Supplementary Material

Synthesis of 1,3,4-oxadiazole derivatives from α-amino acid and acyl hydrazides under thermal heating or microwave irradiation conditions

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Table of Contents

1. General Information

Hydrogen nuclear magnetic resonance (^{1}H NMR) spectra were obtained on a Bruker DPX - 400 MHz or DPX - 200 MHz spectrometer. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in parts per million, referenced to the solvent peak of TMS. Data are reported as follows: chemical shift (d), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, sext = sextet, m = multiplet), and coupling constant (*J*) in Hertz and integrated intensity. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were obtained at 50 MHz or 100 MHz. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$. Selenium nuclear magnetic resonance (^{77}Se NMR) spectra were recorded on a Bruker DPX 400 MHz, at 76.28 MHz with diphenyl diselenide as the ^{77}Se external reference (463 ppm). Accurate mass measurement was performed on XEVO G2 QTOF-Waters mass spectrometer. Optical rotations were carried out on a Perkin Elmer Polarimeter 341. Column chromatography was performed using Merck Silica Gel (230-400 mesh). Thin layer chromatography (TLC) was performed using Merck Silica Gel GF254, 0.25 mm. For visualization, TLC plates were either placed under ultraviolet light or stained with iodine vapor or acidic vanillin. The following solvents were dried and purified by distillation from the reagents indicated: THF from sodium with benzophenone indicator, 1,4-dioxane from KOH and toluene under P_2O_5. All other solvents were ACS or HPLC grade unless otherwise noted.

2. General procedure for the synthesis of 1,3,4-oxadiazoles (1a-6d)

Method A - conventional thermal heating: To a 50 mL round-bottomed flask equipped with a reflux condenser, under argon atmosphere, $POCl_3$ (4.3 mmol) was added to a solution of the appropriate *N*-protected amino acid **1-6** (0.5 mmol) and the aryl hydrazide **a-d** (0.5 mmol) in of dry 1,4-dioxane (8 mL). The reaction mixture was heated under stirring at 80-100 ^{o}C for the time indicated in **Table 1**. After this time, the mixture was cooled to room temperature, and the product was extracted with CH_2Cl_2 (30 mL), added 2 mol/L HCl (10 mL), and washed with saturated sodium bicarbonate solution and then with water. The organic phase was dried over magnesium sulfate and the solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel (hexane-ethyl acetate, 7:3) to afford pure products (**1a-6d**)

Method B: microwave irradiation: To a 5 mL glass tube, $POCl_3$ (4.3 mmol) was added to this mixture of *N*-protected amino acid **1-6** (0.5 mmol) and aryl hydrazide **a-d** (0.5 mmol). For the reactions using *N*-protected selenoamino acid **6** were used 1 mL of 1,4-dioxane to solubilize the starting materials. The reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 100 ± 5 ºC, power 200-250 W. The tube was irradiated in the microwave oven for appropriate time and temperature (according to **Table 2**). After completion of the reaction (monitored by TLC using hexane:ethyl acetate, 7:3). The work-up and purification step was the same used for conventional thermal heating.

Ethyl (*S*)-N-[1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]carbamate (1a). Yield: 51% (Method A) and 62% (Method B). White solid, mp 84 - 86 °C. $[\alpha]_D^{20}$ = -34 (*c* 1.0

AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 6.6 Hz, 2H), 7.56 - 7.46 (m, 3H), 5.49 - 5.45 (m, 1H), 5.26 - 5.17 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 1.68 (d, J = 7.0 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.03, 165.12, 155.68, 131.80, 129.01, 126.94, 123.68, 61.45, 43.56, 19.76, 14.49. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{13}H_{15}N_3NaO_3$ 284.1011, found 284.1017.

Ethyl (*S*)-N-[2-phenyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]carbamate (2a). Yield: 63% (Method A) and 70% (Method B). White solid, mp 87 - 89 °C. $[\alpha]_D^{25}$ = -12 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.66 - 7.62 (m, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.30 - 7.24 (m, 3H), 7.16 (d, J = 6.6 Hz, 2H), 5.56 (d, J = 8.7 Hz, 1H), 5.44 - 5.37 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.32 (d, J = 6.7 Hz, 2H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.31, 163.65, 155.72, 135.31, 134.73, 130.53, 129.71, 129.25, 128.69, 127.29, 125.38, 123.01, 61.51, 48.88, 39.82, 14.42. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{19}H_{19}N_3NaO_3$ 360.1324, found 360.1325.

Ethyl (*S*)-N-[3-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)butyl]carbamate (3a).Yield: 55% (Method A) and 67% (Method B). White solid, mp 67 - 69 °C. $[\alpha]_D^{25}$ = -18 (*c* 1.0 AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ = δ 8.07 - 7.98 (m, 2H), 7.55 - 7.44 (m, 3H), 5.82 (d, J = 9.3 Hz, 1H), 5.29 - 5.15 (m, 1H), 4.16 (q, J = 7.1 Hz, 2H), 1.91 - 1.73 (m, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.00 (d, J = 6.1 Hz, 6H).^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.93, 164.80, 156.08, 131.73, 128.99, 126.86, 123.64, 61.40, 52.16, 38.80, 25.00, 15.15, 14.44, 11.26. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{16}H_{21}N_3NaO_3$ 326.1481, found 326.1477.

Ethyl (*R*)-N-[2-(benzylthio)-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]carbamate (4a). Yield: 40 % (Method A) and 54% (Method B). White solid, mp 79 - 81°C. $[\alpha]_D^{25}$ = -11 (*c* 1.0, AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.04 - 7.94 (m, 2H), 7.57 - 7.43 (m, 3H), 7.32 - 7.21 (m, 5H), 5.70 (d, J = 9.2 Hz, 1H), 5.36 - 5.24 (m, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.70 (s, 2H), 3.06 - 2.95 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.23, 165.17, 155.75, 137.26, 131.90, 129.01, 128.90, 128.61, 127.28, 126.95, 123.42, 61.65, 47.23, 36.42, 34.43, 14.47. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{20}H_{21}N_3NaO_3S$ 406.1201, found 406.1221.

Ethyl (*S*)-N-[3-(methylthio)-1-(5-phenyl-1,3,4-oxadiazol-2-yl)propyl]carbamate (5a). Yield: 58% (Method A) and 63% (Method B). White solid, mp 81 - 83 °C, $[\alpha]_D^{20}$ = -32 (*c* 1.0, AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 - 7.96 (m, 2H), 7.59 - 7.42 (m, 3H), 5.57 - 5.48 (m, 1H), 5.38 - 5.21 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2H), 2.43 - 2.30 (m, 1H), 2.29 - 2.17 (m, 1H), 2.12 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.02, 165.15, 155.87, 131.83, 129.03, 126.98, 123.69, 61.59, 47.00, 33.13, 29.90, 15.48, 14.47. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{15}H_{19}N_3NaO_3S$ 344.1045, found 344.1043.

Ethyl (*R*)-N-[1-(5-phenyl-1,3,4-oxadiazol-2-yl)-2-(phenylselanyl)ethyl]carbamate (6a). Yield: 51% (Method A) and 52% (Method B). White solid, mp 89 - 91 °C, $[\alpha]_D^{20}$ = -3 (*c* 1.0 AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.88 (d, J = 8.0 Hz, 2H), 7.52 - 7.40 (m, 5H), 7.11 (d, J = 7.0 Hz, 2H), 5.95 (d, J = 9.0 Hz, 1H), 5.49 - 5.38 (m, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.50 (d, J = 5.9 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C

NMR (100 MHz, $CDCl_3$): δ = 164.96, 155.56, 133.60, 131.71, 129.13, 128.82, 128.15, 127.59, 126.85, 123.37, 61.53, 47.88, 31.58, 14.40. ^{77}Se (76,28 MHz, $CDCl_3$) δ = 263.5 (*vs.* PhSeSePh at 463.0 ppm as an external standard)[1]. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{19}H_{19}N_3NaO_3Se$ 440.0489, found 440.0490.

Ethyl (*S*)-N[-1-(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)ethyl]carbamate (1b). Yield: 45% (Method A) and 63% (Method B). Yellow solid, mp 93 - 95 °C. $[\alpha]_D^{25}$=-10 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.37 (br s, 1H), 5.24 – 5.13 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 1.66 (d, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.73, 165.28, 155.67, 142.34, 129.71, 126.87, 121.01, 61.43, 43.66, 21.54, 19.81, 14.49. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{14}N_{17}N_3NaO_3$ 298.1168, found 298.1170.

Ethyl (*S*)-N-[2-phenyl-1-(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)ethyl]carbamate (2b). Yield: 40% (Method A) and 72% (Method B). White solid, mp 120 - 122 °C, $[\alpha]_D^{25}$ = -21 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ =7.84 (d, *J* = 8.1 Hz, 2H), 7.29 - 7.23 (m, 5H), 7.15 (d, *J* = 6.6 Hz, 2H), 5.57 (d, *J* = 8.8 Hz, 1H), 5.41 (br s, 1H), 4.11 (q, *J* = 6,8Hz, 2H), 3.35 - 3.28 (m, 2H), 2.41 (s, 3H), 1.21 (t, *J* = 6.8 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.64, 165.10, 155.76, 142.37, 135.30, 129.67, 129.28, 128.63, 127.18, 126.83, 120.71, 61.42, 48.83, 39.84, 21.54, 14.41. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{20}N_{21}N_3NaO_3$ 374.1481, found 374.1494.

Ethyl (*S*)-N-[3-methyl-1-(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)butyl]carbamate (3b). Yield: 41% (Method A) and 60% (Method B). White solid, mp 84 - 86 °C. $[\alpha]_D^{25}$ = -15 (*c* 1,0; AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.70 (d, *J* = 9.3 Hz, 1H), 5.15 - 5.02 (m, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 2.42 (s, 3H), 2.05 (s, 1H), 1.66 - 1.48 (m, 1H), 1.25 (t, *J* = 7.0 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 6H).^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.65, 164.88, 156.09, 142.25, 129.61, 126.73, 120.73, 61.28, 52.06, 38.68, 24.90, 21.50, 15.10, 14.38, 11.22. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{17}N_{23}N_3NaO_3$ 340.1637, found 340.1654.

Ethyl (*R*)-N-[2-(benzylthio)-1-(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)ethyl]carbamate (4b). Yield: 30% (Method A) and 55% (Method B). White solid, mp 88 - 90 °C. $[\alpha]_D^{25}$ = -5,0 (*c* 1,0; AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.2 Hz, 2H), 7.35 - 7.28 (m, 6H), 5.60 - 5.52 (m, 1H), 5.37 - 5.26 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.70 (d, *J* = 5.7 Hz, 2H), 3.02 (dd, *J* = 6.1, 1.8 Hz, 2H), 2.44 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.30, 165.18, 155.70, 137.38, 131.84, 129.00, 128.90, 128.60, 127.28, 126.99, 123.62, 61.63, 47.53, 42.63, 36.62, 34.69, 14.45. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{21}H_{23}N_3NaO_3S$ 420.1358, found 420.1365.

Ethyl (*S*)-N-[3-(methylthio)-1-(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)propyl]carbamate (5b). Yield: 35% (Method A) and 64% (Method B). White solid, mp 90 - 92 °C. $[\alpha]_D^{25}$ = -5,0 (*c* 1,0 AcOEt). ^{1}H NMR (400MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.50 (br s, 1H), 5.32 - 5.25 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.64 (t, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 2.39 - 2.30 (m, 1H), 2.27 - 2.16 (m, 1H), 2.12 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.72, 165.31,

155.89, 142.44, 129.74, 126.95, 120.91, 61.58, 47.01, 33.18, 29.90, 21.54, 15.48, 14.47. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{16}H_{21}N_3NaO_3S$ 358.1201, found 358.1220.

Ethyl (*R*)-N-[2-(phenylselanyl)-1-(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)ethyl]carbamate (6b). Yield: 66% (Method A) and 54% (Method B). White solid, mp 107 - 109 °C. $[\alpha]_D^{25}$= -4,0 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 6.5 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.16 - 7.07 (m, 3H), 5.85 (d, *J* = 8.5 Hz, 1H), 5.41 (br s, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.49 (d, *J* = 5.6 Hz, 2H), 2.41 (s, 3H), 1.25 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ = 165.16, 164.70, 155.61, 142.33, 133.65, 129.56, 129.16, 128.19, 127.63, 126.86, 120.61, 61.56, 47.88, 31.68, 21.57, 14.43. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{20}H_{21}N_3NaO_3Se$ 454.0646, found 454.0616.

Ethyl (*S*)-N-[1-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)ethyl]carbamate (1c). Yield: 40% (Method A) and 57% (Method B). Yellow solid, mp 88 - 91°C, $[\alpha]_D^{25}$ = -45 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, DMSO): δ 7.86 (d, *J* = 8.6 Hz, 2H), 7.15 (br s, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 4.21 - 4.12 (m, 1H), 4.00 (q, *J* = 7.0 Hz, 1H), 3.82 (s, 3H), 1.30 (d, *J* = 7.1 Hz, 2H), 1.17 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO): δ= 171.96, 164.74, 161.85, 155.57, 129.17, 124.62, 113.53, 59.64, 55.26, 48.56, 18.27, 14.46. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{14}N_{17}N_3NaO_4$ 314.1117, found 314.1132.

Ethyl (*S*)-N-[-1-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-2-(phenyl)ethyl]carbamate (2c). Yield: 46% (Method A) and 70% (Method B). White solid, mp 106 - 108 °C. $[\alpha]_D^{25}$ = -17 (*c* 1,0; AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.8 Hz, 2H), 7.31 - 7.21 (m, 3H), 7.20 - 7.10 (m, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 5.51 - 5.33 (m, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 3.31 (d, *J* = 5.9 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.40, 164.97, 162.53, 155.69, 135.46, 129.36, 128.71, 128.67, 127.22, 116.24, 114.54, 61.47, 55.42, 48.99, 40.06, 14.45. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{20}N_{21}N_3NaO_4$ 390.1430, found 390.1436.

Ethyl (*S*)-N-[1-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-3-(methyl)butyl]carbamate (3c). Yield: 46% (Method A) and 70% (Method B). White solid, mp 105 - 107 °C. $[\alpha]_D^{25}$ = -8.0 (*c* 1.0. AcOEt). ^{1}H NMR (400 MHz, DMSO): δ = 7.91 (d, *J* = 8.9 Hz, 2H), 7.76 (br s, 1H), 7.14 (d, *J* = 8.9 Hz, 1H), 4.78 (t, *J* = 8.0 Hz, 1H), 4.03 (q, *J* = 7.0 Hz, 2H), 3.85 (s, 3H), 2.05 - 1.96 (m, 1H), 1.60 - 1.49 (m, 1H), 1.32 - 1.20 (m, 1H), 1.17 (t, *J* = 7.0 Hz, 3H), 0.91 - 0.82 (m, 6H).^{13}C NMR (100 MHz, DMSO): δ = 165.51, 163.83, 162.03, 156.08, 128.30, 115.62, 114.88, 60.19, 55.50, 51.67, 36.97, 24.82, 15.23, 14.49, 10.72. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{17}N_{23}N_3NaO_4$ 356.1586, found 356.1569.

Ethyl (*R*)-N-[2-(benzylthio)-1-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)ethyl] carbamate (4c). Yield: 35% (Method A) and 53% (Method B). White solid, mp 75 - 77 °C. $[\alpha]_D^{25}$= -6.0(*c* 1.0 AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.9 Hz, 2H), 7.33 - 7.25 (m, 5H), 6.99 (d, *J* = 8.9 Hz, 2H), 5.66 (d, *J* = 8.4 Hz, 1H), 5.37 - 5.18 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.71 (s, 2H), 3.02 (dd, *J* = 6.2, 2.0 Hz,

2H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ*= 165.14, 164.71, 162.47, 155.77, 137.35, 128.92, 128.76, 128.61, 127.27, 115.99, 114.47, 61.63, 55.43, 47.30, 36.51, 34.58, 14.48. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{21}H_{23}N_3NaO_4S$ 436.1307, found 436.1289.

Ethyl (*S*)-N-[1-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-3-(methylthio)propyl] carbamate (5c). Yield: 42% (Method A) and 60% (Method B). White solid, mp 52 - 54 °C. $[\alpha]_D^{25}$ = -11 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): *δ*= 7.95 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 5.78 - 5.69 (m, 1H), 5.32 - 5.23 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 2.65 (t, *J* = 7.3 Hz, 2H), 2.40 - 2.30 (m, 1H), 2.28 - 2.17 (m, 1H), 2.12 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ*= 165.45, 165.00, 162.40, 155.91, 128.65, 115.99, 114.42, 61.45, 55.36, 46.81, 32.95, 29.81, 15.39, 14.43. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{16}H_{21}N_3NaO_4S$ 374.1150, found 374.1129.

Ethyl (*R*)-N-[1-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-2-(phenylselanyl)ethyl] carbamate (6c). Yield: 42% (Method A) and 60% (Method B). White solid, mp 101 - 103 °C. $[\alpha]_D^{25}$ = -11 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): *δ*= 7.82 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.16 - 7.08 (m, 3H), 6.94 (d, *J* = 8.3 Hz, 2H), 6.02 (d, *J* = 8.7 Hz, 1H), 5.39 (br s, 1H), 4.13 (q, *J* = 7.0 Hz, 2H), 3.85 (s, 3H), 3.49 (d, *J* = 5.7 Hz, 2H), 1.24 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ*= 164.82, 164.41, 162.23, 155.58, 133.48, 129.05, 128.57, 128.25, 127.47, 115.77, 114.20, 61.41, 55.29, 47.81, 31.40, 14.35. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{20}H_{21}N_3NaO_3Se$ 470.0595, found 470.0598.

Ethyl (*S*)-N-[1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)ethyl]carbamate (1d). Yield: 44% (Method A) and 50% (Method B). White solid, mp 95 - 97 °C. $[\alpha]_D^{25}$= -17 (*c* 1.0 AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): *δ* = 7.98 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 5.46 - 5.37 (m, 1H), 5.27 - 5.15 (m,1H), 4.17 (q, *J* = 7.1 Hz, 2H), 1.68 (d, *J* = 7.0 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=167.03, 165.12, 155.68, 131.80, 129.01, 126.94, 123.68, 61.45, 43.58, 19.76, 14.49. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{13}H_{14}ClN_3NaO_3$ 318.0621, found 318.0616.

Ethyl (*S*)-N-[1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-2-(phenyl)ethyl]carbamate (2d). Yield: 35% (Method A) and 62% (Method B). White solid, mp 129 - 132 °C. $[\alpha]_D^{25}$ = -7.0 (*c* 1.0 AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): *δ* = 7.88 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.32 - 7.12 (m, 5H), 5.85 (d, *J* = 8.7 Hz, 1H), 5.50 - 5.29 (m, *J* = 14.4 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.33 (d, *J* = 6.6 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): *δ* = 166.12, 164.02, 155.72, 137.96, 135.24, 129.25, 129.18, 128.55, 128.02, 127.12, 121.84, 61.36, 48.75, 39.57, 14.35. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{19}H_{18}ClN_3NaO_3$ 394.0934, found 394.0899.

