Electronic supplementary materials *Mendeleev Commun.*, 2022, **32**, 747–749

Synthesis of novel glutarimide derivatives *via* the Ugi multicomponent reaction: affinity towards the E3 ubiquitin ligase substrate receptor Cereblon

Darina Barkhatova, Daniil Zhukovsky, Christopher Heim, Samuel Maiwald, Marcus D. Hartmann and Mikhail Krasavin

Contents

1. Experimental procedures and characterization data

General considerations. (*S*)-3-Aminopiperidine-2,6-dione **1** was prepared according our previously reported procedure, other reagents were purchased from the commercial sources. 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 400 spectrometer (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) in $CDCl_3$ and were referenced to residual solvent proton peaks (δ_H = 7.28) and solvent carbon peaks (δ_C = 77.0).

General procedure for the Ugi reaction towards compounds 2a-c. To a vigorously stirred solution of (*S*)-3-aminopiperidine-2,6-dione **1** (0.5 mmol) in methanol (10 ml), *p*-tolualdehyde (0.5 mmol) was added. The reaction mixture was stirred at room temperature for 30 min, whereupon the carboxylic acid (0.5 mmol) and the isocyanide (0.5 mmol) were added. The reaction mixture was stirred at room temperature for 24 hours. The solvent was removed using a rotary evaporator and the desired products were isolated by a column chromatography on silica gel using 3% methanol in chloroform as eluent.

General procedure for the Ugi reaction towards compounds 3a-d. To a vigorously stirred solution of (*S*)-3-aminopiperidine-2,6-dione **1** (0.5 mmol) in methanol (10 ml), oxo carboxylic acid (0.5 mmol) was added. The reaction mixture was stirred at room temperature for 30 min, whereupon the isocyanide (0.5 mmol) was added. The reaction mixture was stirred at room

temperature for 24 hours. The solvent was removed using a rotary evaporator and the desired products were isolated by a column chromatography on silica gel using 3% methanol in chloroform as eluent.

(*S*)-*N*-*tert*-Butyl-2-(*N*-((*S*)-2,6-dioxopiperidin-3-yl)acetamido)-2-(*p*-tolyl)acetamide (*S,S*)-2a. Crude ratio of diastereomers 2:1. Yield 30% (R_f = 0.27), 56 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.65 (s, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 5.58 (s, 1H), 3.53 (dd, *J* = 11.4, 5.8 Hz, 1H), 2.53 – 2.41 (m, 2H), 2.38 (s, 3H), 2.37 – 2.32 (m, 1H), 2.26 (s, 3H), 2.05 – 1.96 (m, 1H), 1.48 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.30, 170.53, 168.31, 165.25, 139.35, 131.97, 130.05, 129.75, 67.13, 55.60, 52.15, 30.83, 28.60, 22.22, 21.83, 21.27. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{27}N_3O_4$, 374.2074; Found 374.2074.

(*R*)-*N*-*tert*-Butyl-2-(*N*-((*S*)-2,6-dioxopiperidin-3-yl)acetamido)-2-(*p*-tolyl)acetamide (*R,S*)-2a. Yield 62% (R_f = 0.18), 116 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 17.3 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 7.7 Hz, 2H), 6.41 (d, *J* = 10.6 Hz, 1H), 5.36 (s, 1H), 3.73 – 3.48 (m, 1H), 2.95 – 2.74 (m, 1H), 2.76 – 2.60 (m, 1H), 2.43 – 2.31 (m, 5H), 2.13 – 2.10 (m, 3H), 1.40 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.34, 170.77, 170.60, 168.30, 139.34, 131.99, 130.06, 129.76, 67.12, 55.59, 52.14, 30.83, 28.60, 22.22, 21.84, 21.27. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{27}N_3O_4$, 374.2074; Found 374.2074.

(*S*)-*N*-Cyclohexyl-2-(*N*-((*S*)-2,6-dioxopiperidin-3-yl)acetamido)-2-(*p*-tolyl)acetamide (*S,S*)-2b. Crude ratio of diastereomers 3:1. Yield 18% (R_f = 0.21), 36 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, *J* = 7.9 Hz, 1H), 8.36 (s, 1H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 5.61 (s, 1H), 3.94 (dtd, *J* = 10.7, 7.0, 3.7 Hz, 1H), 3.54 (dd, *J* = 11.3, 5.8 Hz, 1H), 2.57 – 2.45 (m, 1H), 2.43 (s, 1H), 2.38 (s, 3H), 2.26 (s, 3H), 2.07 – 1.94 (m, 3H), 1.85 – 1.75 (m, 2H), 1.67 (dt, *J* = 13.0, 3.5 Hz, 1H), 1.50 – 1.29 (m, 4H), 1.29 – 1.19 (m, 1H), 1.18 – 1.06 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.77, 170.78, 168.08, 139.40, 131.66, 130.01, 129.78, 66.64, 55.61, 49.01, 33.07, 32.71, 30.80, 25.41, 25.07, 25.01, 22.09, 21.88, 21.25. HRMS (ESI/Q-TOF) m/z: [M+Na]+ Calcd for $C_{22}H_{29}N_3O_4$, 422.2050; Found 422.2048.

(*R*)-*N*-Cyclohexyl-2-(*N*-((*S*)-2,6-dioxopiperidin-3-yl)acetamido)-2-(*p*-tolyl)acetamide (*R,S*)-2b. Yield 56% (R_f = 0.17), 112 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.71 (s, 1H), 5.43 (s, 1H), 3.83 (dtd, *J* = 11.0, 7.3, 3.9 Hz, 1H), 3.72 – 3.48 (m, 1H), 2.89 – 2.70 (m, 1H), 2.69 – 2.57 (m, 1H), 2.47 – 2.37 (m, 1H), 2.35 (s, 3H), 2.06 (s, 3H), 1.93 (dt, *J* = 13.1, 4.1 Hz, 2H), 1.79 – 1.64 (m, 2H), 1.63 (dt, *J* = 12.6, 3.6 Hz, 1H), 1.47 – 1.28 (m, 2H), 1.28 – 1.07 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ

172.80, 171.85, 170.85, 168.11, 138.95, 131.08, 129.63, 128.86, 66.57, 55.59, 49.02, 32.88, 32.72, 31.36, 25.37, 24.82, 24.79, 22.63, 21.81, 21.25. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{29}N_3O_4$, 400.2231; Found 400.2231.

***N*-((*S*)-2-*tert*-Butylamino-2-oxo-1-(*p*-tolyl)ethyl)-*N*-((*S*)-2,6-dioxopiperidin-3-yl)-isobutyramide (*S,S*)-2c.** Crude ratio of diastereomers 4:1. Yield 8% (R_f = 0.25), 16 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.06 (s, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 5.58 (s, 1H), 3.54 (dd, *J* = 11.2, 5.9 Hz, 1H), 2.95 – 2.81 (m, 1H), 2.54 – 2.44 (m, 1H), 2.44 – 2.37 (m, 1H), 2.39 (s, 3H), 2.38 – 2.29 (m, 1H), 2.04 (ddd, *J* = 17.1, 14.0, 5.6 Hz, 1H), 1.49 (s, 9H), 1.26 (d, *J* = 6.7 Hz, 3H), 1.20 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.35, 172.49, 170.60, 168.80, 139.30, 132.07, 130.05, 129.79, 65.92, 55.59, 52.14, 30.74, 28.64, 21.76, 21.27, 19.80, 18.82. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{31}N_3O_4$, 424.2207; Found 424.2202.

***N*-((*R*)-2-*tert*-Butylamino-2-oxo-1-(*p*-tolyl)ethyl)-*N*-((*S*)-2,6-dioxopiperidin-3-yl)-isobutyramide (*R,S*)-2c.** Yield 30% (R_f = 0.27), 60 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 5.95 (s, 1H), 5.49 (s, 1H), 3.67 – 3.49 (m, 1H), 2.83 – 2.64 (m, 3H), 2.43 (ddd, *J* = 14.1, 6.5, 4.1 Hz, 1H), 2.38 (s, 3H), 2.36 – 2.31 (m, 1H), 1.42 (s, 9H), 1.26 – 1.21 (m, 3H), 1.07 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.21, 171.68, 169.78, 168.60, 139.22, 131.31, 129.85, 129.24, 65.93, 52.17, 31.30, 31.25, 28.61, 21.96, 21.20, 19.59, 19.31. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{31}N_3O_4$, 424.2207; Found 424.2207.

(*S*)-*N*-*tert*-Butyl-1-((*S*)-2,6-dioxopiperidin-3-yl)-2-methyl-5-oxopyrrolidine-2-carboxamide (*S,S*)-3a. Crude ratio of diastereomers 1:1. Yield 42% (R_f = 0.22), 65 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 – 8.56 (m, 1H), 8.05 (s, 1H), 3.73 (dd, *J* = 11.7, 5.6 Hz, 1H), 2.87 – 2.69 (m, 2H), 2.66 – 2.56 (m, 1H), 2.51 – 2.41 (m, 2H), 2.38 (dd, *J* = 10.9, 2.5 Hz, 1H), 2.08 – 1.92 (m, 2H), 1.57 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.02, 175.01, 172.14, 170.74, 67.85, 53.13, 51.57, 34.32, 30.96, 29.02, 28.47, 23.45, 22.93. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{23}N_3O_4$, 310.1761; Found 310.1761.

(*R*)-*N*-*tert*-Butyl-1-((*S*)-2,6-dioxopiperidin-3-yl)-2-methyl-5-oxopyrrolidine-2-carboxamide (*R,S*)-3a. Yield 45% (R_f = 0.18), 70 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 5.55 (s, 1H), 3.84 (dd, *J* = 12.2, 5.3 Hz, 1H), 2.94 (dtd, *J* = 14.0, 12.6, 4.5 Hz, 1H), 2.82 (dddd, *J* = 17.6, 4.4, 2.7, 1.2 Hz, 1H), 2.59 (ddd, *J* = 17.6, 14.1, 5.4 Hz, 1H), 2.51 – 2.45 (m, 2H), 2.36 – 2.22 (m, 2H), 2.11 (ddd, *J* = 12.8, 8.4, 6.3 Hz, 1H), 1.56 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.11, 172.60, 171.44, 169.39, 67.65, 54.06, 51.76, 32.71,

31.57, 29.15, 28.69, 22.61, 22.43. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{23}N_3O_4$, 310.1761; Found 310.1761.

(*S*)-*N*-Cyclohexyl-1-((*S*)-2,6-dioxopiperidin-3-yl)-2-methyl-5-oxopyrrolidine-2-carboxamide (*S,S*)-3b. Crude ratio of diastereomers 3:2. Yield 49% (R_f = 0.26), 82 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.35 (d, *J* = 7.8 Hz, 1H), 3.77 (dd, *J* = 11.7, 5.7 Hz, 1H), 3.69 (ddq, *J* = 11.3, 7.7, 3.6 Hz, 1H), 2.83 – 2.76 (m, 1H), 2.79 – 2.72 (m, 1H), 2.67 – 2.53 (m, 2H), 2.54 – 2.39 (m, 2H), 2.42 – 2.30 (m, 1H), 2.11 – 2.01 (m, 1H), 1.98 (ddd, *J* = 13.1, 5.7, 2.8 Hz, 1H), 1.95 – 1.86 (m, 1H), 1.82 – 1.67 (m, 3H), 1.60 (s, 3H), 1.39 – 1.24 (m, 2H), 1.27 – 1.09 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.13, 171.90, 171.19, 170.87, 67.63, 53.01, 49.02, 34.35, 32.65, 32.59, 30.92, 28.99, 25.37, 25.02, 24.97, 23.52, 23.08. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{25}N_3O_4$, 358.1737; Found 358.1737.

