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SUPPORTING INFORMATION

Vinyl sulfonamide synthesis for irreversible tethering via a novel α-selenoether protection strategy

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1. Synthetic Experimental Considerations

All non-aqueous reactions were carried out under an inert atmosphere (argon) with flame-dried glassware, using standard techniques. Anhydrous solvents were obtained by filtration through drying columns (THF, CH_2Cl_2, toluene).

Normal phase flash column chromatography was performed on an Isolera™ Spektra flash purification system using Biotage® SNAP KP-Sil flash purification cartridges or SNAP Ultra flash purification cartridges, with the indicated solvent gradient. Reversed-phase flash column chromatography was performed using Biotage® SNAP Ultra C18 cartridges.

Analytical thin-layer chromatography (TLC) was performed on precoated aluminium-backed silica gel plates. Visualisation of the developed chromatogram was performed by UV absorbance (254 nm) and/or stained with aqueous potassium permanganate solution, aqueous ceric ammonium molybdate, or a ninhydrin solution in ethanol.

Nuclear magnetic resonance spectra were recorded on a 400 MHz spectrometer. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane with the residual protic solvent resonance as the internal standard (chloroform: δ 7.27 ppm, methanol: δ 3.31 ppm). Data are reported as follows: chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, m = multiplet and br = broad], coupling constant (in Hz), integration). ^{13}C NMR spectra are recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($^{13}CDCl_3$: δ 77.0 ppm, $^{13}CD_3OD$: δ 49.0 ppm). ^{19}F NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million, referenced to fluorobenzene as a standard at δ -113.5 ppm.

Assignments of ^{1}H and ^{13}C spectra were based upon the analysis of δ and *J* values, as well as DEPT, COSY, HMBC and HSQC experiments where appropriate.

Commercial reagents were used as supplied or purified by standard techniques where necessary.

Optical rotations (α') were recorded at the indicated temperature (T ºC) and were converted to the corresponding specific rotations $[\alpha]_D^T$.

2. Synthetic Experimental Details and Characterisation Data

2.1. General Procedures

General Procedure A: *N*-sulfonylation of amines

1-Bromoethane-1-sulfonyl chloride **S–1** (1 equiv) was added dropwise to a solution of NEt_3 (1.5 equiv) and amine (2.0 equiv) in CH_2Cl_2 (0.2 M wrt sulfonyl chloride **S–1**) at 0˚C, and stirred for 1 h at this temperature. The solution was then allowed to warm to rt for 1 h, and the reaction was treated with 1 M HCl (5 mL). The aqueous phase was then extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude products were purified by flash column chromatography using the indicated eluent system, to give the sulfonamide.

General Procedure B: bromide-selenide substitution

$NaBH_4$ (1.5 equiv) was added portionwise to a solution of Ph_2Se_2 (0.5 equiv) in THF and DMF at 0 ºC, and the resulting solution was stirred for 10 min. The solution was then allowed to warm to rt for 2 h. A solution of bromoethylsulfonamide (1.0 equiv) in THF was then added dropwise. The solution was then heated to 40 ºC for 15 h. H_2O and CH_2Cl_2 were added, and the phases were separated. The aqueous layer was further extracted with CH_2Cl_2, the combined organic layers were dried over Na_2SO_4, and the mixture was filtered. The solvent was removed under reduced pressure, and the resulting crude residue was purified by flash column chromatography to yield the phenyl selenide.

General Procedure C: selenide oxidation-elimination

$NaIO_4$ (2.0 equiv) was added to a solution of selenide (1.0 equiv) in EtOH (0.1 M wrt selenide) at rt and was then stirred at 30 ºC for 24 h. Sat. aq. $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure which generally afforded the vinyl sulfonamide products in high purity without need for further purification.

General Procedure D: $ZrCp_2Cl_2$-catalysed amide bond formation

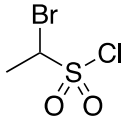
A solution of carboxylic acid (1 equiv), amine (1.2 equiv) and bis(cyclopentadienyl)zirconium(IV) dichloride (5 mol%) in anhydrous toluene (0.05 M wrt carbxylic acid) was heated to reflux under argon for 24 h. The reaction mixture was allowed to cool to rt, filtered through Celite and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (1% MeOH/CH_2Cl_2) to give the corresponding amide.

General Procedure E: HATU-mediated amide bond formation

The requisite amine (1.2 equiv) was added to a solution of carboxylic acid (1.0 equiv), HATU (1.2 equiv) and DIPEA (1.2 equiv) in CH_2Cl_2 (0.05 M wrt carboxylic acid) at rt. The mixture was stirred for 24 h, then filtered through Celite. The solvent was removed under reduced pressure, and the resulting crude residue was purified by reversed-phase flash column chromatography using the indicated conditions to afford the desired amide.

2.2. Compound Synthesis and Characterisation

1-Bromoethane-1-sulfonyl chloride (S–1)

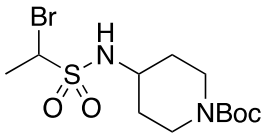


1,1-Dibromoethane (5.00 mL, 54.8 mmol) was added to a solution of sodium sulfite (6.91 g, 54.8 mmol) in water (50 mL) and ethanol (5 mL). After heating the solution at reflux for 48 h the solvent was removed *in vacuo*. The resulting white residue was pulverized and cooled to 0 ºC,

before careful addition of phosphorus pentachloride (34.2 g, 164 mmol) with stirring. When the reaction had subsided the mixture was heated to 80 ºC for 2 h and then cautiously poured into ice (30 g). After the ice had melted the aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The organic layers were combined and successively washed with sat. aq. $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL). The solution was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by serial vacuum distillation (42–46 ºC at 1.5 mbar) to give 1-bromoethanesulfonyl chloride (5.19 g, 46%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (q, *J* = 6.8 Hz, 1 H), 2.22 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 65.6, 21.8.

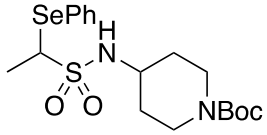
Data are consistent with those previously reported.[1]

tert-Butyl 4-((1-bromoethyl)sulfonamido)piperidine-1-carboxylate (5a)



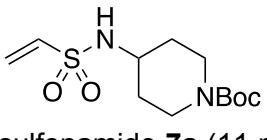
Prepared according to General Procedure A, using 1-bromoethane-1-sulfonyl chloride **S–1** (161 mg, 0.78 mmol), 4-amino-1-Boc-piperidine (312 mg, 1.56 mmol), NEt_3 (163 μL, 1.17 mmol) in CH_2Cl_2 (3.90 mL). The crude material was purified by flash column chromatography (15% grading to 35% EtOAc/pentane), which afforded sulfonamide **5a** (263 mg, 91%) as a colourless oil. R_f 0.45 (25% EtOAc/pentane); ν_{max} (film)/cm^{-1} 3261, 2978, 1672, 1428, 1367, 1330, 1239, 1133, 1081, 910, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (d, *J* = 8.3 Hz, 1 H), 4.84 (d, *J* = 6.8 Hz, 1 H), 4.07–3.93 (m, 2 H), 3.57–3.45 (m, 1 H), 2.88–2.77 (m, 2 H), 2.03–1.94 (m, 5 H), 1.52–1.39 (m, 11 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 79.8, 58.1, 52.4, 42.4 (2 × C), 33.5 (2 × C), 28.3 (3 × C), 20.7; HRMS (ESI$^-$) *m/z* Calculated for $C_{12}H_{22}N_2O_4S^{79}Br^-$ [M-H]$^-$ 369.0484; Found 369.0490 (Δ +1.6 ppm).

tert-Butyl 4-((1-(phenylselanyl)ethyl)sulfonamido)piperidine-1-carboxylate (6a)



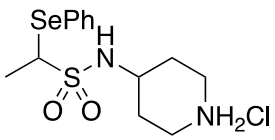
Prepared according to General Procedure B, using $NaBH_4$ (40.0 mg, 1.05 mmol), Ph_2Se_2 (109 mg, 0.35 mmol), bromoethylsulfonamide **5a** (260 mg, 0.70 mmol) in THF (2.92 mL) and DMF (0.58 mL). The crude material was purified by flash column chromatography (10% grading to 20% EtOAc/pentane), which gave the seleno-sulfonamide **6a** (215 mg, 69%) as a colourless oil. R_f 0.39 (25% EtOAc/pentane); ν_{max} (film)/cm^{-1} 3276, 2978, 2934, 2875, 1675, 1427, 1366, 1315, 1237, 1166, 1133, 1080, 907, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.65 (m, 2 H), 7.38–7.28 (m, 3 H), 4.91 (d, *J* = 8.0 Hz, 1 H), 4.23 (q, *J* = 7.1 Hz, 1 H), 4.07–3.88 (m, 2 H), 3.52–3.38 (m, 1 H), 2.87–2.72 (m, 2 H), 1.96–1.79 (m, 2 H), 1.73 (d, *J* = 7.1 Hz, 3 H), 1.43 (s, 9 H), 1.40–1.23 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 135.7 (2 × C), 129.2 (2 × C), 128.9, 126.9, 79.7, 58.6, 52.1, 42.4 (2 × C), 33.4 (2 × C), 28.3 (3 × C), 17.5. HRMS (ESI$^-$) *m/z* Calculated for $C_{18}H_{27}N_2O_4S^{80}Se^-$ [M-H]$^-$ 447.0857; Found 447.0864 (Δ +1.6 ppm).

tert-Butyl 4-(vinylsulfonamido)piperidine-1-carboxylate (7a)



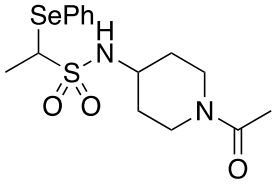
Prepared according to General Procedure C, using seleno-sulfonamide **6a** (23 mg, 0.05 mmol) and $NaIO_4$ (21 mg, 0.10 mmol) in EtOH (0.50 mL). The product was isolated in <95% purity after aqueous workup and was further purified by flash column chromatography (30% grading to 50% EtOAc/pentane), which gave the vinyl sulfonamide **7a** (11 mg, 76%) as a colourless oil. R_f 0.12 (25% EtOAc/pentane); ν_{max} (film)/cm^{-1} 3256, 2977, 2935, 1689, 1669, 1427, 1328, 1239, 1136, 1083, 909, 735; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (dd, *J* = 16.5, 9.8 Hz, 1 H), 6.26 (d, *J* = 16.5 Hz, 1 H), 5.94 (d, *J* = 9.8 Hz, 1 H), 4.46 (d, *J* = 7.5 Hz, 1 H), 4.07–3.89 (m, 2 H), 3.40–3.24 (m, 1 H), 2.93–2.79 (m, 2 H), 1.98–1.87 (m, 2 H), 1.45 (s, 9 H), 1.44–1.35 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 137.0, 126.2, 79.9, 50.9, 42.4 (2 × C), 33.2 (2 × C), 28.4 (3 × C); HRMS (ESI$^-$) *m/z* Calculated for $C_{12}H_{21}N_2O_4S^-$ [M-H]$^-$ 289.1222; Found 289.1220 (Δ -0.7 ppm).

1-(Phenylselanyl)-*N*-(piperidin-4-yl)ethane-1-sulfonamide hydrochloride (S–2)



N-Boc amine **6a** (55 mg, 0.12 mmol) was dissolved in a 4 M solution of HCl in 1,4-dioxane (1.2 mL, 4.8 mmol), and was stirred at rt for 3 h. The solvent was removed under reduced pressure, which gave the amine hydrochloride salt **S–2** (36 mg, 78%) as a white solid. ν_{max} (film)/cm^{-1} 2942, 2808, 2727, 2365, 1705, 1439, 1302, 1268, 1133, 1096, 990, 896, 761; ^{1}H NMR (400 MHz, CD_3OD) δ 7.76–7.71 (m, 2 H), 7.41–7.30 (m, 3 H), 4.57–4.48 (m, 1 H), 3.77–3.56 (m, 2 H), 3.42–3.28 (m, 3 H), 3.11–2.99 (m, 2 H), 2.19–2.04 (m, 2 H), 1.83–1.66 (m, 5 H); ^{13}C NMR (101 MHz, CD_3OD) δ 136.7 (2 × C_{Ph}), 130.3 (2 × C_{Ph}), 129.8, 128.7, 58.7, 50.0, 44.0 (2 × C), 31.3 (2 × C), 18.1; HRMS (ESI$^+$) *m/z* Calculated for $C_{13}H_{21}N_2O_2S^{80}Se^+$ $[M\text{-}Cl]^+$ 349.0489; Found 349.0492 (Δ +0.9 ppm).

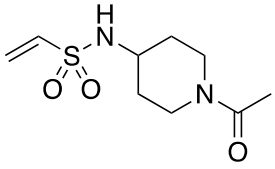
N-(1-Acetylpiperidin-4-yl)-1-(phenylselanyl)ethane-1-sulfonamide (6b)



Acetic anhydride (10 μL, 0.11 mmol), was added dropwise to a solution of amine **S–2** (36 mg, 94 μmol) and NEt_3 (26 μL, 0.19 mmol) in CH_2Cl_2 (0.38 mL), and was stirred at rt for 24 h. Sat. aq. $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash column chromatography (5% grading to 40% EtOAc/pentane), which gave the desired *N*-Ac piperidine **6b** (33 mg, 91%) as a colourless oil. R_f 0.23 (25% EtOAc/pentane); ν_{max} (film)/cm^{-1} 3164, 2929, 1622, 1442, 1323, 1129, 907, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.66 (m, 2 H), 7.40–7.29 (m, 3 H), 5.00–4.95 (m, 1 H), 4.48–4.37 (m, 1 H), 4.29–4.21 (m, 1 H), 3.78–3.68 (m, 1 H), 3.60–3.47 (m, 1 H), 3.15–3.04 (m, 1 H), 2.75–2.64 (m, 1 H), 2.08–2.06 (m, 3 H), 2.03–1.80 (m, 2 H), 1.78–1.72 (m, 3 H), 1.50–1.23 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 135.7, 135.6, 129.31, 129.27, 129.02, 128.99, 127.0, 58.83, 58.78, 52.0, 44.9, 40.3, 40.2, 34.3, 34.2, 33.0, 32.8, 21.4, 17.6, 17.5; HRMS (ESI$^+$) *m/z* Calculated for $C_{15}H_{23}N_2O_3S^{80}Se^+$ $[M+H]^+$ 391.0595; Found 391.0587 (Δ -2.0 ppm).

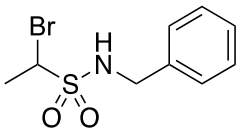
The compound appeared as a mixture of rotamers in the NMR spectra.

N-(1-Acetylpiperidin-4-yl)ethenesulfonamide (7b)



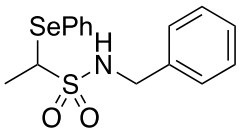
Prepared according to General Procedure C, using seleno-sulfonamide **6b** (33 mg, 85 μmol) and $NaIO_4$ (36 mg, 0.17 mmol) in EtOH (0.85 mL). The crude material was pure following the aqueous work up, which gave the vinyl sulfonamide **7b** (17 mg, 85%) as a white solid. m.p. = 126–129 ºC ($CHCl_3$); ν_{max} (film)/cm^{-1} 3169, 2923, 1607, 1460, 1312, 1260, 1152, 1132, 1090, 1054, 977, 914, 738, 674; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (dd, *J* = 16.5, 9.9 Hz, 1 H), 6.28 (d, *J* = 16.5 Hz, 1 H), 5.95 (d, *J* = 9.9 Hz, 1 H), 5.01 (d, *J* = 7.4 Hz, 1 H), 4.44–4.38 (m, 1 H), 3.81–3.74 (m, 1 H), 3.46–3.34 (m, 1 H), 3.20–3.11 (m, 1 H), 2.85–2.76 (m, 1 H), 2.10 (s, 3 H), 2.08–2.01 (m, 1 H), 1.99–1.92 (m, 1 H), 1.56–1.38 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 137.0, 126.1, 50.6, 44.8, 40.1, 33.7, 32.6, 21.3; HRMS (ESI$^+$) *m/z* Calculated for $C_9H_{17}N_2O_3S^+$ $[M+H]^+$ 233.0960; Found 233.0954 (Δ -2.6 ppm).

N-Benzyl-1-bromoethane-1-sulfonamide (5c)



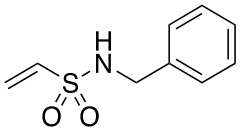
Prepared according to General Procedure A, using 1-bromoethane-1-sulfonyl chloride **S–1** (183 mg, 0.81 mmol), benzylamine (190 mg, 1.77 mmol), NEt_3 (160 μL, 1.17 mmol) in CH_2Cl_2 (4.15 mL). The crude material was purified by flash column chromatography (5% grading to 40% EtOAc/pentane), which afforded the sulfonamide **5c** (218 mg, 97%) as a colourless oil. R_f 0.27 (25% EtOAc/pentane); ν_{max} (film)/cm^{-1} 3294, 1441, 1340, 1311, 1142, 1068, 740; ^{1}H NMR (400 MHz, MeOD) δ 7.45–7.20 (m, 5H), 4.99 (q, *J* = 6.8 Hz, 1H), 4.33 (s, 2H), 1.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, MeOD) δ 139.4, 129.6 (2 × C), 128.9 (2 × C), 128.7, 58.8, 48.7, 21.2; HRMS (ESI$^+$) *m/z* Calculated for $C_9H_{16}N_2O_2S^{79}Br^+$ $[M+NH_4]^+$ 295.0116; Found 295.0121 (Δ +1.7 ppm).

N-Benzyl-1-(phenylselanyl)ethane-1-sulfonamide (6c)



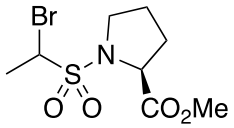
Prepared according to General Procedure B, using $NaBH_4$ (33.0 mg, 0.87 mmol), Ph_2Se_2 (90 mg, 0.29 mmol), bromoethylsulfonamide **5c** (100 mg, 0.36 mmol) in THF (2.60 mL) and DMF (0.51 mL). The crude material was purified by flash column chromatography (10% grading to 30% EtOAc/pentane), which gave the seleno-sulfonamide **6c** (47 mg, 37%) as a colourless oil. R_f 0.29 (25% EtOAc/pentane); ν_{max} (film)/cm^{-1} 3297, 3057, 1438, 1321, 1140, 1067, 742; ^{1}H NMR (400 MHz, MeOD) δ 7.67 (m, 2H), 7.42–7.18 (m, 8H), 4.33–3.98 (m, 3H), 1.64 (d, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, MeOD) δ 139.5, 136.7 (2 × C), 130.2 (2 × C), 129.7, 129.6 (2 × C), 129.0 (2 × C), 128.9, 128.6, 58.9, 48.4, 17.9; HRMS (ESI$^+$) *m/z* Calculated for $C_{15}H_{18}NO_2S^{80}Se^+$ $[M+H]^+$ 355.0145; Found 355.0154 (Δ +2.7 ppm).

N-Benzylethenesulfonamide (7c)



Prepared according to General Procedure C, using seleno-sulfonamide **6c** (23 mg, 65 μmol) and $NaIO_4$ (22 mg, 104 μmol) in EtOH (0.50 mL). The crude material was pure following the aqueous work up, which gave the vinyl sulfonamide **7c** (11.6 mg, 91%) as a colourless oil. ν_{max} (film)/cm^{-1} 3269, 1440, 1327, 1248, 1143, 1021, 911, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.28 (m, 5H), 6.49 (dd, J = 16.6, 9.8 Hz, 1H), 6.27 (d, J = 16.5 Hz, 1H), 5.93 (d, J = 9.9 Hz, 1H), 4.54 (s, 1H), 4.22 (d, J = 5.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6, 136.2, 129.0 (2 × C), 128.3, 128.1 (2 × C), 127.0, 47.2. Data are consistent with those previously reported.[2]

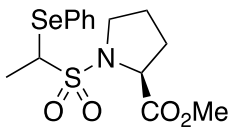
Methyl ((1-bromoethyl)sulfonyl)-L-prolinate (5d)



Prepared according to General Procedure A, using 1-bromoethane-1-sulfonyl chloride **S–1** (146 mg, 0.71 mmol), L-proline methyl ester hydrochloride (235 mg, 1.42 mmol), NEt_3 (248 μL, 1.78 mmol) in CH_2Cl_2 (3.55 mL). The crude material was purified by flash column chromatography (90% CH_2Cl_2/pentane grading to CH_2Cl_2), which afforded the sulfonamide **5d** (167 mg, 78%) as a colourless oil. R_f 0.33 (CH_2Cl_2); ν_{max} (film)/cm^{-1} 2962, 1743, 1443, 1340, 1279, 1204, 1141, 1077, 1021, 722; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (q, J = 6.9 Hz, 0.5 H), 5.05 (q, J = 6.9 Hz, 0.5 H), 4.57 (dd, J = 8.6, 4.4 Hz, 0.5 H), 4.50 (dd, J = 8.6, 4.2 Hz, 0.5 H), 3.80–3.74 (m, 0.5 H), 3.73–3.71 (m, 3 H) 3.69–3.60 (m, 1 H), 3.55–3.47 (m, 0.5 H), 2.36–2.25 (m, 1 H), 2.08–1.92 (m, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 172.5, 61.8, 61.0, 58.3, 57.9, 52.4, 52.4, 50.5, 50.4, 30.9, 30.7, 25.1, 24.9, 20.8, 20.2; HRMS (ESI$^+$) *m/z* Calculated for $C_8H_{15}NO_4S^{79}Br^+$ $[M+H]^+$ 299.9905; Found 299.9915 (Δ +3.3 ppm).

The product was obtained as a 1:1 mixture of diastereoisomers.

Methyl ((1-(phenylselanyl)ethyl)sulfonyl)-L-prolinate (6d)

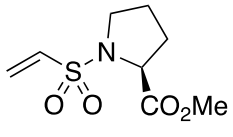


Prepared according to General Procedure B, using $NaBH_4$ (31 mg, 0.83 mmol), Ph_2Se_2 (86 mg, 0.28 mmol), bromoethylsulfonamide **5d** (165 mg, 0.55 mmol) in THF (2.30 mL) and DMF (0.45 mL). The crude material was purified by flash column chromatography (5% grading to 50% EtOAc/pentane), followed by reversed-phase flash column chromatography (H_2O grading to MeOH, with 0.1% v/v HCO_2H additive), which gave the seleno-sulfonamide **6d** (17 mg, 8%, 63:37 *dr*) as a colourless oil. R_f 0.37 (25% EtOAc/pentane); ν_{max} (film)/cm^{-1} 2953, 1743, 1438, 1331, 1209, 1138, 1073, 1021, 742, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.71 (m, 1.76 H), 7.52–7.47 (m, 0.49 H), 7.40–7.29 (m, 2.90 H), 7.27–7.23 (m, 0.62 H), 4.67 (dd, J = 8.6, 4.1 Hz, 0.56 H), 4.60 (q, J = 7.3 Hz, 0.57 H), 4.56–4.52 (m, 0.36 H), 4.50 (t, J = 7.1 Hz, 0.40 H), 3.80–3.71 (m, 4.48 H), 3.66 (t, J = 6.3 Hz, 0.56 H), 3.54–3.46 (m, 0.44 H), 2.95 (t, J = 7.2 Hz, 0.55 H), 2.34–2.21 (m, 1.00 H), 2.11–1.90 (m, 3.04 H), 1.83–1.75 (m, 1.82 H), 1.74–1.67 (m, 2.45 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 136.0, 135.9, 132.5, 129.1, 129.0, 128.8, 128.7, 126.7, 62.3, 61.6, 61.1, 58.6, 58.1, 52.4, 52.3, 50.6, 50.2, 32.7, 31.0, 27.6, 26.4,

25.2, 25.1, 17.6, 17.0; HRMS (ESI$^+$) *m/z* Calculated for $C_{19}H_{23}O_2S^{80}Se^+$ $[M+H]^+$ 395.0584; Found 395.0587 (Δ +0.8 ppm).