Ethyl (*S*)-N-[1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-3-(methyl)butyl]carbamate (3d). Yield: 38% (Method A) and 42% (Method B). White solid, mp 89 - 91 °C. $[\alpha]_D^{25}$ = -5.0 (*c* 1.0 AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): *δ* = 7.97 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 5.48 (d, *J* = 7.5 Hz, 1H), 5.14 (br s, 1H), 4.16 (d, *J* = 7.1 Hz, 2H), 1.88

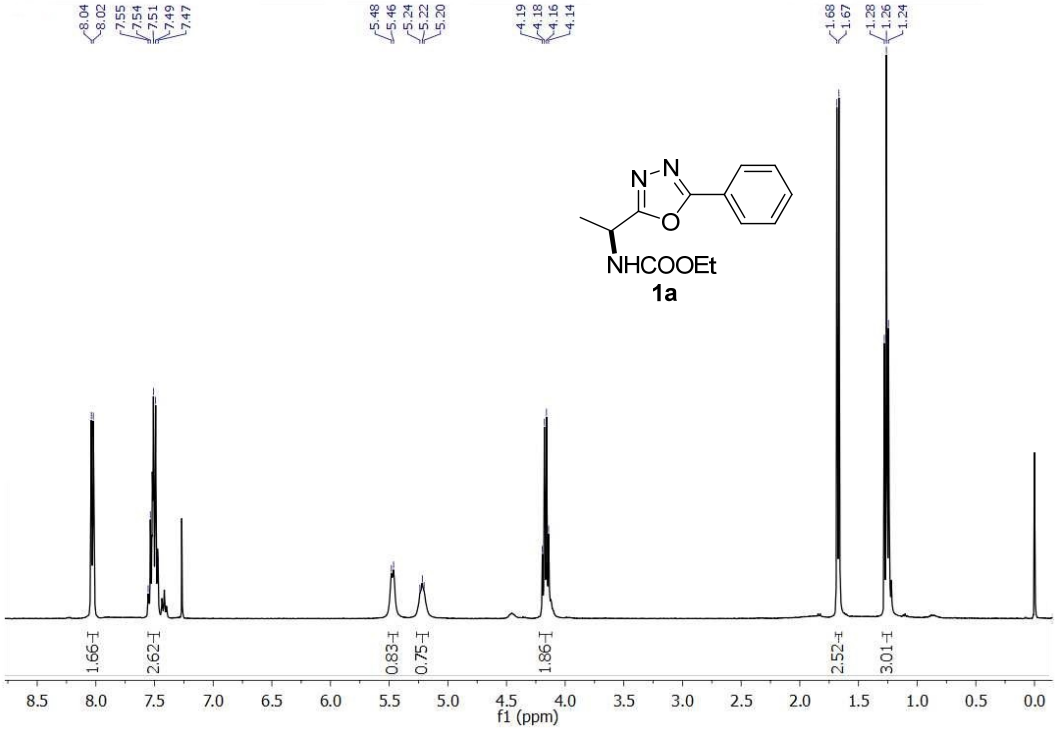
- 1.72 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 2H), 1.00 (d, *J* = 6.3 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.21, 164.05, 155.91, 138.03, 129.35, 128.15, 122.13, 61.41, 46.01, 42.68, 24.59, 22.58, 21.80, 14.44. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{16}H_{20}ClN_3NaO_3$ 360.1091, found 360.1078.

Ethyl (R)-N-[2-(benzylthio)-1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)ethyl] carbamate (4d). Yield: 35% (Method A) and 52% (Method B). Yellow solid, mp 85 - 87°C. $[\alpha]_D^{25}$ = -7.0 (*c* 1.0 AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.28 (s, 5H), 5.74 (d, *J* = 8.6 Hz, 1H), 5.39 - 5.22 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 2H), 3.02 (d, *J* = 6.2 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.63, 164.53, 155.91, 138.38, 137.45, 129.58, 129.06, 128.79, 128.40, 127.48, 122.13, 61.84, 47.46, 36.68, 34.62, 14.64. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{20}H_{20}ClN_3NaO_3S$ 440.0812, found 440.0833.

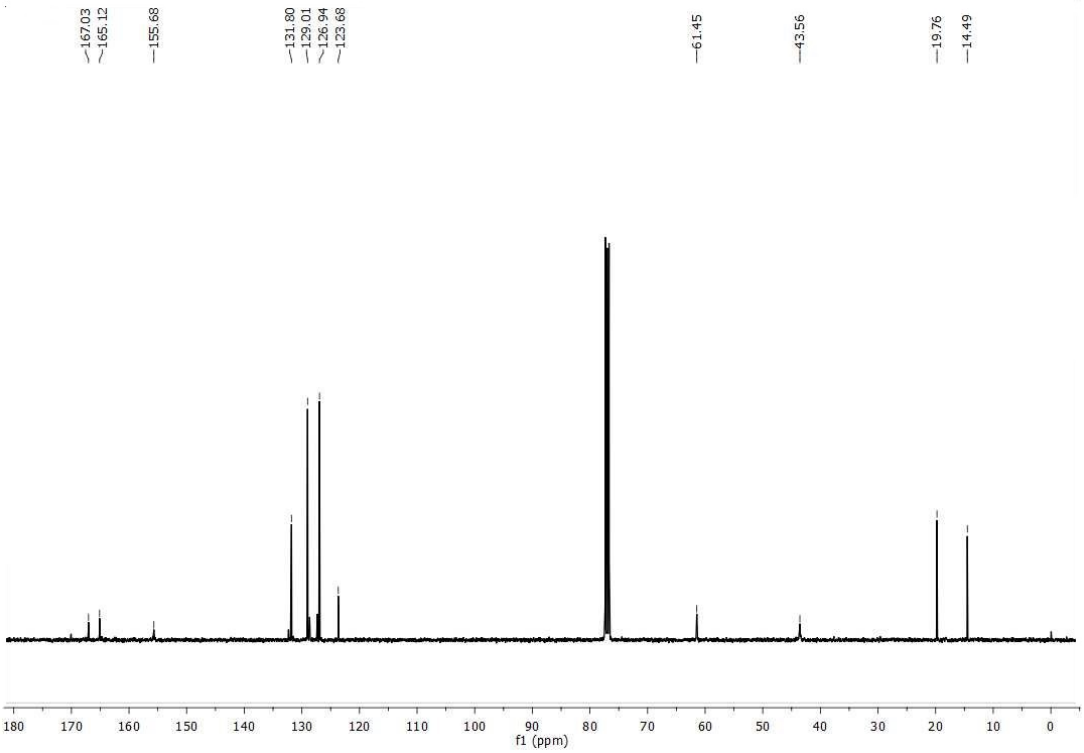
Ethyl (*S*)-N-[1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-3-(methythio)ethyl] carbamate (5d). Yield: 30% (Method A) and 43% (Method B). White solid, mp 57 - 60 °C. $[\alpha]_D^{25}$ = -4.0 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.96 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 5.61 (d, *J* = 8.8 Hz, 1H), 5.38 - 5.28 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.42 - 2.31 (m, *J* = 13.8 Hz, 1H), 2.29 - 2.18 (m, *J* = 7.1 Hz, 1H), 2.12 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.22, 164.31, 155.88, 138.20, 129.42, 128.20, 122.02, 61.60, 46.83, 32.88, 29.83, 15.46, 14.46. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{15}H_{18}ClN_3NaO_3S$ 378.0655, found 378.0660.

Ethyl (*R*)-N-[1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-2-(phenylselanyl)ethyl] carbamate (6d). Yield: 50% (Method A) and 47% (Method B). White solid, mp 103 - 105 °C. $[\alpha]_D^{25}$ = -7.0 (*c* 1.0 AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.6 Hz, 2H), 7.47 – 7.44 (m, 4H), 7.15 – 7.10 (m, 3H), 5.68 (br s, 1H), 5.41 (br s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.49 (d, *J* = 5.9 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.21, 164.26, 155.54, 138.16, 133.75, 129.33, 129.24, 128.22, 127.74, 122.01, 61.70, 48.01, 31.74, 14.46. HRMS (TOF MS ESI+) $[M+Na]^+$: Anal. Calcd for $C_{19}H_{18}ClN_3NaO_3Se$ 474.0100, found 474.0083.

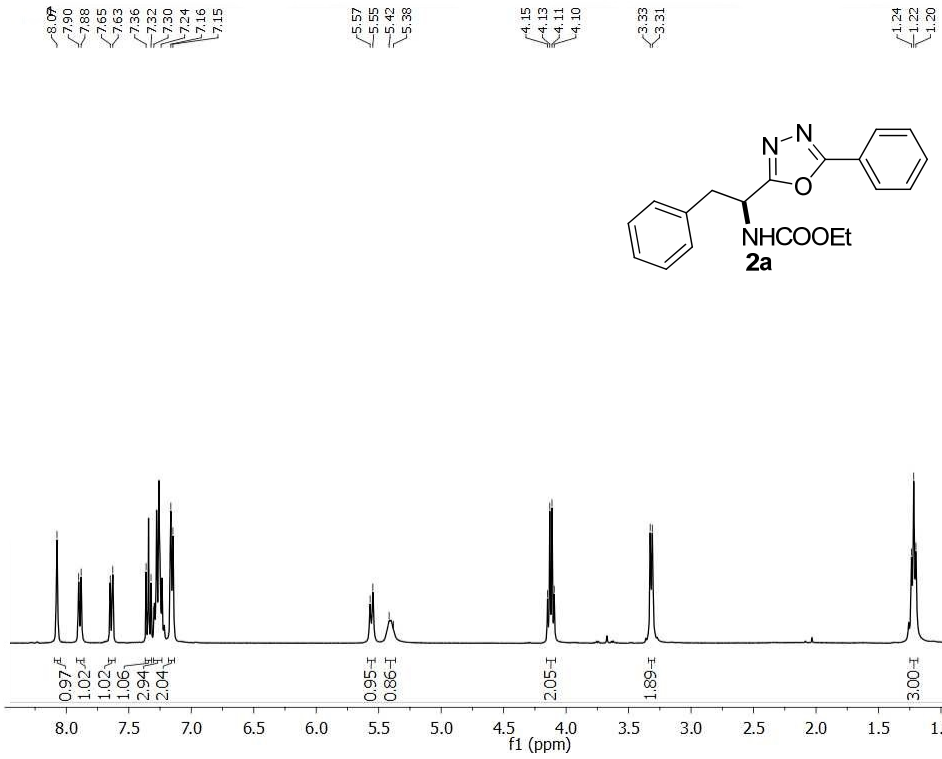
^{1}H and ^{13}C NMR Spectrum of Synthesized Compounds



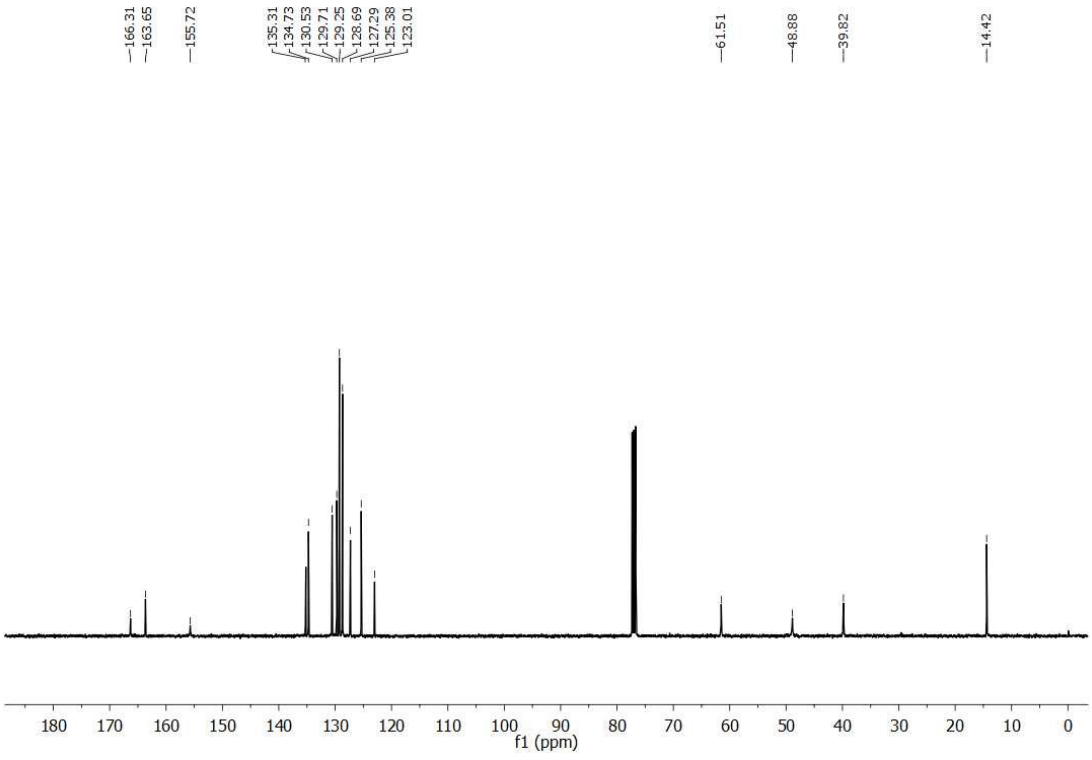
^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of compound **1a** (Table 2, entry 1).



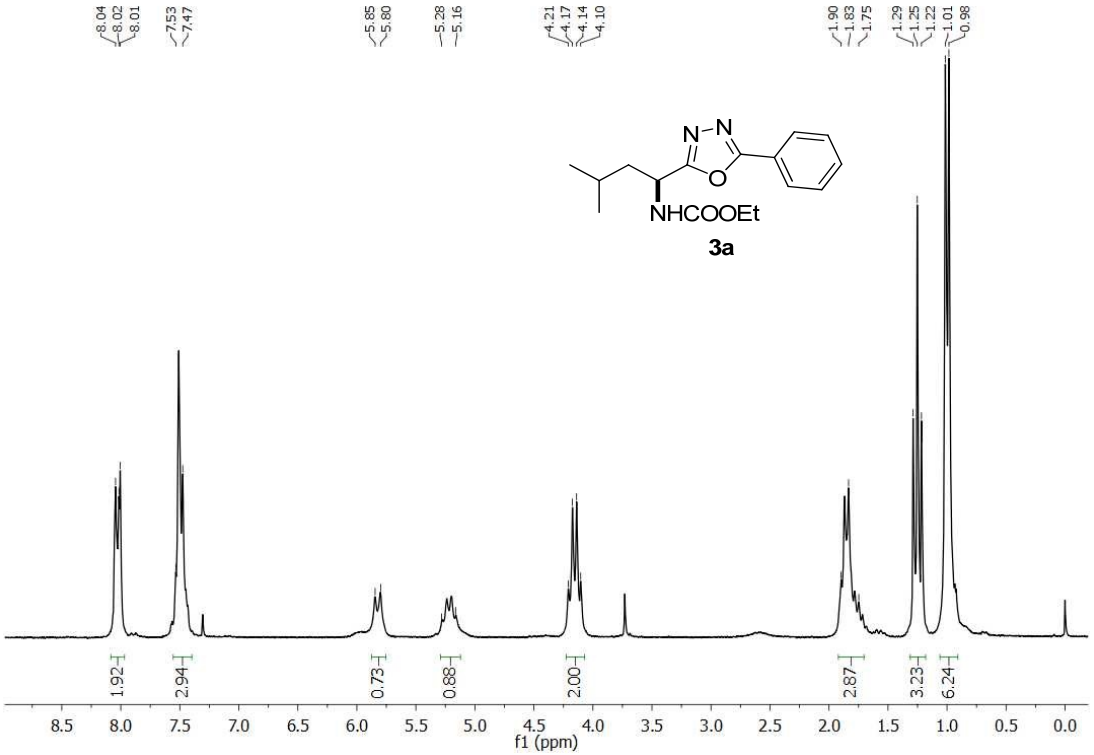
^{13}C NMR (50 MHz, $CDCl_3$) Spectrum of compound **1a** (Table 2, entry 1).



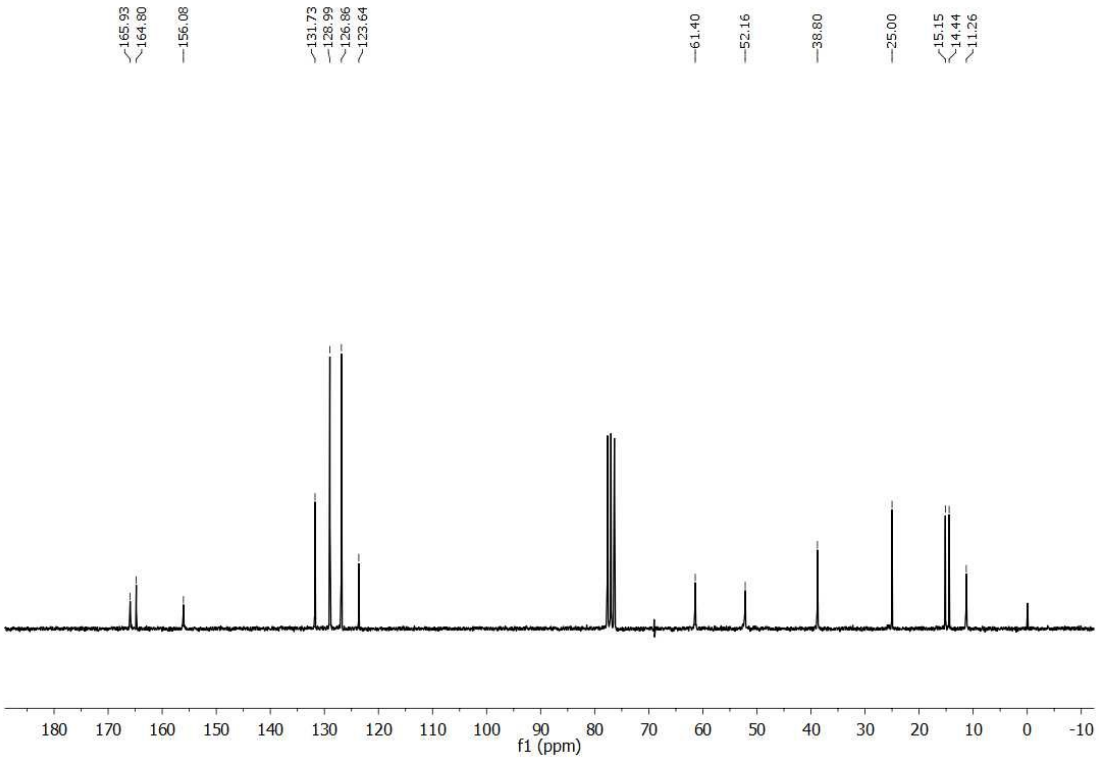
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of compound **2a** (Table 2, entry 2)



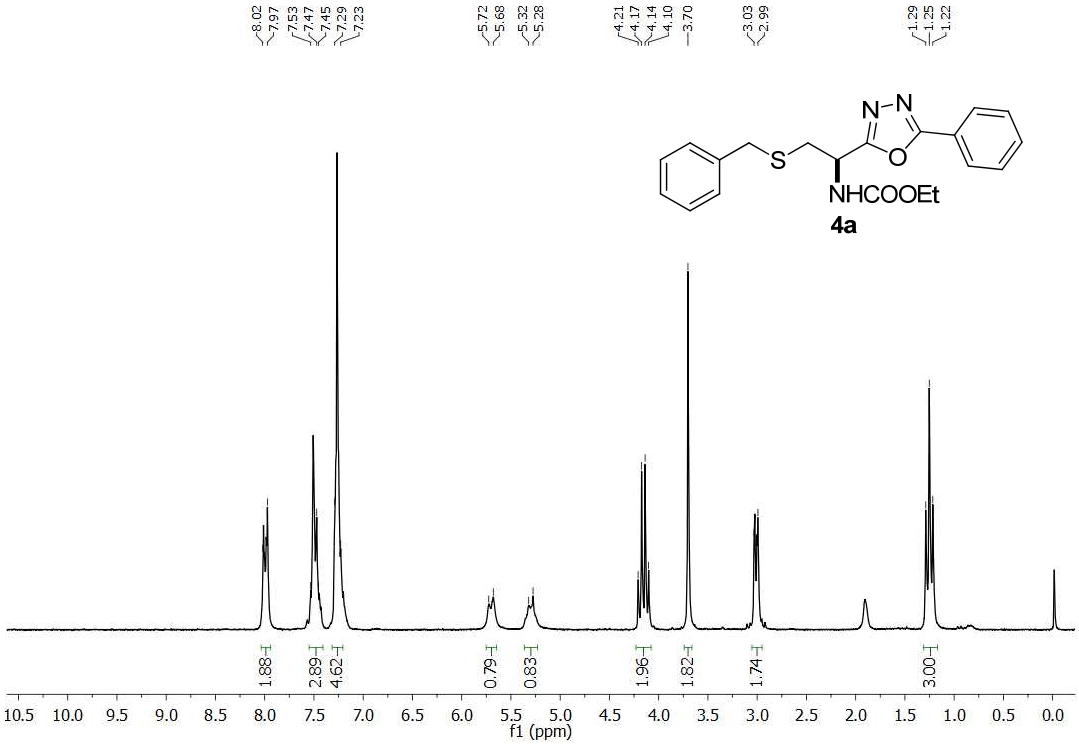
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **2a** (Table 2, entry 2).