(*R*)-*N*-Cyclohexyl-1-((*S*)-2,6-dioxopiperidin-3-yl)-2-methyl-5-oxopyrrolidine-2-carboxamide (*R,S*)-3b. Yield 32% (R_f = 0.22), 54 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 5.70 (d, *J* = 8.1 Hz, 1H), 3.86 (dd, *J* = 12.3, 5.3 Hz, 1H), 3.81 – 3.71 (m, 1H), 2.93 (dtd, *J* = 14.0, 12.6, 4.5 Hz, 1H), 2.77 (d, *J* = 6.3 Hz, 1H), 2.67 – 2.59 (m, 1H), 2.52 – 2.46 (m, 2H), 2.36 – 2.24 (m, 2H), 2.17 – 2.07 (m, 1H), 1.97 – 1.86 (m, 2H), 1.75 (dt, *J* = 13.2, 3.9 Hz, 2H), 1.66 (dt, *J* = 13.0, 3.7 Hz, 1H), 1.58 (s, 3H), 1.47 – 1.32 (m, 2H), 1.24 – 1.09 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.33, 172.59, 171.89, 169.68, 67.42, 54.11, 48.86, 33.01, 32.62, 31.55, 29.16, 25.36, 24.85, 24.83, 22.63, 22.34. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{25}N_3O_4$, 358.1737; Found 358.1740.

(2*S*,3'*S*)-*N*-*tert*-Butyl-2-methyl-2',6,6'-trioxo[1,3'-bipiperidine]-2-carboxamide (*S,S*)-3c. Crude ratio of diastereomers 2:1. Yield 17% (R_f = 0.27), 27 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 12.6 Hz, 1H), 8.23 (s, 1H), 3.66 (dd, *J* = 11.2, 5.6 Hz, 1H), 2.88 – 2.66 (m, 2H), 2.64 – 2.48 (m, 2H), 2.40 (tt, *J* = 9.5, 7.5 Hz, 3H), 2.16 – 1.96 (m, 1H), 1.80 – 1.70 (m, 2H), 1.61 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.90, 171.11, 170.81, 170.56, 67.18, 56.51, 51.84, 36.90, 32.47, 30.90, 28.50, 25.38, 23.03, 16.95. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{25}N_3O_4$, 346.1737; Found 346.1735.

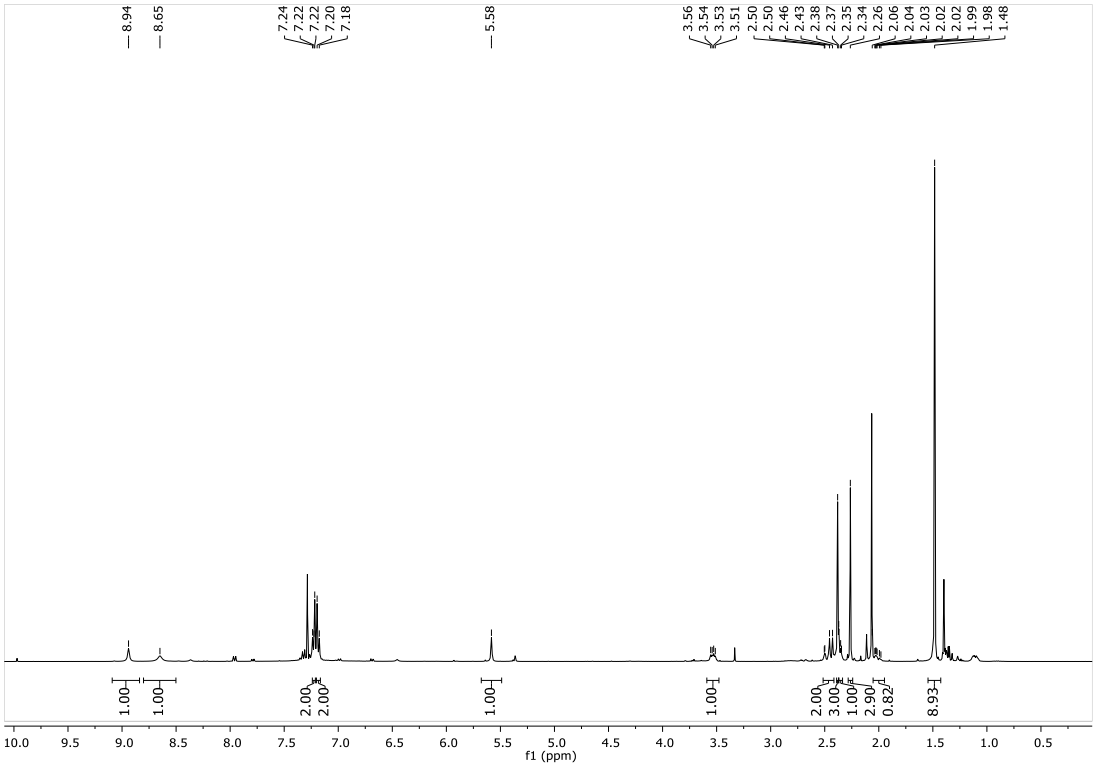
(2*R*,3'*S*)-*N*-*tert*-Butyl-2-methyl-2',6,6'-trioxo[1,3'-bipiperidine]-2-carboxamide (*R,S*)-3c. Yield 9% (R_f = 0.24), 15 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 5.69 (s, 1H), 3.50 (dd, *J* = 11.7, 5.3 Hz, 1H), 3.00 – 2.84 (m, 1H), 2.77 (dddd, *J* = 17.5, 4.3, 2.7, 1.2 Hz, 1H), 2.55 – 2.37 (m, 3H), 2.21 (dtd, *J* = 15.0, 6.7, 6.1, 3.3 Hz, 1H), 2.17 – 2.10 (m, 1H), 2.01 – 1.81 (m, 3H), 1.62 (s, 3H), 1.40 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.06,

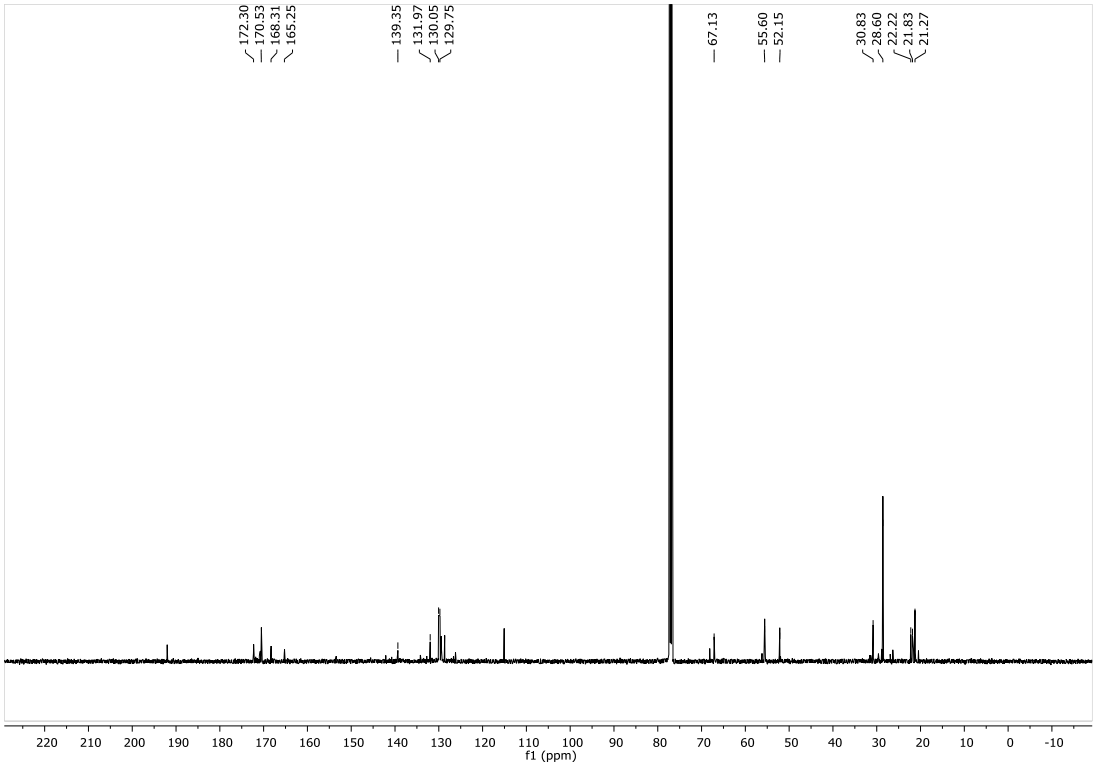
171.30, 170.54, 169.43, 66.95, 57.50, 51.86, 35.90, 32.51, 31.46, 28.65, 23.08, 22.42, 17.29. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{25}N_3O_4$, 324.1918; Found 324.1917.

(*S*)-*N*-*tert*-Butyl-2-((*S*)-2,6-dioxopiperidin-3-yl)-3-oxoisoindoline-1-carboxamide (*S*,*S*)-3d. Crude ratio of diastereomers 4:3. Yield 11% (R*f* = 0.27), 19 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.84 (d, *J* = 7.4 Hz, 1H), 7.77 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.64 (td, *J* = 6.9, 6.4, 1.8 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.47 (s, 1H), 5.09 (s, 1H), 4.24 (dd, *J* = 11.7, 5.6 Hz, 1H), 2.91 (dd, *J* = 16.9, 3.3 Hz, 1H), 2.87 – 2.76 (m, 1H), 2.75 – 2.62 (m, 1H), 2.18 – 2.12 (m, 1H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.51, 170.18, 168.64, 166.45, 141.94, 132.98, 129.68, 129.19, 123.95, 123.07, 65.59, 54.50, 51.81, 31.00, 28.33, 21.70. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{21}N_3O_4$, 344.1605; Found 344.1603.

