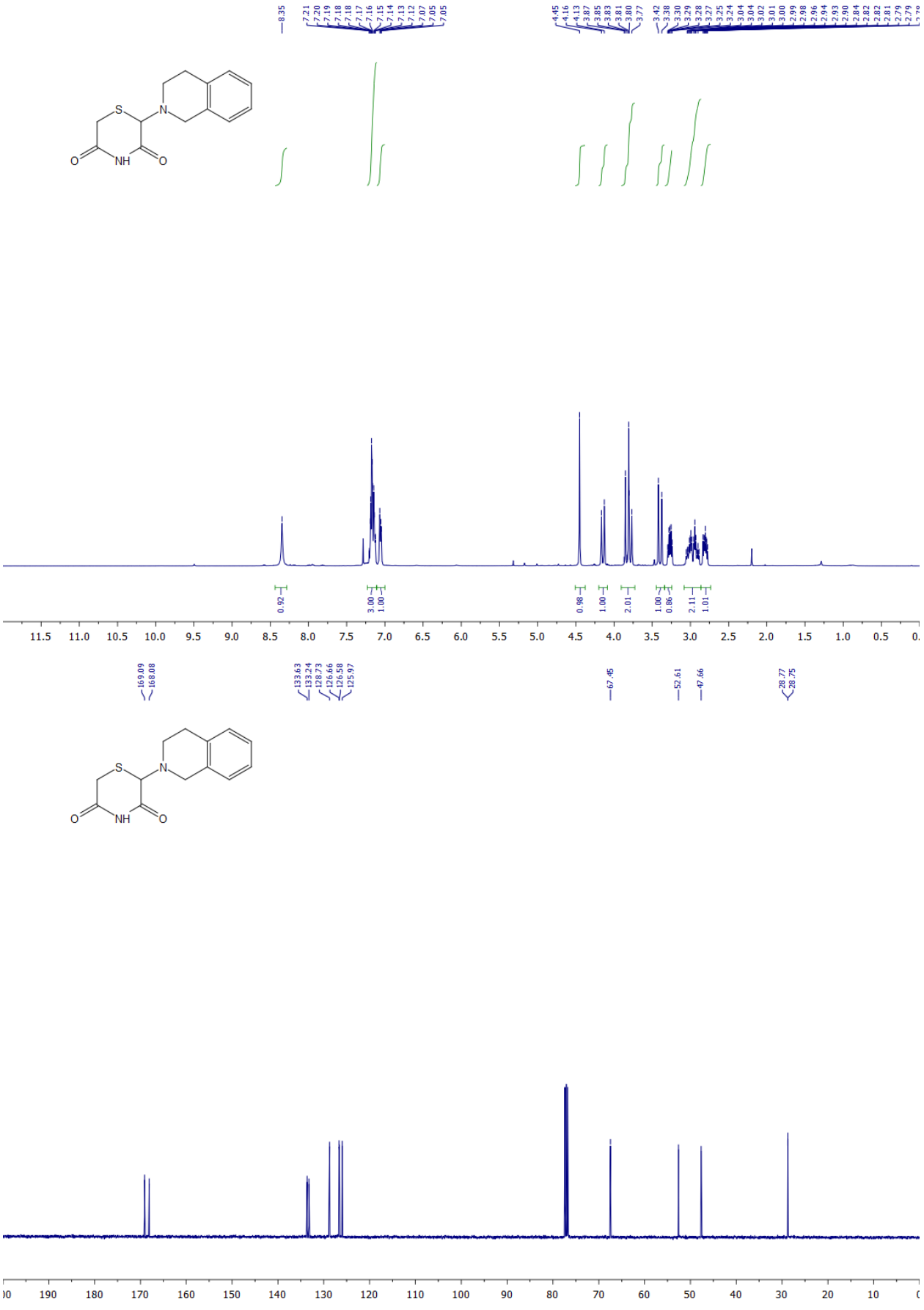




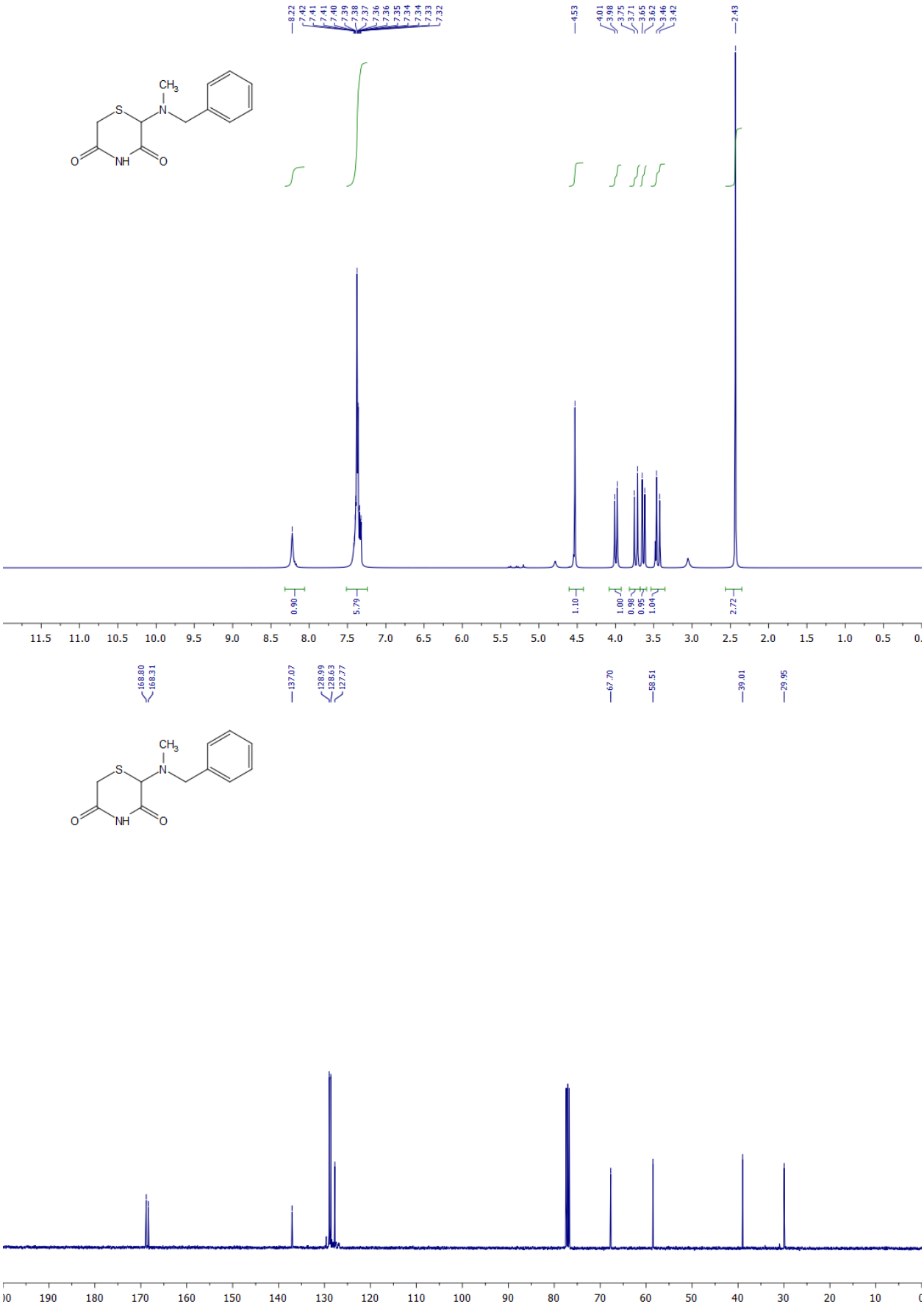
Copies of ^{1}H (400.13 MHz, DMSO-d_6) and ^{13}C{^{1}H} (100.61 MHz, DMSO-d_6) spectra of **3b**