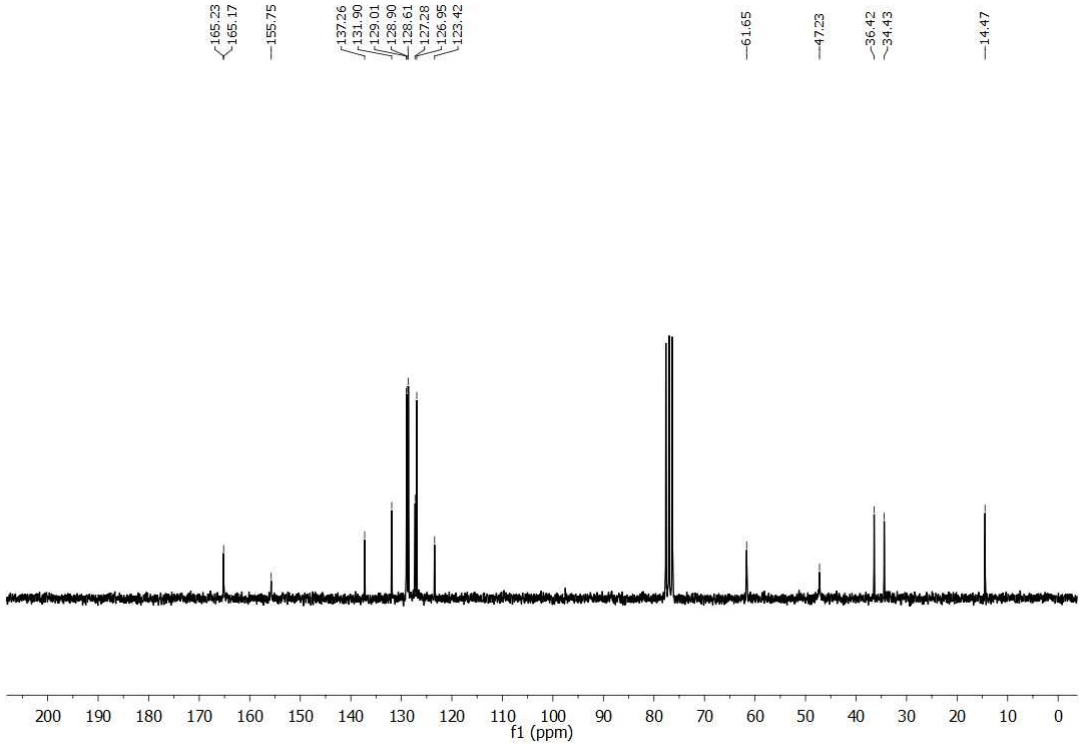
^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of compound **3a** (Table 2, entry 3).



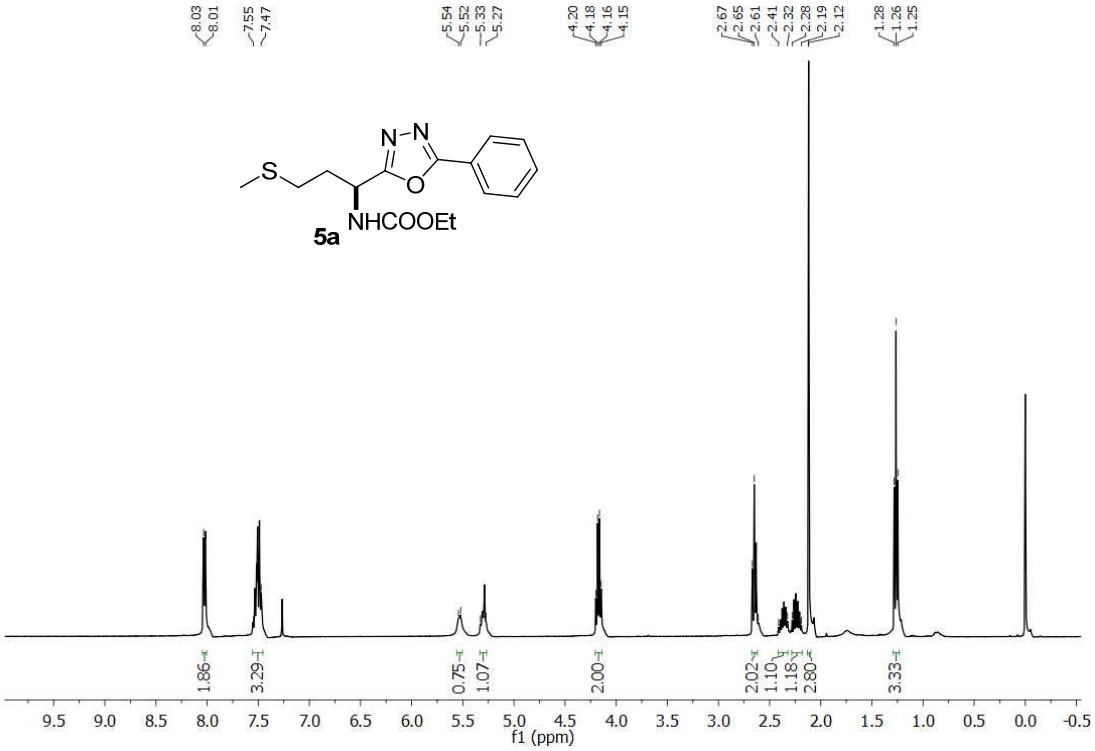
^{13}C NMR (50 MHz, $CDCl_3$) Spectrum of compound **3a** (Table 2, entry 3).



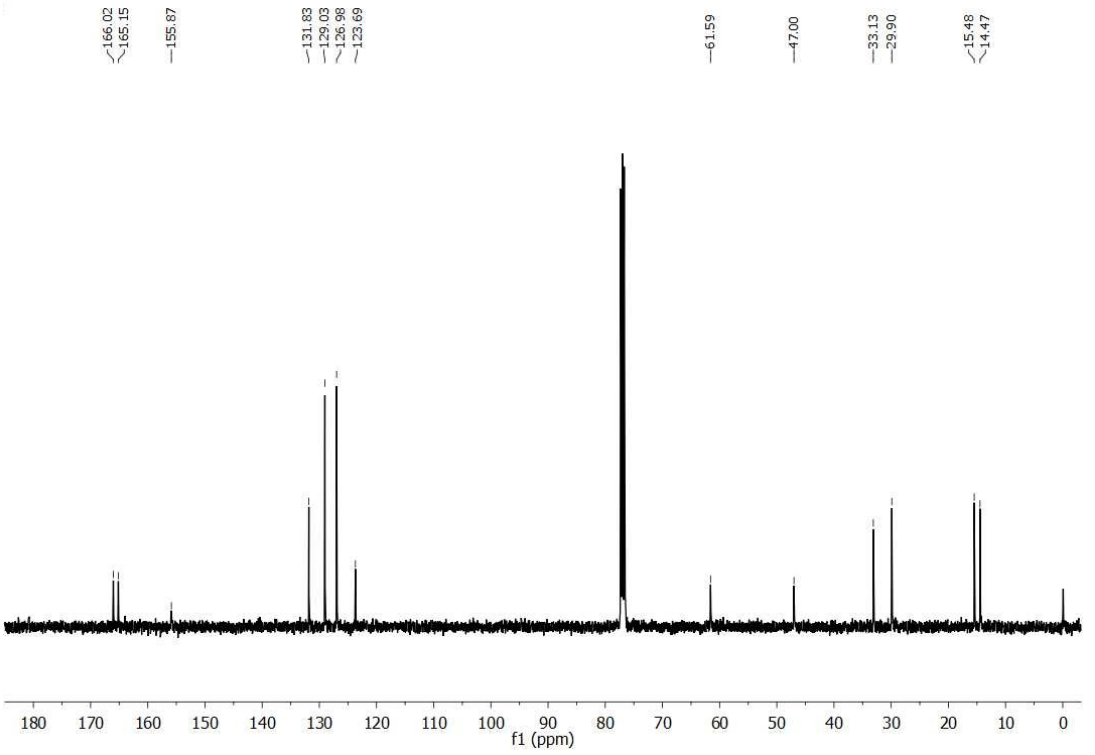
^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of compound **4a** (Table 2, entry 4).



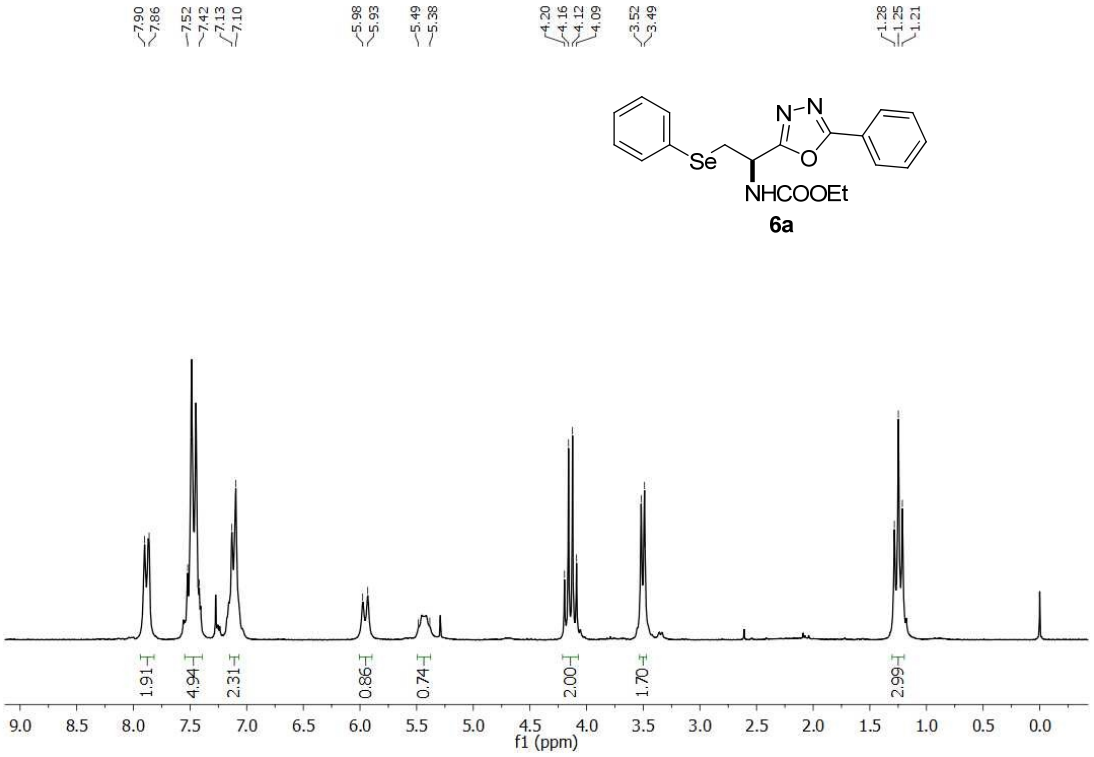
^{3}C NMR (50 MHz, $CDCl_3$) Spectrum of compound **4a** (Table 2, entry 4).



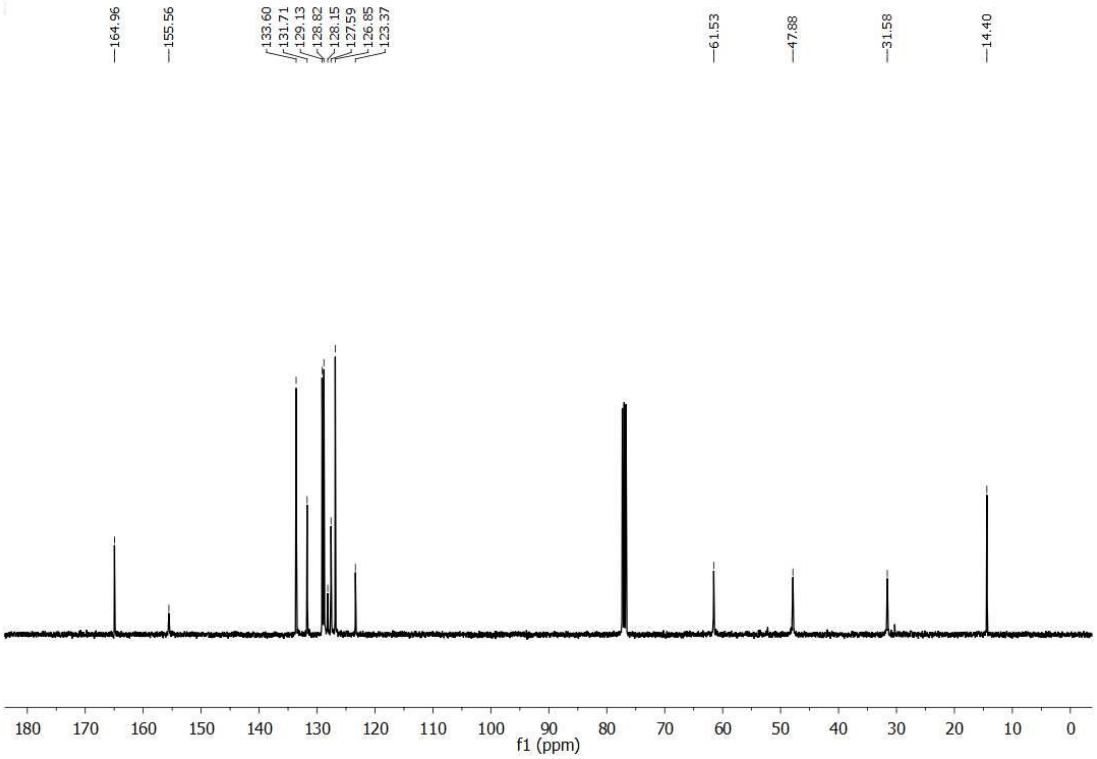
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of compound **5a** (Table 2, entry 5).



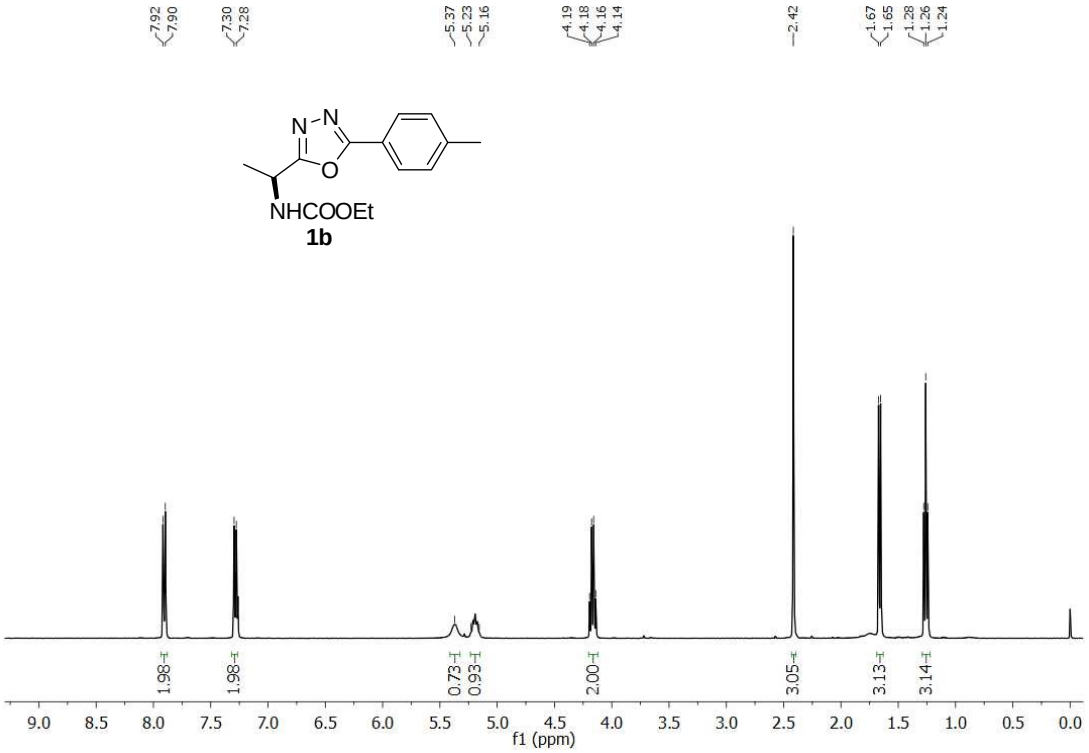
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **5a** (Table 2, entry 5).



