Electronic supplementary materials *Mendeleev Commun.*, 2023, **33**, 67–69

Synthesis of novel glutarimide derivatives *via* the Michael addition of (hetero)aromatic thiols: pronounced effect of sulfur oxidation on cytotoxicity towards multiple myeloma cell lines

Maria Adamchik, Andrey Bubyrev, Daniil Zhukovsky, Petr Zhmurov, Alexander Bunev and Mikhail Krasavin

Contents

Experimental procedures

General

All commercial reagents were used without purification. NMR spectrum were recorded using Bruker Avance III spectrometer in DMSO-d_6 or $CDCl_3$ (^{1}H: 400.13 MHz; ^{13}C: 100.61 MHz; ^{19}F: 376.50 MHz); chemical shifts are reported as parts per million (δ, ppm); the residual solvent peak was used as internal standard; multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets; coupling constants, *J*, are reported in Hz. Mass spectra were recorded with a Shimadzu LCMS-9030 HRMS qTOF spectrometer (ESI or APCI, positive ions detection). Melting points were determined with RD-MP (REACH Devices)melting point apparatus in open capillary tubes. Analytical thin-layer chromatography was carried out on UV-254 silica gel plates using appropriate eluents. Compounds were visualized with short-wavelength UV light.

*General Procedure 1 (GP 1): synthesis of compounds **1a-h.***

To the screw-capped glass vial, glutarimide **3** (250 mg, 2 mmol), the corresponding thiophenol (2.2 mmol), THF (5 ml) and DIPEA (0.87 ml, 5 mmol) were added. The resulting mixture was stirred in an oil bath at 75 °C for 1-3 h, until the full consumption of the starting material (TLC: chloroform/methanol = 92:8, permanganate stain). All volatiles were removed under vacuum, the residue was diluted with EtOAc (50 ml) and washed with 1 M HCl (1×30 ml) and brine (1×30 ml). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography.

3-(Mesitylthiomethyl)piperidine-2,6-dione (1a)

Compound was synthesized according GP 1. Yield: 387 mg (70%). Eluent: chloroform/methanol gradient from 99:1 to 95:5. White powder; mp 93−95 °C. ^{1}H NMR (400 MHz $CDCl_3$) δ 8.16 (s, 1H), 6.93 (s, 2H), 3.30 (dd, *J* = 13.0, 3.6 Hz, 1H), 2.83 – 2.63 (m, 2H), 2.59 – 2.46 (m, 8H), 2.43 – 2.33 (m, 1H), 2.26 (s, 3H), 2.00 – 1.84 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 172.4, 142.8, 138.6, 129.5, 129.3, 42.1, 35.4, 31.5, 23.2, 22.0, 21.1. HRMS (APCI), *m/z* calcd for $C_{15}H_{20}NO_2S$ $[M+H]^+$ 278.1209 found 278.1211.

3-((3-Fluoro-4-methoxyphenyl)thiomethyl)piperidine-2,6-dione (1b)

Compound was synthesized according GP 1. Yield: 407 mg (72%). Eluent: chloroform/methanol gradient from 99:1 to 95:5. White powder; mp. 152-154 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 7.32 (dd, *J* = 11.9, 2.2 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.16 – 7.10 (m, 1H), 3.83 (s, 3H), 3.42 (dd, *J* = 13.6, 4.1 Hz, 1H), 3.06 (dd, *J* = 13.6, 8.3 Hz, 1H), 2.77 – 2.65 (m, 1H), 2.61 – 2.44 (m, 2H, overlapping with DMSO-d_6), 2.09 – 2.00 (m, 1H), 1.86 – 1.72 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.13, 173.26, 151.40 (d, J_{C-F} = 246.7 Hz), 146.17 (d, J_{C-F} = 10.5 Hz), 127.02 (d, J_{C-F} = 6.6 Hz), 126.64 (d, J_{C-F} = 3.4 Hz), 117.65 (d, J_{C-F} = 19.1 Hz), 114.52 (d, J_{C-F} = 2.3 Hz), 56.08, 40.72, 34.52, 30.87, 22.17. ^{19}F NMR (376 MHz, DMSO) δ -133.92. HRMS (APCI), m/z calcd for $C_{13}H_{15}FNO_3S$ $[M + H]^+$ 284.0751 found 284.0754.

3-((2,3-Dichloro-4-methoxyphenyl)thiomethyl)piperidine-2,6-dione (1c)

Compound was synthesized according GP 1. Yield: 440 mg (66%). Eluent: chloroform/methanol gradient from 99:1 to 95:5. White powder; mp. 179-183 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (s, 1H), 7.49 (d, *J* = 8.9 Hz, 1H), 7.19 (d, *J* = 9.0 Hz, 1H), 3.89 (s, 3H), 3.46 (dd, *J* = 13.4, 4.1 Hz, 1H), 3.10 (dd, *J* = 13.4, 8.2 Hz, 1H), 2.81 – 2.70 (m, 1H), 2.62 – 2.43 (m, 2H, overlapping with DMSO-d_6), 2.13 – 2.03 (m, 1H), 1.89 – 1.74 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.51, 173.72, 154.96, 132.95, 129.62, 127.67, 121.48, 112.29, 57.22, 40.94, 33.91, 31.44, 22.85. HRMS (APCI), m/z calcd for $C_{13}H_{14}Cl_2NO_3S$ $[M + H]^+$ 334.0066 found 334.0069.

3-{[2-(Morpholinocarbonyl)phenyl]thiomethyl}piperidine-2,6-dione (1d)

Compound was synthesized according GP 1. Yield: 473 mg (68%). Eluent: chloroform/methanol gradient from 99:1 to 95:5. White powder; mp. 77-81 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 7.59 – 7.48 (m, 1H), 7.47 – 7.36 (m, 1H), 7.37 – 7.26 (m, 1H), 7.27 – 7.12 (m, 1H), 3.69 – 3.58 (m, 4H), 3.58 – 3.43 (m, 3H), 3.18 – 2.98 (m, 3H), 2.81 – 2.66 (m, 1H), 2.50 (s, 2H, overlapping with DMSO-d_6), 2.06 (dd, *J* = 12.8, 8.5 Hz, 1H), 1.88 – 1.64 (m, 1H). ^{13}C NMR

(101 MHz, DMSO-d_6) δ 174.03, 173.26, 167.23, 137.41, 132.64, 129.52, 126.60, 126.45, 66.12, 65.95, 46.79, 41.47, 40.62, 30.93, 22.34. HRMS (APCI), m/z calcd for $C_{17}H_{21}N_2O_4S$ $[M + H]^+$ 349.1217 found 349.1220.

3-((4-Methoxyphenyl)thiomethyl)piperidine-2,6-dione (1e)

Compound was synthesized according GP 1. Yield: 487 mg (92%). Eluent: chloroform/methanol gradient from 99:1 to 95:5. White powder; mp. 137-140 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (s, 1H), 7.43 – 7.30 (m, 2H), 7.02 – 6.85 (m, 2H), 3.74 (s, 3H), 3.36 (dd, J = 13.5, 3.9 Hz, 1H), 2.99 (dd, J = 13.5, 8.6 Hz, 1H), 2.71 – 2.59 (m, 1H), 2.52 – 2.46 (m, 2H, overlapping with DMSO-d_6), 2.11 – 1.99 (m, 1H), 1.85 – 1.72 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.19, 173.27, 158.50, 132.29, 125.82, 114.85, 55.17, 40.71, 35.17, 30.84, 22.10. HRMS (APCI), m/z calcd for $C_{13}H_{16}NO_3S$ $[M + H]^+$ 266.0845 found 266.0848.

3-((4-(*tert*-Butyl)phenyl)thiomethyl)piperidine-2,6-dione (1f)

Compound was synthesized according GP 1. Yield: 471 mg (81%). Eluent: chloroform/methanol gradient from 99:1 to 95:5. White powder; mp. 122-125 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (s, 1H), 7.38 – 7.27 (m, 4H), 3.46 (dd, J = 13.6, 3.9 Hz, 1H), 3.06 (dd, J = 13.5, 8.5 Hz, 1H), 2.79 – 2.67 (m, 1H), 2.61 – 2.41 (m, 2H, overlapping with DMSO-d_6), 2.11 – 2.02 (m, 1H), 1.86 – 1.73 (m, 1H), 1.26 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.14, 173.26, 148.67, 132.48, 128.48, 126.00, 40.68, 34.12, 33.25, 31.00, 30.86, 22.23. HRMS (APCI), m/z calcd for $C_{16}H_{22}NO_2S$ $[M + H]^+$ 292.1366 found 292.1368.

3-((3,4-Dimethoxyphenyl)thiomethyl)piperidine-2,6-dione (1g)

Compound was synthesized according GP 1. Yield: 542 mg (92%). Eluent: chloroform/methanol gradient from 99:1 to 95:5. White powder; mp. 110-114 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (s, 1H), 7.10 – 6.82 (m, 3H), 3.82 – 3.68 (m, 6H), 3.41 (dd, J = 13.6, 3.9 Hz, 1H), 3.03 (dd, J = 13.6, 8.5 Hz, 1H), 2.74 – 2.64 (m, 1H), 2.59 – 2.45 (m, 2H, overlapping with DMSO-d_6), 2.13 – 2.00 (m, 1H), 1.87 – 1.72 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.23, 173.29, 149.04, 148.08, 126.25, 122.87, 114.19, 112.45, 55.58, 55.55, 40.79, 34.78, 30.86, 22.15. HRMS (APCI), m/z calcd for $C_{14}H_{18}NO_4S$ $[M + H]^+$ 296.0951 found 296.0955.

Methyl 3-((2,6-dioxopiperidin-3-yl)methylthio)benzoate (1h)

Compound was synthesized according GP 1. Yield: 480 mg (82%). Eluent: chloroform/methanol gradient from 99:1 to 95:5. White powder; mp. 107-110 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (s, 1H), 7.89 – 7.85 (m, 1H), 7.79 – 7.75 (m, 1H), 7.70 – 7.62 (m, 1H), 7.52 – 7.45 (m,

1H), 3.86 (s, 3H), 3.55 (dd, *J* = 13.4, 4.1 Hz, 1H), 3.18 (dd, *J* = 13.4, 8.1 Hz, 1H), 2.86 – 2.74 (m, 1H), 2.63 – 2.42 (m, 2H, overlapping with DMSO-d_6), 2.05 (dd, *J* = 17.8, 8.8 Hz, 1H), 1.88 – 1.73 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.99, 173.23, 165.70, 137.33, 132.60, 130.49, 129.56, 128.16, 126.49, 52.28, 40.59, 32.66, 30.95, 22.37. HRMS (APCI), m/z calcd for $C_{14}H_{16}NO_4S$ $[M + H]^+$ 294.0795 found 294.0800.

*General Procedure 2 (GP 2): synthesis of compounds **1i-l***

To a screw-capped glass vial, glutarimide **3** (250 mg, 2 mmol), thiopyridine/thiopyrimidine (2.2 mmol) and pyridine (5 ml) were added. The resulting mixture was stirred in a n oil bath at 75 °C until the full consumption of the starting material (TLC: chloroform/methanol = 90:10, permanganat stain). All volatiles were removed under vacuum, the residue was diluted with EtOAc (50 ml) and washed with water (1×30 ml) and brine (1×30 ml). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography.

3-((4,6-Dimethylpyrimidin-2-yl)thiomethyl)piperidine-2,6-dione (1i)

Compound was synthesized according GP 2. Yield: 233 mg (44%). Eluent: chloroform/methanol gradient from 99:1 to 90:10. White powder; mp. 126-128 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 6.94 (s, 1H), 3.75 (dd, *J* = 13.8, 4.6 Hz, 1H), 3.23 (dd, *J* = 13.8, 7.4 Hz, 1H), 3.02 – 2.83 (m, 1H), 2.67 – 2.40 (m, 2H, overlapping with DMSO-d_6), 2.34 (s, 6H), 2.12 – 1.95 (m, 1H), 1.93 – 1.64 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.36, 173.30, 169.54, 166.91, 115.92, 40.95, 31.11, 29.68, 23.33, 22.36. HRMS (APCI), m/z calcd for $C_{12}H_{16}N_3O_2S$ $[M + H]^+$ 266.0958 found 266.0962.

3-((4-Cyclopropylpyrimidin-2-yl)thiomethyl)piperidine-2,6-dione (1j)

Compound was synthesized according GP 2. Yield: 210 mg (38%). Eluent: chloroform/methanol gradient from 99:1 to 95:5. White powder; mp. 116-120°C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (s, 1H), 8.37 (d, *J* = 5.2 Hz, 1H), 7.13 (d, *J* = 5.2 Hz, 1H), 3.74 (dd, *J* = 13.9, 4.4 Hz, 1H), 3.13 (dd, *J* = 13.9, 7.7 Hz, 1H), 2.98 – 2.79 (m, 1H), 2.68 – 2.43 (m, 2H, overlapping with DMSO-d_6), 2.12 – 1.95 (m, 2H), 1.89 – 1.65 (m, 1H), 1.10 – 1.00 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.30, 173.30, 171.97, 170.08, 156.51, 115.03, 40.91, 31.12, 29.88, 22.43, 16.34, 11.13, 11.06. HRMS (APCI), m/z calcd for $C_{13}H_{16}N_3O_2S$ $[M + H]^+$ 278.0958 found 278.0962.

3-((4-Methylpyrimidin-2-yl)thiomethyl)piperidine-2,6-dione (1k)

Compound was synthesized according GP 2. Yield: 215 mg (43%). Eluent: chloroform/methanol gradient from 99:1 to 90:10. White powder; mp 149−152 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ

10.75 (s, 1H), 8.46 (d, *J* = 5.1 Hz, 1H), 7.08 (d, *J* = 5.1 Hz, 1H), 3.76 (dd, *J* = 13.8, 4.6 Hz, 1H), 3.23 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.99 – 2.86 (m, 1H), 2.64 – 2.44 (m, 2H, overlapping with DMSO-d_6), 2.40 (s, 3H), 2.11 – 1.96 (m, 1H), 1.83 – 1.64 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.4, 173.3, 170.1, 167.5, 157.2, 116.7, 40.9, 31.2, 29.8, 23.6, 22.4. HRMS (APCI), *m/z* calcd for $C_{11}H_{14}N_3O_2S$ $[M+H]^+$ 252.0801 found 252.0801.

3-((5-Bromopyrimidin-2-yl)thiomethyl)piperidine-2,6-dione (1l)

Compound was synthesized according GP 2. Used in the next step without purification and characterization.

*General Procedure 3 (GP 3): synthesis of compounds **2a-h.***

A stirred solution of **1a-h** (0.7 mmol) in THF (4 ml) and methanol (4 ml) was cooled to 0 °C in an ice bath. Solution of Oxone® (1.28 g, 2.1 mmol) in water (7 ml) was added in one portion. The reaction mixture was warmed to room temperature and stirred at that temperature until the full consumption of the starting material (1-4 hours). The reaction mixture was diluted with water (30 ml) and extracted with EtOAc (4×20 ml). The combined organic extracts were washed with water (1×30 ml) and brine (1×30 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography.

*Characterization data of compounds **2a-h***

3-(Mesitylsulfonylmethyl)piperidine-2,6-dione (2a)

Compound was synthesized according GP 3. Yield: 177 mg (82%). Eluent: chloroform/methanol gradient from 99:1 to 95:5. White powder; mp. 125-129 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 6.87 (s, 2H), 4.07 – 3.96 (m, 1H), 3.29 (br s, 1H), 3.12 (br s, 1H), 2.92 – 2.59 (m, 2H), 2.56 (s, 3H), 2.53 (s, 3H), 2.50 – 2.38 (m, 1H), 2.28 (s, 3H), 2.10 – 1.87 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.13, 172.14, 141.58, 138.24, 131.18, 38.42, 37.74, 32.04, 24.97, 23.15, 21.13, 19.22. HRMS (APCI), m/z calcd for $C_{15}H_{20}NO_4S$ $[M + H]^+$ 310.1108 found 310.1110.

3-((3-Fluoro-4-methoxyphenyl)sulfonylmethyl)piperidine-2,6-dione (2b)

Compound was synthesized according GP 3. Yield: 172 mg (78%). Eluent: chloroform/methanol gradient from 99:1 to 95:5. White powder; mp. 195-199 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 7.86 – 7.68 (m, 2H), 7.43 (t, *J* = 8.4 Hz, 1H), 3.96 (s, 3H), 3.83 (dd, *J* = 14.7, 2.8 Hz, 1H), 3.48 (dd, *J* = 14.7, 8.8 Hz, 1H), 3.09 – 2.90 (m, 1H), 2.62 (ddd, *J* = 17.8, 12.8, 5.3 Hz, 1H), 2.53 – 2.41 (m, 1H, overlapping with DMSO-d_6), 2.15 – 2.02 (m, 1H), 1.95 – 1.76 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.94, 172.78, 151.74 (d, J_{C-F} = 10.3 Hz), 150.81 (d, J_{C-F} = 249.4 Hz), 130.95 (d, J_{C-F} = 5.5 Hz), 125.60 (d, J_{C-F} = 3.6 Hz), 115.53 (d, J_{C-F} = 20.9 Hz),

114.15 (d, J_{C-F} = 1.9 Hz), 56.59, 55.04, 36.41, 31.05, 23.14. ^{19}F NMR (376 MHz, DMSO-d_6) δ -132.42. HRMS (APCI), m/z calcd for $C_{13}H_{15}FNO_5S$ $[M + H]^+$ 316.0649 found 316.0652.

3-((2,3-Dichloro-4-methoxyphenyl)sulfonylmethyl)piperidine-2,6-dione (2c)

Compound was synthesized according GP 3. Yield: 168 mg (66%). Eluent: chloroform/methanol gradient from 99:1 to 95:5. White powder; mp. 204-208 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 8.00 (d, *J* = 8.9 Hz, 1H), 7.39 (d, *J* = 9.1 Hz, 1H), 4.16 (dd, *J* = 14.8, 3.2 Hz, 1H), 4.01 (s, 3H), 3.67 – 3.54 (m, 1H), 3.07 – 2.93 (m, 1H), 2.68 – 2.53 (m, 1H), 2.48 (s, 1H, overlapping with DMSO-d_6), 2.16 – 2.05 (m, 1H), 2.02 – 1.78 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.89, 172.69, 159.75, 131.17, 130.84, 129.54, 122.87, 110.91, 57.40, 53.93, 36.54, 31.11, 23.19. HRMS (APCI), m/z calcd for $C_{13}H_{14}Cl_2NO_5S$ $[M + H]^+$ 365.9964 found 365.9968.

3-{[2-(Morpholinocarbonyl)phenyl)sulfonyl]methyl}piperidine-2,6-dione (2d)

Compound was synthesized according GP 3. Yield: 110 mg (45%). Eluent: chloroform/methanol gradient from 99:1 to 95:5. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) rotameric mixture δ 8.57 (s, 1H, rotamer), 8.52 (s, 1H, rotamer), 8.04 (d, J = 7.8 Hz, 1H), 7.74 – 7.66 (m, 1H), 7.65 – 7.54 (m, 1H), 7.40 – 7.31 (m, 1H), 4.28 (dd, J = 14.6, 2.4 Hz, 1H, rotamer), 4.04 – 3.88 (m, 2H), 3.83 – 3.66 (m, 3H), 3.65 – 3.48 (m, 2H), 3.36 (dd, J = 14.6, 9.1 Hz, 1H, rotamer), 3.26 – 3.08 (m, 3H), 2.80 – 2.46 (m, 2H), 2.40 – 2.27 (m, 1H, rotamer), 2.06 – 1.73 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) rotameric mixture δ 172.14, 172.10, 171.93, 171.83, 167.94, 167.86, 137.15, 136.81, 136.76, 134.40, 134.30, 130.41, 130.14, 130.02, 129.89, 127.56, 66.29, 66.05, 66.02, 56.53, 56.51, 47.94, 42.43, 37.25, 36.77, 31.78, 31.62, 24.07, 23.81. HRMS (APCI), m/z calcd for $C_{17}H_{21}N_2O_6S$ $[M + H]^+$ 381.1115 found 381.1121

3-((4-Methoxyphenyl)sulfonylmethyl)piperidine-2,6-dione (2e)

Compound was synthesized according GP 3. Yield: 172 mg (83%). Eluent: chloroform/methanol gradient from 99:1 to 95:5. White powder; mp. 170-174 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 7.88 – 7.84 (m, 2H), 7.20 – 7.16 (m, 2H), 3.87 (s, 3H), 3.77 (dd, *J* = 14.6, 2.6 Hz, 1H), 3.42 (dd, *J* = 14.6, 9.0 Hz, 1H), 3.03 – 2.93 (m, 1H), 2.68 – 2.52 (m, 2H, overlapping with DMSO-d_6), 2.14 – 2.01 (m, 1H), 1.92 – 1.78 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.94, 172.84, 163.36, 130.86, 129.93, 114.74, 55.80, 55.22, 36.46, 31.04, 23.10. HRMS (APCI), m/z calcd for $C_{13}H_{16}NO_5S$ $[M + H]^+$ 298.0744 found 298.0749.

3-((4-*tert*-Butylphenyl)sulfonylmethyl)piperidine-2,6-dione (2f)

Compound was synthesized according GP 3. Yield: 131 mg (58%). Eluent: chloroform/methanol gradient from 99:1 to 95:5. White powder; mp. 210-214 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 7.89 – 7.83 (m, 2H), 7.76 – 7.65 (m, 2H), 3.79 (dd, *J* = 14.6, 2.6 Hz, 1H), 3.46 (dd, *J* = 14.6, 9.1 Hz, 1H), 3.09 – 2.97 (m, 1H), 2.70 – 2.57 (m, 1H), 2.54 – 2.41 (m, 1H, overlapping with DMSO-d_6), 2.21 – 2.09 (m, 1H), 2.01 – 1.78 (m, 1H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.93, 172.81, 157.12, 136.62, 127.48, 126.42, 54.96, 36.30, 34.98, 31.02, 30.71, 23.13. HRMS (APCI), m/z calcd for $C_{16}H_{22}NO_4S$ $[M + H]^+$ 324.1264 found 324.1263.

3-((3,4-Dimethoxyphenyl)sulfonylmethyl)piperidine-2,6-dione (2g)

Compound was synthesized according GP 3. Yield: 196 mg (86%). Eluent: chloroform/methanol gradient from 99:1 to 95:5. White powder; mp. 157-160 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 7.51 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.39 (d, *J* = 2.2 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 1H), 3.88 – 3.85 (m, 6H), 3.80 (dd, *J* = 14.6, 2.6 Hz, 1H), 3.45 (dd, *J* = 14.6, 9.1 Hz, 1H), 3.05 – 2.95 (m, 1H), 2.68 – 2.54 (m, 1H), 2.52 – 2.43 (m, 1H, overlapping with DMSO-d_6), 2.12 – 2.01 (m, 1H), 1.92 – 1.78 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.95, 172.88, 153.10, 148.87, 130.71, 121.58, 111.51, 110.11, 55.94, 55.11, 37.63, 36.50, 31.05, 23.09. HRMS (APCI), m/z calcd for $C_{14}H_{18}NO_6S$ $[M + H]^+$ 328.0849 found 328.0850.

Methyl 3-((2,6-dioxopiperidin-3-yl)methylsulfonyl)benzoate (5h)

Compound was synthesized according GP 3. Yield: 195 mg (86%). Eluent: chloroform/Methanol gradient from 99:1 to 95:5. White powder; mp. 156-160°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 8.44 – 8.39 (m, 1H), 8.36 – 8.27 (m, 1H), 8.26 – 8.21 (m, 1H), 7.89 – 7.81 (m, 1H), 3.99 – 3.82 (m, 4H), 3.60 (dd, *J* = 14.7, 8.5 Hz, 1H), 3.16 – 2.97 (m, 1H), 2.70 – 2.57 (m, 1H), 2.54 – 2.43 (m, 1H, overlapping with DMSO-d_6), 2.18 – 2.05 (m, 1H), 2.00 – 1.80 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.92, 172.71, 164.86, 140.15, 134.31, 132.16, 130.83, 130.46, 128.06, 54.83, 52.67, 36.25, 31.03, 23.20. HRMS (APCI), m/z calcd for $C_{14}H_{16}NO_6S$ $[M + H]^+$ 326.0693 found 326.0694.

