# Synthesis of Enantiopure 3-Substituted Morpholines

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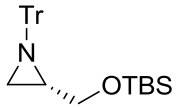
**Supporting Information**

## General Information

All reactions requiring inert conditions were performed in oven or flame-dried glassware under an inert atmosphere of nitrogen or argon using standard Schlenk and syringe-septum technique. Anhydrous THF, $CH_2Cl_2$ and DMSO were obtained from commercial sources. All other solvent were HPLC grade and used as received. PE refers to petroleum ether of bp 50-70 °C. Flash chromatography (FC) was performed on silica gel (silica gel 60, mesh 230-400). Purified compounds were further dried under high vacuum. Thin layer chromatography (TLC) was performed on aluminium backed plated pre-coated with silica and the products were visualized by UV detection or by staining with ninhydrin. Optical rotation values are given in units of $deg \times cm^3 \times g^{-1} \times dm^{-1}$; concentration *c* is listed in $g \times 100\ mL^{-1}$. $^1H$ chemical shifts ($\delta_H$) are quoted in parts per million (ppm) relative to $Me_4Si$ (or sodium 3-(trimethylsilyl)propionate-2,2,3,3-$d_4$ ($d_4$-TSP) when spectra were recorded in $D_2O$) as internal standard unless stated otherwise and *J* values are given in Hertz. $^{13}C$ chemical shifts ($\delta_C$) are quoted in ppm relative to residual solvent peaks ($CDCl_3$ = 77.16) or $d_4$-TSP when spectra were recorded in $D_2O$. HRMS were recorded by ESI-TOF. Melting points were determined in open-end capillary tubes and are uncorrected. Analytical HPLC measurements were performed with the stated chiral stationary phase. Grignard reagents were obtained from commercial sources and the concentration was determined prior to use by titration with iodine.[1] (*S*)-methyl 1-tritylaziridine-2-carboxylate **1** was prepared in three steps starting from L-serine following literature procedures and recrystallised from ethanol.[2-4] (*S*)-(1-tritylaziridin-2-yl)methanol was prepared from **1** by the procedure of Utsunomiya *et al*.[5] Benzothiazole-2-sulfonyl chloride was prepared from 2-mercaptobenzothiazole according to Bornholdt *et al*.[6] Pentafluorophenyl benzothiazole-2-sulfonate was prepared according to Bornholdt *et al*.[7] Diphenylvinylsulfonium trifluoromethanesulfonate was prepared according to Yar et al.[8] and obtained as a low melting grey solid when stored at +4 °C. Other reagents were obtained from commercial sources and were used as received.

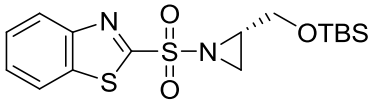
**(*S*)-2-((tert-butyldimethylsilyloxy)methyl)-1-tritylaziridine (2)**




(*S*)-(1-tritylaziridin-2-yl)methanol (28.10 g, 89.08 mmol) and imidazole (15.16 g, 222.7 mmol, 2.5 equiv.) were dissolved in dry $CH_2Cl_2$ (450 mL) under argon at 0 °C. Tert-butyldimethylsilyl chloride (14.09 g, 93.50 mmol) was added neat all at once. A white precipitate quickly formed. The mixture was stirred 1.5 h on a melting ice bath. By then TLC ( EtOAc:PE, 1:9) showed full conversion of starting material ($R_f$ 0.14) into **2** ($R_f$ 0.80). The reaction mixture was diluted with $CH_2Cl_2$ (200 mL) and washed with sat. $NH_4Cl$ (2×400 mL), water (400 mL) and brine (200 mL). The organic layer was dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The solid residue was recrystallised from *n*-hexane to afford the title compound **2** (34.78 g, 91 %) as a colourless solid.

Mp 79.5-80.0 °C (*n*-hexane). $[\alpha]^{20}_D$ = -23.4 (c 1.08, $CH_2Cl_2$). Litt. $[\alpha]_D$[(*R*)-isomer] = +24.0 (c 1.22, $CH_2Cl_2$).[9] $[\alpha]^{20}_D$ = -31.2 (c 1.03, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 6H), 7.30 – 7.15 (m, 10H), 3.96 (dd, *J* = 5.0, 10.7, 1H), 3.65 (dd, *J* = 5.6, 10.7, 1H), 1.68 (d, *J* = 3.1, 1H), 1.46 – 1.37 (m, 1H), 1.13 (d, *J* = 6.2, 1H), 0.87 (s, 9H), 0.04 (s, 3H), 0.02 (d, *J* = 2.6, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 144.8, 129.7, 127.5, 126.7, 73.8, 66.0, 34.6, 26.1, 25.5, 18.5, -5.07, -5.10.

**(*S*)-2-(2-((tert-butyldimethylsilyloxy)methyl)-aziridin-1-ylsulfonyl)benzo[d]thiazole (3)**

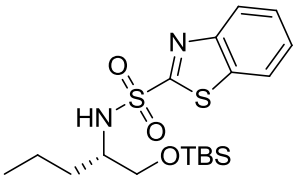



Trifluoroacetic acid (5.51 mL, 72 mmol) was added dropwise by syringe to a stirred solution of **2** (7.73 g, 18 mmol) and triethylsilane (11.5 mL, 72 mmol) in dry $CH_2Cl_2$ (90 mL) at -5 °C under argon. The mixture was stirred 2.5 h at -5 °C to +4 °C until TLC showed full deprotection of the trityl group to triphenylmethane. The reaction mixture was quenched by pouring it into cold 2 M $K_2CO_3$ (90 mL) under vigorous stirring. The layers were separated and the aqueous layer extracted with ether (2×30 mL). The combined organic layers were concentrated *in vacuo* (gently - the aziridine is volatile!) to remove the $CH_2Cl_2$. The residue was dissolved in EtOAc (80 mL), 2 M $K_2CO_3$ (35 mL) was added and the mixture cooled to 0 °C in an ice bath. Benzothiazole-2-sulfonyl chloride (4.00 g, 17.1 mmol) was added solid in small portions under vigorous stirring. Stirring was continued for 2 h at 0 °C and the mixture

was then allowed to warm to ambient. At this point TLC still indicated the presences of some unreacted benzothiazole-2-sulfonyl chloride (BtsCl). To avoid decomposition of BtsCl and formation of by-products during work up and purification excess benzothiazole-2-sulfonyl chloride was quenched by adding 25 % $NH_4OH$ (2×200 µL) until TLC showed full conversion of BtsCl. The reaction mixture was then diluted with EtOAc (20 mL) and the layers separated. The aqueous layer was extracted with ether (40 mL). The combined organic layers were washed with 0.5 M $NaH_2PO_4$ (40 mL), water (40 mL) and sat. $Na_2SO_4$ (40 mL), dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The residue was purified by FC on silica (EtOAc/PE, 5:95 to 14:86) providing 4.96 g of the title compound containing 3 % of a chloride ring opened by-product and some triethylsilyl containing by-products. Recrystallisation from methanol by dissolving it in 40 °C warm methanol and cooling to -78 °C afforded the title compound **3** (3.30 g, 50 %) as a slightly rose coloured solid.

Mp 56.5-57.5 °C. $[\alpha]^{20}_D$ = -32.0 (c 1.10, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.31 – 8.20 (m, 1H), 8.05 – 7.95 (m, 1H), 7.69 – 7.54 (m, 2H), 3.84 – 3.72 (m, 2H), 3.31 – 3.19 (m, 1H), 2.93 (d, *J* = 7.0, 1H), 2.50 (d, *J* = 4.8, 1H), 0.80 (s, 9H), -0.02 (s, 3H), -0.04 (s, 3H). $^{13}$C NMR (75 MHz, CDCl3) δ 163.1, 152.5, 137.0, 128.2, 127.7, 125.8, 122.3, 61.8, 42.2, 32.2, 25.8, 18.4, -5.3, -5.4. HRMS calcd for $C_{16}H_{25}N_2O_3S_2Si$ [M+H] 385.1075; found 385.1061

**General procedure I for ring opening of 3b with Grignard reagents exemplified by the synthesis of (*S*)-*N*-(1-(tert-butyldimethylsilyloxy)pentan-2-yl)benzo[d]thiazole-2-sulfonamide (4b)**

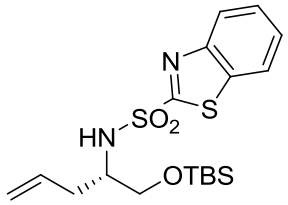



Copper(I) bromide dimethyl sulfide (72 mg, 0.35 mmol) was added to a flame dried Schlenk flask under argon. Dry THF (14 mL) was added and the slurry was stirred at rt for 15 min and then cooled to -55 °C (externally). Ethylmagnesium bromide (3.10 mL, 0.97 M, 3.00 mmol) in THF was added dropwise at -55 °C. The resulting mixture was stirred at -55 to -50 °C for 30 min and then cooled to -78 °C. **3** (769 mg, 2.00 mmol) in dry THF (3.5 mL) was added dropwise by syringe. The reaction mixture was stirred at -78 °C for 1 h and then quenched with 8 mL of an aqueous $(NH_4)_2SO_4$ / $NH_3$ solution (1 mol $(NH_4)_2SO_4$ and 30 ml 25 % $NH_4OH$ diluted to 500 mL with water) at -78 °C and then allowed to warm to ambient in open air. The mixture was

transferred to a 100 mL flask (using some THF, water and $(NH_4)_2SO_4$ / $NH_3$ solution and concentrated *in vacuo* to remove THF. The aqueous residue was extracted with ether (1×25 mL and 2×15 mL) and the combined organic phases were washed with 0.05 M $Na_2EDTA$ (10 mL) and brine (20 mL), dried with $Na_2SO_4$, filtered and concentrated *in vacuo*. The residue was purified by FC on silica (EtOAc/PE, 0:100 to 1:3) to afford the title compound **4b** (545 mg, 66 %) as a colourless solid after storage at +4 °C.

Mp 49.5-50.5 °C. $[\alpha]^{20}_D$ = -10.2 (c 1.07, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.19 – 8.13 (m, 1H), 8.00 – 7.94 (m, 1H), 7.65 – 7.51 (m, 2H), 5.25 (d, *J* = 8.4, 1H), 3.71 – 3.48 (m, 3H), 1.61 – 1.50 (m, 2H), 1.47 – 1.23 (m, 2H), 0.87 (t, *J* = 7.3, 3H), 0.81 (s, 9H), -0.05 (s, 3H), -0.08 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.0, 152.6, 136.6, 127.7, 127.5, 125.3, 122.3, 64.3, 56.1, 34.5, 25.9, 19.0, 18.4, 13.9, -5.5. HRMS calcd for $C_{18}H_{31}N_2O_3S_2Si$ [M+H] 415.1545; found 415.1532.

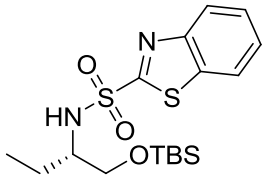
**(*S*)-*N*-(1-(tert-butyldimethylsilyloxy)pent-4-en-2-yl)-benzo[d]thiazole-2-sulfonamide (4c)**




Following the general procedure **I**, the reaction of $CuBr{\cdot}Me_2S$ (74 mg, 0.36 mmol), vinylmagnesium bromide (3.20 mL, 0.94 M, 3.00 mmol) in THF and **3** (769 mg, 2.00 mmol) gave an oily residue. Purification by FC on silica (EtOAc/PE, 8:92) afforded the title compound **4c** (722 mg, 87 %) as a colourless solid after standing at +4 °C

Mp 50-51 °C. $[\alpha]^{20}_D$ = -4.2 (c 1.07, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.20 – 8.13 (m, 1H), 8.01 – 7.94 (m, 1H), 7.66 – 7.51 (m, 2H), 5.67 (ddt, *J* = 7.2, 10.0, 17.2, 1H), 5.28 (d, *J* = 8.1, 1H), 5.09 – 4.95 (m, 2H), 3.76 – 3.65 (m, 1H), 3.64 – 3.54 (m, 2H), 2.36 (t, *J* = 6.9, 2H), 0.82 (s, 9H), -0.02 (s, 3H), -0.05 (d, *J* = 3.0, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.8, 152.6, 136.6, 133.5, 127.7, 127.5, 125.3, 122.3, 118.8, 63.7, 55.6, 36.6, 25.9, 18.3, -5.46, -5.50. HRMS calcd for $C_{18}H_{29}N_2O_3S_2Si$ [M+H] 413.1389; found 413.1362. HRMS calcd for $C_{18}H_{27}N_2O_3S_2Si$ [M-H] 411.1232; found 411.1235.

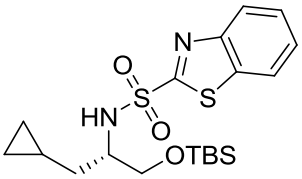
**(*S*)-*N*-(1-(tert-butyldimethylsilyloxy)butan-2-yl)-benzo[d]thiazole-2-sulfonamide (4a)**



Following the general procedure **I**, the reaction of $CuBr{\cdot}Me_2S$ (74 mg, 0.36 mmol), methylmagnesium bromide (3.00 mL, 1.00 M, 3.00 mmol) in ether and **3** (769 mg, 2.00 mmol) gave an oily residue. Purification by FC on silica (EtOAc/PE, 0:100 to 16:84) afforded the title compound **4a** (727 mg, 91 %) as a colourless solid.

Mp 86-87 °C. $[\alpha]^{20}_D$ = -34.2 (c 1.00, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.19 – 8.14 (m, 1H), 8.00 – 7.94 (m, 1H), 7.64 – 7.51 (m, 2H), 5.28 (d, *J* = 7.9, 1H), 3.60 – 3.48 (m, 3H), 1.67 – 1.56 (m, 2H), 0.89 (t, *J* = 7.4, 3H), 0.81 (s, 9H), -0.04 (s, 3H), -0.07 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.0, 152.6, 136.6, 127.7, 127.5, 125.3, 122.3, 63.9, 57.7, 25.9, 25.4, 18.4, 10.3, -5.5. HRMS calcd for $C_{17}H_{29}N_2O_3S_2Si$ [M+H] 401.1389; found 401.1381.

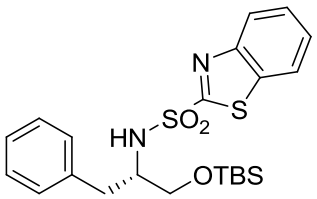
**(*S*)-*N*-(1-(tert-butyldimethylsilyloxy)-3-cyclopropylpropan-2-yl)-benzo[d]thiazole-2-sulfonamide (4d)**



Following the general procedure **I**, the reaction of $CuBr{\cdot}Me_2S$ (74 mg, 0.36 mmol), cyclopropylmagnesium bromide (7.9 mL, 0.38 M, 3.0 mmol) in THF and **3** (769 mg, 2.00 mmol) gave an oily residue. Purification twice by FC on silica (EtOAc/PE, 0:100 to 1:9) afforded the title compound **4d** (653 mg, 76.6 %) as a colourless solid after prolonged standing at 4 °C as well as some **4d** (93 mg, 10.8 %) containing minor impurities by TLC.

Mp 38.5-40 °C. $[\alpha]^{20}_D$ = -29.5 (c 1.08, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.21 – 8.15 (m, 1H), 8.03 – 7.95 (m, 1H), 7.67 – 7.53 (m, 2H), 5.35 (d, *J* = 8.1, 1H), 3.83 – 3.61 (m, 3H), 1.63 – 1.42 (m, 2H), 0.84 (s, 9H), 0.72 – 0.57 (m, 1H), 0.46 – 0.32 (m, 2H), 0.12 – -0.02 (m, 2H), -0.00 (s, 3H), -0.03 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.0, 152.6, 136.6, 127.7, 127.5, 125.3, 122.3, 64.1, 56.9, 37.1, 25.9, 18.4, 7.6, 4.8, 4.4, -5.4, -5.5. HRMS calcd for $C_{19}H_{31}N_2O_3S_2Si$ [M+H] 427.1545; found 427.1550.

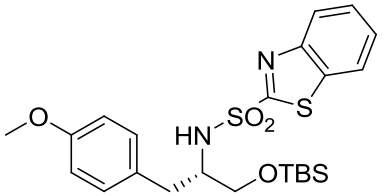
**(*S*)-*N*-(1-(tert-butyldimethylsilyloxy)-3-phenylpropan-2-yl)-benzo[d]thiazole-2-sulfon-amide (4e)**




Following the general procedure **I**, the reaction of $CuBr{\cdot}Me_2S$ (70 mg, 0.34 mmol), phenylmagnesium chloride (1.75 mL, 1.72 M, 3.00 mmol) in THF and **3** (769 mg, 2.00 mmol) gave an oily residue. Purification by FC on silica (EtOAc/PE, 0:100 to 3:7) afforded the title compound **3e (**803 mg, 87 %) as a colourless solid.

Mp 73-74 °C. $[\alpha]^{20}_D$ = -39.8 (c 1.03, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.16 – 8.09 (m, 1H), 7.98 – 7.88 (m, 1H), 7.64 – 7.49 (m, 2H), 7.16 – 6.98 (m, 5H), 5.29 (d, *J* = 8.3, 1H), 3.95 – 3.82 (m, 1H), 3.61 – 3.48 (m, 2H), 2.97 – 2.80 (m, 2H), 0.87 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.5, 152.5, 137.1, 136.7, 129.4, 128.5, 127.7, 127.4, 126.7, 125.3, 122.2, 63.4, 57.4, 38.2, 26.0, 18.4, -5.4, -5.5. HRMS calcd for $C_{22}H_{31}N_2O_3S_2Si$ [M+H] 463.1545; found 463.1534.

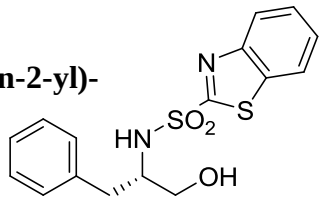
**(*S*)-*N*-(1-(tert-butyldimethylsilyloxy)-3-(4-methoxyphenyl)-propan-2-yl)-benzo[d]thiazole-2-sulfonamide (4f)**




Following the general procedure **I**, the reaction of $CuBr{\cdot}Me_2S$ (67 mg, 0.33 mmol), 4-methoxy-phenylmagnesium bromide (6.7 mL, 0.45 M, 3.0 mmol) in THF and **3** (769 mg, 2.00 mmol) gave an oily residue. Purification by FC on silica (EtOAc/PE, 0:100 to 1:3) afforded the title compound **4f** as a colourless solid (635 mg, 64 %) as well as some **4f** (78 mg) containing minor impurities. Recrystallisation of the impure **4f** from *n*-hexane gave pure **4f** as a colourless solid (53 mg, 6 %).

Mp 101-102 °C. $[\alpha]^{20}_D$ = -38.6 (c 1.03, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.16 – 8.08 (m, 1H), 7.98 – 7.89 (m, 1H), 7.66 – 7.49 (m, 2H), 7.05 – 6.94 (m, 2H), 6.68 – 6.57 (m, 2H), 5.26 (d, *J* = 8.3, 1H), 3.90 – 3.77 (m, 1H), 3.67 (s, 3H), 3.55 (d, *J* = 3.8, 2H), 2.91 – 2.73 (m, 2H), 0.87 (s, 9H), 0.01 (s, 3H), -0.02 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.5, 158.4, 152.5, 136.7, 130.4, 129.0, 127.6, 127.5, 125.3, 122.2, 113.9, 63.4, 57.5, 55.2, 37.2, 26.0, 18.4, -5.36, -5.43. HRMS calcd for $C_{23}H_{33}N_2O_4S_2Si$ [M+H] 493.1651; found 493.1643.

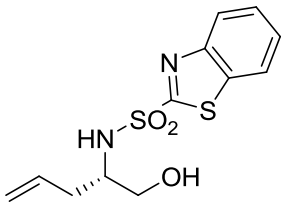
**General procedure II for the deprotection of the TBS group exemplified by the synthesis of (*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-benzo[d]thiazole-2-sulfonamide (5e)**




HF (55 µL, 40 % (aq), 1.23 mmol, 1.5 equiv) was added to a stirred solution of **4e** (381 mg, 0.823 mmol) in acetonitrile (1.1 mL) cooled to 0 °C in an ice bath. The mixture was stirred 30 min at 0 °C and then at ambient for 2 h while the reaction progress was monitored by TLC and UPLC-MS. The reaction mixture was then neutralized with sat. $NaHCO_3$ and concentrated *in vacuo* to remove acetonitrile. The residue was partitioned between brine (10 mL) and EtOAc (15 mL). The aqueous layer was extracted with EtOAc (2×15 ml). The combined organic layers were washed brine (10 mL), dried over $Na_2SO_4$ and concentrated *in vacuo*. The solid residue was purified by FC on silica (EtOAc/PE, 7:13) to afford the title compound **5e** as a colourless solid (249 mg, 87 %).

Mp 119-120 °C. $[\alpha]^{20}_D$ = -29.8 (c 1.02, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.14 – 8.08 (m, 1H), 7.97 – 7.91 (m, 1H), 7.65 – 7.52 (m, 2H), 7.15 – 7.02 (m, 5H), 5.44 (d, *J* = 7.7, 1H), 4.05 – 3.92 (m, 1H), 3.75 (dd, *J* = 3.8, 11.6, 1H), 3.60 (dd, *J* = 4.9, 11.5, 1H), 3.00 – 2.85 (m, 2H), 2.78 (s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.1, 151.9, 136.6, 136.6, 129.4, 128.7, 127.9, 127.6, 126.9, 125.1, 122.3, 63.7, 58.2, 38.4. HRMS calcd for $C_{16}H_{17}N_2O_3S_2$ [M+H] 349.0681; found 349.0648. HRMS calcd for $C_{16}H_{15}N_2O_3S_2$ [M-H] 347.0524; found 347.0514.

**(*S*)-*N*-(1-hydroxypent-4-en-2-yl)benzo[d]thiazole-2-sulfonamide (5c)**

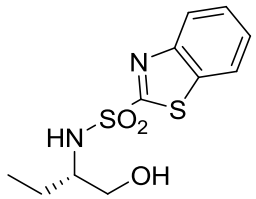



Following the general procedure **II**, the reaction of **4c** (460 mg, 1.11 mmol) and HF (74 µL, 40 %) in acetonitrile (1.48 mL) gave a solid residue. Purification by FC on silica (EtOAc/PE, 7:13) afforded the title compond **5c** (274 mg, 83 %) as a colourless solid.