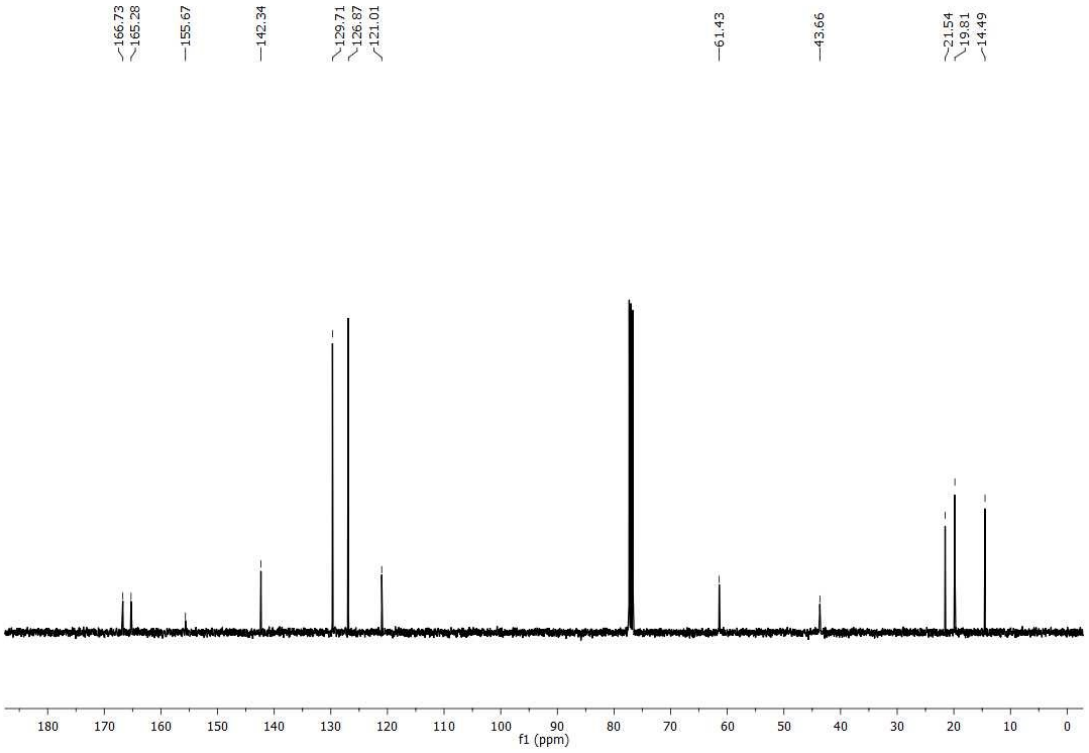
^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of compound **6a** (Table 2, entry 6).



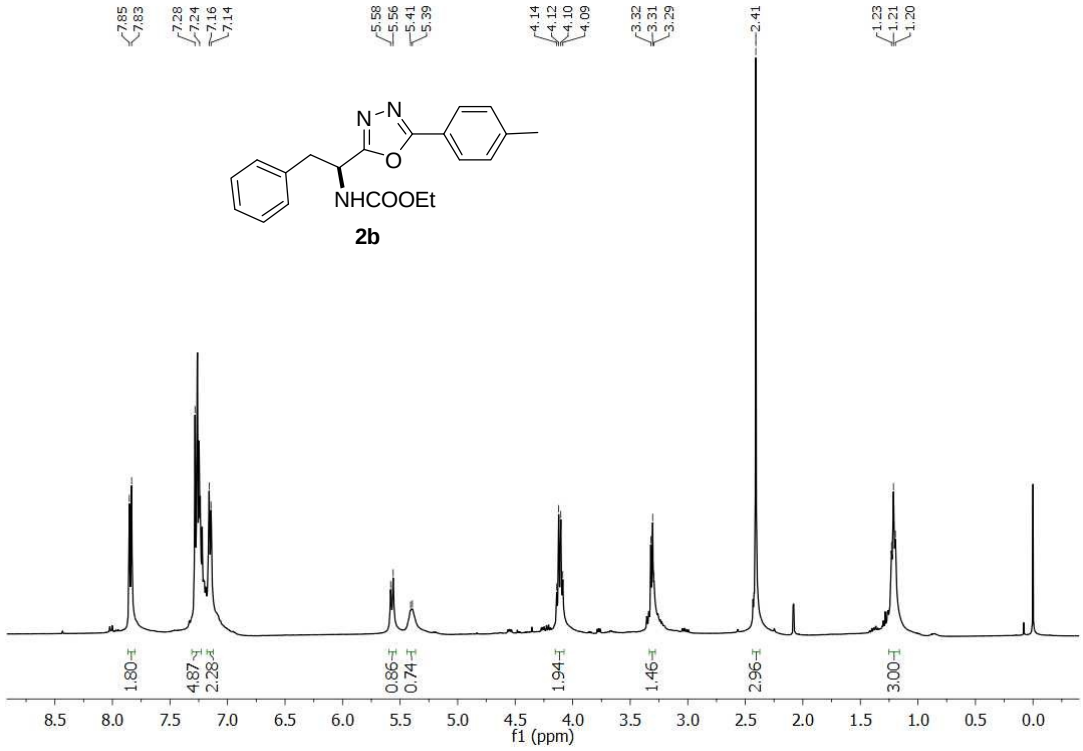
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **6a** (Table 2, entry 6)



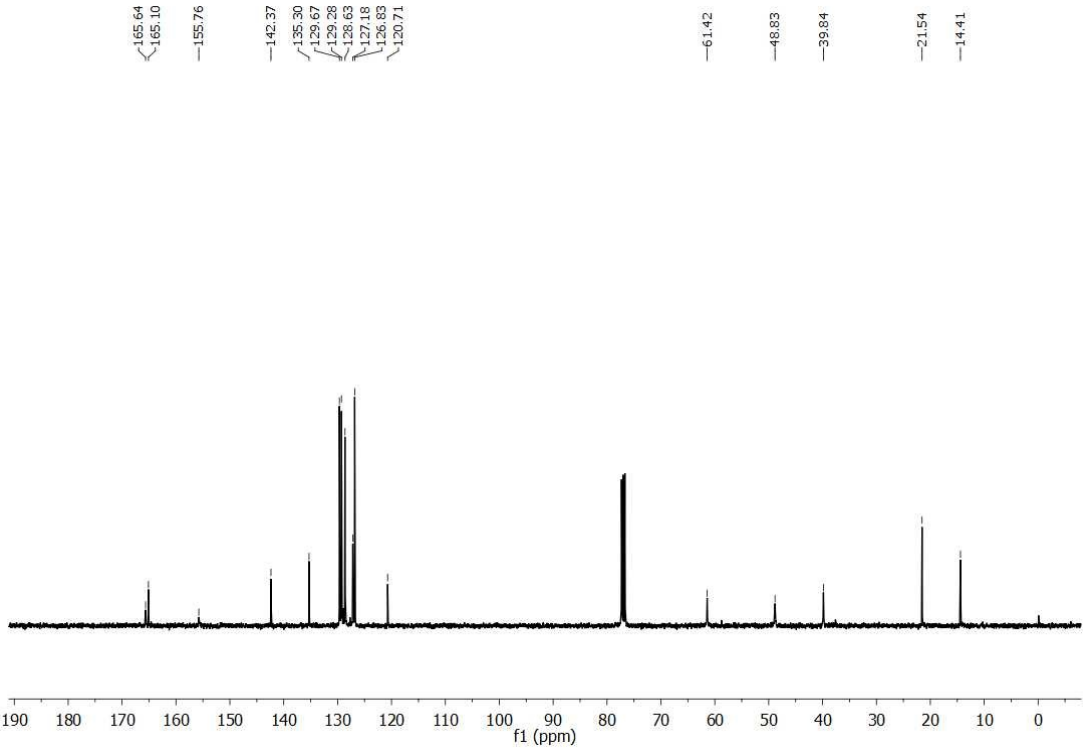
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of compound **1b** (Table 2, entry 7).



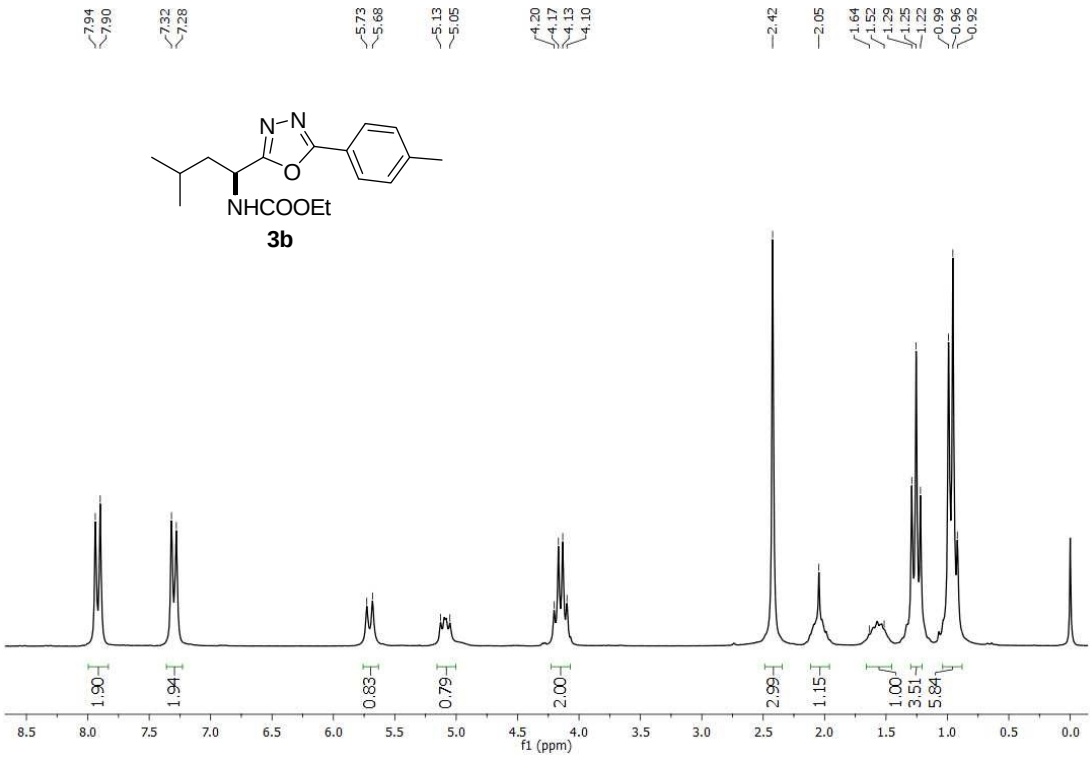
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **1b** (Table 2, entry 7).



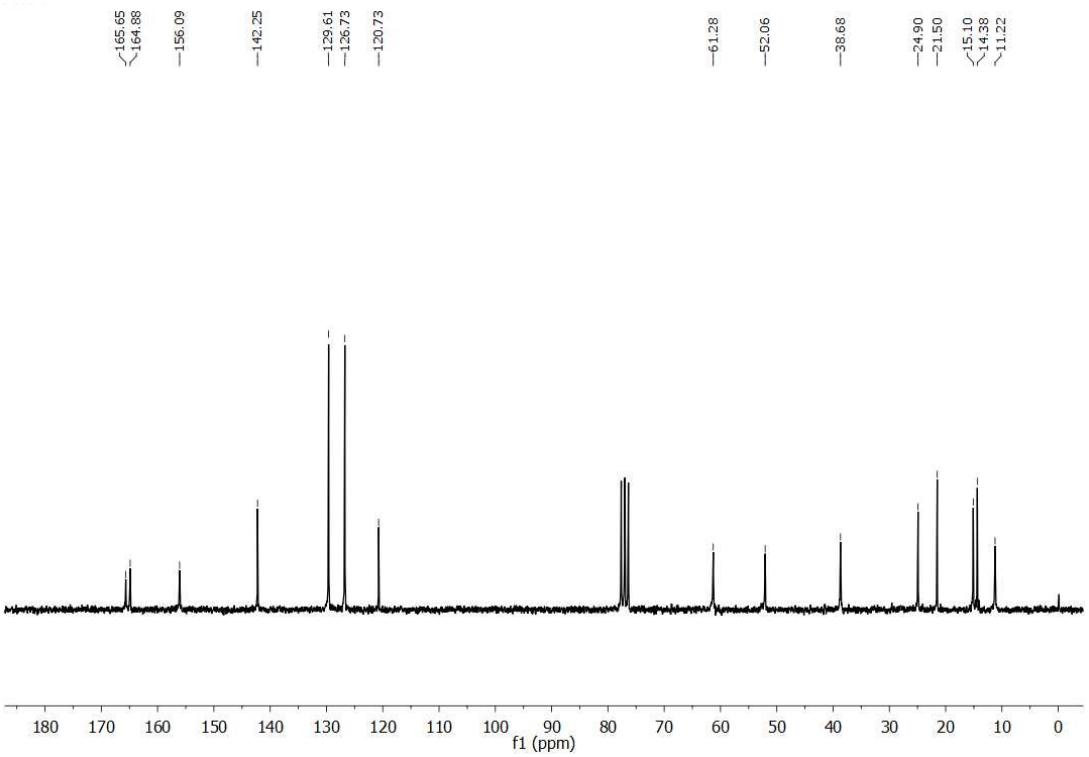
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of compound **2b** (Table 2, entry 8)



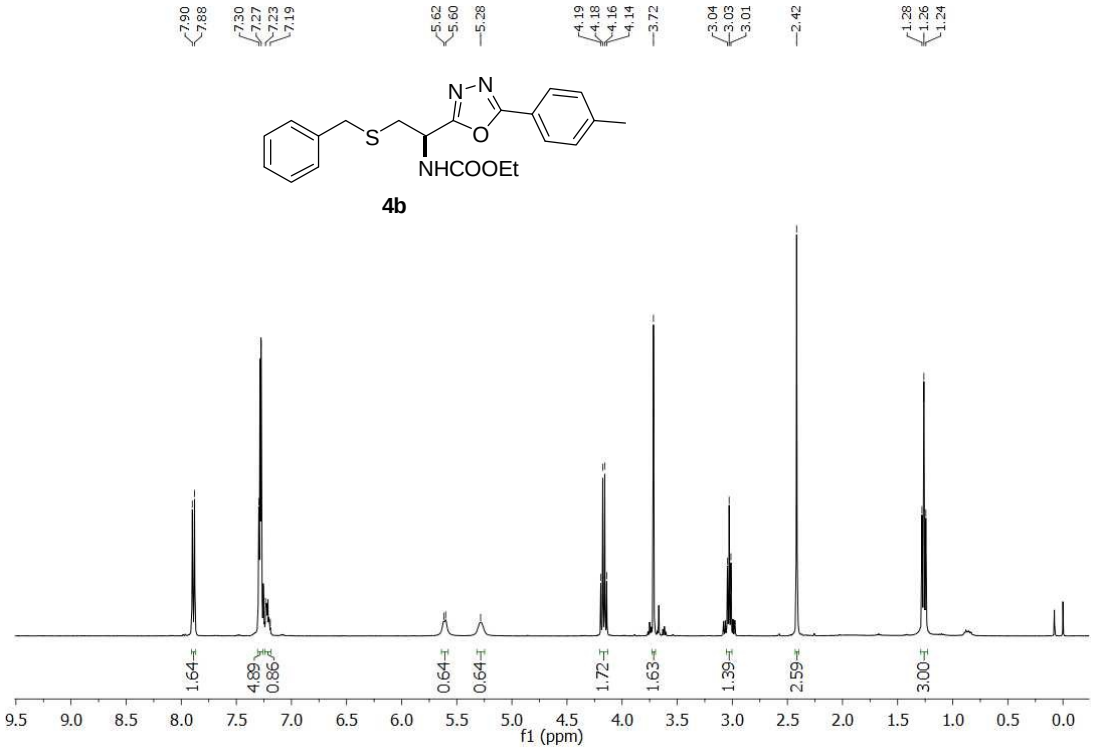
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **2b** (Table 2, entry 8).



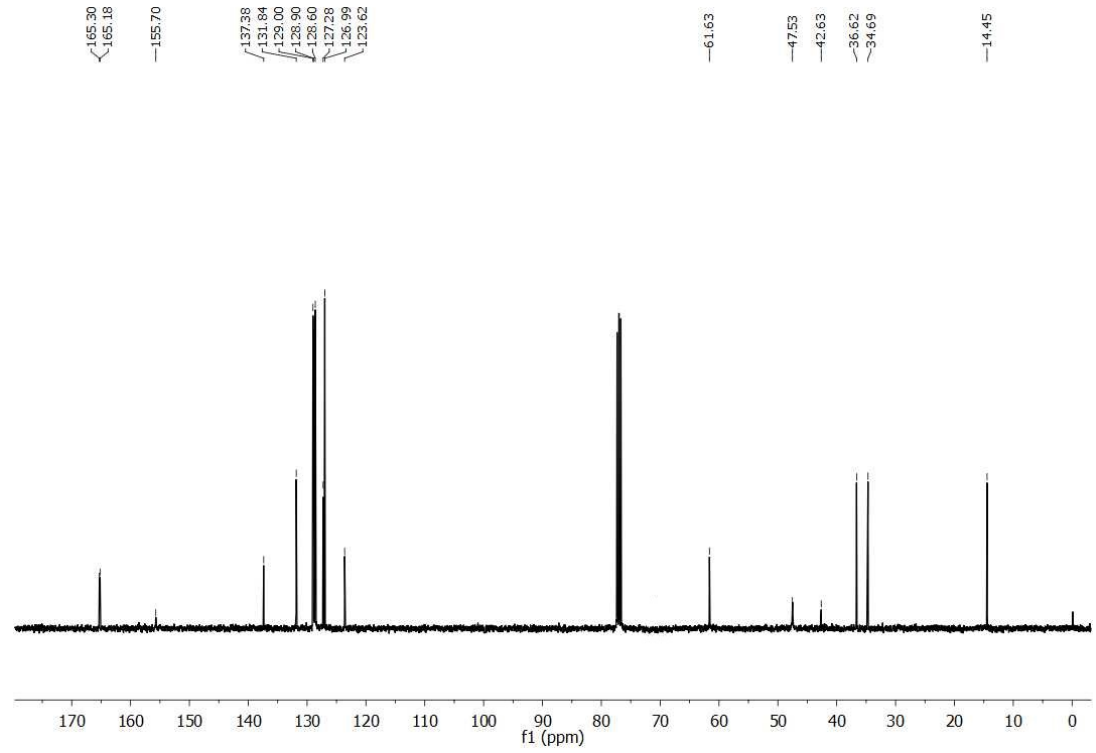
^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of compound **3b** (Table 2, entry 9).