*General Procedure 4 (GP 4): synthesis of compounds **2i-l***

A stirred solution of **1i-l** (0.5 mmol) in THF (4 ml) and MeOH (4 ml) was cooled to 0 °C in an ice bath. Solution of Oxone® (0.92 g, 1.5 mmol) in water (7 ml) was added in one portion. The reaction mixture was warmed to room temperature and stirred overnight. The mixture was diluted with water (30 ml) and extracted with EtOAc (6×20 ml). The combined organic extracts

were washed with water (1×30 ml) and brine (1×30 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography.

3-((4,6-Dimethylpyrimidin-2-yl)sulfonylmethyl)piperidine-2,6-dione (2i)

Compound was synthesized according GP 4. Yield: 58 mg (39%). Eluent: chloroform/methanol gradient from 99:1 to 90:10. White powder; mp. 205-207 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 7.60 (s, 1H), 4.26 (dd, *J* = 14.8, 3.5 Hz, 1H), 3.66 (dd, *J* = 14.8, 8.4 Hz, 1H), 3.23 – 3.13 (m, 1H), 2.75 – 2.57 (m, 1H), 2.55 (s, 6H), 2.51 (s, 1H, overlapping with DMSO-d_6), 2.24 – 2.11 (m, 1H), 2.02 – 1.84 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.98, 172.89, 168.90, 164.40, 123.20, 50.36, 36.21, 31.17, 23.37, 23.13. HRMS (APCI), m/z calcd for $C_{12}H_{16}N_3O_4S$ $[M + H]^+$ 298.0856 found 298.0861.

3-((4-Cyclopropylpyrimidin-2-yl)sulfonylmethyl)piperidine-2,6-dione (2j)

Compound was synthesized according GP 4. Yield: 54 mg (35%). Eluent: chloroform/methanol gradient from 99:1 to 90:10. White powder; mp. 174-178 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 8.81 (d, *J* = 5.2 Hz, 1H), 7.82 – 7.60 (m, 1H), 4.33 (dd, *J* = 14.9, 3.3 Hz, 1H), 3.62 (dd, *J* = 14.9, 8.5 Hz, 1H), 3.19 – 3.08 (m, 1H), 2.70 – 2.57 (m, 1H), 2.45 (s, 1H, overlapping with DMSO-d_6), 2.37 – 2.23 (m, 1H), 2.22 – 2.08 (m, 1H), 2.00 – 1.79 (m, 1H), 1.25 – 1.15 (m, 2H), 1.17 – 1.09 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.48, 172.97, 172.83, 164.90, 157.58, 121.78, 50.18, 36.31, 31.15, 23.12, 16.73, 12.56, 12.49. HRMS (APCI), m/z calcd for $C_{13}H_{16}N_3O_4S$ $[M + H]^+$ 310.0856 found 310.0861.

3-((4-Methylpyrimidin-2-yl)sulfonylmethyl)piperidine-2,6-dione (2k)

Compound was synthesized according GP 4. Yield: 58 mg (41%). Eluent: chloroform/methanol gradient from 99:1 to 90:10. White powder; mp. 167-171 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 8.91 (d, *J* = 5.1 Hz, 1H), 7.73 (d, *J* = 5.1 Hz, 1H), 4.29 (dd, *J* = 14.8, 3.6 Hz, 1H), 3.68 (dd, *J* = 14.9, 8.3 Hz, 1H), 3.24 – 3.14 (m, 1H), 2.61 (s, 3H), 2.46 (s, 1H, overlapping with DMSO-d_6), 2.20 – 2.10 (m, 1H), 1.99 – 1.86 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.97, 172.88, 169.81, 164.72, 158.27, 124.05, 50.42, 36.22, 31.16, 23.64, 23.11. HRMS (APCI), m/z calcd for $C_{11}H_{14}N_3O_4S$ $[M + H]^+$ 284.0700 found 284.0700.

3-((5-Bromopyrimidin-2-yl)sulfonylmethyl)piperidine-2,6-dione (2l)

Compound was synthesized according GP 4. Yield: 81 mg (47%). Eluent: chloroform/methanol gradient from 99:1 to 90:10. White powder; mp. 203-207 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 9.31 (s, 2H), 4.29 (dd, *J* = 14.9, 4.1 Hz, 1H), 3.69 (dd, *J* = 14.9, 7.9 Hz, 1H), 3.25 – 3.12 (m, 1H), 2.70 – 2.57 (m, 1H), 2.23 – 2.12 (m, 1H), 2.08 (s, 1H), 2.00 – 1.85 (m, 1H). ^{13}C

NMR (101 MHz, DMSO-d_6) δ 172.95, 172.90, 163.14, 159.63, 123.31, 51.02, 36.34, 31.18, 23.07. HRMS (APCI), m/z calcd for $C_{10}H_{11}BrN_3O_4S$ $[M + H]^+$ 347.9648 found 347.9651.

3-(Phenylaminomethyl)piperidine-2,6-dione (4)

To a screw-capped glass vial, glutarimide **3** (250 mg, 2 mmol), aniline (0.219 ml, 2.4 mmol), THF (5 ml) and DIPEA (0.87 ml, 5 mmol) were added. The resulting mixture was stirred in an oil bath at 75 °C overnight. All volatiles were removed under vacuum, the residue was diluted with EtOAc (50 ml) and washed with H_2O (1×30 ml) and brine (1×30 ml). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography. Yield: 218 mg (50%). Eluent: chloroform/methanol gradient from 99:1 to 90:10. White powder; mp. 150-153°C ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 7.14 – 7.00 (m, 2H), 6.68 – 6.46 (m, 3H), 5.69 – 5.60 (m, 1H), 3.58 – 3.44 (m, 1H), 3.28 – 3.09 (m, 1H), 2.82 – 2.66 (m, 1H), 2.60 – 2.45 (m, 2H, overlapping with DMSO-d_6), 2.07 – 1.95 (m, 1H), 1.86 – 1.65 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.78, 173.42, 148.47, 128.92, 115.80, 112.02, 42.71, 40.25, 30.76, 21.49. HRMS (APCI), m/z calcd for $C_{12}H_{15}N_2O_2$ $[M + H]^+$ 219.1128 found 219.1126.

Procedures for biological testing of compounds

Cell culture

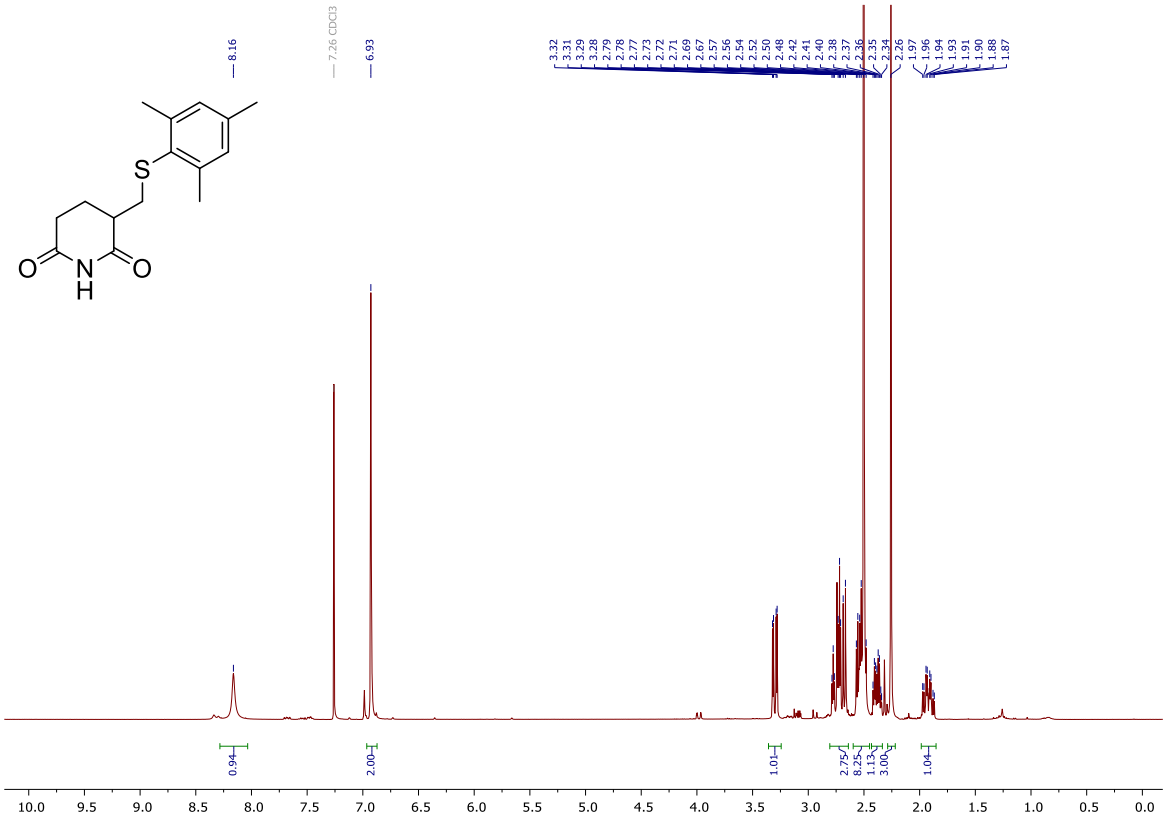
Multiple myeloma cell line MOLP-8 and KMS-12-PE were purchased from the DSMZ. Cells were maintained in RPMI-1640 (Gibco, UK) supplemented with 20% fetal bovine serum (FBS, Gibco, UK), penicillin (100 UI ml^{-1}), streptomycin (100 μg ml^{-1}) and GlutaMax (2 mM, Gibco, UK). All cells line cultivation under a humidified atmosphere of 95% air/5% CO_2 at 37 °C. The number of viable cells was determined by trypan blue exclusion.

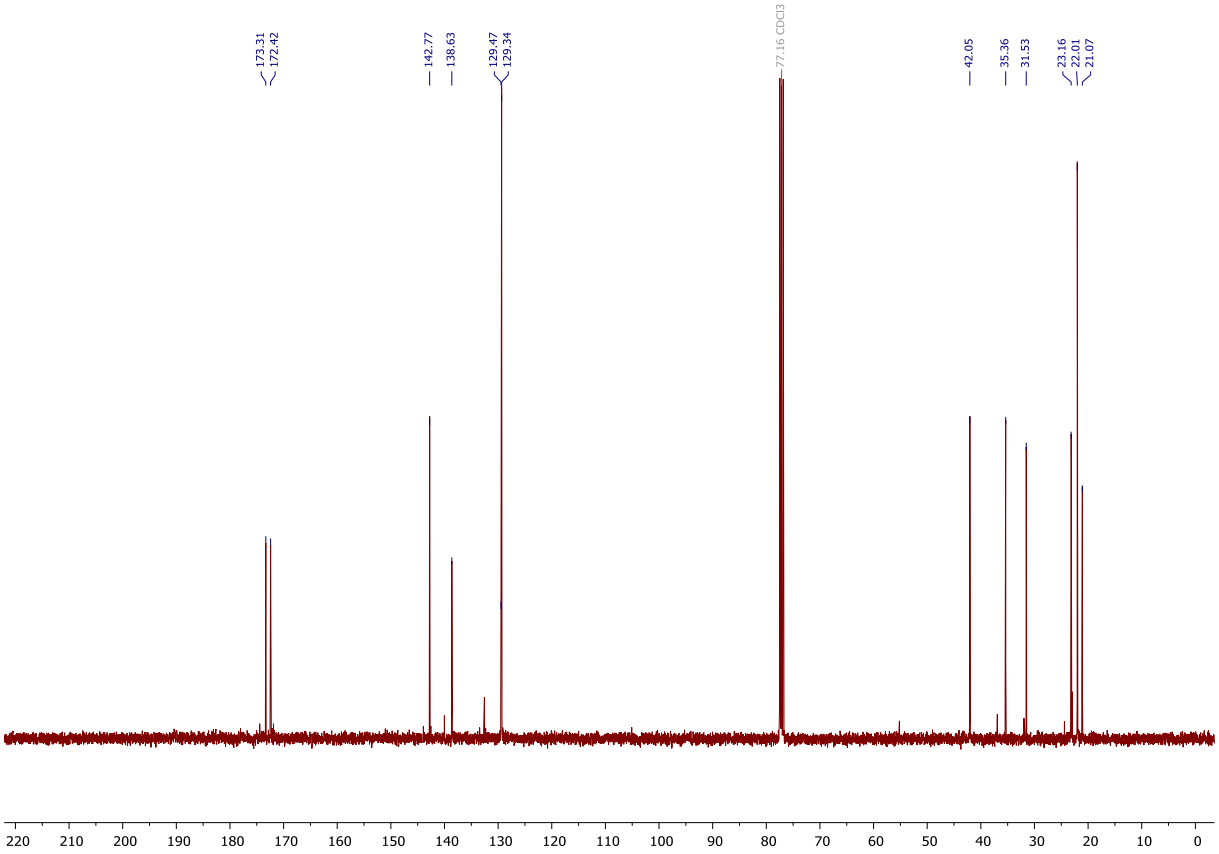
MTT assay

All examined cells were diluted with the growth medium to 3.0×10^5 cells per ml and the aliquots (15×10^3 cells per 50 μl) were placed in individual wells in white 96-multiplates (Nunc, USA). Triplicate wells were treated with test compounds starting at 500.0 μM concentration and diluted 12 at various concentrations or DMSO (Sigma, USA) as control with final concentration 0.1%. Plates were incubated for 48 h at 37 °C in 5% CO_2 atmosphere. After incubation, the cells were then treated with 100 μL CellTiter-Glo® One Solution (Promega, USA). The plates were shaken for 10 min. The luminescence was determined using a microplate reader GloMax Multi+ (Promega, USA). Each of the tested compounds was evaluated for cytotoxicity in three separate experiments.

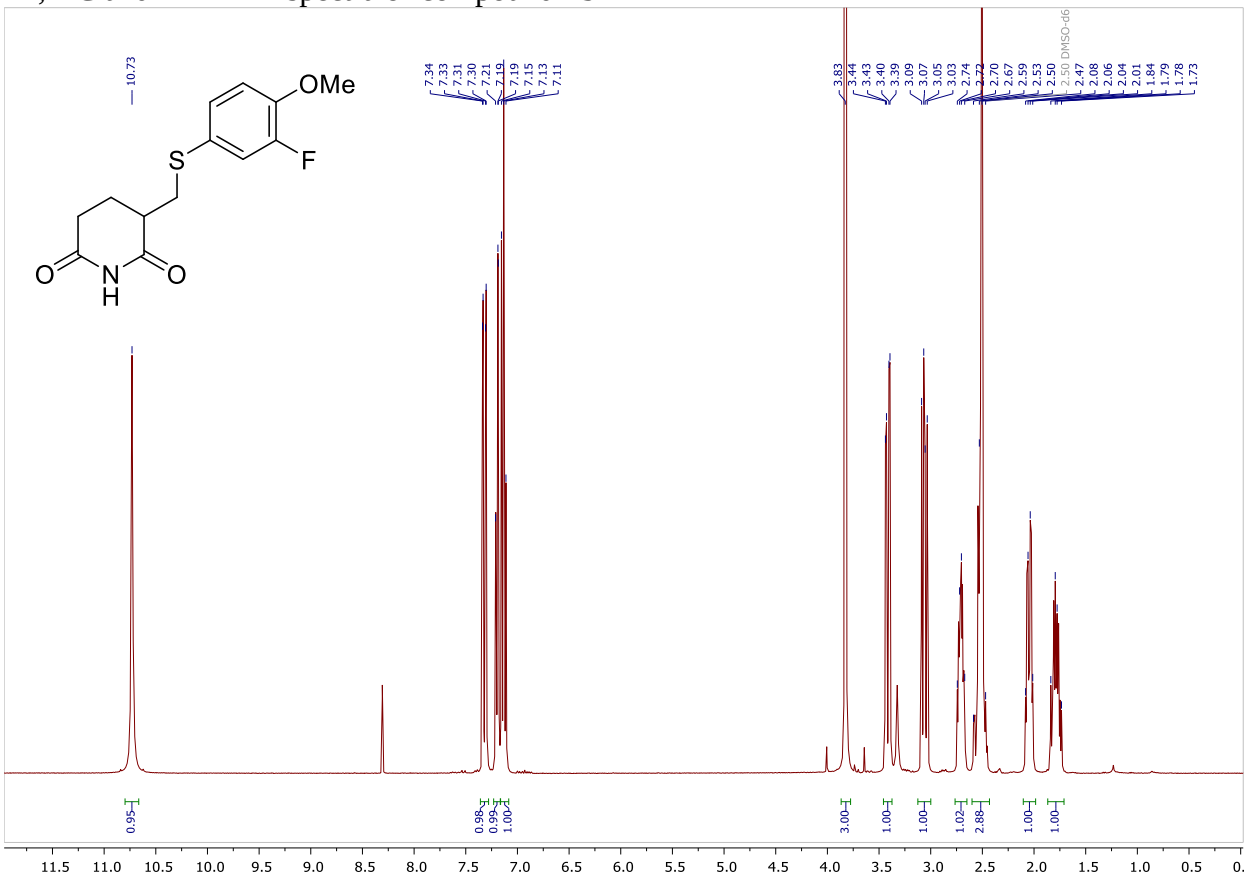
Copies of ^{1}H, ^{13}C NMR and ^{19}F spectra

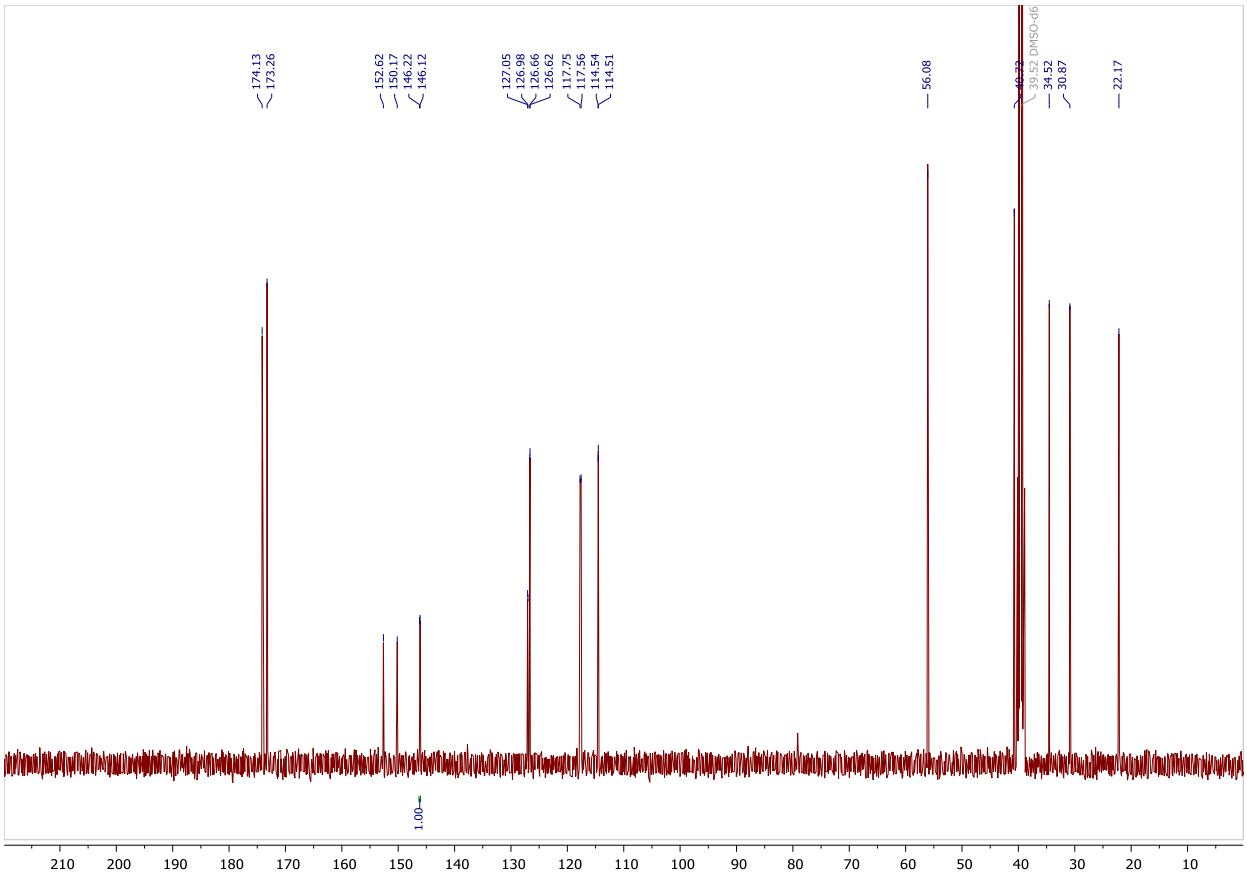
^{1}H and ^{13}C NMR spectra of compound of **1a**