Mp 120-121 °C. $[\alpha]^{20}_D$ = +18.0 (c 1.04, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.17 – 8.10 (m, 1H), 8.01 – 7.93 (m, 1H), 7.65 – 7.53 (m, 2H), 5.72 (ddt, *J* = 7.2, 10.0, 17.2, 1H), 5.42 (d, *J* = 7.5, 1H), 5.17 – 5.02 (m, 2H), 3.87 – 3.71 (m, 2H), 3.63 (dd, *J* = 5.1, 11.6, 1H), 2.98 (br s, 1H), 2.45 – 2.35 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.6, 151.7, 136.4, 133.1, 127.9,

127.7, 125.0, 122.4, 119.3, 64.0, 56.6, 36.8. HRMS) calcd for $C_{12}H_{15}N_2O_3S_2$ [M+H] 299.0524; found 299.0518.

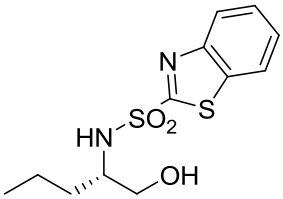
**(S)-*N*-(1-hydroxybutan-2-yl)benzo[d]thiazole-2-sulfonamide (5a)**




Following the general procedure **II**, the reaction of **4a** (726 mg, 1.81 mmol) and HF (121 µL, 40 %) in acetonitrile (2.4 mL) gave a solid residue. Purification by FC on silica (EtOAc/PE, 7:13) afforded the title compound (432 mg, 83 %) as a colourless solid.

Mp 107-108 °C. $[\alpha]^{20}_D$ = -2.8 (c 1.07, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.14 – 8.06 (m, 1H), 8.00 – 7.92 (m, 1H), 7.64 – 7.51 (m, 2H), 5.63 (d, *J* = 7.6, 1H), 3.75 – 3.55 (m, 3H), 3.37 – 2.77 (m, 1H), 1.74 – 1.51 (m, 2H), 0.95 (t, *J* = 7.4, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.9, 151.7, 136.4, 127.9, 127.7, 124.9, 122.4, 64.2, 59.0, 25.5, 10.4. HRMS calcd for $C_{11}H_{15}N_2O_3S_2$ [M+H] 287.0524; found 287.0526.

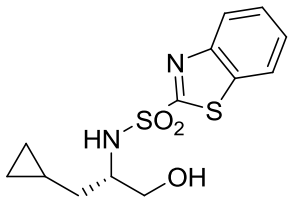
**(S)-*N*-(1-hydroxypentan-2-yl)benzo[d]thiazole-2-sulfonamide (5b)**




Following the general procedure **II**, the reaction of **4b** (415 mg, 1.30 mmol) and HF (87 µL, 40 %) in acetonitrile (2.30 mL) gave a solid residue. Purification by FC on silica (EtOAc/PE, 7:13) afforded the title compound (361 mg, 92 %) as a colourless solid.

Mp 136-137 °C. $[\alpha]^{20}_D$ = +4.5 (c 1.00, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.12 – 8.06 (m, 1H), 7.98 – 7.93 (m, 1H), 7.62 – 7.51 (m, 2H), 5.74 (d, *J* = 8.1, 1H), 3.80 – 3.65 (m, 2H), 3.57 (dd, *J* = 5.7, 11.8, 1H), 3.26 (s, 1H), 1.61 – 1.50 (m, 2H), 1.49 – 1.28 (m, 2H), 0.88 (t, *J* = 7.2, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.9, 151.6, 136.4, 127.9, 127.7, 124.9, 122.4, 64.6, 57.4, 34.5, 19.0, 13.8. HRMS calcd for $C_{12}H_{17}N_2O_3S_2$ [M+H] 301.0681; found 301.0693.

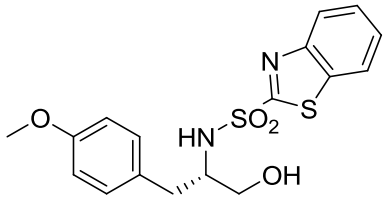
**(*S*)-*N*-(1-cyclopropyl-3-hydroxypropan-2-yl)-benzo[d]thiazole-2-sulfonamide (5d)**




Following the general procedure **II**, the reaction of **4d** (724 mg, 1.70 mmol) and HF (113 µL, 40 %) in acetonitrile (2.7 mL) gave a solid residue. Purification by FC on silica (EtOAc/PE, 7:13) afforded the title compound **5d** (485 mg, 91 %) as a colourless solid.

Mp 136-137 °C. $[\alpha]^{20}_{D}$ = -0.2 (c 1.05, EtOAc). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.16 – 8.08 (m, 1H), 8.00 – 7.93 (m, 1H), 7.64 – 7.52 (m, 2H), 5.53 (d, *J* = 7.7, 1H), 3.91 – 3.75 (m, 2H), 3.68 (dd, *J* = 5.3, 11.5, 1H), 3.04 (s, 1H), 1.64 – 1.42 (m, 3H), 0.75 – 0.61 (m, 1H), 0.50 – 0.35 (m, 2H), 0.12 – 0.02 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.7, 151.7, 136.4, 127.9, 127.7, 125.0, 122.4, 64.3, 58.1, 37.3, 7.6, 4.8, 4.6. HRMS calcd for $C_{13}H_{17}N_2O_3S_2$ [M+H] 313.0681; found 313.0692.

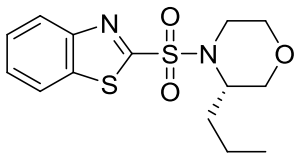
**(S)-N-(1-hydroxy-3-(4-methoxyphenyl)propan-2-yl)-benzo[d]thiazole-2-sulfonamide (5f)**




Following the general procedure **II**, the reaction of **4f** (684 mg, 1.39 mmol) and HF (93 µL, 40 %) in acetonitrile (2.3 mL) gave a solid residue. Purification by FC on silica (EtOAc/PE, 7:13) afforded a colourless oil. Crystallisation from ether afforded the title compound **5f** (473 mg, 90 %) as a colourless solid.

Mp 95.5-97 °C. $[\alpha]^{20}_{D}$ = -27.8 (c 1.00, EtOAc). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.14 – 8.08 (m, 1H), 7.96 – 7.90 (m, 1H), 7.64 – 7.51 (m, 2H), 7.05 – 6.97 (m, 2H), 6.67 – 6.60 (m, 2H), 5.55 (d, *J* = 7.7, 1H), 3.99 – 3.87 (m, 1H), 3.75 (dd, *J* = 3.8, 11.5, 1H), 3.67 (s, 3H), 3.60 (dd, *J* = 4.9, 11.5, 1H), 3.18 – 2.50 (m, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.1, 158.6, 151.9, 136.5, 130.4, 128.5, 127.8, 127.6, 125.1, 122.3, 114.1, 63.8, 58.3, 55.3, 37.4. HRMS (ES TOF) calcd for $C_{17}H_{19}N_2O_4S_2$ [M+H] 379.0786; found 379.0785.

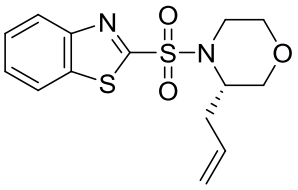
**General procedure III for the annulation reaction of 5a-f to 6a-f exemplified by the synthesis of (S)-3-propyl-4-(benzo[d]thiazol-2-ylsulfonyl)morpholine (6b)**



Triethylamine (600 μL, 4.26 mmol, 4 equiv) was added dropwise by syringe through a septum to a stirred mixture of **5b** (320 mg, 1.07 mmol) in dry $CH_2Cl_2$ (8 mL) in a 20 mL capped microwave vial cooled in an ice bath and under argon. Undissolved **5b** dissolved when triethylamine was added. The mixture was stirred 5 min at 0 °C and then diphenylvinylsulfonium trifluoromethanesulfonate (584 mg, 1.60 mmol) in dry $CH_2Cl_2$ (7 mL) was added dropwise by syringe. The mixture was stirred 1 h at 0 °C. By then UPLC-MS showed full conversion of **5b** into a uncyclised sulfonium intermediate. The reaction mixture was then heated to 90 °C (3-4 bar) in a microwave reactor for 15 min. If any uncyclised sulfonium salt was still present by UPLC-MS the reaction mixture was reheated to 90 °C for 5 min extra. The reaction mixture was then partitioned between 1 M $NaH_2PO_4$ (16 mL) and $CH_2Cl_2$ (10 mL) and the aqueous layer extracted with $CH_2Cl_2$ (2×15 mL). Drying over $Na_2SO_4$ and concentration *in vacuo* gave an oily residue. Purification by FC on silica (EtOAc/$CH_2Cl_2$/PE, 1:1:8) gave a colourless oil that solidified after standing at 4 °C to afford the title compound **6b** (300 mg, 86 %) as a colourless solid.

Mp 69-70 °C. $[\alpha]^{20}_D$ = +59.0 (c 1.06, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.21 – 8.15 (m, 1H), 8.01 – 7.95 (m, 1H), 7.65 – 7.52 (m, 2H), 3.96 (td, *J* = 2.9, 7.5, 1H), 3.87 – 3.65 (m, 3H), 3.57 – 3.37 (m, 3H), 1.84 – 1.64 (m, 2H), 1.47 – 1.31 (m, 2H), 0.93 (t, *J* = 7.3, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 167.0, 152.7, 136.5, 127.7, 127.6, 125.3, 122.3, 68.5, 66.1, 54.5, 41.8, 30.9, 19.5, 13.9. HRMS calcd for $C_{14}H_{19}N_2O_3S_2$ [M+H] 327.0837; found 327.0823.

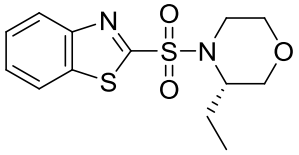
**(S)-3-allyl-4-(benzo[d]thiazol-2-ylsulfonyl)morpholine (6c)**



Following the general procedure **III**, the reaction of triethylamine (770 μL, 5.54 mmol), **5c** (413 mg, 1.38 mmol) and diphenylvinylsulfonium trifluoromethanesulfonate (752 mg, 2.08

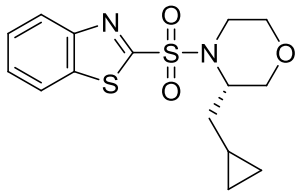
mmol) in $CH_2Cl_2$ (9 + 9 mL) gave an oily residue. Purification by FC on silica (EtOAc/$CH_2Cl_2$/PE, 1:1:8) afforded the title compound **6c** (339 mg, 75 %) as a colourless oil. $[\alpha]^{20}_D$ = +50.5 (c 1.07, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.21 – 8.15 (m, 1H), 8.00 – 7.95 (m, 1H), 7.66 – 7.53 (m, 2H), 5.83 – 5.67 (m, 1H), 5.16 – 5.01 (m, 2H), 4.08 – 3.98 (m, 1H), 3.89 – 3.73 (m, 3H), 3.57 – 3.43 (m, 3H), 2.66 – 2.53 (m, 1H), 2.52 – 2.40 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.8, 152.7, 136.5, 133.8, 127.8, 127.6, 125.3, 122.3, 118.7, 67.8, 66.3, 54.1, 41.9, 33.4. HRMS calcd for $C_{14}H_{17}N_2O_3S_2$ [M+H] 325.0681; found 325.0669.

**(S)-4-(benzo[d]thiazol-2-ylsulfonyl)-3-ethylmorpholine (6a)**



Following the general procedure **III**, the reaction of triethylamine (820 μL, 5.87 mmol), **5a** (420 mg, 1.47 mmol) and diphenylvinylsulfonium trifluoromethanesulfonate (804 mg, 2.20 mmol) in $CH_2Cl_2$ (10 + 9 mL) gave an oily residue. Purification by FC on silica (EtOAc/$CH_2Cl_2$/PE, 1:1:8) afforded the title compound **6a** (382 mg, 83 %) as a colourless oil. $[\alpha]^{20}_D$ = +45.7 (c 1.09, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.21 – 8.15 (m, 1H), 8.01 – 7.95 (m, 1H), 7.66 – 7.53 (m, 2H), 3.92 – 3.81 (m, 2H), 3.80 – 3.69 (m, 2H), 3.56 – 3.39 (m, 3H), 1.89 – 1.71 (m, 2H), 0.96 (t, *J* = 7.5, 3H). $^{13}$C NMR (151 MHz, $CDCl_3$) δ 166.93, 152.67, 136.42, 127.76, 127.61, 125.26, 122.30, 68.06, 66.11, 56.07, 41.77, 21.76, 10.78. HRMS calcd for $C_{13}H_{17}N_2O_3S_2$ [M+H] 313.0681; found 313.0674.

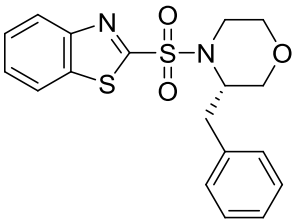
**(*S*)-4-(benzo[d]thiazol-2-ylsulfonyl)-3-cyclopropylmethyl)-morpholine (6d)**



Following the general procedure **III**, the reaction of triethylamine (830 μL, 5.94 mmol), **5d** (464 mg, 1.48 mmol) and diphenylvinylsulfonium trifluoromethanesulfonate (808 mg, 2.23 mmol) in $CH_2Cl_2$ (10 + 9 mL) gave an oily residue. Purification by FC on silica (EtOAc/$CH_2Cl_2$/PE, 1:1:8) afforded a colourless oil that solidified on standing at 4 °C, affording the title compound **6d** (383 mg, 76%) as a colourless solid.

Mp 76-77 °C. $[\alpha]^{20}_{D}$ = +55.3 (c 1.03, EtOAc). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.20 – 8.15 (m, 1H), 8.01 – 7.94 (m, 1H), 7.65 – 7.52 (m, 2H), 4.11 – 4.02 (m, 1H), 3.93 – 3.76 (m, 3H), 3.60 – 3.41 (m, 3H), 1.79 – 1.58 (m, 2H), 0.69 (pd, *J* = 4.9, 7.4, 1H), 0.53 – 0.41 (m, 2H), 0.18 – 0.03 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.9, 152.7, 136.5, 127.7, 127.6, 125.3, 122.3, 68.3, 66.3, 55.1, 42.0, 33.6, 8.1, 5.2, 4.2. HRMS calcd for $C_{15}H_{18}N_2O_3S_2$ [M+H] 339.0837; found 339.0829.

**(*S*)-4-(benzo[d]thiazol-2-ylsulfonyl)-3-benzylmorpholine (6e)**



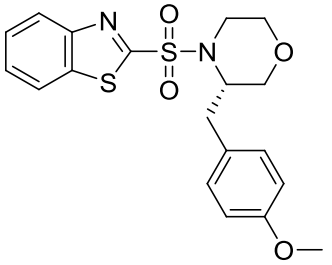
Following the general procedure **III**, the reaction of triethylamine (440 µL, 3.15 mmol), **5e** (274.5 mg, 0.788 mmol) and diphenylvinylsulfonium trifluoromethanesulfonate (434 mg, 1.20 mmol) in $CH_2Cl_2$ (6 + 5 mL) gave an oily residue. Purification by FC on silica (EtOAc/PE, 3:17) afforded the title compound **6e** (224 mg, 76 %) as a colourless solid.

Mp 85.5-86.5 °C. $[\alpha]^{20}_{D}$ = -30.6 (c 1.10, EtOAc). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.19 – 8.13 (m, 1H), 7.98 – 7.93 (m, 1H), 7.64 – 7.51 (m, 2H), 7.29 – 7.13 (m, 5H), 4.22 – 4.12 (m, 1H), 3.96 – 3.86 (m, 2H), 3.71 – 3.50 (m, 3H), 3.45 (ddd, *J* = 1.0, 3.0, 11.8, 1H), 3.17 (dd, *J* = 10.6, 13.1, 1H), 2.90 (dd, *J* = 4.8, 13.1, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.6, 152.7, 137.4, 136.5, 129.7, 128.8, 127.8, 127.6, 126.9, 125.3, 122.3, 67.1, 66.6, 56.1, 42.1, 35.0. HRMS calcd for $C_{18}H_{19}N_2O_3S_2$ [M+H] 375.0837; found 375.0833.

Chirale HPLC analysis : A single peak at 16.4 min (>99% ee) was observed under the following conditions: Chiralpak AD-H (0.46 cm×25 cm); ethanol (0.1% $Et_3N$, 0.1% AcOH):heptane (0.1% $Et_3N$, 0.1% AcOH), 2:8; flow: 0.7 ml/min; λ = 280 nm.

Mixture of **(*R*)-6e** and **(*S*)-6e**: $t_R$ [**(*R*)-6e**] = 14.2 min; $t_R$ [**(*S*)-6e**] = 16.4 min.

**(*S*)-4-(benzo[d]thiazol-2-ylsulfonyl)-3-(4-methoxybenzyl)-morpholine (6f)**



Following the general procedure **III**, the reaction of triethylamine (590 µL, 4.24 mmol), **5f** (410 mg, 1.09 mmol) and diphenylvinylsulfonium

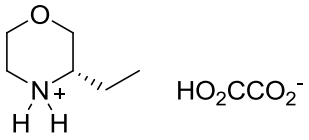
trifluoromethanesulfonate (646 mg, 1.78 mmol) in $CH_2Cl_2$ (7 + 8 mL) gave an oily residue. Purification by FC on silica (EtOAc/$CH_2Cl_2$/PE, 12:12:76) and crystallisation from methanol afforded the title compound **6f** (318.1 mg, 72 %) as a colourless solid.

Mp 96-97 °C. $[\alpha]^{20}_D$ = -37.8 (c 1.00, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.19 – 8.13 (m, 1H), 7.99 – 7.93 (m, 1H), 7.64 – 7.51 (m, 2H), 7.12 (d, *J* = 8.5, 2H), 6.77 (d, *J* = 8.6, 2H), 4.17 – 4.07 (m, 1H), 3.94 – 3.86 (m, 2H), 3.74 (s, 3H), 3.71 – 3.40 (m, 4H), 3.11 (dd, *J* = 10.5, 13.3, 1H), 2.84 (dd, *J* = 5.0, 13.3, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.6, 158.6, 152.7, 136.5, 130.6, 129.4, 127.7, 127.6, 125.3, 122.3, 114.2, 67.1, 66.6, 56.2, 55.3, 42.0, 34.1. HRMS calcd for $C_{19}H_{21}N_2O_4S_2$ [M+H] 405.0943; found 405.0941.

**General procedure IV for the deprotection of the benzothiazolesulfonyl group and isolation of the morpholins as hydrogen oxalates**

2-mercaptoacetic acid (137 µL, 2 mmol, 2 eq, freshly distilled) was added to a stirred suspension of lithium hydroxide monohydrate (168 mg, 4 mmol, 4 eq) in DMSO (2 mL) under argon. The mixture was stirred 5 min at rt. **6a-f** (1.0 mmol) in DMSO (1 mL) was added and the mixture stirred at rt until TLC / UPLC-MS showed full conversion of **6a-f** (5 min – 30 min). The reaction mixture was partitioned between 2 M $K_2CO_3$ (12 mL) and ether (16 mL). The aqueous layer was extracted 3-5 times with ether (16 mL) until TLC (MeOH/$CH_2Cl_2$, 1:4, ninhydrin) showed only insignificant amounts of product in the extract. The combined organic layers were dried twice over solid crushed KOH. Anhydrous oxalic acid (99 mg, 1.1 mmol, 1.1 eq) in dry ether (1-2 mL) was added and the solid formed filtered through a glas sintered funnel size 4, washed with dry ether and dried in high vacuum.

**(*S*)-3-ethylmorpholinum hydrogenoxalate (7a)**

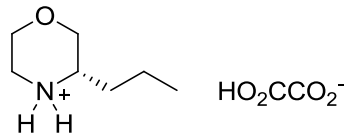



Following the general procedure **IV**, the reaction of 2-mercaptoacetic acid (171 µL, 2.46 mmol), lithium hydroxide monohydrate (206 mg, 4.92 mmol) and **6a** (384.4 mg, 1.230 mmol) afforded a mixture of (*S*)-3-ethylmorpholinum oxalate and (*S*)-3-ethylmorpholinum hydrogenoxalate (180 mg, 81 %) as a colourless solid.

$^{1}$H NMR (600 MHz, $D_2O$) δ 4.10 (dd, *J* = 3.5, 13.0, 1H), 4.08 – 4.04 (m, 1H), 3.81 – 3.74 (m, 1H), 3.56 (dd, *J* = 10.3, 12.9, 1H), 3.37 (dt, *J* = 2.3 13.2, 1H), 3.31 (dtd, *J* = 3.6, 7.0, 10.5, 1H), 3.25 (ddd, *J* = 3.8, 11.5, 13.2, 1H), 1.69 – 1.57 (m, 2H), 0.98 (t, *J* = 7.6, 3H). $^{13}$C NMR (151 MHz, $D_2O$) δ 171.6, 70.7, 66.3, 58.9, 45.9, 24.8, 11.6. Elemental analysis calcd (%) for $C_8H_{15}NO_5$ (hydrogenoxalate): C 46.82; H 7.37; N 6.83; found: C 49.55 ; H 7.88 ; N 7.61. With no signs of impurities in the $^{1}$H- and $^{13}$C NMR spectra the elemental analysis result can be explained assuming the material is a mixture of hydrogenoxalate and oxalate. Elemental analysis calcd (%) for $C_8H_{15}NO_5 \cdot (C_{14}H_{28}N_2O_6)_{0.595}$: C 49.55; H 8.06; N 7.75; found C 49.55 ; H 7.88 ; N 7.61.

Recrystallisation from acetone containing oxalic acid gave a colourless solid. Mp 92.2-93.0 °C (acetone). $[\alpha]^{25}_{D}$ = -9.0 (c 1.02, $H_2O$). Elemental analysis calcd (%) for $C_8H_{15}NO_5$ (hydrogenoxalate): C 46.82; H 7.37; N 6.83; found: C 46.91 ; H 7.32 ; N 6.66.

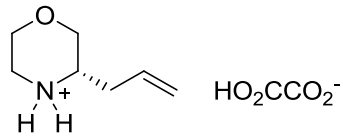
**(*S*)-3-propylmorpholinum hydrogenoxalate (7b)**




Following the general procedure **IV**, the reaction of 2-mercaptoacetic acid (117 µL, 1.68 mmol), lithium hydroxide monohydrate (141 mg, 3.36 mmol) and **6b** (275 mg, 0.842 mmol) afforded the title compound **7b** (137 mg, 74 %) as a colourless solid.