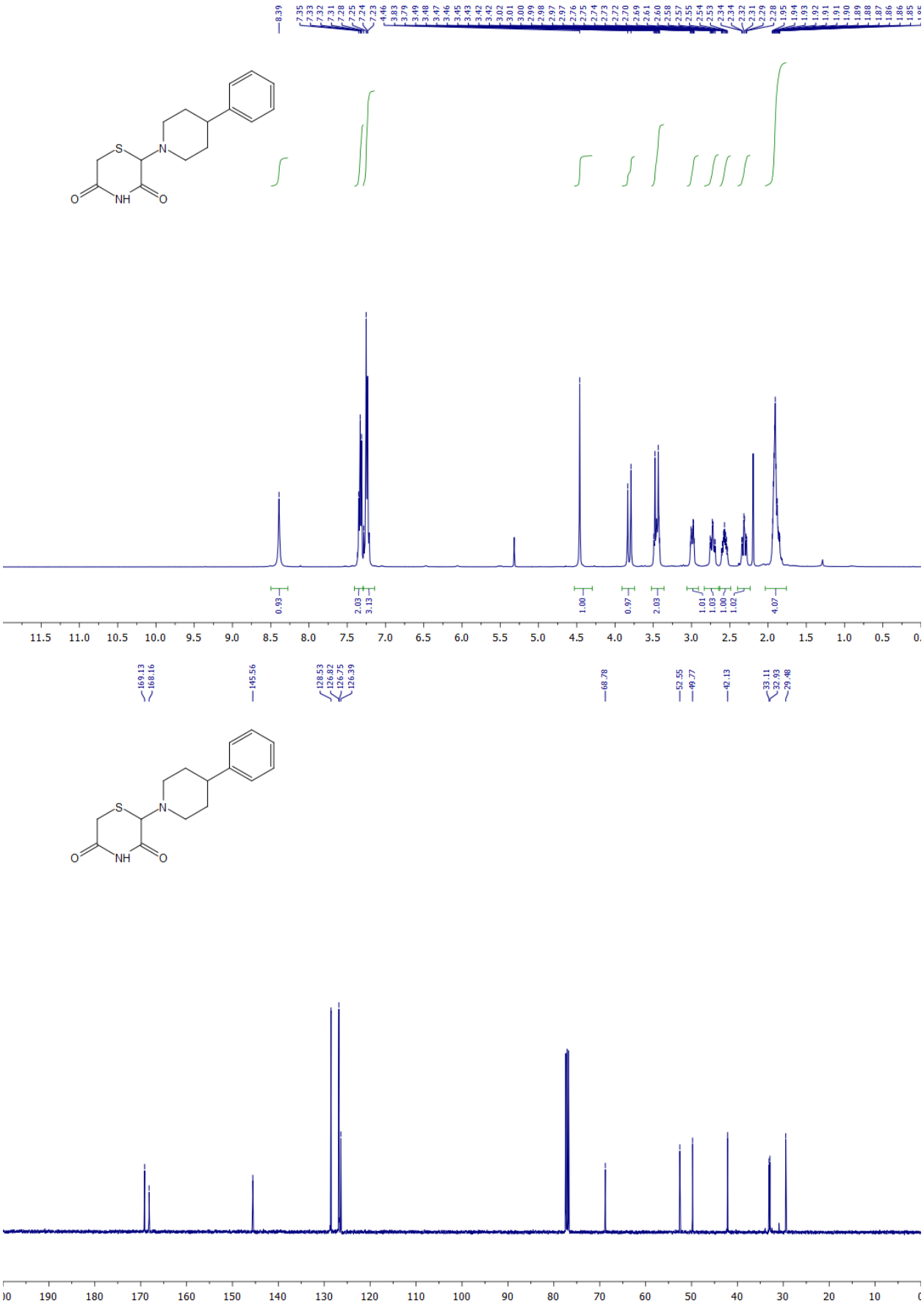
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4a**



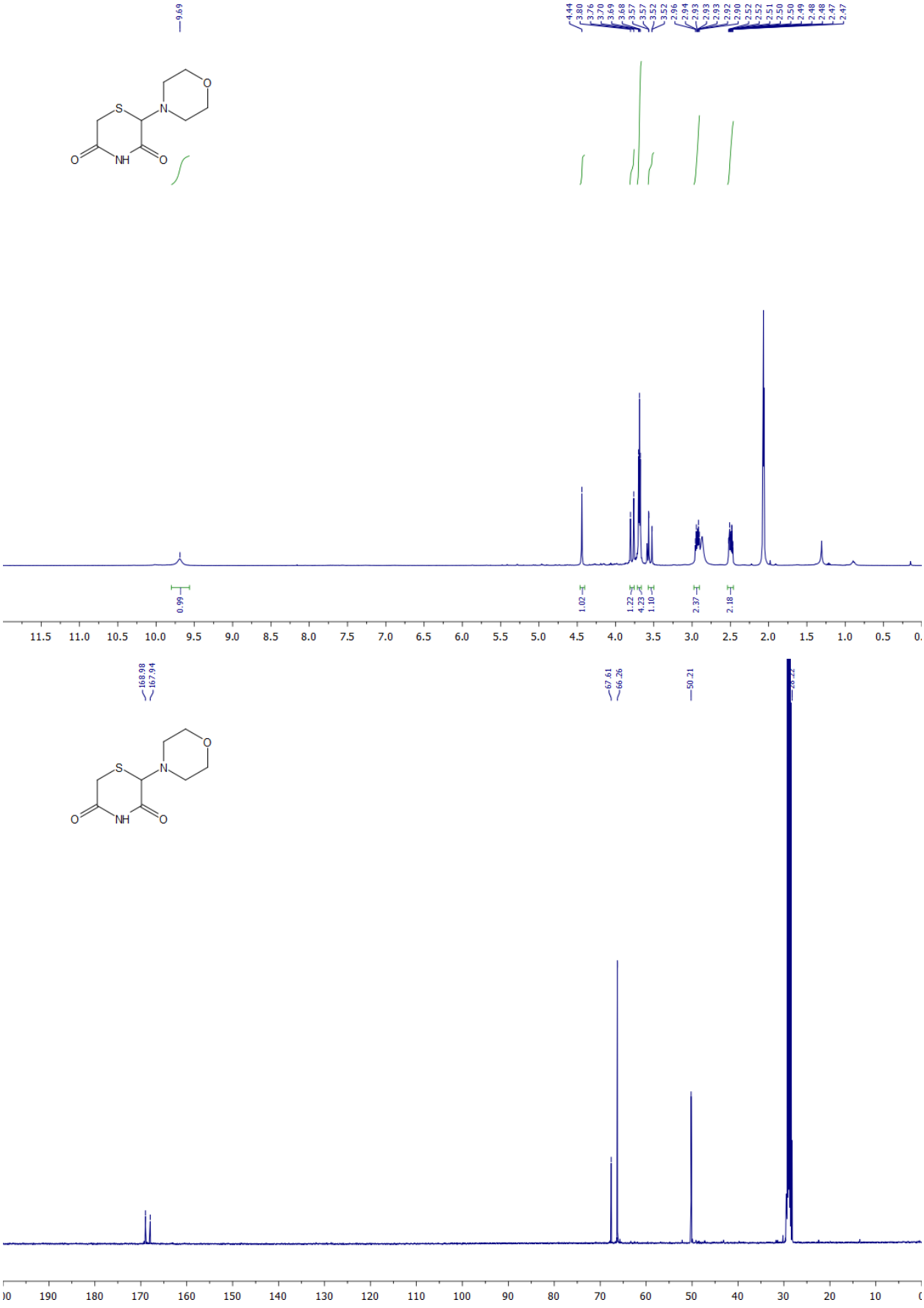
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4b**