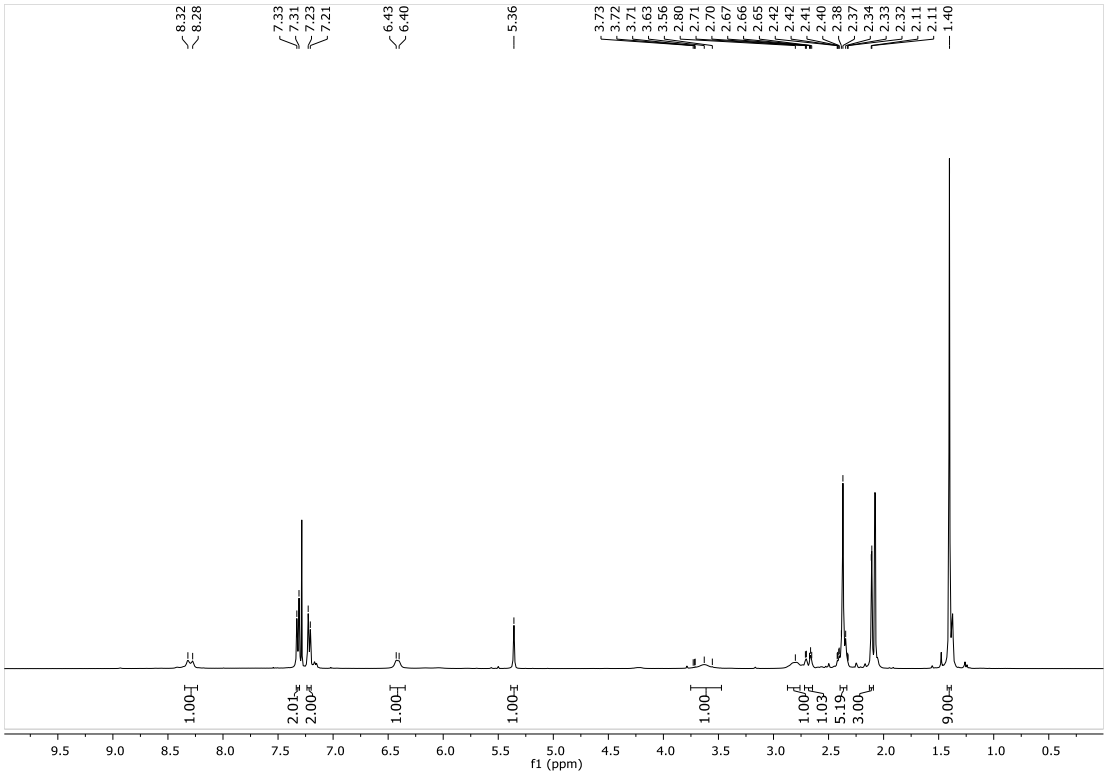
(*R*)-*N*-*tert*-Butyl-2-((*S*)-2,6-dioxopiperidin-3-yl)-3-oxoisoindoline-1-carboxamide (*R*,*S*)-3d. Yield 7% (R_f = 0.24), 12 mg. White amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.60 – 7.54 (m, 1H), 6.25 (s, 1H), 5.04 (s, 1H), 4.95 (dd, *J* = 13.4, 5.0 Hz, 1H), 2.97 (ddd, *J* = 17.7, 4.6, 2.4 Hz, 1H), 2.80 (ddd, *J* = 17.9, 13.5, 5.3 Hz, 1H), 2.70 – 2.52 (m, 1H), 2.30 (dtd, *J* = 12.8, 5.2, 2.4 Hz, 1H), 1.25 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.54, 170.50, 170.19, 166.27, 141.69, 133.08, 129.70, 129.39, 124.31, 122.61, 65.19, 53.44, 51.79, 31.69, 28.31, 22.54. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{21}N_3O_4$, 344.1605; Found 344.1606.

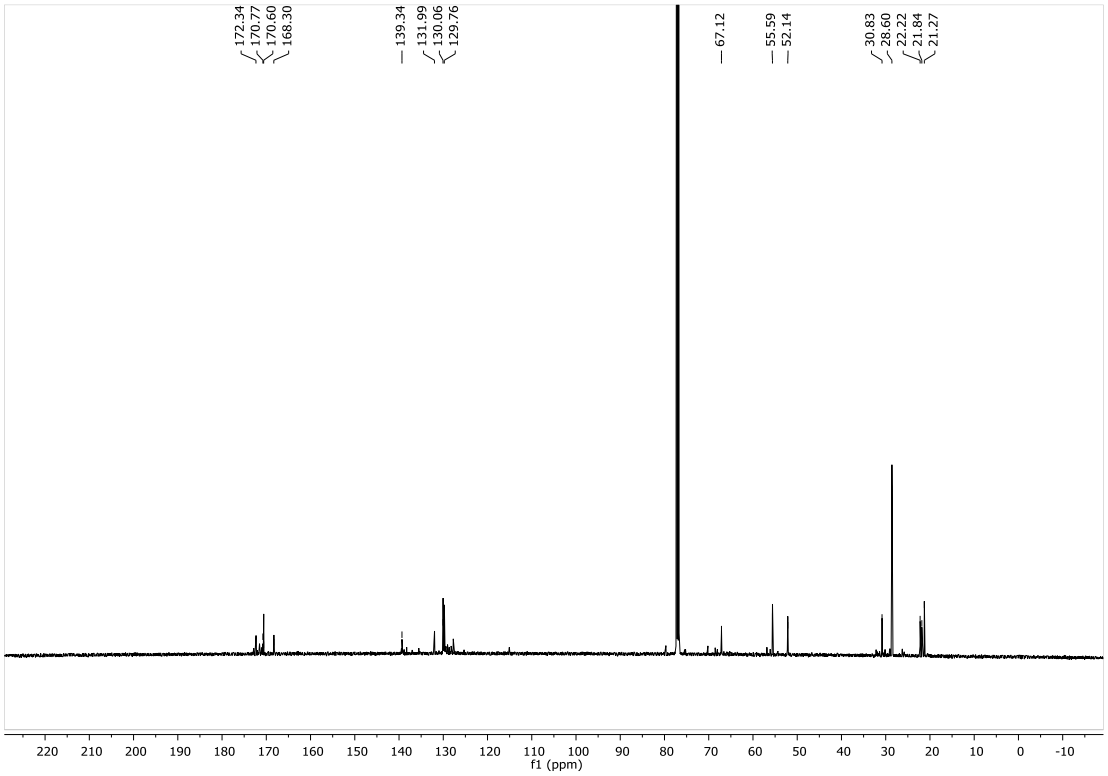
^{1}H and ^{13}C NMR spectra for compound **(*S*,*S*)-2a**



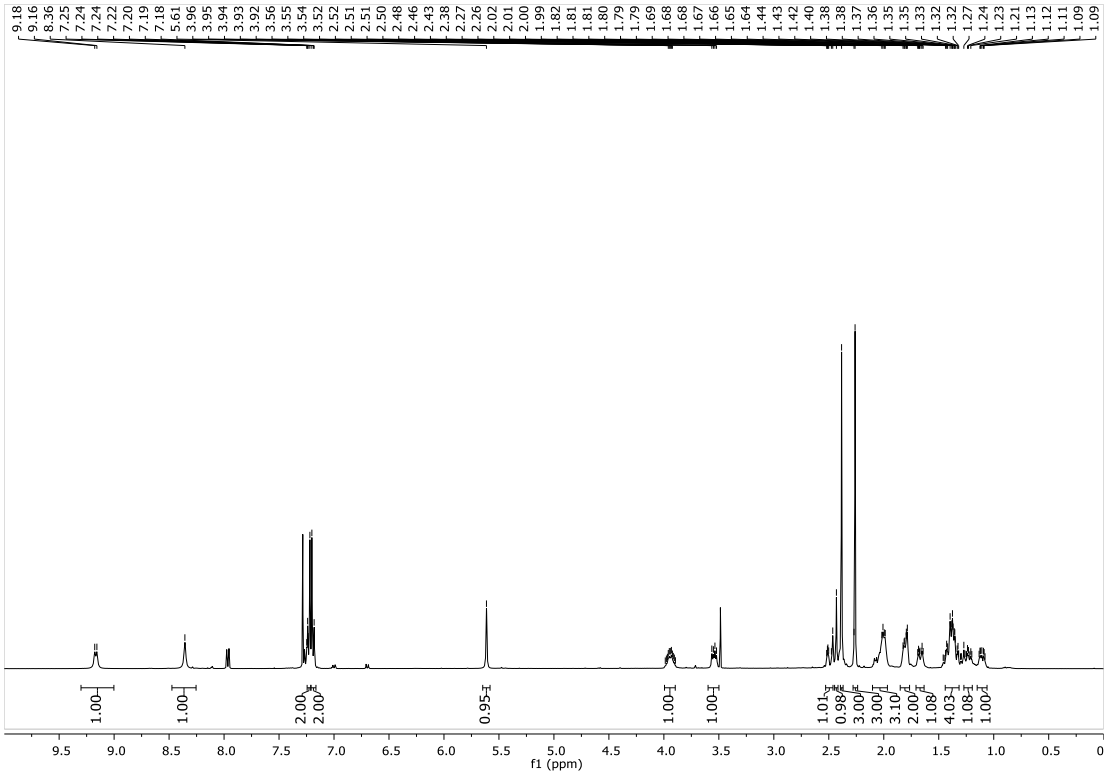


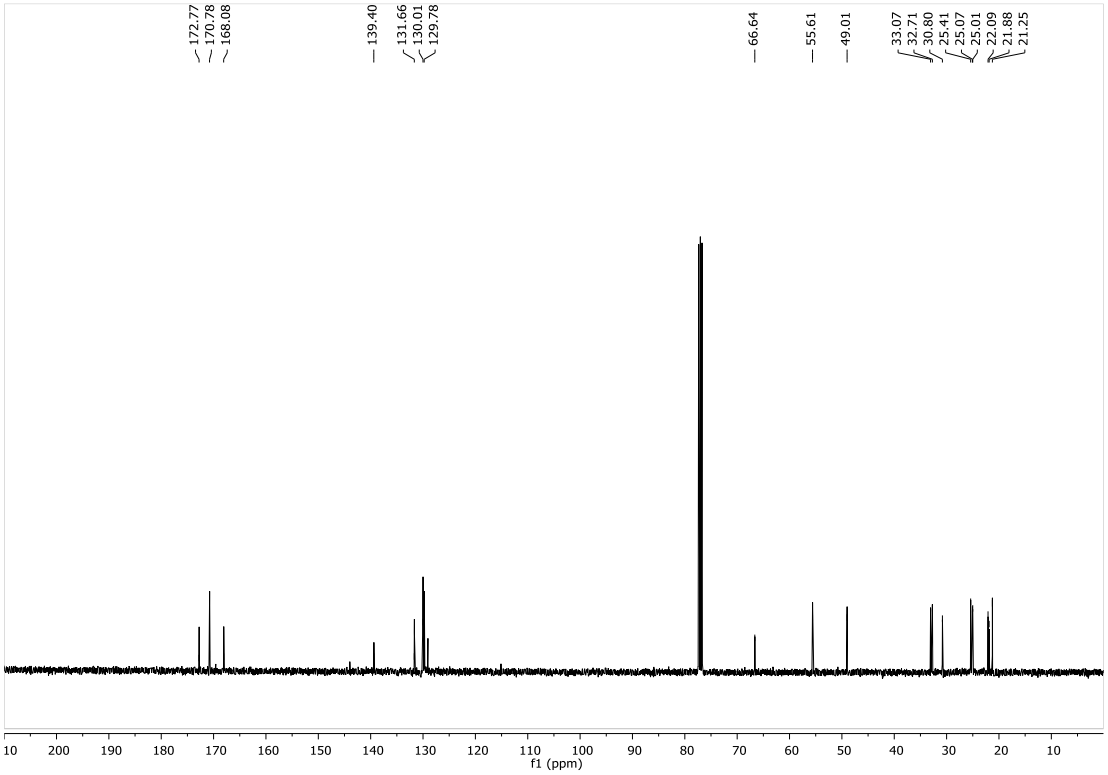
^{1}H and ^{13}C NMR spectra for compound **(*R*,*S*)-2a**