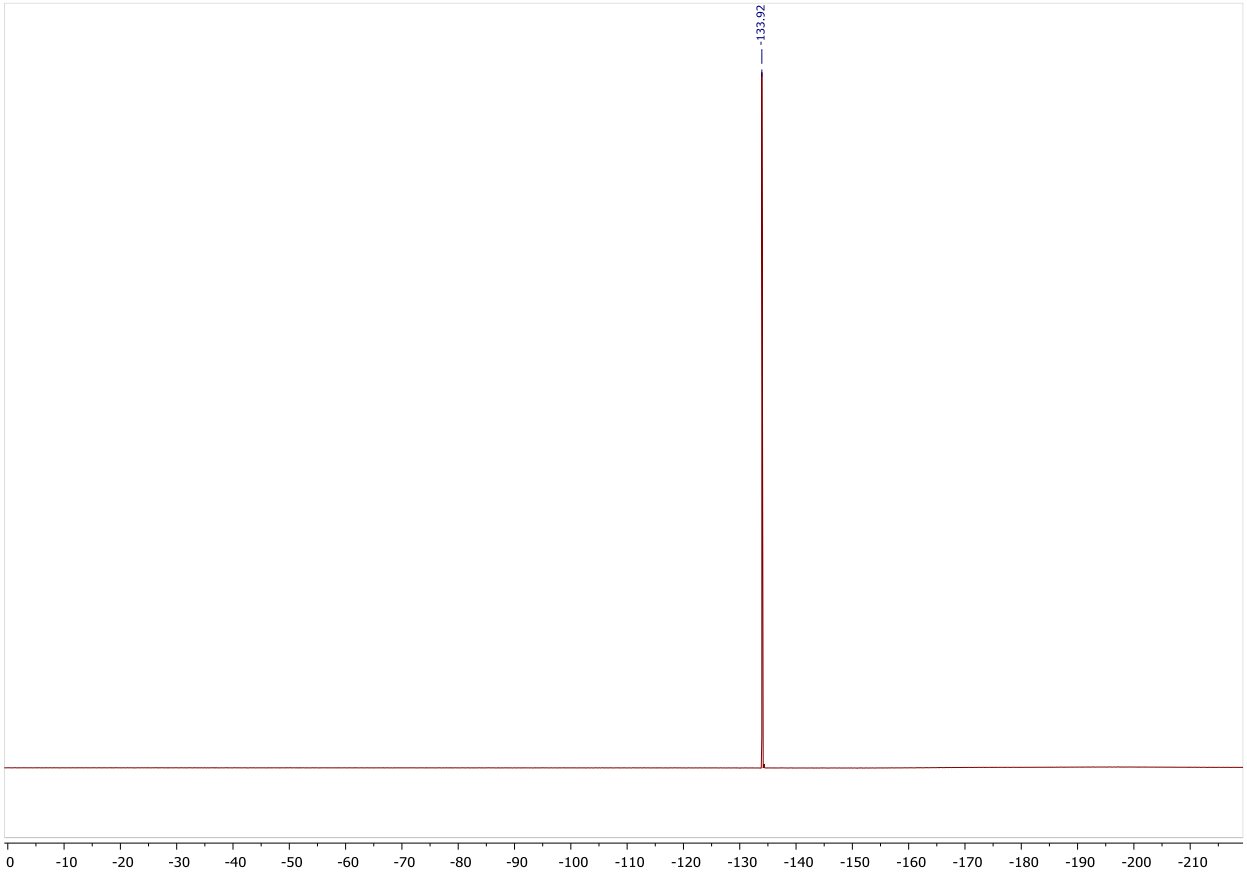




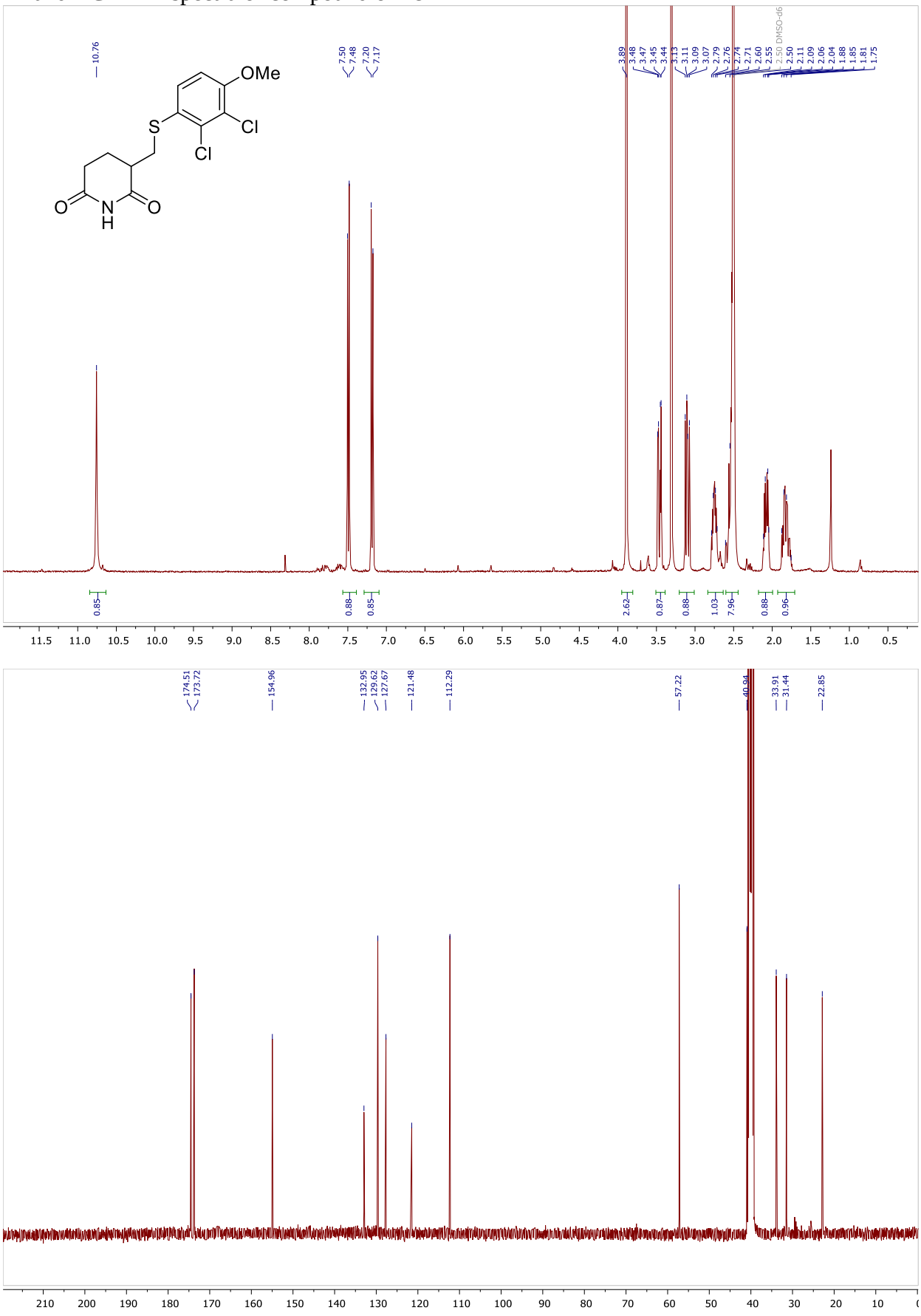
^{1}H, ^{13}C and ^{19}F NMR spectra of compound **1b**



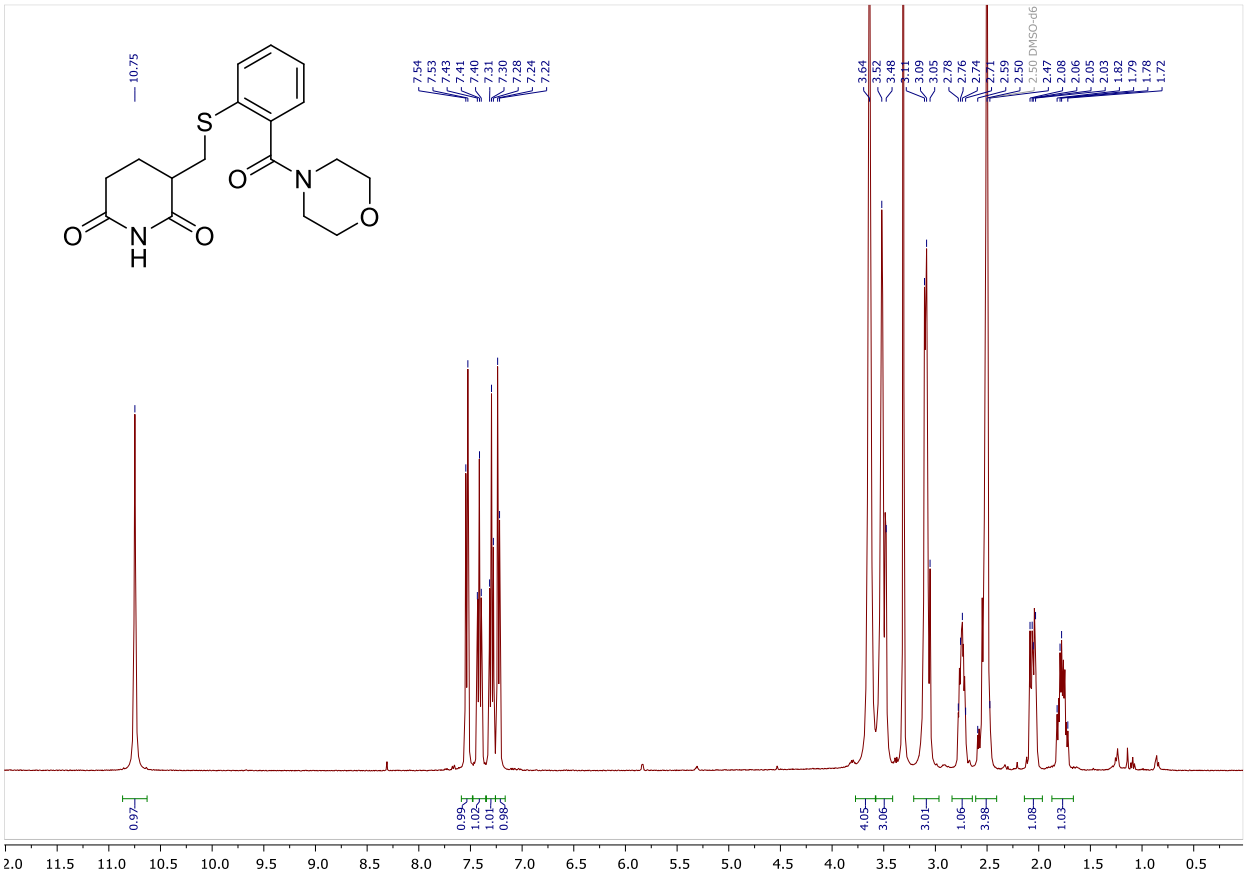


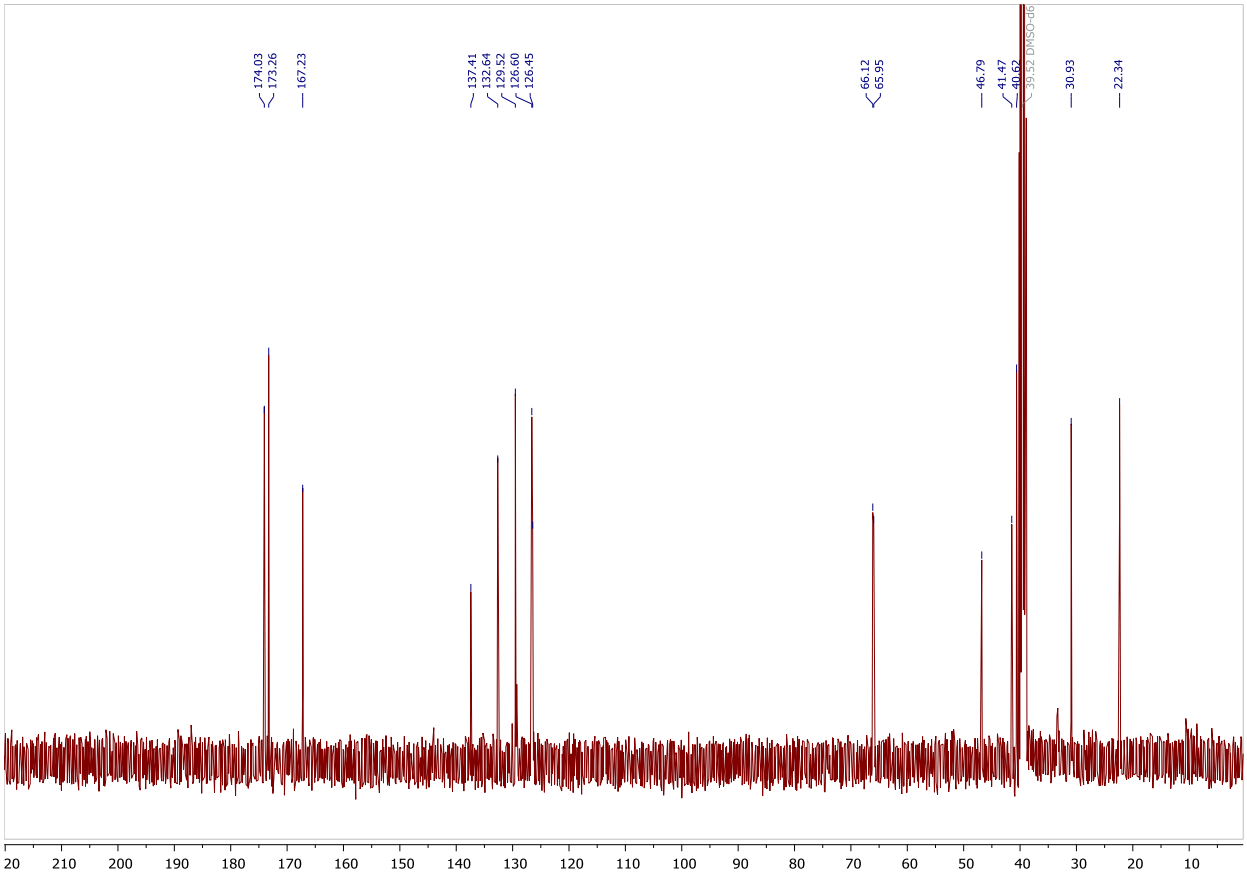

-133.92
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210

^{1}H and ^{13}C NMR spectra of compound of **1c**

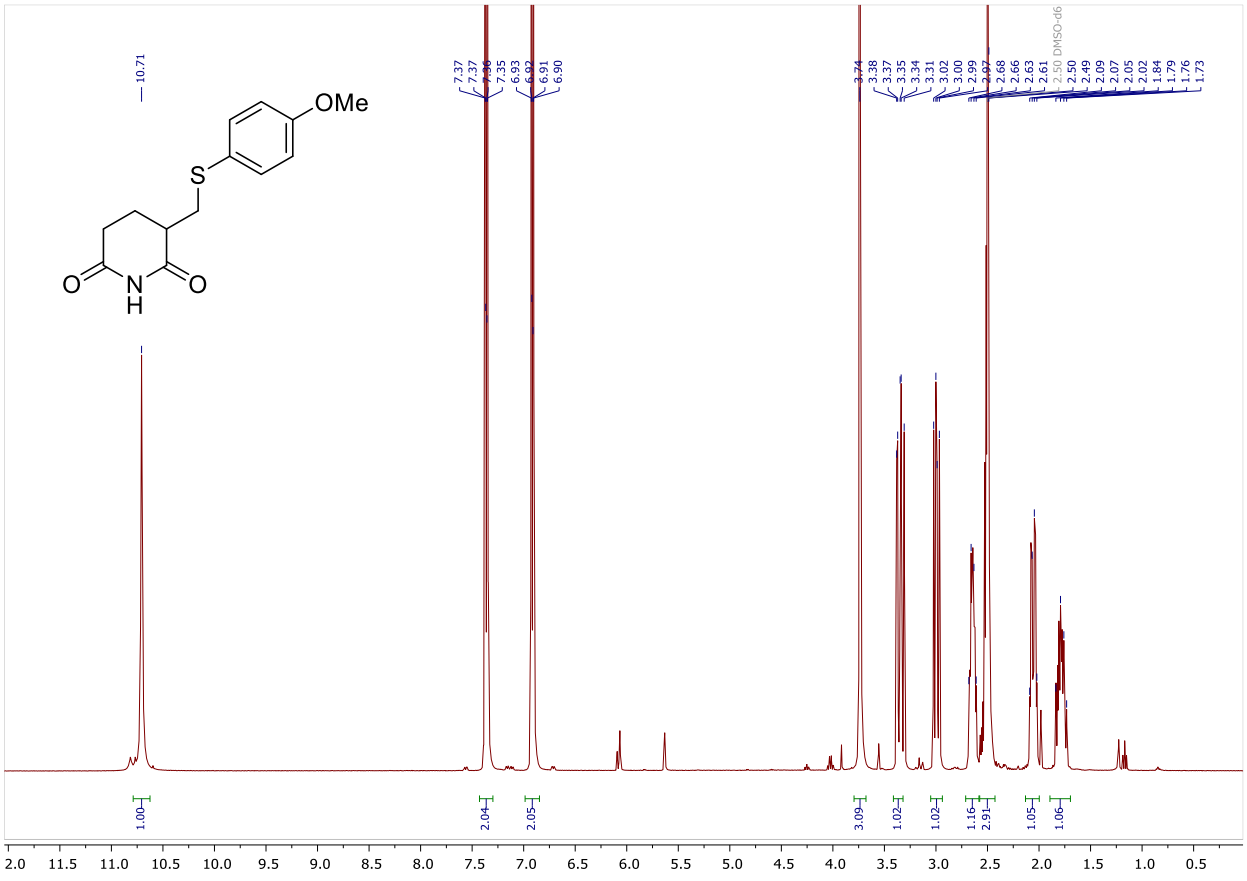


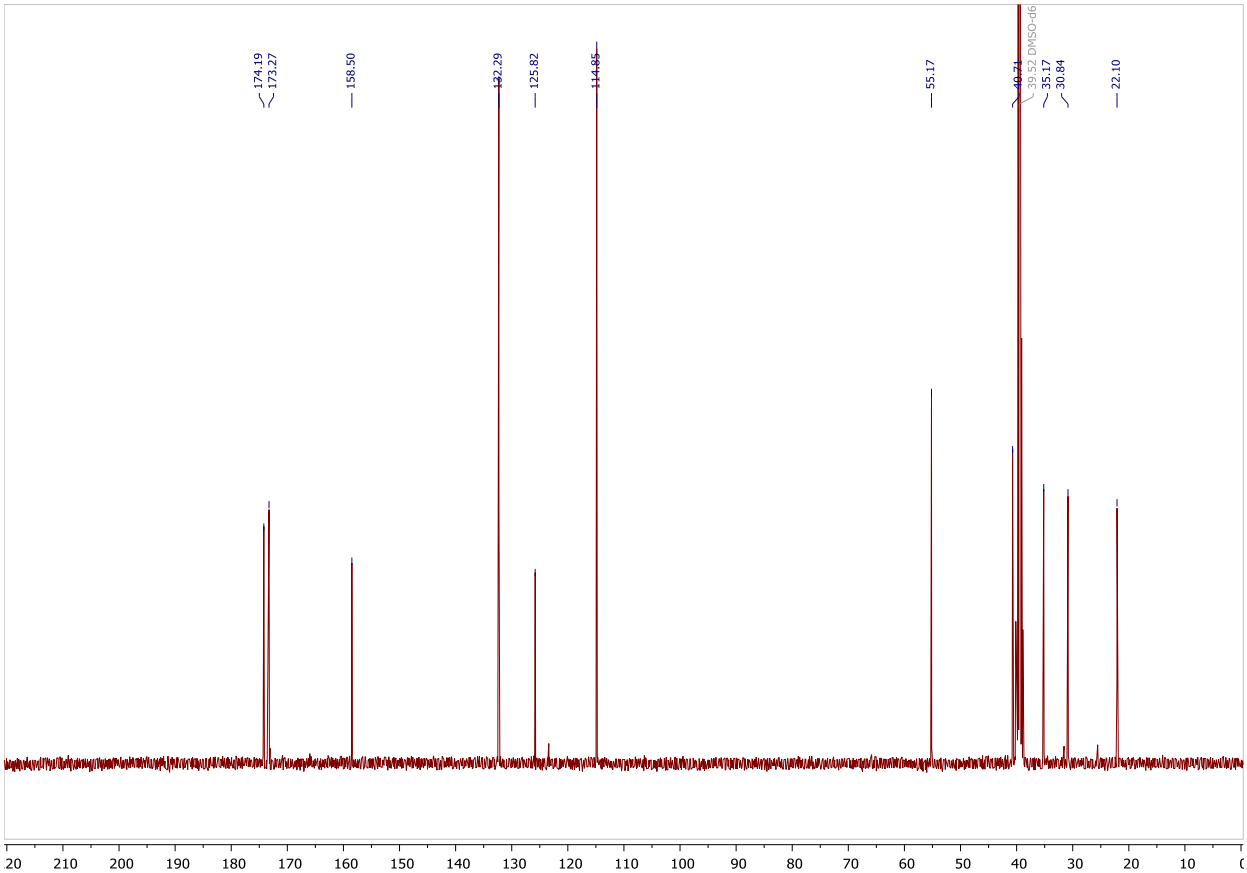
^{1}H and ^{13}C NMR spectra of compound of **1d**



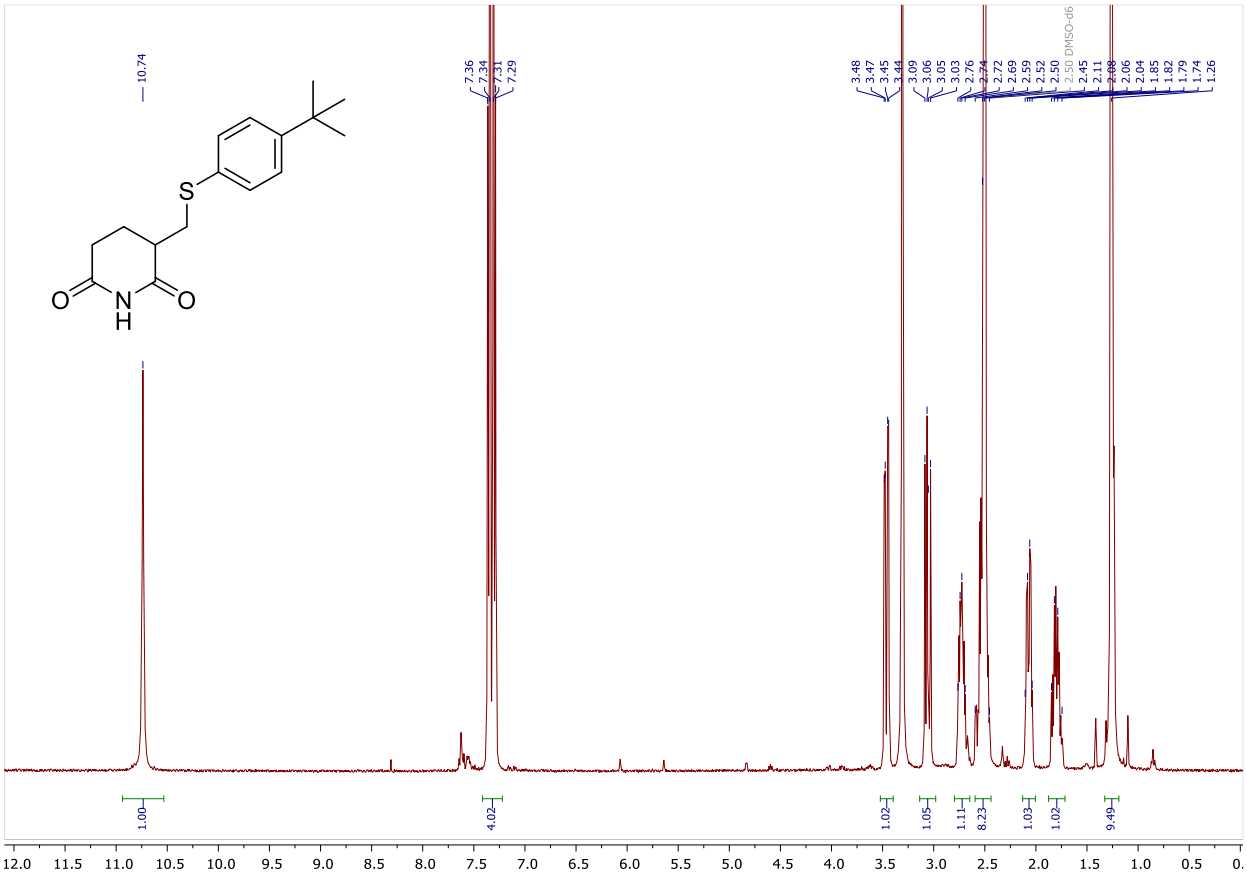


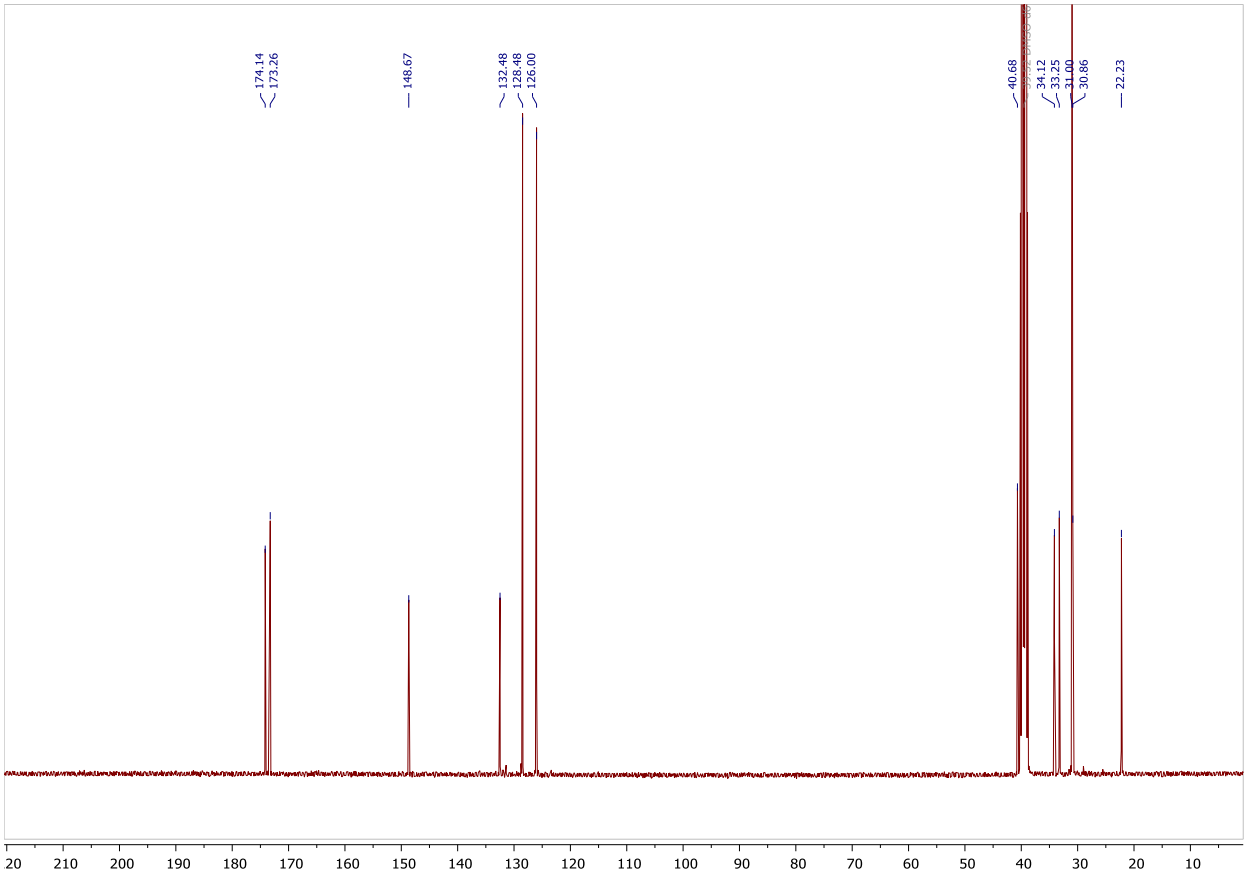
^{1}H and ^{13}C NMR spectra of compound of **1e**