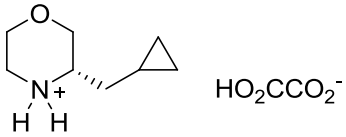
Mp 78-79 °C. $[\alpha]^{25}_{D}$ = -8.9 (c 1.03, $H_2O$). $^{1}$H NMR (600 MHz, $D_2O$) δ 4.12 – 4.03 (m, 2H), 3.80 – 3.74 (m, 1H), 3.56 (dd, *J* = 10.3, 13.0, 1H), 3.42 – 3.34 (m, 2H), 3.25 (ddd, *J* = 3.8, 11.6, 13.2, 1H), 1.62 – 1.52 (m, 2H), 1.46 – 1.33 (m, 2H), 0.92 (t, *J* = 7.4, 3H). $^{13}$C NMR (151 MHz, $D_2O$) δ 169.3, 70.9, 66.3, 57.4, 46.0, 33.4, 20.6, 15.9. Elemental analysis calcd (%) for $C_9H_{17}NO_5$: C 49.31; H 7.82; N 6.39; found: C 49.40; H 7.50; N 6.24.

**(*S*)-3-allylmorpholinum hydrogenoxalate (7c)**




Following the general procedure **IV**, the reaction of 2-mercaptoacetic acid (151 µL, 2.17 mmol), lithium hydroxide monohydrate (182 mg, 4.34 mmol) and **6c** (352.1 mg, 1.085 mmol) afforded the title compound **7c** (176 mg, 75 %) as a colourless solid.

Mp 78-82 °C. $[\alpha]^{25}_{D}$ = +2.3 (c 1.06, $H_2O$). $^1$H NMR (600 MHz, $D_2O$) δ 5.82 – 5.73 (m, 1H), 5.32 – 5.24 (m, 2H), 4.07 (ddd, *J* = 2.9, 9.3, 13.2, 2H), 3.81 – 3.74 (m, 1H), 3.59 (dd, *J* = 10.3, 12.9, 1H), 3.50 – 3.43 (m, 1H), 3.36 (dt, *J* = 2.3, 13.3, 1H), 3.25 (ddd, *J* = 3.8, 11.6, 13.3, 1H), 2.48 – 2.41 (m, 1H), 2.36 – 2.29 (m, 1H). $^{13}$C NMR (151 MHz, $D_2O$) δ 169.1, 133.7, 123.7, 70.7, 66.3, 56.7, 46.1, 35.9. Elemental analysis calcd (%) for $C_9H_{15}NO_5$: C 49.76; H 6.96; N 6.45; found: C 49.94; H 6.87; N 6.36.

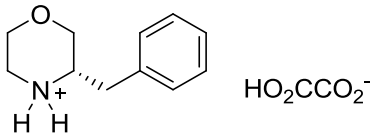
**(*S*)-3-(cyclopropylmethyl)morpholinum hydrogenoxalate (7d)** 

Following the general procedure **IV**, 2-mercaptoacetic acid (138 μL, 1.98 mmol), lithium hydroxide monohydrate (166 mg, 3.96 mmol) and **6d** (335.5 mg, 0.991 mmol) were reacted together. Adding oxalic acid gave a sticky gum impossible to filter. The gum was dissolved in small amount of water and put through the workup procedure once more. Adding oxalic acid gave a gum once more. Cooling in a dry ice-acetone bath seemed to give a solid but when it was filtered it returned to being a gum. The gum was dried in high vacuum over night and crystallised on the glass sintered funnel by adding a few mL of acetone. This afforded **7d** as a colourless solid (130 mg, 57 %).

$^1$H NMR (600 MHz, $D_2O$) δ 4.14 (dd, *J* = 3.4, 12.8, 1H), 4.10 – 4.05 (m, 1H), 3.78 (ddd, *J* = 2.6, 11.7, 13.2, 1H), 3.60 (dd, *J* = 10.5, 12.8, 1H), 3.54 – 3.48 (m, 1H), 3.38 (dt, *J* = 2.1, 13.2, 1H), 3.27 (ddd, *J* = 3.9, 11.8, 13.2, 1H), 1.62 (dt, *J* = 6.5, 14.5, 1H), 1.40 (dt, *J* = 7.6, 14.9, 1H), 0.78 – 0.68 (m, 1H), 0.60 – 0.50 (m, 2H), 0.17 – 0.08 (m, 2H). $^{13}$C NMR (151 MHz, D2O) δ 169.5, 70.9, 66.3, 58.4, 46.2, 36.1, 8.7, 7.0, 6.5. Elemental analysis calcd (%) for $C_{10}H_{17}NO_5$: C 51.94; H 7.41; N 6.06; found: C 52.45; H 7.28; N 6.10.

Recrystallisation from EtOH-TBME gave a colourless solid. Mp 102.4-103.5 °C (EtOH-TBME). $[\alpha]^{25}_{D}$ = -8.2 (c 1.01, $H_2O$). Elemental analysis calcd (%) for $C_{10}H_{17}NO_5$: C 51.94; H 7.41; N 6.06; found: C 51.96; H 7.32; N 5.93.

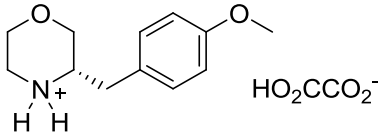
**(*S*)-3-benzylmorpholinum hydrogenoxalate (7e)**



Following the general procedure **IV**, the reaction of 2-mercaptoacetic acid (70 μL, 1.00 mmol), lithium hydroxide monohydrate (84.0 mg, 2.00 mmol) and **6e** (187 mg, 0.498 mmol) afforded the title compound **7e** (100 mg, 75 %) as a colourless solid.

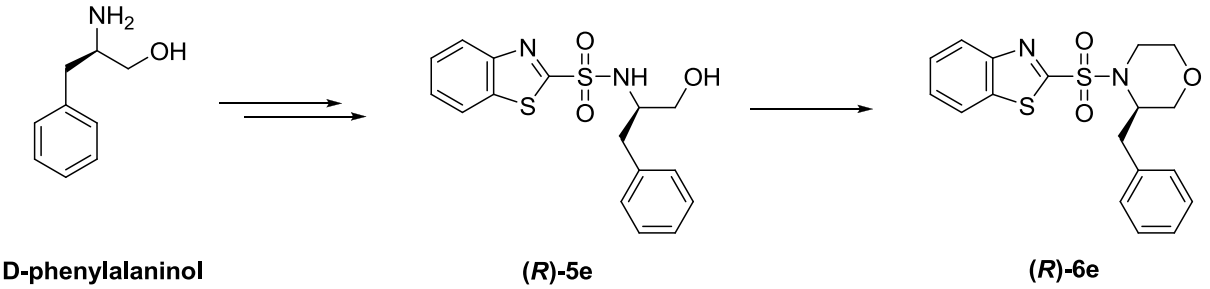
$^1$H NMR (600 MHz, $D_2O$) δ 7.45 – 7.41 (m, 2H), 7.40 – 7.35 (m, 1H), 7.32 (d, *J* = 7.2, 2H), 4.12 – 4.03 (m, 2H), 3.82 – 3.75 (m, 1H), 3.70 – 3.63 (m, 2H), 3.35 (dt, *J* = 2.2, 13.3, 1H), 3.20 (ddd, *J* = 3.8, 11.5, 13.3, 1H), 3.06 – 3.00 (m, 1H), 2.91 – 2.85 (m, 1H). $^{13}$C NMR (151 MHz, $D_2O$) δ 169.7, 137.2, 132.3, 132.2, 130.8, 70.7, 66.3, 58.7, 46.2, 37.5. Elemental analysis calcd (%) for $C_{13}H_{17}NO_5$: C 58.42; H 6.41; N 5.24; found: C 58.91; H 6.34; N 5.27. Recrystallisation from ethanol-TBME gave a colourless solid. Mp 156.2-157.3 °C (ethanol-TBME). $[\alpha]^{25}_D$ = -39.8 (c 1.04, $H_2O$). Elemental analysis calcd (%) for $C_{13}H_{17}NO_5$: C 58.42; H 6.41; N 5.24; found: C 58.18; H 6.39; N 5.05.

**(S)-3-(4-methoxybenzyl)morpholinum hydrogenoxalate (7f)**



Following the general procedure **IV**, the reaction of 2-mercaptoacetic acid (102 μL, 1.46 mmol), lithium hydroxide monohydrate (122 mg, 2.91 mmol) and **6f** (295 mg, 0.729 mmol) afforded the title compound **7f** as a colourless solid (170 mg, 78 %). Mp 154-156 °C (sintering and effervescence was observed). $[\alpha]^{25}_D$ = -38.3 (c 1.07, $H_2O$). $^1$H NMR (600 MHz, $D_2O$) δ 7.27 – 7.23 (m, 2H), 7.03 – 6.99 (m, 2H), 4.09 – 4.03 (m, 2H), 3.83 (s, 3H), 3.82 – 3.76 (m, 1H), 3.67 – 3.59 (m, 2H), 3.35 (dt, *J* = 2.2, 13.3, 1H), 3.20 (ddd, *J* = 3.8, 11.5, 13.3, 1H), 2.99 – 2.94 (m, 1H), 2.85 – 2.80 (m, 1H). $^{13}$C NMR (151 MHz, $D_2O$) δ 168.9, 161.3, 133.6, 129.6, 117.6, 70.7, 66.3, 58.7, 58.4, 46.2, 36.6. Elemental analysis calcd (%) for $C_{14}H_{19}NO_6$: C 56.56; H 6.44; N 4.71; found: C 56.34; H 6.33; N 4.63.

**(*R*)-4-(benzo[d]thiazol-2-ylsulfonyl)-3-benzylmorpholine [(*R*)-6e]**




**D-phenylalaninol** **(*R*)-5e** **(*R*)-6e**

D-phenylalaninol was treated with TBSCl, $Et_3N$ and DMAP.[10] The product was *N*-sulfonylated by treatment with BtsOPFP and DIPEA.[7] The TBS group was deprotected with 40 % HF in $CH_3CN$ according to the general procedure **II** to afford [**(*R*)-5e]**. The reason for installing the *O*-TBS group was to study its deprotection.

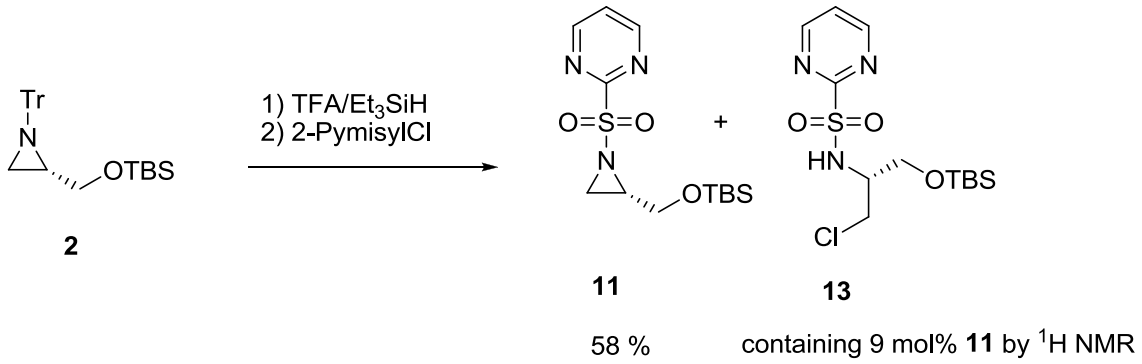
Compound **(*R*)-5e** (184 mg, 0.528 mmol) was dissolved in dry $CH_2Cl_2$ (5 mL) at 0 °C under argon. DIPEA (203 µL, 1.16 mmol) was added and the mixture was stirred for 5 min at 0 °C after which diphenylvinylsulfonium trifluoromethanesulfonate (240 mg, 0.66 mmol) in dry $CH_2Cl_2$ (2 mL) was added dropwise by syringe. The mixture was stirred 1 h at 0 °C and then allowed to warm to ambient. The mixture was stirred at ambient for 4 days. The reaction mixture was diluted with $CH_2Cl_2$ (8 mL) and washed with sat. $NH_4Cl$ (10 mL). The aqueous layer was extracted with $CH_2Cl_2$ (5 mL) and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by FC on silica (EtOAc/PE, 0:100 to 16:84) to afford the title compound **[(*R*)-6e] (**92 mg, 47 %) as a colourless solid. Mp 85-86 °C. $[\alpha]^{20}_D$ = +30.5 (c 1.05, EtOAc). Spectroscopic data were similar to compound **6e**.

Chirale HPLC analysis : A single peak at 14.2 min (>99% ee) was observed under the following conditions: Chiralpak AD-H (0.46 cm×25 cm); ethanol (0.1% $Et_3N$, 0.1% AcOH):heptane (0.1% $Et_3N$, 0.1% AcOH), 2:8; flow: 0.7 ml/min; λ = 280 nm.

Mixture of **(*R*)-6e** and **(*S*)-6e**: $t_R$ [**(*R*)-6e**] = 14.2 min; $t_R$ [**(*S*)-6e**] = 16.4 min.

**Synthesis of 11, Ring Opening Reactions of 11 with Organocuprates and Attempts to Deprotect the TBS group from 12d**

Starting from **2** the trityl group was deprotected with TFA and triethylsilane[9] and the aziridinium salt free based with 2 M $K_2CO_3$ and directly reacted with a freshly prepared 2-pyrimidinesulfonyl chloride solution affording **11** in a moderate yield (route A, scheme 1). The formation of **11** was accompanied by a small amounts of **13** (~ 9 mol%) resulting from opening of the aziridine by chloride ions. Separation by FC proved very difficult so impure **11** was tested directly in the cuprate-opening reaction. When impure **11** was treated with 4-methoxyphenylmagnesium bromide and $CuBr{\cdot}Me_2S$ the ring-opening reaction worked well and **12d** was isolated in 83 % yield along with 2 % unreacted **13** (see tabel 1).

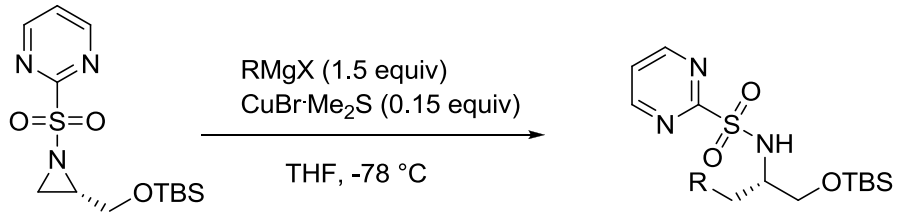



**Scheme 1**

We attributed the problem of forming **11** free of **13** to be a matter of quickly and effectively quenching the HCl formed before it could react with an aziridine, and keep the chloride iones tied up in aqueous solution. Since we didn't experience any problems with 2-methylaziridine in place of *O*-TBS(aziridin-2-yl)methanol in an earlier project, we thought it could be a matter of lowered hydrophilicity of the aziridinium salt. (submitted for pub) To encourage that we experimented with the rate of addition of the sulfonyl chloride and with adding varying amounts of ether to the reaction mixture. All though it did lower the amount of chloride ring opened product **13** somewhat, the problem with forming **11** free from **13** was eventually solved by using pentafluorophenyl 2-pyrimidine sulfonate **10** (route B) instead of the sulfonyl chloride. Pentafluorophenyl 2-pyrimidine sulfonate **10** is a shelf stable equivalent to pymisyl chloride with pentafluorophenolate acting as the leaving group.[7] Although some unknown

ring opening products was observed, pure **11** was obtained by FC in 65 % yield. **11** was reacted with a small number of different Grignard reagents (tabel 1) providing **12a-c** in good yields (83-89 %), see tabel 1.

**Tabel 1. Ring-opening of 11 with Grignard reagents**




| entry | R | product | yield [%][a] |
|---|---|---|---|
| 1 | Vinyl | **12a** | 89 |
| 2 | Cyclopropyl | **12b** | 83 |
| 3 | Ph | **12c** | 86 |
| 4 | 4-MeOPh | **12d** | 83 |

[a] Isolated yields after chromatographic purification.

Next, we tried to remove the TBS group from **12d** with TBAF in THF. Unfortunately the TBS group could not be deprotected to give the desired product **14** without extensive formation of two isomeric byproducts through loss of sulfurdioxide. Based on UPLC-HRMS (ESI-TOF) analysis we tentatively assigns structure **15** and **16** to the byproducts with **15** being the major isomer, see figure 2. We propose that **15** is formed from **14** by a Smiles type rearrangement, involving intramolecular nucleophilic aromatic substitution with expelsion of $SO_2$ and that **15** can undergo a second Smiles rearrangement to form **16**.[11-13]

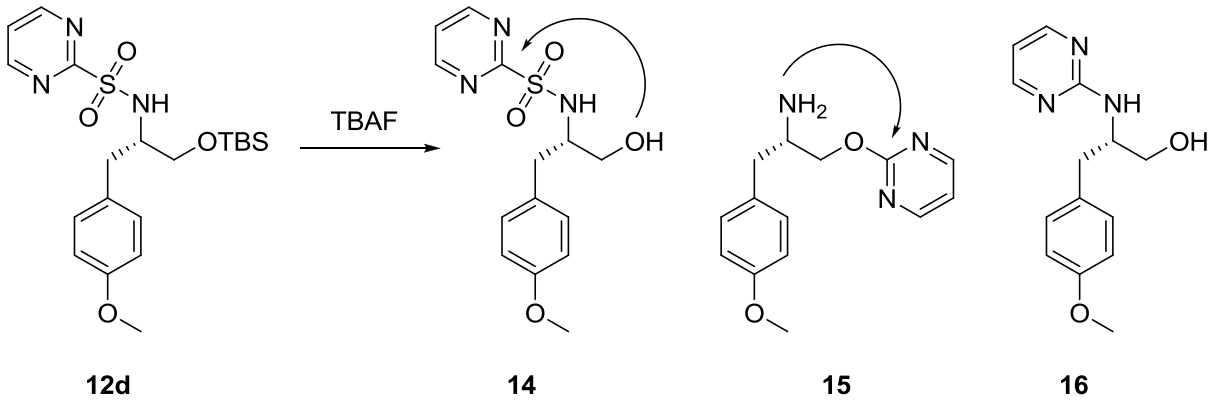
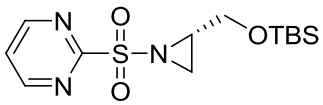



**Figure 2. Proposed structures and mechanisms**

Numerous other reagents and conditions for deprotection of a TBS group e.g. 40 % HF in $CH_3CN$[14], HCl or Dowex 50W-X8 in MeOH[15], $FeCl_3$[16], PMA on $SiO_2$[17], vanilin/ $BF_3{\cdot}Et_2O$[18] and HF-pyridine[19] were tried but formation of **14** was always accompanied by formation of **15** and **16**. Since formation of these byproducts originates from the instability of the pymisyl group in these substrates under the reaction conditions (both acidic and basic reaction conditions were tried), we decide to abandon the pymisyl group and search for alternatives. Although we didn't pursue it, we note that deprotection of the pymisyl group from **12a-12d** with thiolates while the TBS group is still in place could be a useful way of making enantiomerically pure *O*-TBS protected β-amino alcohols ready for further manipulation.

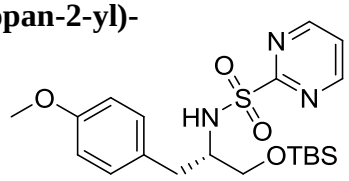
**(S)-2-(2-((tert-butyldimethylsilyloxy)methyl)-aziridin-1-ylsulfonyl)pyrimidine (11). Route A.**




Trifluoroacetic acid (3.45 mL, 45 mmol, 3 eq) was added dropwise by syringe to a stirred solution of **2** (6.44 g, 15 mmol) and triethylsilane (4.80 mL, 30 mmol, 2 eq) in dry $CH_2Cl_2$ (75 mL) at -5 °C under argon. The mixture was stirred 1 h at -5 °C. TLC (EtOAc/petrol, 1:19) showed very little formation of triphenylmethane so extra trifluoroacetic acid (1.15 mL, 15 mmol, 1 eq) and triethylsilane (2.40 mL, 15 mmol, 1 equiv) was added and stirring was continued for 2-3 h at 0 °C. The reaction mixture was quenched by pouring it into cold 2 M $K_2CO_3$ (50 mL) under vigorous stirring. Sodium hypochlorite (33.2 mL, 1.86 M, 61.9 mmol)

was slowly added to a mechanically stirred suspension of 2-mercaptopyrimidine (2.10 g, 18.8 mmol) in 1 M HCl (15 wt% $CaCl_2$) (94 mL) and $CH_2Cl_2$ (94 mL) keeping the internal temperature at -10 °C to -5 °C with the aid of an acetone – dry ice cooling bath. After addition of sodium hypochlorite was complete stirring was continued for 20 min at -10 °C to -5 °C. Excess chlorine was quenched with cold 1 M $Na_2S_2O_3$ at -10 °C. The organic layer was separated off in a pre-cooled separatory funnel and added to the two-phase mixture of the aziridine under vigorous stirring at -5 °C. After stirring at -5 to 0 °C for 30 min, the layers were separated and the organic layer washed with sat. $NaHCO_3$ (50 mL), 0.5 M $KH_2PO_4$ (50 mL) and water (50 ml), dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by FC on silica (EtOAc/petrol) affording the title compound **11** (2.85 g, 58 %) as a colorless solid containing ~9 mol% of **13** by $^1$HNMR.