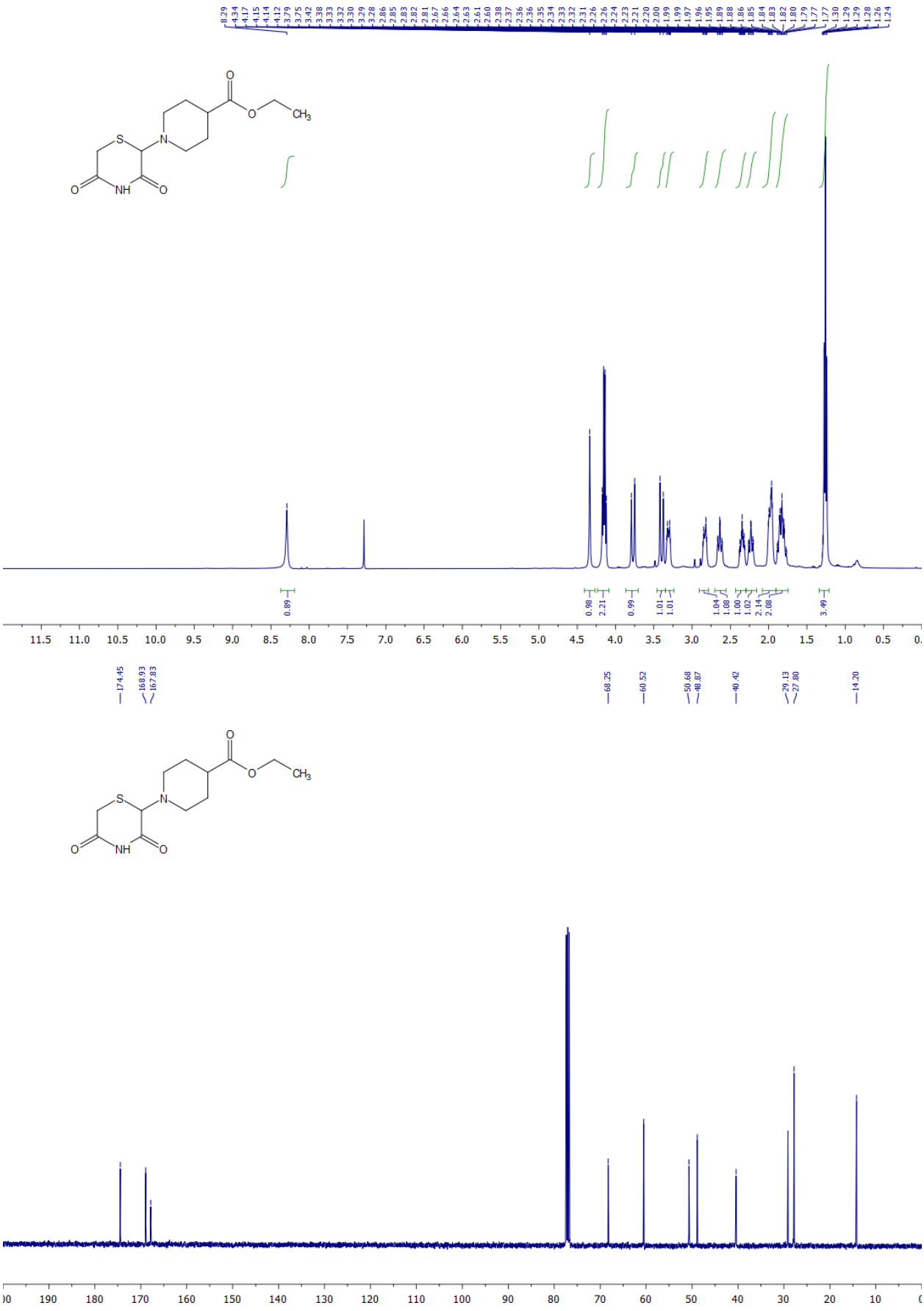
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4c**



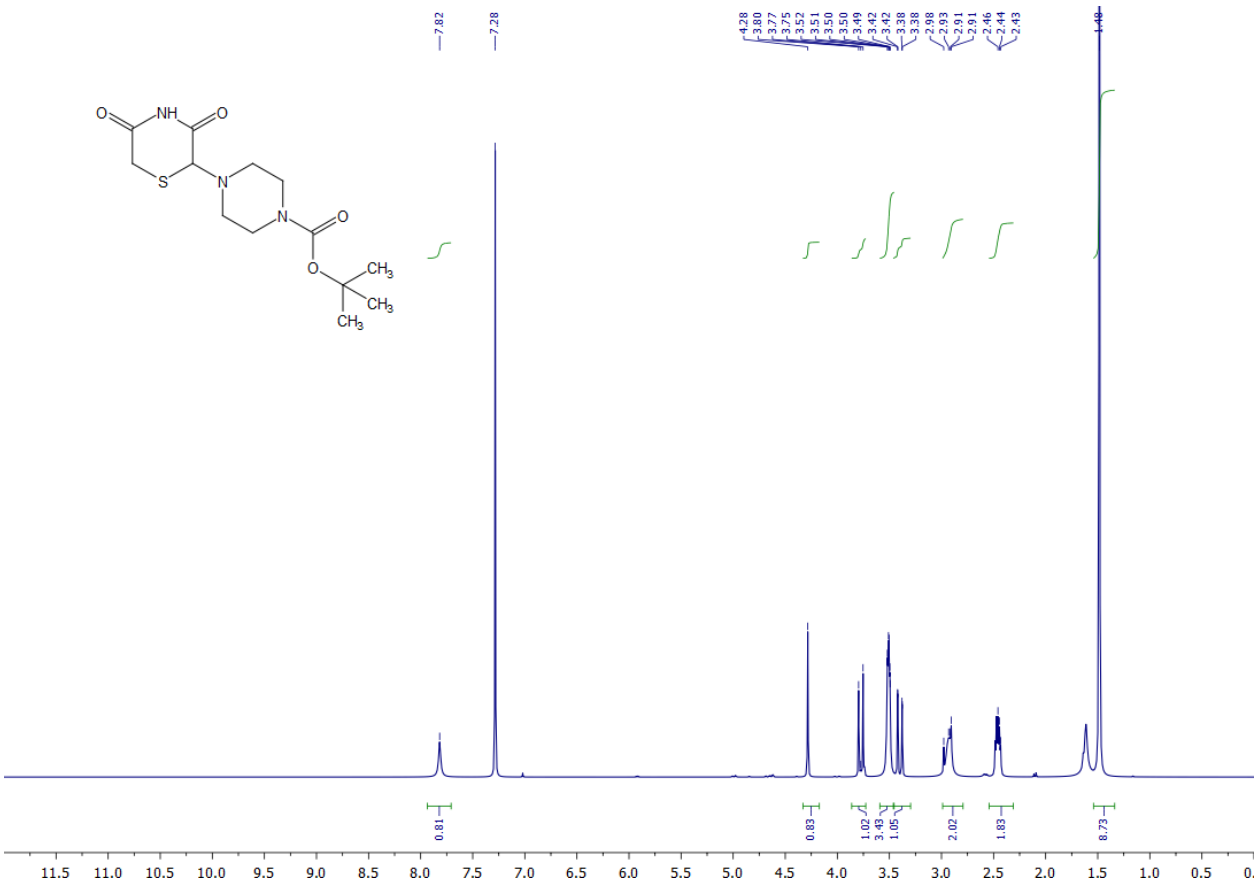
Copies of ^{1}H (400.13 MHz, Acetone-d_6) and $^{13}C\{^{1}H\}$ (125.73 MHz, Acetone-d_6) spectra of **4d**