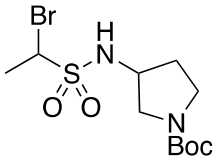
The product was obtained as a 63:37 mixture of diastereoisomers, although the *dr* of the product in the crude reaction mixture was 1:1.

Methyl (vinylsulfonyl)-L-prolinate (7d)



Prepared according to General Procedure C, using seleno-sulfonamide **6d** (18 mg, 48 μmol) and $NaIO_4$ (21 mg, 96 μmol) in EtOH (0.48 mL). The crude material was pure following the aqueous work up, which gave the vinyl sulfonamide **7d** (8.5 mg, 81%) as a colourless oil. ν_{max} (film)/cm^{-1} 2942, 1745, 1442, 1340, 1205, 1146, 1082, 1019, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (dd, *J* = 16.6, 9.9 Hz, 1 H), 6.27 (d, *J* = 16.6 Hz, 1 H), 5.97 (d, *J* = 9.9 Hz, 1 H), 4.42 (dd, *J* = 8.6, 3.5 Hz, 1 H), 3.76 (s, 3 H), 3.44–3.39 (m, 2 H), 2.31–2.21 (m, 1 H), 2.11–1.95 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 134.5, 127.0, 60.4, 52.4, 47.7, 31.0, 24.8; HRMS (ESI$^+$) *m/z* Calculated for $C_8H_{14}NO_4S^+$ $[M+H]^+$ 220.0644; Found 220.0646 (Δ +0.9 ppm).

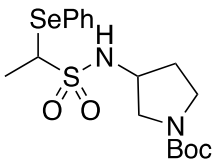
tert-Butyl 3-((1-bromoethyl)sulfonamido)pyrrolidine-1-carboxylate (5e)



Prepared according to General Procedure A, using 1-bromoethane-1-sulfonyl chloride **S–1** (179 mg, 0.87 mmol), *tert*-butyl 3-aminopyrrolidine-1-carboxylate (318 μL, 1.74 mmol), NEt_3 (182 μL, 1.31 mmol) in CH_2Cl_2 (4.35 mL). The crude material was purified by flash column chromatography (pentane grading to 40% EtOAc/pentane), which afforded the sulfonamide **5e** (233 mg, 75%) as a colourless oil. R_f 0.35 (25% EtOAc/pentane); ν_{max} (film)/cm^{-1} 2979, 1669, 1412, 1334, 1151, 1125, 909, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88–5.77 (m, 1 H), 4.90–4.82 (m, 1 H), 4.15–4.04 (m, 1 H), 3.70–3.54 (m, 1 H), 3.54–3.20 (m, 3 H), 2.23–2.04 (m, 1 H), 2.02–1.87 (m, 4 H), 1.45–1.37 (m, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 79.7, 57.9, 57.7, 54.3, 54.2, 53.6, 53.4, 52.1, 52.0, 51.3, 51.0, 43.7, 43.5, 32.8, 31.8, 31.7, 28.3, 20.6; HRMS (ESI$^+$) *m/z* Calculated for $C_{11}H_{21}N_2O_4NaS^{79}Br^+$ $[M+Na]^+$ 379.0303; Found 379.0318 (Δ +4.0 ppm).

The compound appeared as a mixture of rotamers and diastereoisomers in the NMR spectra.

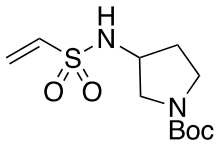
tert-Butyl 3-((1-(phenylselanyl)ethyl)sulfonamido)pyrrolidine-1-carboxylate (6e)



Prepared according to General Procedure B, using $NaBH_4$ (34 mg, 0.90 mmol), Ph_2Se_2 (94 mg, 0.30 mmol), bromoethylsulfonamide **5e** (214 mg, 0.60 mmol) in THF (2.50 mL) and DMF (0.50 mL). The crude material was purified by reversed-phase flash column chromatography (H_2O grading to MeOH, with 0.1% v/v HCO_2H additive), which gave the seleno-sulfonamide **6e** (80 mg, 31%) as a colourless oil. ν_{max} (film)/cm^{-1} 3236, 2983, 2885, 1671, 1409, 1366, 1320, 1164, 1125, 911, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.66 (m, 2 H), 7.40–7.29 (m, 3 H), 5.02–4.94 (m, 1 H), 4.26 (q, *J* = 7.1 Hz, 1 H), 4.10–3.97 (m, 1 H), 3.67–3.50 (m, 1 H), 3.49–3.27 (m, 2 H), 3.26–3.05 (m, 1 H), 2.20–1.80 (m, 2 H), 1.79–1.69 (m, 3 H), 1.49–1.41 (m, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 135.7, 135.6, 129.3, 129.1, 126.9, 79.7, 58.4, 54.1, 53.5, 52.2, 52.0, 51.4, 43.8, 43.4, 33.2, 33.1, 32.1, 31.8, 28.4, 17.5; HRMS (ESI$^+$) *m/z* Calculated for $C_{17}H_{27}N_2O_4S^{80}Se^+$ $[M+H]^+$ 435.0857; Found 435.0854 (Δ -0.7 ppm).

The compound appeared as a mixture of rotamers and diastereoisomers in the NMR spectra.

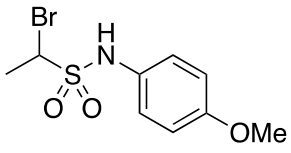
tert-Butyl 3-(vinylsulfonamido)pyrrolidine-1-carboxylate (7e)



Prepared according to General Procedure C, using seleno-sulfonamide **6e** (15 mg, 33 μmol) and $NaIO_4$ (14 mg, 0.66 μmol) in EtOH (0.33 mL). The crude material was pure following the aqueous work up, which gave the vinyl sulfonamide **7e** (9.0 mg, 99%) as a

colourless oil. ν_{max} (film)/cm^{-1} 3220, 2929, 1669, 1408, 1331, 1148, 1121, 1017, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (dd, *J* = 16.5, 9.8 Hz, 1 H), 6.30 (d, *J* = 16.5 Hz, 1 H), 5.98 (d, *J* = 9.8 Hz, 1 H), 4.73 (d, *J* = 7.5 Hz, 1 H), 3.96–3.86 (m, 1 H), 3.61 (dd, *J* = 11.6, 6.2 Hz, 1 H), 3.52–3.32 (m, 2 H), 3.25 (dd, *J* = 11.6, 4.9 Hz, 1 H), 2.21–2.10 (m, 1 H), 2.00–1.82 (m, 1 H), 1.46 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 136.5, 126.9, 79.9, 52.9, 52.0, 51.4, 43.7, 43.4, 32.8, 31.8, 29.7, 28.4; HRMS (ESI$^+$) *m/z* Calculated for $C_{11}H_{19}N_2O_4S^+$ $[M+H]^+$ 275.1066; Found 275.1070 (Δ +1.5 ppm).

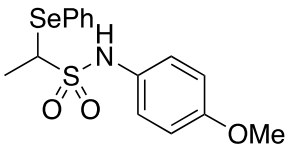
1-Bromo-*N*-(4-methoxyphenyl)ethane-1-sulfonamide (5f)



Prepared according to General Procedure A, using 1-bromoethane-1-sulfonyl chloride **S–1** (167 mg, 0.81 mmol), *p*-anisidine (208 mg, 1.62 mmol), NEt_3 (169 μL, 1.22 mmol) in CH_2Cl_2 (4.05 mL). The crude material was purified by flash column chromatography (5% grading to 40% EtOAc/pentane), which afforded the sulfonamide **5f** (157 mg, 66%) as a colourless oil. R_f 0.23 (25% EtOAc/pentane); ν_{max} (film)/cm^{-1} 3261, 2965, 2840, 1508, 1443, 1333, 1248, 1151, 1030, 920; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (m, 2 H), 6.91 (d, *J* = 8.4 Hz, 2 H), 6.81–6.74 (m, 1 H), 4.88–4.74 (m, 1 H), 3.83 (s, 3 H), 2.03–1.84 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 158.4, 128.0, 127.8, 125.8, 125.6, 114.7, 65.8, 55.5, 55.3, 19.9, 18.8; HRMS (ESI$^+$) *m/z* Calculated for $C_9H_{13}NO_3S^{79}Br^+$ $[M+H]^+$ 293.9800; Found 293.9805 (Δ +1.7 ppm).

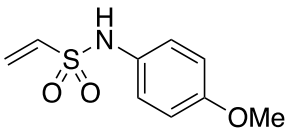
The compound appeared as a mixture of rotamers in the NMR spectra.

N-(4-Methoxyphenyl)-1-(phenylselanyl)ethane-1-sulfonamide (6f)



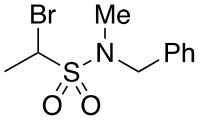
Prepared according to General Procedure B, using $NaBH_4$ (28 mg, 0.75 mmol), Ph_2Se_2 (78 mg, 0.25 mmol), bromoethylsulfonamide **5f** (149 mg, 0.50 mmol) in THF (2.1 mL) and DMF (0.42 mL). The crude material was purified by reversed-phase flash column chromatography (50 mM aq. NH_4HCO_3 grading to MeCN), which gave the seleno-sulfonamide **6f** (42 mg, ~85% purity) as a colourless oil. The product was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.65 (m, 2 H), 7.41–7.29 (m, 3 H), 7.18–7.14 (m, 2 H), 6.87–6.82 (m, 2 H), 6.75 (br s, 1 H), 4.29 (q, *J* = 7.3 Hz, 1 H), 3.81 (s, 3 H), 1.75–1.70 (m, 3 H).

N-(4-Methoxyphenyl)ethenesulfonamide (7f)



Prepared according to General Procedure C, using seleno-sulfonamide **6f** (42 mg, 0.11 mmol) and $NaIO_4$ (47 mg, 0.22 mmol) in EtOH (1.1 mL). The crude material was impure following the aqueous work up. The crude residue was purified by flash column chromatography (10% Et_2O/pentane grading to Et_2O), which gave the vinyl sulfonamide **7f** (19 mg, 80%) as a colourless oil. R_f 0.34 (50% Et_2O/pentane); ν_{max} (film)/cm^{-1} 3257, 1610, 1505, 1327, 1249, 1144, 1025, 913, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.13 (m, 2 H), 6.89–6.83 (m, 2 H), 6.59–6.51 (m, 2 H), 6.19 (d, *J* = 16.6 Hz, 1 H), 5.93 (d, *J* = 9.9 Hz, 1 H), 3.79 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 135.1, 128.6, 128.1, 125.0 (2 × C), 114.6 (2 × C), 55.5; HRMS (ESI$^+$) *m/z* Calculated for $C_9H_{10}N_1O_3S^-$ $[M–H]^-$ 212.0381; Found 212.0376 (Δ -2.4 ppm).

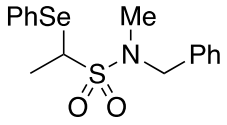
N-Benzyl-1-bromo-*N*-methylethane-1-sulfonamide (5g)



Prepared according to General Procedure A, using 1-bromoethane-1-sulfonyl chloride **S–1** (208 mg, 1.01 mmol), *N*-benzylmethylamine (260 μL, 2.02 mmol), NEt_3 (211 μL, 1.52 mmol) in CH_2Cl_2 (5.00 mL). The crude material was purified by flash column chromatography (10% Et_2O/pentane grading to Et_2O), which afforded the sulfonamide **5g** (252 mg, 85%) as a colourless oil. R_f 0.69 (25% EtOAc/pentane); ν_{max} (film)/cm^{-1} 2978, 2934, 1335, 1150, 989, 941, 910, 776, 737, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5 H), 5.00 (q, *J* = 6.9 Hz, 1 H),

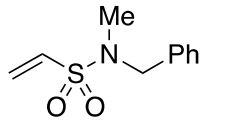
4.59 (d, *J* = 14.8 Hz, 1 H), 4.36 (d, *J* = 14.8 Hz, 1 H), 2.88 (s, 3 H), 2.06 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.5, 128.6 (2 × C), 128.0 (2 × C), 127.9, 56.8, 55.2, 35.3, 20.9; HRMS (ESI^+) *m/z* Calculated for $C_{10}H_{15}NO_2S^{79}Br^+$ $[M+H]^+$ 292.0007; Found 292.0014 (Δ +2.4 ppm).

N-Benzyl-*N*-methyl-1-(phenylselanyl)ethane-1-sulfonamide (6g)



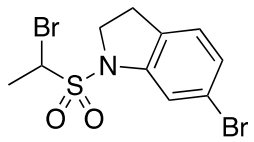
Prepared according to General Procedure B, using $NaBH_4$ (49 mg, 1.29 mmol), Ph_2Se_2 (134 mg, 0.43 mmol), bromoethylsulfonamide **5g** (251 mg, 0.86 mmol) in THF (3.60 mL) and DMF (0.72 mL). The crude material was purified by reversed-phase flash column chromatography (H_2O grading to MeOH, with 0.1% v/v HCO_2H additive), which gave the seleno-sulfonamide **6g** (44 mg, 14%) as a colourless oil. ν_{max} (film)/cm^{-1} 2921, 1439, 1324, 1148, 1129, 990, 941, 771, 736, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.69 (m, 2 H), 7.42–7.28 (m, 8 H), 4.49–4.36 (m, 3 H), 2.82 (s, 3 H), 1.83–1.78 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0, 135.6 (2 × C), 129.3 (2 × C), 128.9, 128.6 (2 × C), 128.2 (2 × C), 127.8, 127.1, 57.4, 55.0, 35.2, 17.9; HRMS: not found using ESI, EI or CI

N-Benzyl-*N*-methylethenesulfonamide (7g)



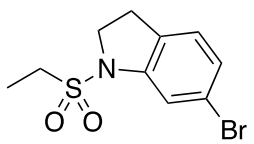
Prepared according to General Procedure C, using seleno-sulfonamide **6g** (43 mg, 0.12 mmol) and $NaIO_4$ (51 mg, 0.24 mmol) in EtOH (1.2 mL). The crude material was pure following the aqueous work up, which gave the vinyl sulfonamide **7g** (20 mg, 79%) as a yellow oil. R_f 0.69 (50% Et_2O/pentane); ν_{max} (film)/cm^{-1} 2895, 1453, 1334, 1148, 972, 935, 775; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5 H), 6.46 (dd, *J* = 16.6, 9.9 Hz, 1 H), 6.27 (d, *J* = 16.6 Hz, 1 H), 6.01 (d, *J* = 9.9 Hz, 1 H), 4.26 (s, 2 H), 2.70 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6, 133.3, 128.7, 128.4, 128.0, 127.6, 53.8, 34.0; HRMS (ESI^+) *m/z* Calculated for $C_{10}H_{14}N_1O_2S^+$ $[M+H]^+$ 212.0745; Found 212.0747 (Δ +0.9 ppm).

6-Bromo-1-((1-bromoethyl)sulfonyl)indoline (5h)



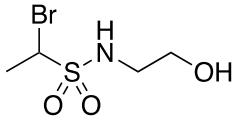
Prepared according to General Procedure A, using 1-bromoethane-1-sulfonyl chloride **S–1** (164 mg, 0.80 mmol), 6-bromoindoline (317 mg, 1.60 mmol), NEt_3 (167 μL, 1.20 mmol) in CH_2Cl_2 (2.0 mL). The crude material was purified by flash column chromatography (5% grading to 20% EtOAc/pentane), which afforded the sulfonamide **5h** (226 mg, 77%) as a white solid. m.p = 88–90 ºC ($CHCl_3$); R_f 0.69 (25% EtOAc/pentane); ν_{max} (film)/cm^{-1} 2975, 1600, 1473, 1412, 1352, 1324, 1151, 1109, 1039, 976, 809, 750, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 1.7 Hz, 1 H), 7.12 (d, *J* = 8.0, 1.7 Hz, 1 H), 7.08–7.03 (m, 1 H), 5.05 (q, *J* = 6.9 Hz, 1 H), 4.30 (td, *J* = 10.3, 6.3 Hz, 1 H), 4.15 (td, *J* = 10.3, 7.7 Hz, 1 H), 3.23–3.02 (m, 2 H), 2.05 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 130.3, 126.54, 126.51, 120.9, 116.6, 55.4, 52.4, 27.5, 20.4; HRMS: not found using ESI, EI or CI.

6-Bromo-1-(ethylsulfonyl)indoline (8)



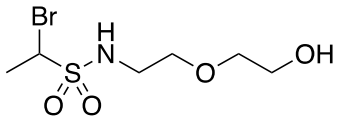
Prepared according to General Procedure B, using $NaBH_4$ (33 mg, 0.89 mmol), Ph_2Se_2 (92 mg, 0.30 mmol), bromoethylsulfonamide **5h** (219 mg, 0.59 mmol) in THF (2.46 mL) and DMF (0.49 mL). The crude material was purified by flash column chromatography (pentane grading to 15% EtOAc/pentane), which gave the dehalogenated sulfonamide **8** (67 mg, 37%) as an off-white solid. m.p. = 71–74 ºC (CH_2Cl_2); R_f 0.30 (15% EtOAc/pentane); ν_{max} (film)/cm^{-1} 2942, 1597, 1472, 1411, 1341, 1147, 1109, 1039, 970, 866, 776, 751, 710; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 1.7 Hz, 1 H), 7.09 (d, *J* = 8.0, 1.7 Hz, 1 H), 7.06–7.01 (m, 1 H), 4.04 (t, *J* = 8.6 Hz, 2 H), 3.15–3.05 (m, 4 H), 1.38 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4, 130.0, 126.4, 126.0, 121.2, 116.4, 50.7, 44.1, 27.5, 7.6; HRMS (ESI^+) *m/z* Calculated for $C_{10}H_{13}NO_2S^{79}Br^+$ $[M+H]^+$ 289.9850; Found 289.9856 (Δ +2.1 ppm).

1-Bromo-*N*-(2-hydroxyethyl)ethane-1-sulfonamide (S–3)



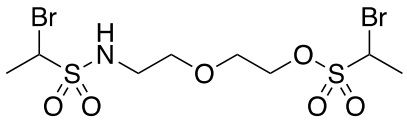
Prepared according to General Procedure A, using sulfonyl chloride **S–1** (505 mg, 2.36 mmol), ethanolamine (340 μL, 4.98 mmol) and NEt_3 (694 μL, 4.98 mmol) in CH_2Cl_2 (20 mL). The crude reaction mixture was purified by flash column chromatography (70% EtOAc/hexane), which afforded sulfonamide **S–3** (458 mg, 84%) as a colourless oil. ν_{max} (film)/cm^{-1} 3285, 2915, 1434, 1319, 1133, 1040; ^{1}H NMR (400 MHz, CD_3OD) δ 5.21 (q, *J* = 6.8 Hz, 1 H), 3.62 (t, *J* = 5.8 Hz, 2 H), 3.26 (t, *J* = 5.8 Hz, 2 H), 1.95 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (101 MHz, CD_3OD) δ 62.6, 58.5, 47.2, 21.2; HRMS (ESI$^+$) *m/z* Calculated for $C_4H_{10}NO_3S^{79}BrNa^+$ [M+Na]$^+$ 253.9457; Found 253.9462 (Δ +3.9 ppm).

1-Bromo-*N*-(2-(2-hydroxyethoxy)ethyl)ethane-1-sulfonamide (S–4)



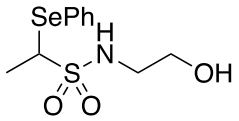
Prepared according to General Procedure A, using sulfonyl chloride **S–1** (50 mg, 0.22 mmol), 2-(2-aminoethoxy)ethan-1-ol (47 μL, 0.47 mmol), and NEt_3 (65 μL, 0.47 mmol) in CH_2Cl_2 (20 mL). The crude reaction mixture was purified by flash column chromatography (70% EtOAc/hexane), which afforded sulfonamide **S–4** (45 mg, 74%) as a colourless oil and bis-sulfonylated compound **S–5** (5 mg, 5%) as a colourless oil. ν_{max} (film)/cm^{-1} 3405, 3311, 2978, 1444, 1332, 1151, 921; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (s, 1 H), 4.95 (q, *J* = 6.8 Hz, 1 H), 3.82–3.76 (m, 2 H), 3.68–3.61 (m, 4 H), 3.51–3.49 (m, 1 H), 3.48–3.43 (m, 2 H), 2.04 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 72.0, 70.8, 69.1, 58.0, 44.6, 21.0; HRMS: not found using ESI, EI or CI.

2-(2-((1-Bromoethyl)sulfonamido)ethoxy)ethyl 1-bromoethane-1-sulfonate (S–5)



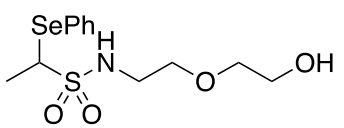
ν_{max} (film)/cm^{-1} 3310, 2978, 1444, 1351, 1332, 1151, 1005, 921; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20–5.12 (m, 1 H), 5.02 (qd, *J* = 6.7, 1.4 Hz, 1 H), 4.94, (q, *J* = 6.9 Hz, 1 H), 4.58–4.54 (m, 2 H), 3.81–3.76 (m, 2 H), 3.70–3.66 (m, 2 H), 3.51–3.45 (m, 2 H), 2.09 (d, *J* = 6.7 Hz, 3 H), 2.04 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 71.9, 70.6, 68.9, 57.8, 54.3, 44.4, 20.9, 20.7; HRMS (ESI$^+$) *m/z* Calculated for $C_8H_{17}NO_6NaS_2{}^{79}Br_2{}^+$ [M+Na]$^+$ 467.8762; Found 467.8789 (Δ +5.8 ppm).

N-(2-Hydroxyethyl)-1-(phenylselanyl)ethane-1-sulfonamide (11)



$NaBH_4$ (301 mg, 7.93 mmol) was added portionwise to a solution of Ph_2Se_2 (1.34 g, 3.96 mmol) in THF (3.0 mL) and DMF (1.7 mL) at 0 ºC, and the resulting solution was stirred for 10 min. The solution was then allowed to warm to rt for 2 h. A solution of bromoethylsulfonamide **S–3** (458 mg, 1.98 mmol) in THF (5.3 mL) was then added dropwise. The solution was then heated to 40 ºC for 15 h. H_2O and CH_2Cl_2 were added, and the phases were separated. The aqueous layer was further extracted with CH_2Cl_2, the combined organic layers were dried over Na_2SO_4, and the mixture was filtered. The solvent was removed under reduced pressure, and the resulting crude residue was purified by flash column chromatography (2% MeOH/CH_2Cl_2), which gave the seleno-sulfonamide **11** (196 mg, 32%) as a yellow oil. ν_{max} (film)/cm^{-1} 3289, 2910, 1432, 1320, 1125, 1065; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.69 (m, 2 H), 7.41–7.30 (m, 3 H), 5.22–5.15 (m, 1 H), 4.35 (q, *J* = 7.3, 1 H), 3.72–3.67 (m, 2 H), 3.33–3.23 (m, 1 H), 3.21–3.12 (m, 1 H), 1.80–1.75 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7 (2 × C), 129.3 (2 × C), 129.0, 127.1, 62.1, 58.0, 46.2, 17.4; HRMS (ESI$^+$) *m/z* Calculated for $C_{10}H_{15}NNaO_3S^{80}Se^+$ [M+Na]$^+$ 331.9830; Found 331.9828 (Δ +3.1 ppm).