**(S)-N-(1-(tert-butyldimethylsilyloxy)-3-(4-methoxyphenyl)propan-2-yl)-pyrimidine-2-sulfonamide (12d)**

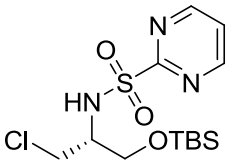



Copper(I) bromide dimethyl sulfide (275 mg, 1.25 mmol) was added to a flame dried Schlenk flask under argon. Dry THF (45 mL) was added and the slurry was stirred at rt for 15 min and then cooled to -65 °C (externally). 4-methoxyphenylmagnesium bromide (25.0 mL, 0.5 M, 12.5 mmol) in THF was added dropwise keeping the internal temperature at -60 to -55 °C. The resulting mixture was stirred at -60 to -50 °C for 30 min and then cooled to -78 °C. Impure **3** (2.75 g, 8.34 mmol) in dry THF (12 mL) was added dropwise by syringe. The reaction mixture was stirred at -78 °C for 40 min and then quenched with 2 M $(NH_4)_2SO_4$ (20 mL) and allowed to warm to ambient in open air. The reaction mixture was transferred to a 250 mL flask (using some THF, water and 2 M $(NH_4)_2SO_4$) and concentrated *in vacuo* to remove THF. The aqueous residue was extracted with $CH_2Cl_2$ (3×40 mL) and the combined organic phases dried with $Na_2SO_4$, filtered and concentrated *in vacuo*. The residue was purified twice by FC on silica (EtOAc/PE) to afford the title compound **12d** (3.025 g, 83 %) as a pale green solid (99 % pure by $^1$H NMR). Recrystallisation from EtOAc/PE afforded **12d** as a colourless solid.

Mp 87-87.5 °C (EtOAc/PE). $[\alpha]^{20}_D$ = -34.9 (c 1.03, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.82 (d, *J* = 4.8, 2H), 7.43 (t, *J* = 4.8, 1H), 7.08 – 6.97 (m, 2H), 6.79 – 6.66 (m, 2H), 5.17 (d, *J*

= 8.4, 1H), 3.87 – 3.74 (m, 4H), 3.56 (d, *J* = 3.7, 2H), 2.90 – 2.73 (m, 2H), 0.90 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.4, 158.5, 158.3, 130.5, 129.5, 122.9, 114.0, 63.6, 57.4, 55.4, 37.3, 26.0, 18.4, -5.3, -5.4. HRMS calcd for $C_{20}H_{32}N_3O_4SSi$ [M+H] 438.1883; found 438.1888.

**(*R*)-*N*-(1-(tert-butyldimethylsilyloxy)-3-chloropropan-2-yl)-pyrimidine-2-sulfonamide (13)**

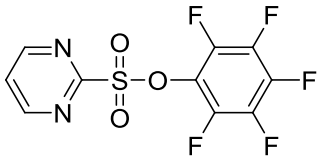



FC also afforded compound **13** (87 mg, 2 %) as a colourless solid.

Recrystallisation from EtOAc/PE afforded an analytically pure sample of the title compound **13** as a colourless solid.

Mp 62-63 °C (EtOAc/PE). $[\alpha]^{20}_{D}$ = -14.1 (c 1.04, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.93 (d, *J* = 4.8, 2H), 7.53 (t, *J* = 4.9, 1H), 5.39 (d, *J* = 8.1, 1H), 3.98 – 3.86 (m, 2H), 3.79 (dd, *J* = 3.9, 10.9, 1H), 3.74 – 3.63 (m, 2H), 0.88 (s, 9H), 0.06 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.4, 158.7, 123.4, 61.5, 56.1, 43.7, 25.9, 18.4, -5.4. HRMS calcd for $C_{13}H_{25}ClN_3O_3SSi$ [M+H] 366.1074; found 366.1079.

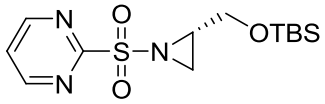
**Pentafluorophenyl 2-pyrimidine sulfonate (10)**




Cold (+4 °C) sodium hypochlorite (106.4 mL, 1.86 M, 198 mmol) was added dropwise to a mechanical stirred mixture of 2-mercaptopyrimidine (6.73 g, 60 mmol) in $CH_2Cl_2$ (300 ml) and 1 M HCl in 15 wt% $CaCl_2$ (300 mL) in a three-necked 1 L round bottomed flask keeping the internal temperature at -10 to -5 °C (closer to -10 °C). Stirring was continued for 15 min at -10 °C to -5 °C after the addition was completed. Excess $Cl_2$ (indicated by a greenish color) was quenched by adding 1M $Na_2SO_3$ (~18 mL) at -10 °C and stirring the mixture for 2 min. The mixture was transferred to a pre cooled separating funnel ($CH_2Cl_2$ and some dry-ice) and the $CH_2Cl_2$ layer was transferred to a dry ice - acetone cooled addition funnel. The 2-pyrimidinesulfonyl chloride solution was added dropwise to a solution of pentafluorophenol (11.04 g, 60 mmol ) and triethylamine (8.8 mL, 63 mmol) in dry $CH_2Cl_2$ (40 mL) in a 500 mL three necked flask under argon keeping the internal temperature below -30 °C. After the addition was complete stirring was continued for 1 h while the reaction mixture was slowly

warmed to -10 °C. The mixture was finally allowed to warm to 0 °C. The reaction mixture was washed with 1 M $KH_2PO_4$ (2×100 mL), 1M $K_2CO_3$ (2×100 mL) and water (100 ml), dried with $MgSO_4$ and concentrated *in vacuo* to afford 16.74 g (85 %) of crude product. $^1$H-NMR ($CDCl_3$) showed ~ 4% of some unidentified pyrimidines and 2-3 % triethylamine salt present. The crude product was taken up in ether (250 mL) and washed with 0.5 M $KH_2PO_4$ (100 mL) and water (50 mL). The solution was dried with $MgSO_4$ and concentrated *in vacuo*. The solid was recrystallised from diisopropyl ether (~20 ml) affording the title compound (14.04 g, 72 %) as white needles. Mp 84.7-85.1 °C (diisopropylether) (litt. mp 85.9-86.7 °C).[7] $^1$H- and $^{13}$C data were identical to previously reported data.[7]

**(S)-2-(2-((tert-butyldimethylsilyloxy)-methyl)aziridin-1-ylsulfonyl)pyrimidine (11). Route B.**

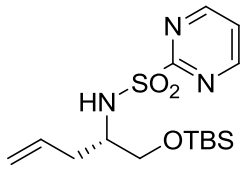



Trifluoroacetic acid (3.06 mL, 40 mmol, 4 equiv) was added dropwise by syringe to a stirred solution of **2** (4.29 g, 10 mmol) and triethylsilane (6.40 mL, 40 mmol, 4 equiv) in dry $CH_2Cl_2$ (50 mL) at 0 °C to under argon. The mixture was stirred at 0 °C to 4 °C while reaction was monitored by TLC (ethyl actetate/petrol, 1:19). The reaction mixture was quenched after 2.5-3h by pouring it into cold 2 M $K_2CO_3$ (50 mL) under vigorous stirring while cooling in a dry ice – acetone bath so the internal temperature was around -10 °C. The aqueous layer was extracted with ether (2×30 mL) and the combined organic layers dried over $Na_2SO_4$, filtered and concentrated *in vacuo* at + 20 °C. The residue was dissolved in acetonitrile (25 mL) and diisopropylethylamine (3.48 mL, 10 mmol) added. The solution was cooled to 0 °C in an ice-bath. Pentafluorophenyl 2-pyrimidine sulfonate (3.26 g, 10 mmol) in acetonitrile (5 mL) was added dropwise. After the addition was complete the reaction mixture was stirred at ambient for 50 min. The reaction mixture was partitioned between 1 M $KH_2PO_4$ (80 mL) and $CH_2Cl_2$ (150 mL). The aqueous layer was extracted with $CH_2Cl_2$ (60 mL). The combined organic phases were washed with 1M $K_2CO_3$ (80 mL) and water (80 mL), dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by FC on silica (EtOAc/PE, 2:3) afforded the title compound **11** (1.50 g, 46 %) as an oil that solidified at +4 °C after drying in high vacuum. Impure fractions were repurified by FC to afford **11** (619 mg, 19 %) (+95 % purity).

Recrystallisation of a small sample from methanol by dissolving it at 40 °C and cooling to -78 °C gave an analytical pure sample of **11** as a colourless solid.

Mp 46-47 °C (methanol). $[\alpha]^{20}_{D}$ = -45.6 (c 1.07, EtOAc). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.98 (d, *J* = 4.9, 2H), 7.58 (t, *J* = 4.8, 1H), 3.86 (dd, *J* = 4.4, 11.6, 1H), 3.76 (dd, *J* = 4.3, 11.6, 1H), 3.29 – 3.20 (m, 1H), 2.94 (d, *J* = 7.0, 1H), 2.47 (d, *J* = 4.8, 1H), 0.84 (s, 9H), 0.00 (s, 6H).$^{13}$C NMR (75 MHz, $CDCl_3$) δ 164.6, 158.8, 123.9, 61.9, 41.5, 31.8, 25.9, 18.4, -5.3, -5.3. HRMS calcd for $C_{13}H_{24}N_3O_3SSi$ [M+H] 330.1308; found 330.1317.

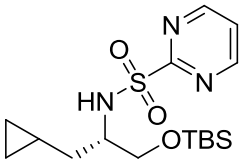
**General procedure V for ring opening of 11 with Grignard reagents exemplified by the synthesis of (*S*)-*N*-(1-(tert-butyldimethylsilyloxy)-pent-4-en-2-yl)pyrimidine-2-sulfonamide (12a)**




Copper(I) bromide dimethyl sulfide (54 mg, 0.26 mmol) (~0.15 eq) was added to a flame dried Schlenk flask under argon. Dry THF (11 mL) was added and the slurry was stirred at rt for 15 min and then cooled to -65 °C (externally). Vinylmagnesium bromide (2.39 mL, 0.94 M, 2.25 mmol) in THF was added dropwise at -65 to -60 °C. The resulting mixture was stirred at -65 to -60 °C for 30 min and then cooled to -78 °C. **11** (494 mg, 1.50 mmol) in dry THF (3 mL) was added dropwise by syringe. The reaction mixture was stirred at -78 °C for 1 h and then quenched with 6 mL of an aqueous $(NH_4)_2SO_4$ / $NH_3$ solution (1 mol $(NH_4)_2SO_4$ and 30 ml 25 % $NH_4OH$ diluted to 500 mL with water) at -78 °C and then allowed to warm to ambient in open air. The mixture was transferred to a 100 mL flask (using THF, water and $(NH_4)_2SO_4$ / $NH_3$ solution and concentrated *in vacuo* to remove THF. The aqueous residue was extracted with $CH_2Cl_2$ (1×20 mL and 2×10 mL) and the combined organic phases dried with $Na_2SO_4$, filtered and concentrated *in vacuo*. The residue was purified by FC on silica (EtOAc/PE, 1:3 to 1:1) to afford the title compound **12a** (479 mg, 89 %) as a colourless solid after standing at +4 °C.

Mp 34-36 °C. $[\alpha]^{20}_{D}$ = -15.2 (c 1.02, EtOAc). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.92 (d, *J* = 4.9, 2H), 7.51 (t, *J* = 4.9, 1H), 5.66 (ddt, *J* = 7.2, 10.1, 17.3, 1H), 5.19 (d, *J* = 8.1, 1H), 5.08 – 4.95 (m, 2H), 3.75 – 3.55 (m, 3H), 2.35 (t, *J* = 6.9, 2H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.6, 158.6, 133.8, 123.2, 118.5, 64.0, 55.4, 36.6, 25.9, 18.4, -5.4. HRMS calcd for $C_{15}H_{28}N_3O_3SSi$ [M+H] 358.1621; found 358.1634.

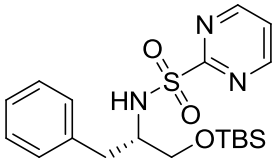
**(*S*)-*N*-(1-(tert-butyldimethylsilyloxy)-3-cyclopropylpropan-2-yl)-pyrimidine-2-sulfonamide (12b)**



Following the general procedure **V**, the reaction of $CuBr{\cdot}Me_2S$ (52 mg, 0.25 mmol), cyclopropylmagnesium bromide (5.75 mL, 0.39 M, 2.25 mmol) in THF and **11** (494 mg, 1.50 mmol) gave an oily residue. Purification by FC on silica (EtOAc/PE, 0:100 to 2:3) afforded the title compound **12b** (464 mg, 83 %) as a colourless solid after standing at +4 °C.

Mp 85.5-86.5 °C. $[\alpha]^{20}_{D}$ = -28.7 (c 1.19, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.92 (d, *J* = 4.8, 2H), 7.51 (t, *J* = 4.9, 1H), 5.21 (d, *J* = 7.9, 1H), 3.76 – 3.60 (m, 3H), 1.59 – 1.38 (m, 2H), 0.90 – 0.82 (m, 9H), 0.68 – 0.52 (m, 1H), 0.45 – 0.32 (m, 2H), 0.06 – -0.01 (m, 2H), 0.02 (s, 3H), 0.01 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.7, 158.6, 123.1, 64.3, 56.6, 37.1, 26.0, 18.4, 7.6, 4.8, 4.3, -5.4. HRMS calcd for $C_{16}H_{30}N_3O_3SSi$ [M+H] 372.1777; found 372.1783.

**(*S*)-*N*-(1-(tert-butyldimethylsilyloxy)-3-phenylpropan-2-yl)-pyrimidine-2-sulfonamide (12c)**



Following the general procedure **V**, the reaction of $CuBr{\cdot}Me_2S$ (52 mg, 0.25 mmol), phenylmagnesium chloride (5.75 mL, 0.39 M, 2.25 mmol) in THF and **11** (494 mg, 1.50 mmol) gave an oily residue. Purification by FC on silica (EtOAc/PE, 0:100 to 3:2) afforded the title compound **12c** (525 mg, 86 %) as a colourless solid.

Mp 116-117 °C. $[\alpha]^{20}_{D}$ = -36.0 (c 1.24, EtOAc). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.82 (d, *J* = 4.9, 2H), 7.43 (t, *J* = 4.9, 1H), 7.23 – 7.08 (m, 5H), 5.22 (d, *J* = 8.4, 1H), 3.93 – 3.81 (m, 1H), 3.56 (d, *J* = 3.7, 2H), 2.96 – 2.81 (m, 2H), 0.90 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.3, 158.5, 137.5, 129.6, 128.6, 126.7, 123.0, 63.5, 57.3, 38.3, 26.0, 18.4, -5.35, -5.39. HRMS calcd for $C_{19}H_{30}N_3O_3SSi$ [M+H] 408.1777; found 408.1773.

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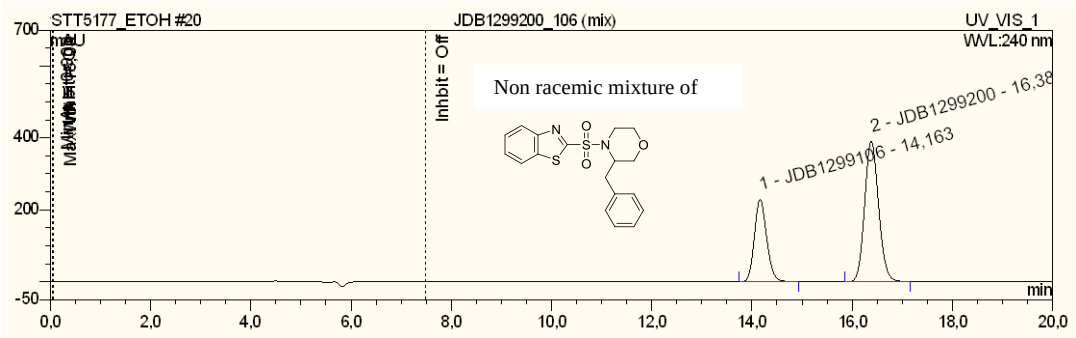
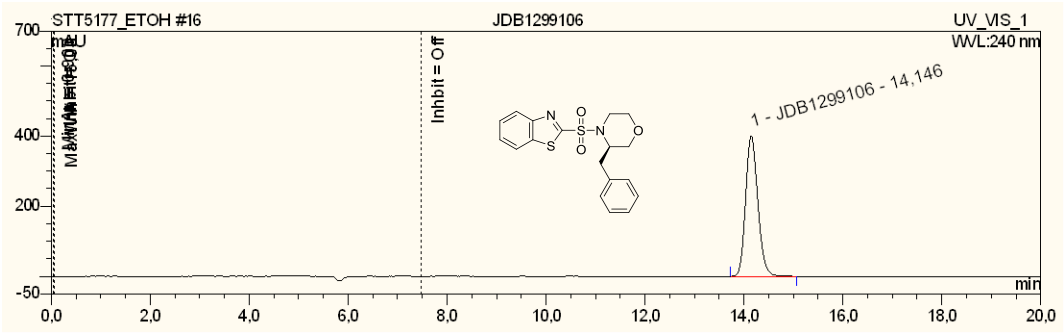
**Chirale HPLC of compound (*R*)-6e and 6e:**

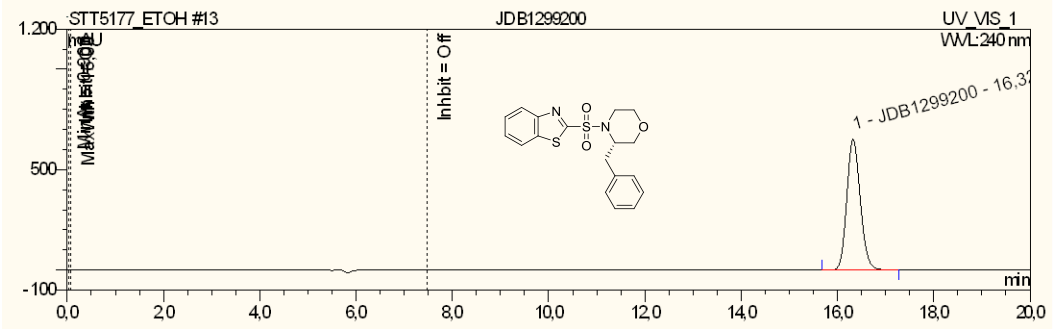
Chiral HPLC of a mixture of **6e** and **(*R*)-6e**:




Chiral HPLC of **(*R*)-6e**:




Chiral HPLC of **6e**:




Column: Chiralpak AD-H (0.46 cm × 25 cm)

Flow: 0.7 mL/min

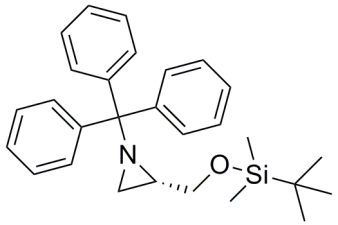
Method: Isocratic
20 % ethanol (0.1 % triethylamine, 0.1 % acetic acid)
80 % *n*-heptane (0.1 % triethylamine, 0.1 % acetic acid)