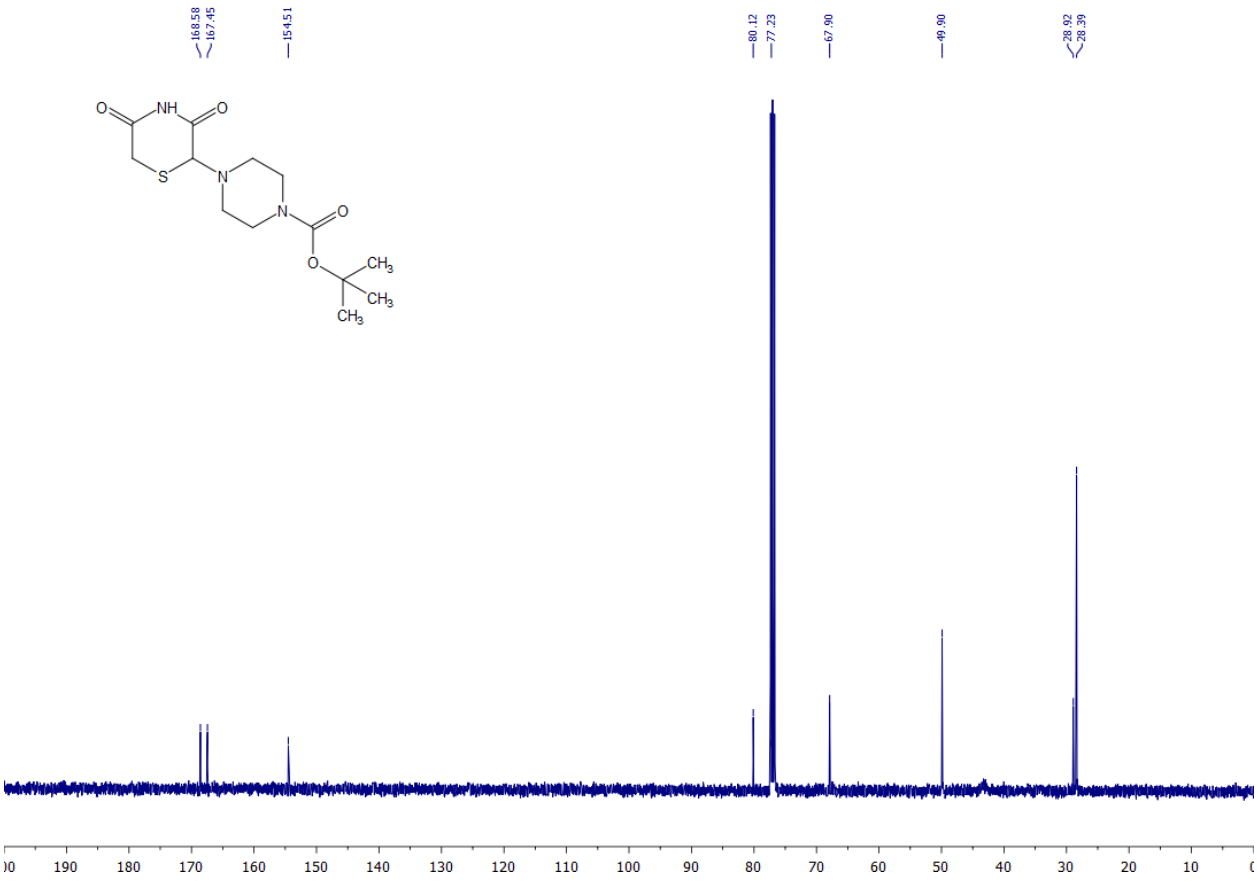


Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4e**

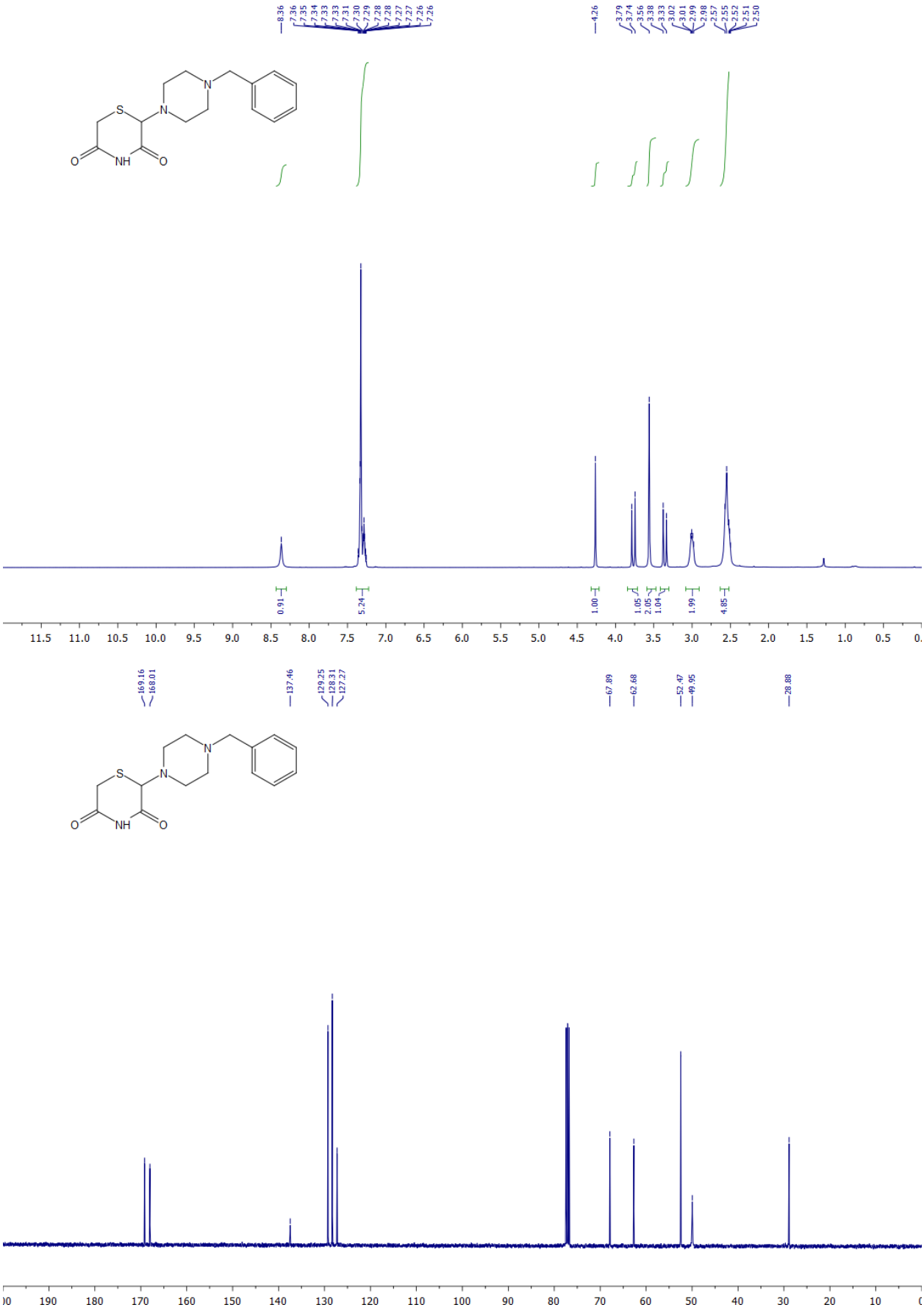


Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4f**

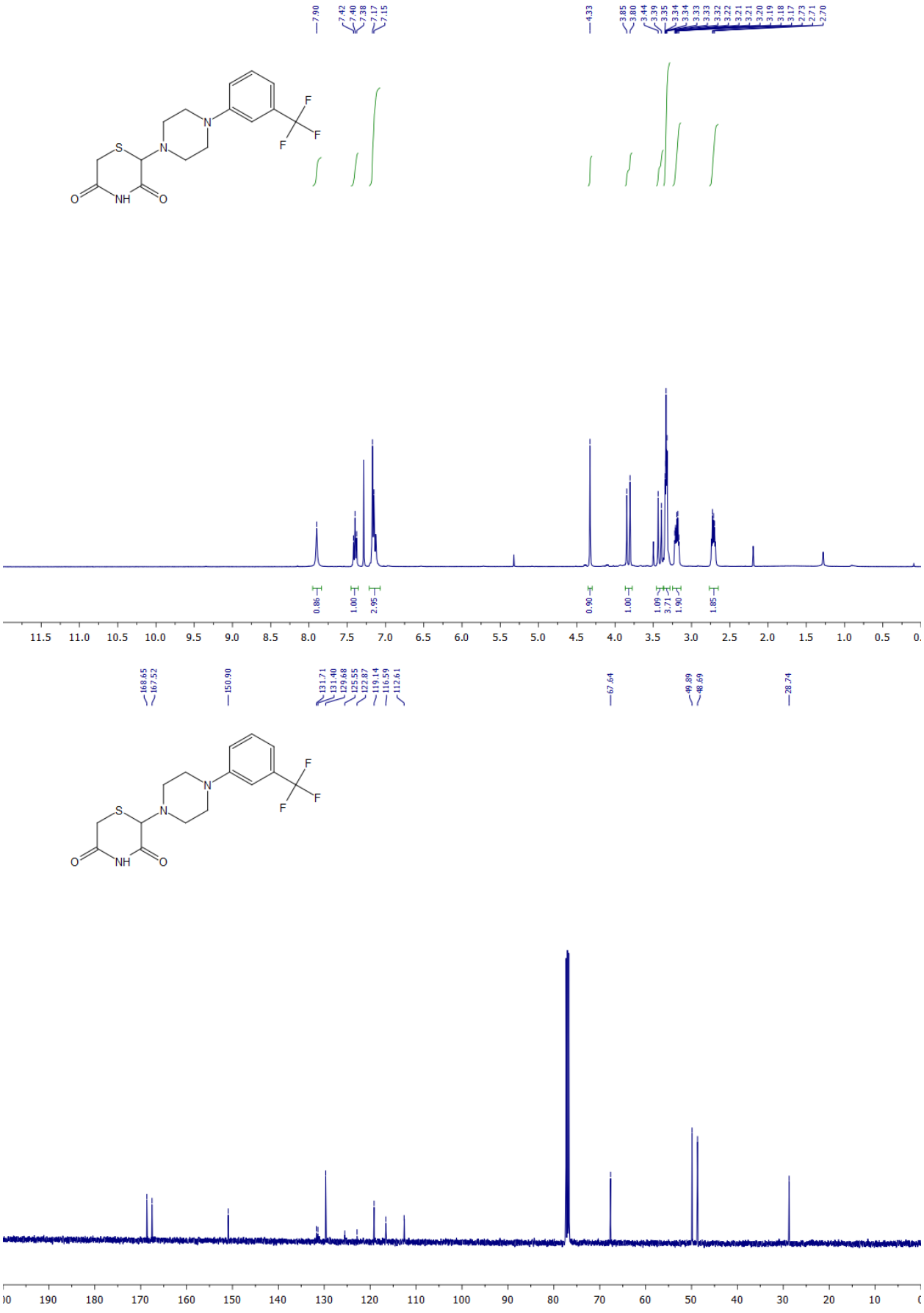