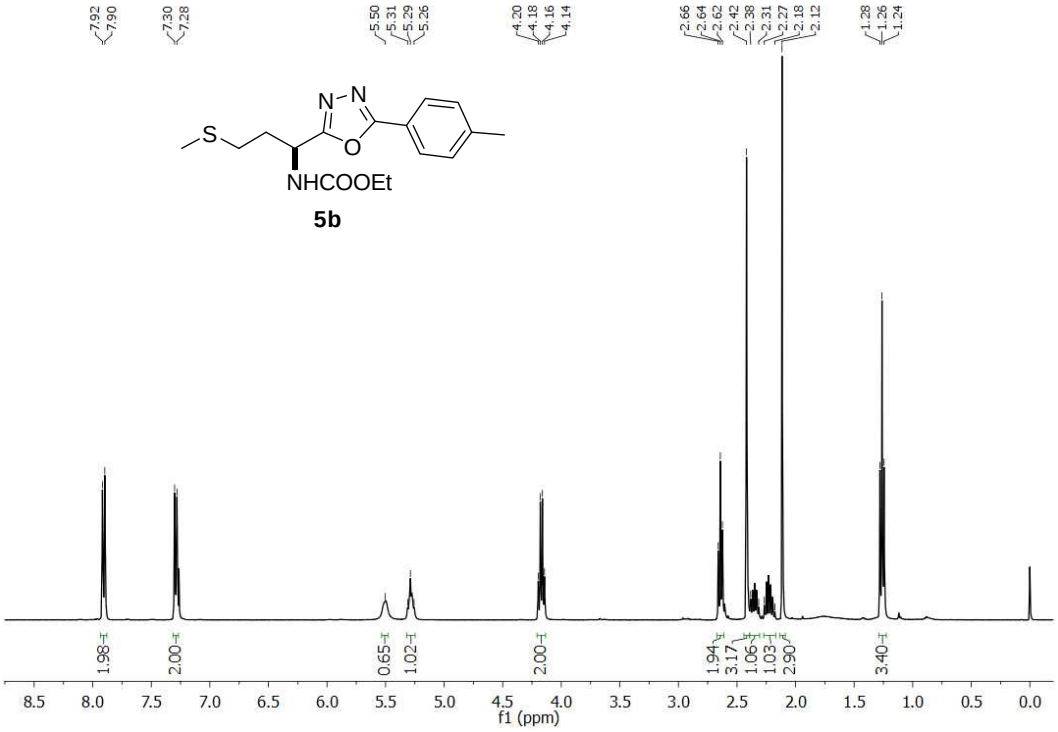
^{13}C NMR (50 MHz, $CDCl_3$) Spectrum of compound **3b** (Table 2, entry 9).



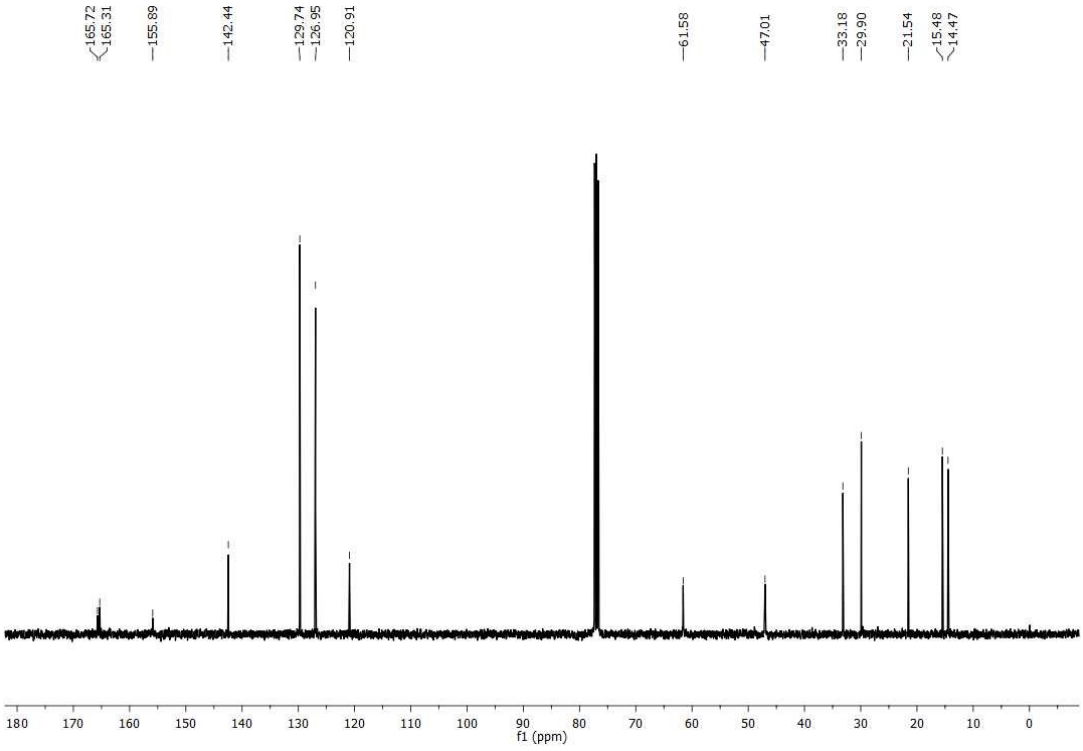
^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of compound **4b** (Table 2, entry 10).



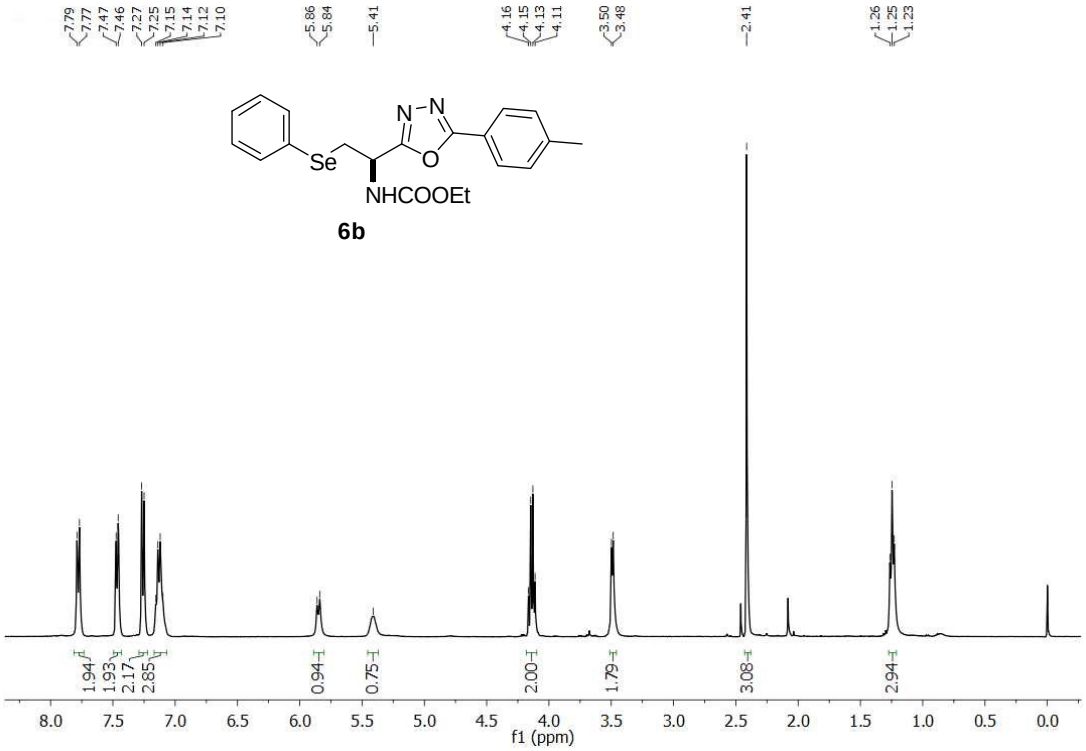
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **4b** (Table 2, entry 10).



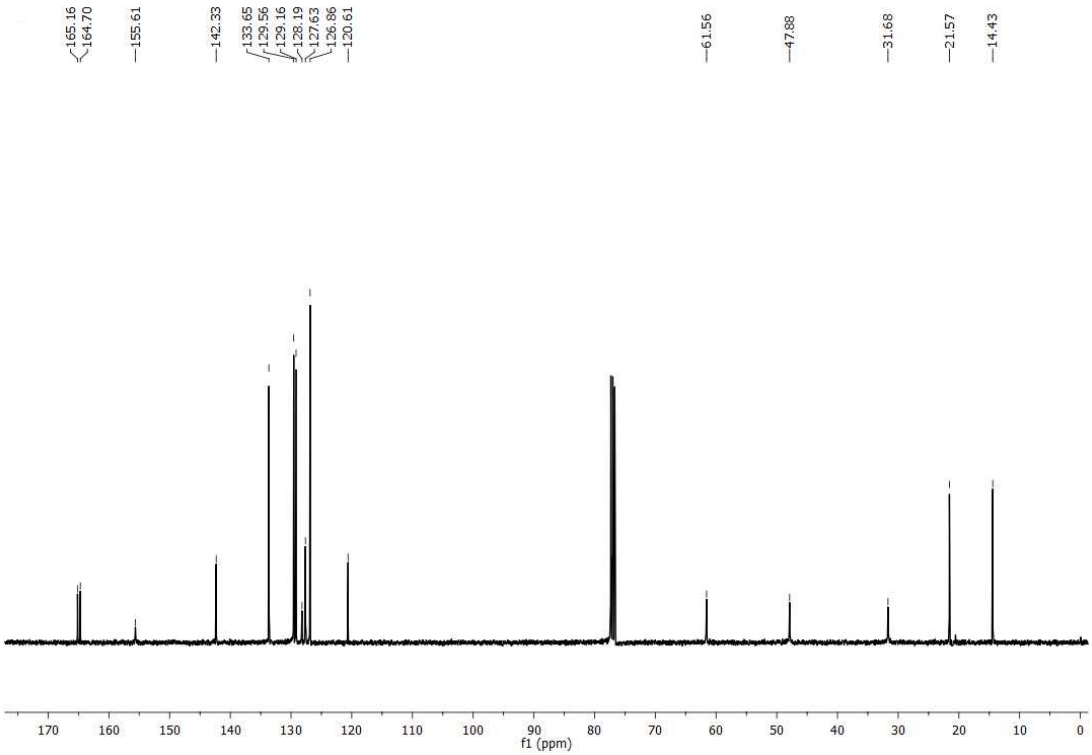
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of compound **5b** (Table 2, entry 11).



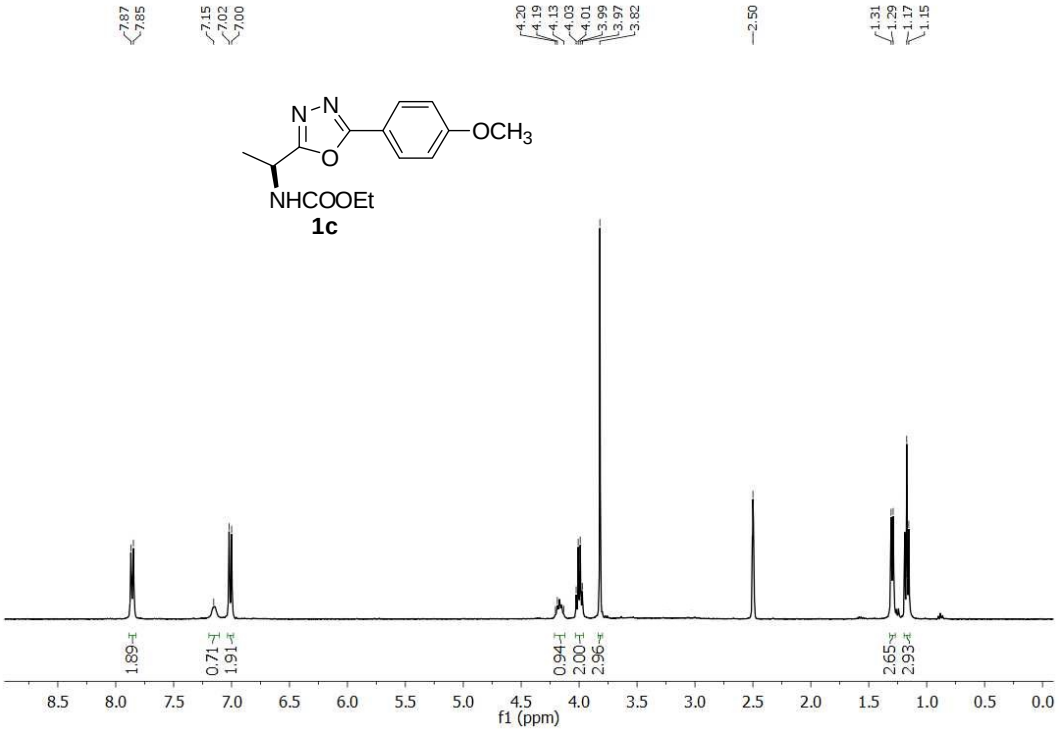
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **5b** (Table 2, entry 11).



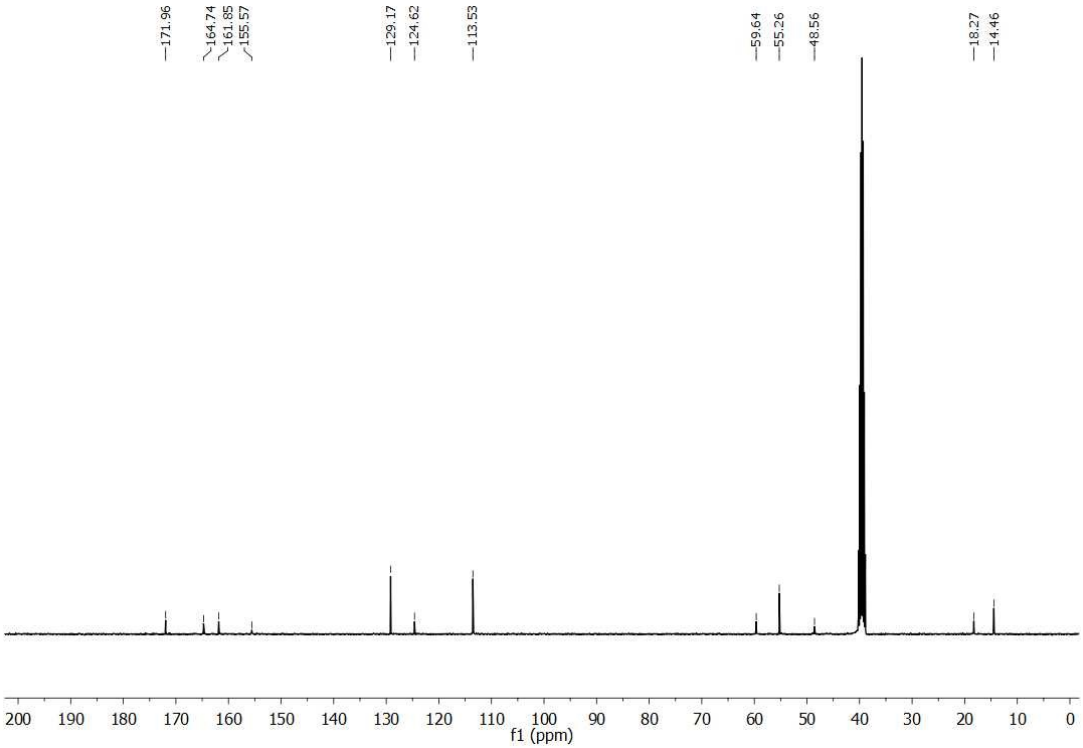
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of compound **6b** (Table 2, entry 12).



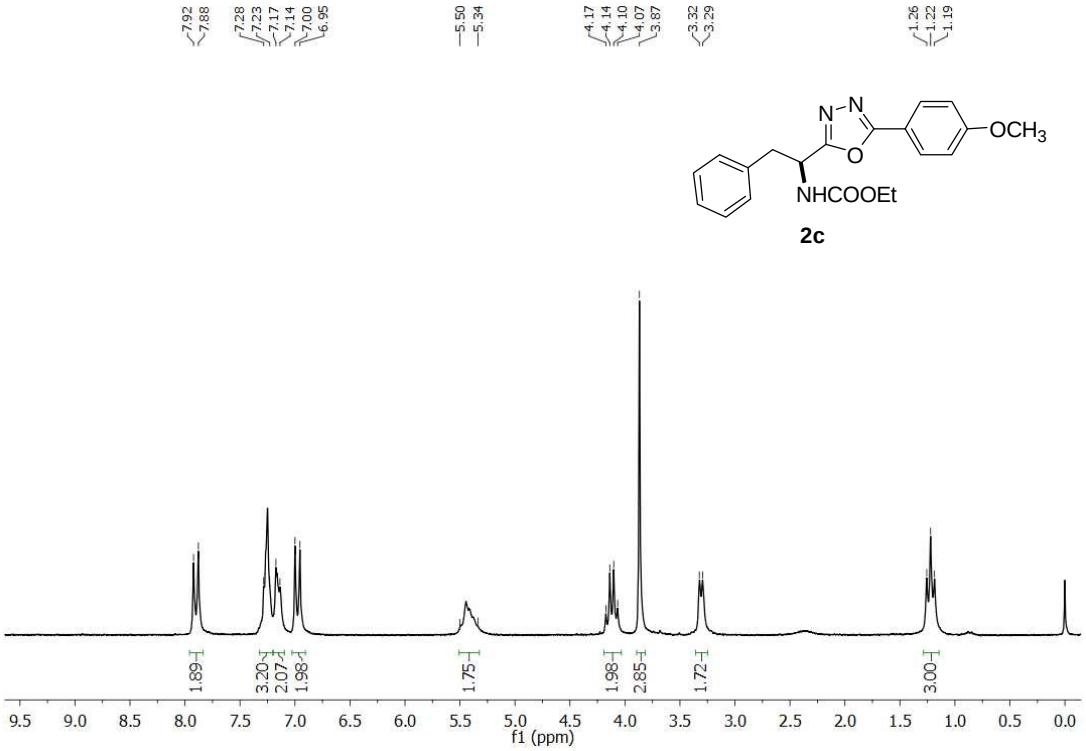
^{13}C NMR (100MHz, $CDCl_3$) Spectrum of compound **6b** (Table 2, entry 12).



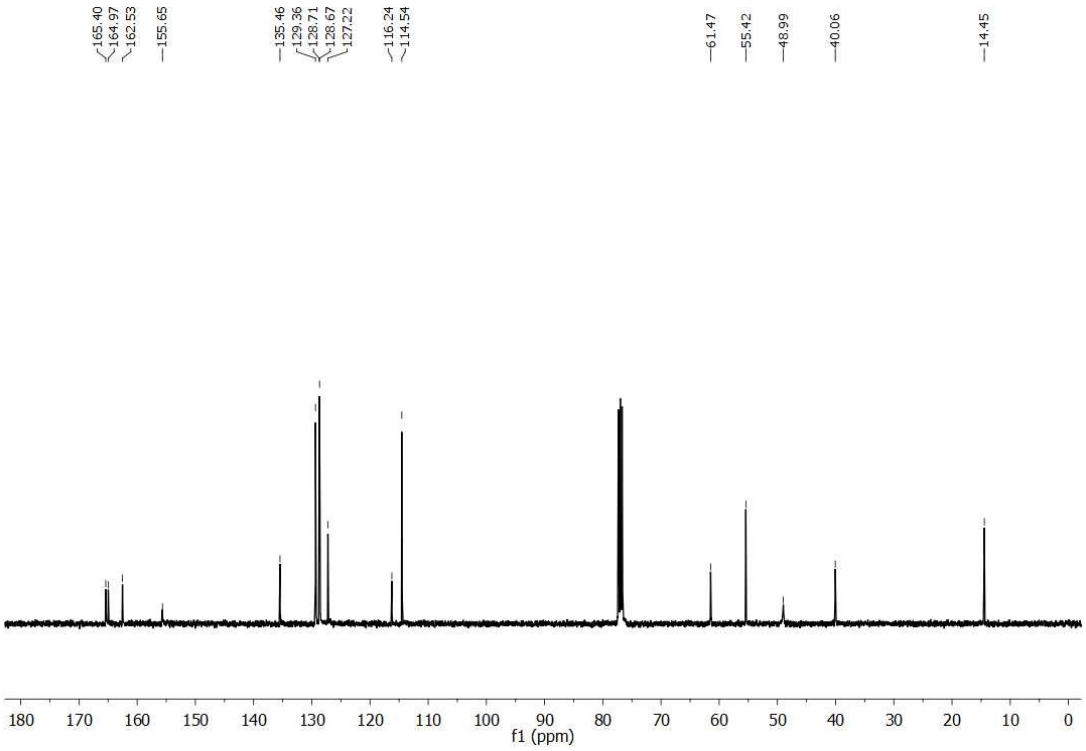
^{1}H NMR (400 MHz, DMSO) Spectrum of compound **1c** (Table 2, entry 13).