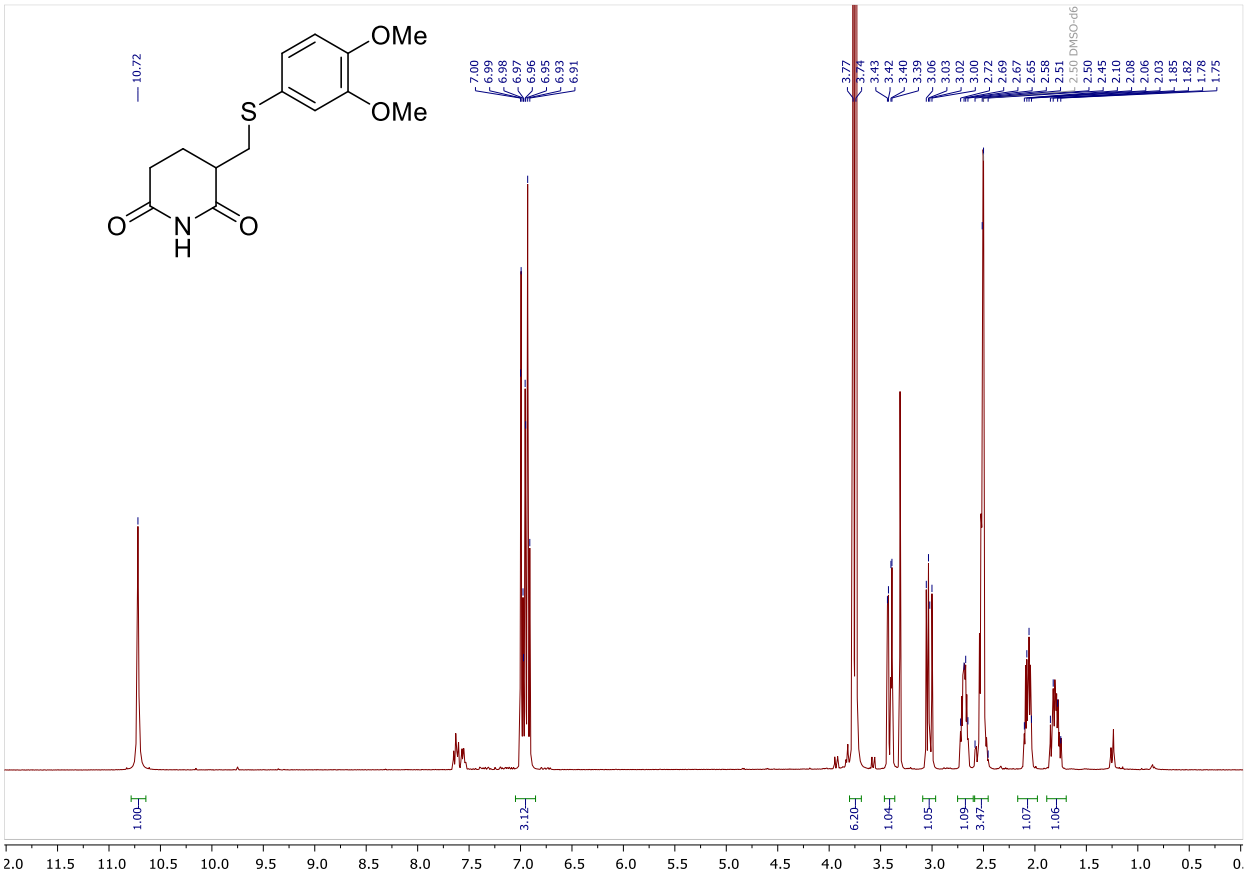


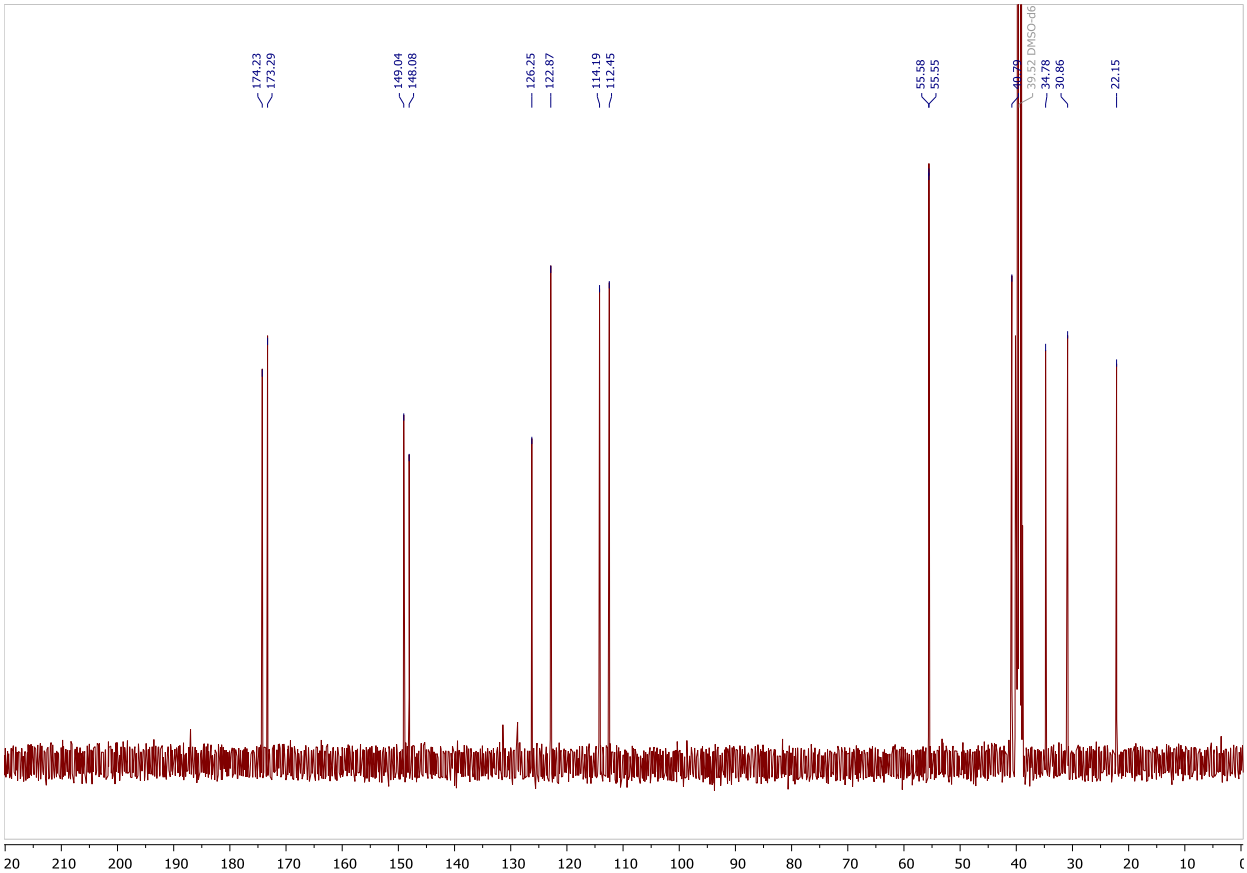
^{1}H and ^{13}C NMR spectra of compound of **1f**



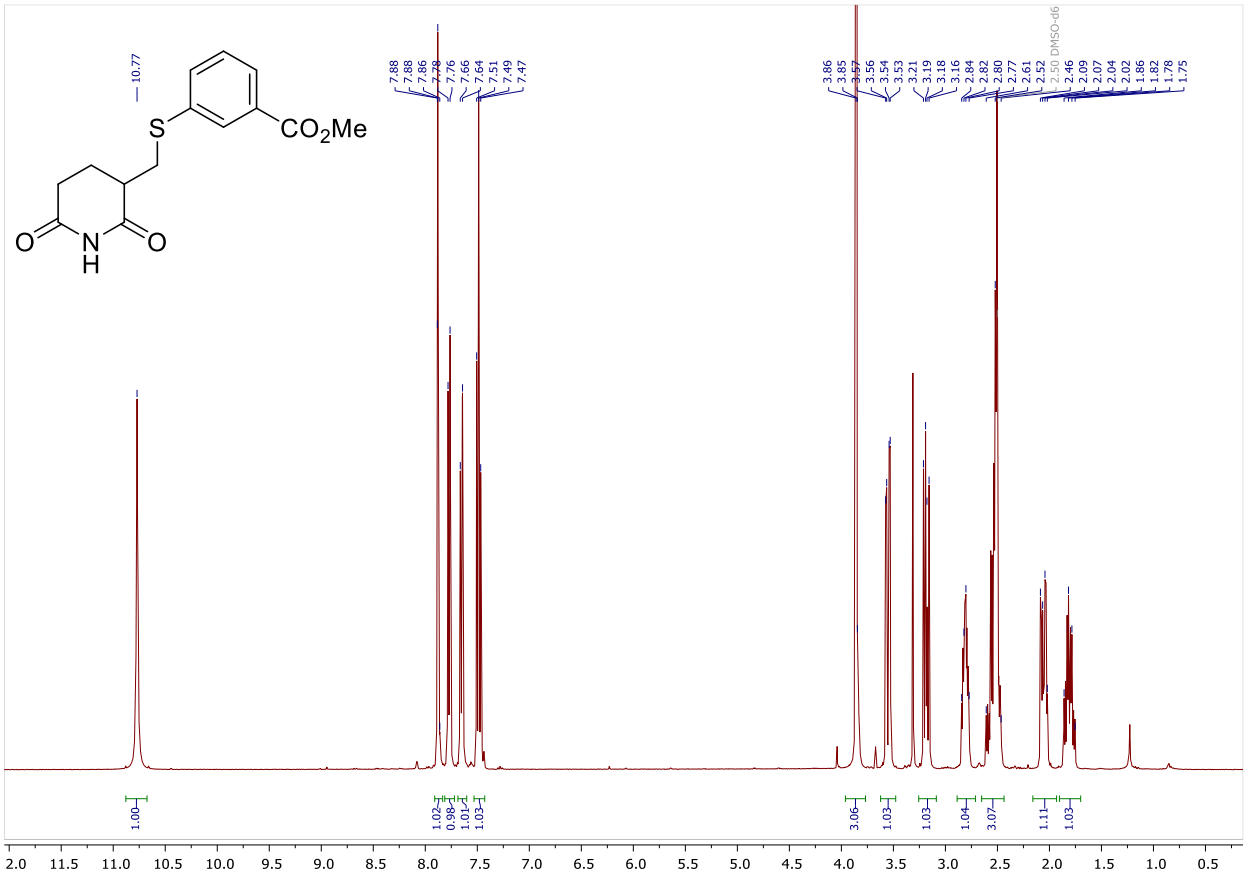


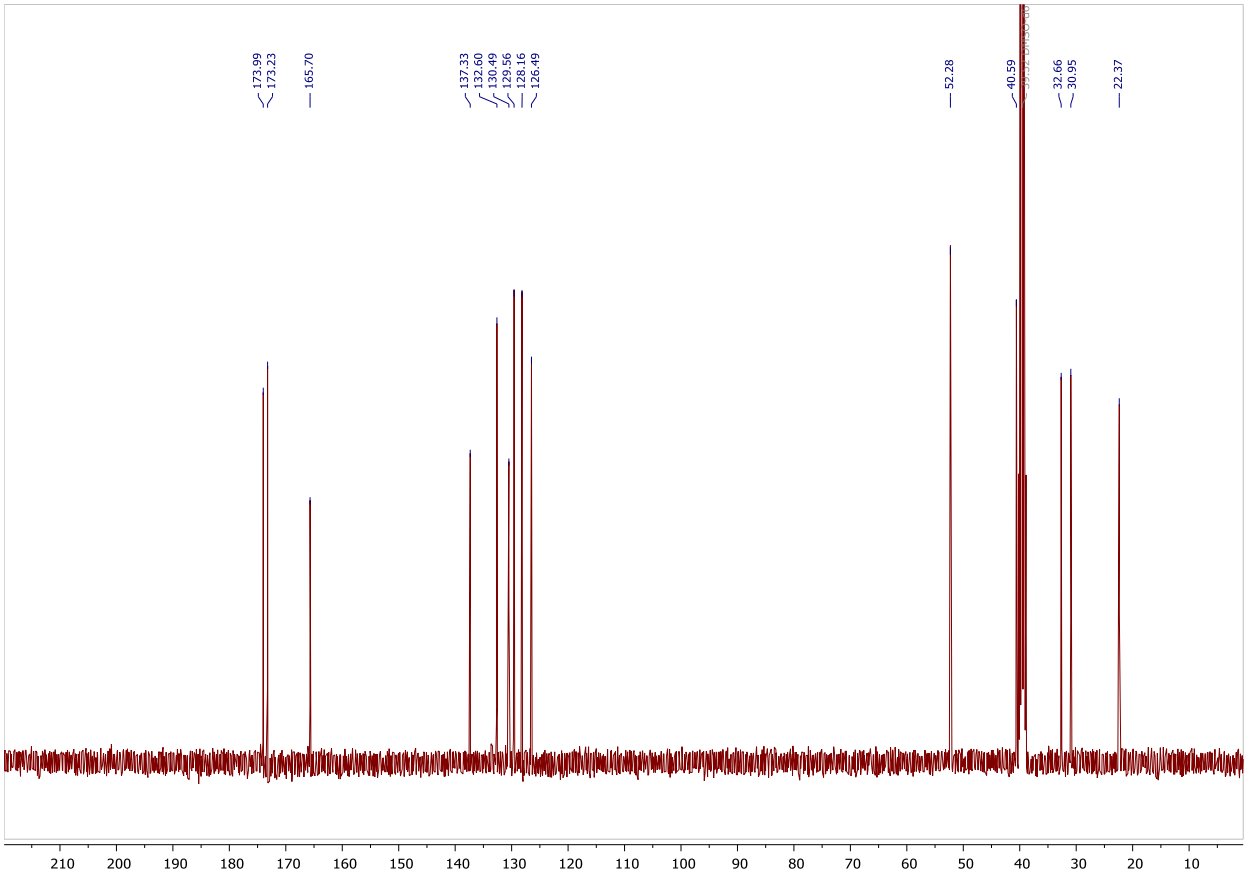
^{1}H and ^{13}C NMR spectra of compound of **1g**



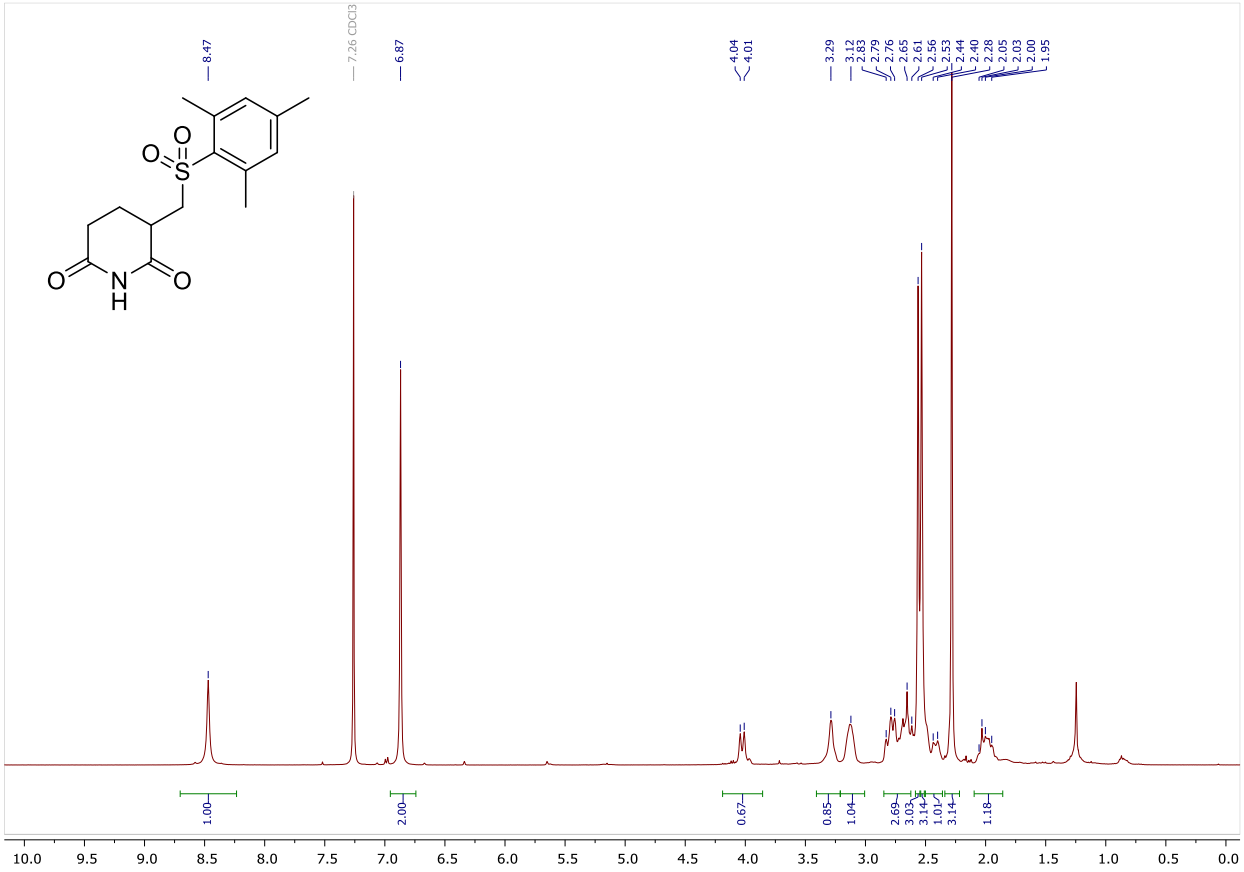


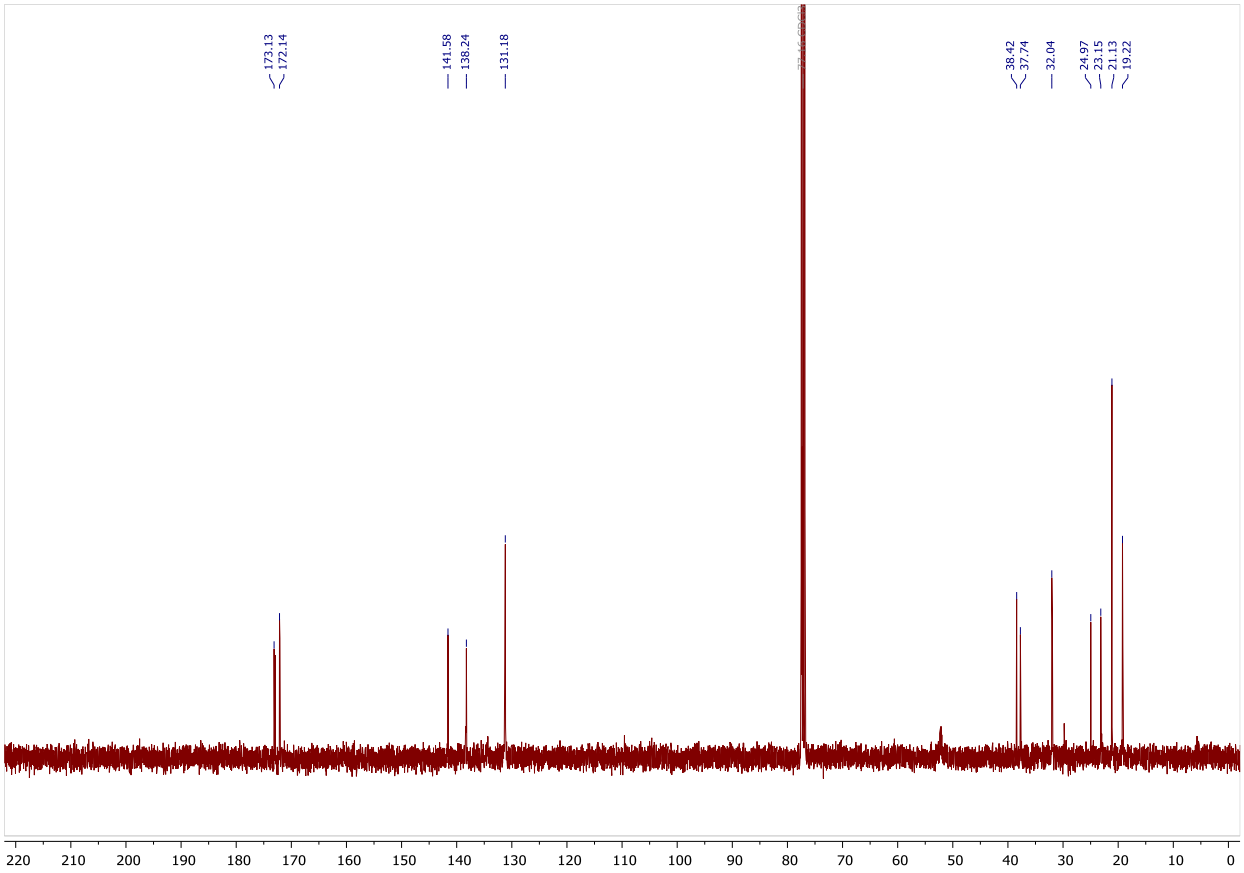
^{1}H and ^{13}C NMR spectra of compound of **1h**