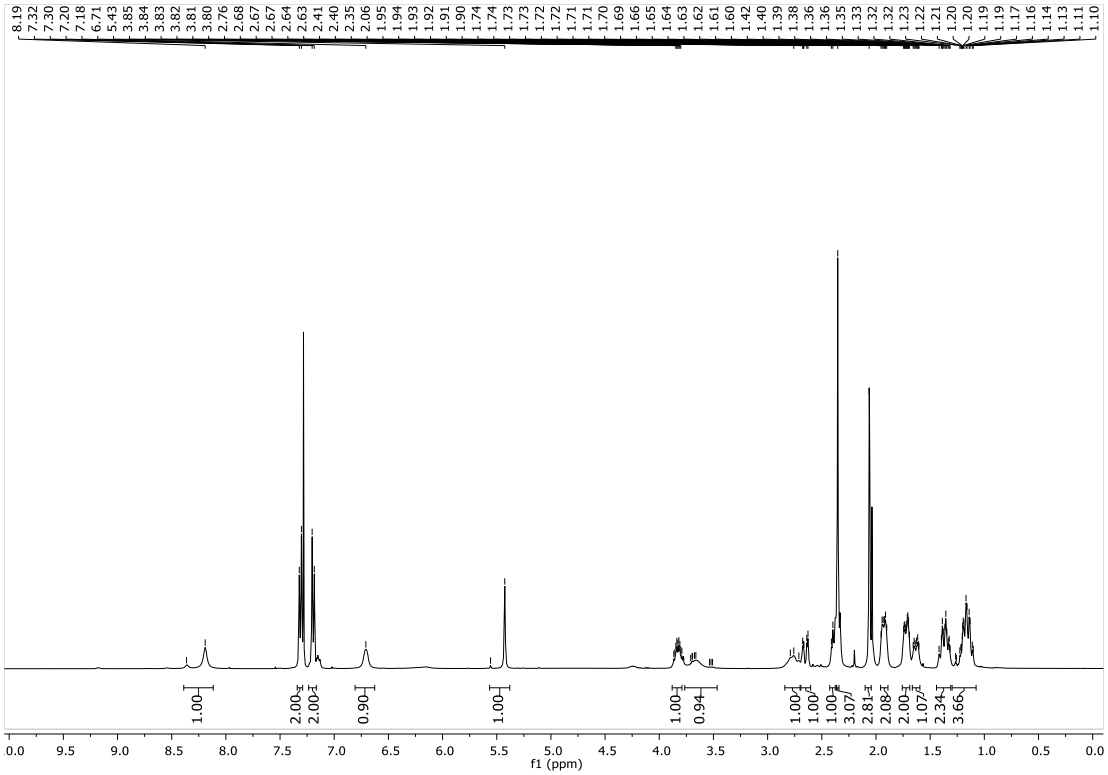


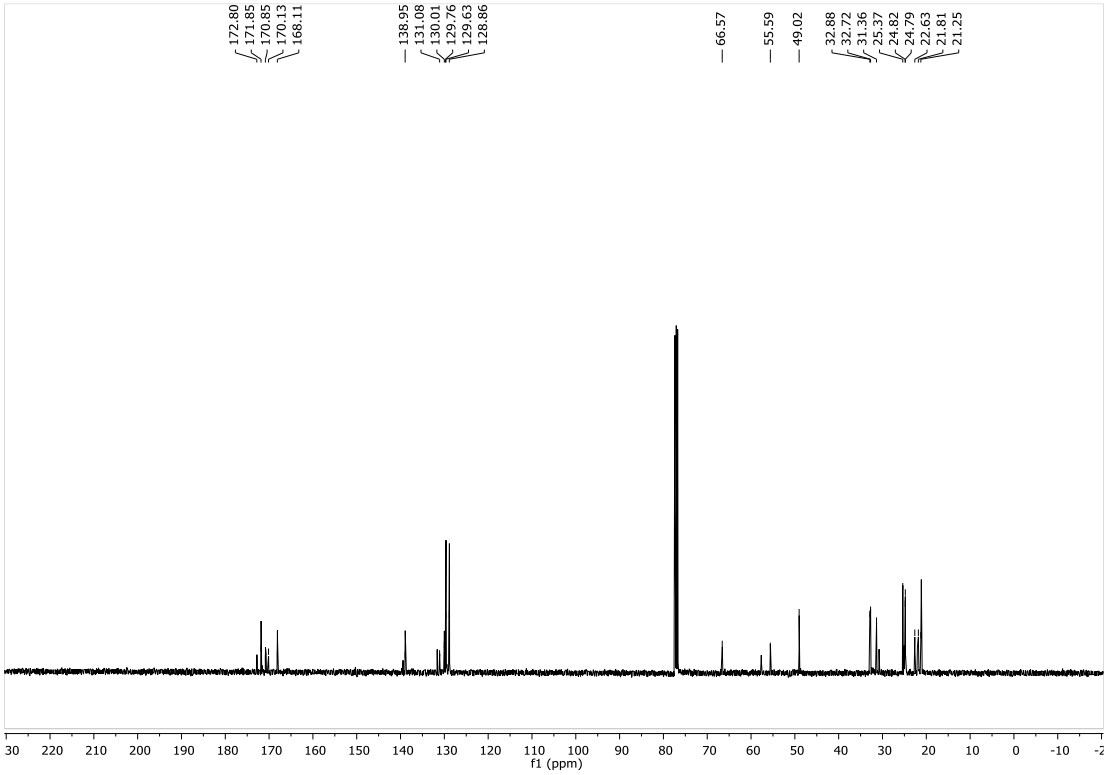
^{1}H and ^{13}C NMR spectra for compound **(*S*,*S*)-2b**



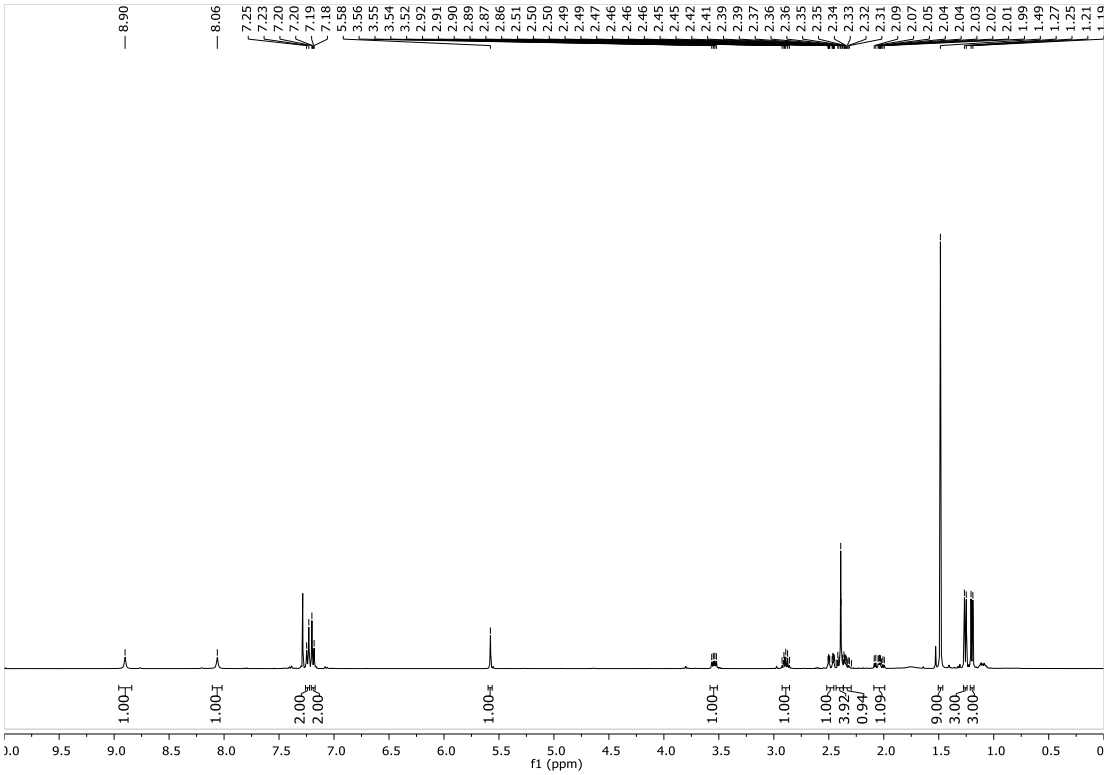


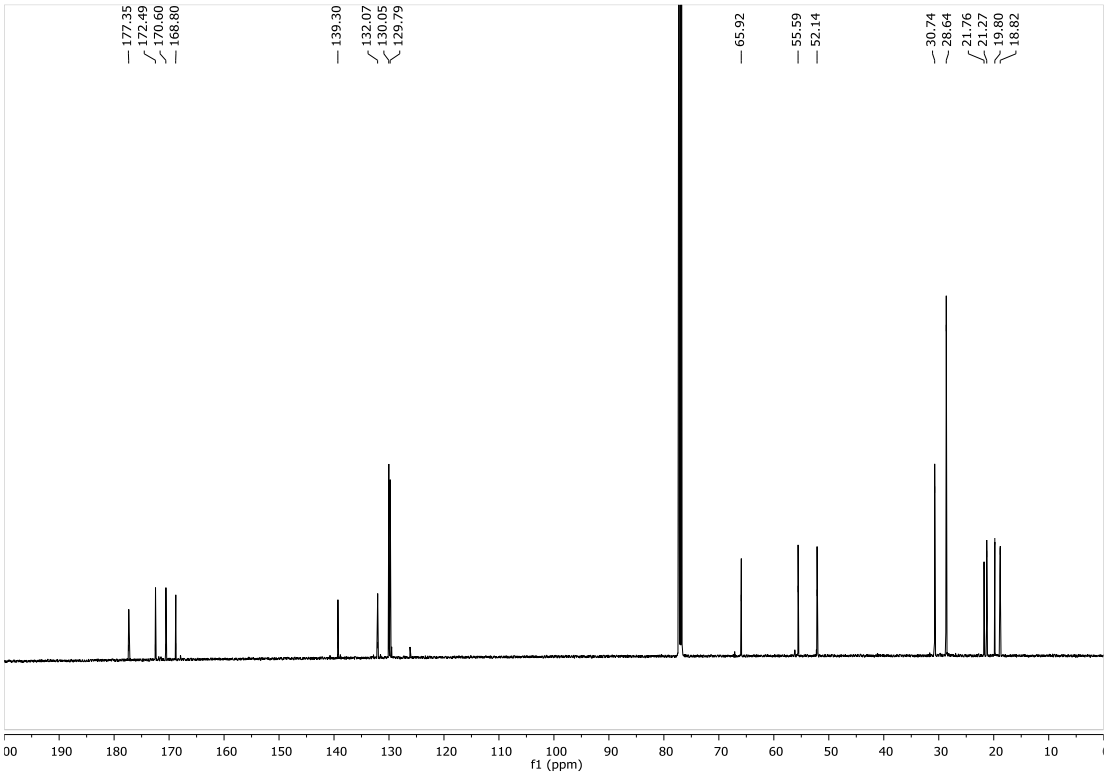
^{1}H and ^{13}C NMR spectra for compound **(*R*,*S*)-2b**