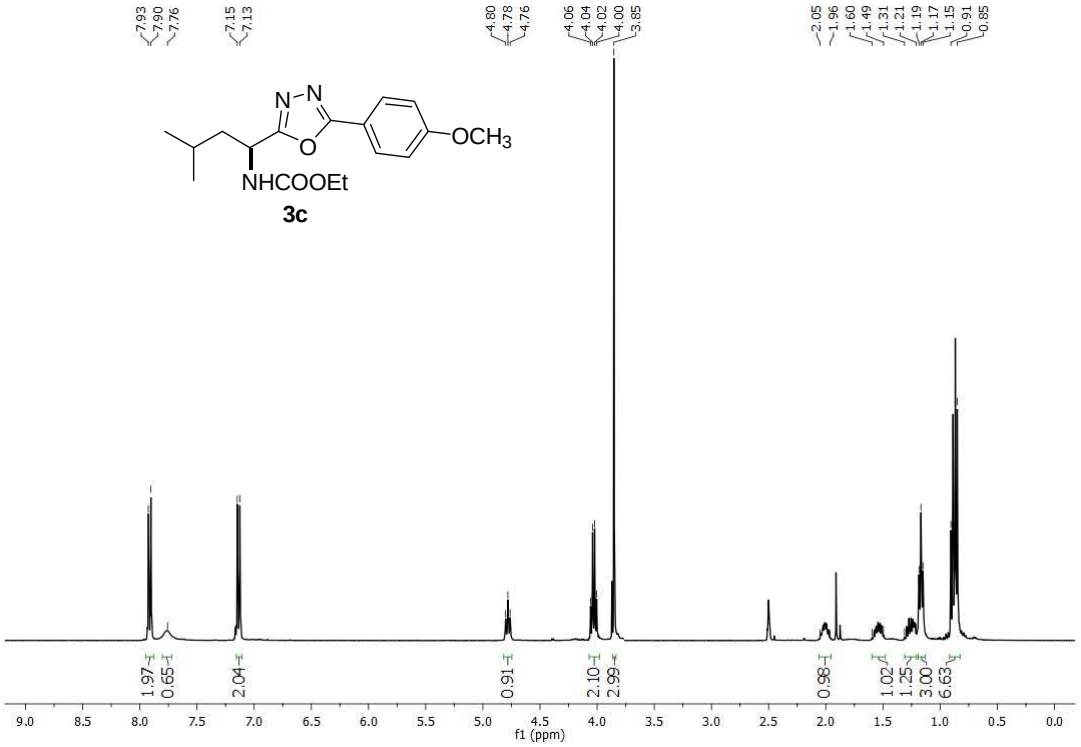
^{13}C NMR (100 MHz, DMSO) Spectrum of compound **1c** (Table 2, entry 13).



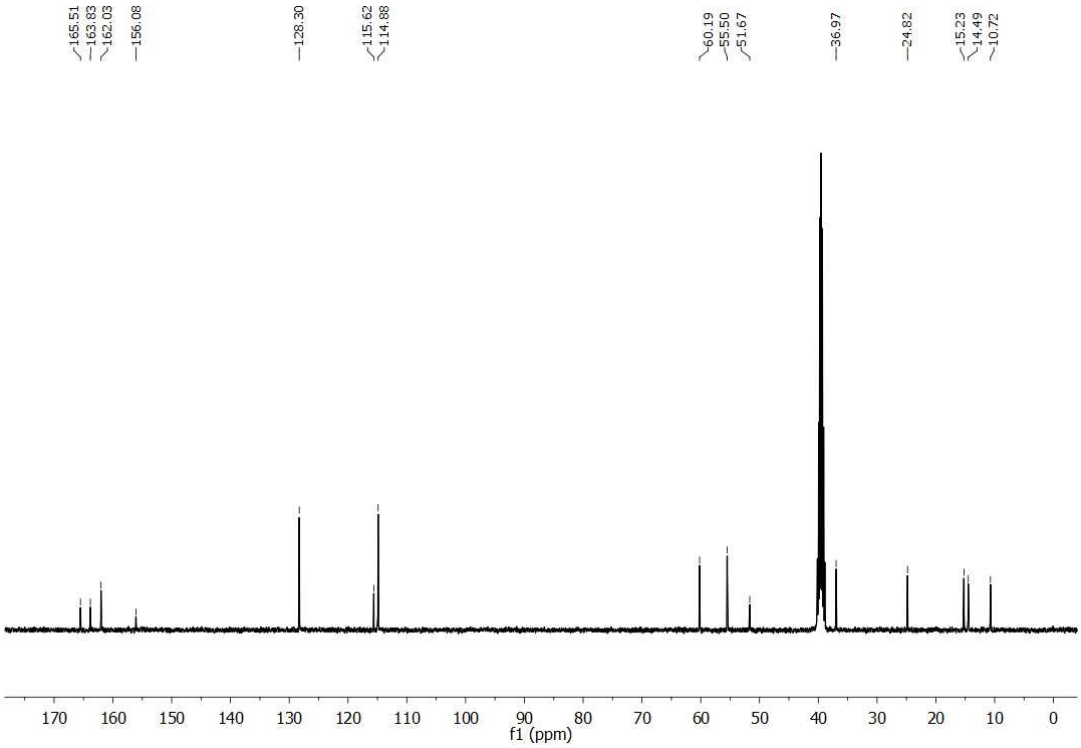
^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of compound **2c** (Table 2, entry 14).



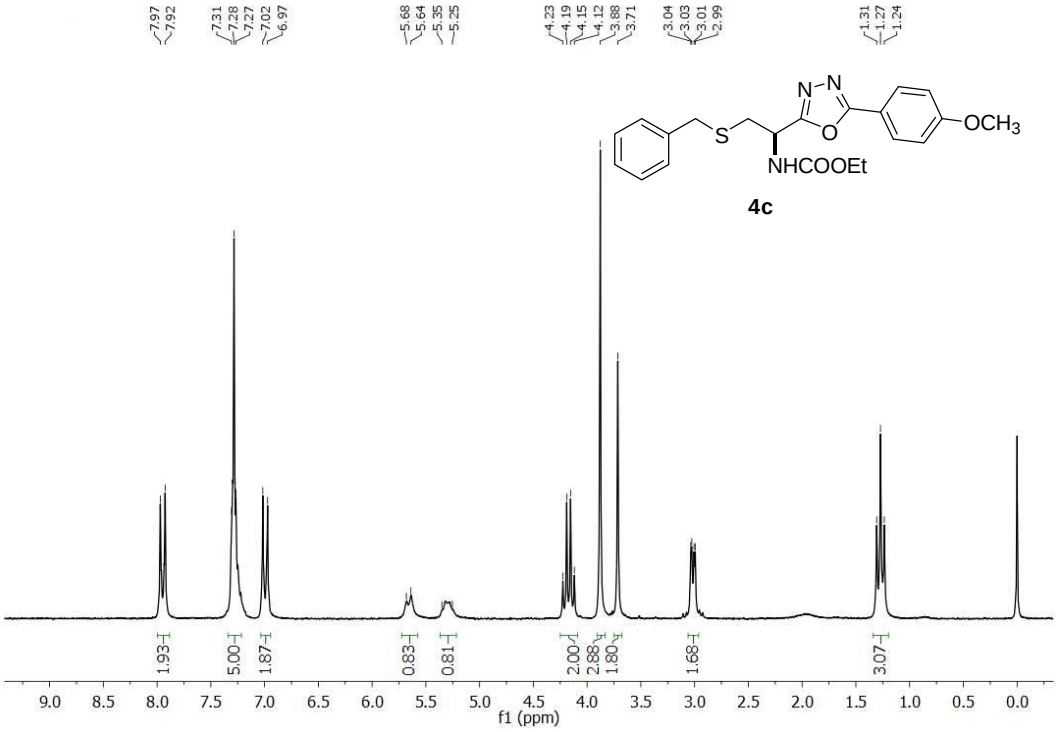
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **2c** (Table 2, entry 14).



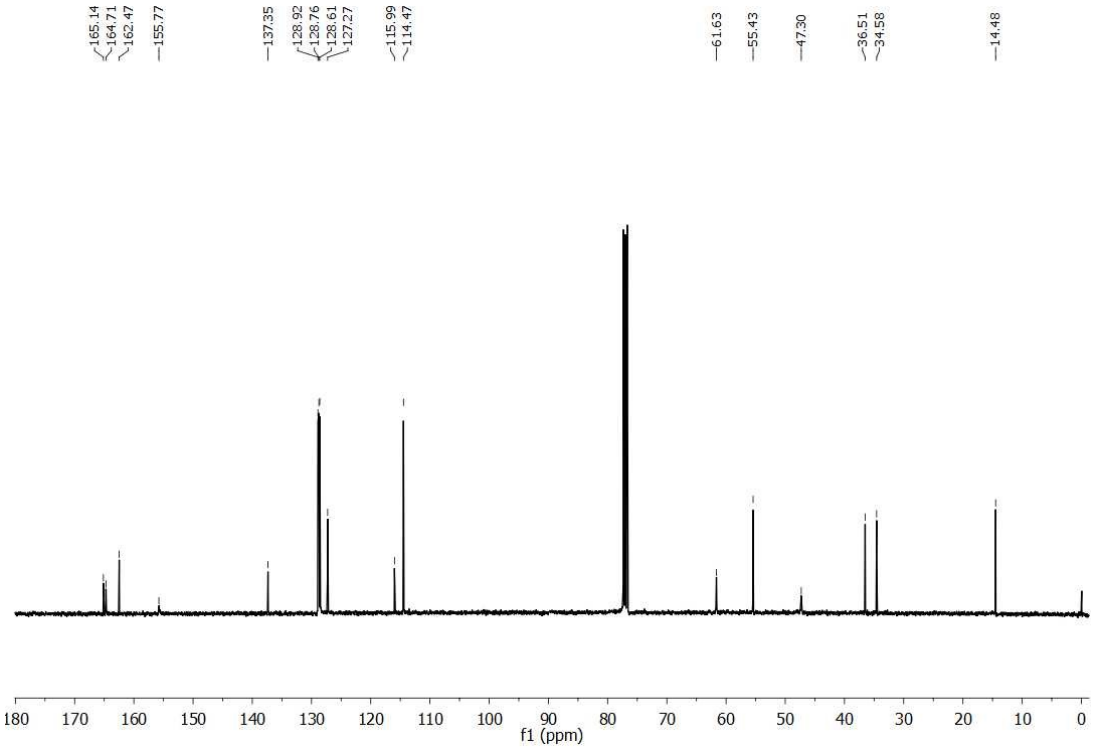
^{1}H NMR (400 MHz, DMSO) Spectrum of compound **3c** (Table 2, entry 15).



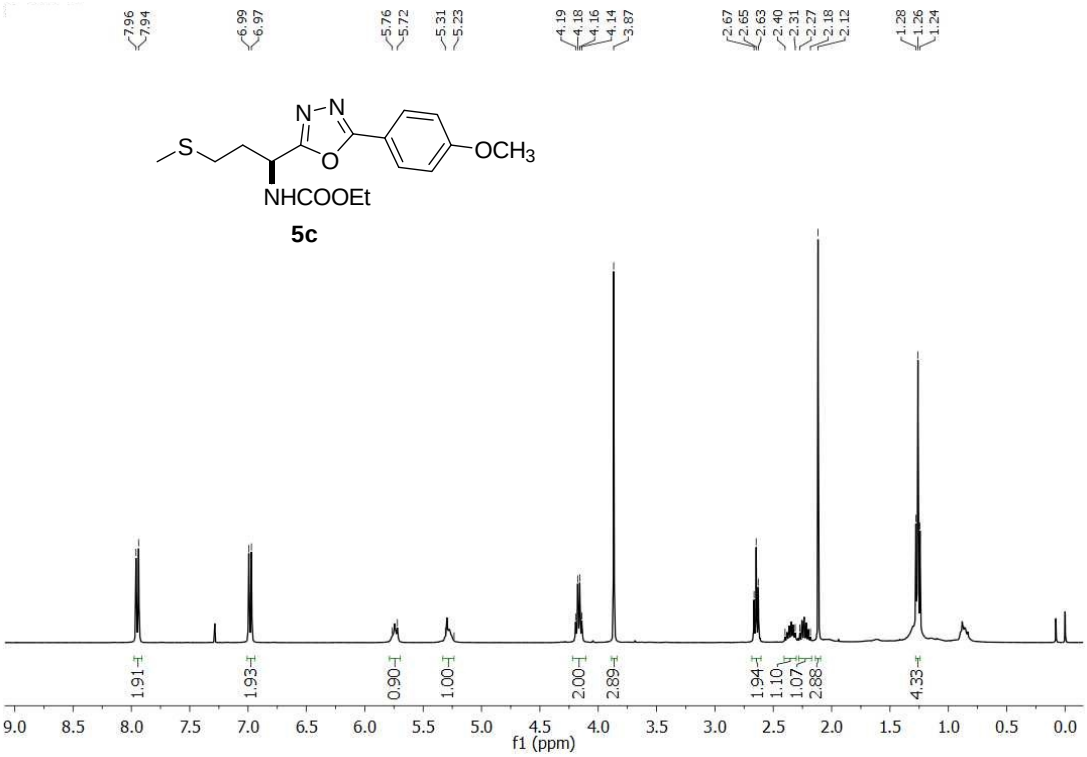
^{13}C NMR (100 MHz, DMSO) Spectrum of compound **3c** (Table 2, entry 15).



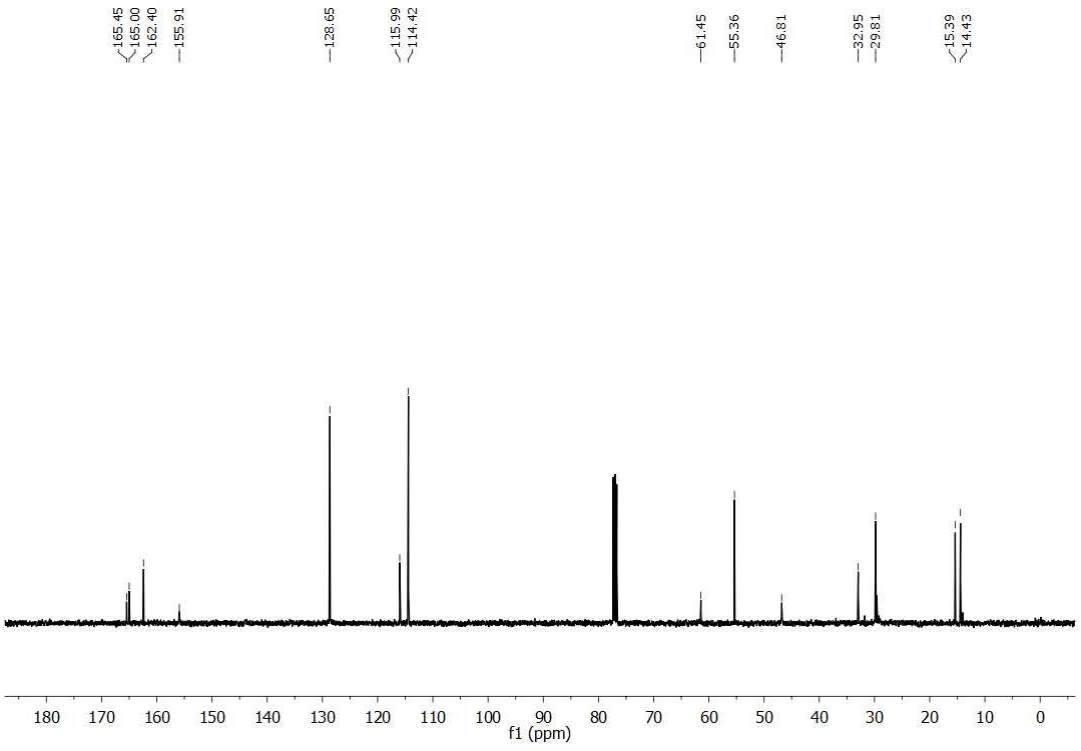
^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of compound **4c** (Table 2, entry 16).



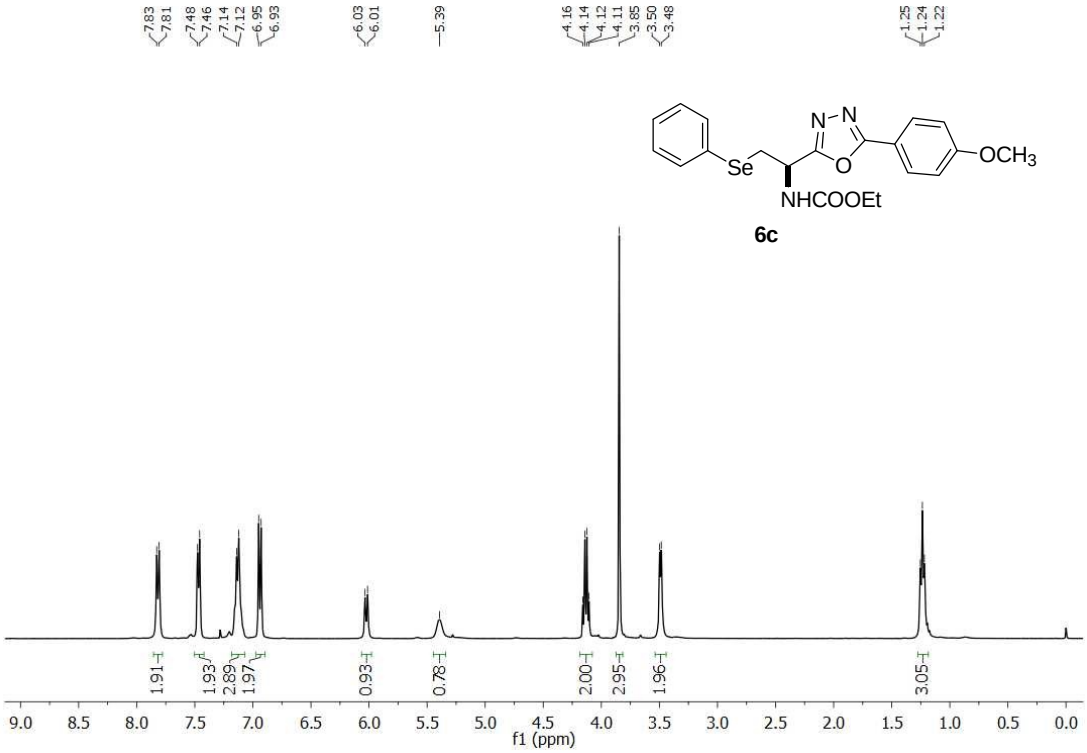
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **4c** (Table 2, entry 16).