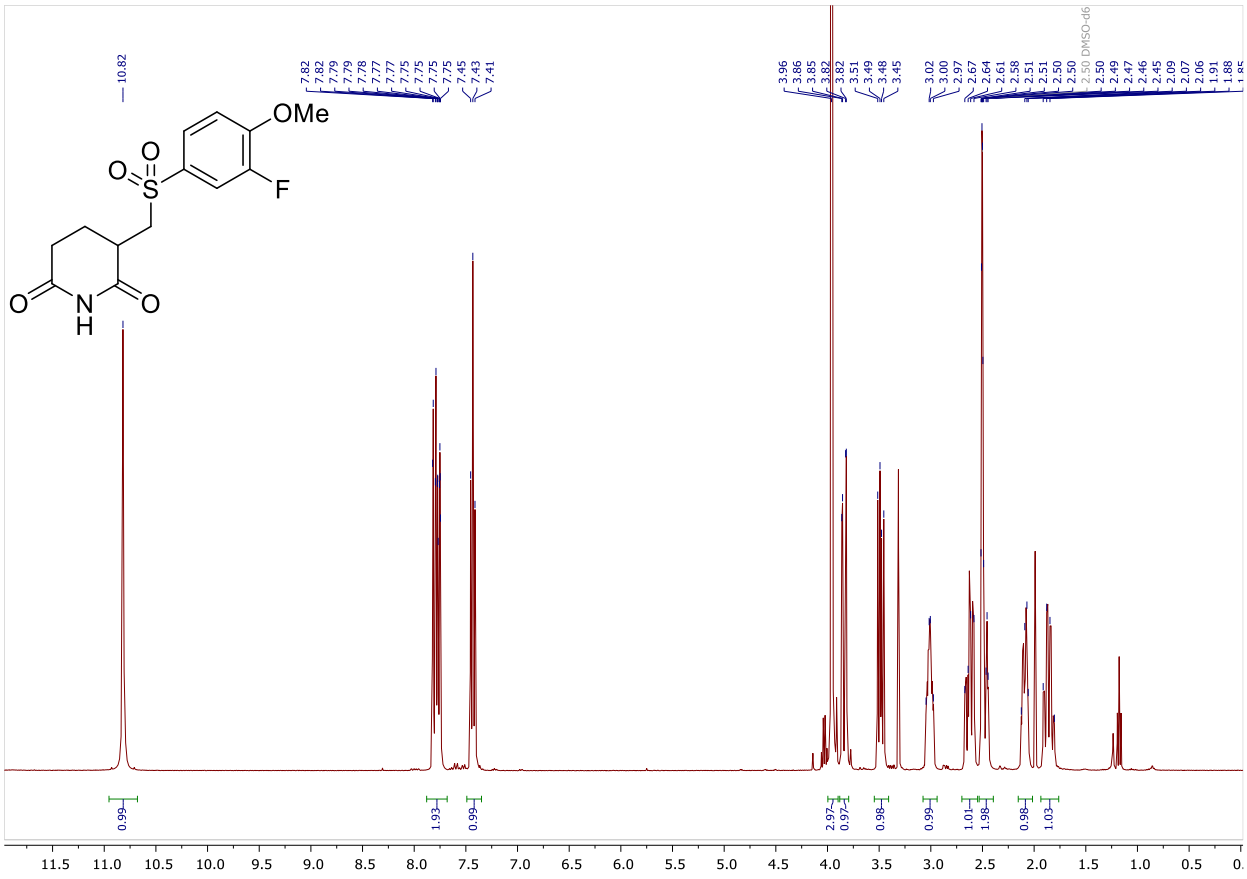


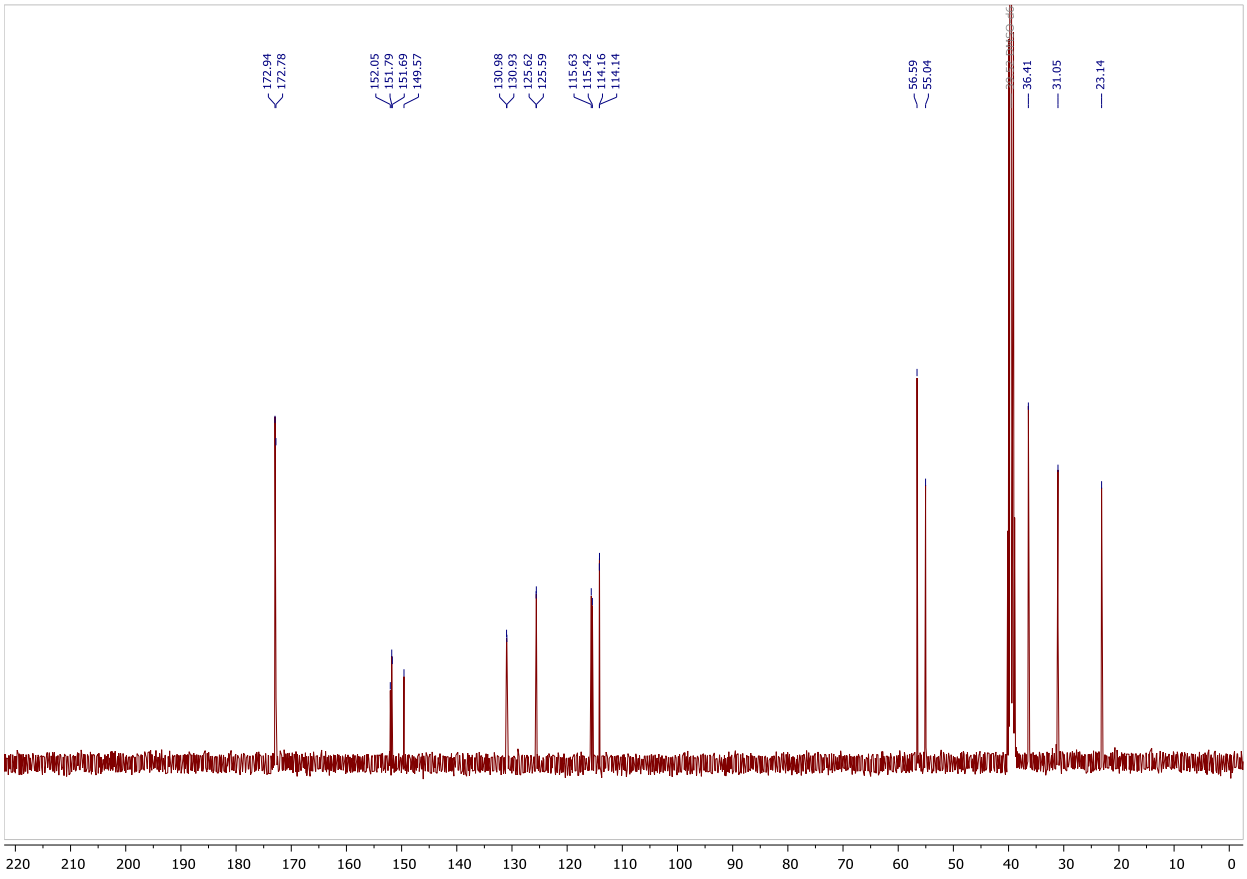
^{1}H and ^{13}C NMR spectra of compound of **2a**

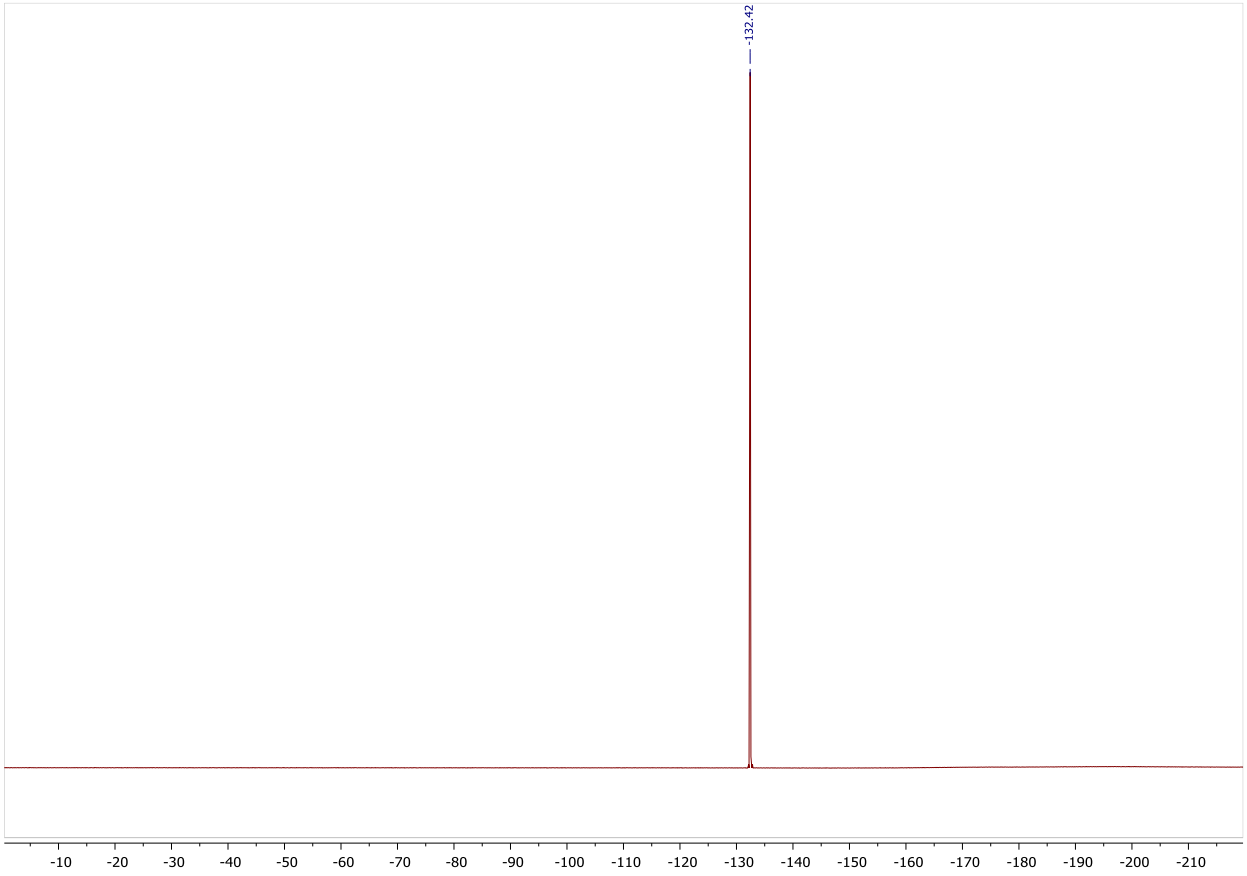




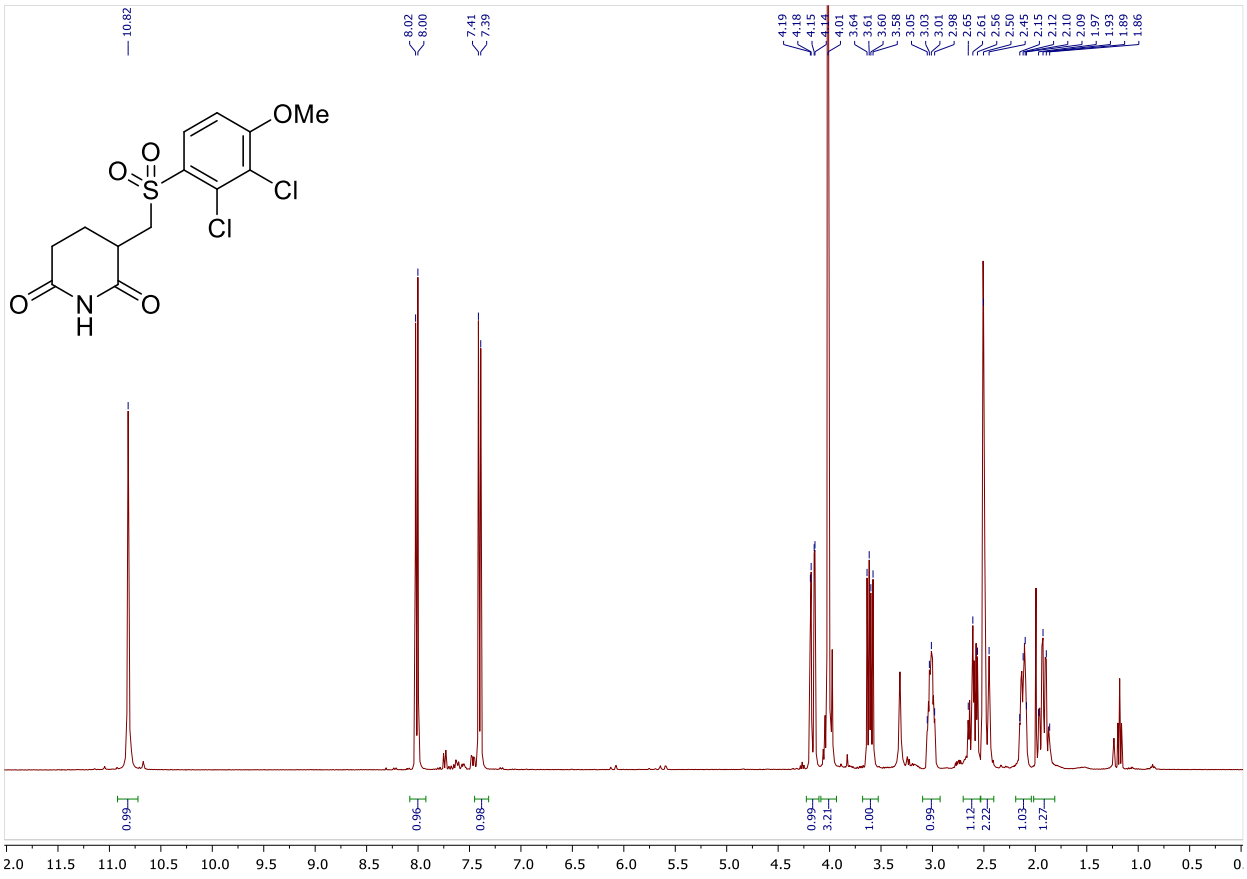
^{1}H, ^{13}C and ^{19}F NMR spectra of compound **2b**

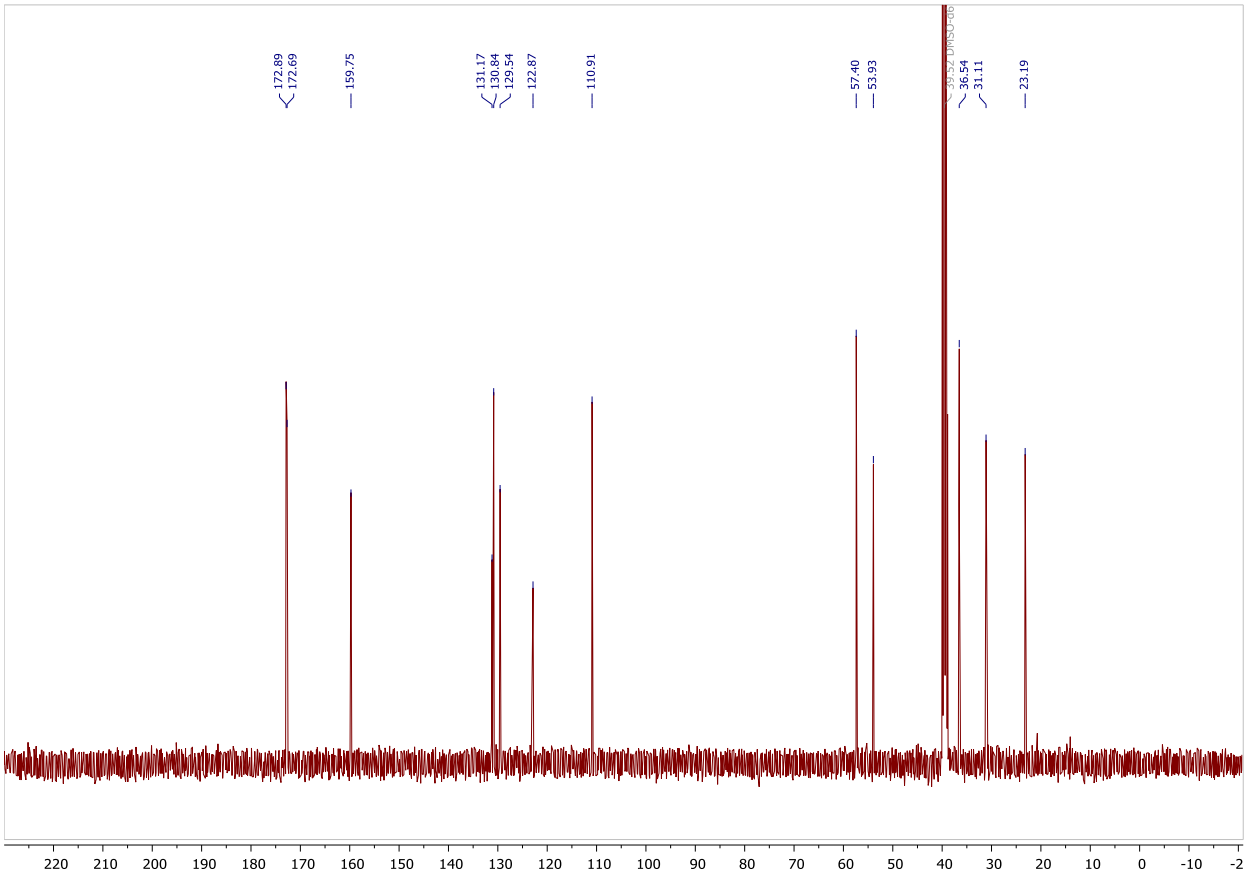




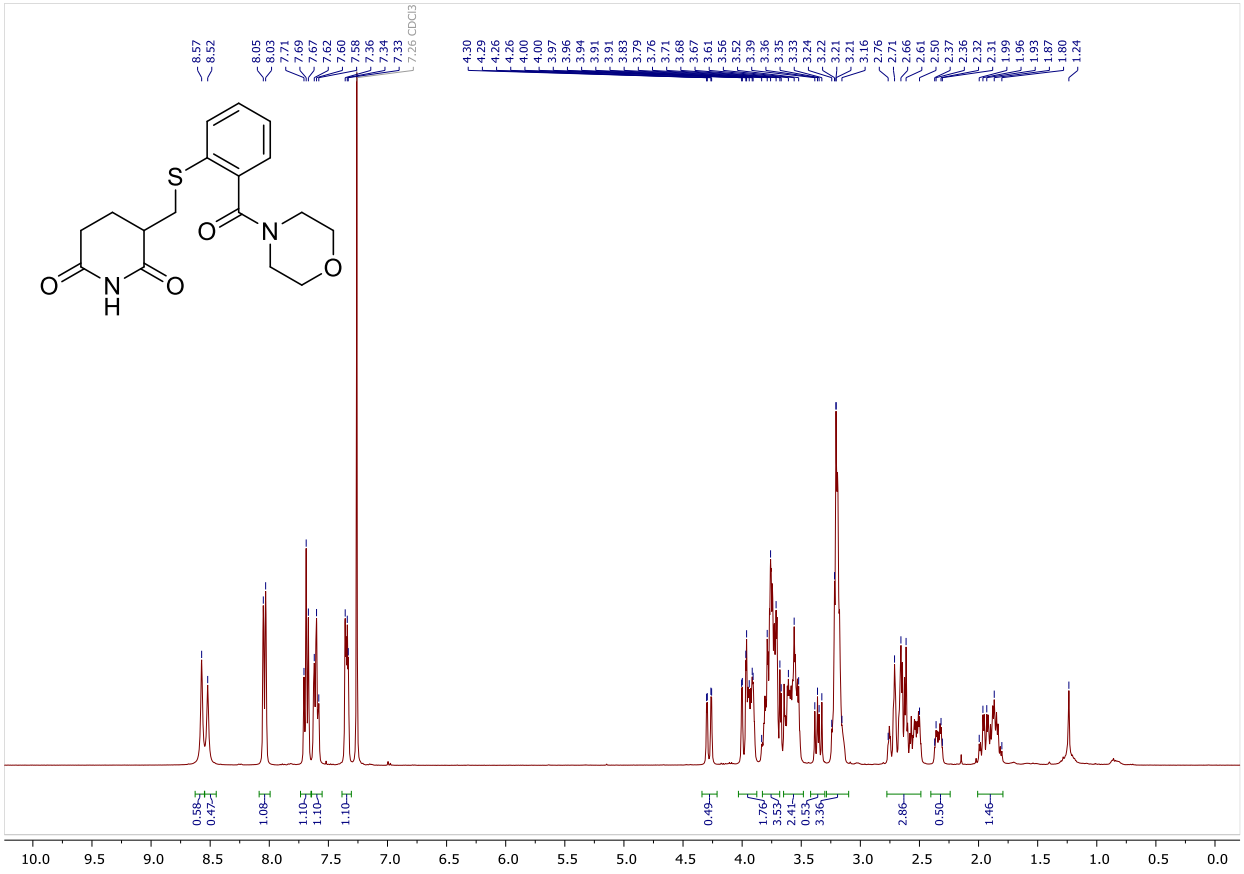

-132.42
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210

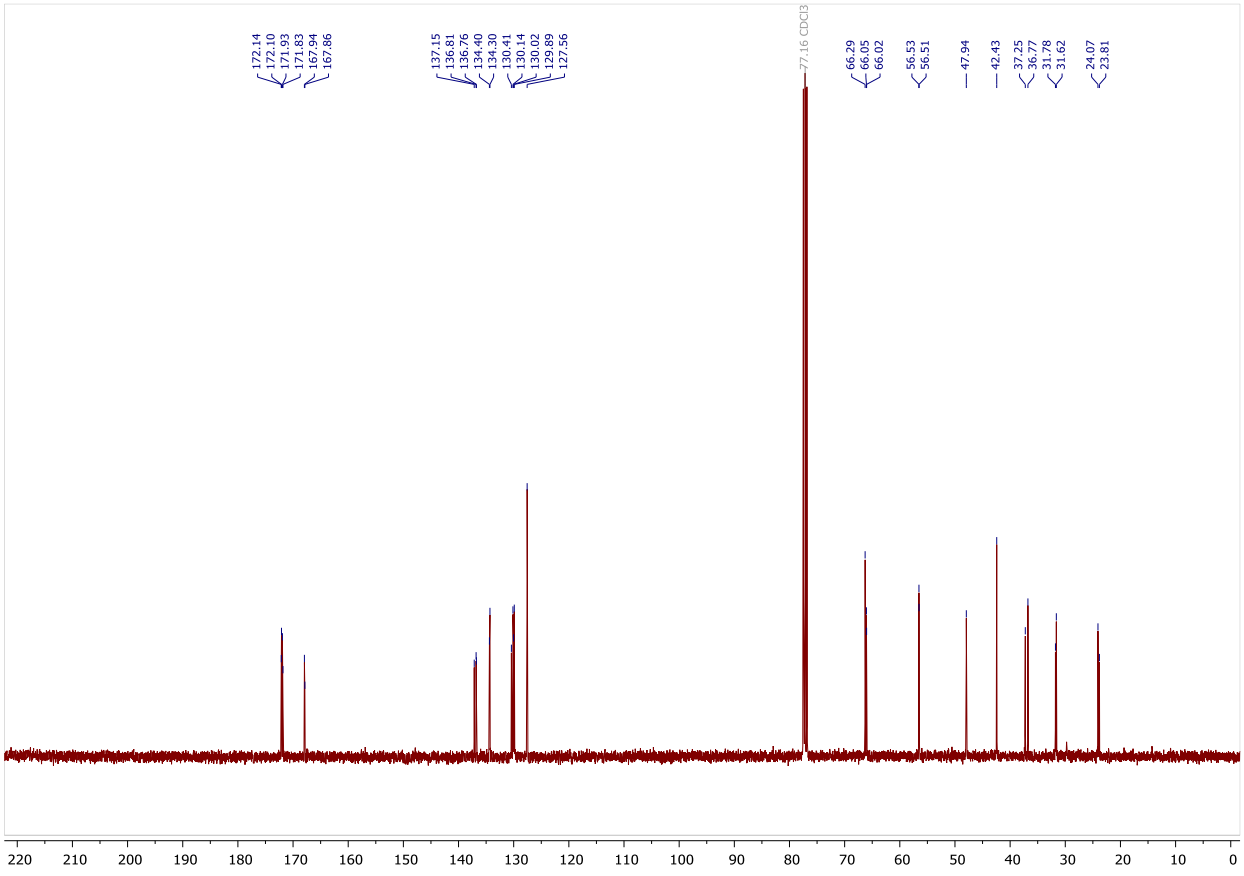
^{1}H and ^{13}C NMR spectra of compound of **2c**