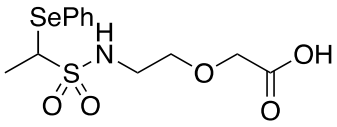
N-(2-(2-Hydroxyethoxy)ethyl)-1-(phenylselanyl)ethane-1-sulfonamide (12)



$NaBH_4$ (171 mg, 4.51 mmol) was added portionwise to a solution of Ph_2Se_2 (705 mg, 2.26 mmol) in THF (4.0 mL) and DMF (1.9 mL) at 0 ºC, then the solution was allowed to warm to rt for 30 min. A solution of

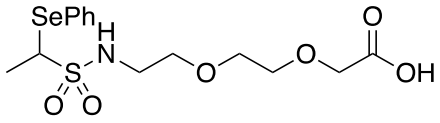
bromoethylsulfonamide **S–4** (310 mg, 1.13 mmol) in THF (5.4 mL) was then added dropwise. The solution was then heated to 40 ºC for 8 h. H_2O and CH_2Cl_2 were added, and the phases were separated. The aqueous layer was further extracted with CH_2Cl_2, the combined organic layers were dried over Na_2SO_4, and the mixture was filtered. The solvent was removed under reduced pressure, and the resulting crude residue was purified by flash column chromatography (2% MeOH/CH_2Cl_2), which gave the seleno-sulfonamide **12** (113 mg, 25%) as a yellow oil. ν_{max} (film)/cm^{-1} 3282, 2929, 1438, 1319, 1129, 1065; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.69 (m, 2 H), 7.41–7.30 (m, 3 H), 5.19 (br s, 1 H), 4.33 (q, *J* = 7.2 Hz, 1 H), 3.79–3.74 (m, 2 H), 3.61–3.56 (m, 4 H), 3.40–3.25 (m, 2 H), 2.01 (br s, 1 H), 1.79–1.74 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8 (2 × C), 129.3 (2 × C), 129.0, 127.1, 72.3, 70.3, 61.7, 58.1, 44.1, 17.4; HRMS (ESI$^+$) *m/z* Calculated for $C_{12}H_{19}NO_4NaS^{80}Se^+$ $[M+Na]^+$ 376.0098; Found 376.0121 (Δ +6.1 ppm).

2-(2-((1-(Phenylselanyl)ethyl)sulfonamido)ethoxy)acetic acid (13)



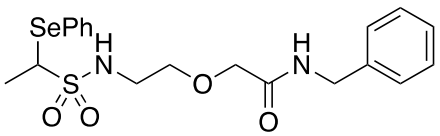
NaH (60% dispersion in mineral oil, 60 mg, 1.48 mmol) was added portionwise to a solution of alcohol **11** (114 mg, 0.37 mmol) in THF (4.5 mL) at 0˚C. After stirring at rt for 30 min, bromoacetic acid (56 mg, 0.41 mmol) was added and the reaction was heated to relux for 1 h. The reaction was treated with H_2O (2 mL) and then extracted with Et_2O (10 mL). The aqueous layer was acidified with 1 M HCl (2 mL) and then extracted with CH_2Cl_2 (3 × 15 mL). The combined CH_2Cl_2 layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure, which afforded carboxylic acid **13** (137 mg, 99%) as a yellow oil. ν_{max} (film)/cm^{-1} 3274, 2925, 1729, 1438, 1315, 1133; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (br s, 1 H), 7.73–7.68 (m, 2 H), 7.39–7.28 (m, 3 H), 5.59 (t, *J* = 5.8 Hz, 1 H), 4.35 (q, *J* = 7.2 Hz, 1 H), 4.14 (s, 2 H), 3.64 (t, *J* = 4.9 Hz, 2 H), 3.42–3.26 (m, 2 H), 1.78–1.73 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 135.7 (2 × C), 129.2 (2 × C), 128.9, 127.1, 71.1, 67.7, 58.1, 43.9, 17.4; HRMS (ESI$^+$) *m/z* Calculated for $C_{12}H_{17}NO_5NaS^{80}Se^+$ $[M+H]^+$ 389.9890; Found 389.9910 (Δ +5.1 ppm).

2-(2-(2-((1-(Phenylselanyl)ethyl)sulfonamido)ethoxy)ethoxy)acetic acid (14)



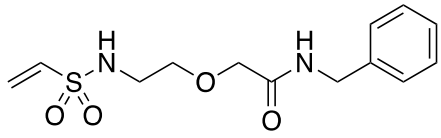
NaH (60% dispersion in mineral oil, 52 mg, 1.28 mmol) was added portionwise to a solution of alcohol **12** (110 mg, 0.32 mmol) in THF (3.9 mL) at 0˚C. After stirring at rt for 30 min, bromoacetic acid (48 mg, 0.35 mmol) was added and the reaction was heated to reflux for 1 h. The reaction was treated with H_2O (2 mL) and then extracted with Et_2O (10 mL). The aqueous layer was acidified with 1 M HCl (2 mL) and then extracted with CH_2Cl_2 (3 × 15 mL). The combined CH_2Cl_2 layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure, which afforded carboxylic acid **14** (120 mg, 95%) as a yellow oil. ν_{max} (film)/cm^{-1} 3282, 2924, 1734, 1438, 1319, 1121; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.68 (m, 2 H), 7.40–7.29 (m, 3 H), 7.18 (s, 1 H), 5.36–5.29 (m, 1 H), 4.32 (q, *J* = 7.3 Hz, 1 H), 4.18 (s, 2 H), 3.77–3.73 (m, 2 H), 3.69–3.65 (m, 2 H), 3.60 (t, *J* = 5.0 Hz, 2 H), 3.40–3.24 (m, 2 H), 1.75 (d, *J* = 7.3 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 135.8 (2 × C), 129.3 (2 × C), 129.2, 127.1, 71.2, 70.7, 70.2, 68.5, 58.1, 44.0, 17.4; HRMS (ESI$^+$) *m/z* Calculated for $C_{14}H_{21}NO_6NaS^{80}Se^+$ $[M+Na]^+$ 434.0152; Found 434.0156 (Δ +0.9 ppm).

N-Benzyl-2-(2-((1-(phenylselanyl)ethyl)sulfonamido)ethoxy)acetamide (S–6)



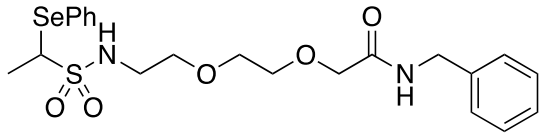
Prepared according to General Procedure D, using carboxylic acid **13** (32 mg, 87 μmol) and benzylamine (11 μL, 0.10 mmol), which afforded amide **S–6** (26 mg, 78%) as a yellow oil. R_f 0.30 (4% MeOH/CH_2Cl_2); ν_{max} (film)/cm^{-1} 3303, 2928, 1651, 1537, 1438, 1317, 1133; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.62 (m, 2 H), 7.38–7.22 (m, 8 H), 7.14–7.07 (m, 1 H), 5.22 (t, *J* = 6.0 Hz, 1 H), 4.47 (d, *J* = 6.1 Hz, 2 H), 4.25 (q, *J* = 7.3 Hz, 1 H), 3.99 (s, 2 H), 3.56–3.51 (m, 2 H), 3.36–3.28 (m, 1 H), 3.26–3.17 (m, 1 H), 1.71 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 138.1, 135.7 (2 × C), 129.4 (2 × C), 129.1, 128.7 (2 × C), 127.9 (2 × C), 127.5, 127.1, 70.8, 70.5, 58.2, 43.8, 42.8, 17.3; HRMS (ESI$^+$) *m/z* Calculated for $C_{19}H_{25}N_2O_4S^{80}Se^+$ $[M+H]^+$ 457.0700; Found 457.0706 (Δ +1.3 ppm).

N-Benzyl-2-(2-(vinylsulfonamido)ethoxy)acetamide (15a)



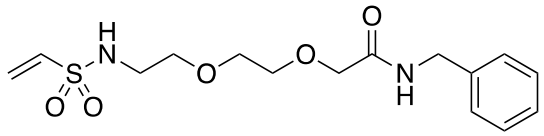
Prepared according to General Procedure C, using seleno-sulfonamide **S–6** (29 mg, 76 μmol). The crude material was pure following the aqueous work up, which gave vinyl sulfonamide **15a** (18 mg, 79%) as a colourless oil. ν_{max} (film)/cm^{-1} 3086, 2929, 2176, 1693, 1656, 1454, 1327, 1148; ^{1}H NMR (400 MHz, CD_3OD) δ 7.34–7.22 (m, 5 H), 6.63 (dd, *J* = 16.6, 10.0 Hz, 1 H), 6.12 (d, *J* = 16.6 Hz, 1 H), 5.92 (d, J = 10.0 Hz, 1 H), 4.44 (s, 2 H), 4.03 (s, 2 H), 3.61 (t, *J* = 5.2 Hz, 2 H), 3.17 (t, *J* = 5.2 Hz, 2 H); ^{13}C NMR (101 MHz, CD_3OD) δ 172.2, 139.8, 137.8, 129.6 (2 × C), 128.6 (2 × C), 128.3, 126.4, 71.6, 71.1, 43.6, 43.5; HRMS (ESI$^+$) *m/z* Calculated for $C_{13}H_{18}N_2O_4NaS^+$ [M+Na]$^+$ 321.0885; Found 321.0885 (Δ +0.6 ppm).

N-Benzyl-2-(2-(2-((1-(phenylselanyl)ethyl)sulfonamido)ethoxy)ethoxy)acetamide (S–7)



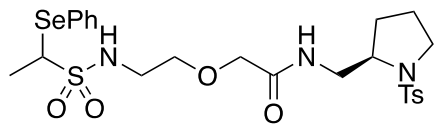
Prepared according to General Procedure D, using carboxylic acid **14** (19 mg, 46 μmol) and benzylamine (5 μL, 46 μmol), which afforded amide **S–7** (14 mg, 62%) as a yellow oil. ν_{max} (film)/cm^{-1} 3315, 2926, 1660, 1534, 1438, 1321, 1140; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.66 (m, 2 H), 7.40–7.27 (m, 8 H), 7.16–7.06 (m, 1 H), 4.85 (t, *J* = 5.9 Hz, 1 H), 4.50 (d, *J* = 6.0 Hz, 2 H), 4.25 (q, *J* = 7.2 Hz, 1 H), 4.07 (s, 2 H), 3.71–3.66 (m, 2 H), 3.63–3.59 (m, 2 H), 3.49 (t, *J* = 5.1 Hz, 2 H), 3.28–3.11 (m, 2 H), 1.72 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 138.2, 135.8 (2 × C), 129.3 (2 × C), 129.0, 128.7 (2 × C), 127.8 (2 × C), 127.5, 127.0, 70.9, 70.7, 70.6, 70.2, 58.1, 44.0, 42.8, 17.4; HRMS (ESI$^+$) *m/z* Calculated for $C_{21}H_{28}N_2O_5NaS^{80}Se^+$ [M+Na]$^+$ 523.0782; Found 523.0779 (Δ -0.6 ppm).

N-Benzyl-2-(2-(2-(vinylsulfonamido)ethoxy)ethoxy)acetamide (16a)



Prepared according to General Procedure C, using seleno-sulfonamide **S–7** (14 mg, 28 μmol). The crude material was pure following the aqueous work up, which gave vinyl sulfonamide **16a** (8 mg, 84%) as a colourless oil. ν_{max} (film)/cm^{-1} 3308, 2931, 1659, 1536, 1328, 1149; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5 H), 7.08 (br s, 1 H), 6.47 (dd, *J* = 16.6, 9.9 Hz, 1 H), 6.22 (d, *J* = 16.6 Hz, 1 H), 5.91 (d, *J* = 9.9 Hz, 1 H), 4.72–4.65 (m, 1 H), 4.52 (d, *J* = 5.9 Hz, 2 H), 4.07 (s, 2 H), 3.72–3.66 (m, 2 H), 3.64–3.58 (m, 2 H), 3.53 (t, *J* = 5.1 Hz, 2 H), 3.08 (q, *J* = 5.4 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 138.1, 135.9, 128.7 (2 × C), 127.8 (2 × C), 127.6, 126.5, 70.9, 70.6, 70.2, 69.9, 42.8, 42.6; HRMS (ESI$^+$) *m/z* Calculated for $C_{15}H_{23}N_2O_5S^+$ [M+H]$^+$ 343.1328; Found 343.1322 (Δ -1.7 ppm).

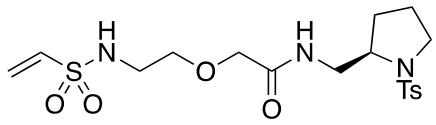
2-(2-((1-(Phenylselanyl)ethyl)sulfonamido)ethoxy)-*N*-(((*R*)-1-tosylpyrrolidin-2-yl)methyl)acetamide (S–8)



Prepared according to General Procedure D, using carboxylic acid **13** (33 mg, 88 μmol) and (*R*)-[1-(toluene-4-sulfonyl)-pyrrolidin-2-yl]-methylamine (27 mg, 0.11 mmol), which afforded amide **S–8** (38 mg, 71%) as a white solid. m.p. = 45 ºC ($CHCl_3$); $[\alpha]_D^{21}$ +0.52 (*c* 0.05, $CHCl_3$); ν_{max} (film)/cm^{-1} 3349, 2924, 2340, 1665, 1537, 1439, 1320, 1157; ^{1}H NMR (400 MHz, CD_3OD) δ 7.78–7.73 (m, 2 H), 7.73–7.68 (m, 2 H), 7.43–7.37 (m, 2 H), 7.37–7.27 (m, 3 H), 4.54–4.46 (m, 1 H), 3.98 (s, 2 H), 3.89–3.80 (m, 1 H), 3.61 (t, *J* = 5.1 Hz, 2 H), 3.44–3.16 (m, 6 H), 2.42 (s, 3 H), 1.86–1.75 (m, 1 H), 1.73–1.67 (m, 3 H), 1.68–1.58 (m, 1 H), 1.53–1.42 (m, 2 H); ^{13}C NMR (101 MHz, CD_3OD) δ 172.7, 145.4, 136.7 (2 × C), 135.3, 131.0 (2 × C), 130.2 (2 × C), 129.8, 128.84 (2 × C), 128.79, 72.30 (0.5 × C), 72.27 (0.5 × C), 71.1, 60.4, 58.6 (0.5 × C), 58.5 (0.5 × C), 50.4, 44.5, 44.3, 30.1, 24.8, 21.5, 18.0; HRMS (ESI$^+$) *m/z* Calculated for $C_{24}H_{33}N_3O_6NaS_2{}^{80}Se^+$ [M+H]$^+$ 626.0874; Found 626.0892 (Δ +2.9 ppm).

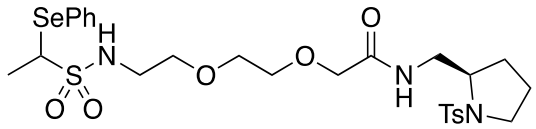
The compound appeared as a mixture of diastereoisomers in the NMR spectra.

(*R*)-*N*-((1-Tosylpyrrolidin-2-yl)methyl)-2-(2-(vinylsulfonamido)ethoxy)acetamide (15b)



Prepared according to General Procedure C, using seleno-sulfonamide **S–8** (38 mg, 63 μmol). The crude material was pure following the aqueous work up, which gave vinyl sulfonamide **15b** (24 mg, 78%) as a colourless oil. $[\alpha]_D^{21}$ +0.54 (*c* 0.04, $CHCl_3$); ν_{max} (film)/cm^{-1} 3292, 2924, 1654, 1542, 1328, 1154; ^{1}H NMR (400 MHz, CD_3OD) δ 7.76 (d, *J* = 8.3 Hz, 2 H), 7.42 (d, *J* = 8.0 Hz, 2 H), 6.68 (dd, *J* = 16.5, 10.0 Hz, 1 H), 6.15 (d, *J* = 16.5 Hz, 1 H), 5.96 (d, *J* = 10.0 Hz, 1 H), 4.01 (s, 2 H), 3.90–3.82 (m, 1 H), 3.65 (t, *J* = 5.2 Hz, 2 H), 3.45–3.35 (m, 3 H), 3.25–3.17 (m, 3 H), 2.44 (s, 3 H), 1.88–1.76 (m, 1 H), 1.68–1.59 (m, 1 H), 1.55–1.43 (m, 2 H); ^{13}C NMR (101 MHz, CD_3OD) δ 172.8, 145.4, 137.8, 135.4, 131.0 (2 × C), 128.9 (2 × C), 126.5, 71.6, 71.1, 60.4, 50.4, 44.3, 43.7, 30.0, 24.8, 21.5; HRMS (ESI$^+$) *m/z* Calculated for $C_{18}H_{28}N_3O_6S_2^+$ $[M+H]^+$ 446.1420; Found 446.1419 (Δ -0.2 ppm).

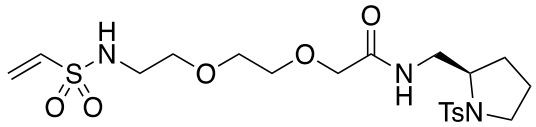
2-(2-(2-((1-(Phenylselanyl)ethyl)sulfonamido)ethoxy)ethoxy)-*N*-(((*R*)-1-tosylpyrrolidin-2-yl)methyl)acetamide (S–9)



Prepared according to General Procedure D, using carboxylic acid **14** (21 mg, 53 μmol) and (*R*)-[1-(toluene-4-sulfonyl)-pyrrolidin-2-yl]-methylamine (14 mg, 56 μmol), which afforded amide **S–9** (14 mg, 47%) as a white solid. $[\alpha]_D^{21}$ +0.22 (*c* 0.02, $CHCl_3$); ν_{max} (film)/cm^{-1} 3345, 2926, 2360, 1666, 1533, 1439, 1326, 1158; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.69 (m, 4 H), 7.62–7.55 (m, 1 H), 7.38–7.28 (m, 5 H), 5.37 (q, *J* = 5.6 Hz, 1 H), 4.34 (qd, *J* = 7.3, 1.1 Hz, 1 H), 4.07–4.03 (m, 2 H), 3.85–3.77 (m, 1 H), 3.76–3.67 (m, 4 H), 3.66–3.61 (m, 2 H), 3.57–3.50 (m, 1 H), 3.47–3.30 (m, 4 H), 3.24–3.16 (m, 1 H), 2.44 (s, 3 H), 1.84–1.70 (m, 4 H), 1.66–1.53 (m, 2 H), 1.50–1.40 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 143.9, 135.8 (2 × C), 133.8, 129.8 (2 × C), 129.2 (2 × C), 128.8, 127.6 (2 × C), 127.1, 71.2, 70.7, 70.6, 70.2, 59.6, 57.9 (0.5 × C), 57.8 (0.5 × C), 49.4, 44.0, 43.2, 29.5, 24.1, 21.5, 17.5; HRMS (ESI$^+$) *m/z* Calculated for $C_{26}H_{38}N_3O_7S_2{}^{80}Se^+$ $[M+H]^+$ 648.1316; Found 648.1286 (Δ -4.6 ppm).

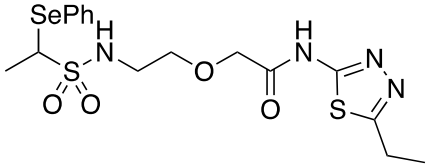
The compound appeared as a mixture of diastereoisomers in the NMR spectra.

(*R*)-*N*-((1-Tosylpyrrolidin-2-yl)methyl)-2-(2-(2-(vinylsulfonamido)ethoxy)ethoxy)acetamide (16b)



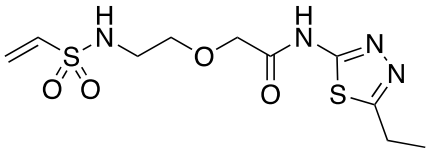
Prepared according to General Procedure C, using seleno-sulfonamide **S–9** (19 mg, 33 μmol). The crude material was pure following the aqueous work up, which gave vinyl sulfonamide **16b** (15 mg, 92%) as a colourless oil. $[\alpha]_D^{21}$ +0.26 (*c* 0.025, $CHCl_3$); ν_{max} (film)/cm^{-1} 2932, 2510, 1659, 1461, 1331, 1158; ^{1}H NMR (400 MHz, CD_3OD) δ 7.81–7.76 (m, 2 H), 7.47–7.42 (m, 2 H), 6.70 (dd, *J* = 16.6, 10.0 Hz, 1 H), 6.16 (d, *J* = 16.6 Hz, 1 H), 5.96 (d, *J* = 10.0 Hz, 1 H), 4.05 (s, 2 H), 3.91–3.84 (m, 1 H), 3.77–3.71 (m, 2 H), 3.72–3.68 (m, 2 H), 3.64 (t, *J* = 5.5 Hz, 2 H), 3.48–3.40 (m, 3 H), 3.27–3.21 (m, 1 H), 3.19 (t, *J* = 5.5 Hz, 2 H), 2.46 (s, 3 H), 1.89–1.78 (m, 1 H), 1.69–1.61 (m, 1 H), 1.55–1.45 (m, 2 H); ^{13}C NMR (101 MHz, CD_3OD) δ 173.2, 145.4, 137.9, 135.4, 131.0 (2 × C), 128.9 (2 × C), 126.2, 72.1, 71.3, 71.23, 71.17, 60.5, 50.5, 44.2, 43.8, 30.0, 24.8, 21.5; HRMS (ESI$^+$) *m/z* Calculated for $C_{20}H_{31}N_3O_7NaS_2^+$ $[M+Na]^+$ 512.1501; Found 512.1503 (Δ +0.4 ppm).

N-(5-Ethyl-1,3,4-thiadiazol-2-yl)-2-(2-((1-(phenylselanyl)ethyl)sulfonamido)ethoxy)acetamide (S–10)



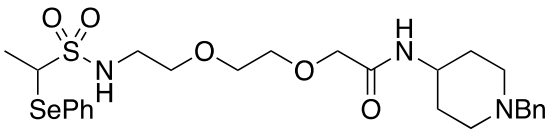
Prepared according to General Procedure D, using carboxylic acid **13** (32 mg, 86 μmol) and 5-ethyl-1,3,4-thiadiazol-2-amine (14 mg, 0.10 mmol), which afforded amide **S–10** (19 mg, 55%) as a yellow oil. ν_{max} (film)/cm^{-1} 3280, 2931, 1701, 1530, 1438, 1307, 1137; ^{1}H NMR (400 MHz, CD_3OD) δ 7.73–7.67 (m, 2 H), 7.37–7.26 (m, 3 H), 4.55 (q, *J* = 7.2 Hz, 1 H), 4.26 (s, 2 H), 3.64 (t, *J* = 5.1 Hz, 2 H), 3.40–3.25 (m, 2 H), 3.05 (q, *J* = 7.6 Hz, 2 H), 1.71 (d, *J* = 7.2 Hz, 3 H), 1.39 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (101 MHz, CD_3OD) δ 170.3, 169.2, 136.7 (2 × C), 130.2 (2 × C), 129.8, 128.9, 72.5, 70.7, 58.6, 44.4, 24.1, 18.0, 14.4 (1 × C_{Ar} quat. signal missing); HRMS (ESI$^+$) *m/z* Calculated for $C_{16}H_{23}N_4O_4S_2{}^{80}Se^+$ $[M+H]^+$ 479.0326; Found 479.0334 (Δ +1.7 ppm).