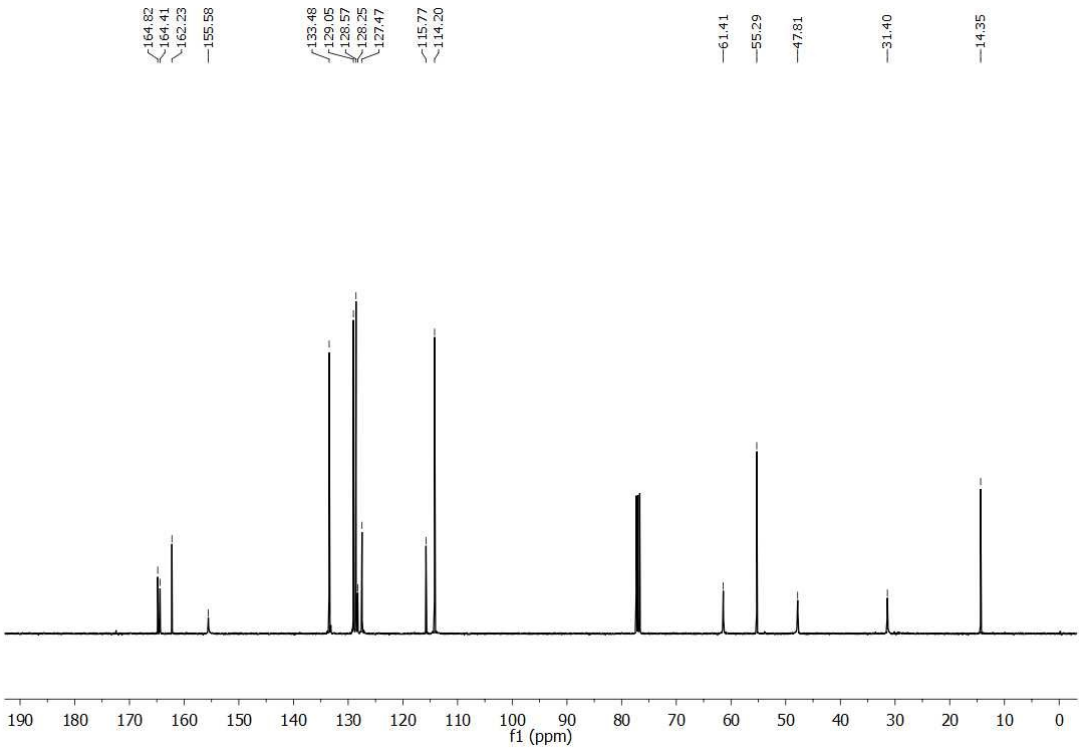
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of compound **5c** (Table 2, entry 17).



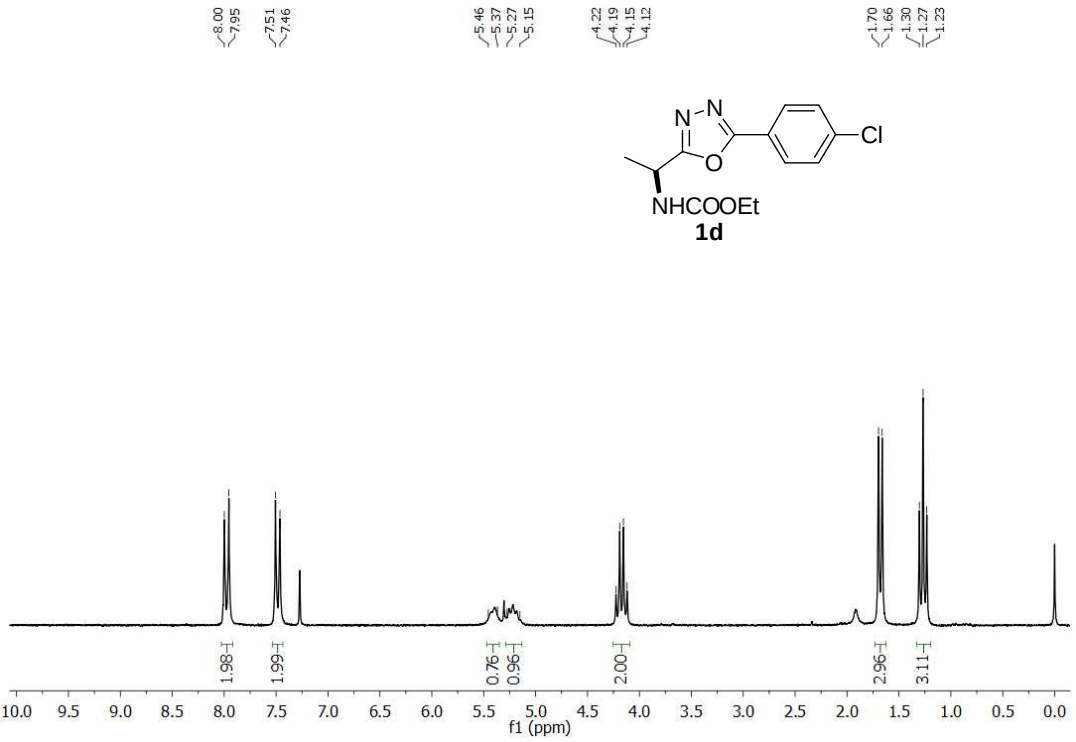
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **5c** (Table 2, entry 17).



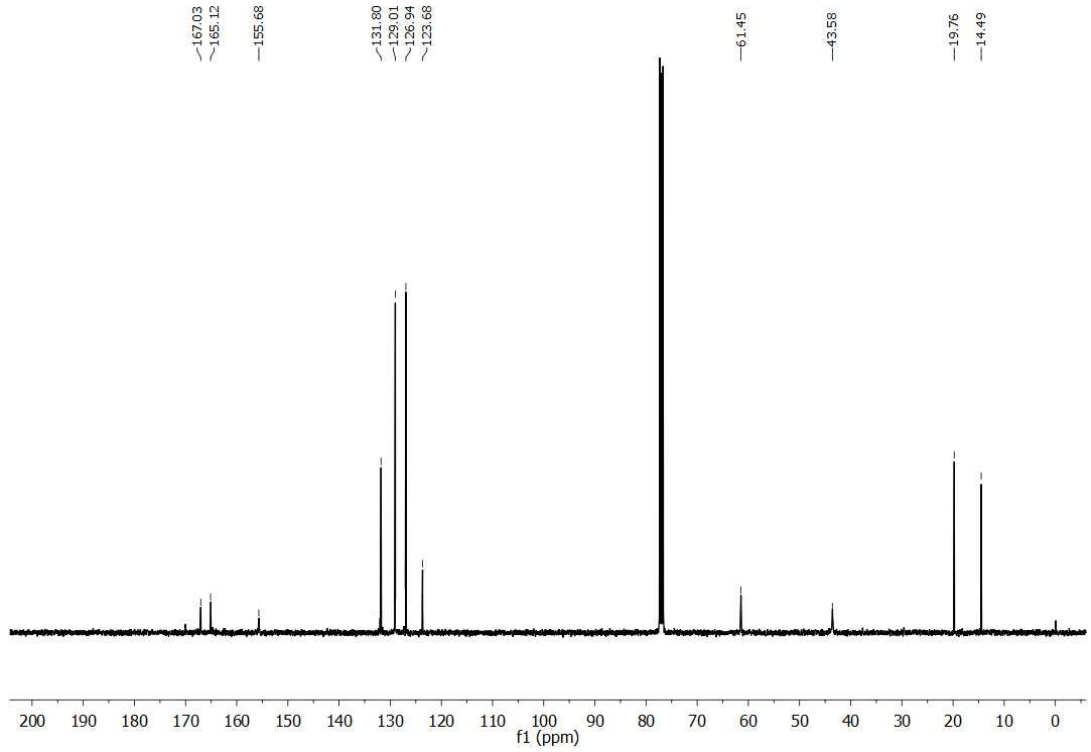
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of compound **6c** (Table 2, entry 18).



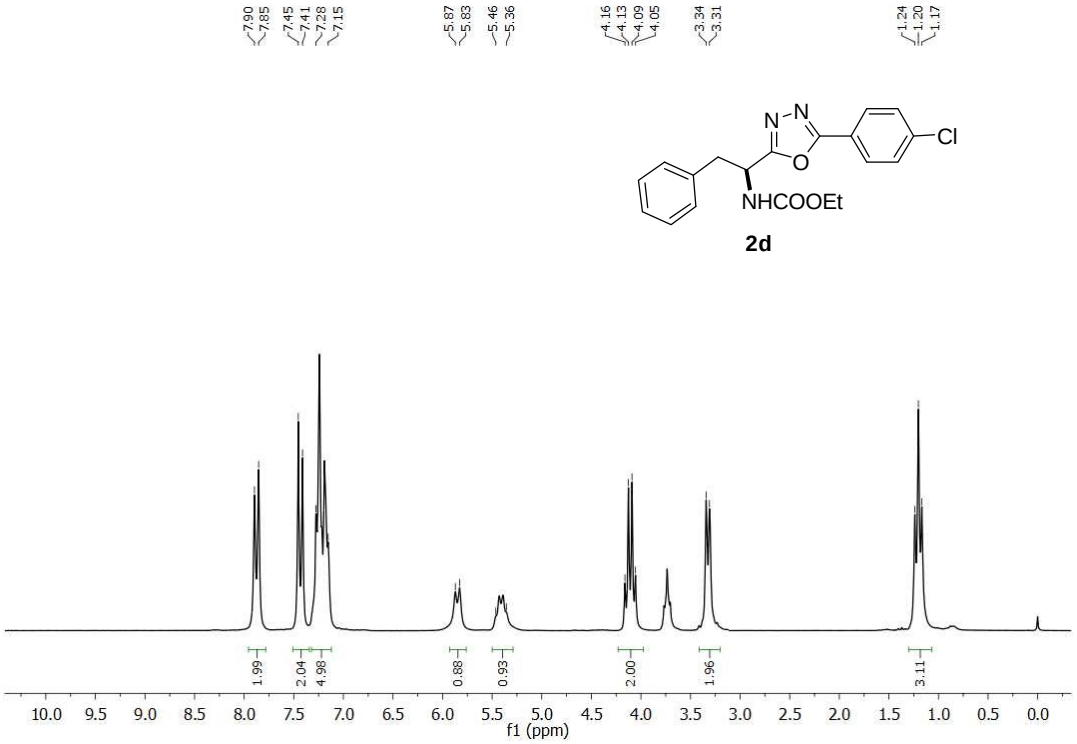
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **6c** (Table 2, entry 18).



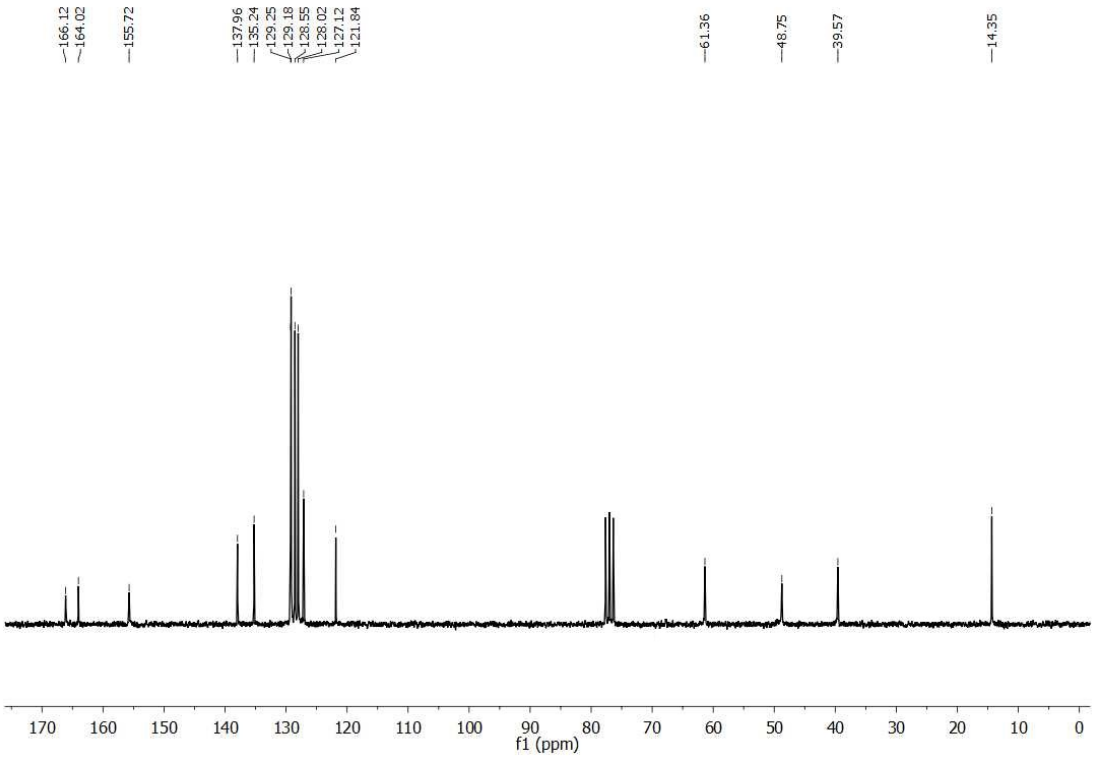
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of compound **1d** (Table 2, entry 19).



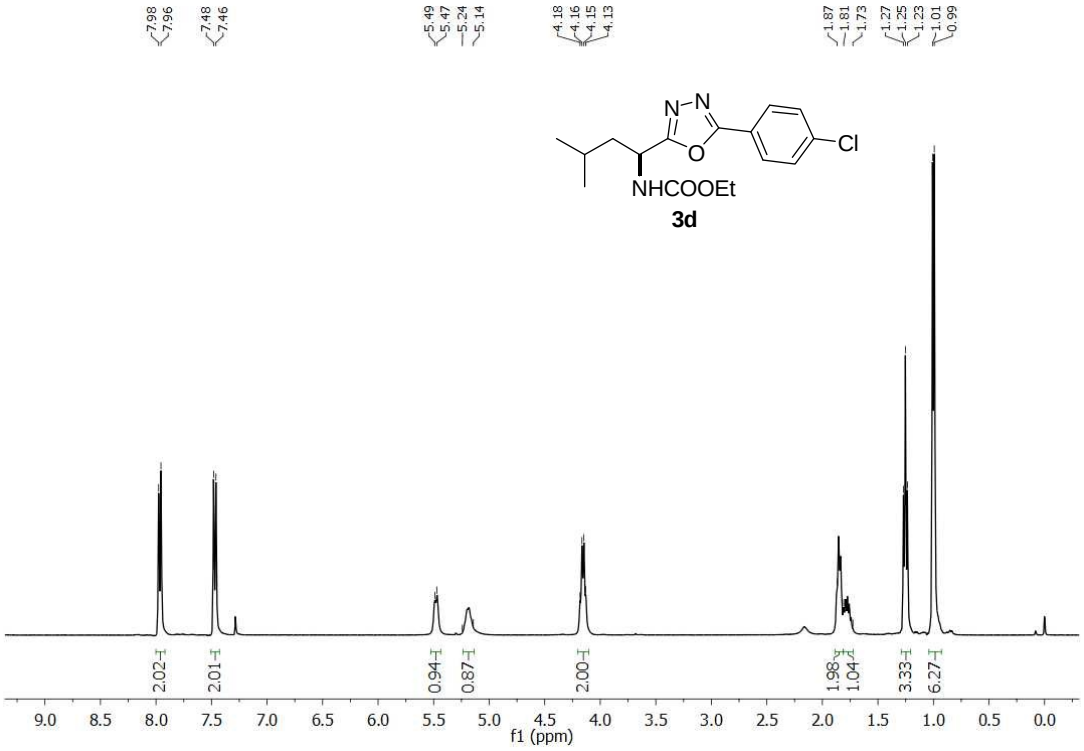
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **1d** (Table 2, entry 19).



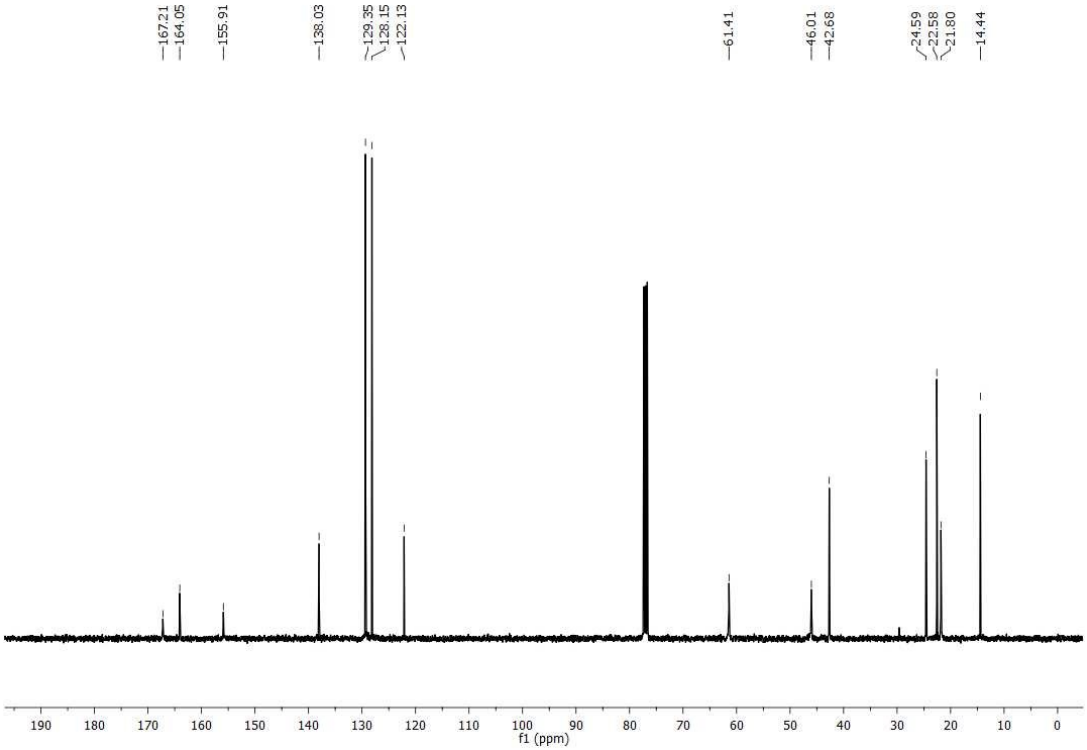
^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of compound **2d** (Table 2, entry 20).