Wavelength: 280 nm

Mixed sample: $t_R$ [**(*S*)-6e**] = 16.4 min, : $t_R$ [**(*R*)-6e**] = 14.2 min

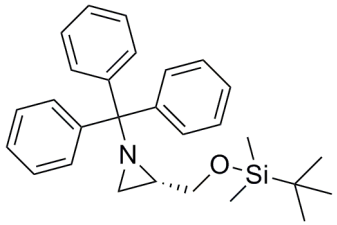
1H NMR of compound **2**

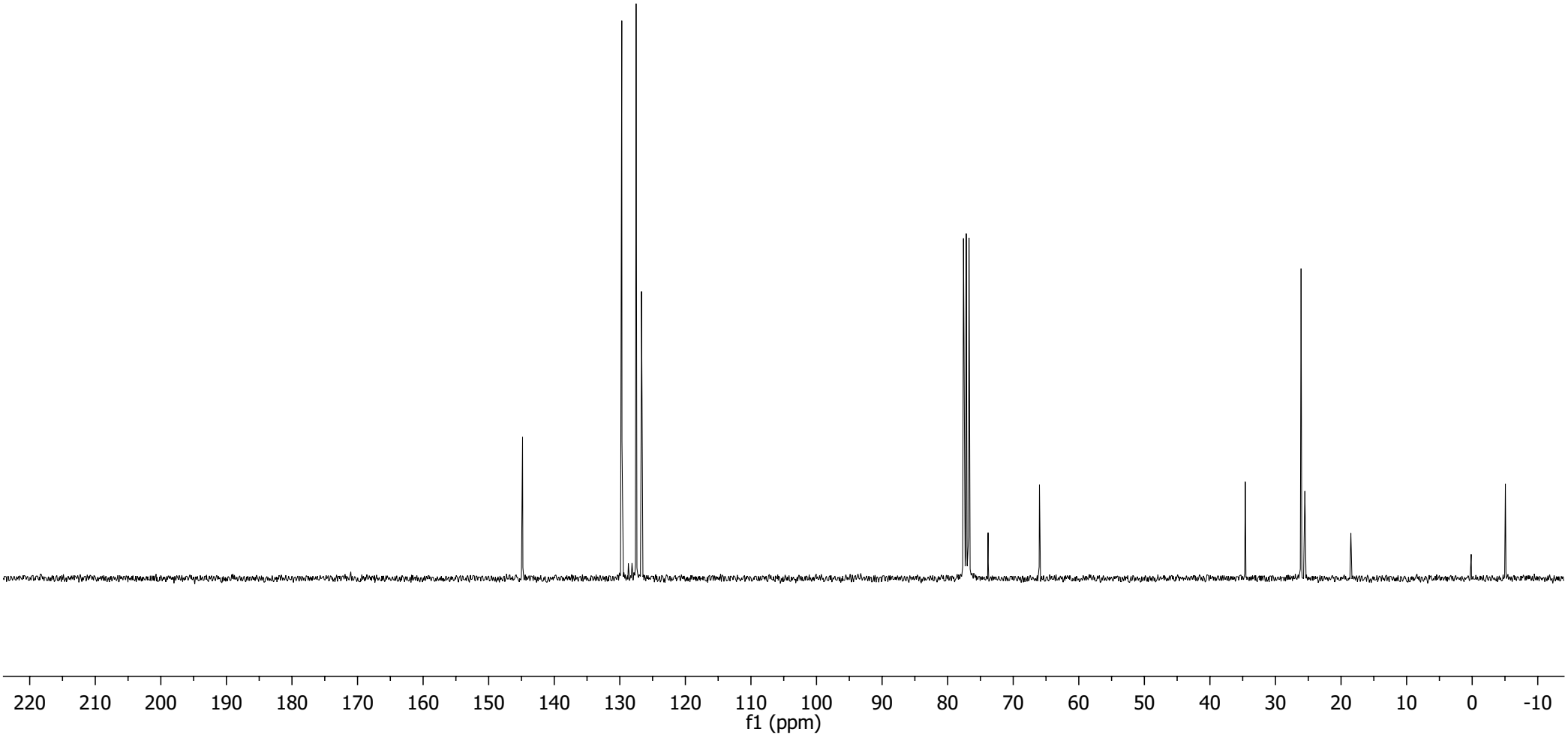




13C NMR of compound **2**

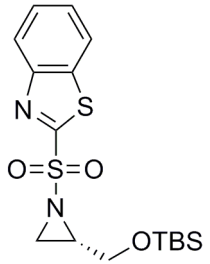




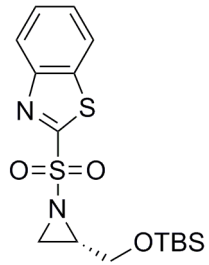
1H NMR of compound **3**

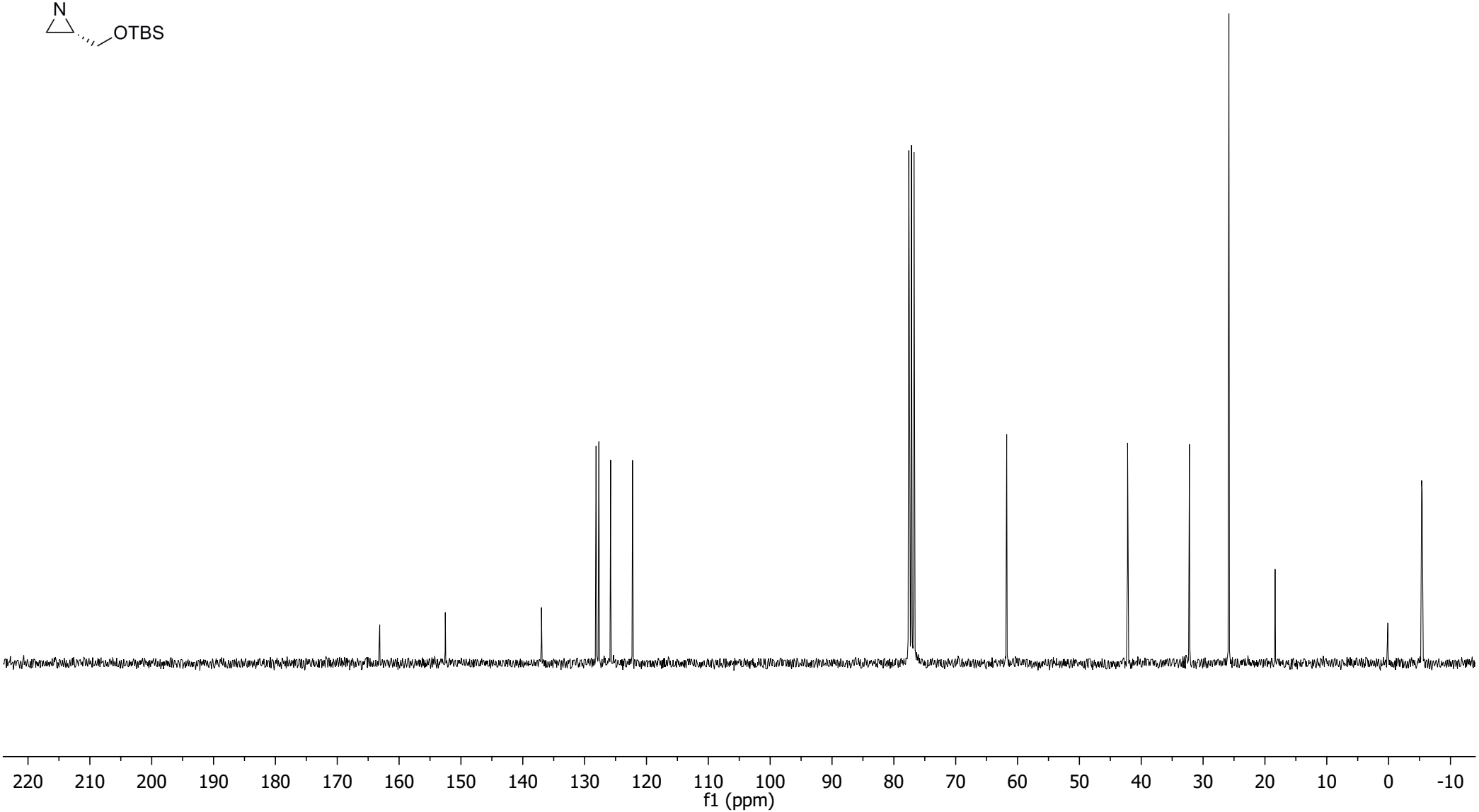




13C NMR of compound **3**

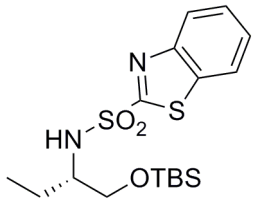




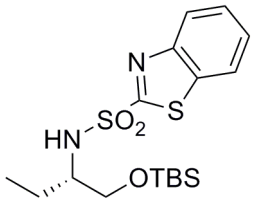
1H NMR of compound **4a**

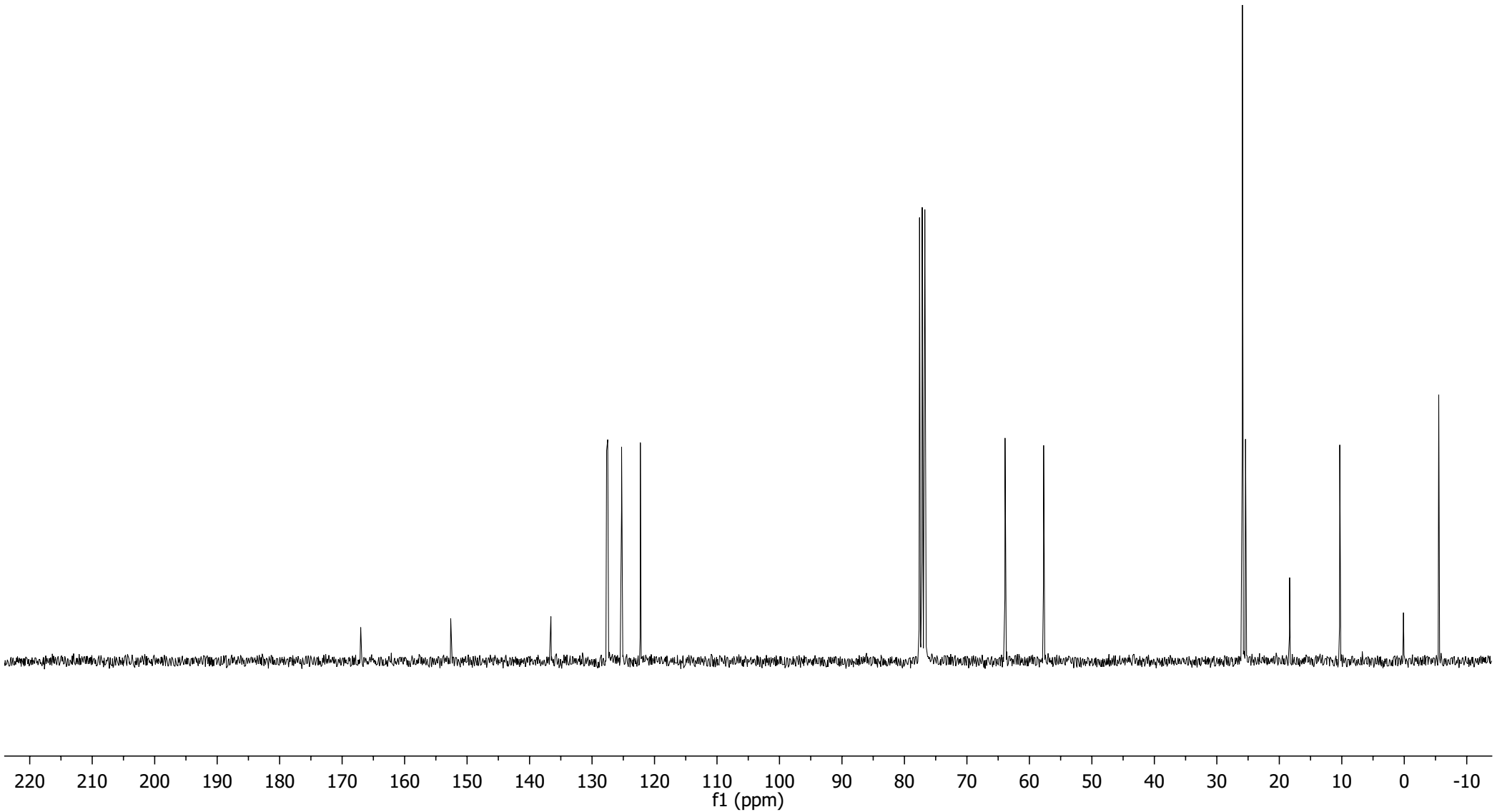




13C NMR of compound **4a**

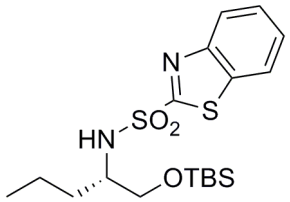




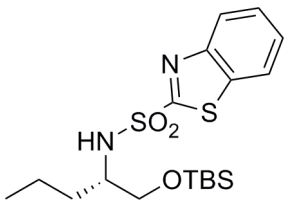
1H NMR of compound **4b**

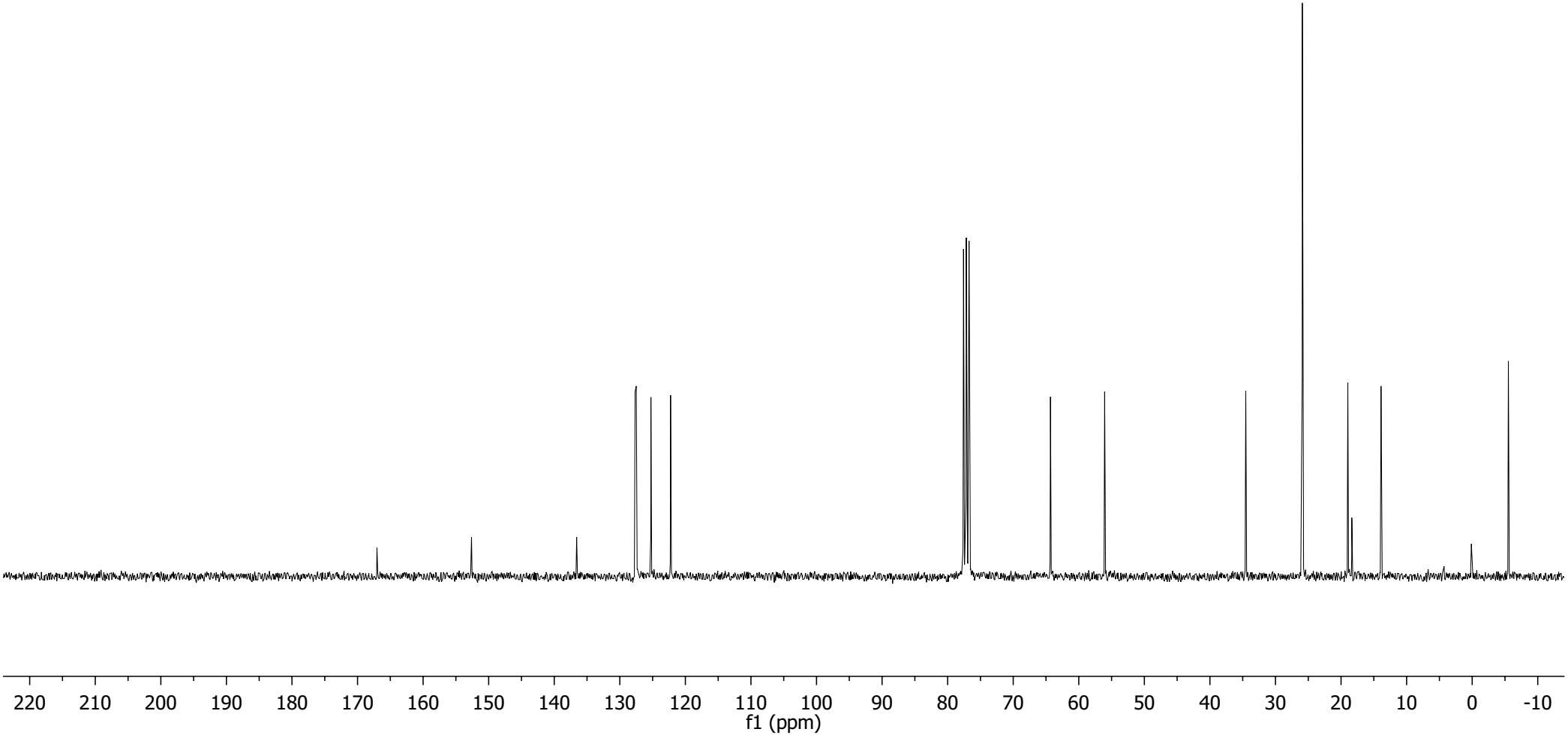




13C NMR of compound **4b**

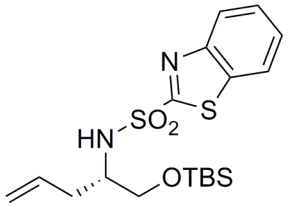




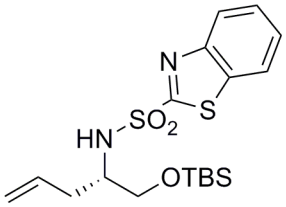



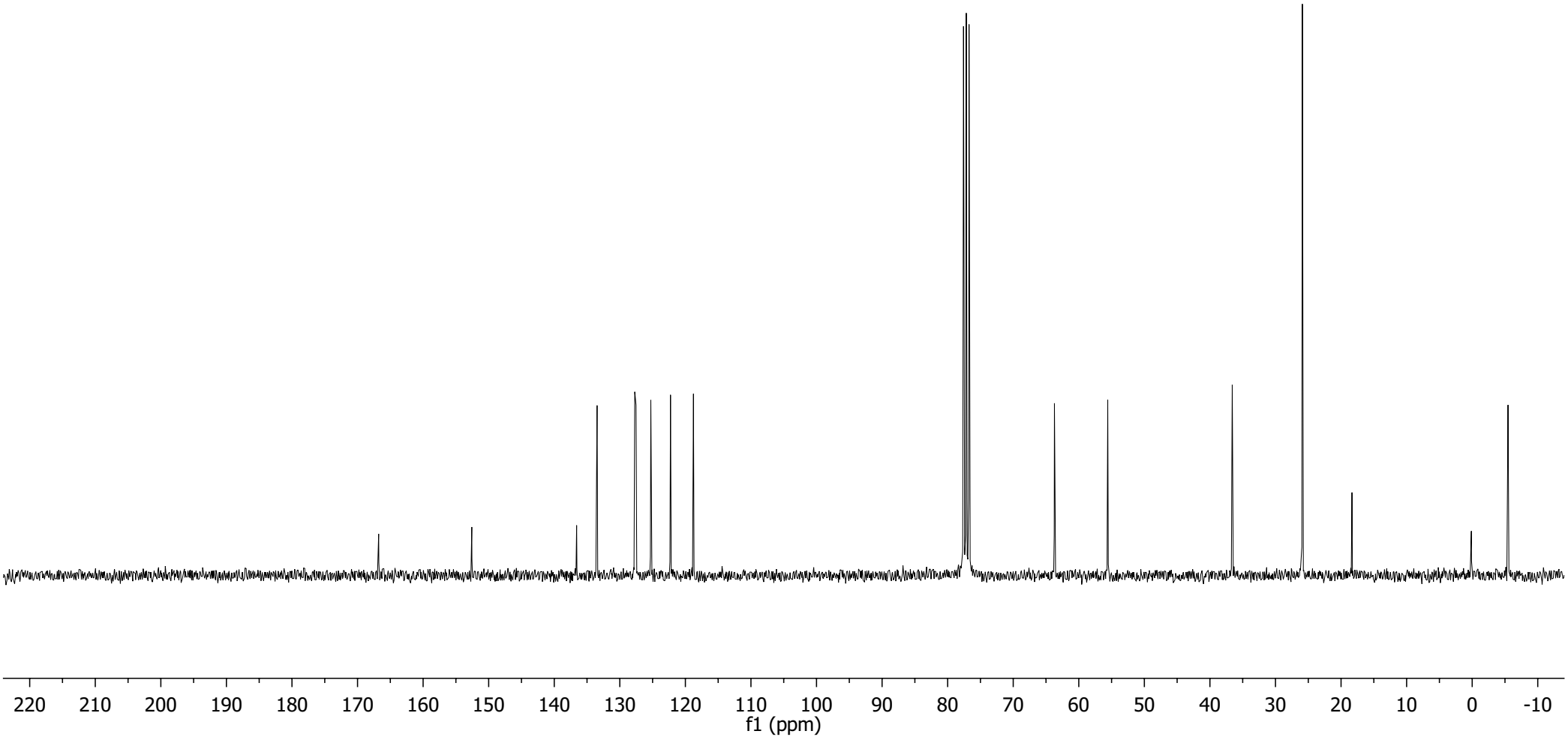
1H NMR of compound **4c**





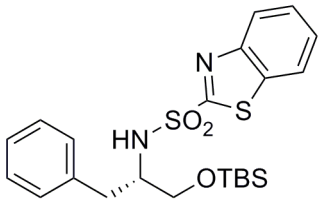
13C NMR of compound **4c**



1H NMR of compound **4e**





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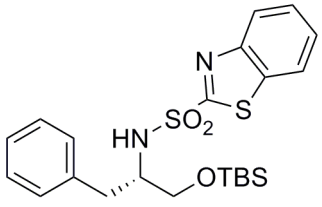
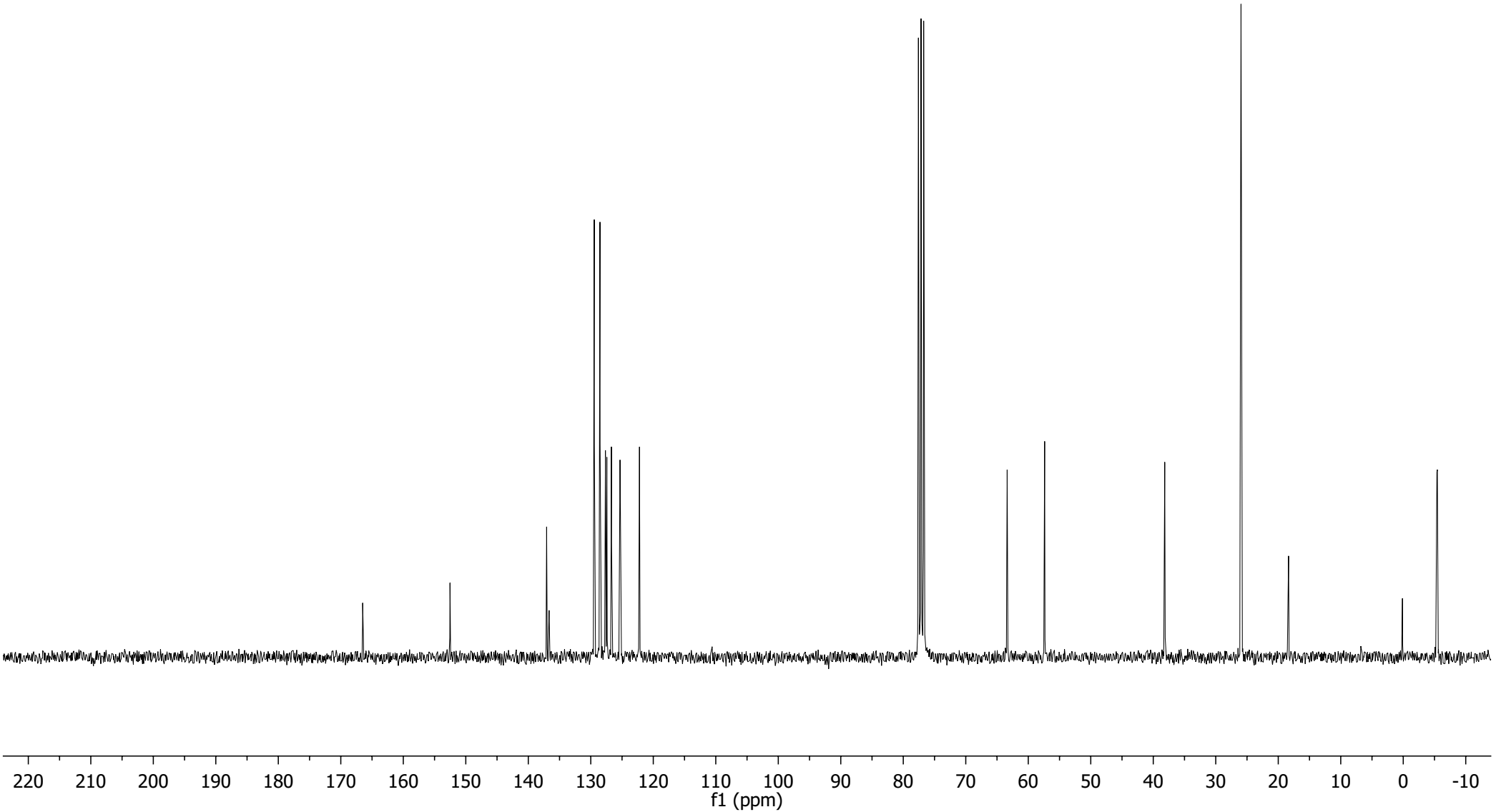
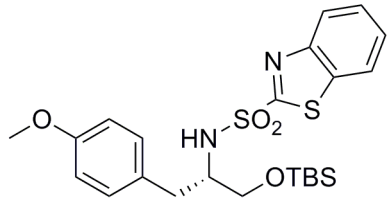