N-(5-Ethyl-1,3,4-thiadiazol-2-yl)-2-(2-(vinylsulfonamido)ethoxy)acetamide (15c)



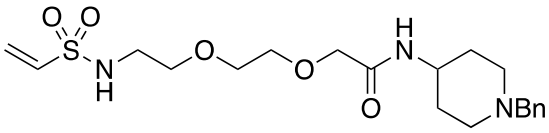
Prepared according to General Procedure C, using seleno-sulfonamide **S–10** (19 mg, 39 μmol). The crude material was pure following the aqueous work up, which gave vinyl sulfonamide **15c** (19 mg, 72%) as a white solid. m.p. = 79–82 ºC (CH_2Cl_2); ν_{max} (film)/cm^{-1} 3263, 2937, 1698, 1530, 1432, 1325, 1143, 1095; ^{1}H NMR (400 MHz, CD_3OD) δ 6.72 (dd, *J* = 16.6, 10.0 Hz, 1 H), 6.19 (d, *J* = 16.6 Hz, 1 H), 5.98 (d, *J* = 10.0 Hz, 1 H), 4.32 (s, 2 H), 3.72 (t, *J* = 5.2 Hz, 2 H), 3.25 (t, *J* = 5.2 Hz, 2 H), 3.08 (q, *J* = 7.6 Hz, 2 H), 1.41 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (101 MHz, CD_3OD) δ 170.5, 169.1, 159.8, 137.9, 126.4, 71.8, 70.8, 43.6, 24.1, 14.4; HRMS (ESI$^+$) *m/z* Calculated for $C_{10}H_{17}N_4O_4S_2^+$ $[M+H]^+$ 321.0691; Found 321.0688 (Δ -0.9 ppm).

N-(1-Benzylpiperidin-4-yl)-2-(2-(2-((1-(phenylselanyl)ethyl)sulfonamido)ethoxy)ethoxy)acetamide (S–11)



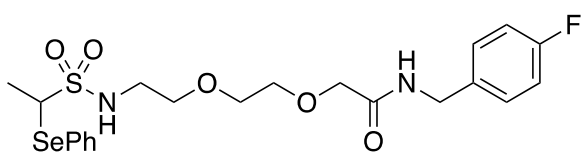
Prepared according to General Procedure E, using carboxylic acid **14** (20 mg, 49 μmol). The crude material was purified by reversed-phase flash column chromatography (H_2O grading to MeOH, with 0.1% v/v HCO_2H additive), which gave the amide **S–11** (19 mg, 65%) as a colourless oil. R_f 0.50 (10% MeOH/CH_2Cl_2); ν_{max} (film)/cm^{-1} 1663, 1539, 1439, 1318, 1143, 839, 734, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (br s, 0.5 H), 7.73–7.66 (m, 2 H), 7.46–7.28 (m, 8.5 H), 6.11 (br s, 1 H), 4.38 (q, *J* = 7.1 Hz, 1 H), 4.19 (s, 2 H), 4.10–3.98 (m, 1 H), 3.95 (s, 2 H), 3.68–3.48 (m, 8 H), 3.39–3.22 (m, 2 H), 2.89 (t, *J* = 11.5 Hz, 2 H), 2.16–1.94 (m, 4 H), 1.74 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 135.6, 130.9, 129.9, 129.4, 129.3, 129.2, 128.9, 127.2, 70.9, 70.3, 70.1, 69.5, 61.1, 58.0, 51.5, 43.7, 43.5, 29.1, 17.5; HRMS (ESI$^+$) *m/z* Calculated for $C_{26}H_{38}N_3O_5S^{80}Se^+$ $[M+H]^+$ 584.1697; Found 584.1702 (Δ +0.9 ppm).

N-(1-Benzylpiperidin-4-yl)-2-(2-(2-(vinylsulfonamido)ethoxy)ethoxy)acetamide (16d)



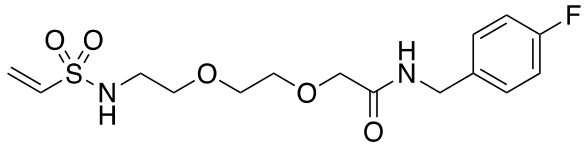
Prepared according to General Procedure C, using seleno-sulfonamide **S–11** (18 mg, 31 μmol) and $NaIO_4$ (13 mg, 62 μmol) in EtOH (0.31 mL). The crude material was impure following the aqueous work up and was subjected to reversed-phase flash column chromatography (H_2O grading to MeOH, with 0.1% v/v HCO_2H additive), which gave the vinyl sulfonamide **16d** (5 mg, 38%) as a colourless oil. ν_{max} (film)/cm^{-1} 2929, 1666, 1535, 1453, 1327, 1148, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5 H), 6.88–6.82 (m, 1 H), 6.56 (dd, *J* = 16.6, 9.9 Hz, 1 H), 6.23 (d, *J* = 16.6 Hz, 1 H), 5.91 (d, *J* = 9.9 Hz, 1 H), 3.98–3.86 (m, 3 H), 3.70–3.61 (m, 8 H), 3.22 (t, *J* = 5.0 Hz, 2 H), 3.08–2.99 (m, 2 H), 2.32–2.21 (m, 2 H), 1.99–1.90 (m, 2 H), 1.76–1.65 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) □ 169.3, 136.1, 129.8, 128.8, 128.5, 126.3, 122.8, 70.9, 70.4, 70.0, 62.3, 51.9, 42.4, 31.3, 29.7, 28.9; HRMS (ESI$^+$) *m/z* Calculated for $C_{20}H_{32}N_3O_5S^+$ $[M+H]^+$ 426.2063; Found 426.2077 (Δ +3.3 ppm).

N-(4-Fluorobenzyl)-2-(2-(2-((1-(phenylselanyl)ethyl)sulfonamido)ethoxy)ethoxy)acetamide (S–12)



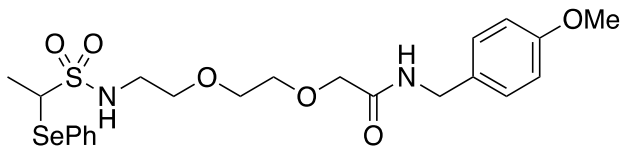
Prepared according to General Procedure E, using carboxylic acid **14** (22 mg, 54 μmol). The crude material was purified by flash column chromatography (CH_2Cl_2 grading to 10% MeOH/CH_2Cl_2) followed by reversed-phase flash column chromatography (H_2O grading to MeOH, with 0.1% v/v HCO_2H additive), which gave the amide **S–12** (17 mg, 60%) as a colourless oil. R_f 0.36 (5% MeOH/CH_2Cl_2); ν_{max} (film)/cm^{-1} 3300, 2931, 1663, 1542, 1514, 1442, 1320, 1220, 1143, 1123, 744, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.66 (m, 2 H), 7.40–7.25 (m, 5 H), 7.17–7.08 (m, 1 H), 7.05–6.96 (m, 2 H), 4.97–4.90 (m, 1 H), 4.46 (d, *J* = 6.1 Hz, 2 H), 4.27 (q, *J* = 7.3 Hz, 1 H), 4.06 (s, 2 H), 3.70–3.65 (m, 2 H), 3.64–3.59 (m, 2 H), 3.54–3.47 (m, 2 H), 3.32–3.14 (m, 2 H), 1.76–1.69 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 162.2 (d, *J* = 245 Hz), 135.8 (2 × C), 134.1 (d, *J* = 2.9 Hz), 129.5 (d, *J* = 8.0 Hz, 2 × C), 129.3 (2 × C), 129.0, 127.0, 115.5 (d, *J* = 22 Hz, 2 × C), 70.9, 70.7, 70.6, 70.2, 58.2, 44.0, 42.1, 17.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.0; HRMS (ESI$^+$) *m/z* Calculated for $C_{21}H_{28}N_2O_5S^{80}SeF^+$ $[M+H]^+$ 519.0868; Found 519.0851 (Δ -3.3 ppm).

N-(4-Fluorobenzyl)-2-(2-(2-(vinylsulfonamido)ethoxy)ethoxy)acetamide (16e)



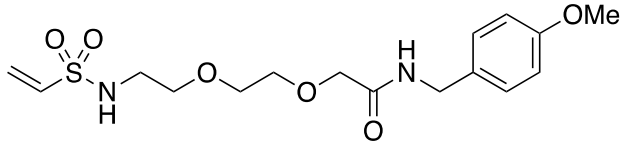
Prepared according to General Procedure C, using seleno-sulfonamide **S–12** (16 mg, 31 μmol) and $NaIO_4$ (13 mg, 62 μmol) in EtOH (0.31 mL). The crude material was pure following the aqueous work up, which gave the vinyl sulfonamide **16e** (9.1 mg, 81%) as a colourless oil. ν_{max} (film)/cm^{-1} 3287, 2902, 1662, 1537, 1511, 1435, 1327, 1221, 1138, 967, 834; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2 H), 7.12–7.06 (m, 1 H), 7.06–6.98 (m, 2 H), 6.49 (dd, *J* = 16.6, 9.9 Hz, 1 H), 6.23 (d, *J* = 16.6 Hz, 1 H), 5.93 (d, *J* = 9.9 Hz, 1 H), 4.86–4.77 (m, 1 H), 4.47 (d, *J* = 6.1 Hz, 2 H), 4.06 (s, 2 H), 3.71–3.66 (m, 2 H), 3.64–3.60 (m, 2 H), 3.58–3.53 (m, 2 H), 3.14–3.09 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 162.2 (d, *J* = 245 Hz), 135.9, 134.0 (d, *J* = 2.4 Hz), 129.6 (d, *J* = 7.9 Hz, 2 × C), 126.6, 115.5 (d, *J* = 21 Hz, 2 × C), 70.9, 70.7, 70.2, 69.9, 42.6, 42.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.9; HRMS (ESI$^+$) *m/z* Calculated for $C_{15}H_{22}N_2O_5SF^+$ $[M+H]^+$ 361.1233; Found 361.1233 (Δ 0.0 ppm).

N-(4-Methoxybenzyl)-2-(2-(2-((1-(phenylselanyl)ethyl)sulfonamido)ethoxy)ethoxy)acetamide (S–13)



Prepared according to General Procedure E, using carboxylic acid **14** (21 mg, 50 μmol). The crude material was purified by reversed-phase flash column chromatography (H_2O grading to MeOH, with 0.1% v/v HCO_2H additive), which gave the amide **S–13** (16 mg, 62%) as a colourless oil. ν_{max} (film)/cm^{-1} 3291, 2926, 1654, 1533, 1513, 1438, 1319, 1247, 1139, 1114, 1033, 743, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.67 (m, 2 H), 7.40–7.28 (m, 3 H), 7.26–7.20 (m, 2 H), 7.09–7.01 (m, 1 H), 6.89–6.83 (m, 2 H), 4.88 (t, *J* = 6.1 Hz, 1 H), 4.43 (d, *J* = 5.9 Hz, 2 H), 4.26 (q, *J* = 7.2 Hz, 1 H), 4.05 (s, 2 H), 3.79 (s, 3 H), 3.69–3.64 (m, 2 H), 3.62 (m, 2 H), 3.51–3.46 (m, 2 H), 3.28–3.11 (m, 2 H), 1.76–1.70 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 159.0, 135.8 (2 × C), 130.2, 129.3 (2 × C), 129.2 (2 × C), 129.0, 127.0, 114.1 (2 × C), 70.9, 70.7, 70.6, 70.1, 58.1, 55.3, 44.0, 42.3, 17.4; HRMS (ESI$^-$) *m/z* Calculated for $C_{22}H_{29}N_2O_6S^{80}Se^-$ $[M-H]^-$ 529.0912; Found 529.0916 (Δ +0.8 ppm).

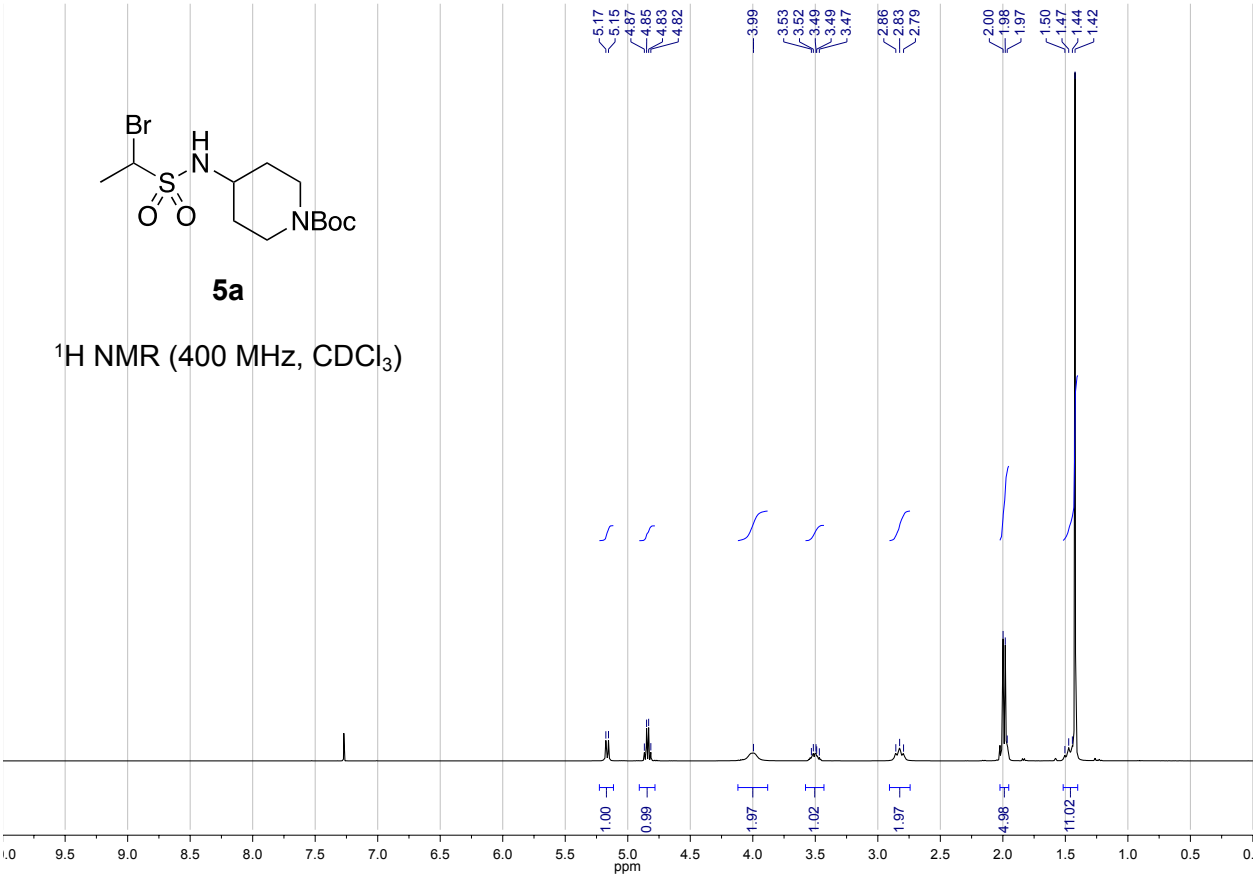
N-(4-Methoxybenzyl)-2-(2-(2-(vinylsulfonamido)ethoxy)ethoxy)acetamide (16f)



Prepared according to General Procedure C, using seleno-sulfonamide **S–13** (16 mg, 30 μmol) and $NaIO_4$ (13

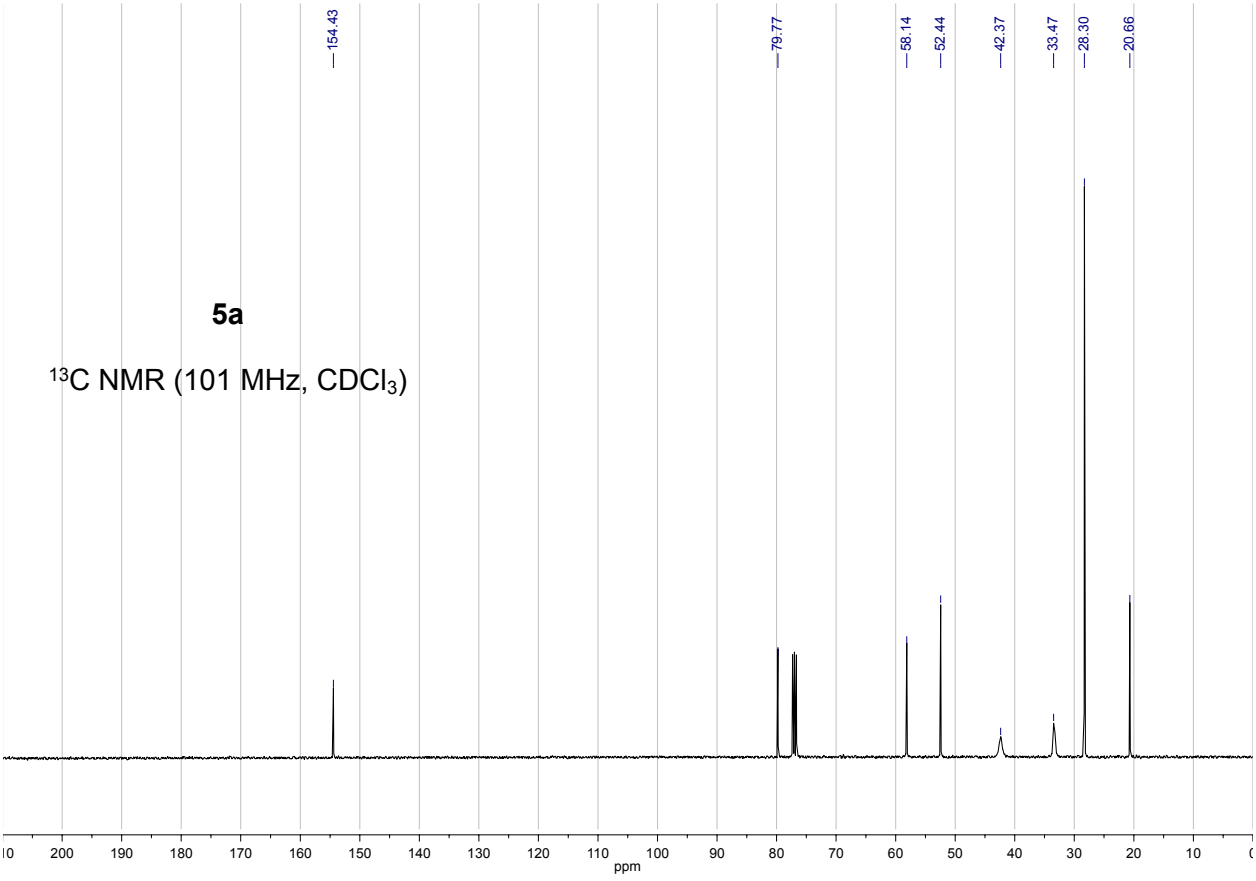
mg, 60 μmol) in EtOH (0.30 mL). The crude material was pure following the aqueous work up, which gave the vinyl sulfonamide **16f** (9.3 mg, 83%) as a colourless oil. ν_{max} (film)/cm^{-1} 3286, 2906, 1658, 1513, 1445, 1325, 1246, 1146, 1109, 1030, 965, 812, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.23 (m, 2 H), 7.07–6.99 (m, 1 H), 6.92–6.87 (m, 2 H), 6.50 (dd, *J* = 16.6, 9.9 Hz, 1 H), 6.23 (d, *J* = 16.6 Hz, 1 H), 5.93 (d, *J* = 9.9 Hz, 1 H), 4.76–4.68 (m, 1 H), 4.45 (d, *J* = 5.8 Hz, 2 H), 4.06 (s, 2 H), 3.82 (s, 3 H), 3.71–3.66 (m, 2 H), 3.64–3.60 (m, 2 H), 3.57–3.51 (m, 2 H), 3.12–3.06 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 159.1, 136.0, 130.2, 129.2 (2 × C), 126.5, 114.1 (2 × C), 70.9, 70.7, 70.2, 70.0, 55.3, 42.6, 42.4; HRMS (ESI^{+}) ***m/z*** Calculated for $C_{16}H_{25}N_2O_6S^{+}$ $[M+H]^{+}$ 373.1433; Found 373.1440 (Δ +1.9 ppm).