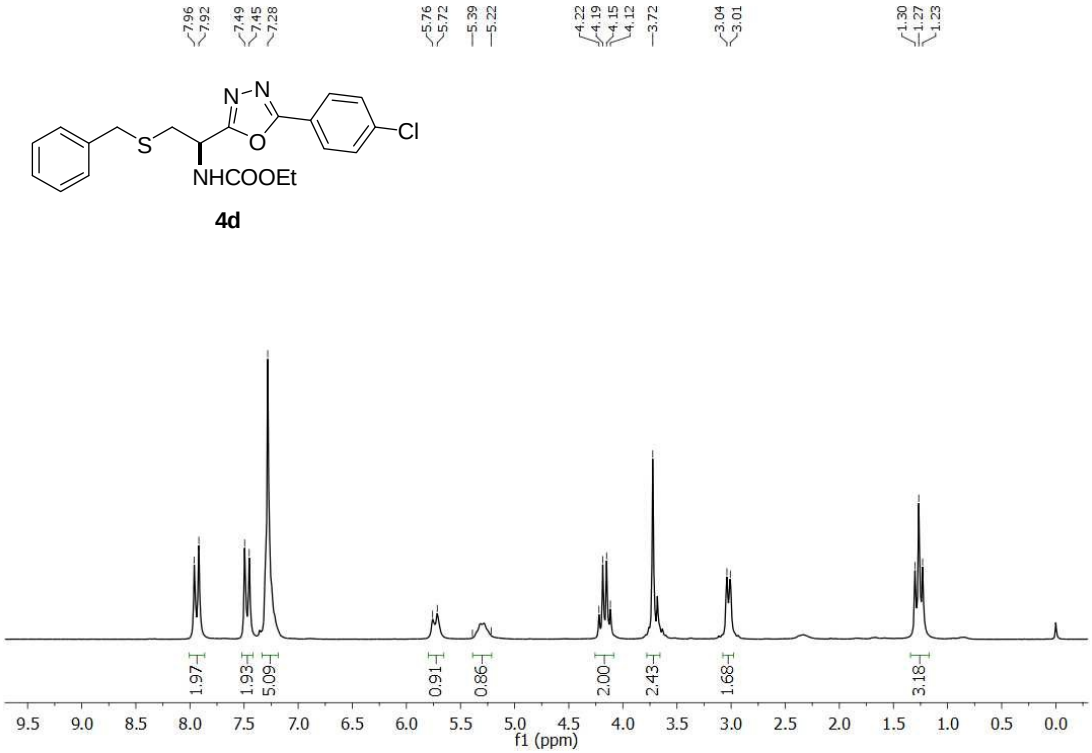
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **2d** (Table 2, entry 20).



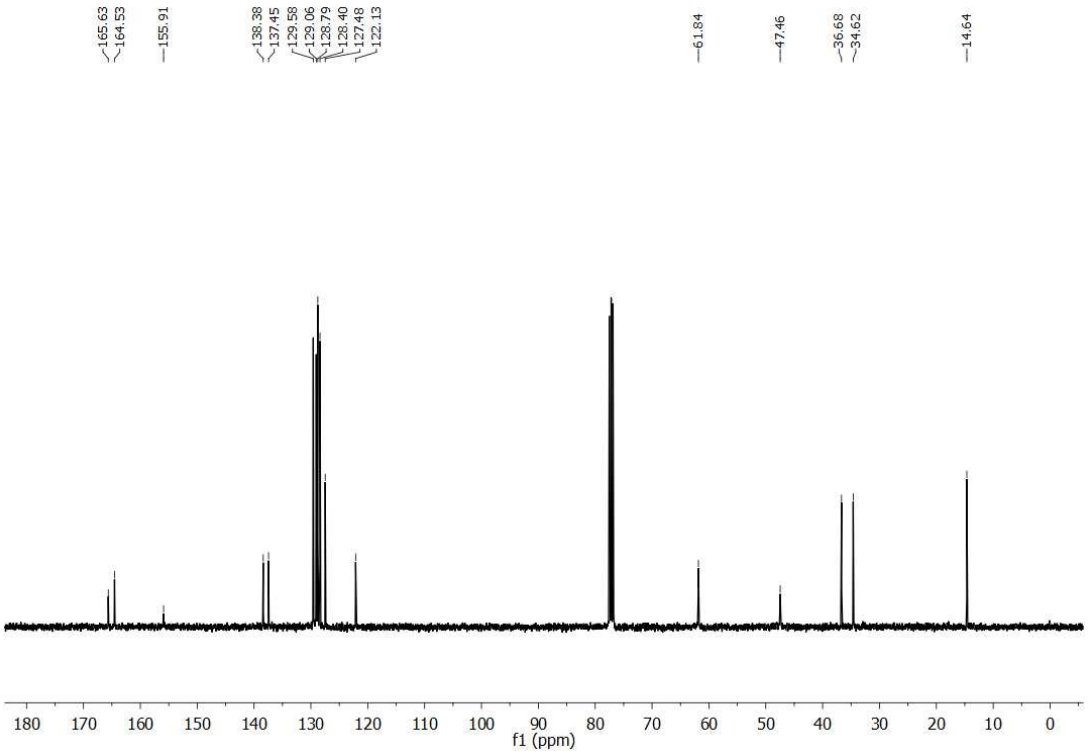
^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of compound **3d** (Table 2, entry 21).



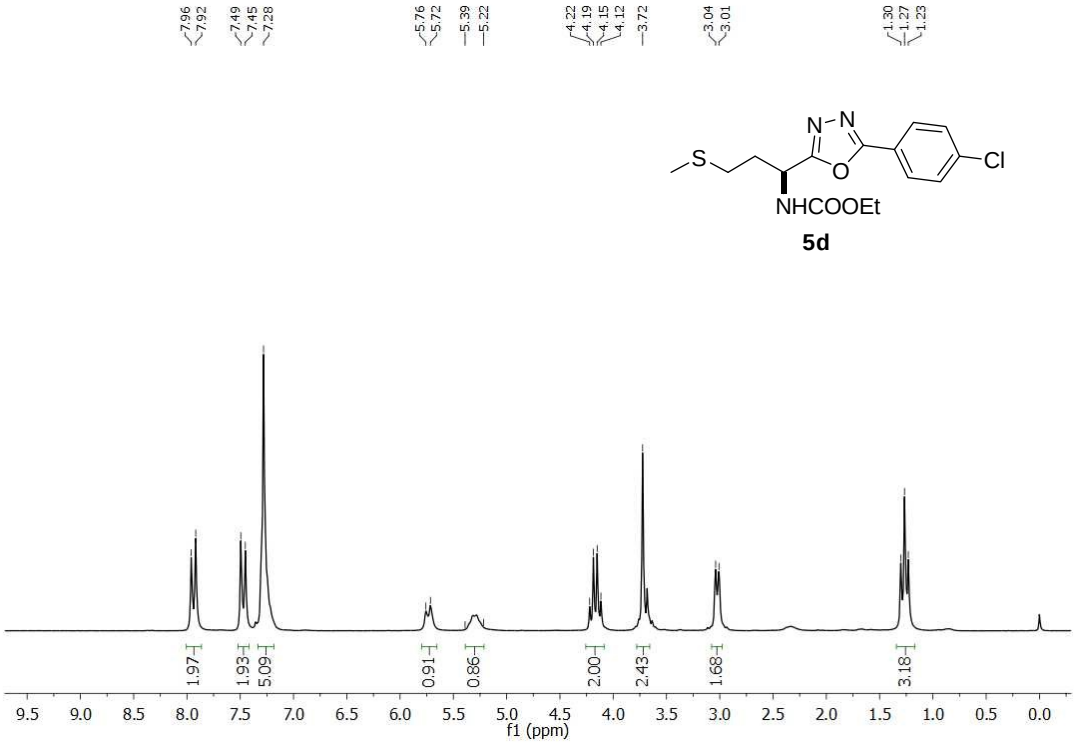
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **3d** (Table 2, entry 21).



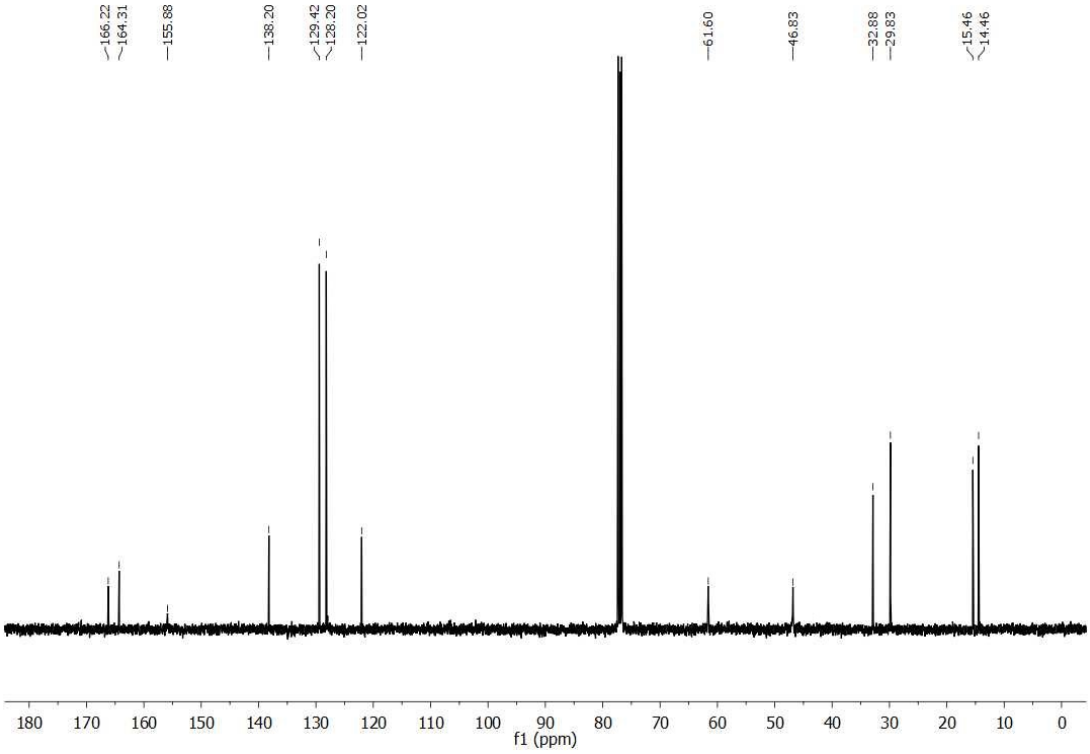
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of compound **4d** (Table 2, entry 22).



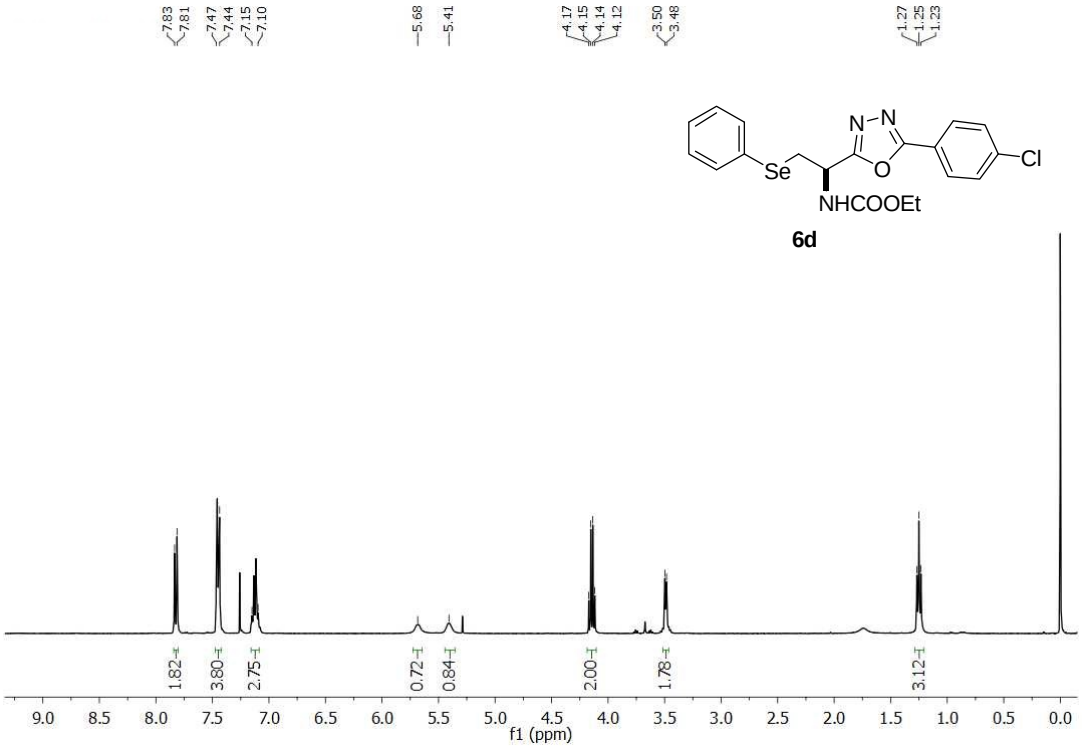
^{13}C NMR (100MHz, $CDCl_3$) Spectrum of compound **4d** (Table 2, entry 22).



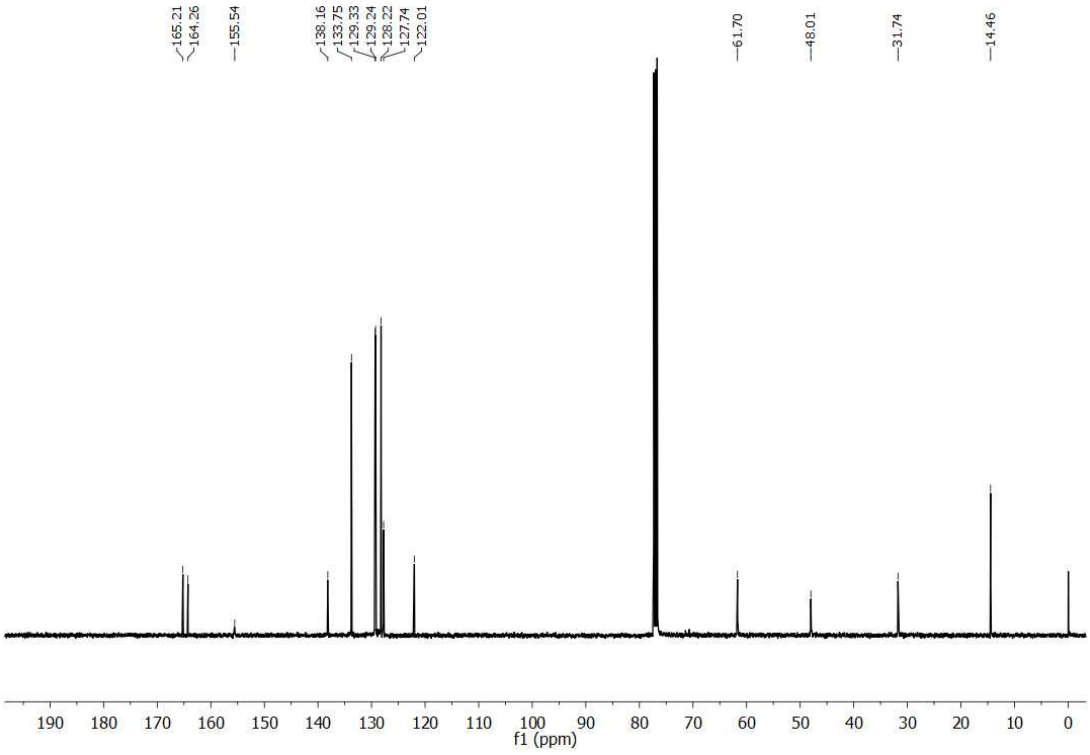
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of compound **5d** (Table 2, entry 23).



^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **5d** (Table 2, entry 23).

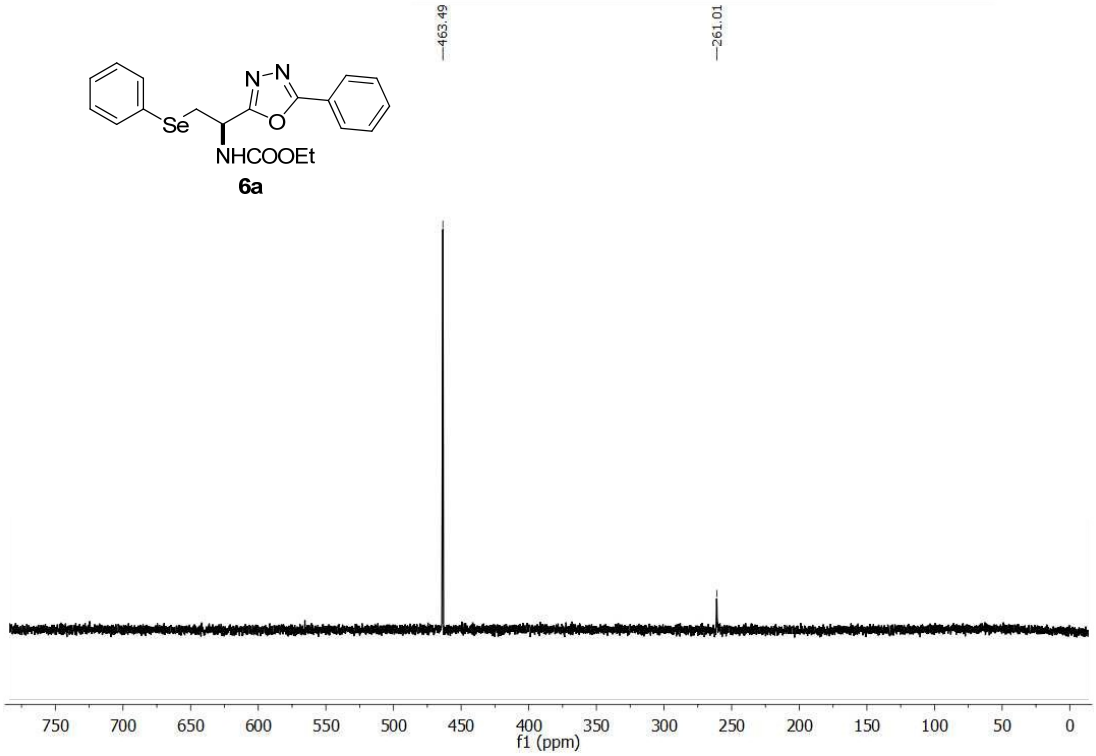


^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of compound **6d** (Table 2, entry 24).



^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of compound **6d** (Table 2, entry 24).

4. ^{77}Se NMR Spectrum of compound 6a



^{77}Se NMR (76.28 MHz, $CDCl_3$) Spectrum of compound **6a** (Table 2, entry 6).

5. References

1. Menezes, P. H.; Gonsalves, S. M. C.; Hallwass, F.; Silva, R. O.; Bieber, L. W.; Simas, A. M. *Org. Lett*. **2003**, 5, 1601