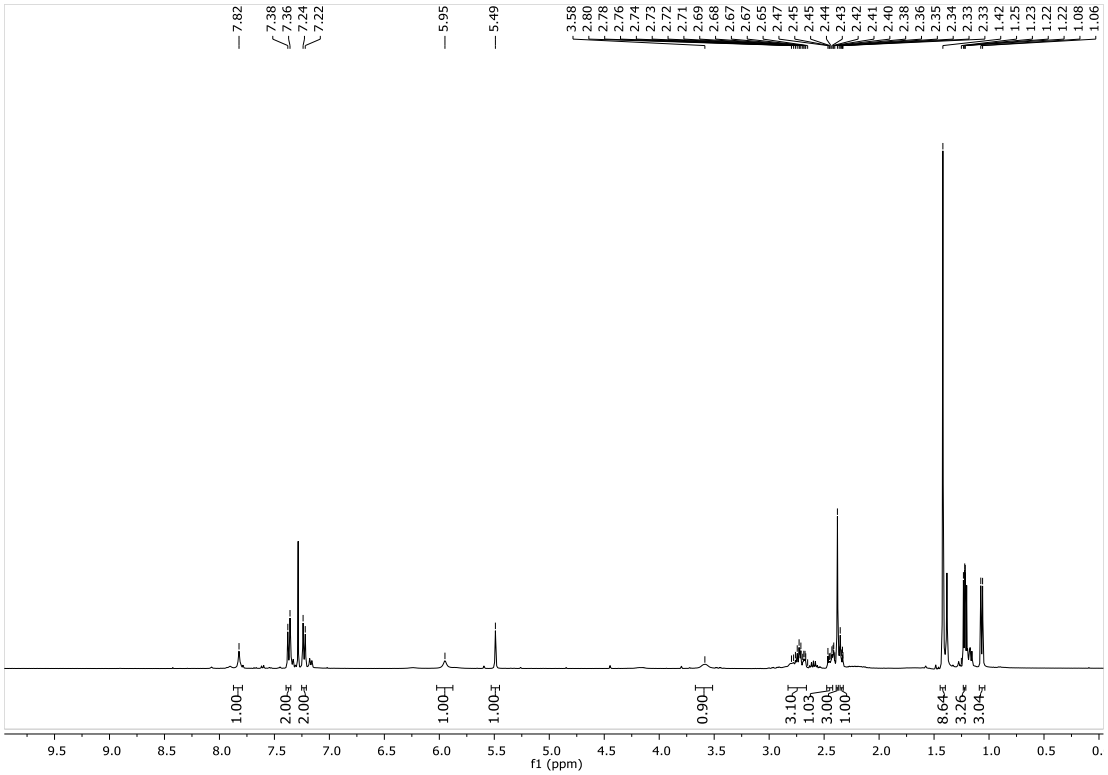


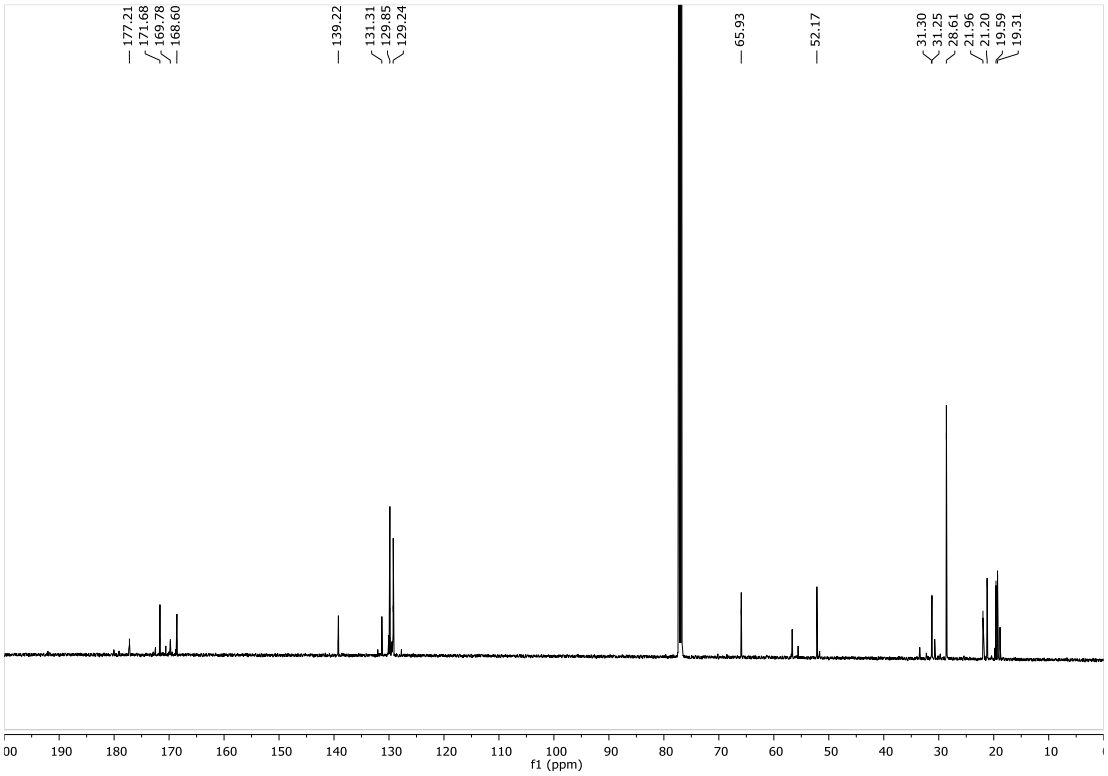
^{1}H and ^{13}C NMR spectra for compound **(*S*,*S*)-2c**



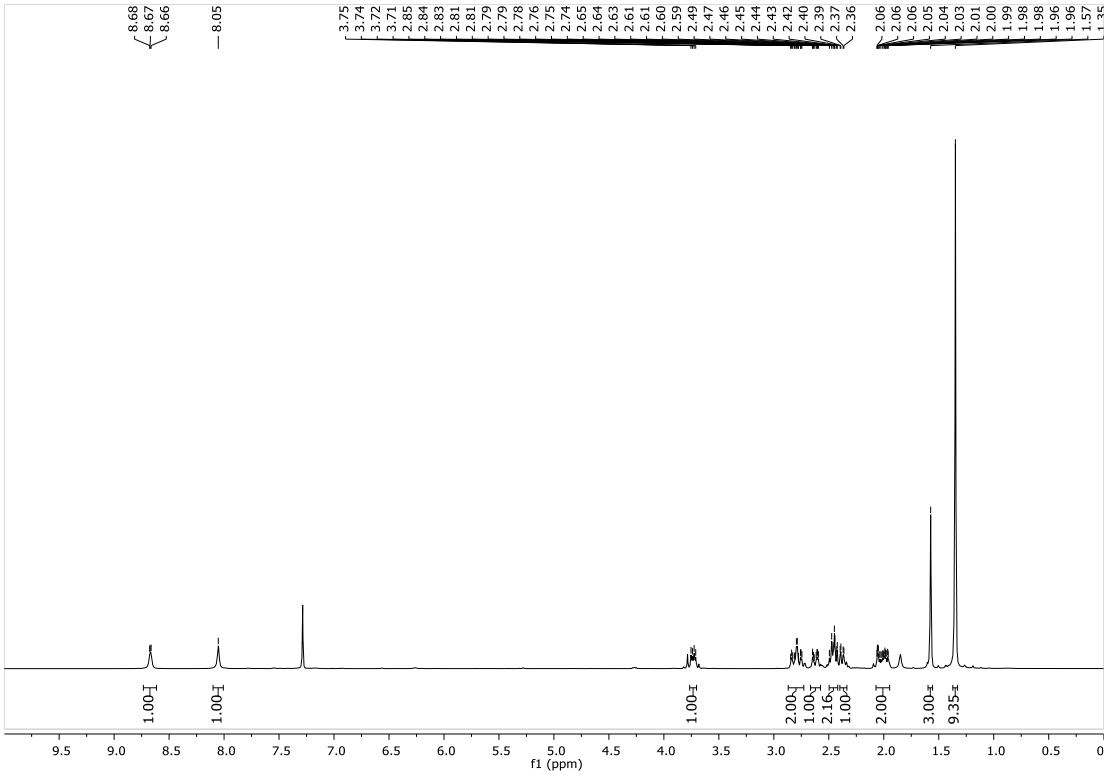


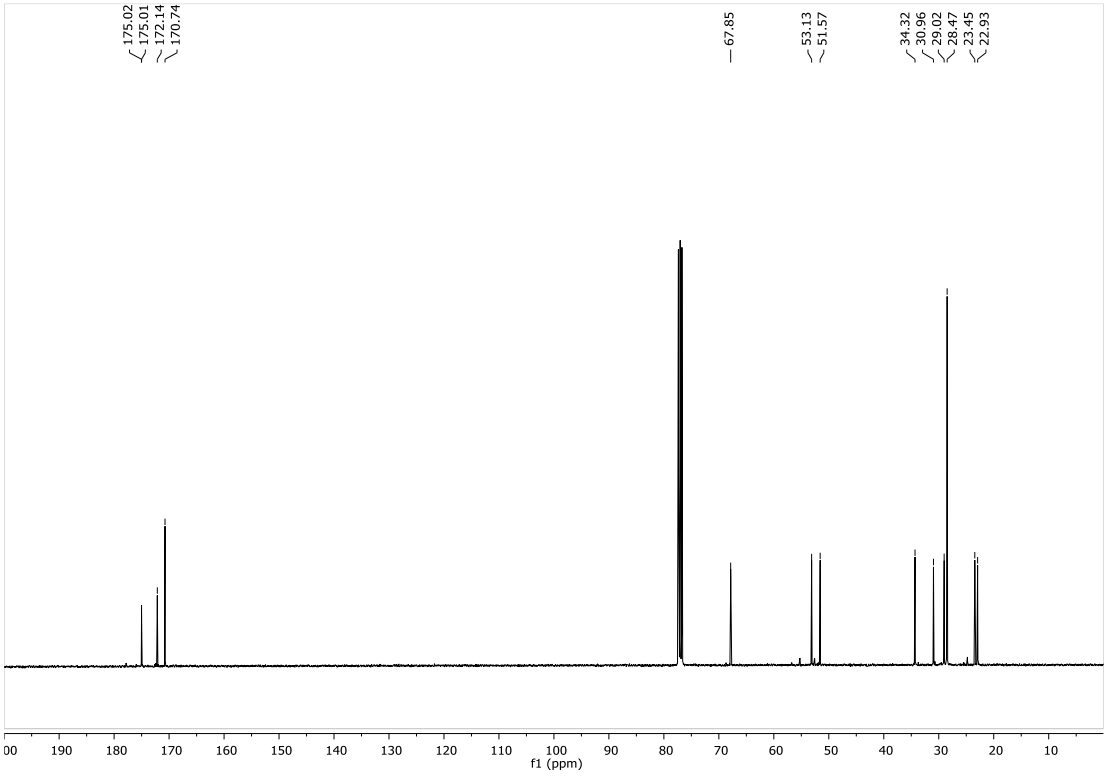
^{1}H and ^{13}C NMR spectra for compound **(*R*,*S*)-2c**