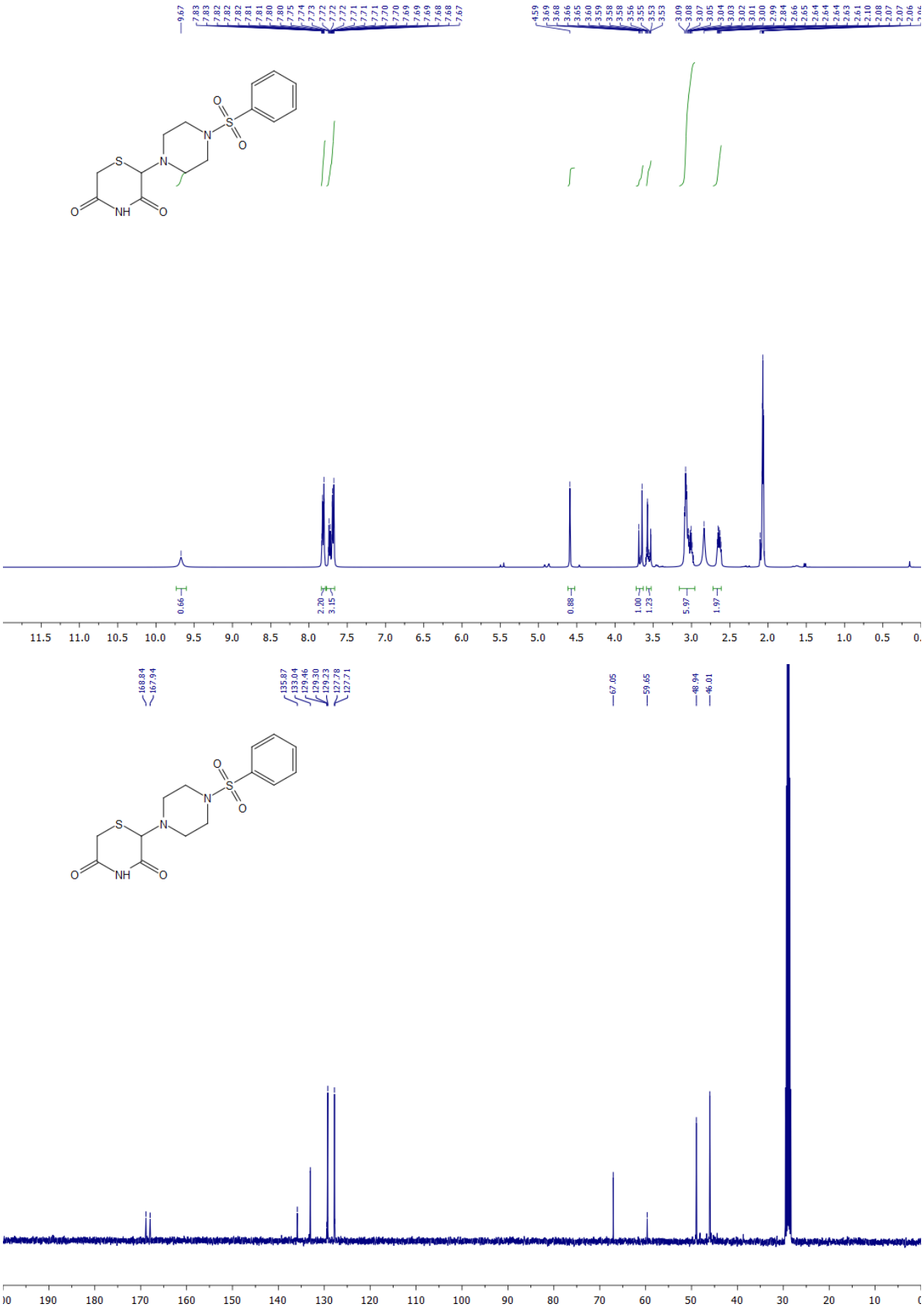
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4g**



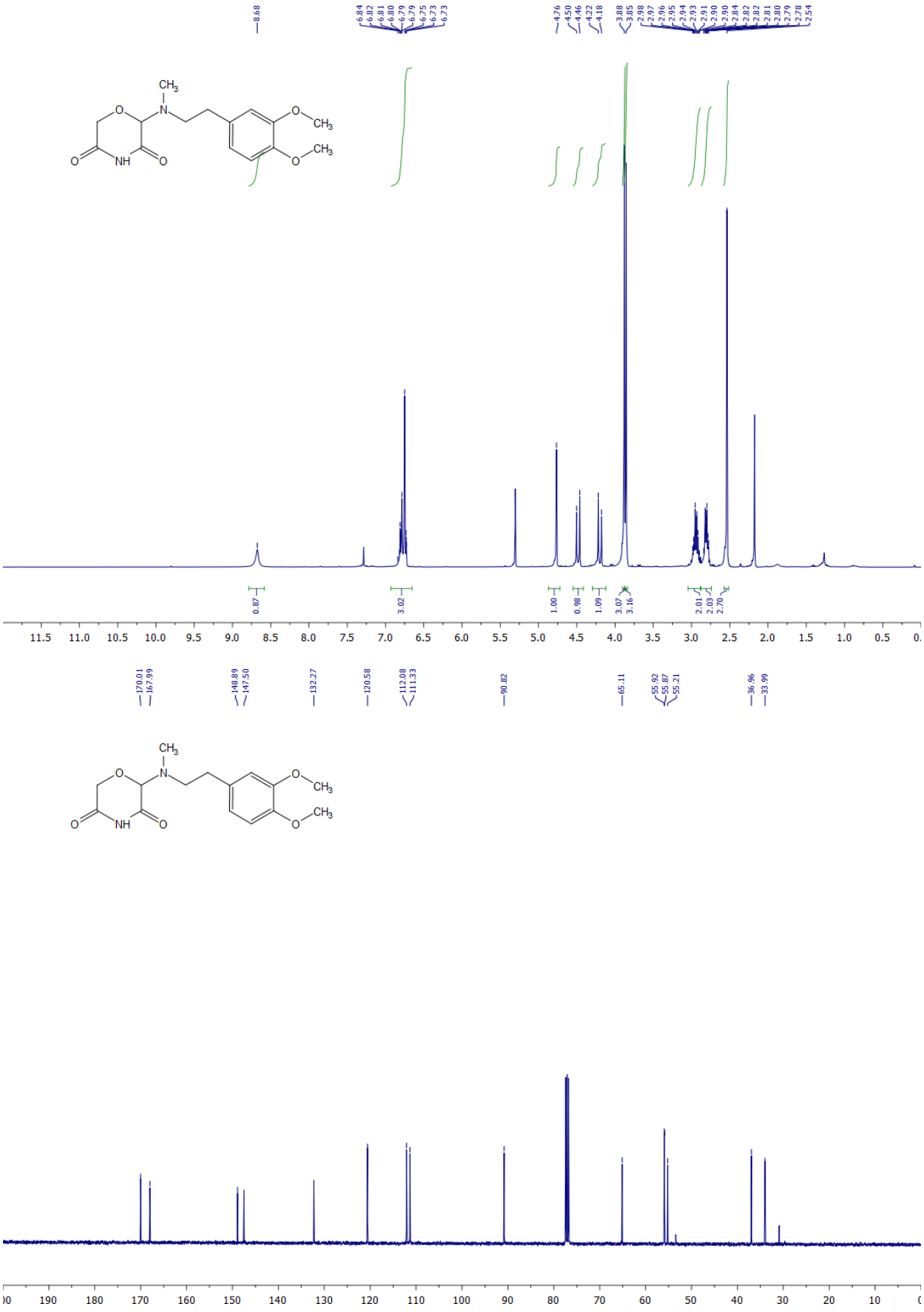
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **4h**