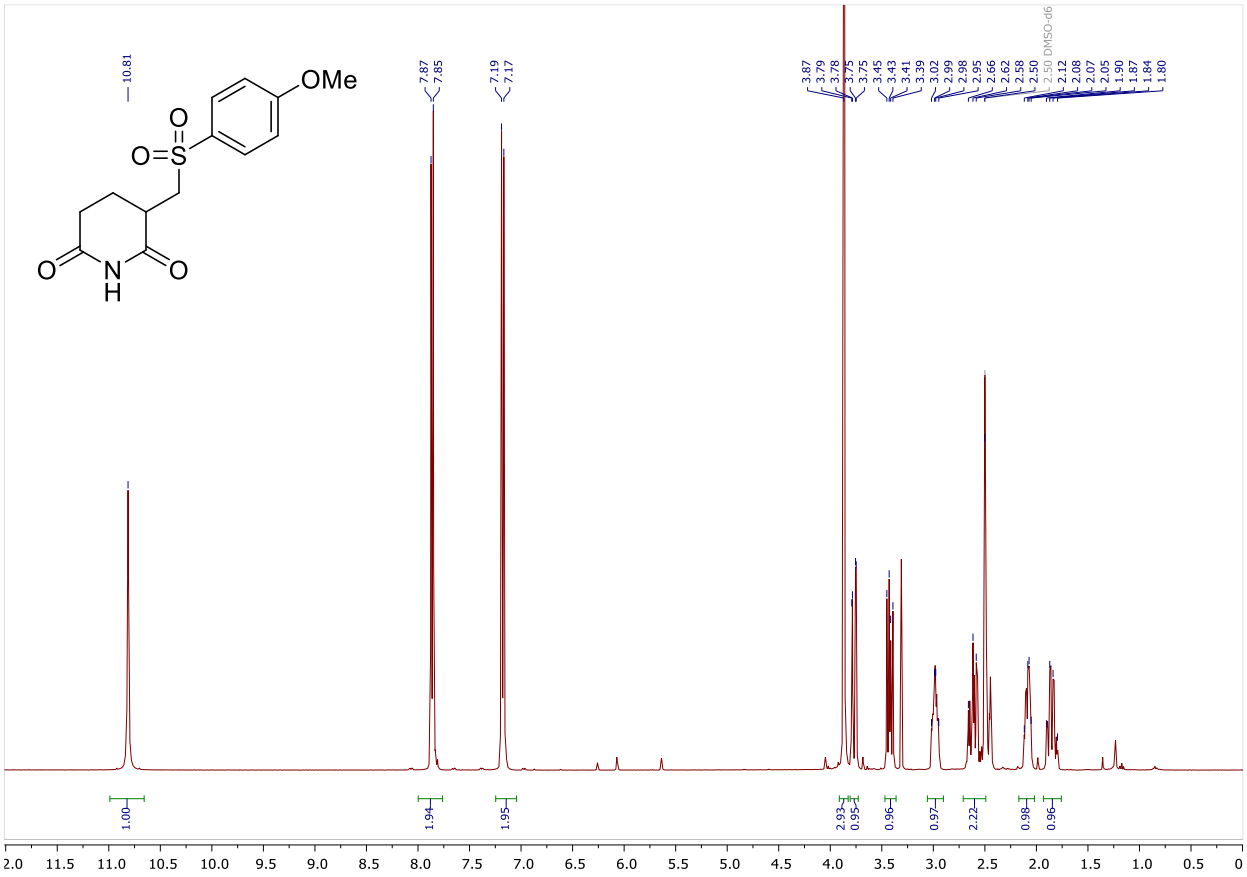


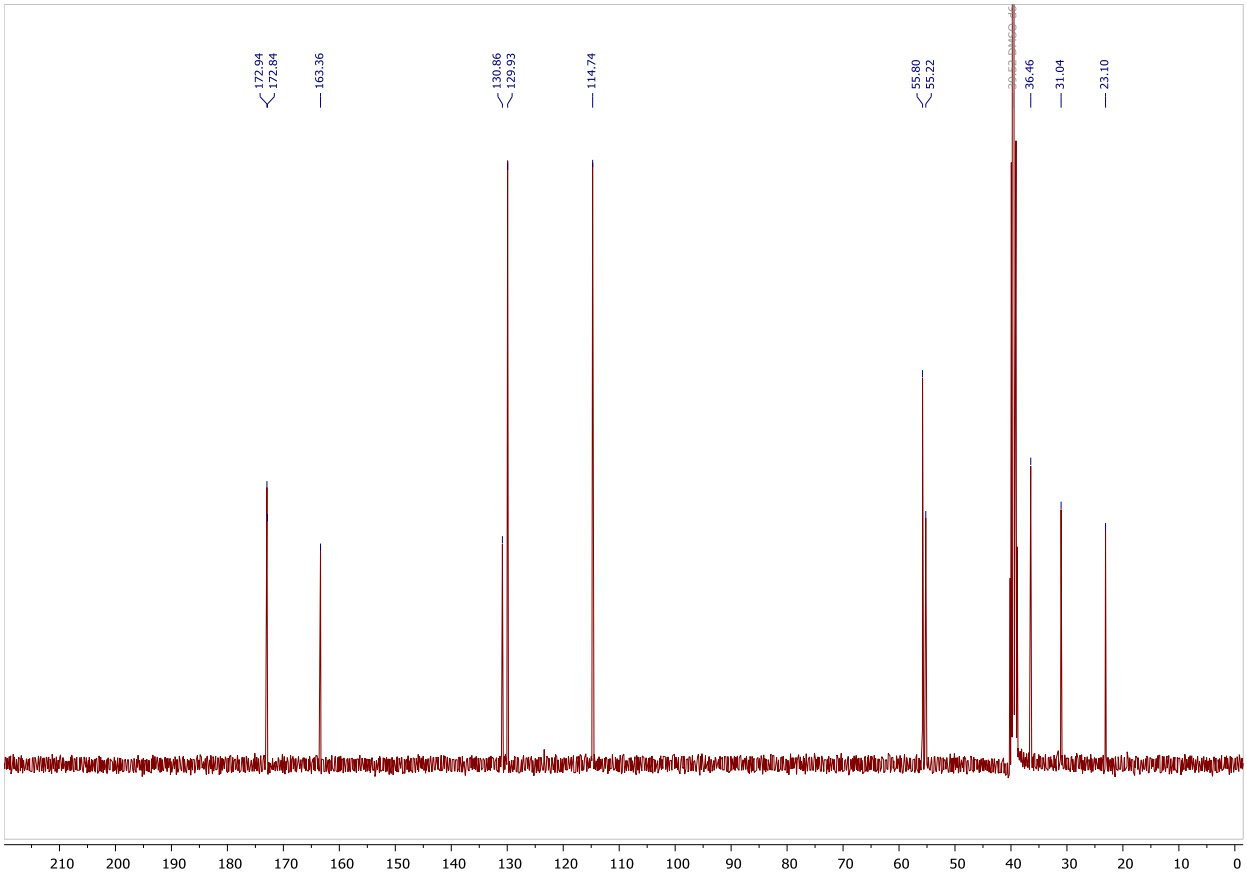
^{1}H and ^{13}C NMR spectra of compound of **2d**



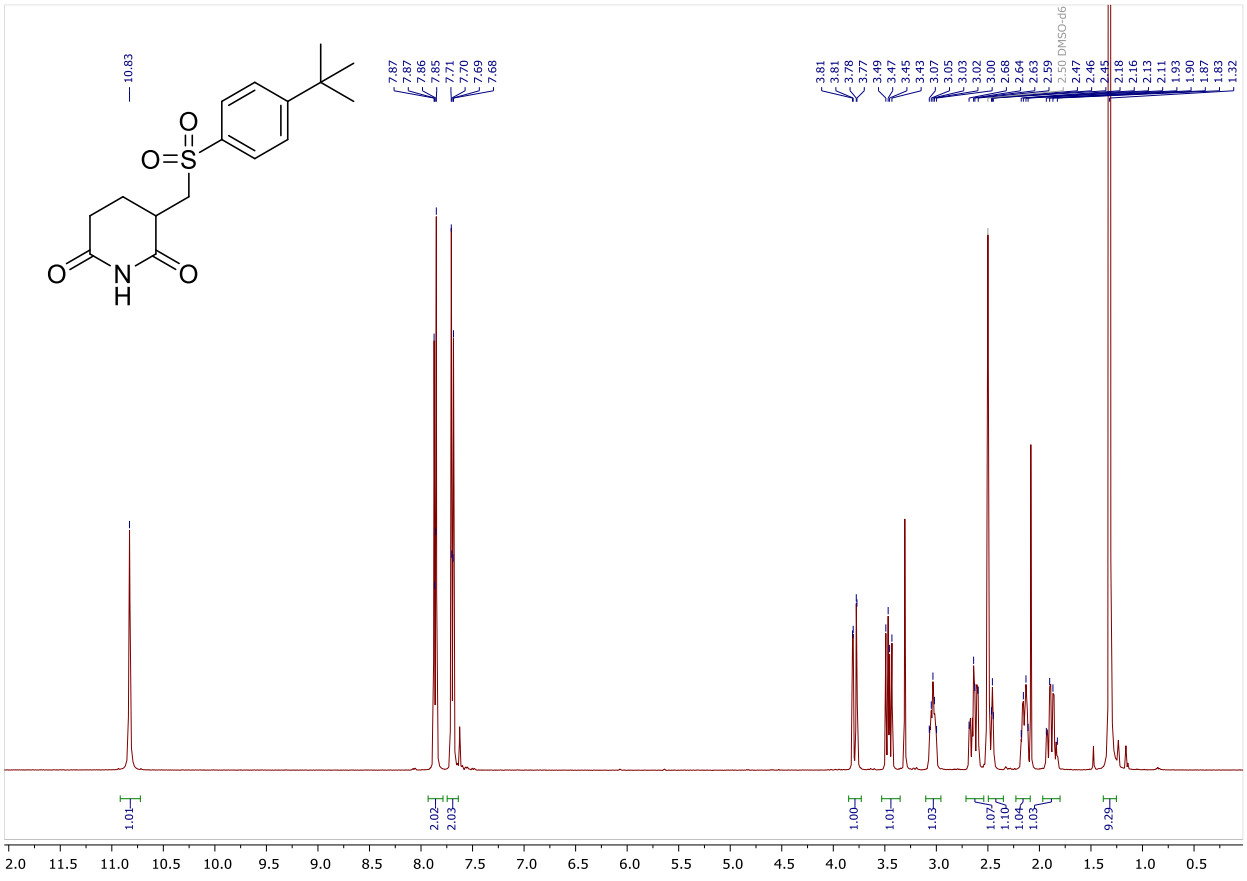


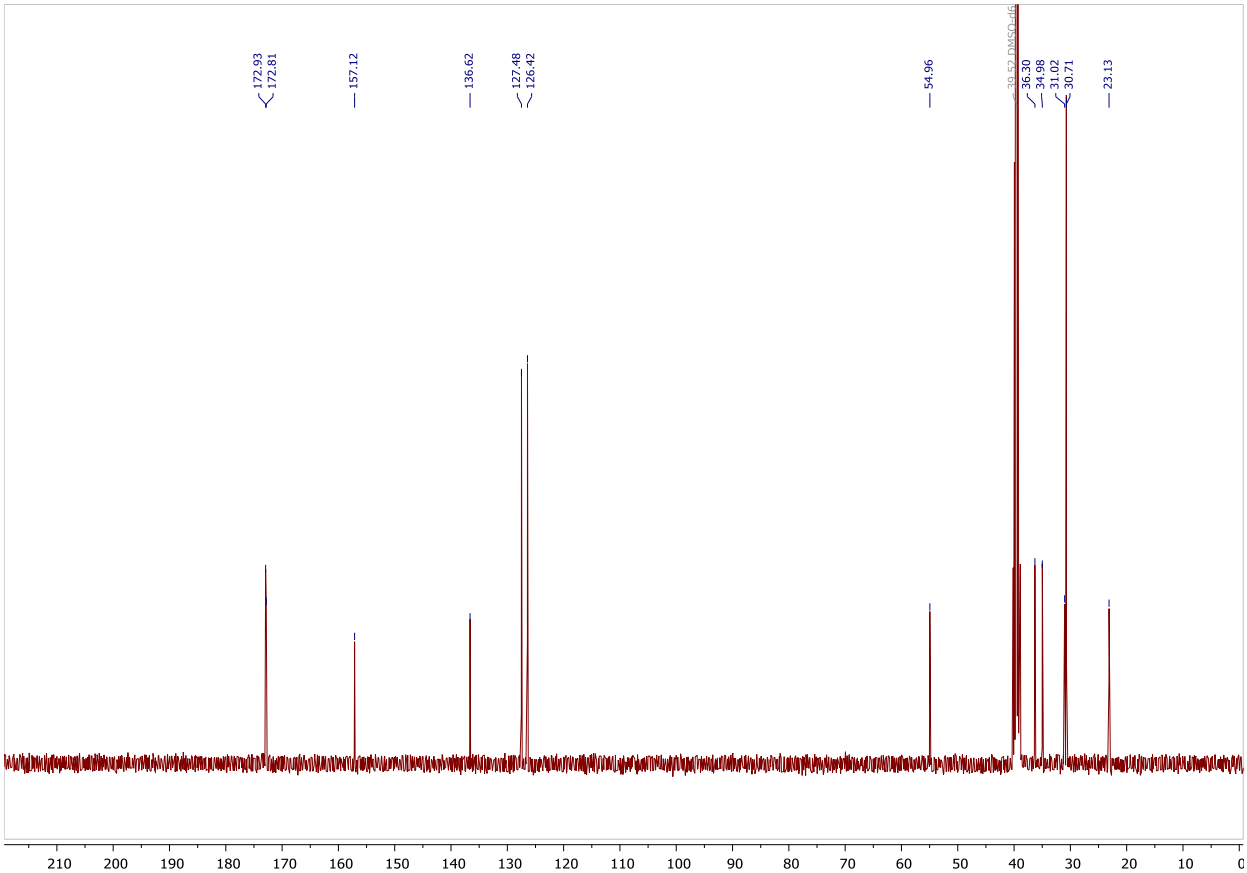
^{1}H and ^{13}C NMR spectra of compound of **2e**



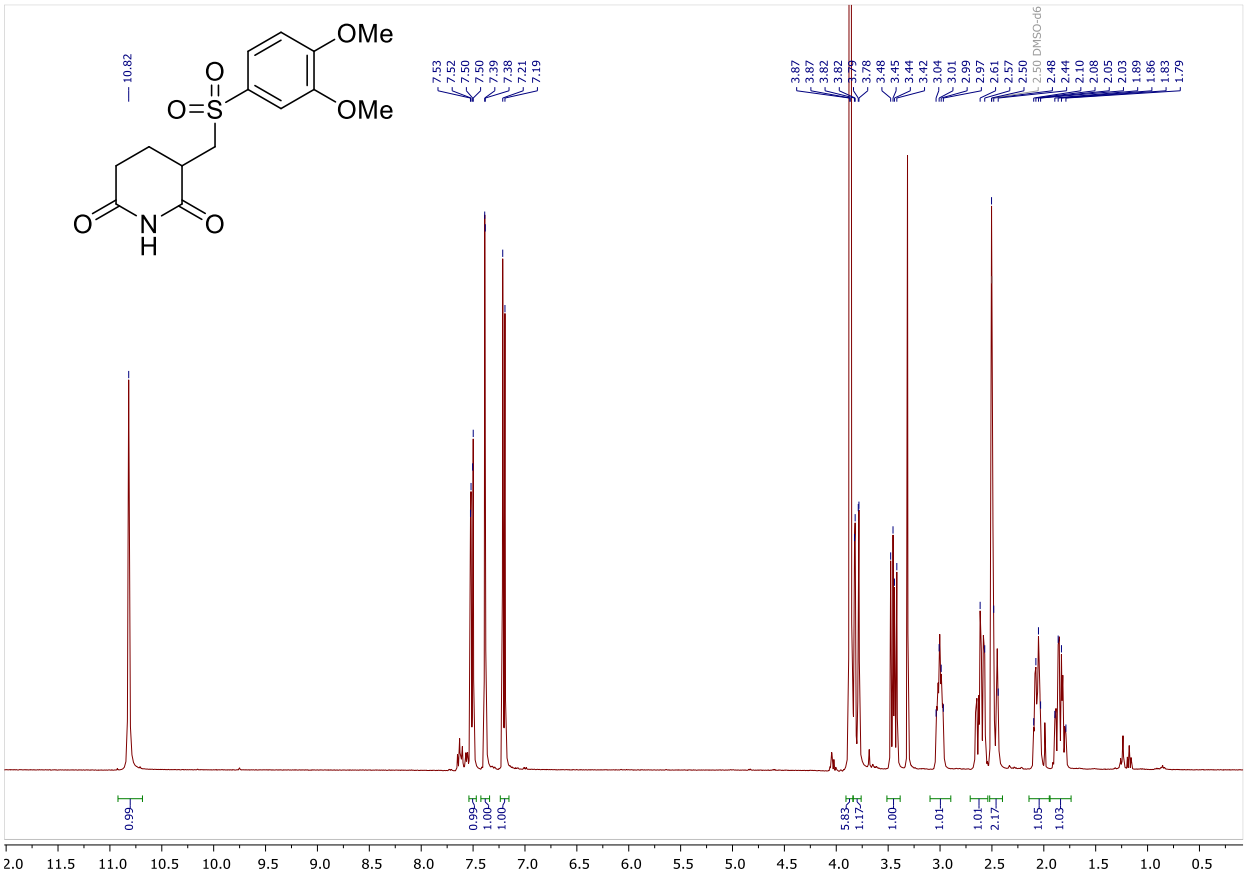


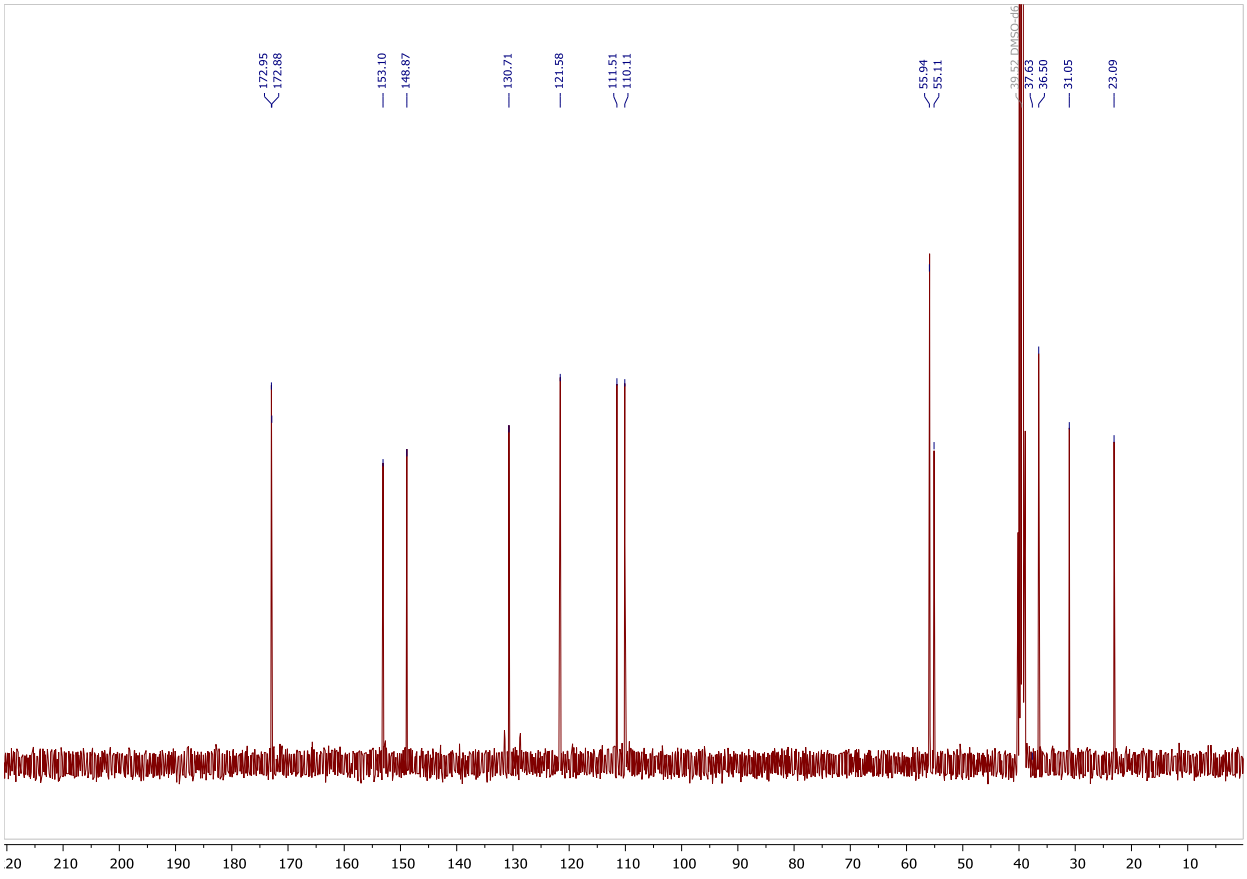
^{1}H and ^{13}C NMR spectra of compound of **2f**