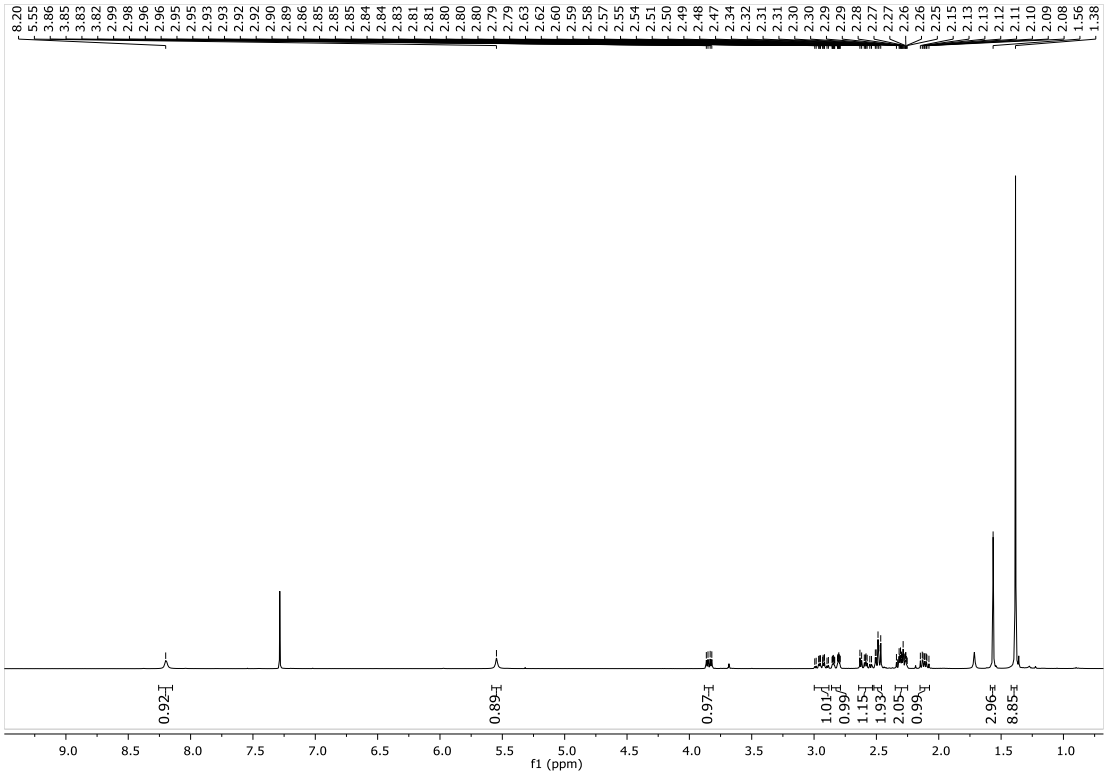


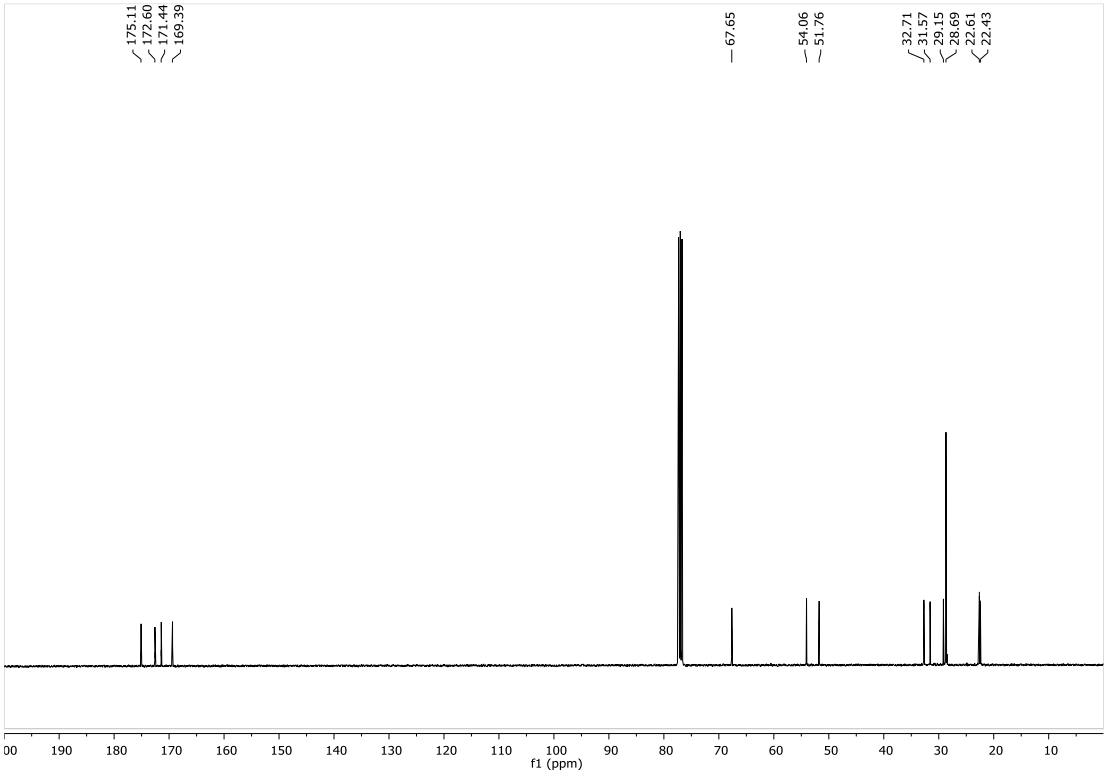
^{1}H and ^{13}C NMR spectra for compound **(*S*,*S*)-3a**



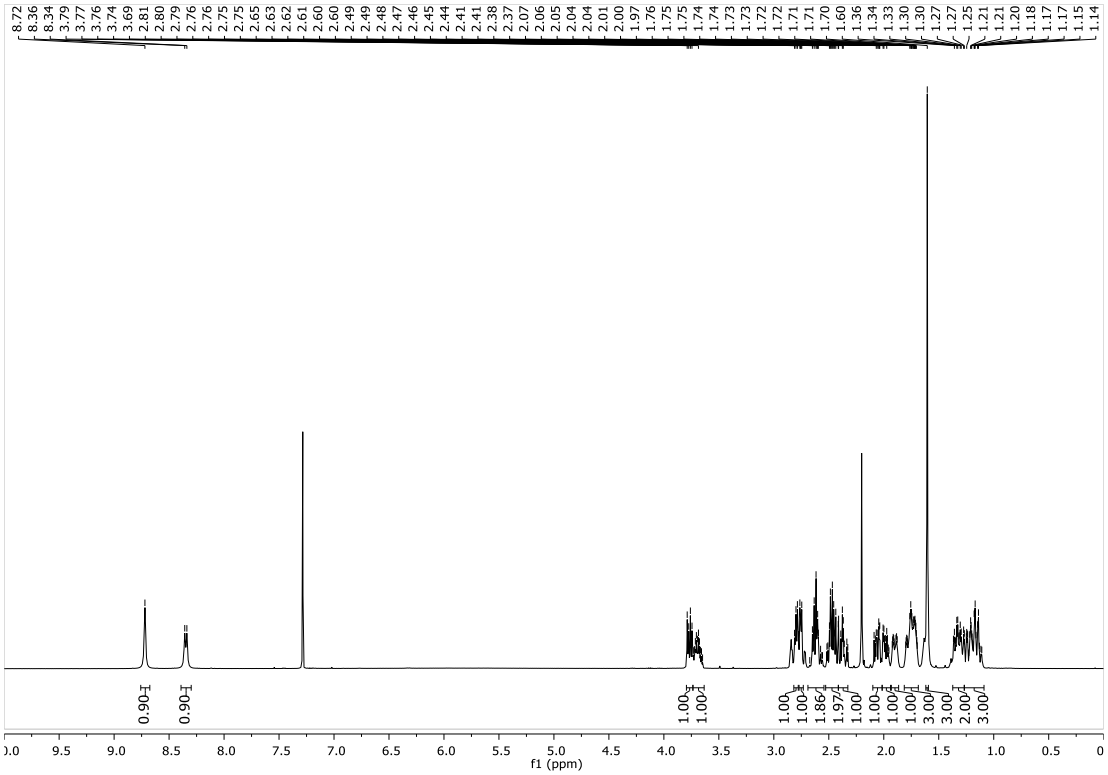


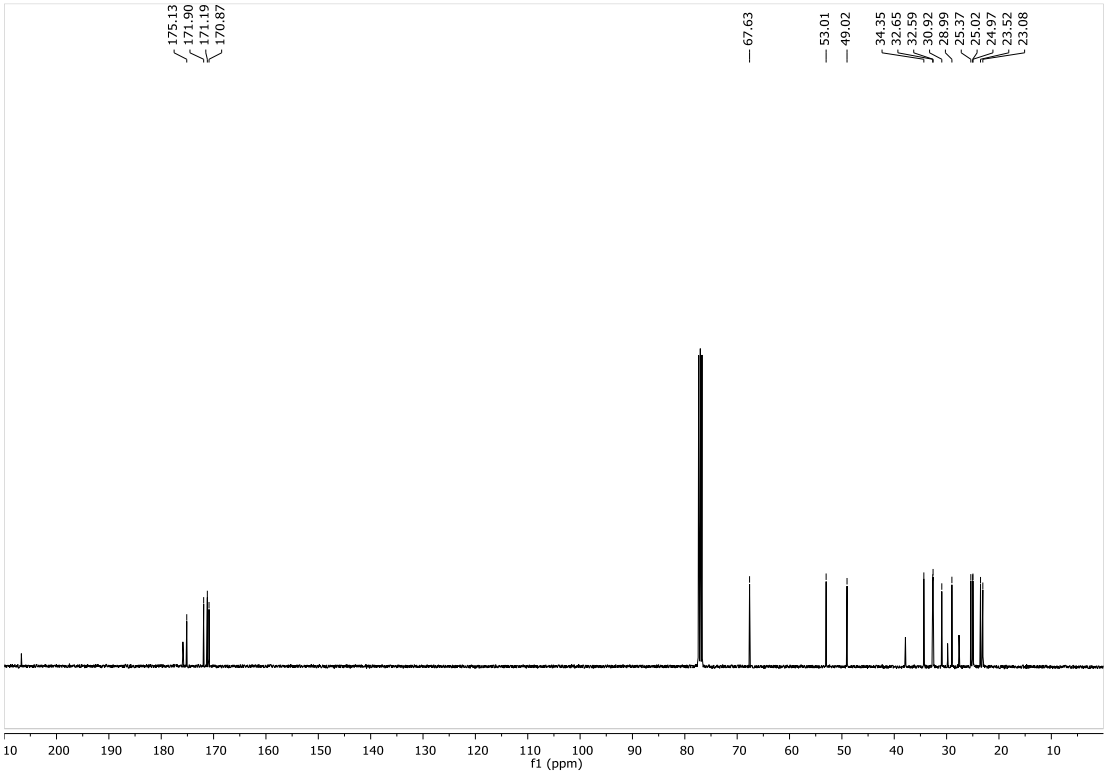
^{1}H and ^{13}C NMR spectra for compound **(*R*,*S*)-3a**