3. ^{1}H and ^{13}C NMR Spectra of Selected Compounds



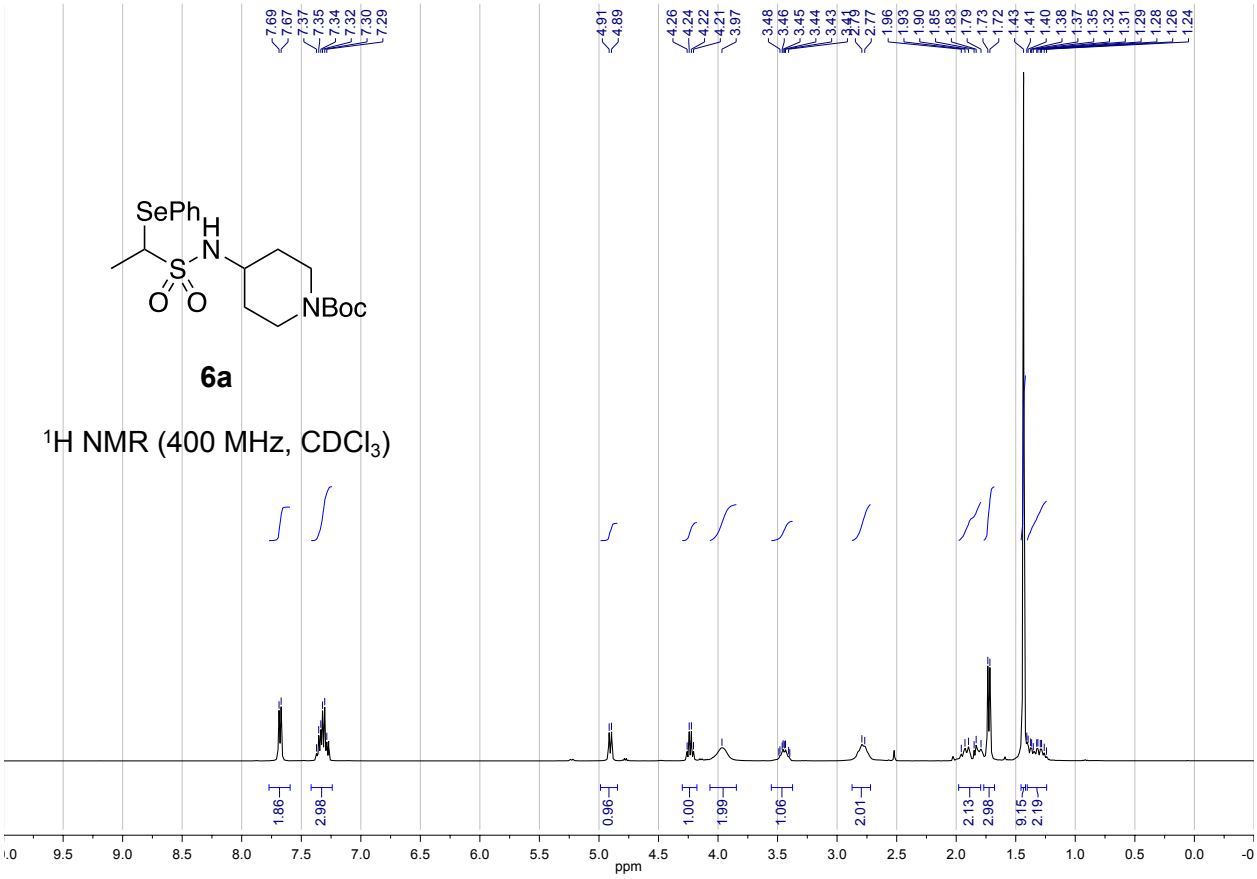
5a

^{1}H NMR (400 MHz, $CDCl_3$)



5a

^{13}C NMR (101 MHz, $CDCl_3$)

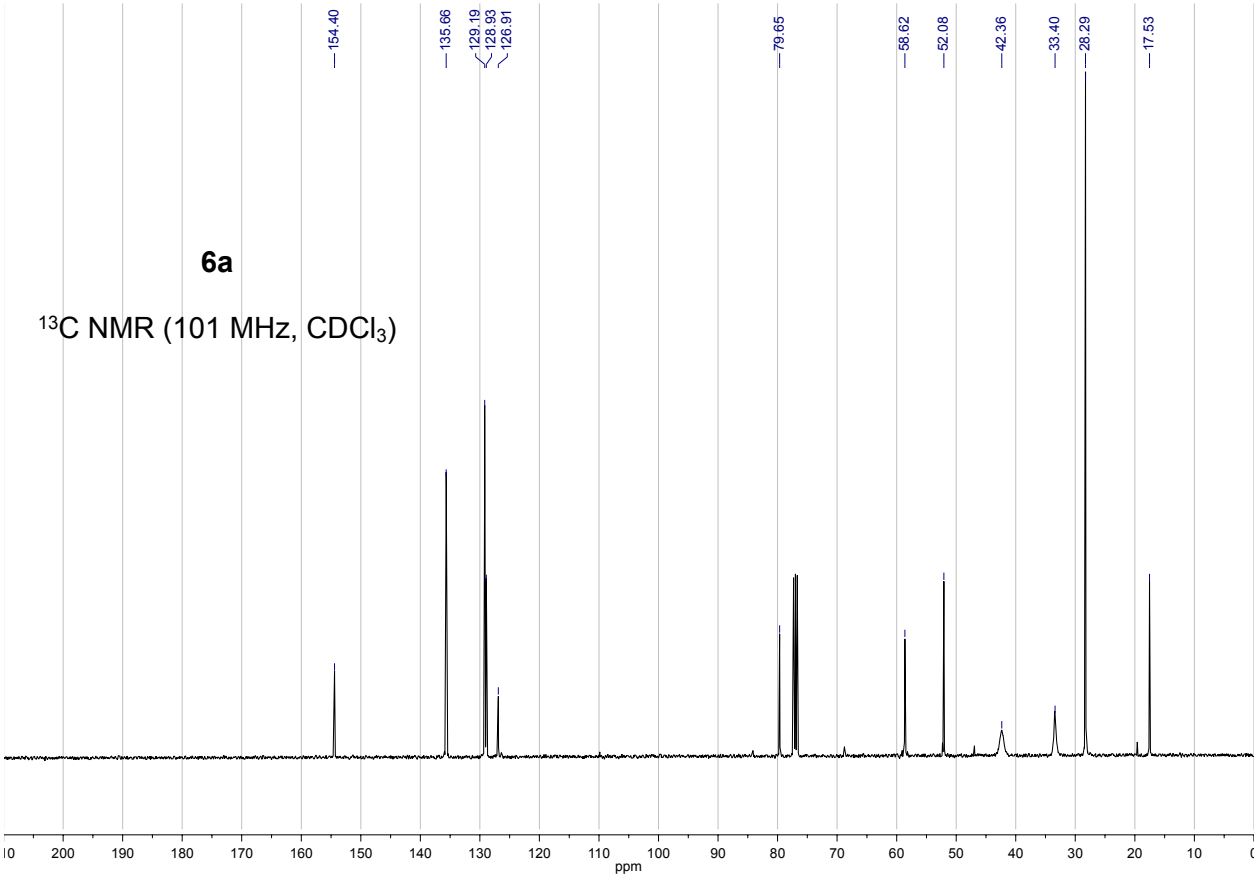


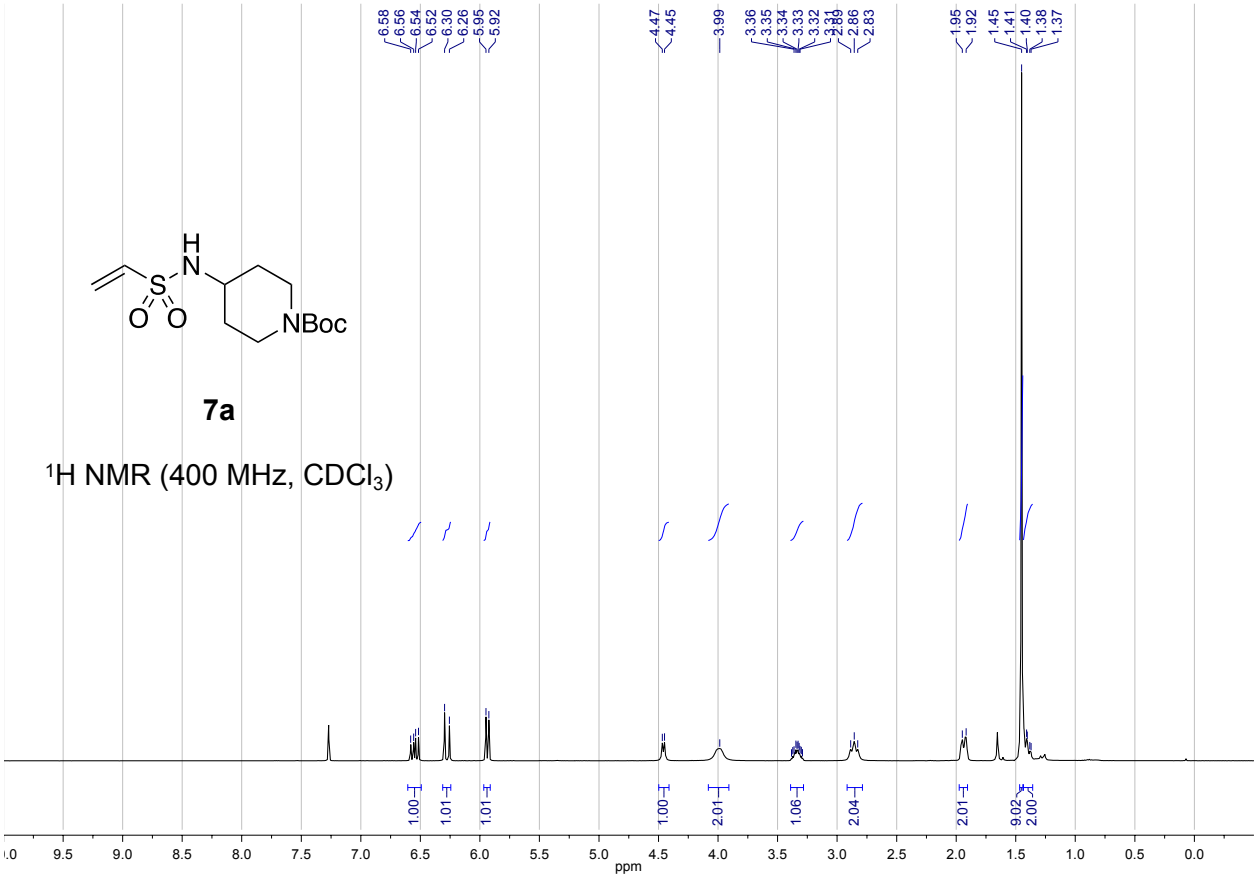
6a

^{1}H NMR (400 MHz, $CDCl_3$)

6a

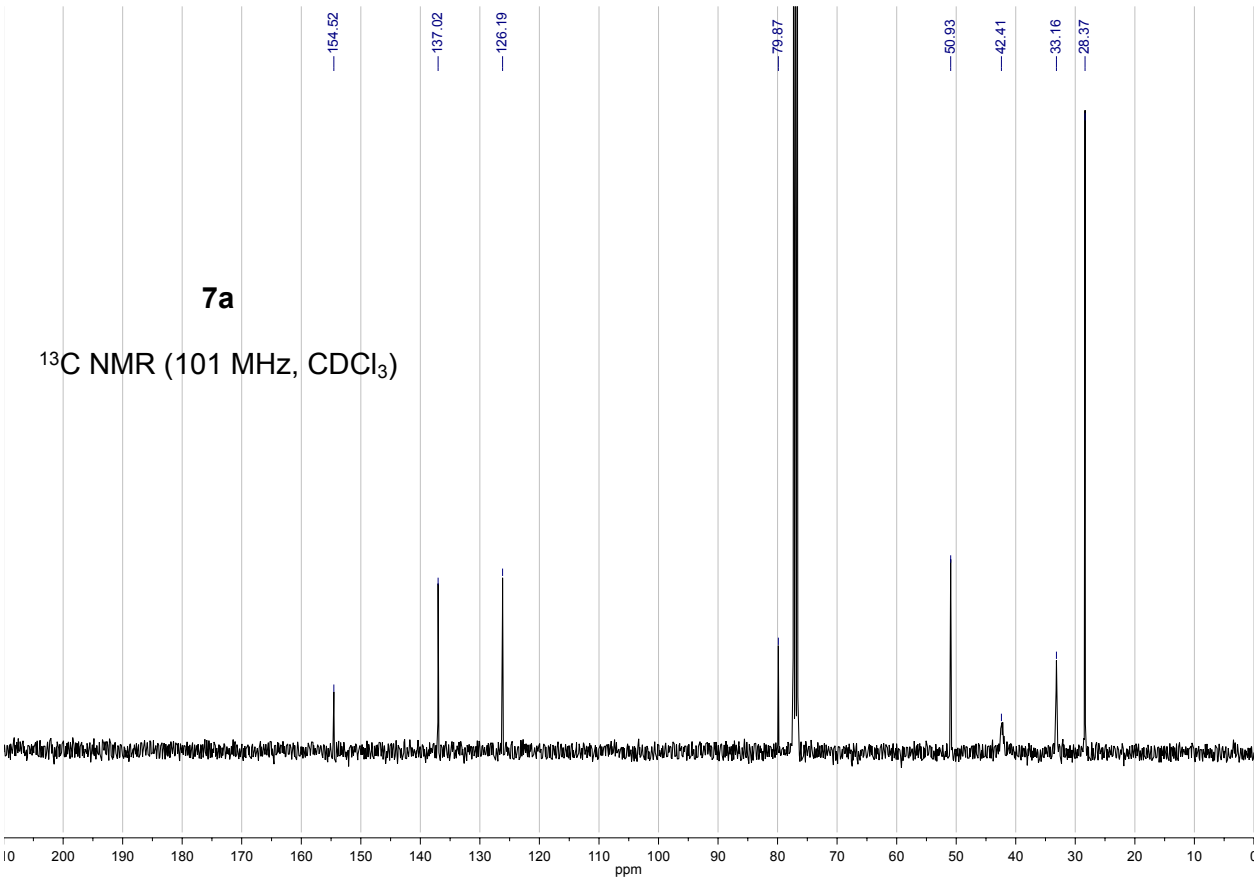
^{13}C NMR (101 MHz, $CDCl_3$)





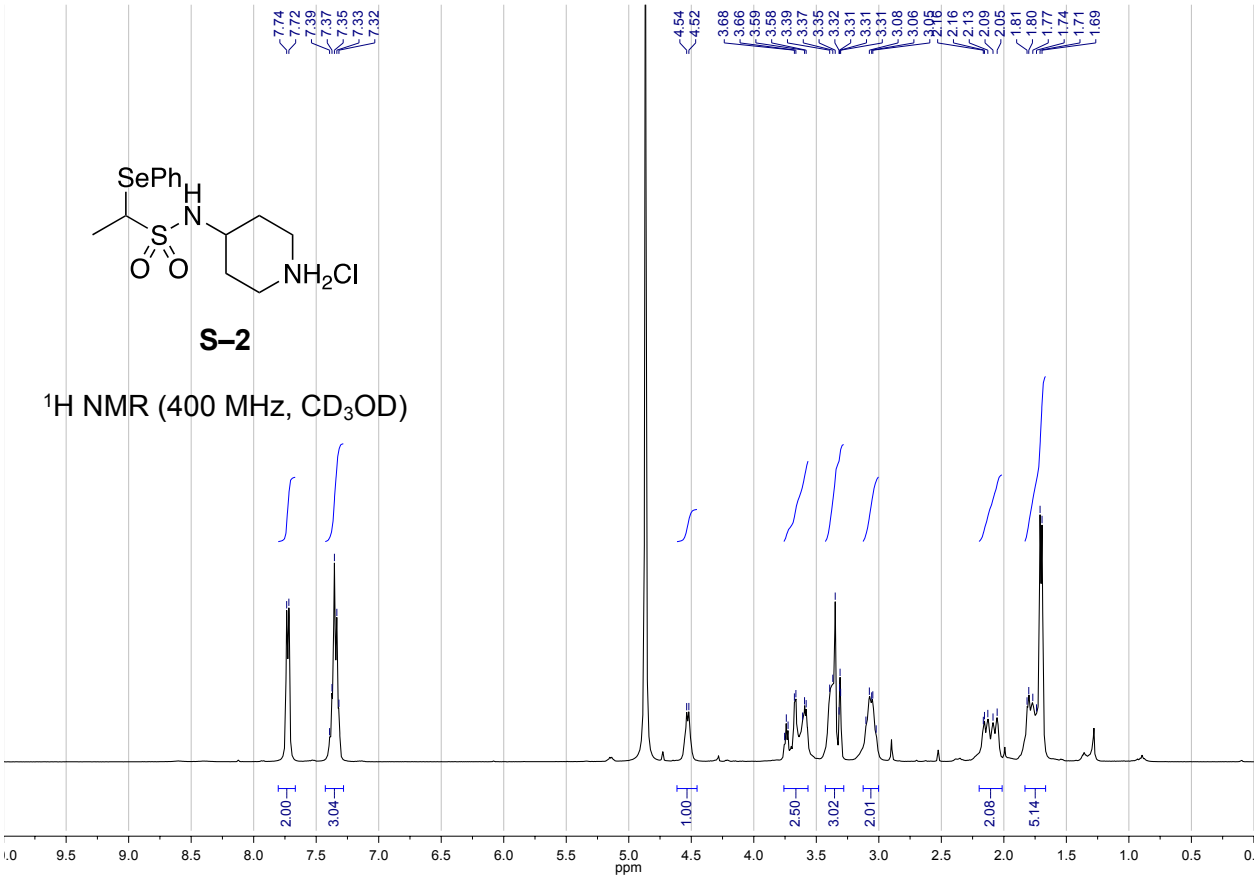
7a

^{1}H NMR (400 MHz, $CDCl_3$)



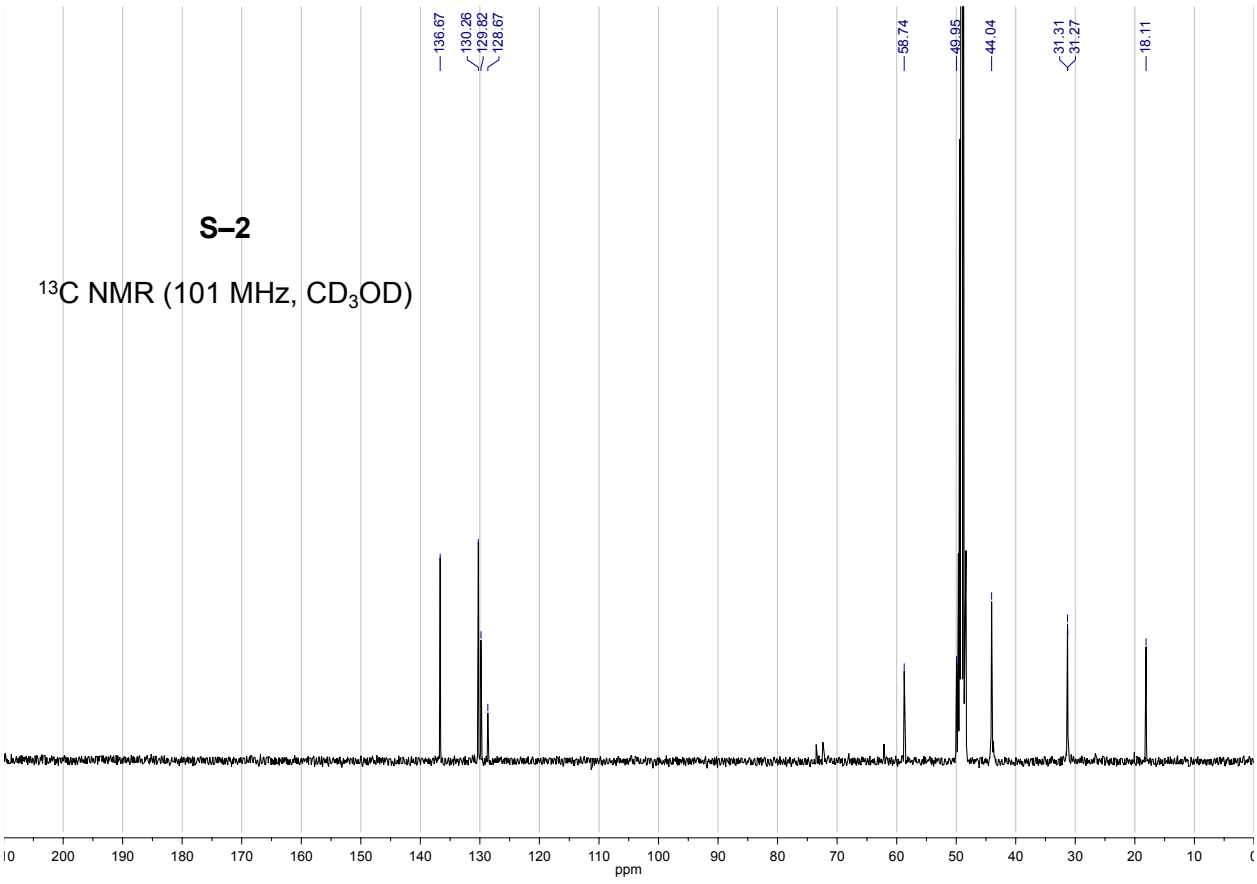
7a

^{13}C NMR (101 MHz, $CDCl_3$)



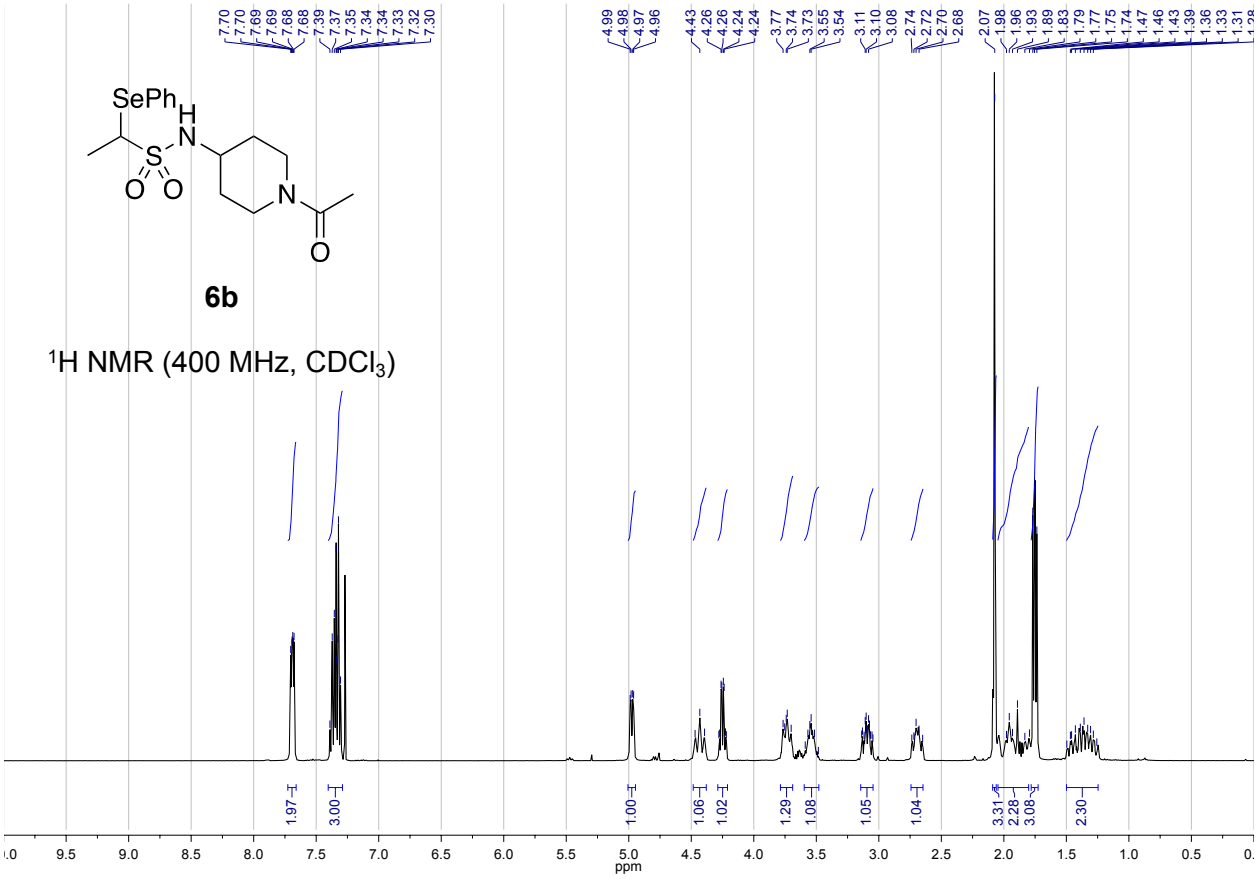
S–2

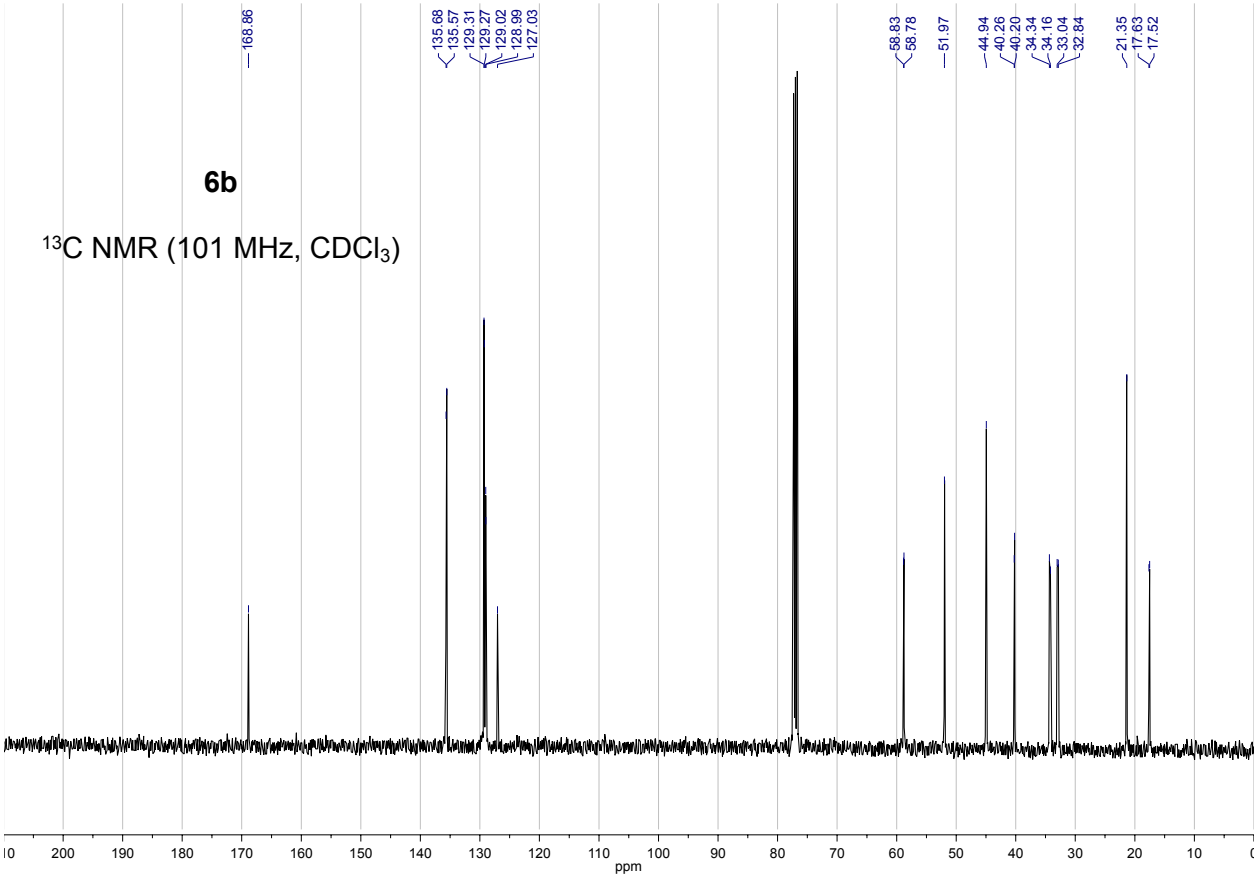
^{1}H NMR (400 MHz, CD_3OD)