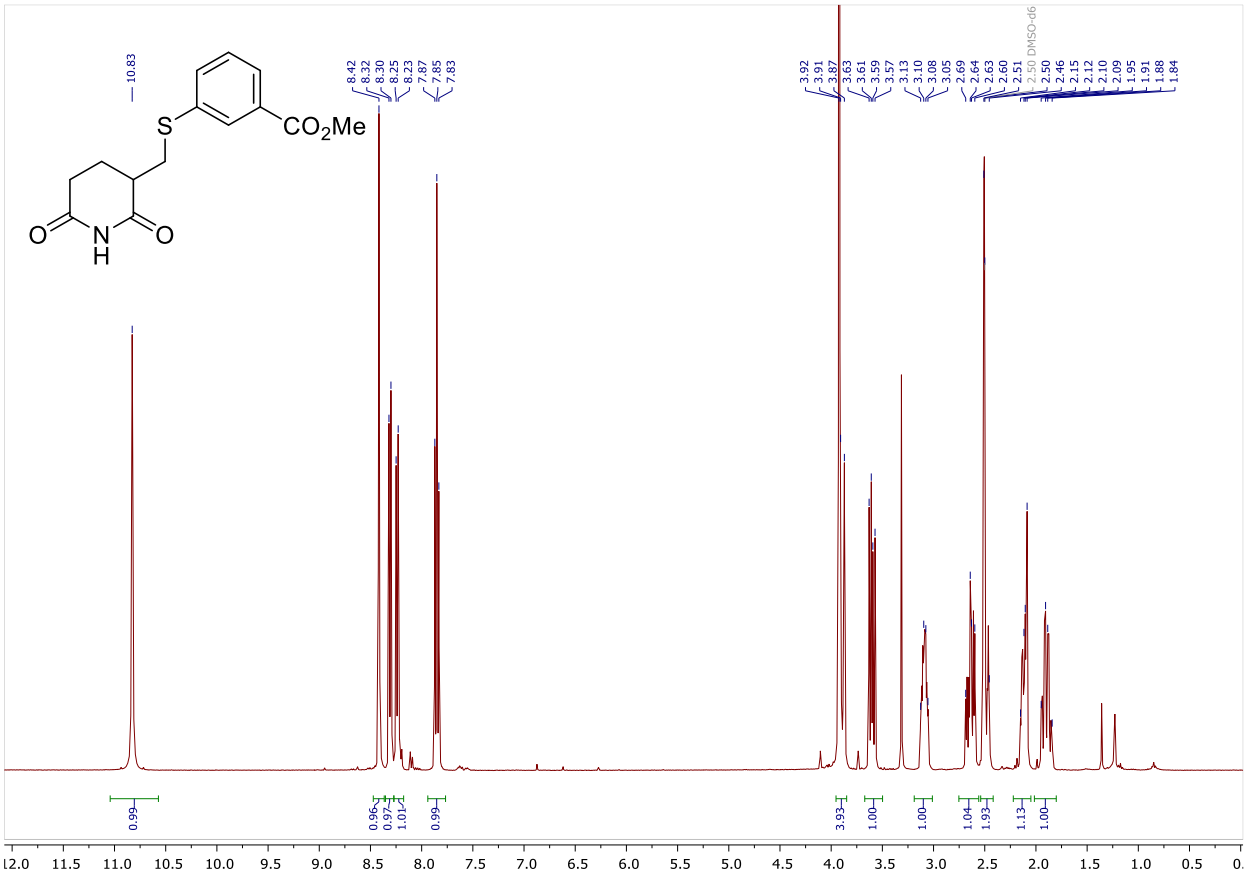


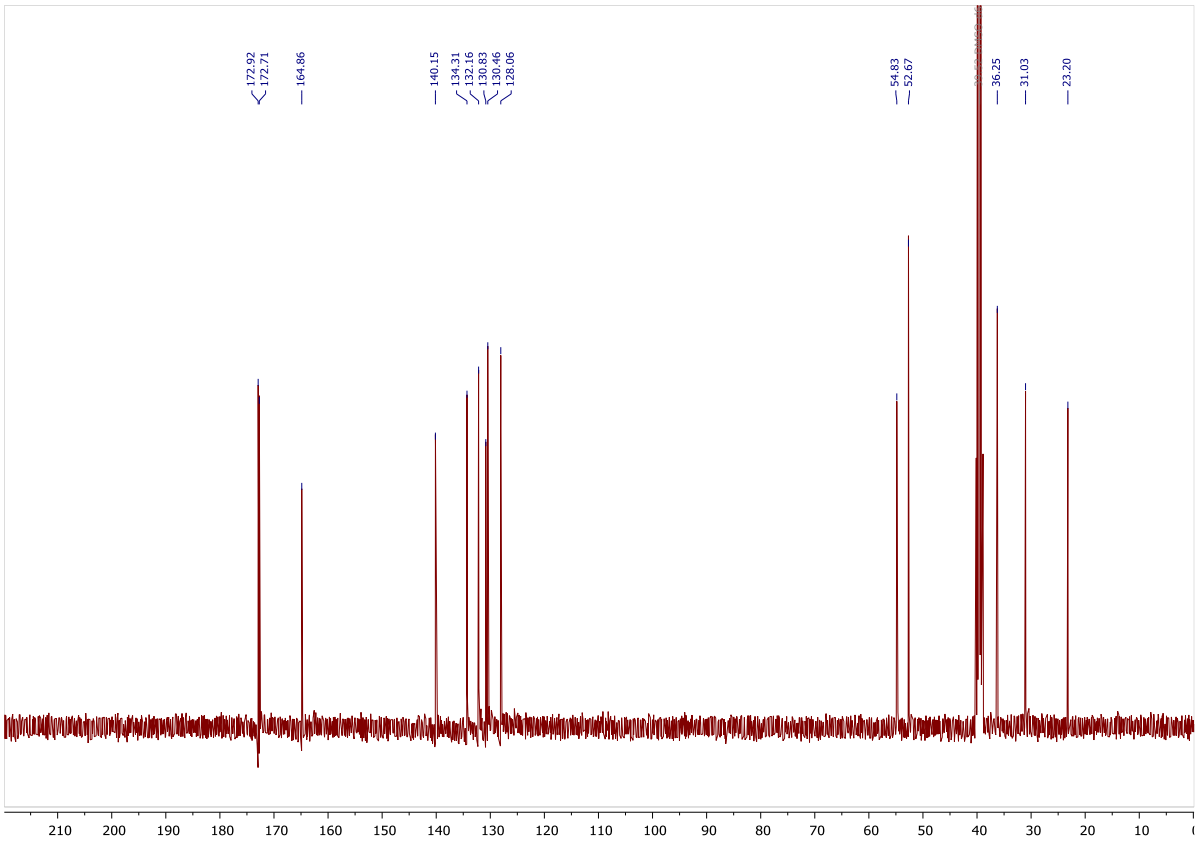
^{1}H and ^{13}C NMR spectra of compound of **2g**



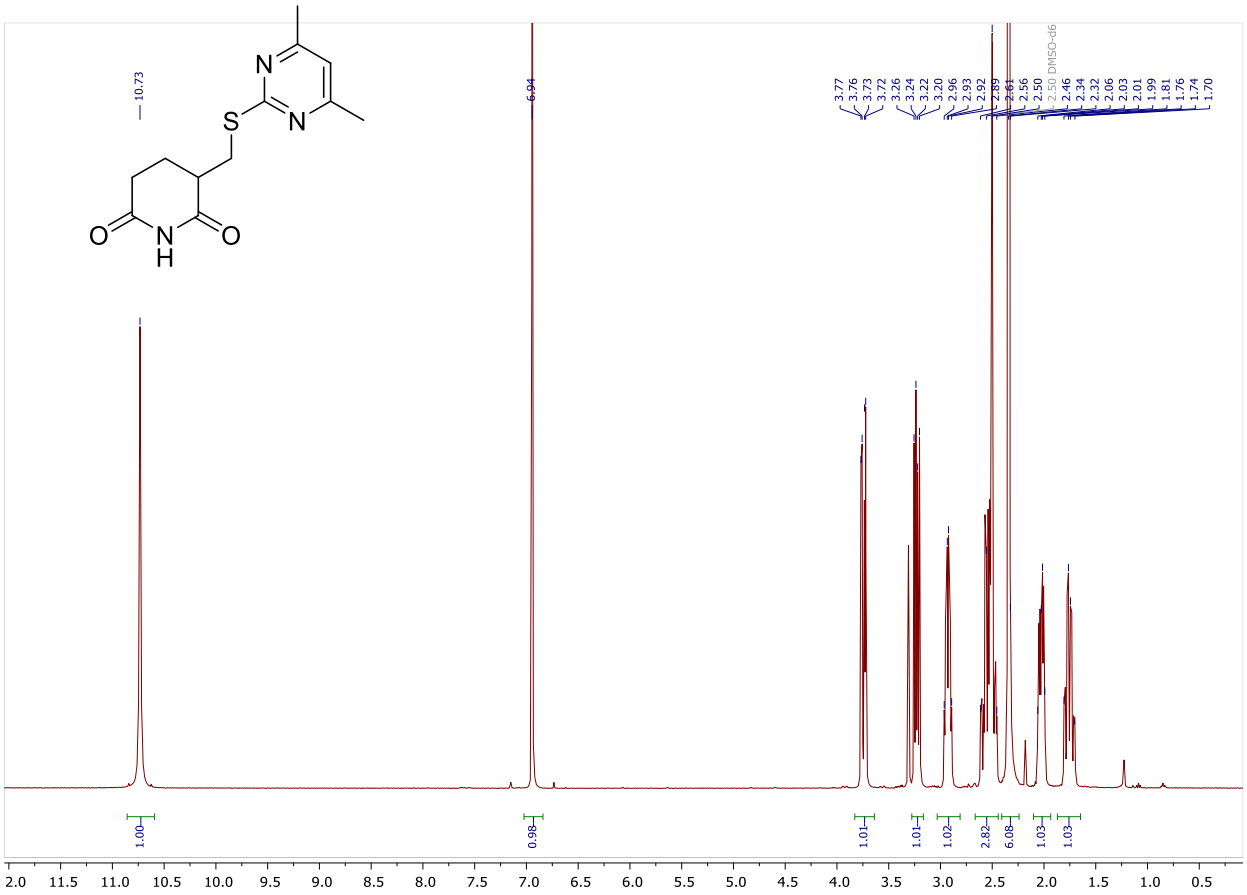


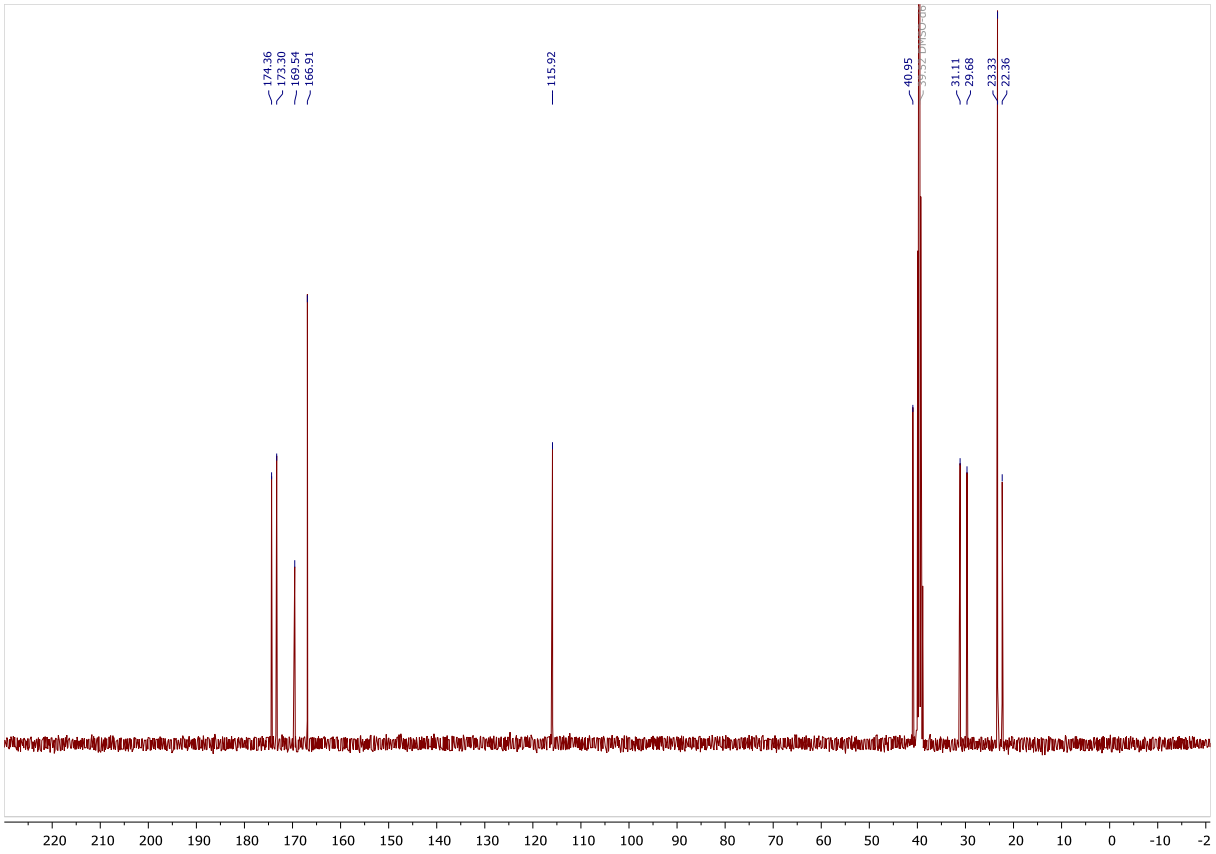
^{1}H and ^{13}C NMR spectra of compound of **1h**



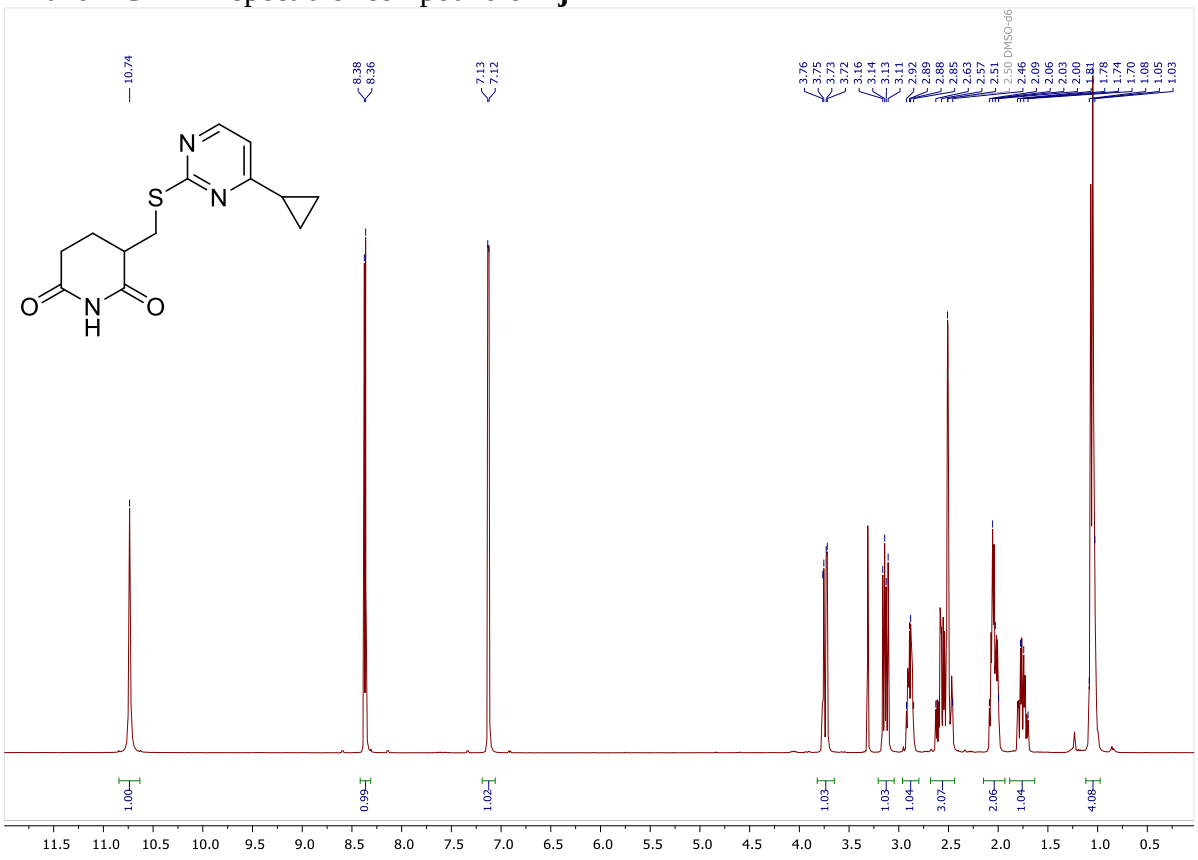


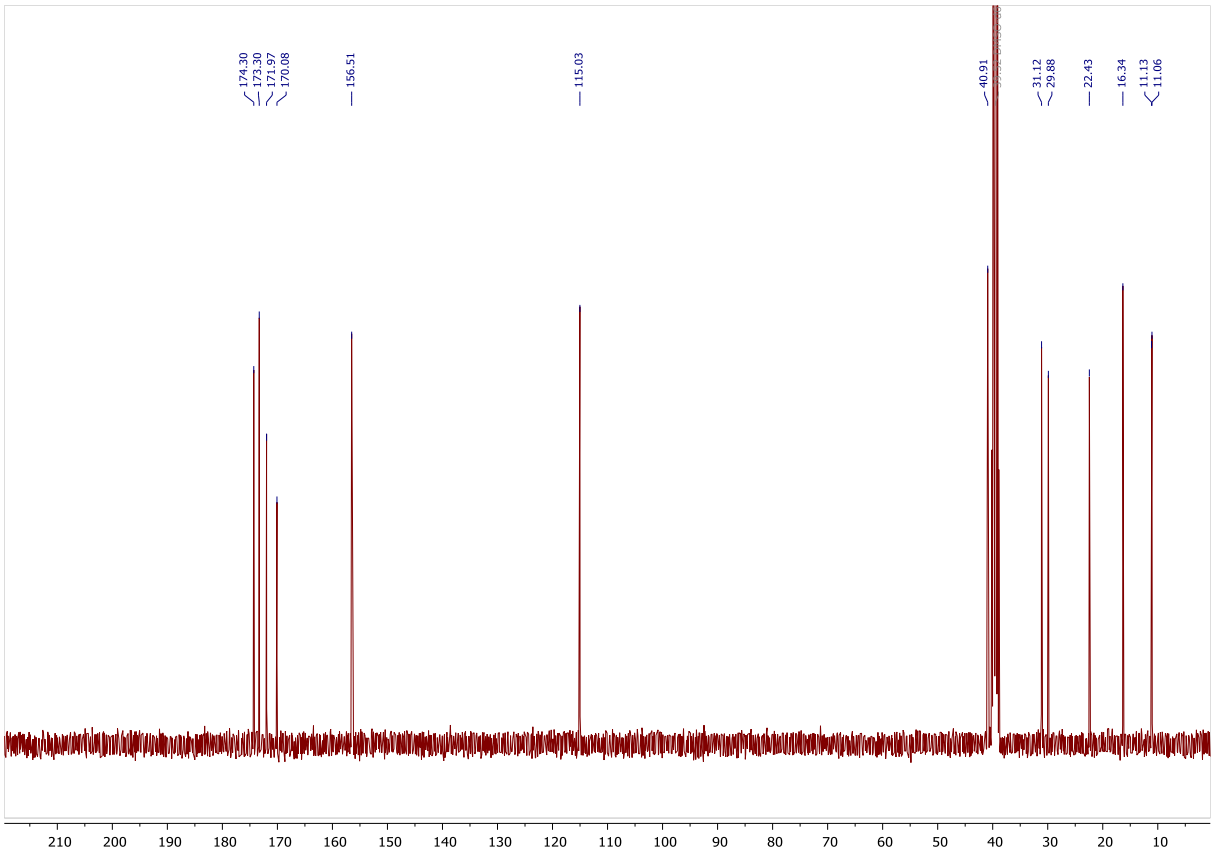
^{1}H and ^{13}C NMR spectra of compound of **1i**