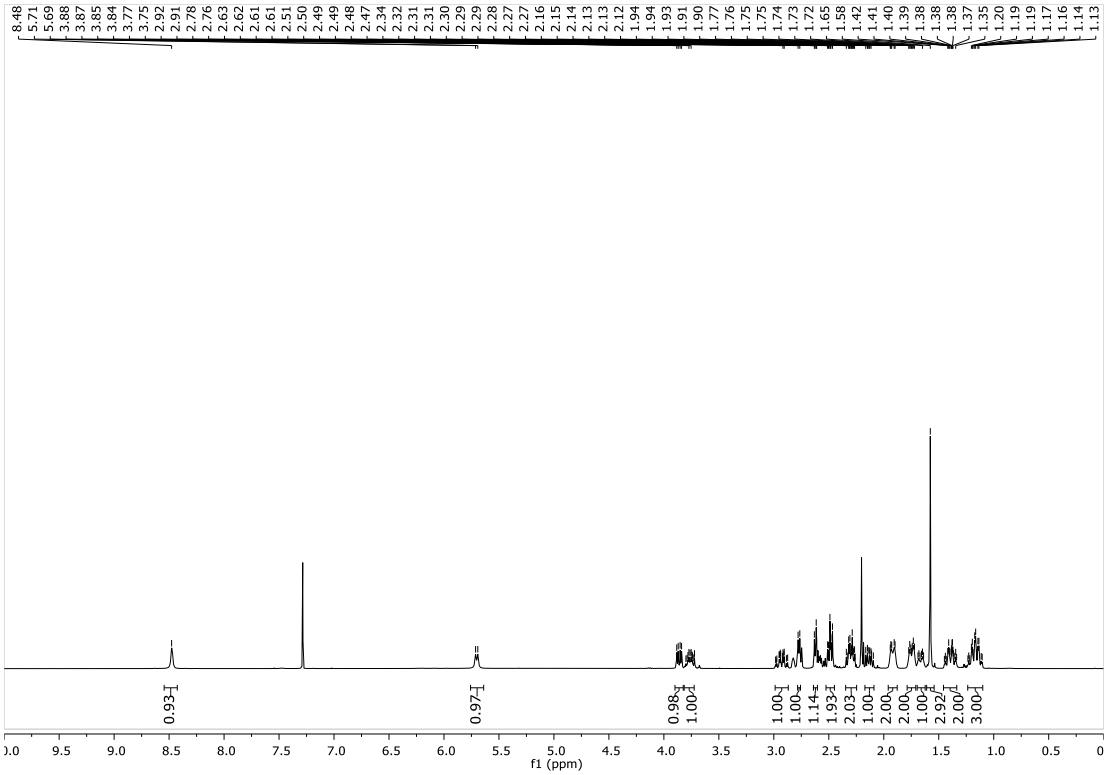


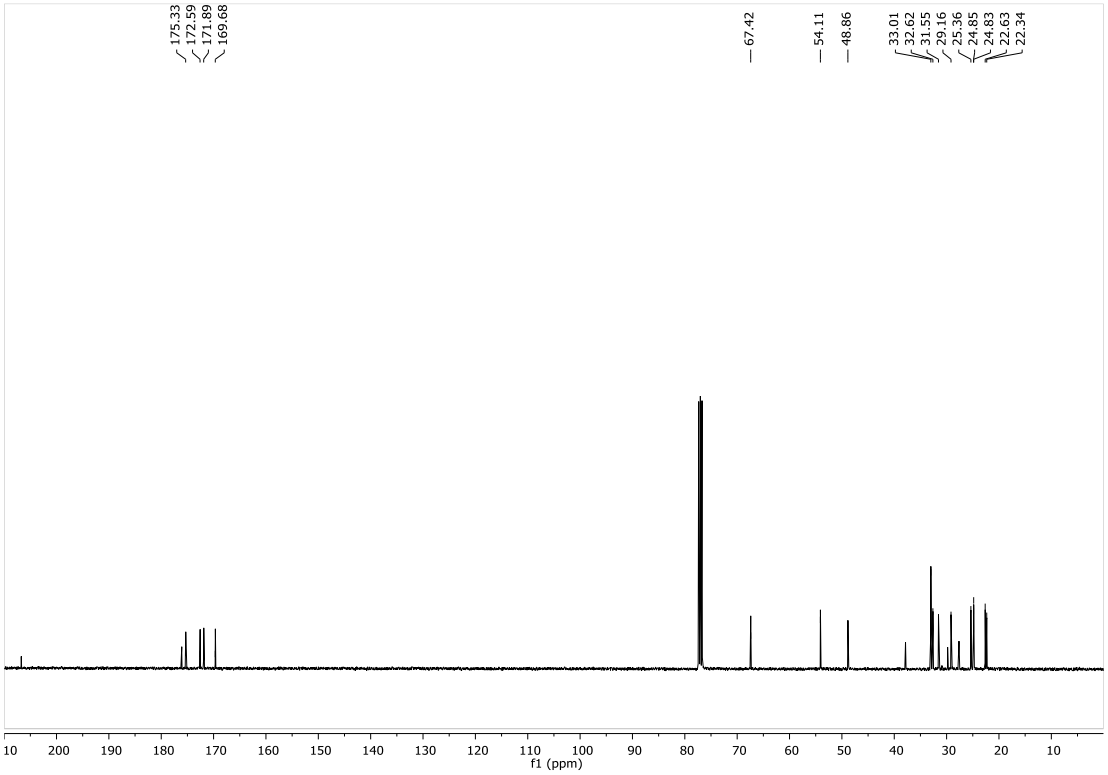
^{1}H and ^{13}C NMR spectra for compound **(*S*,*S*)-3b**



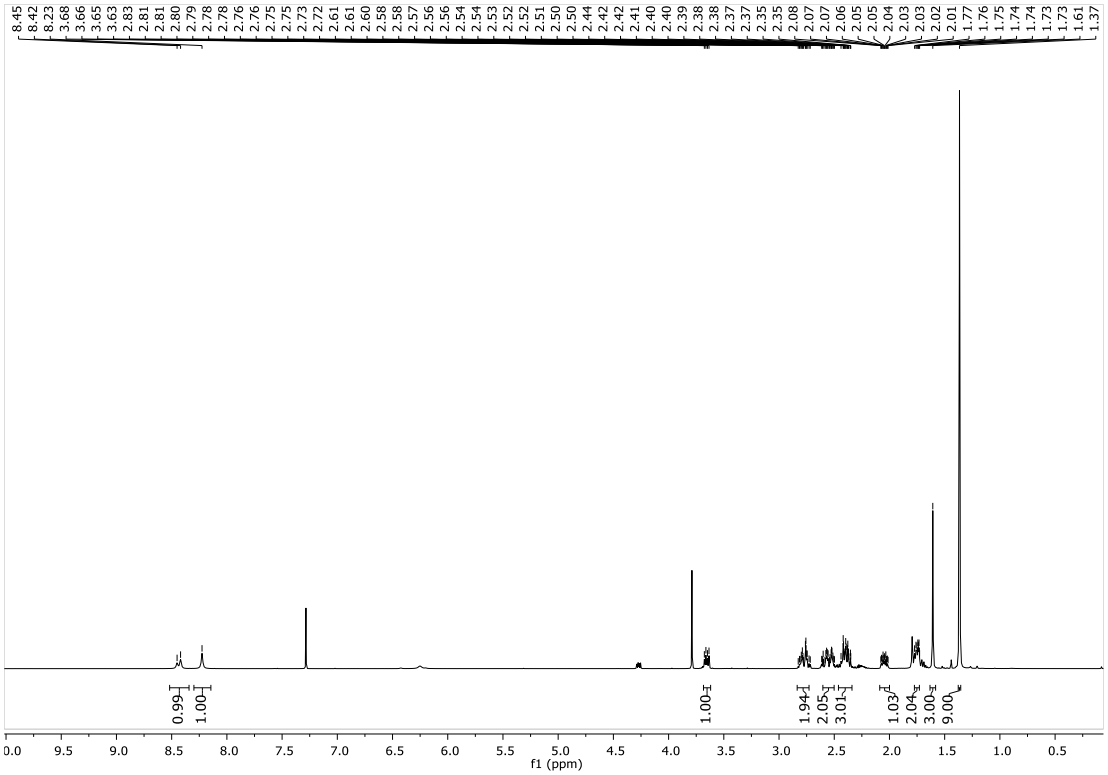


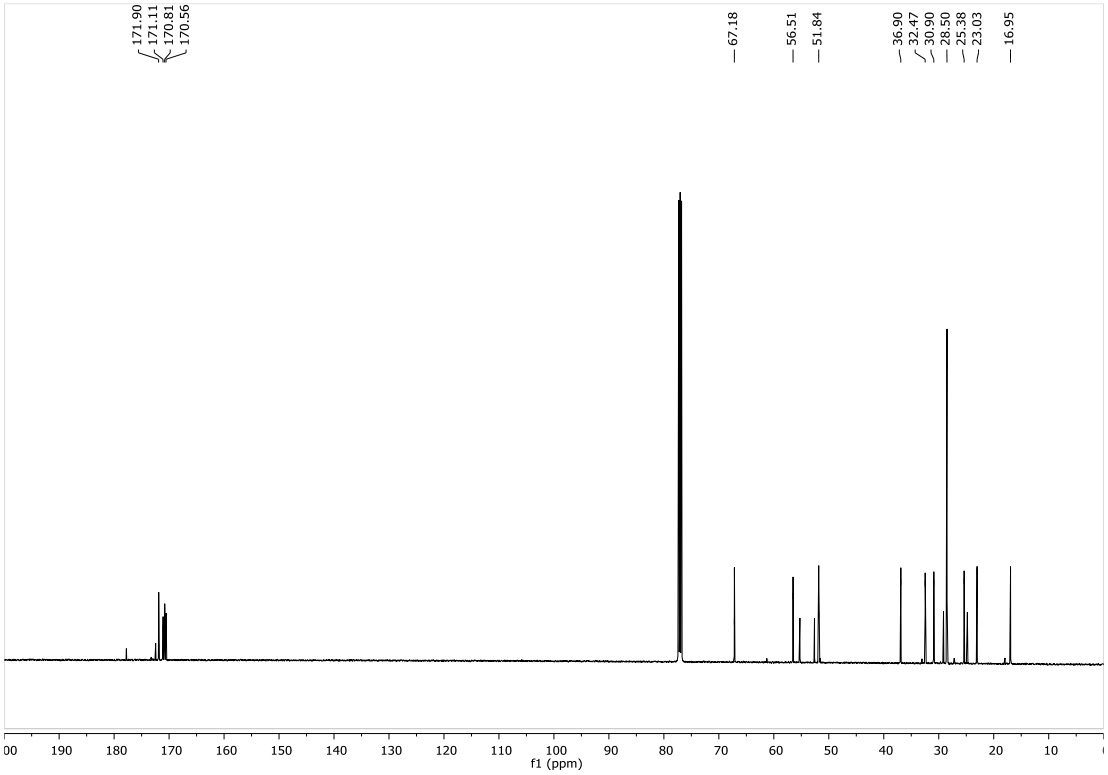
^{1}H and ^{13}C NMR spectra for compound **(*R*,*S*)-3b**