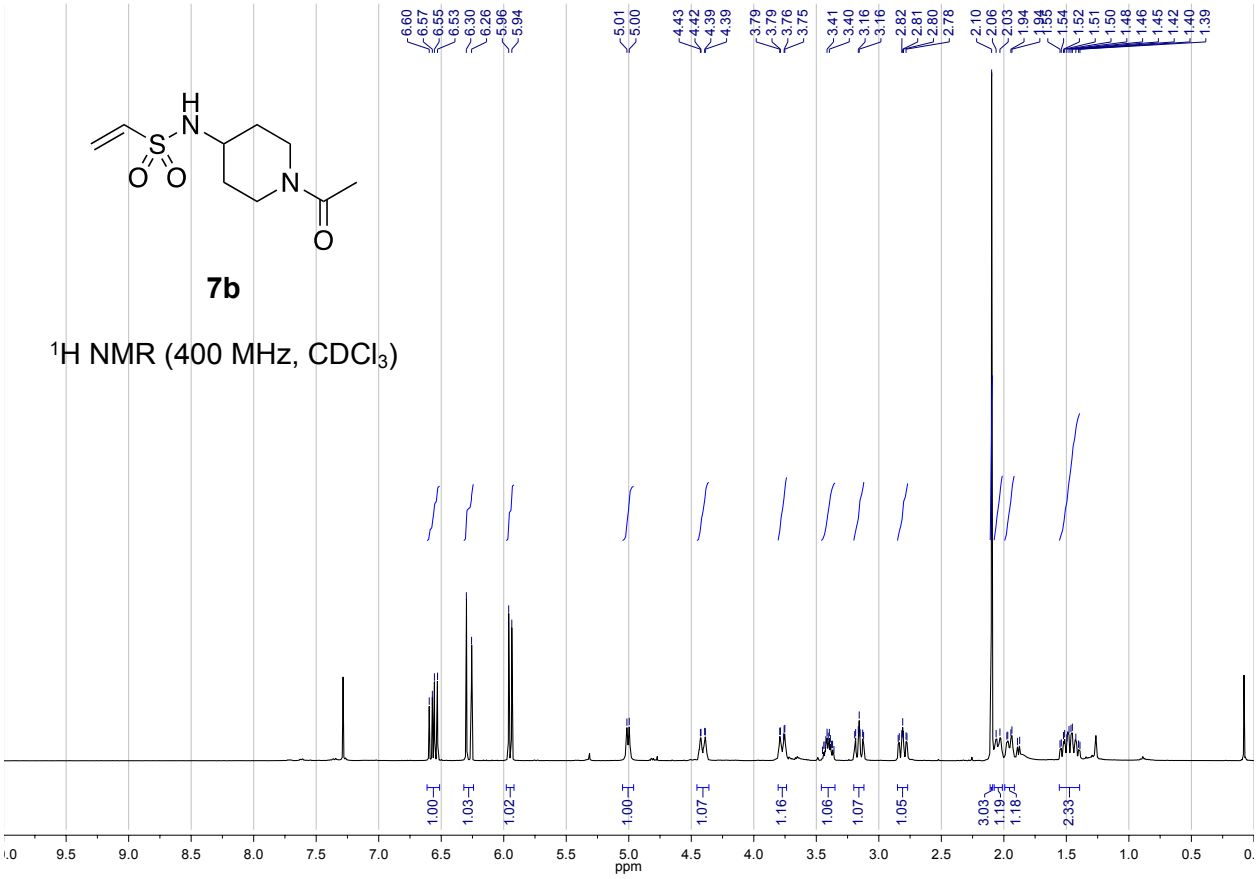


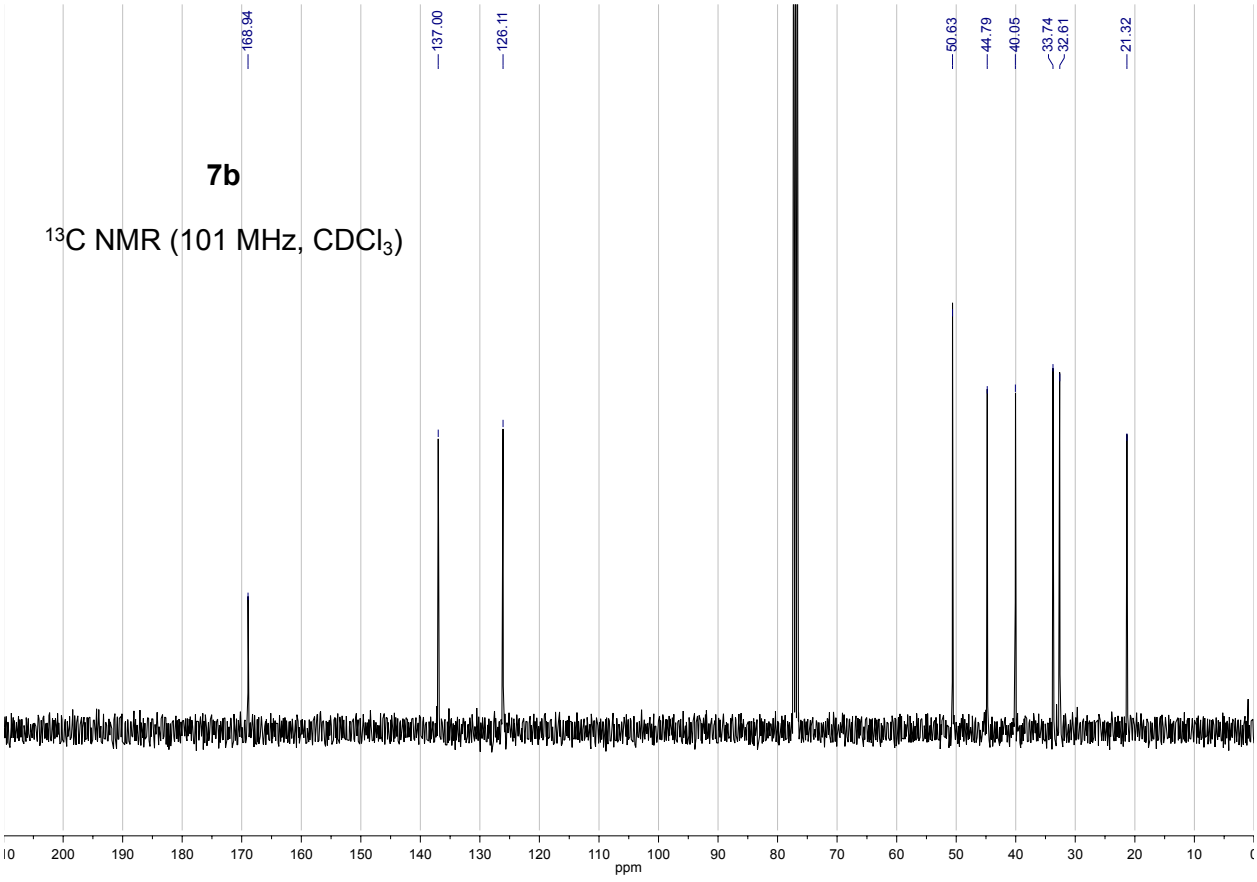
S–2

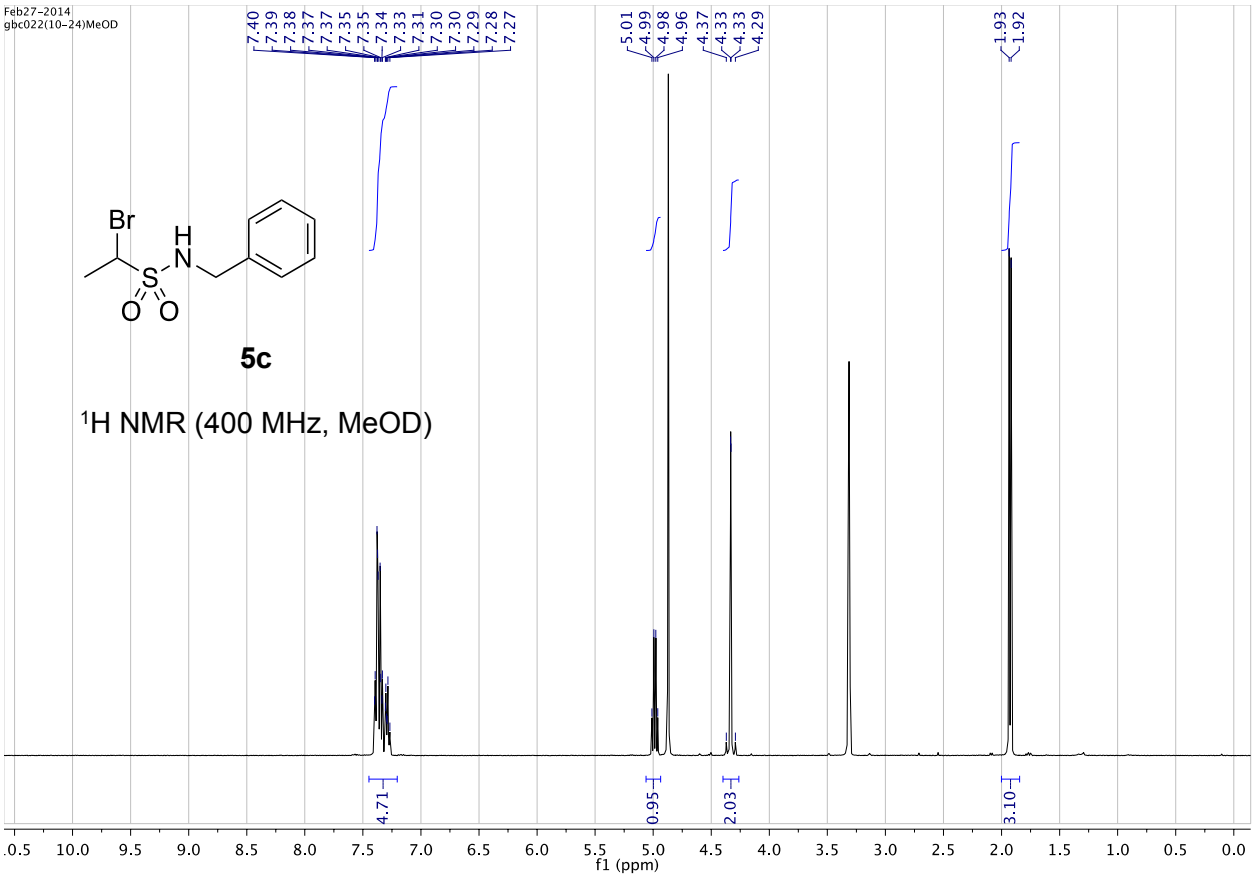
^{13}C NMR (101 MHz, CD_3OD)