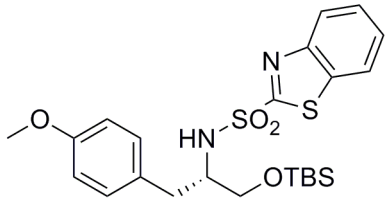



1H NMR of compound **4f**



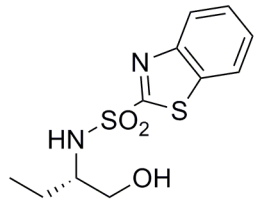
13C NMR of compound **4f**





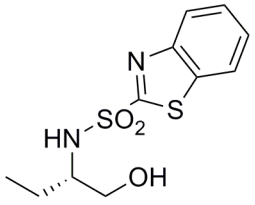
1H NMR of compound **5a**





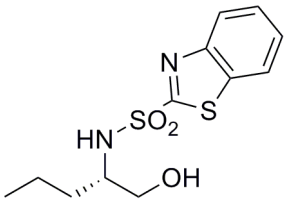
13C NMR of compound **5a**

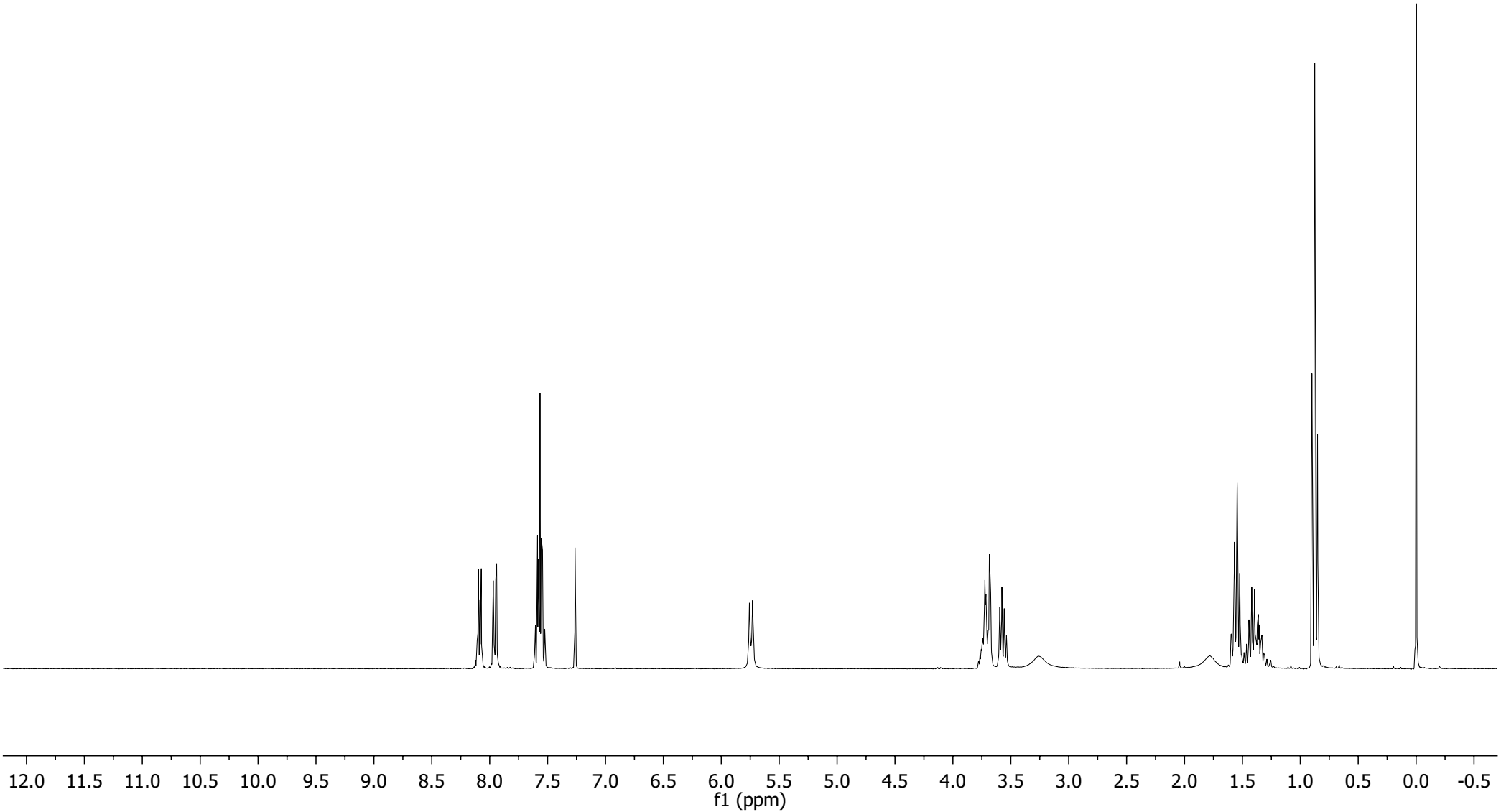




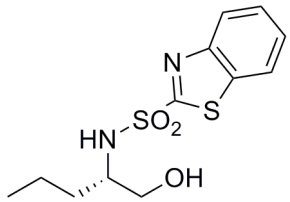
1H NMR of compound **5b**





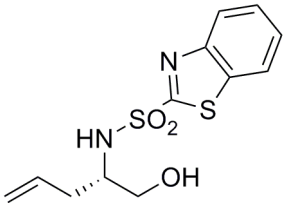



13C NMR of compound **5b**

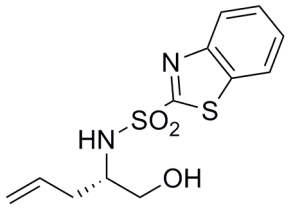


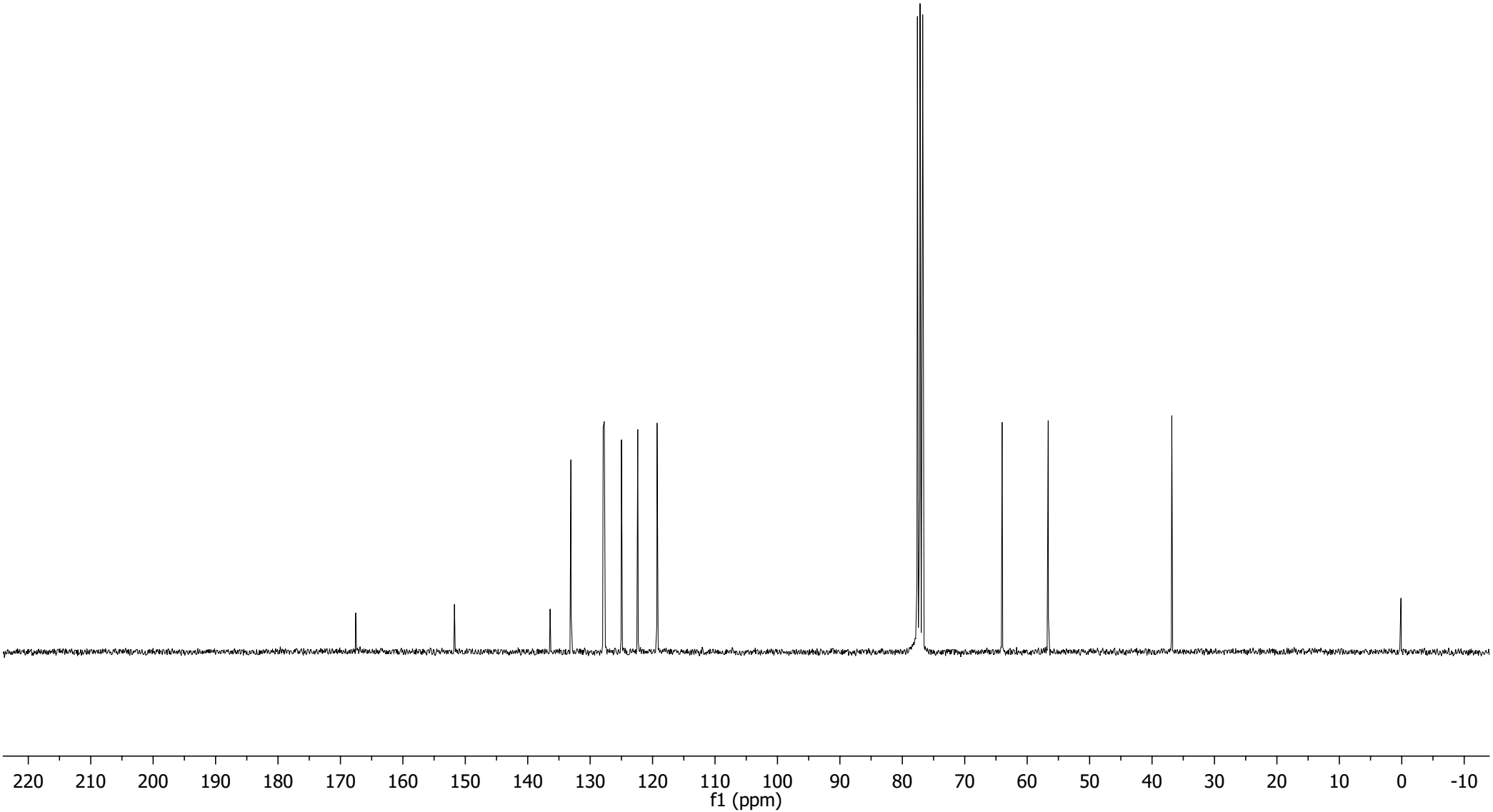
1H NMR of compound **5c**





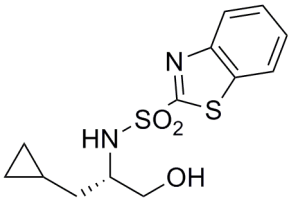
13C NMR of compound **5c**



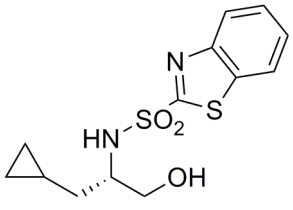
1H NMR of compound **5d**





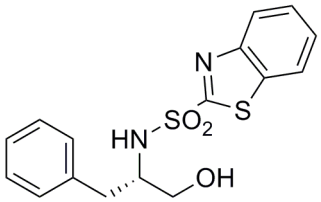
13C NMR of compound **5d**

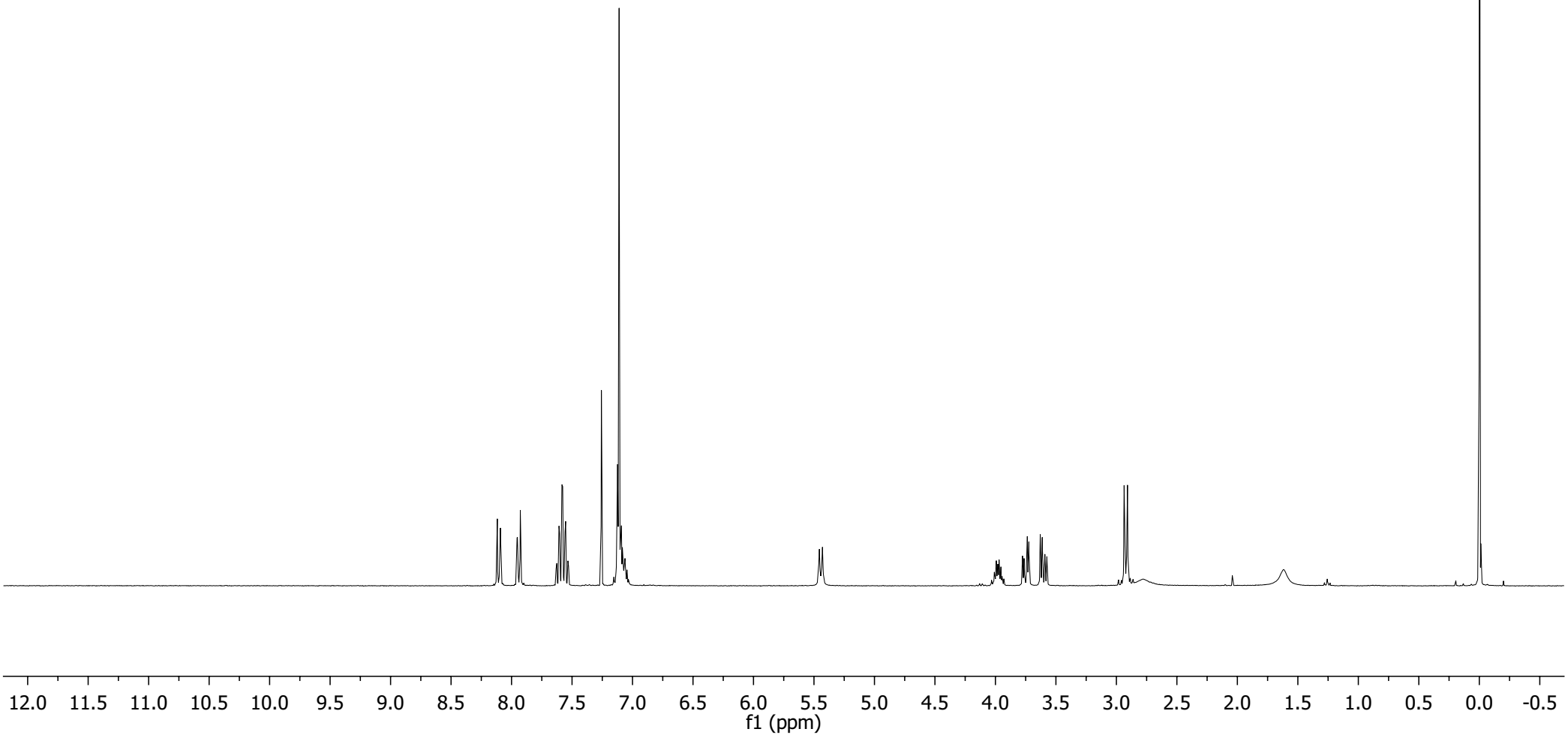




1H NMR of compound **5e**

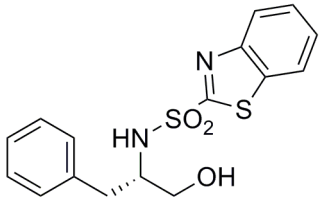




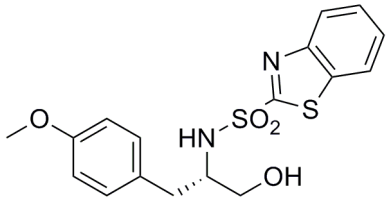
13C NMR of compound **5e**





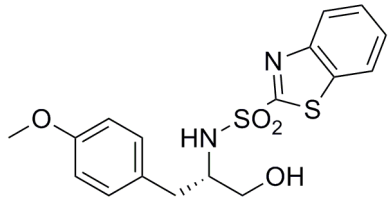
1H NMR of compound **5f**





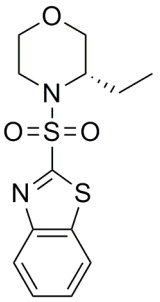
13C NMR of compound **5f**





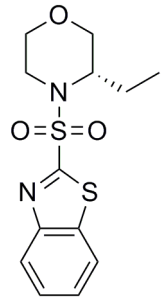
1H NMR of compound **6a**



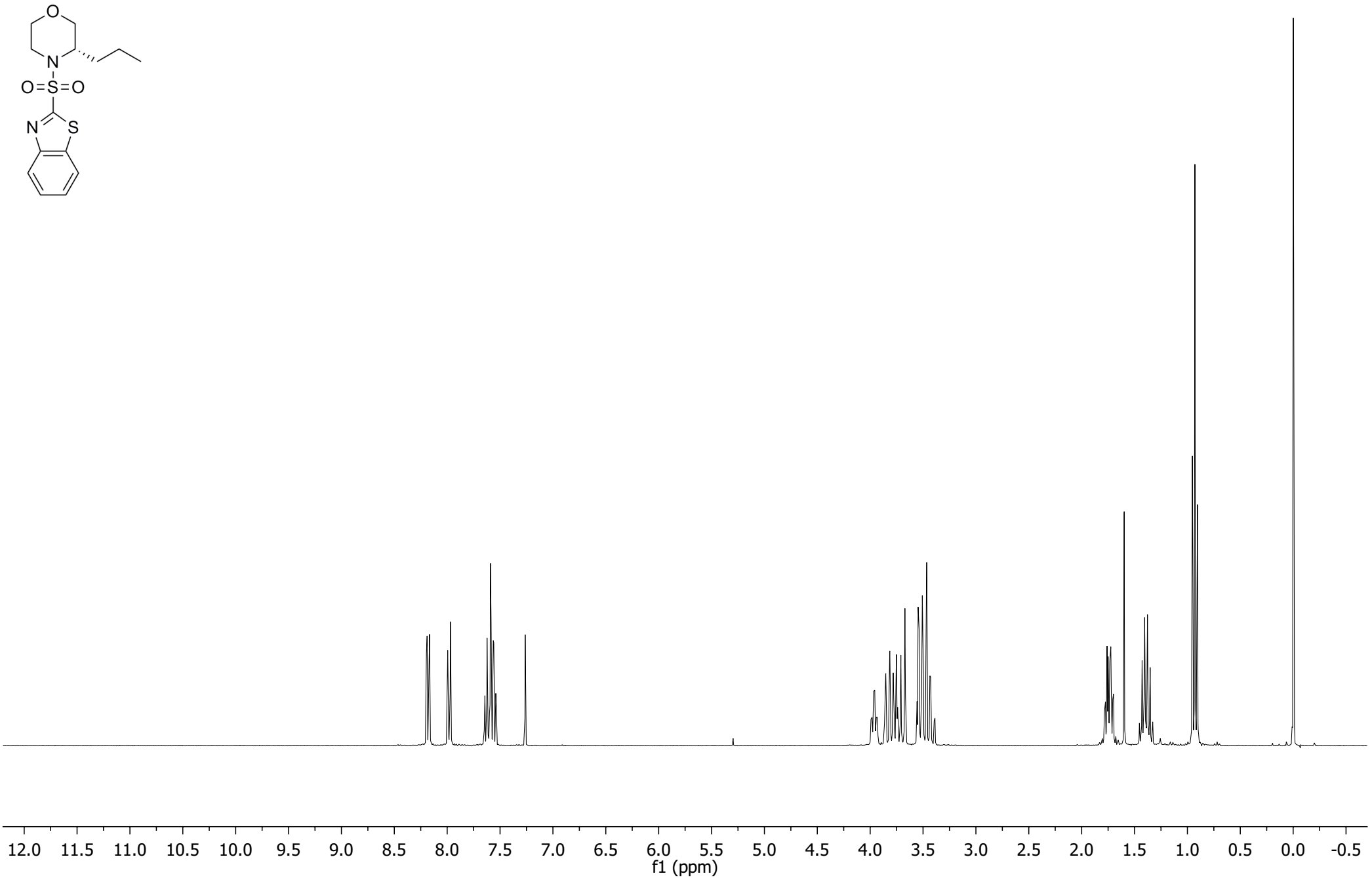


13C NMR of compound **6a**



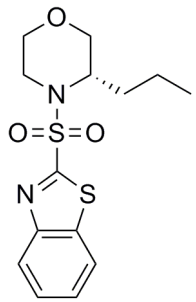


1H NMR of compound **6b**



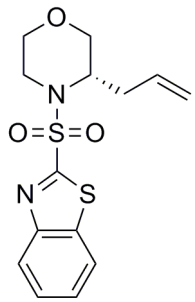
13C NMR of compound **6b**