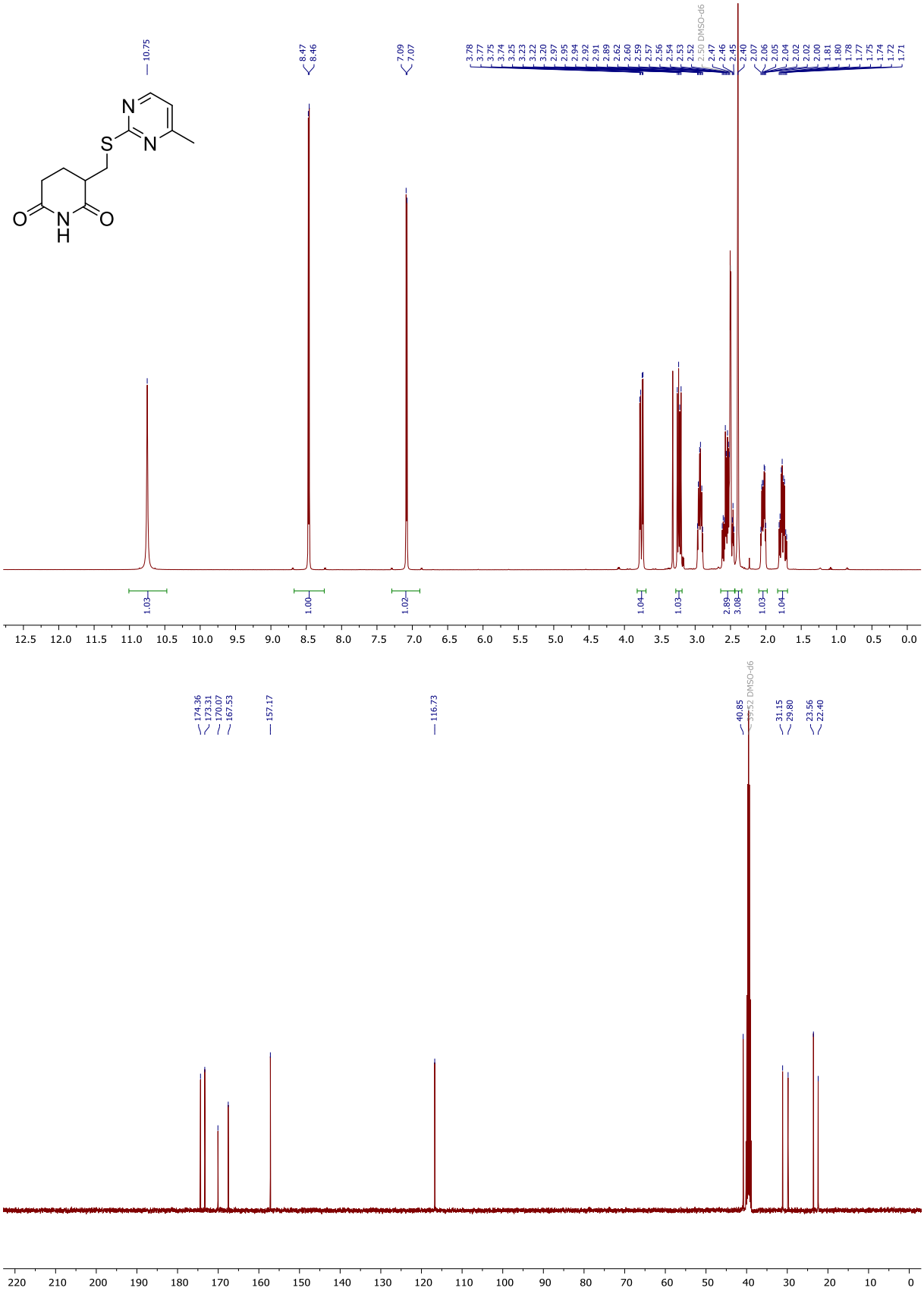


^{1}H and ^{13}C NMR spectra of compound of **1j**

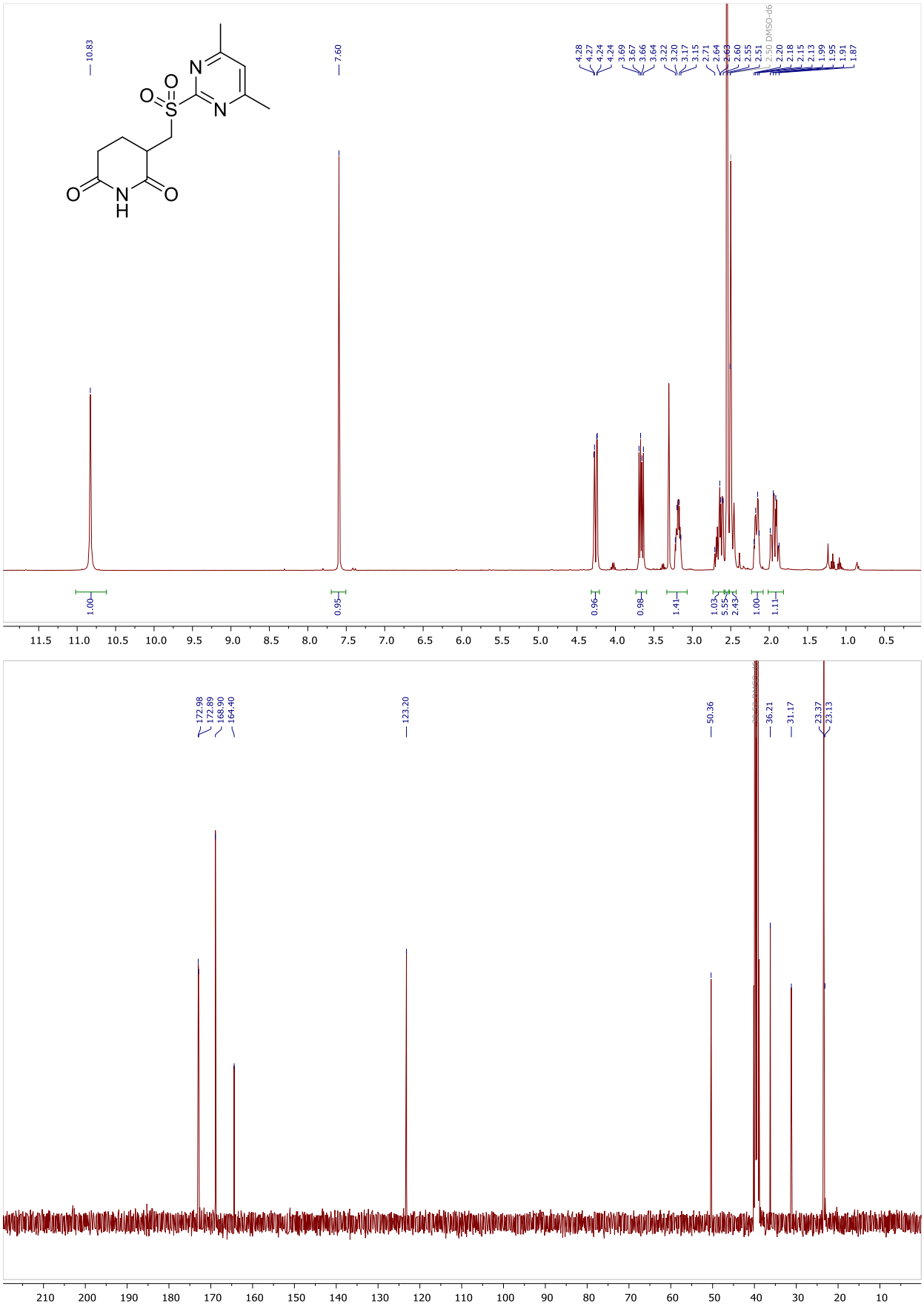




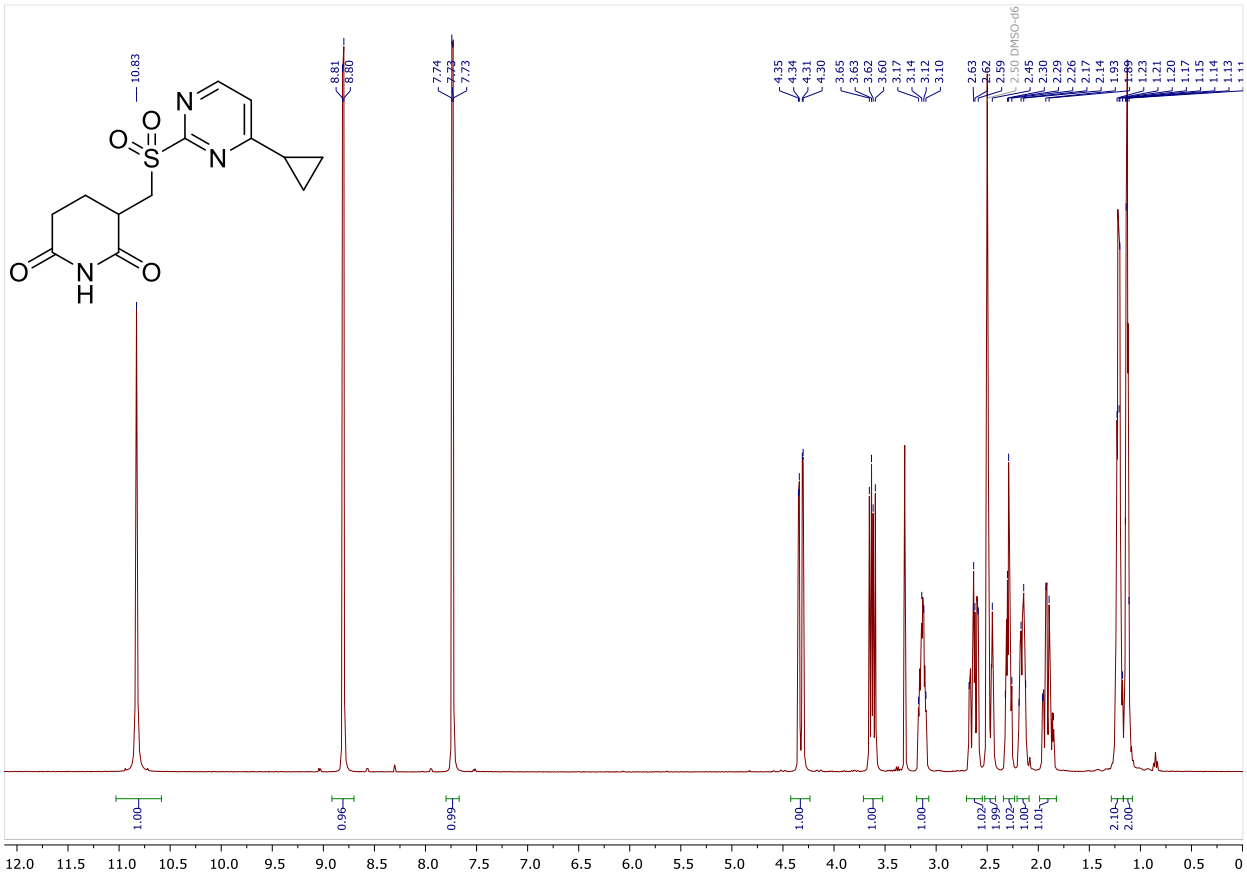
^{1}H and ^{13}C NMR spectra of compound of **1k**

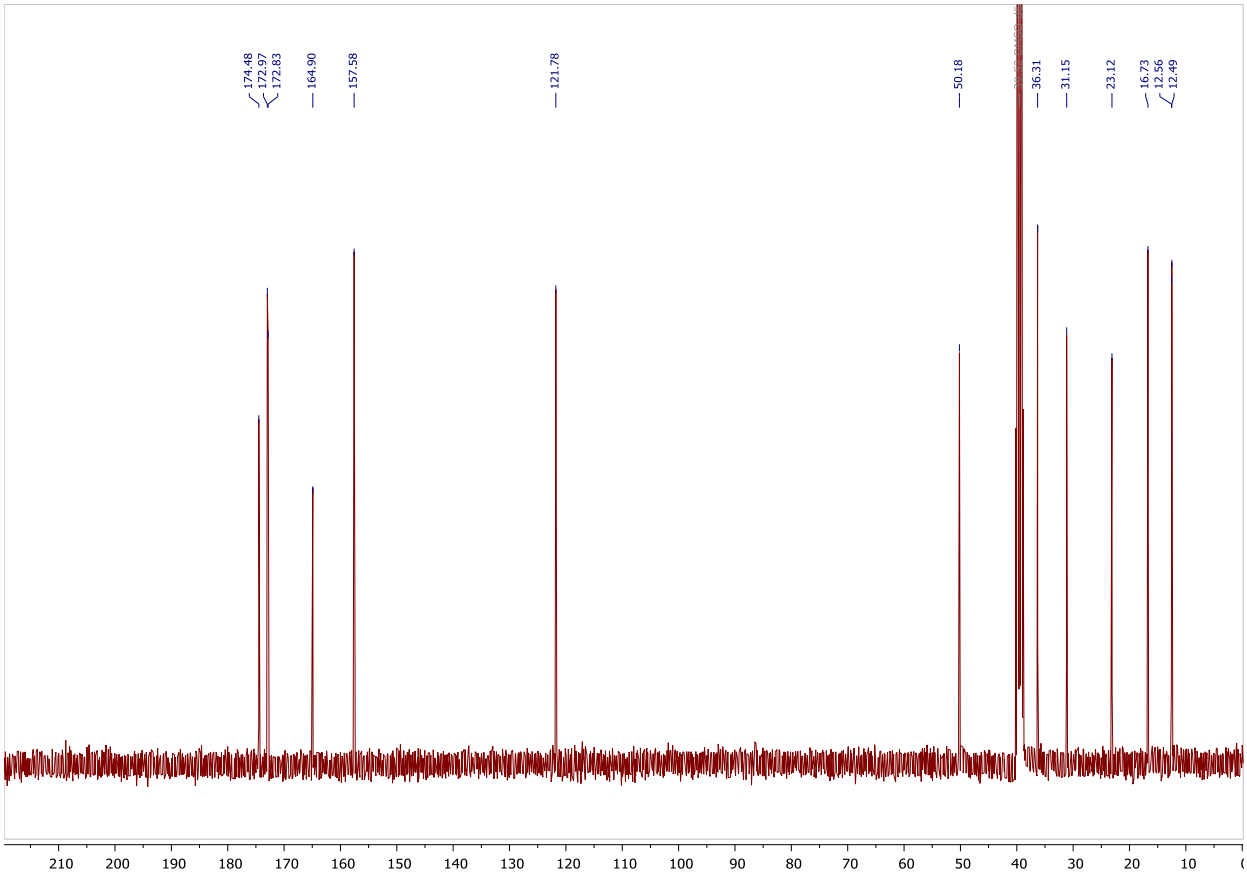


^{1}H and ^{13}C NMR spectra of compound of **2i**

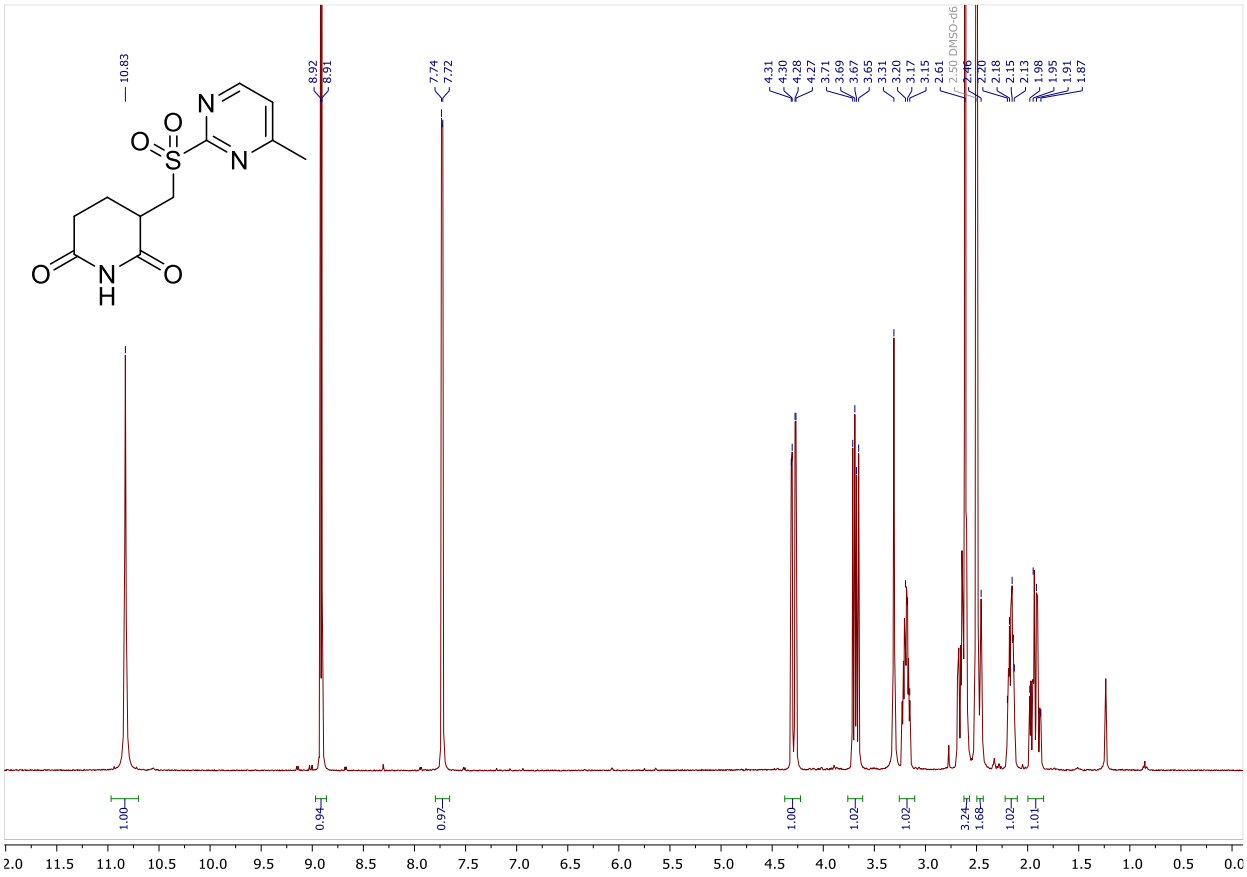


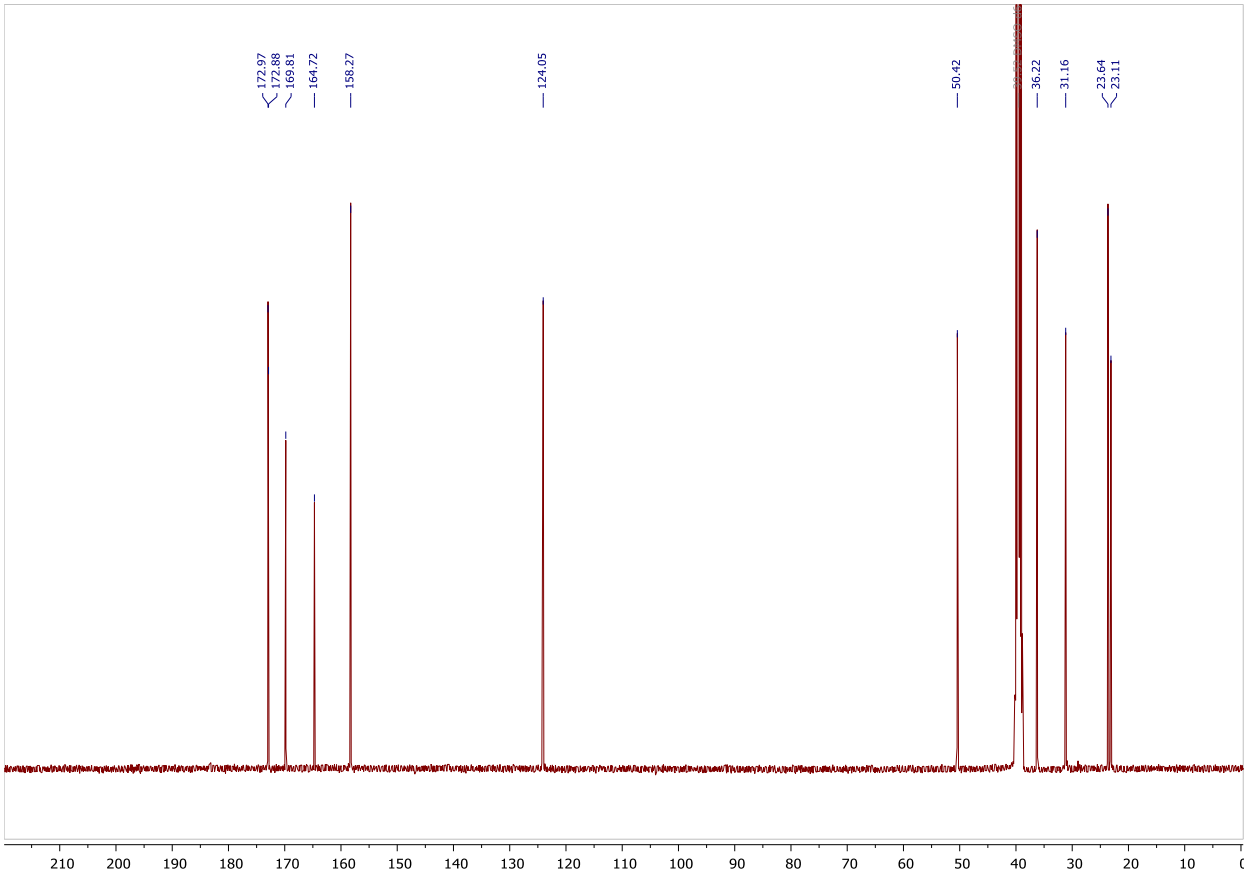
^{1}H and ^{13}C NMR spectra of compound of **2j**



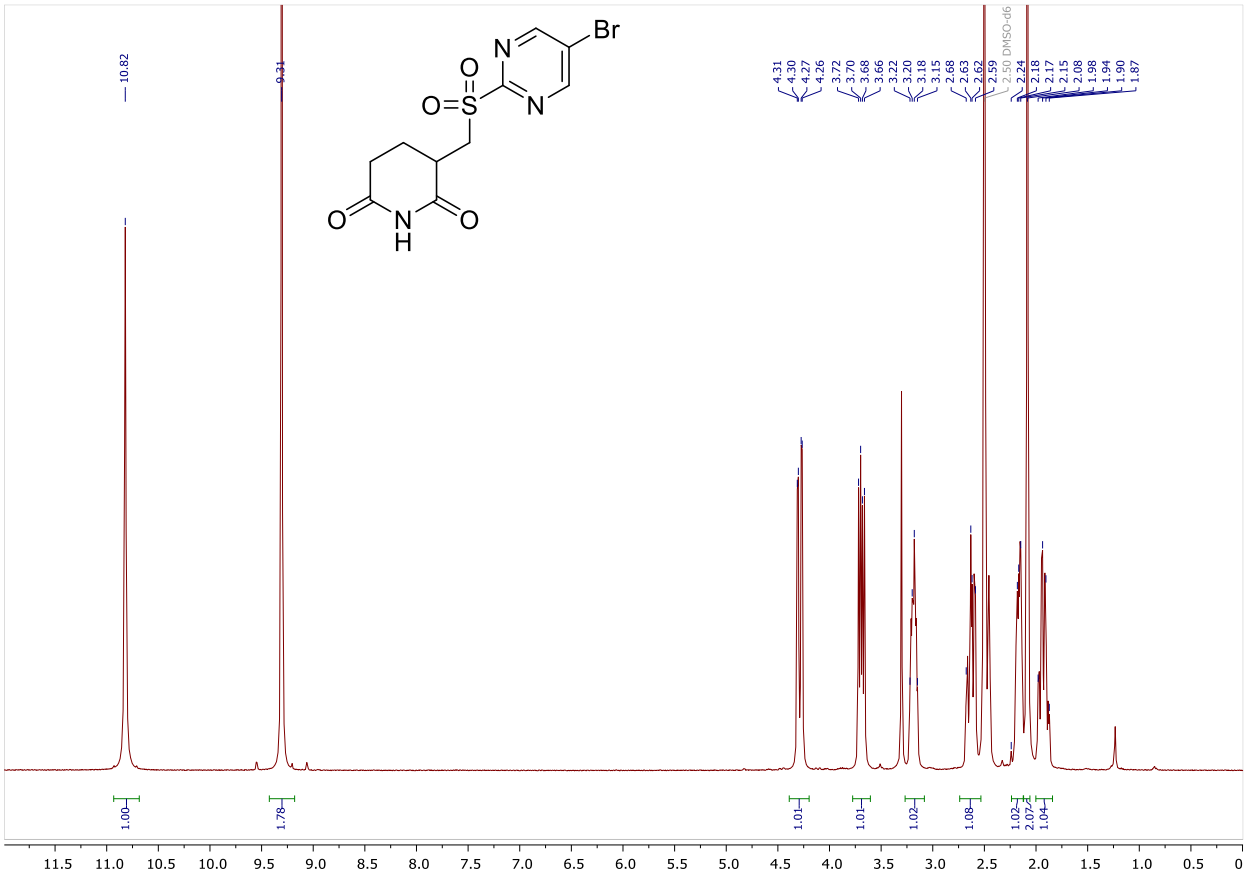


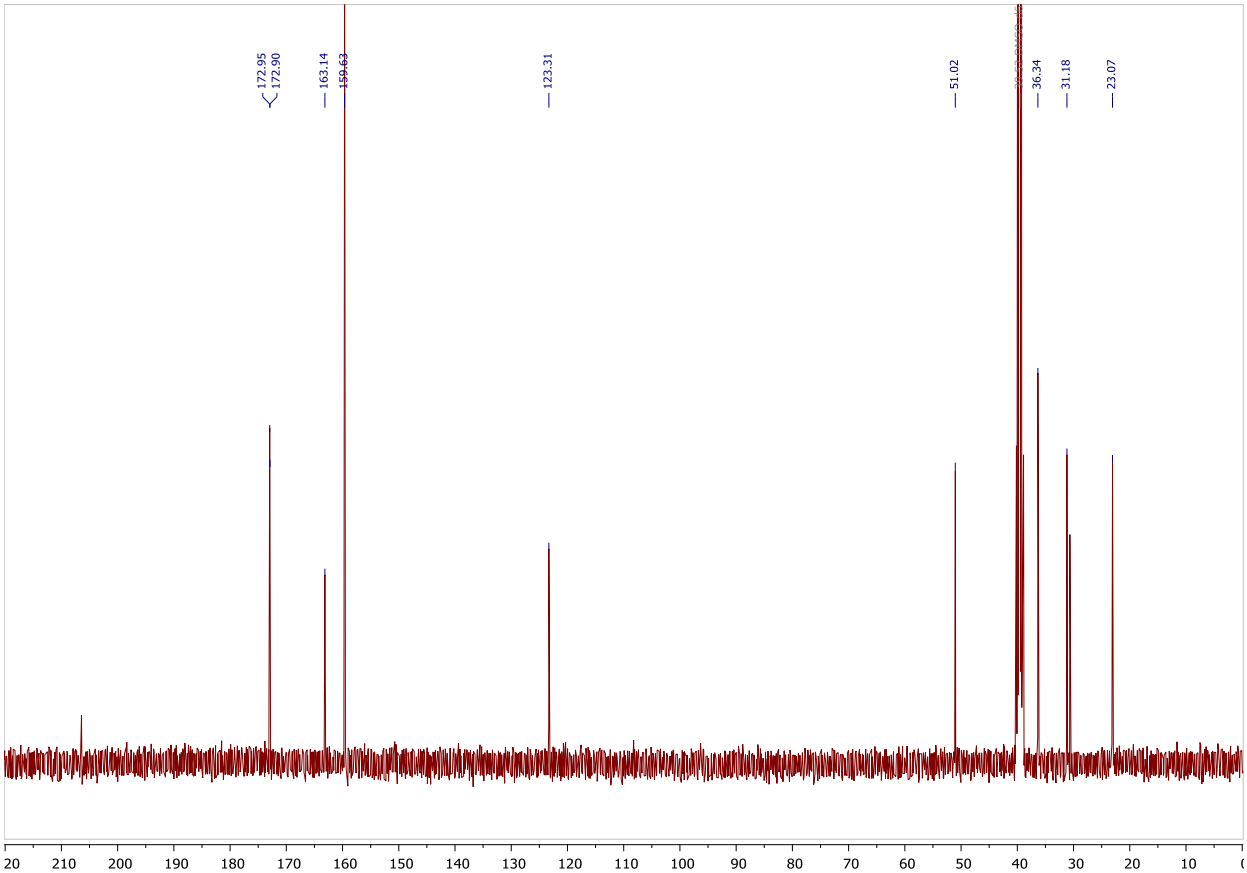
^{1}H and ^{13}C NMR spectra of compound of **2k**





^{1}H and ^{13}C NMR spectra of compound of **2l**





^{1}H and ^{13}C NMR spectra of compound of **4**