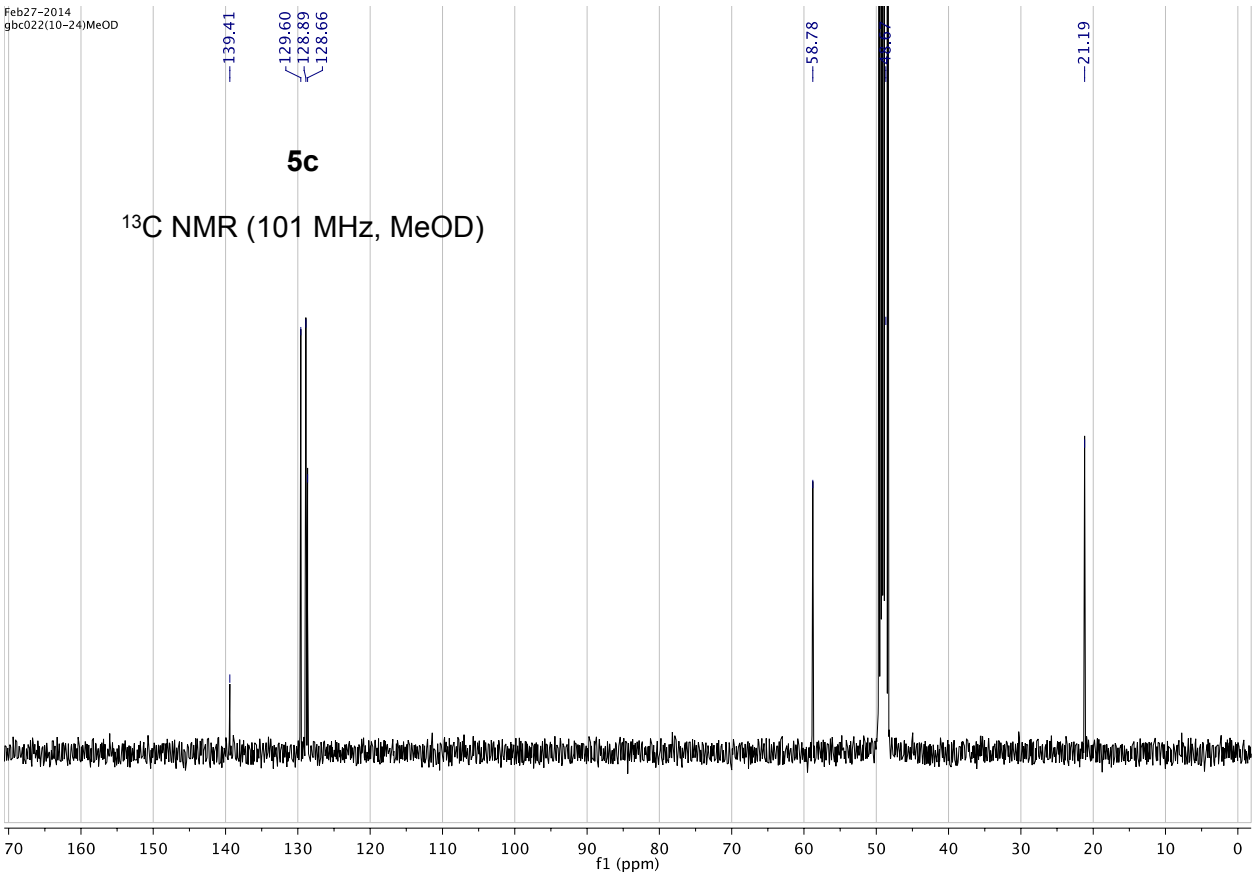

SePh
H
N
S
O
O
N
O
6b
^{1}H NMR (400 MHz, $CDCl_3$)
ppm

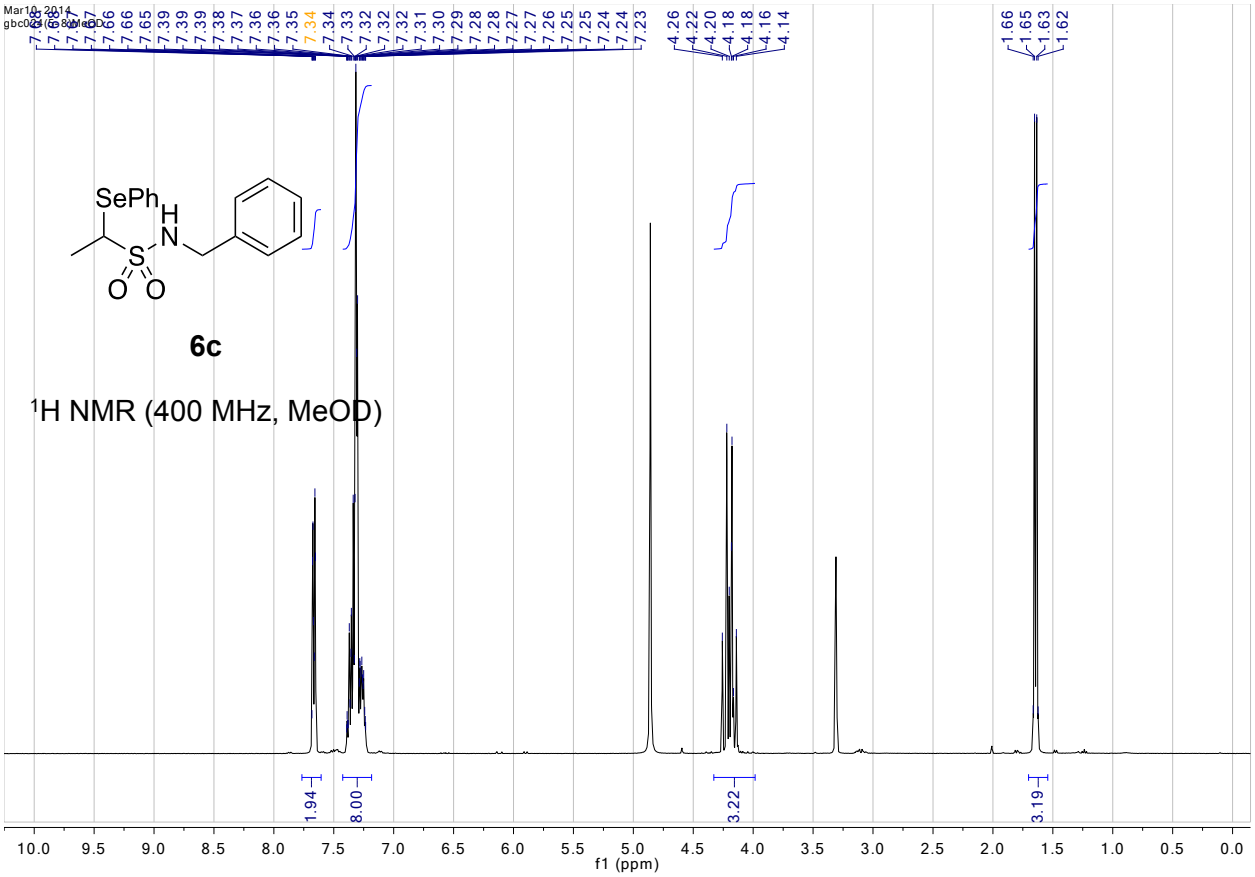

6b
^{13}C NMR (101 MHz, $CDCl_3$)
ppm

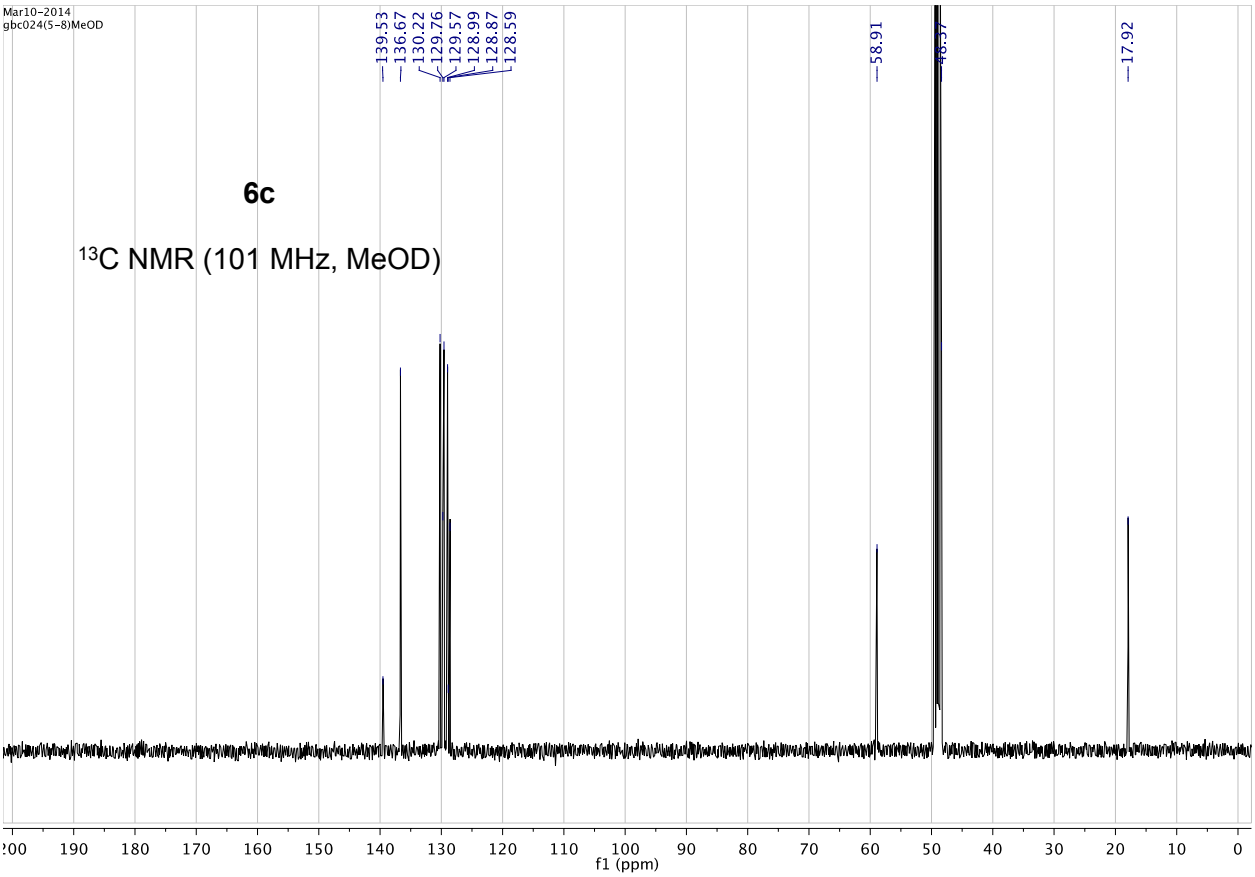

7b
1H NMR (400 MHz, CDCl3)
ppm

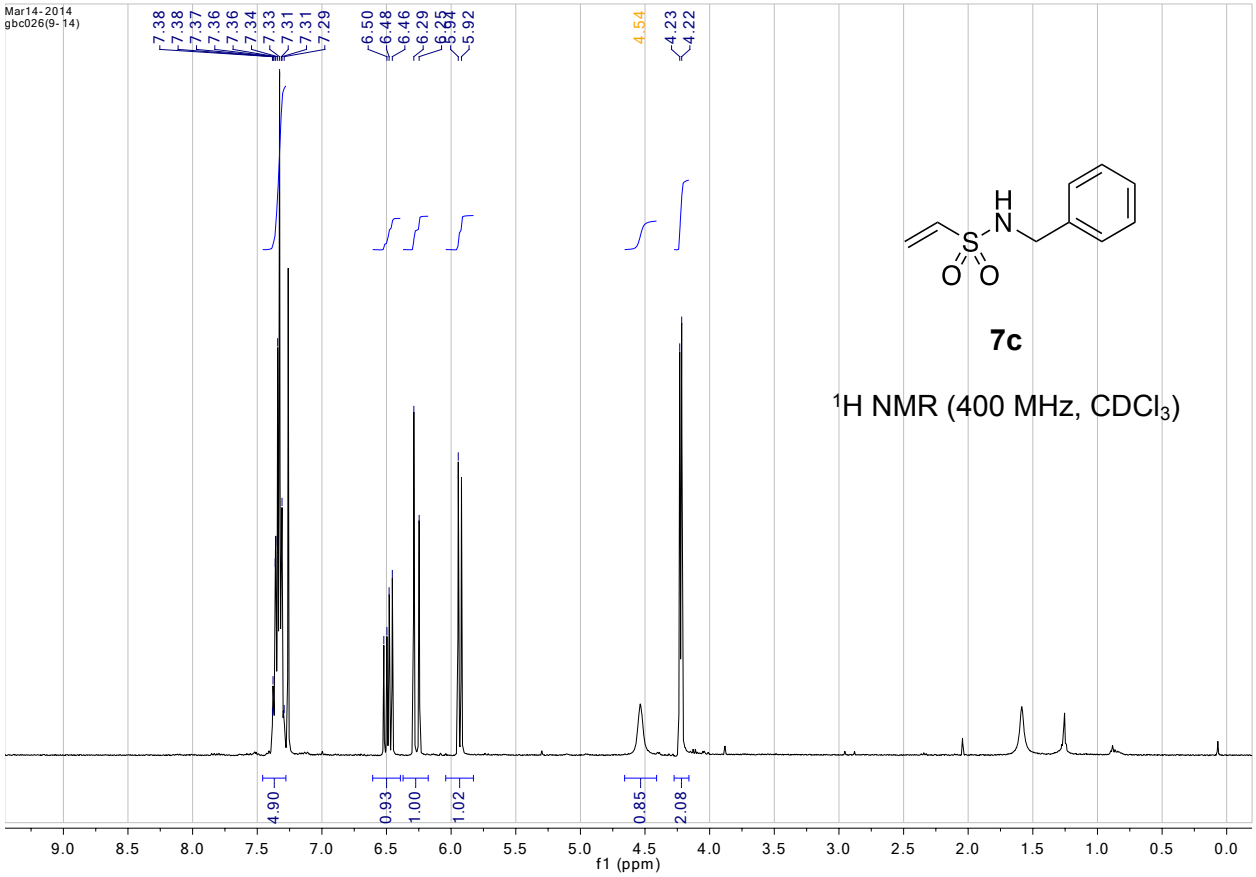

7b
13C NMR (101 MHz, CDCl3)
ppm

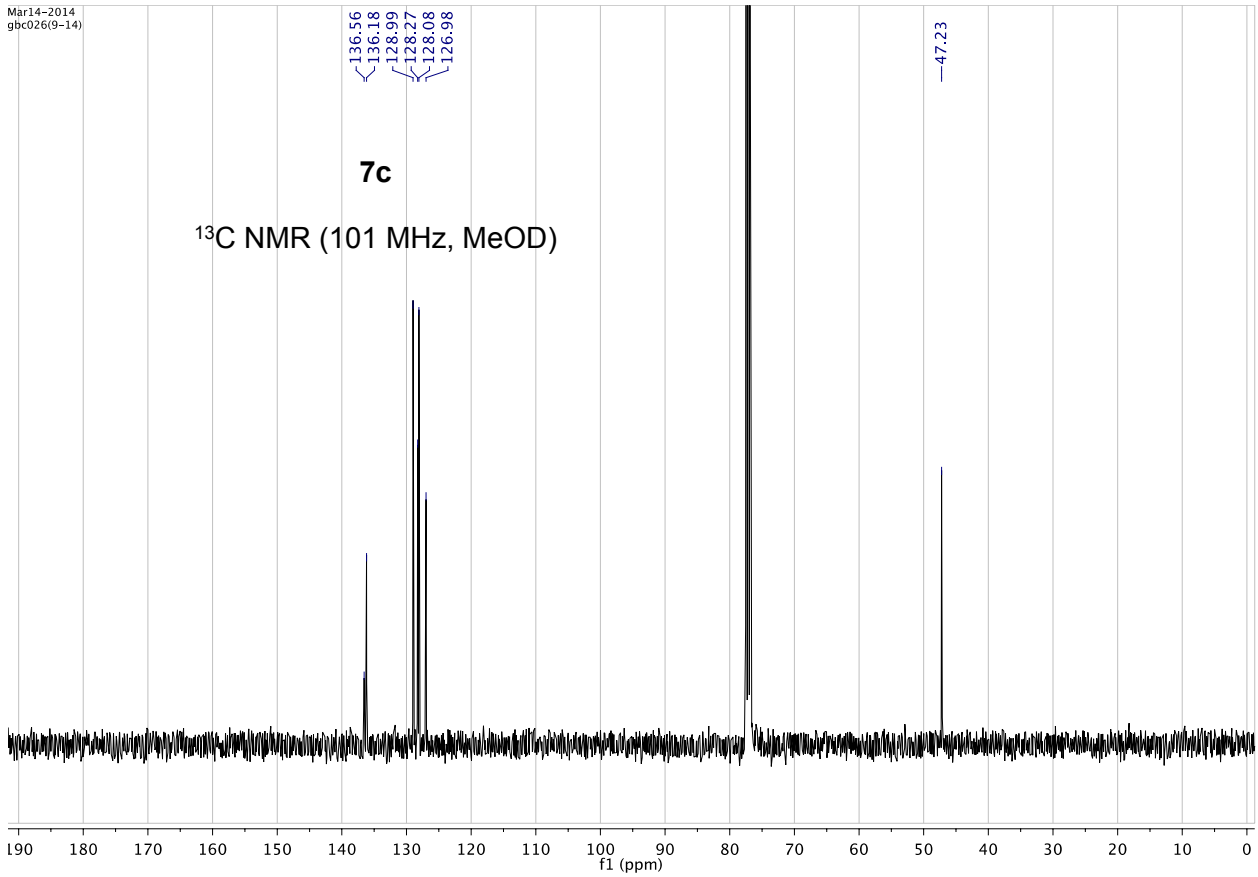

Feb27-2014
gbc022(10-24)MeOD
7.40
7.39
7.38
7.37
7.37
7.35
7.35
7.34
7.33
7.31
7.30
7.30
7.29
7.28
7.27
5.01
4.99
4.98
4.96
4.37
4.33
4.33
4.29
1.93
1.92
Br
H
N
S
O
O
5c
1H NMR (400 MHz, MeOD)
4.71
0.95
2.03
3.10
f1 (ppm)

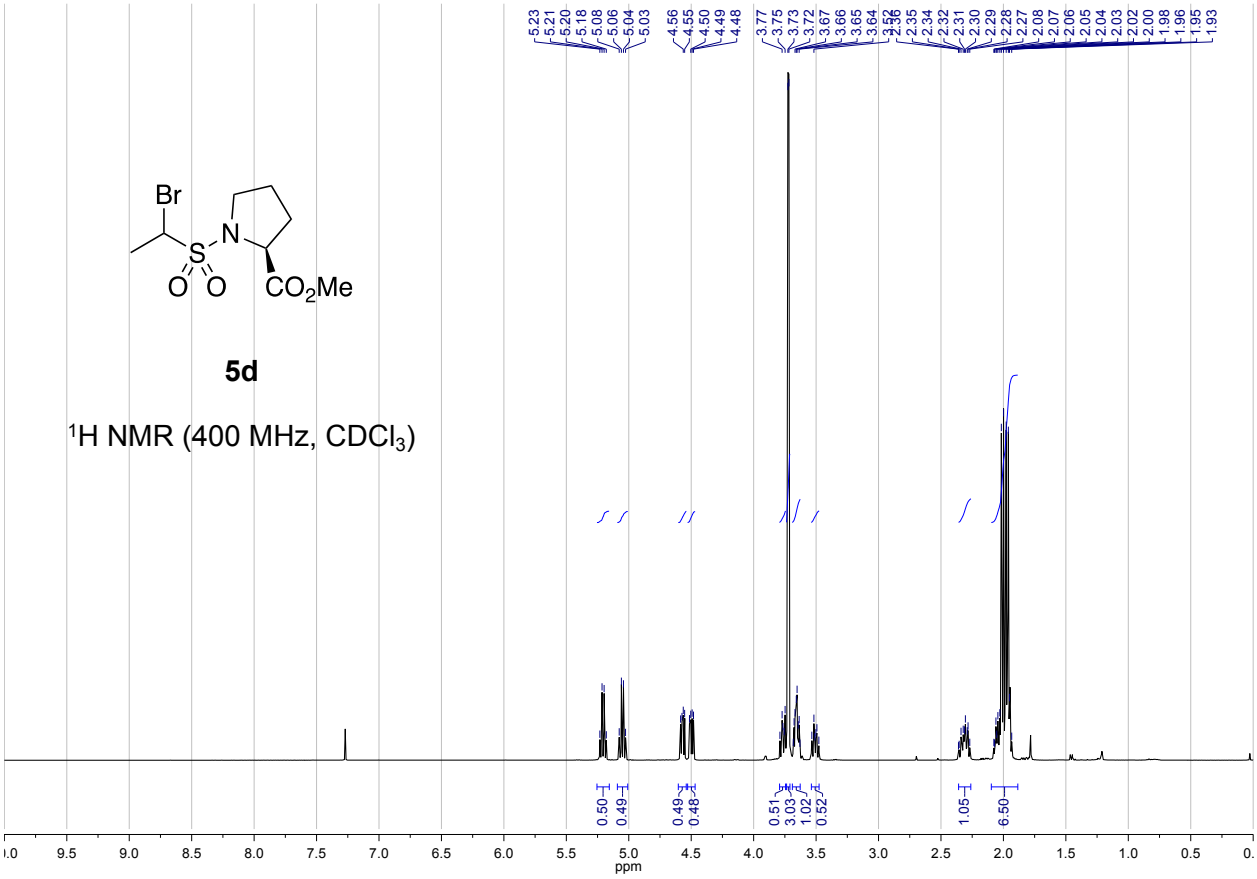

Feb27-2014
gbc022(10-24)MeOD
139.41
129.60
128.89
128.66
58.78
21.19
5c
13C NMR (101 MHz, MeOD)
f1 (ppm)


SePh
H
N
S
O
O
6c
^{1}H NMR (400 MHz, MeOD)
1.94
8.00
3.22
3.19
f1 (ppm)


Mar10-2014
gbc024(5-8)MeOD
139.53
136.67
130.22
129.76
129.57
128.99
128.87
128.59
58.91
46.37
17.92
6c
^{13}C NMR (101 MHz, MeOD)
f1 (ppm)

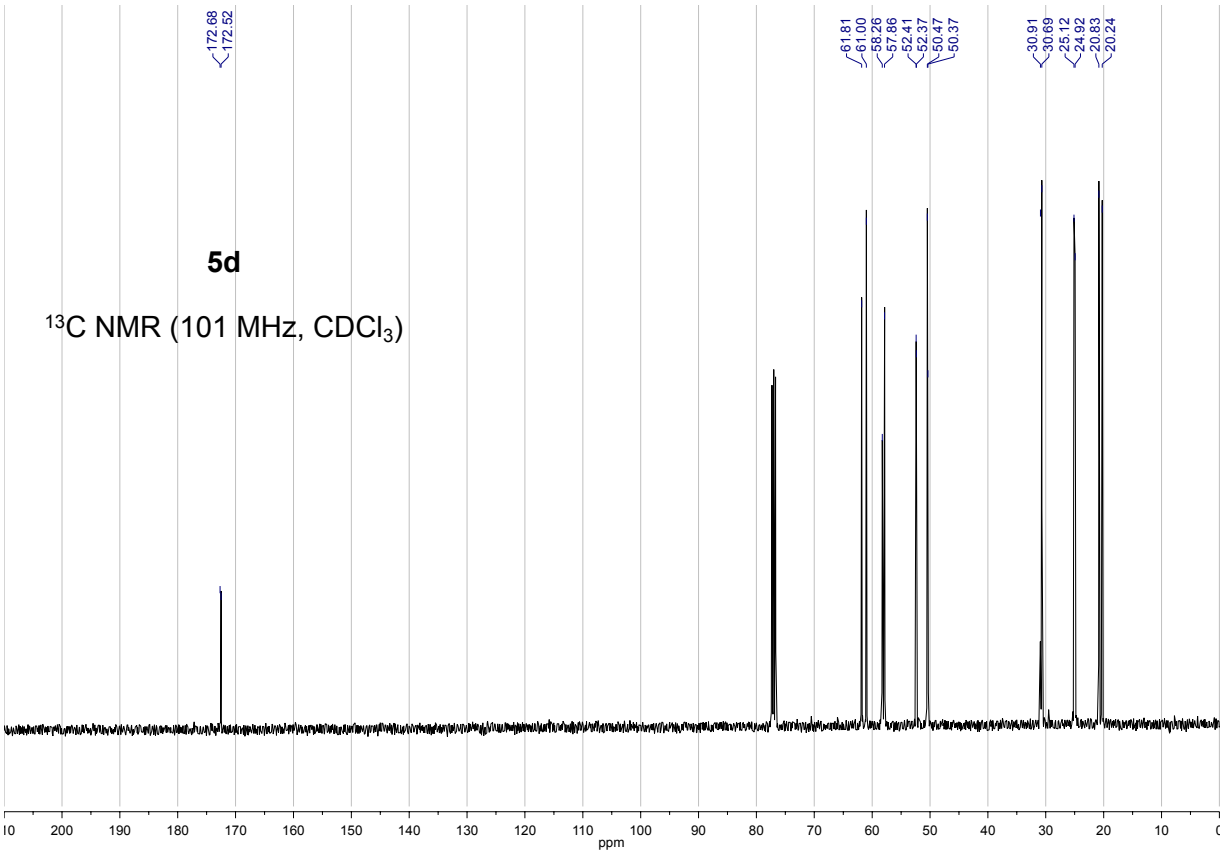

Mar14-2014
gbc026(9-14)
7.38
7.38
7.37
7.36
7.36
7.34
7.33
7.31
7.31
7.29
6.50
6.48
6.46
6.29
6.25
5.92
4.54
4.23
4.22
4.90
0.93
1.00
1.02
0.85
2.08
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
H
N
S
O
O
7c
1H NMR (400 MHz, CDCl3)


Mar14-2014
gbc026(9-14)
136.56
136.18
128.99
128.27
128.08
126.98
47.23
7c
13C NMR (101 MHz, MeOD)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



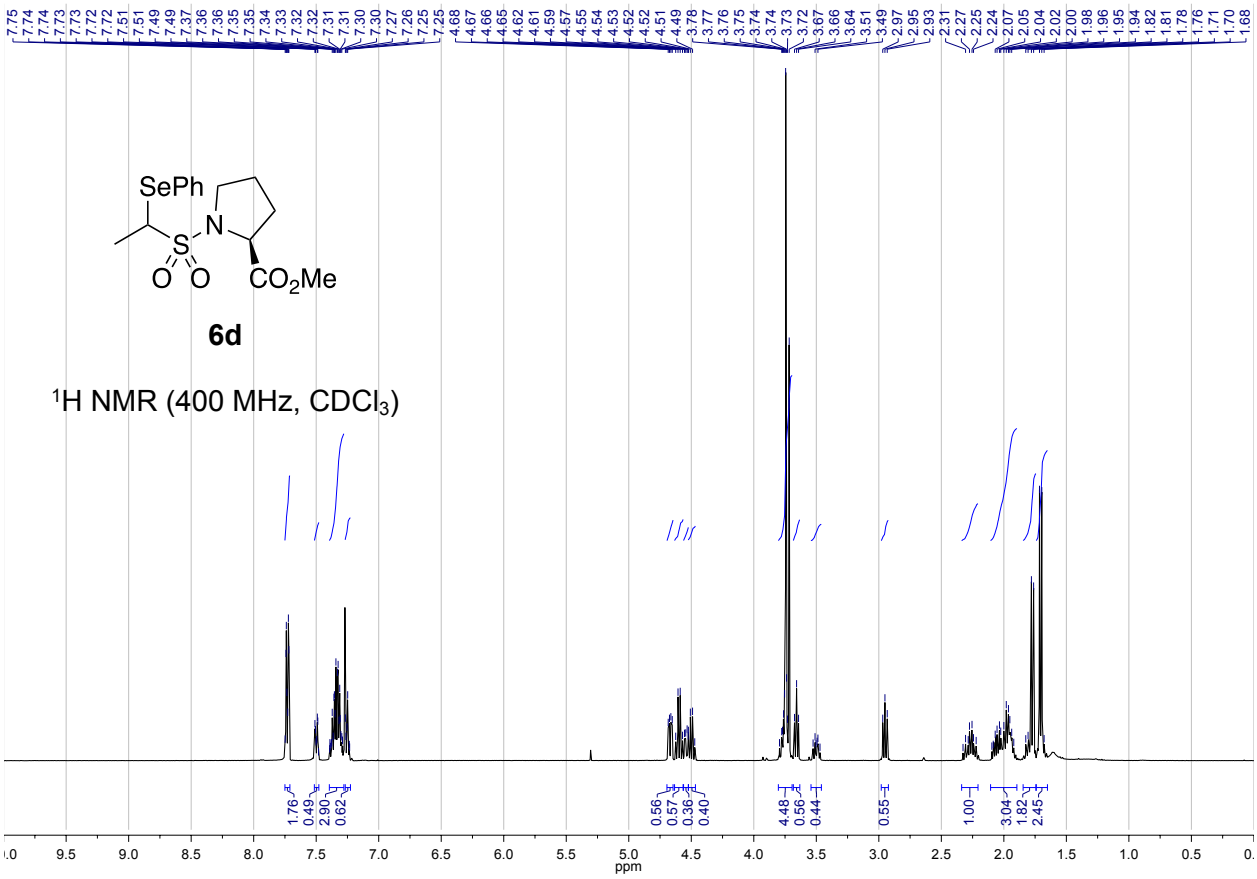
5d

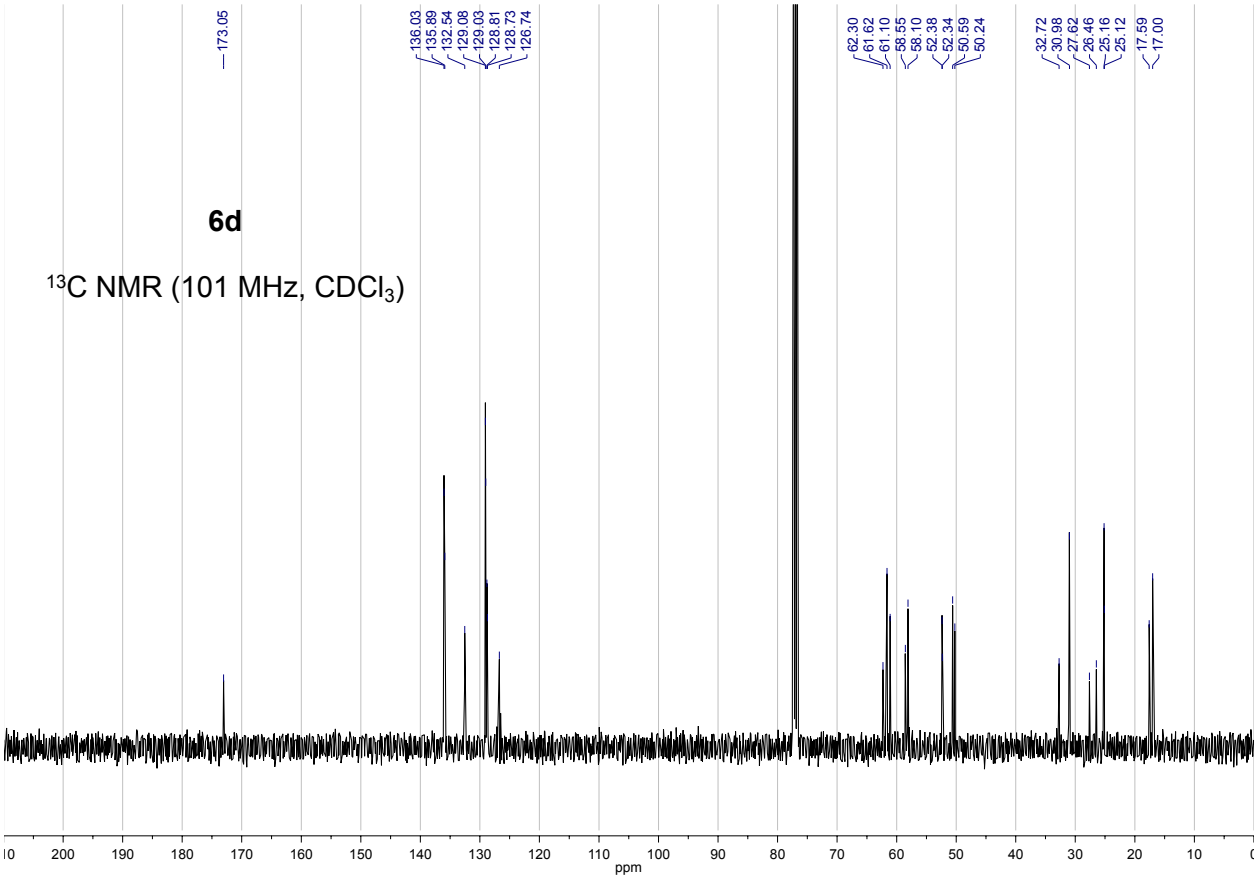
^{1}H NMR (400 MHz, $CDCl_3$)