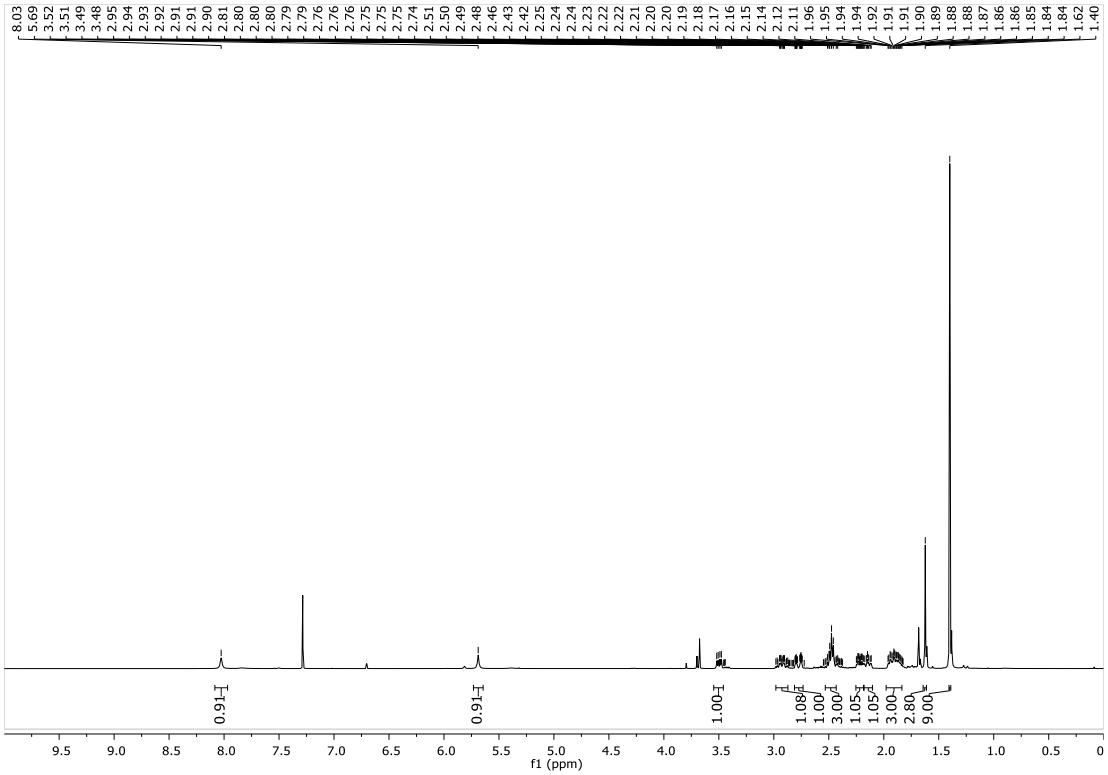


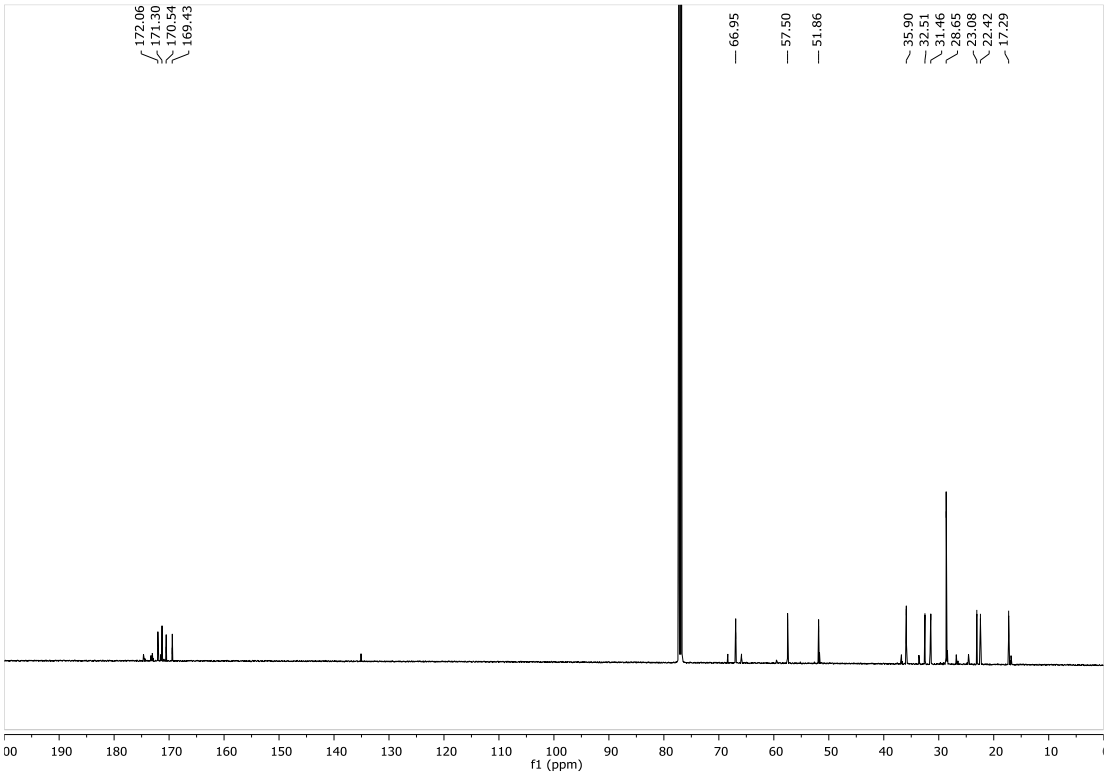
^{1}H and ^{13}C NMR spectra for compound **(*S*,*S*)-3c**



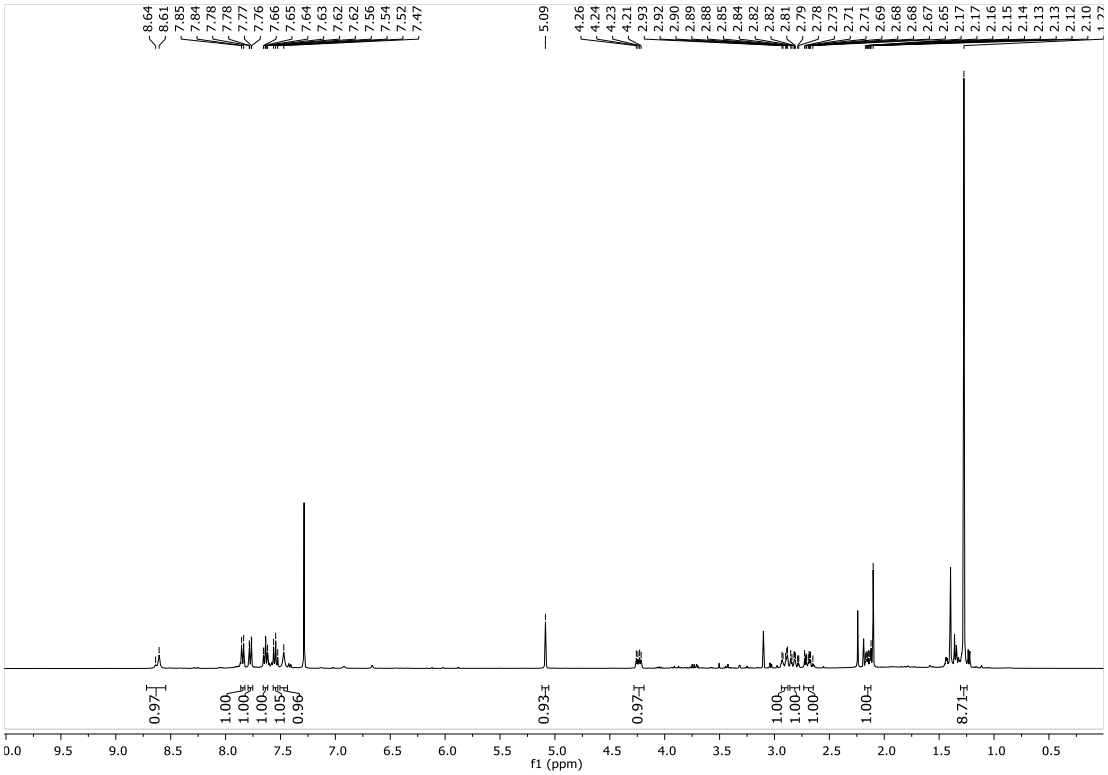


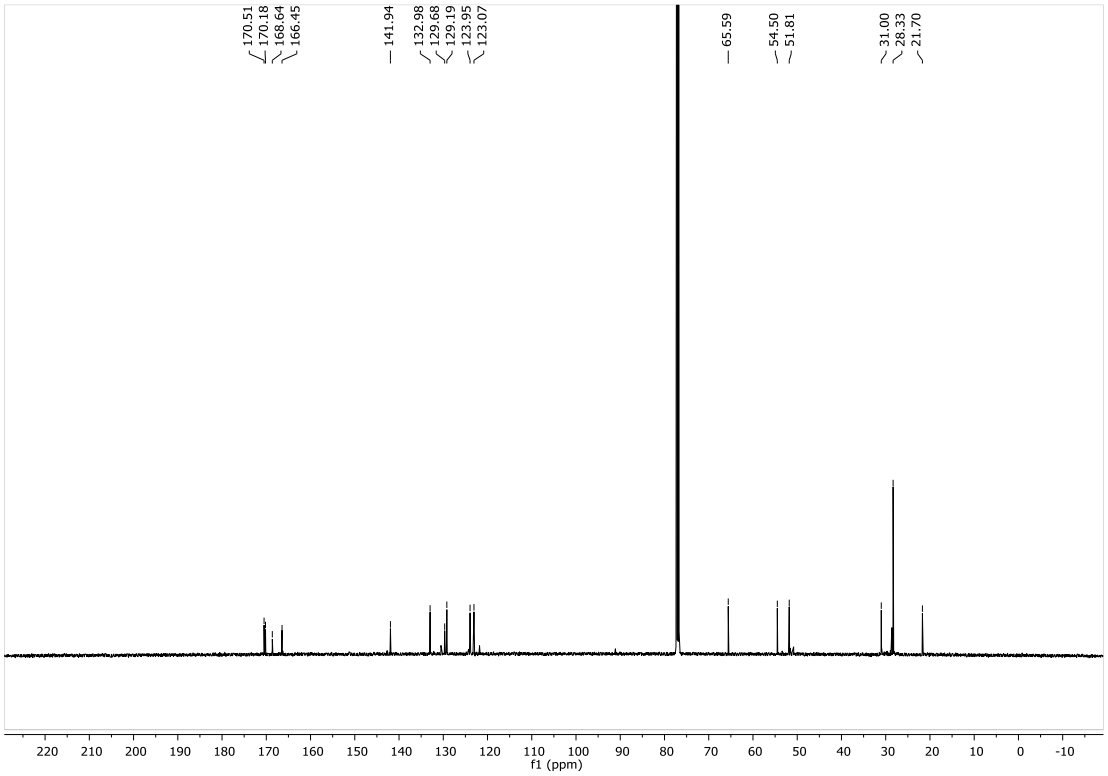
^{1}H and ^{13}C NMR spectra for compound **(*R*,*S*)-3c**





^{1}H and ^{13}C NMR spectra for compound **(*S*,*S*)-3d**





^{1}H and ^{13}C NMR spectra for compound **(*R*,*S*)-3d**