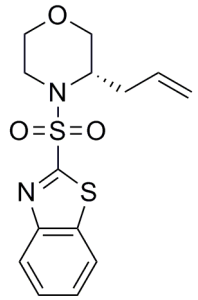
1H NMR of compound **6c**





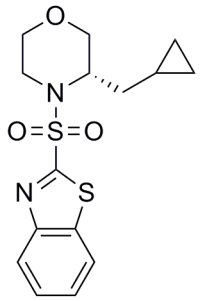
13C NMR of compound **6c**





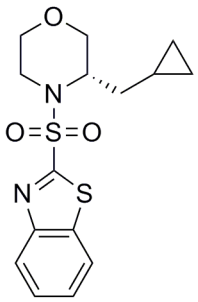
1H NMR of compound **6d**

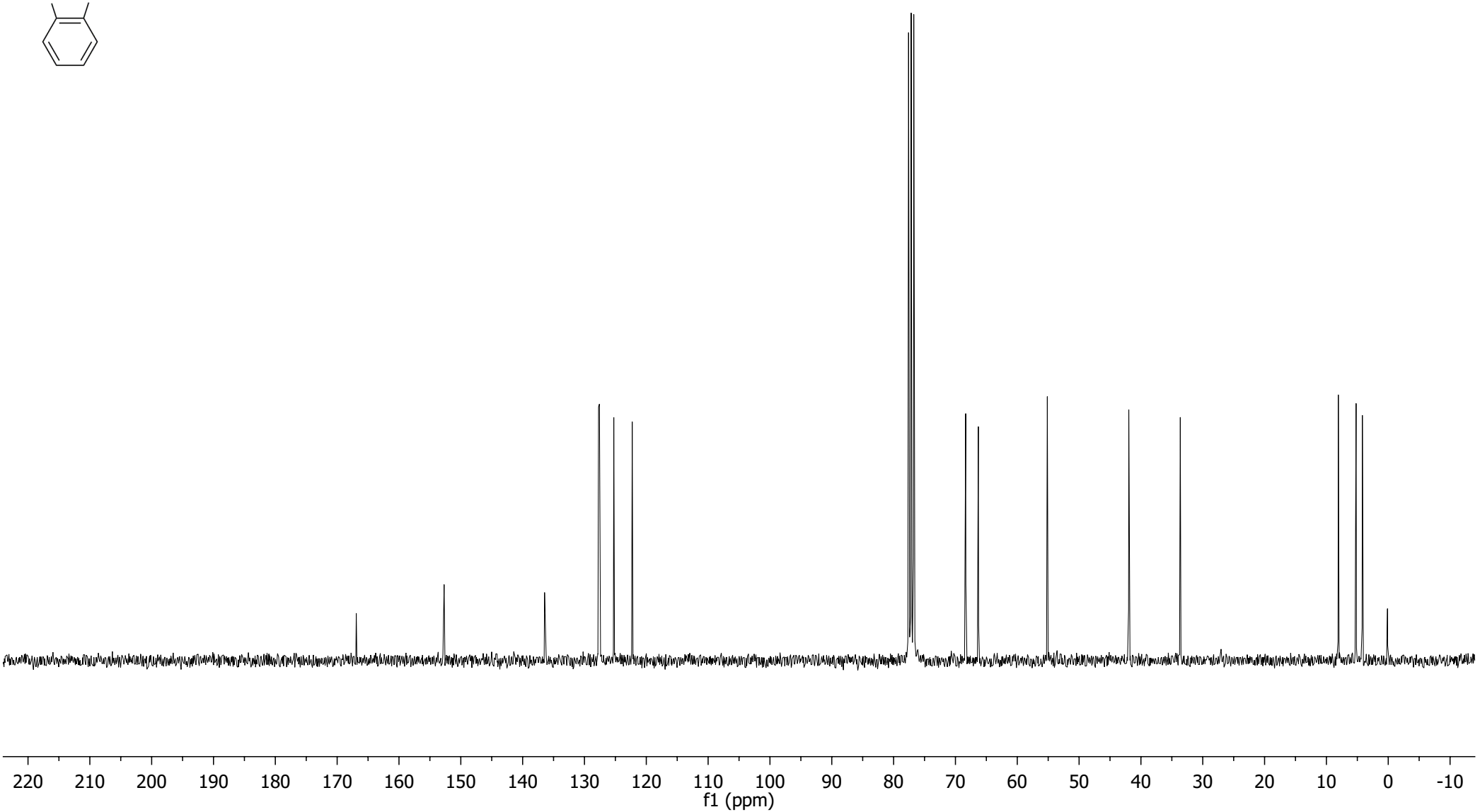




13C NMR of compound **6d**

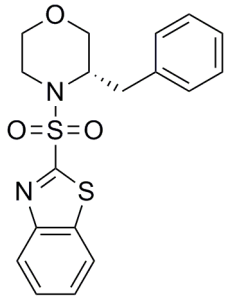




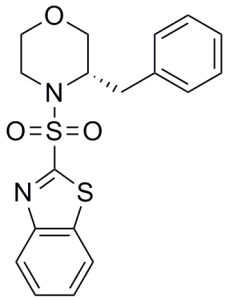
1H NMR of compound **6e**





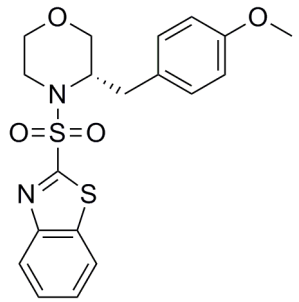
13C NMR of compound **6e**

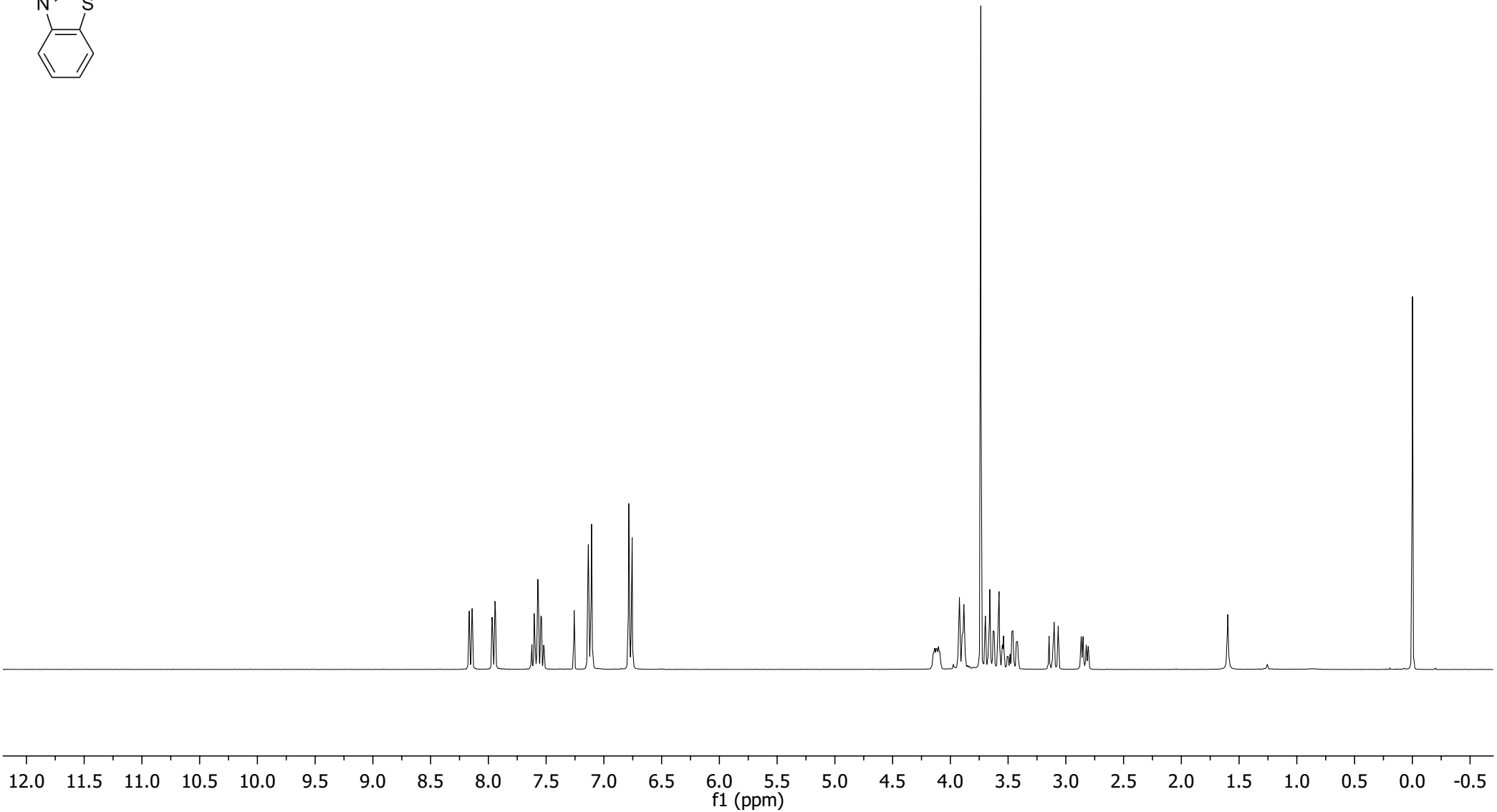




1H NMR of compound **6f**

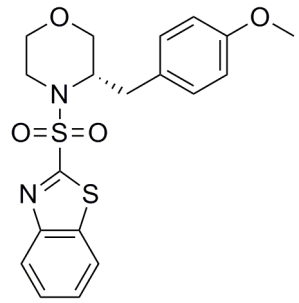




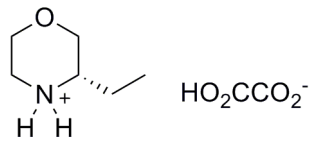
13C NMR of compound **6f**





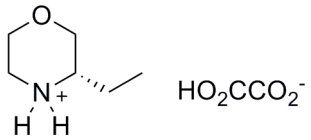
1H NMR of compound **7a**

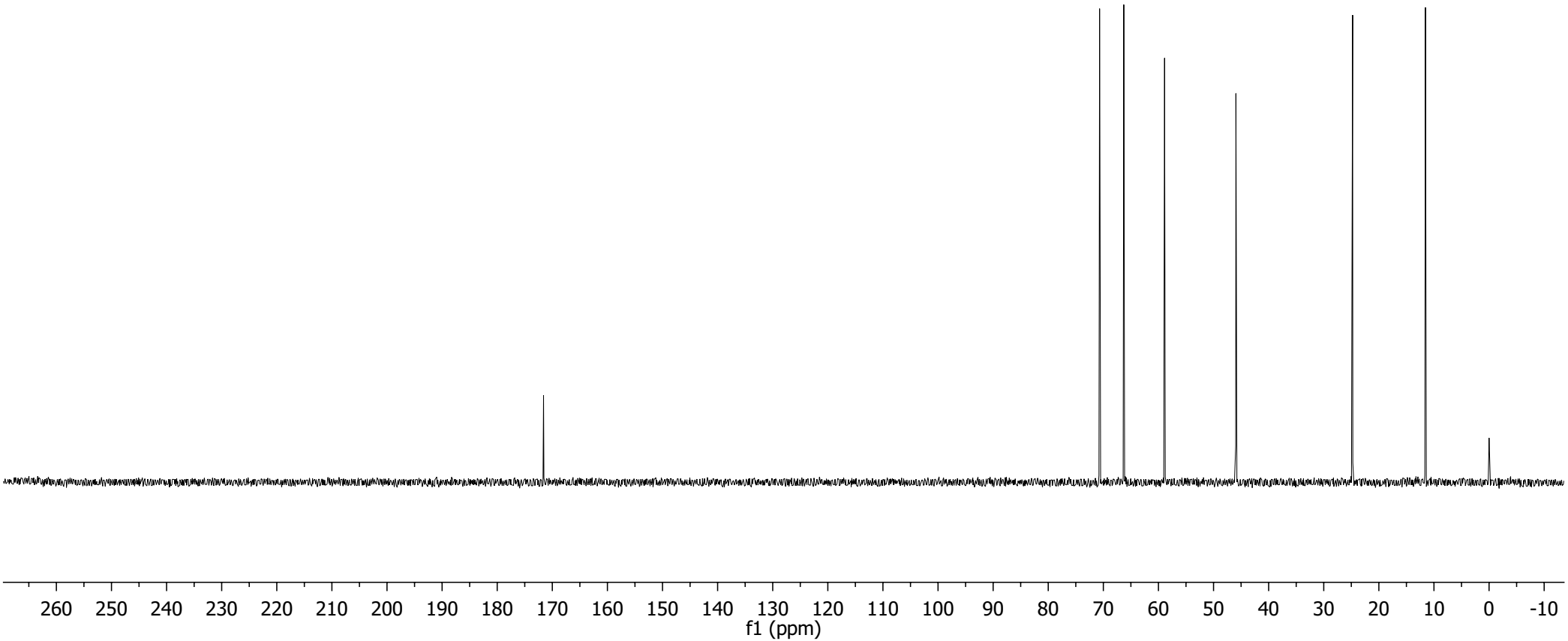




13C NMR of compound **7a**

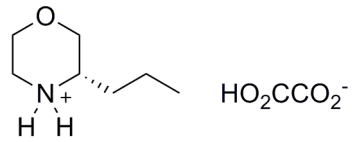




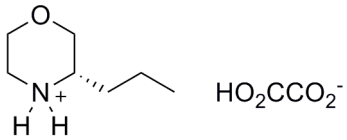
1H NMR of compound **7b**

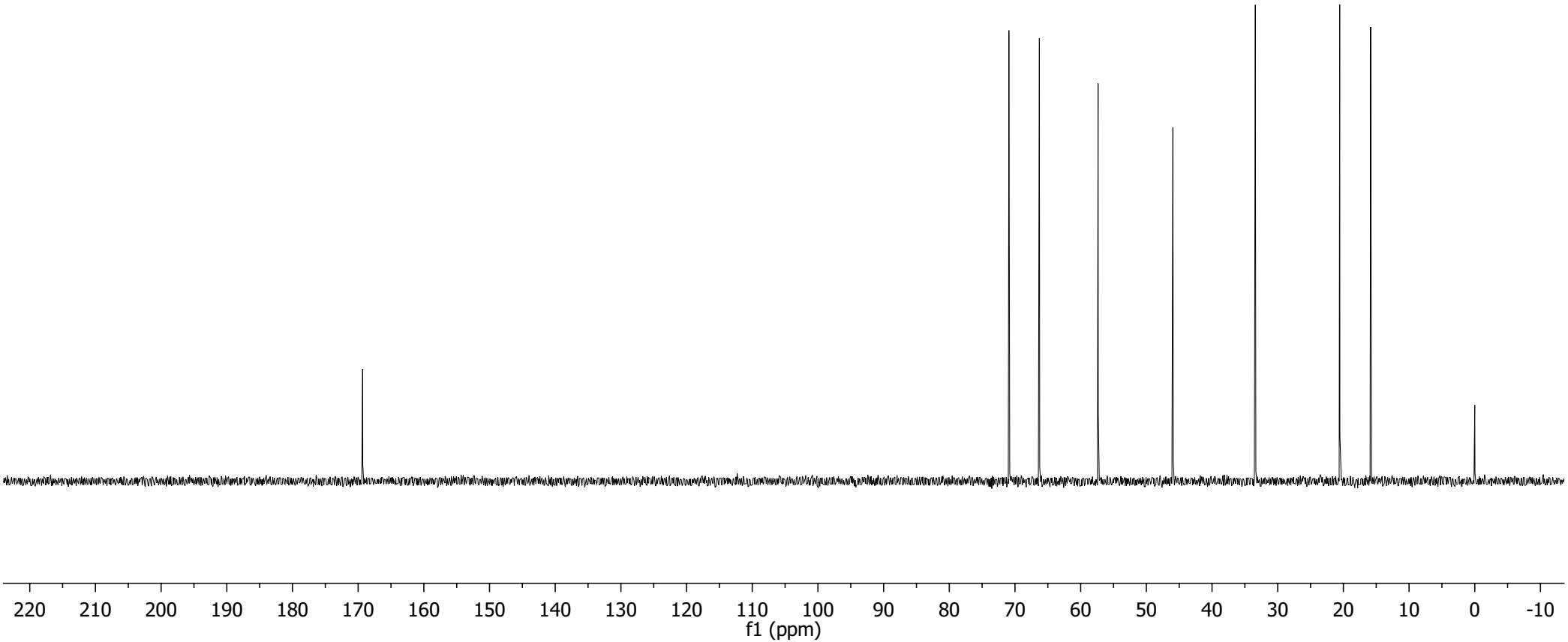




13C NMR of compound **7b**

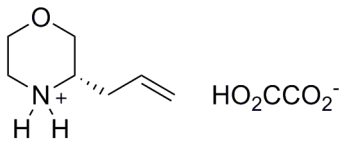




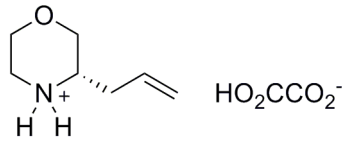
1H NMR of compound **3c**

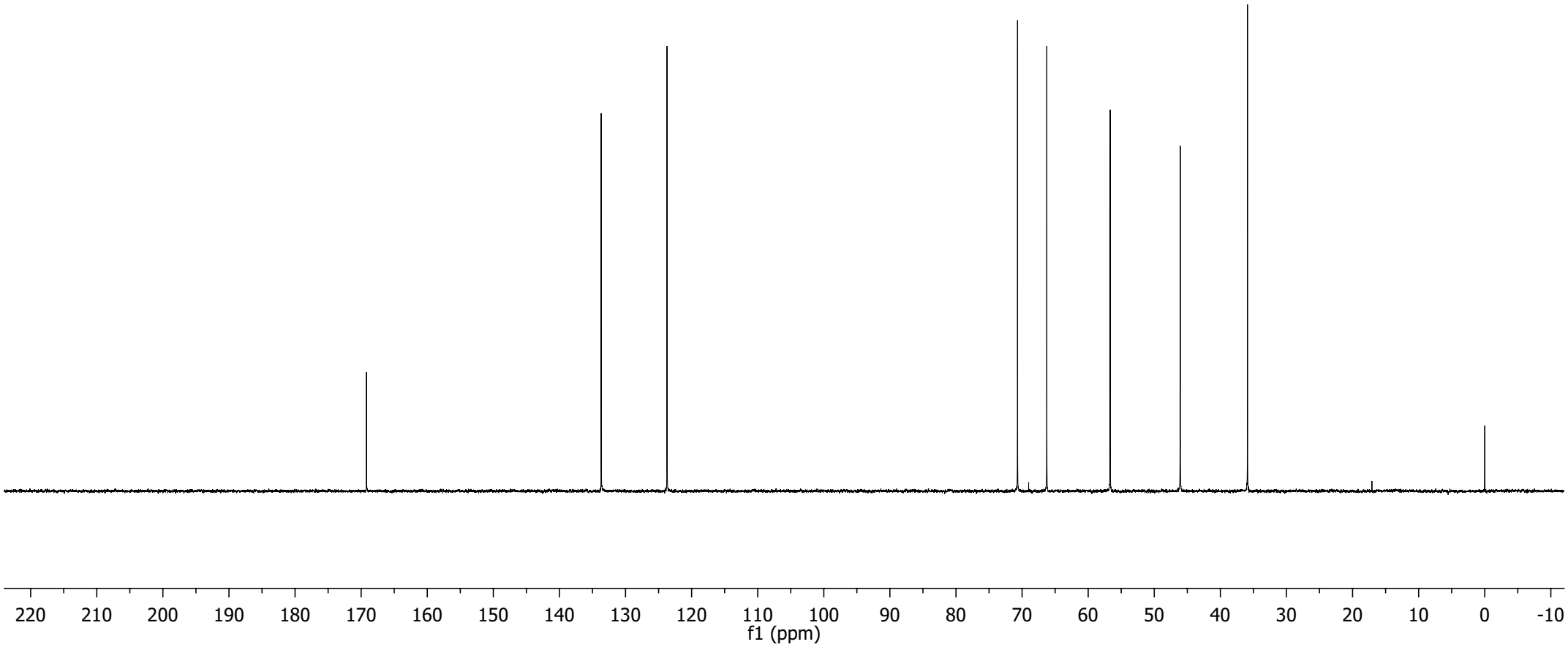




13C NMR of compound **7c**

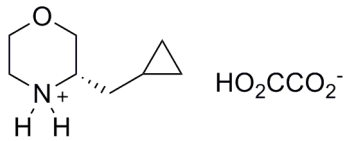




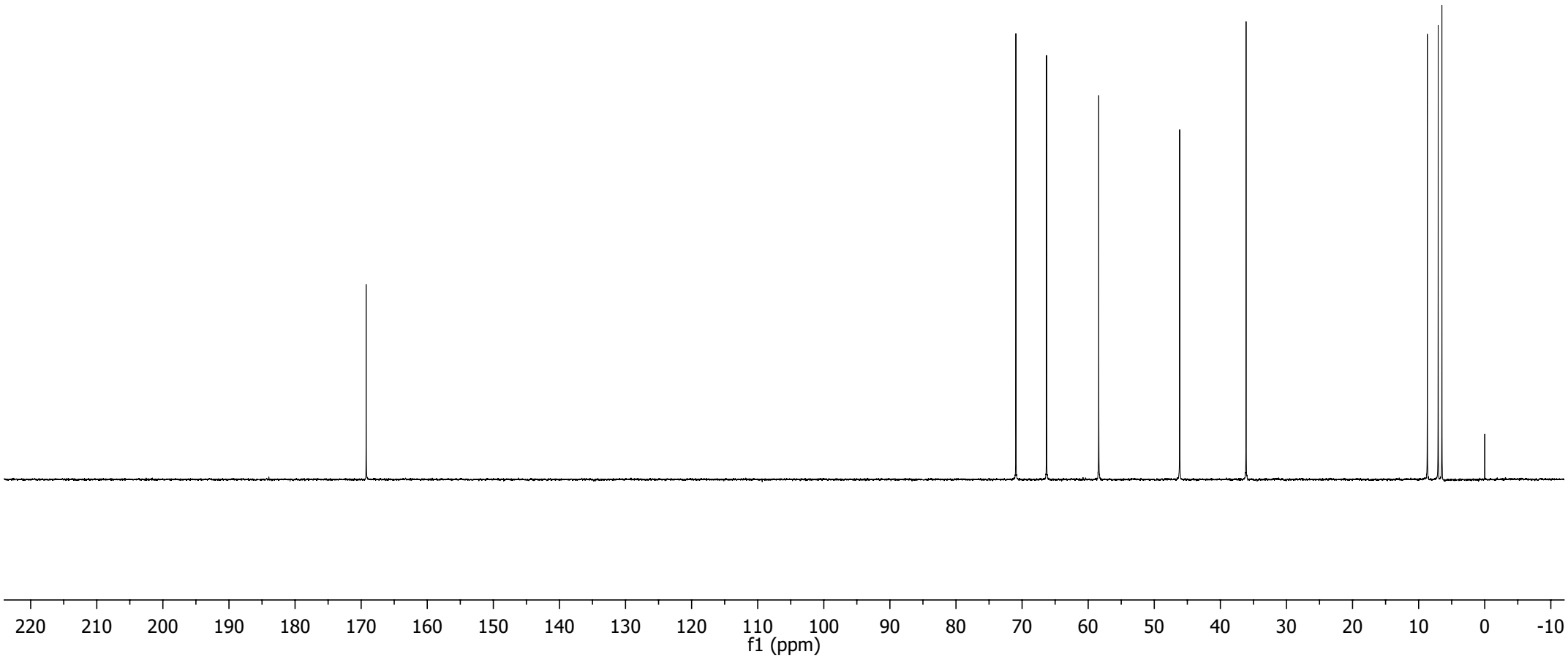
1H NMR of compound **7d**





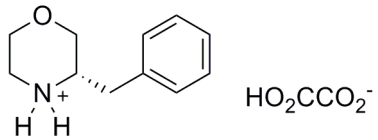
13C NMR of compound **7d**



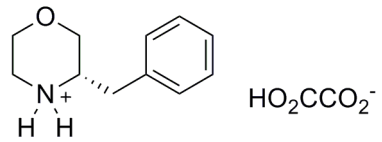
1H NMR of compound **7e**