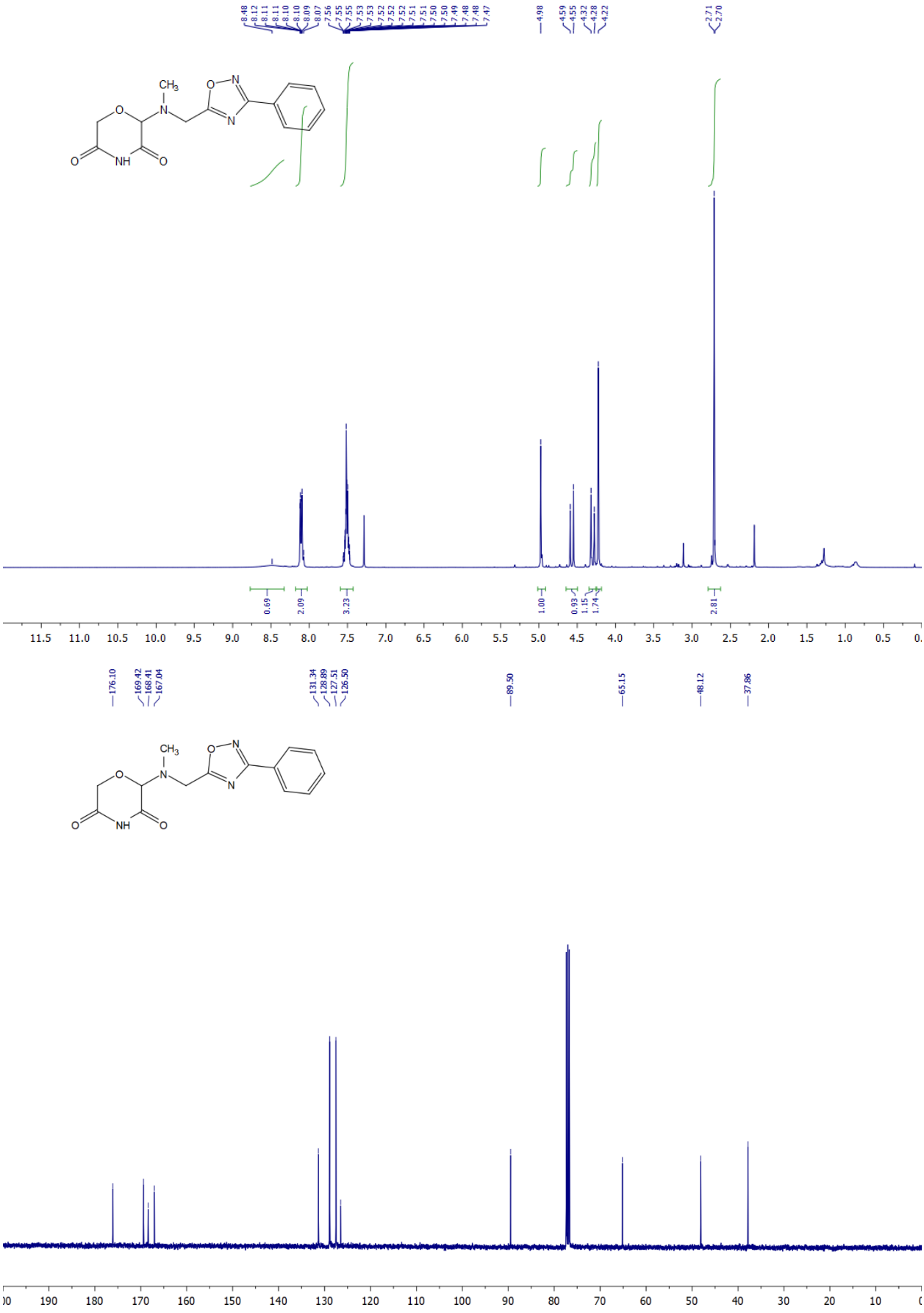
Copies of ^{1}H (400.13 MHz, Acetone-d_6) and $^{13}C\{^{1}H\}$ (100.61 MHz, Acetone-d_6) spectra of **4i**



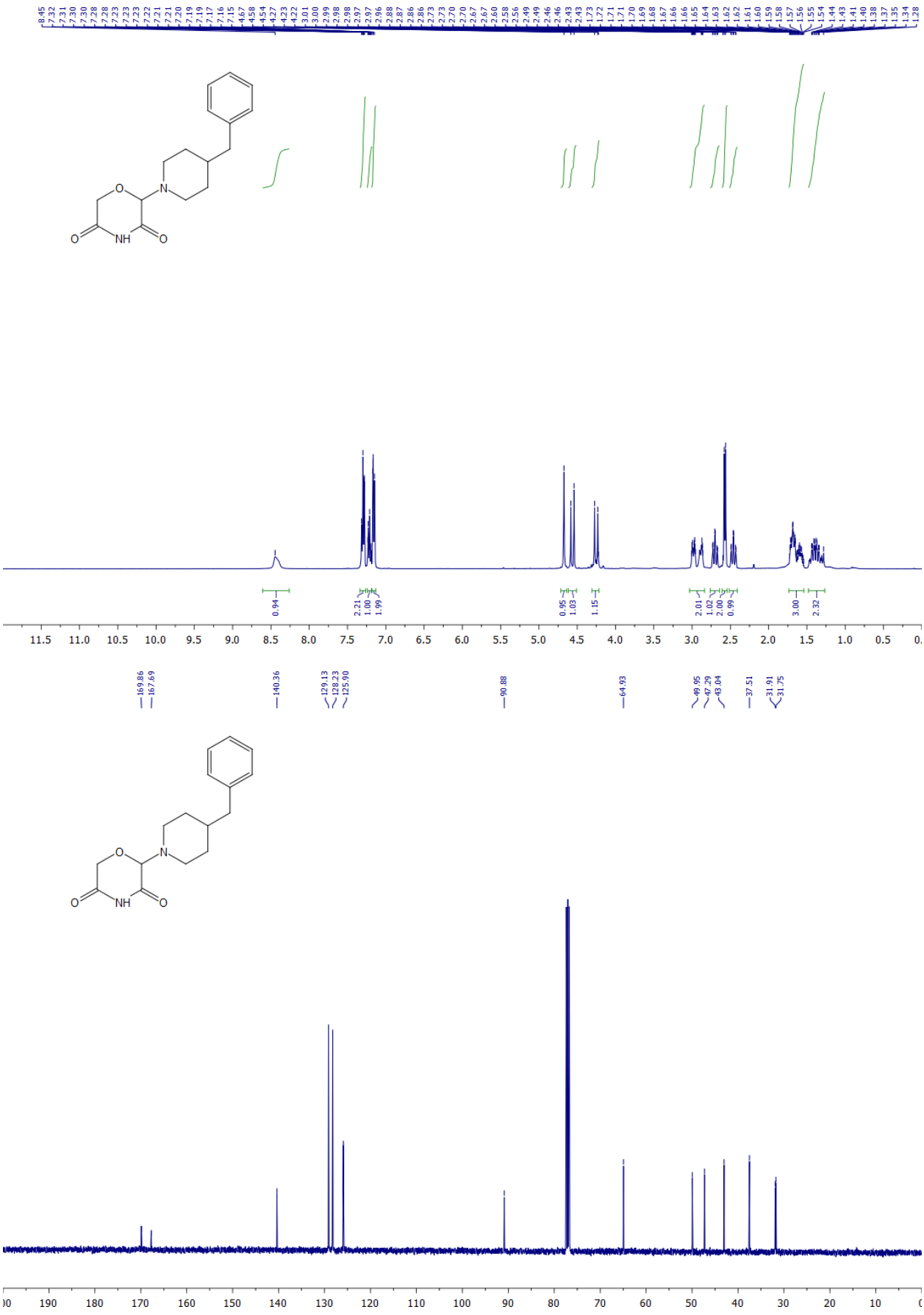
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **5a**