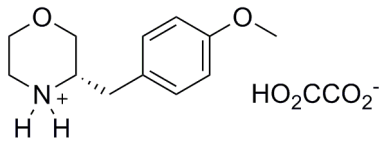
13C NMR of compound **7e**



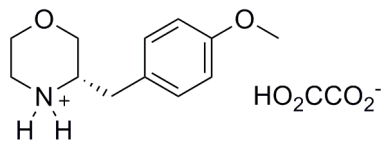


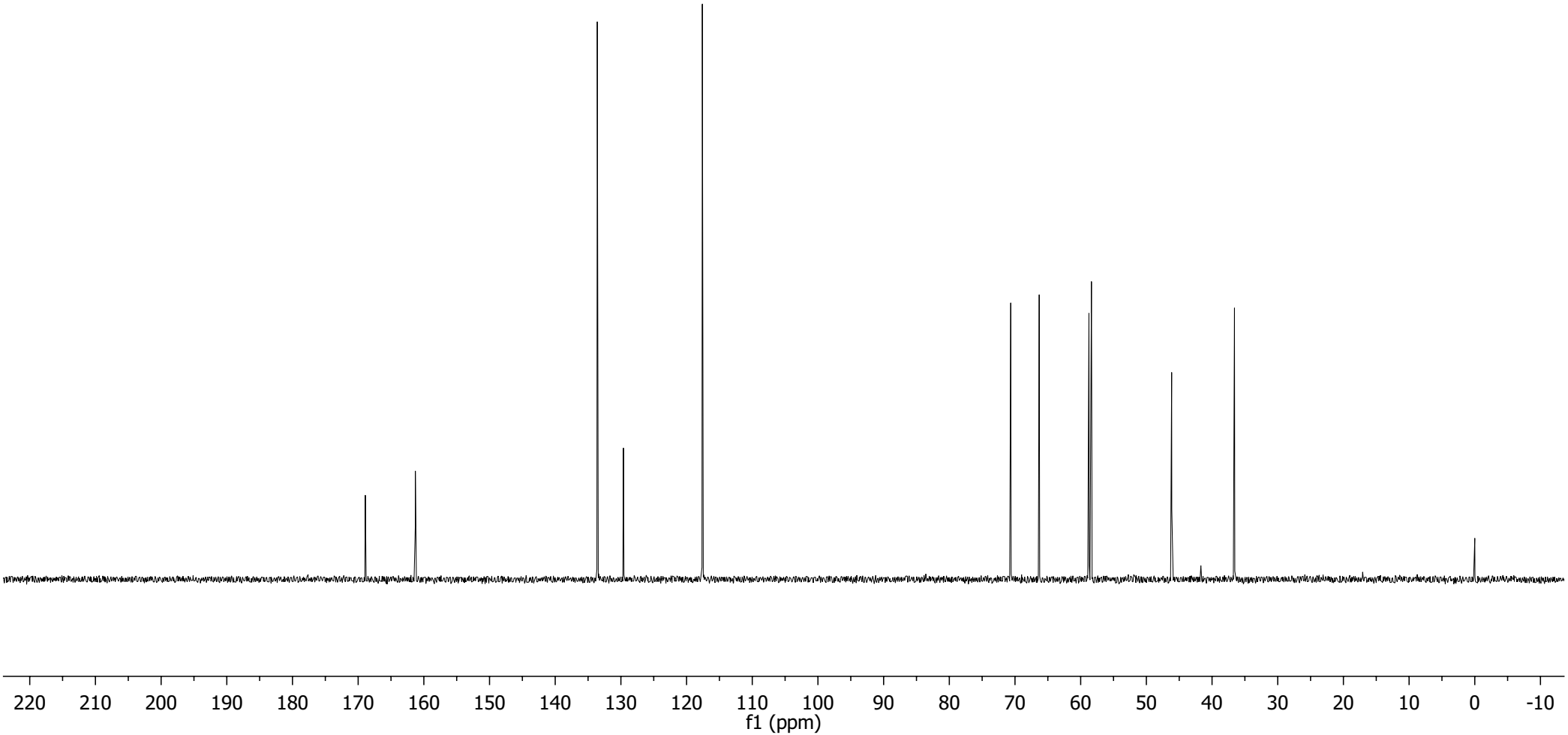
1H NMR of compound **7f**





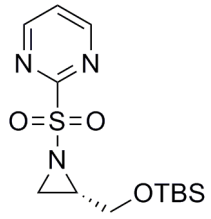
13C NMR of compound **7f**



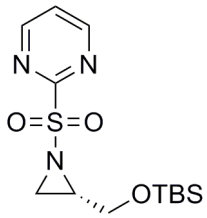
1H NMR of compound **11**

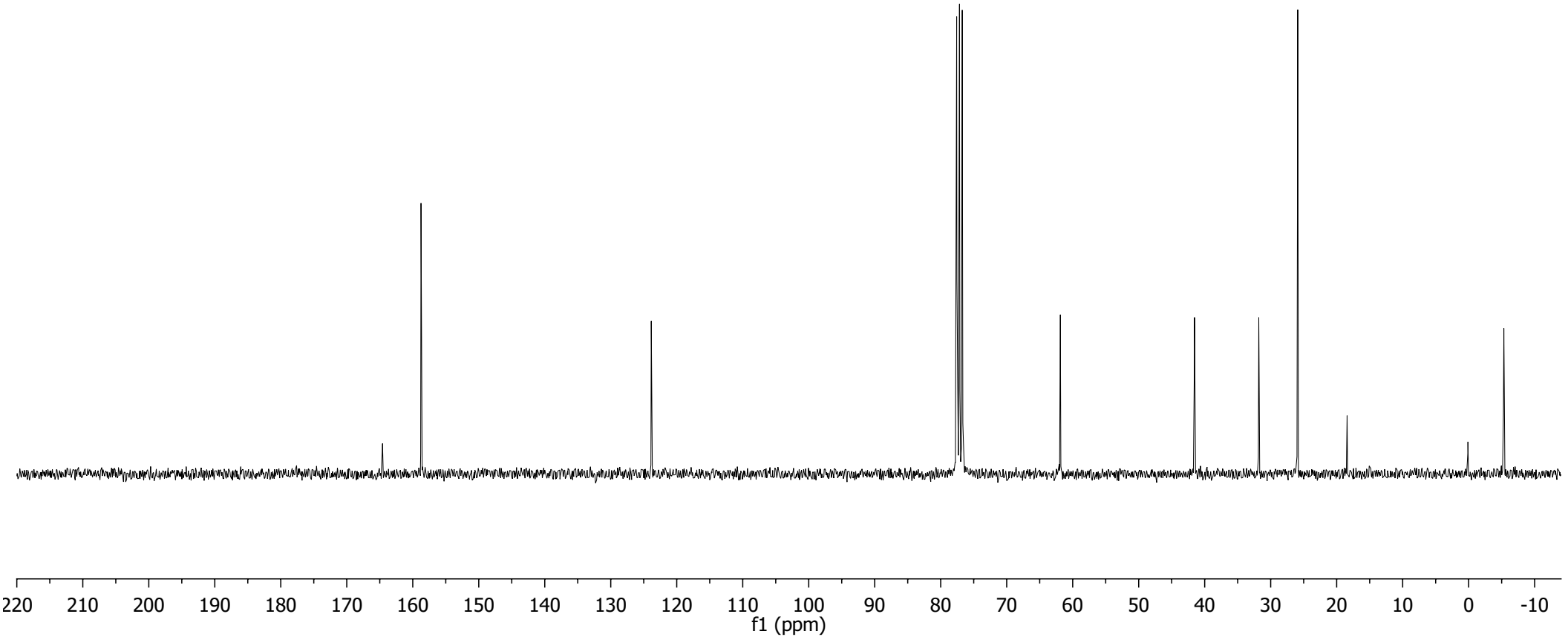




13C NMR of compound **11**

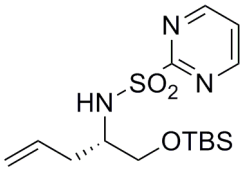




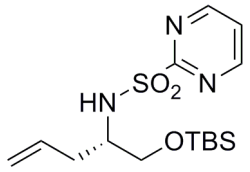
1H NMR of compound **12a**

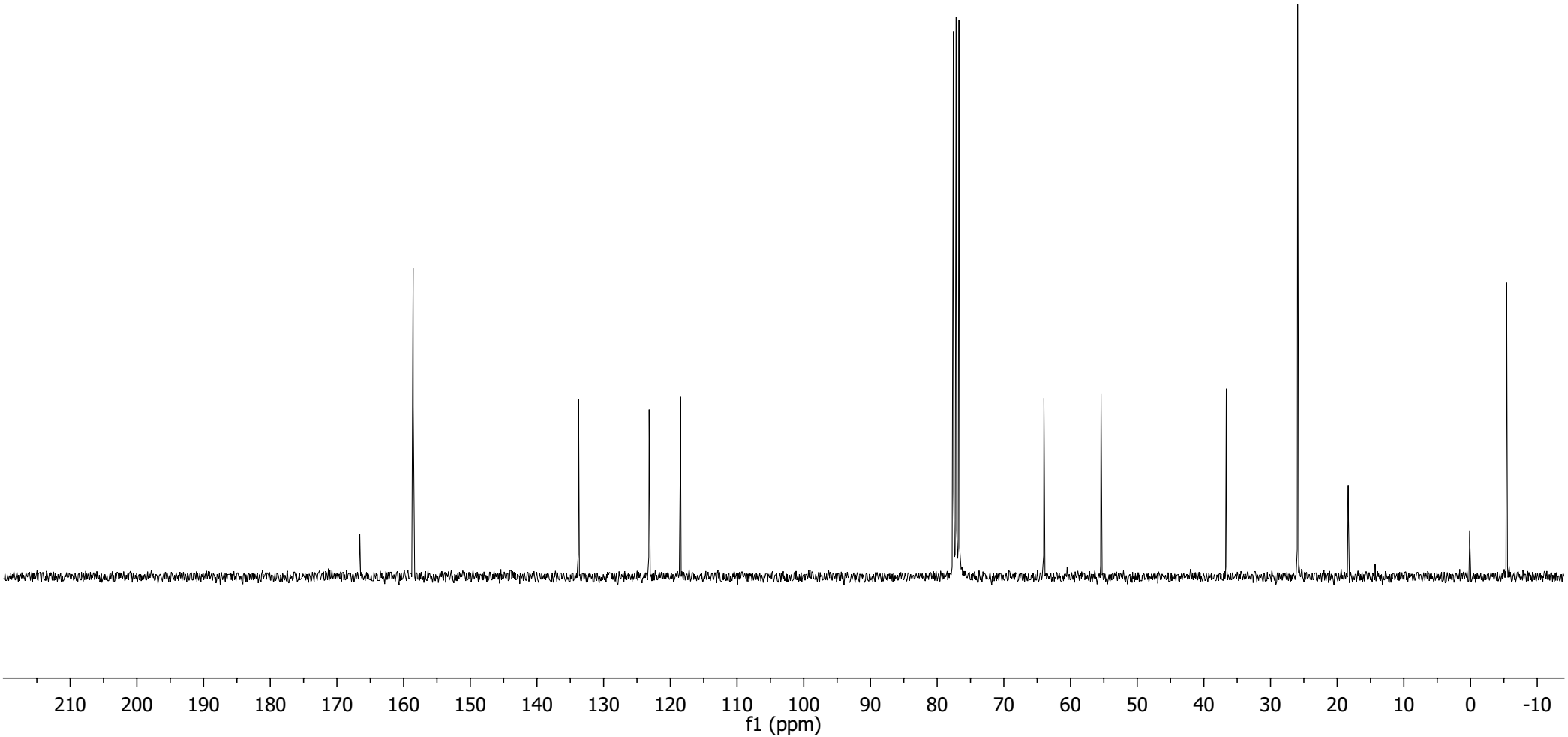




13C NMR of compound **12a**

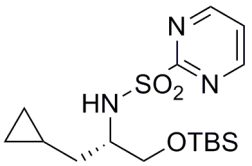




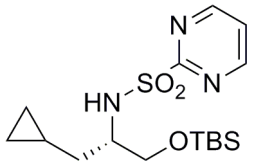
1H NMR of compound **12b**

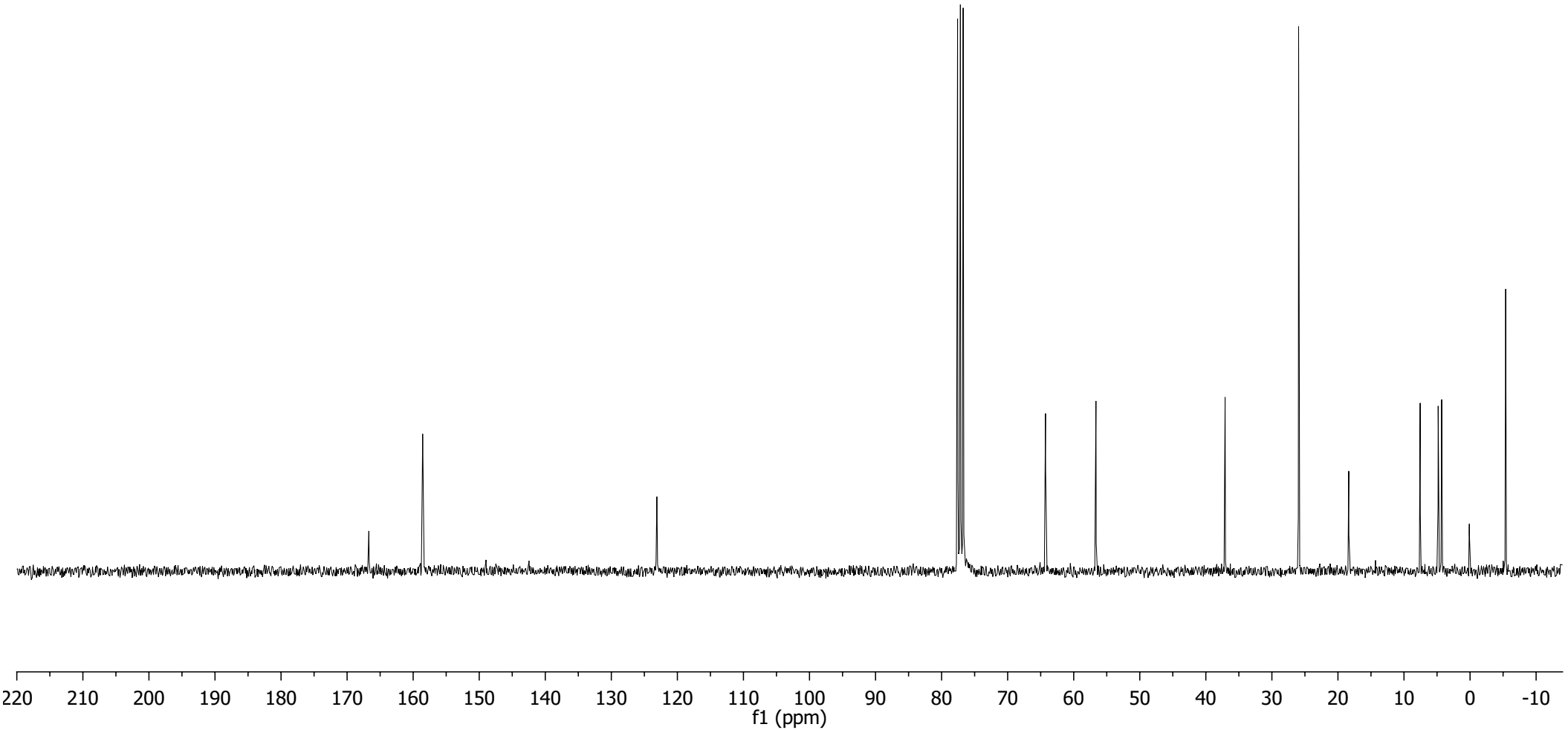




13C NMR of compound **12b**

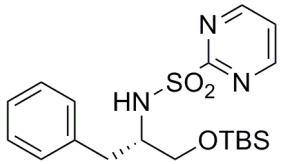




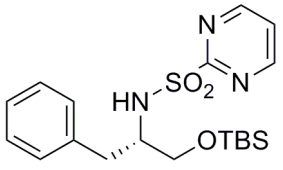



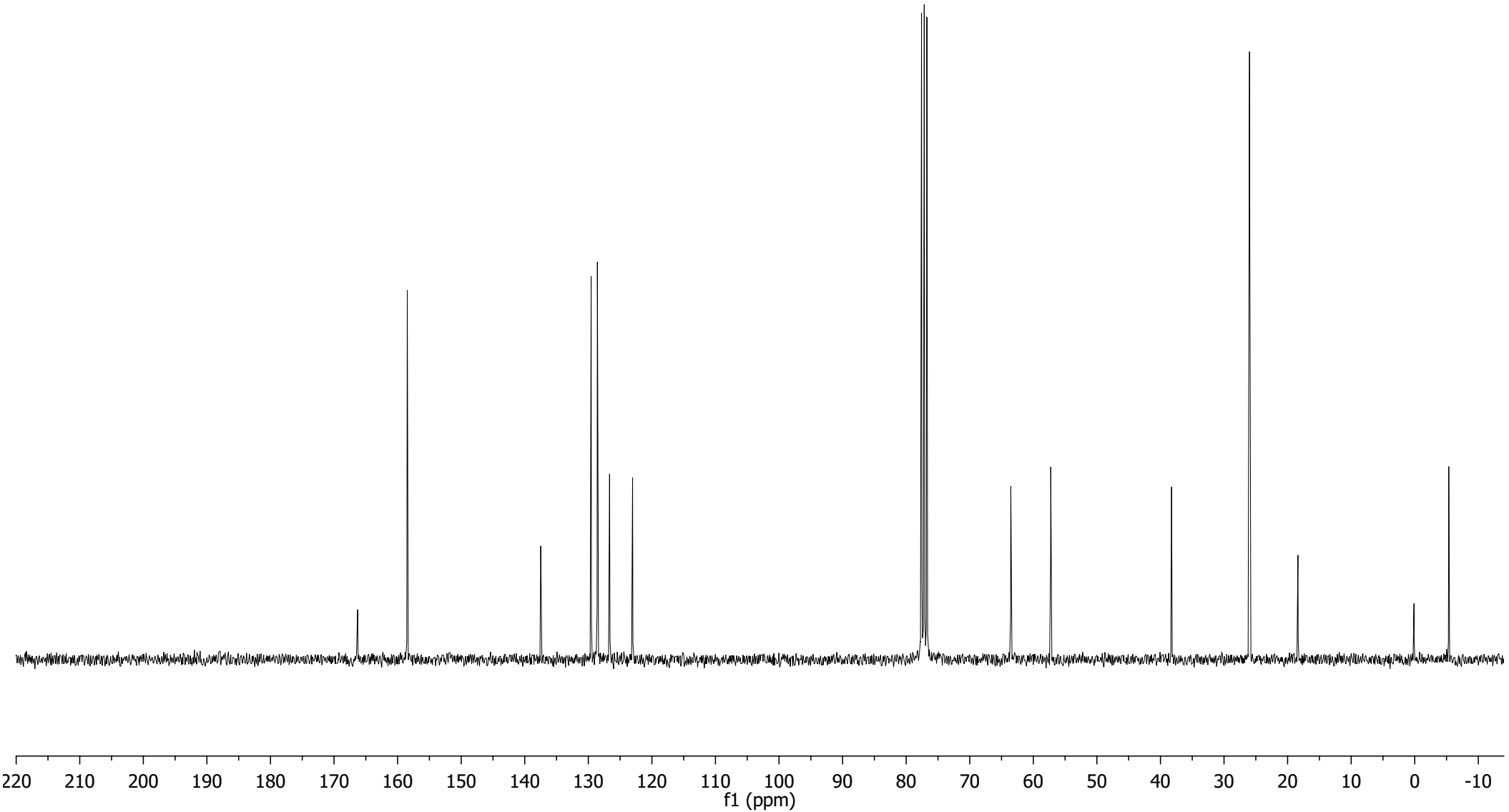
1H NMR of compound **12c**





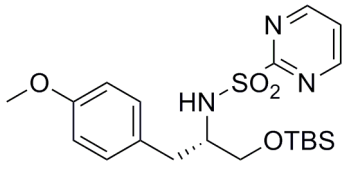
13C NMR of compound **12c**



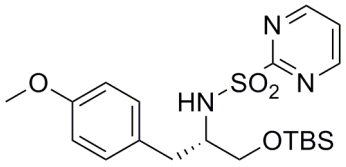
1H NMR of compound **12d**

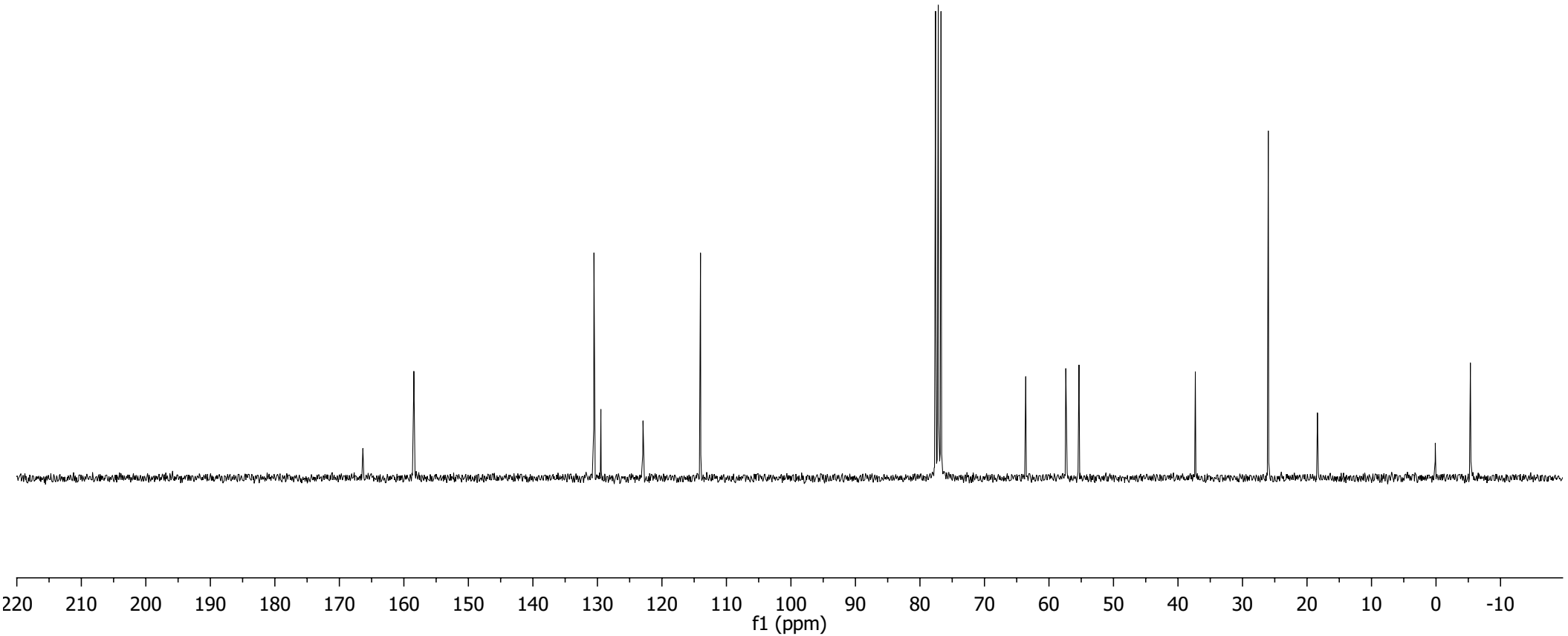


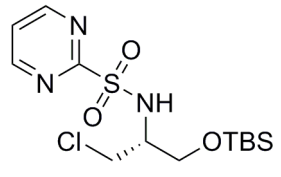


13C NMR of compound **12d**






N
N
O
S
O
NH
Cl
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12.0
11.5
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2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

13C NMR of compound **13**