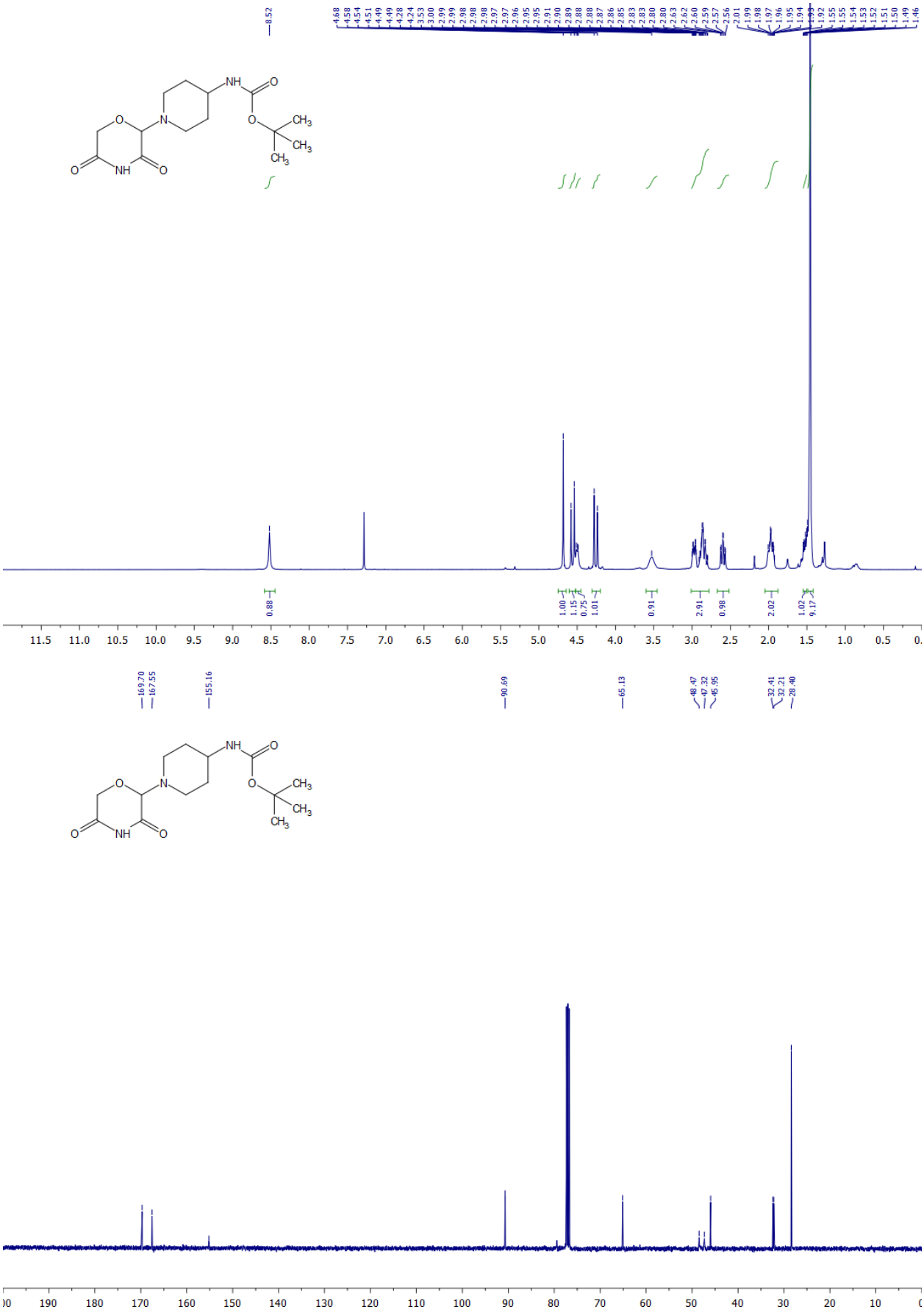
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **5b**



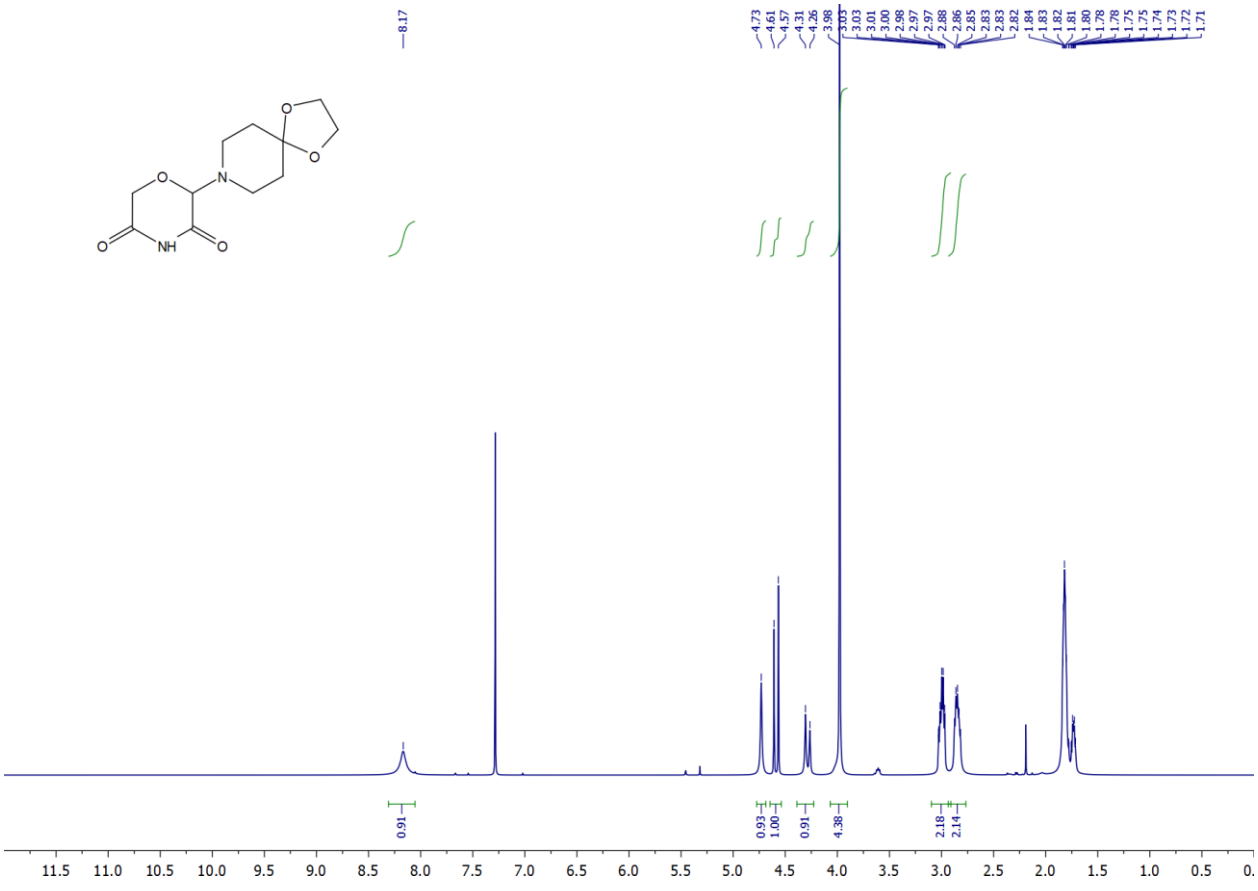
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **5c**

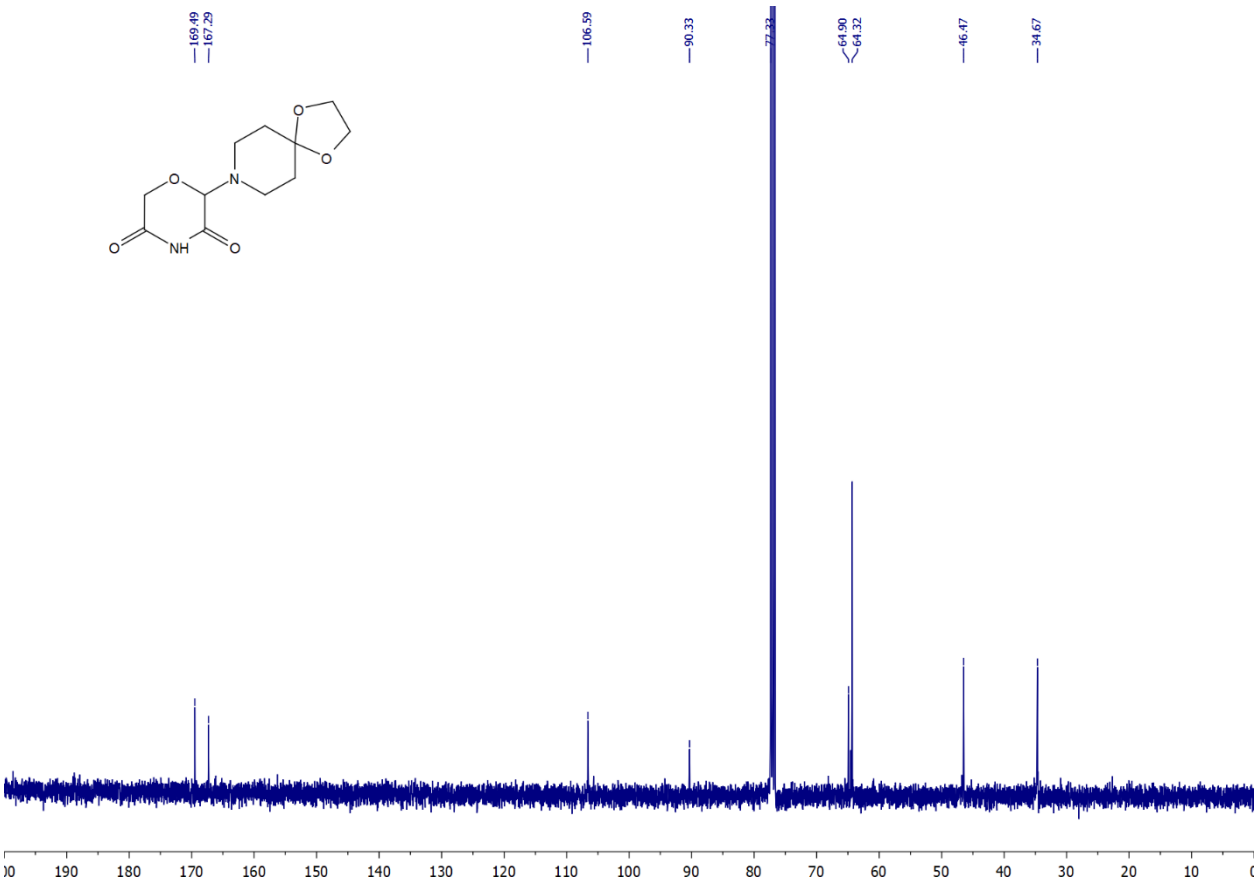


Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **5d**

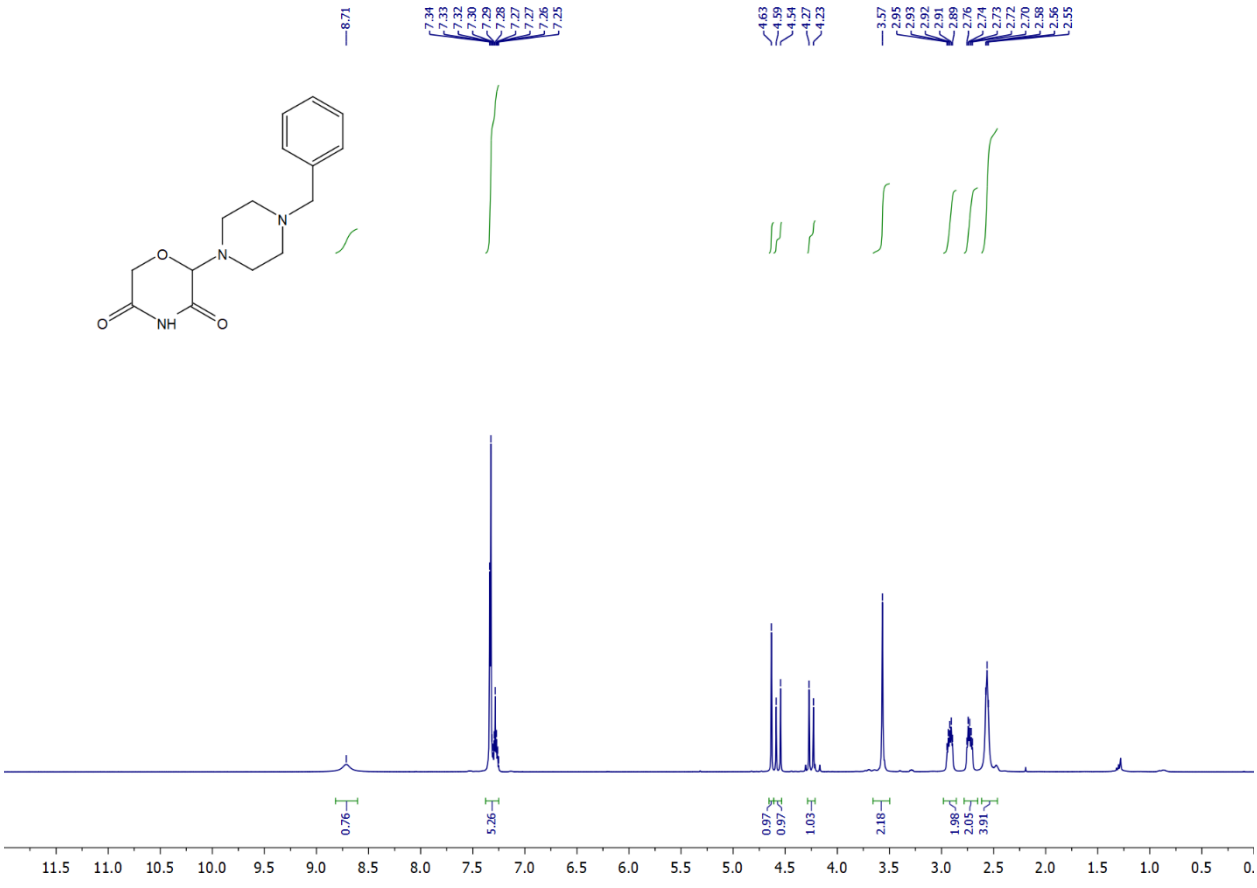


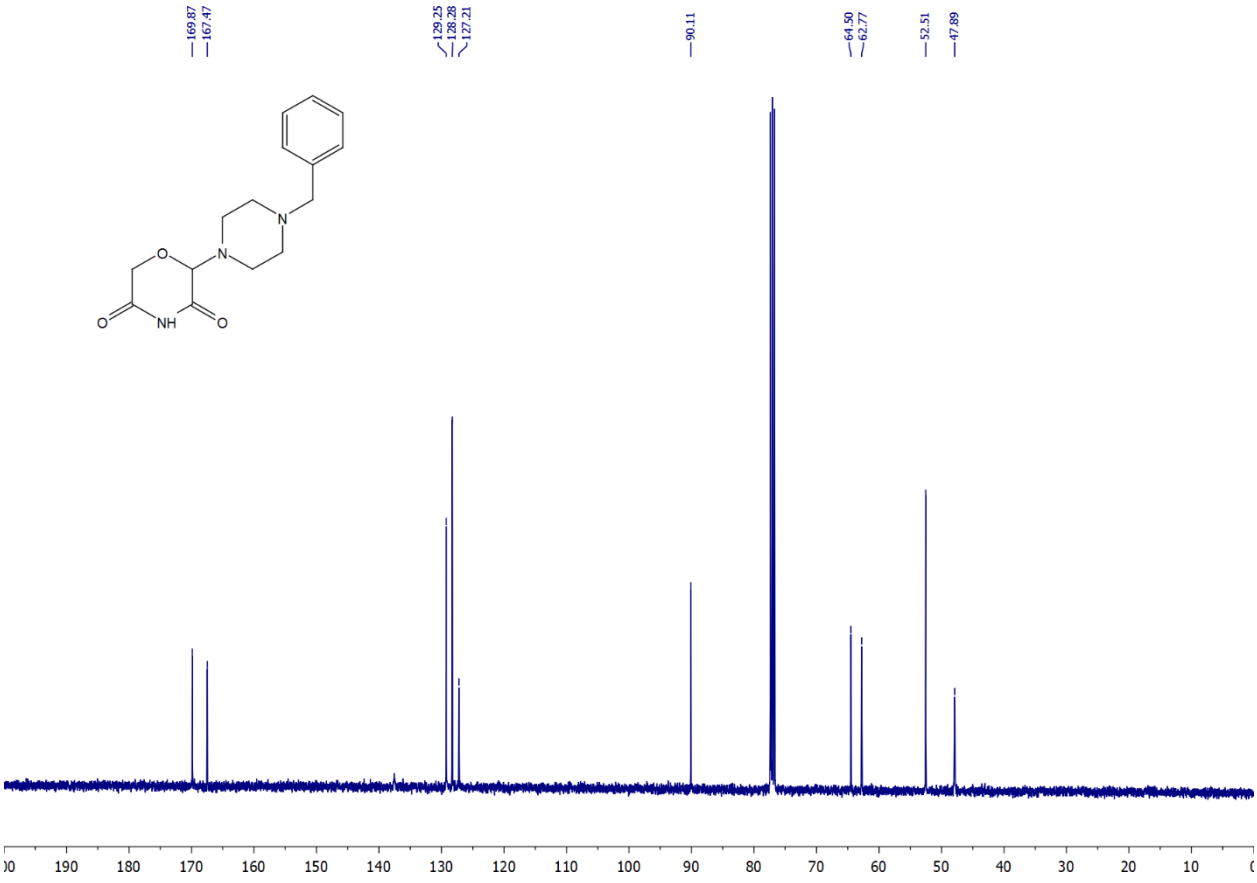
Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **5e**





Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **5f**





Copies of ^{1}H (400.13 MHz, $CDCl_3$) and $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$) spectra of **5g**