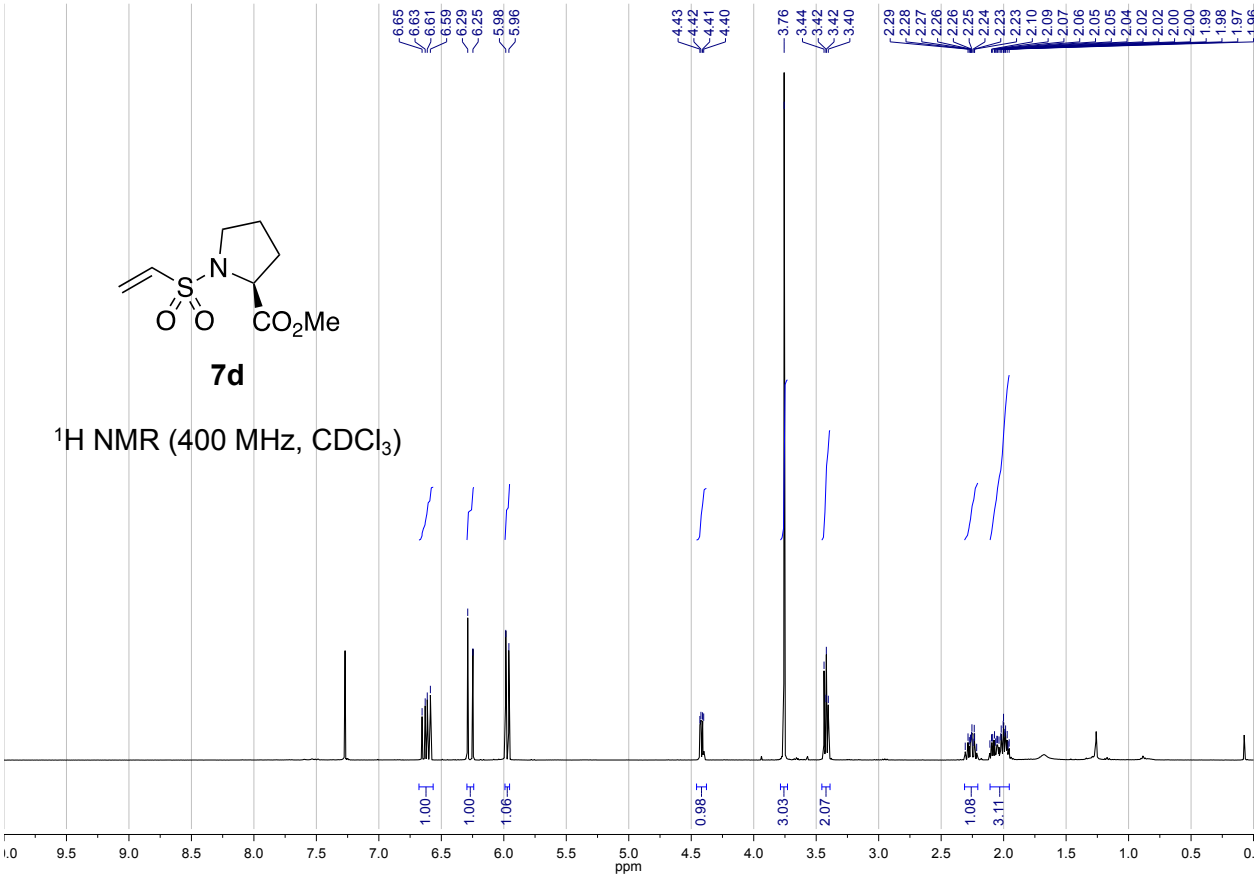


5d

^{13}C NMR (101 MHz, $CDCl_3$)

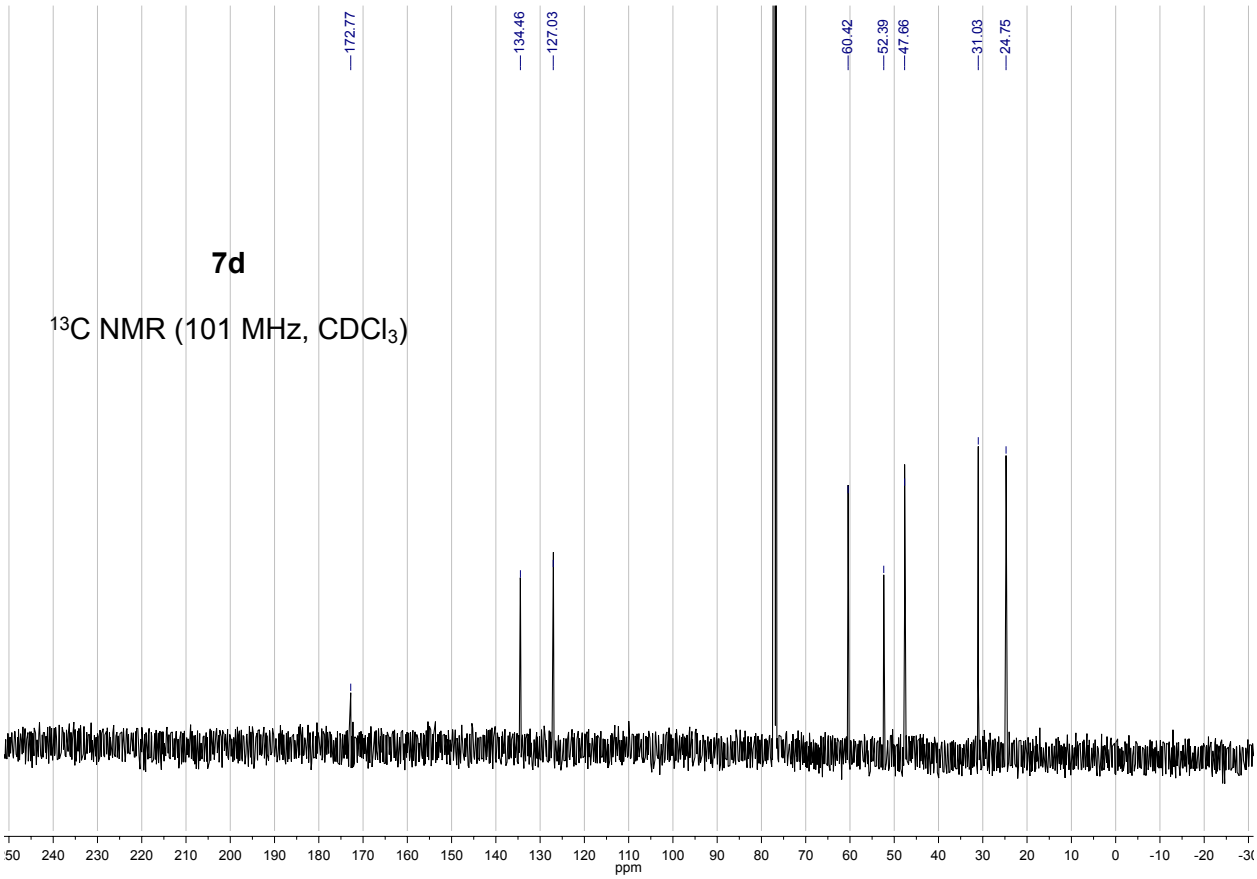

SePh
N
S
O
O
CO2Me
6d
1H NMR (400 MHz, CDCl3)
ppm


6d
13C NMR (101 MHz, CDCl3)
ppm



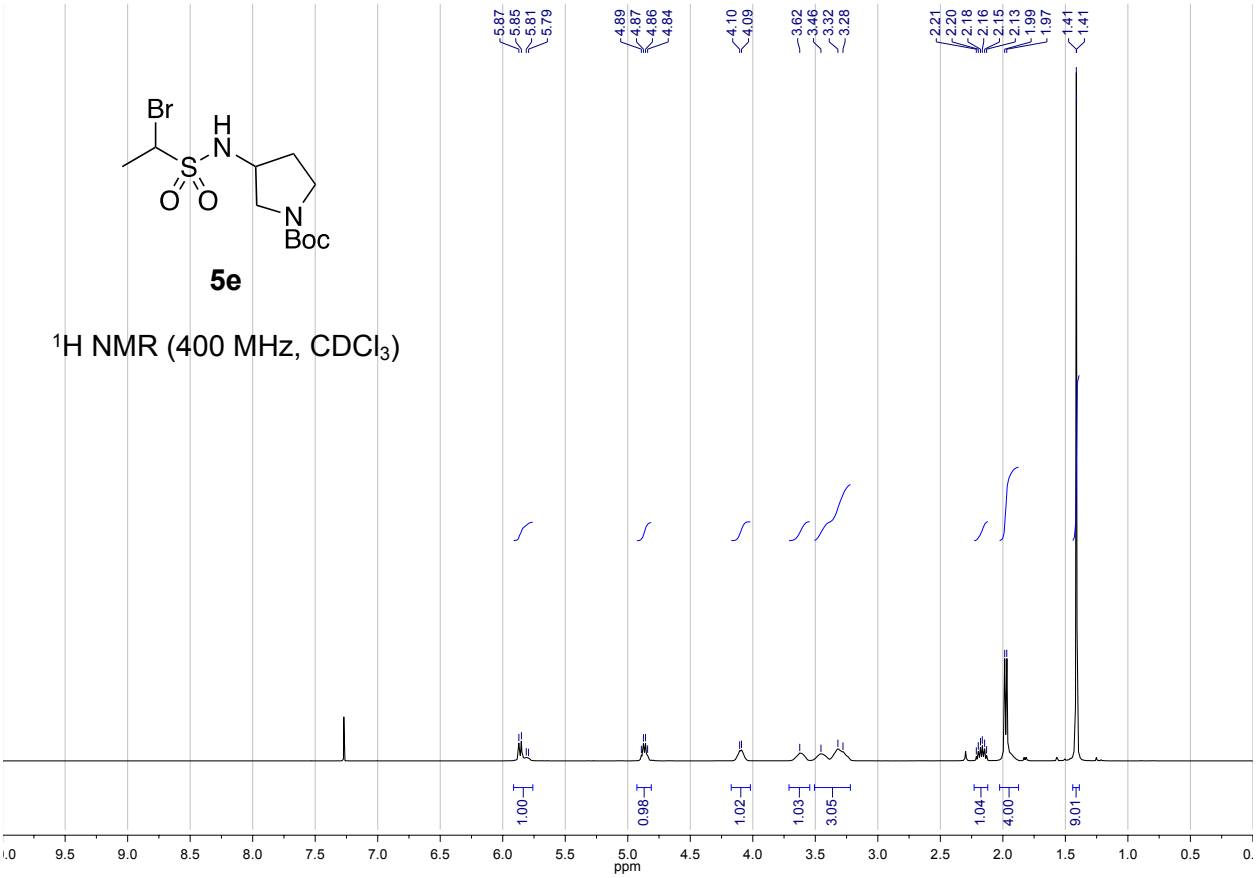
7d

^{1}H NMR (400 MHz, $CDCl_3$)



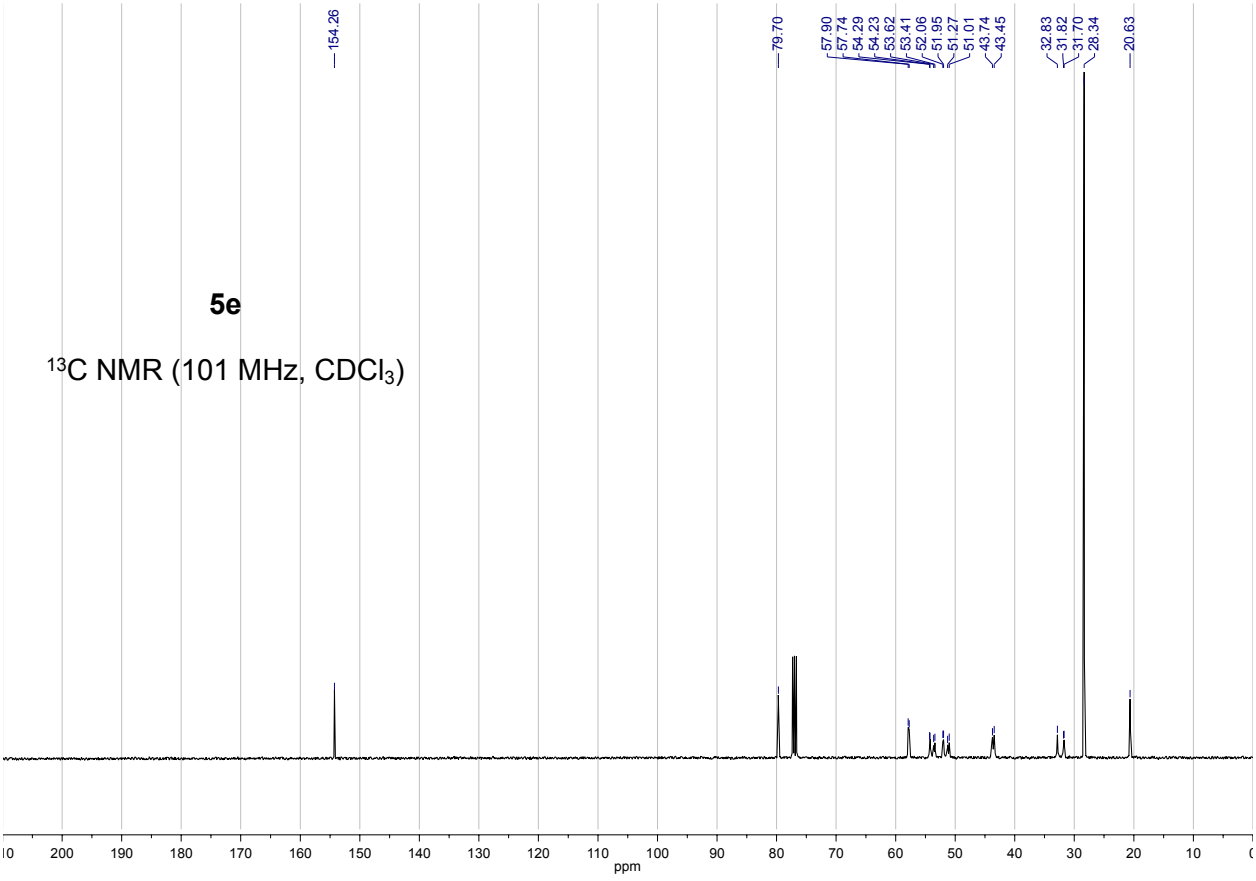
7d

^{13}C NMR (101 MHz, $CDCl_3$)



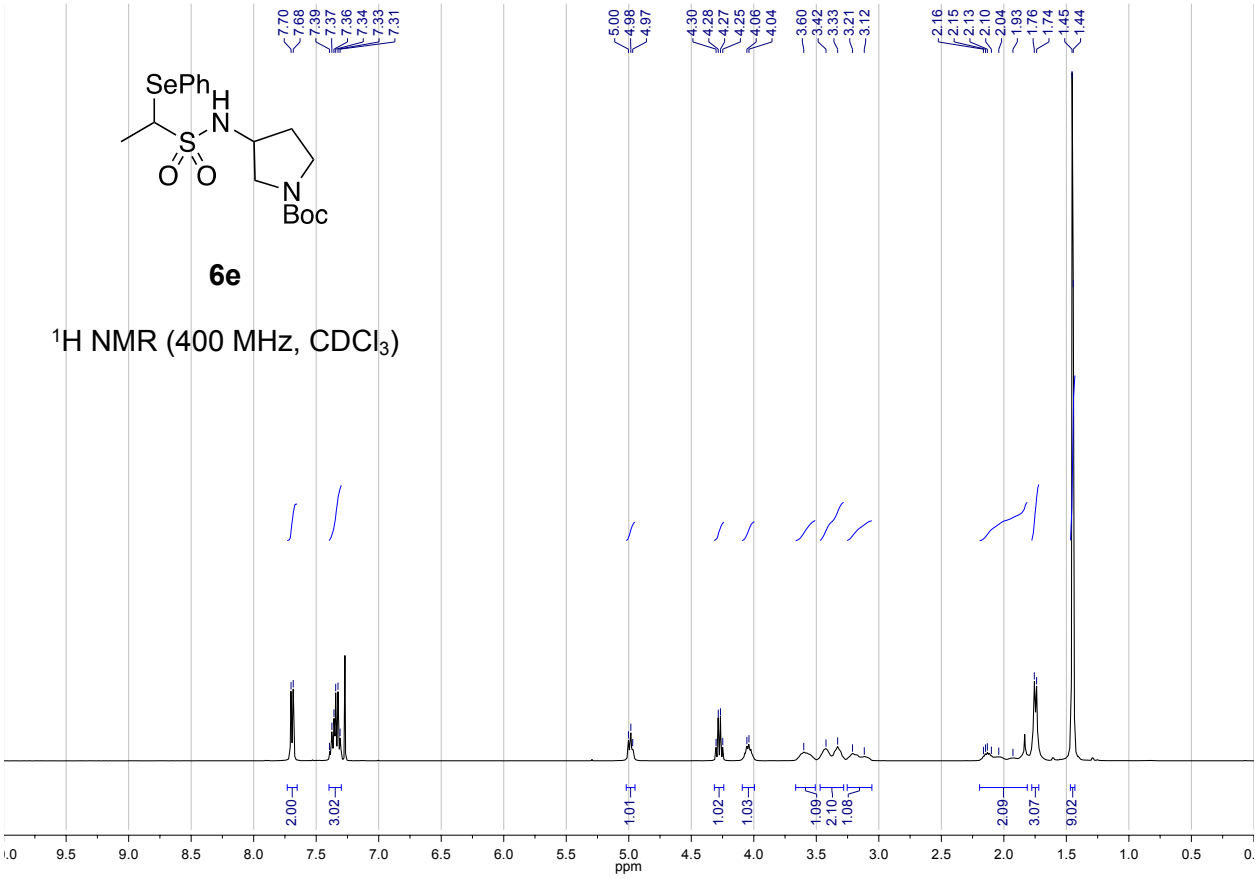
5e

^{1}H NMR (400 MHz, $CDCl_3$)



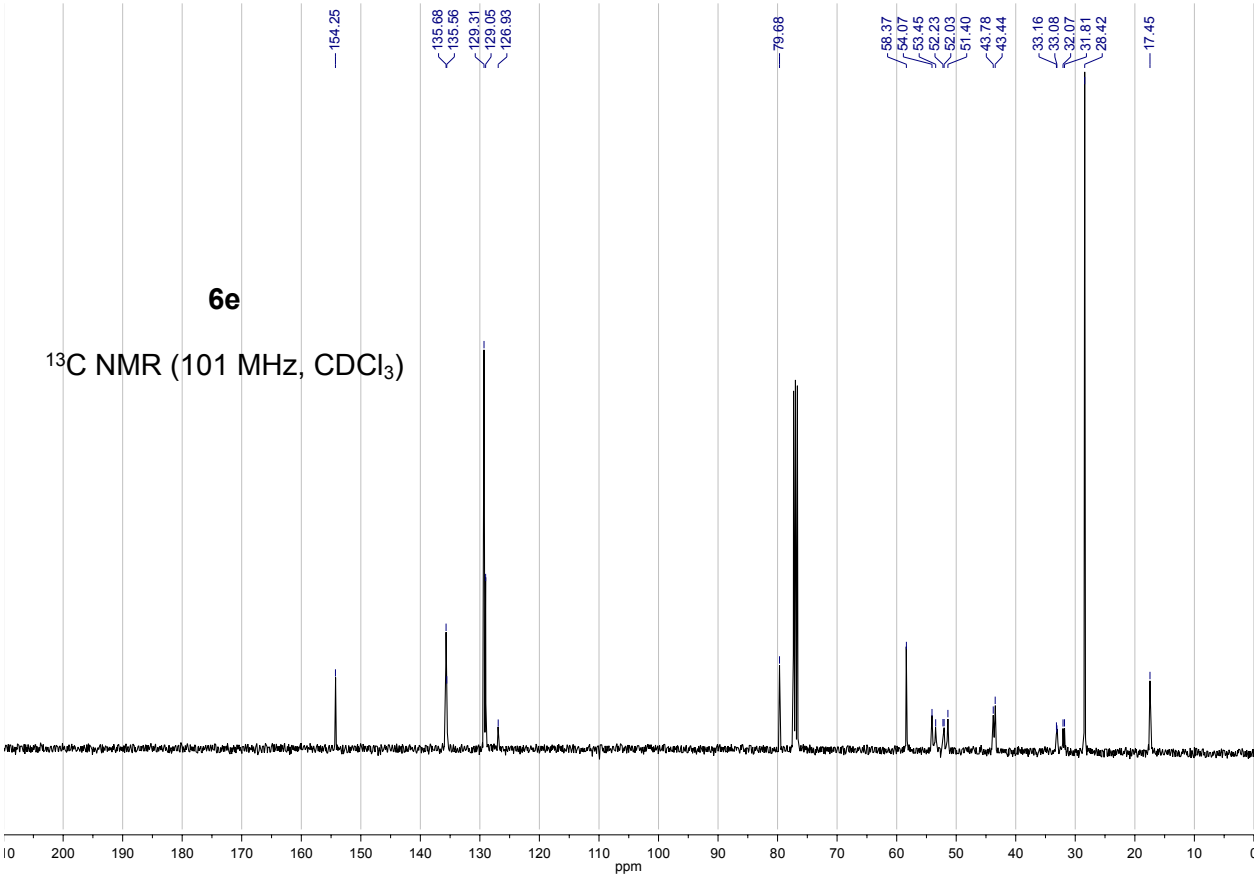
5e

^{13}C NMR (101 MHz, $CDCl_3$)



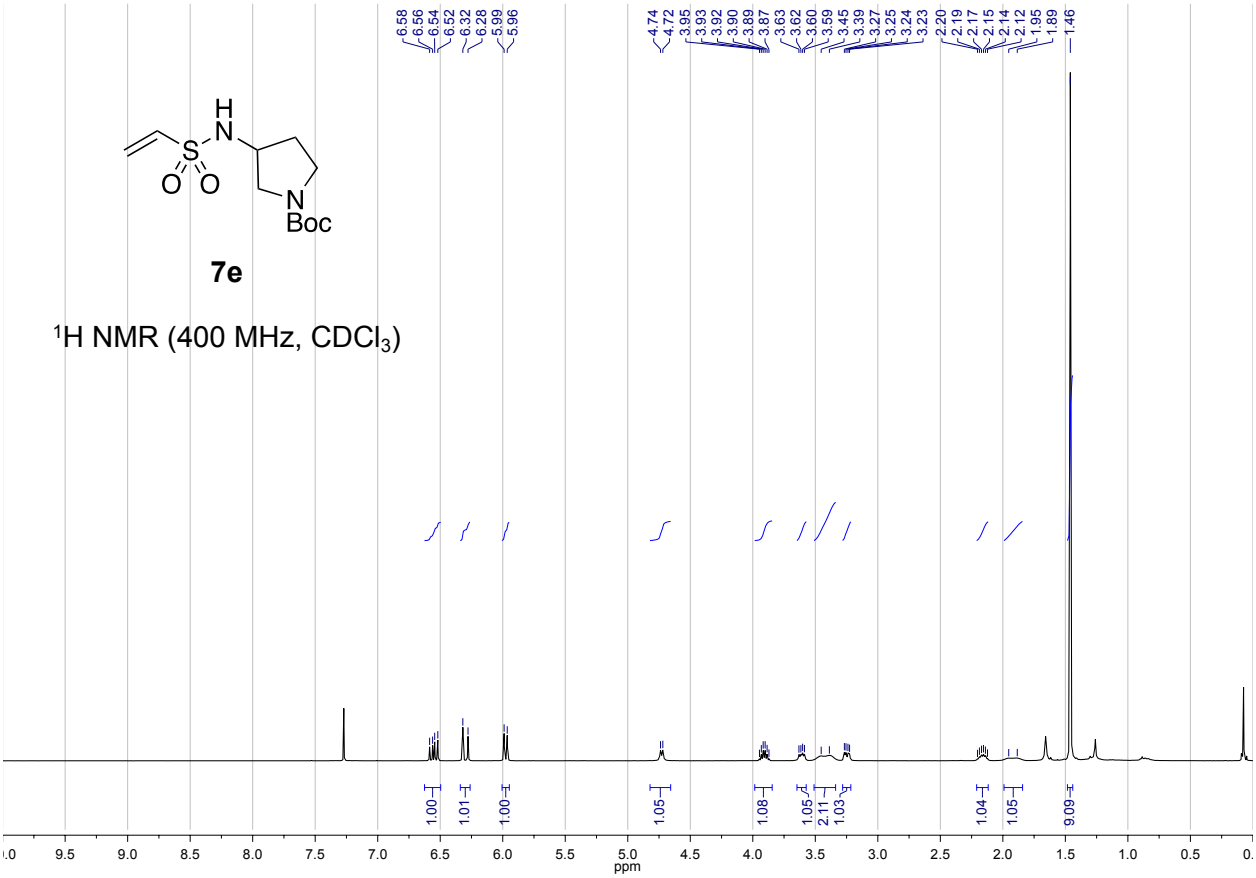
6e

^{1}H NMR (400 MHz, $CDCl_3$)



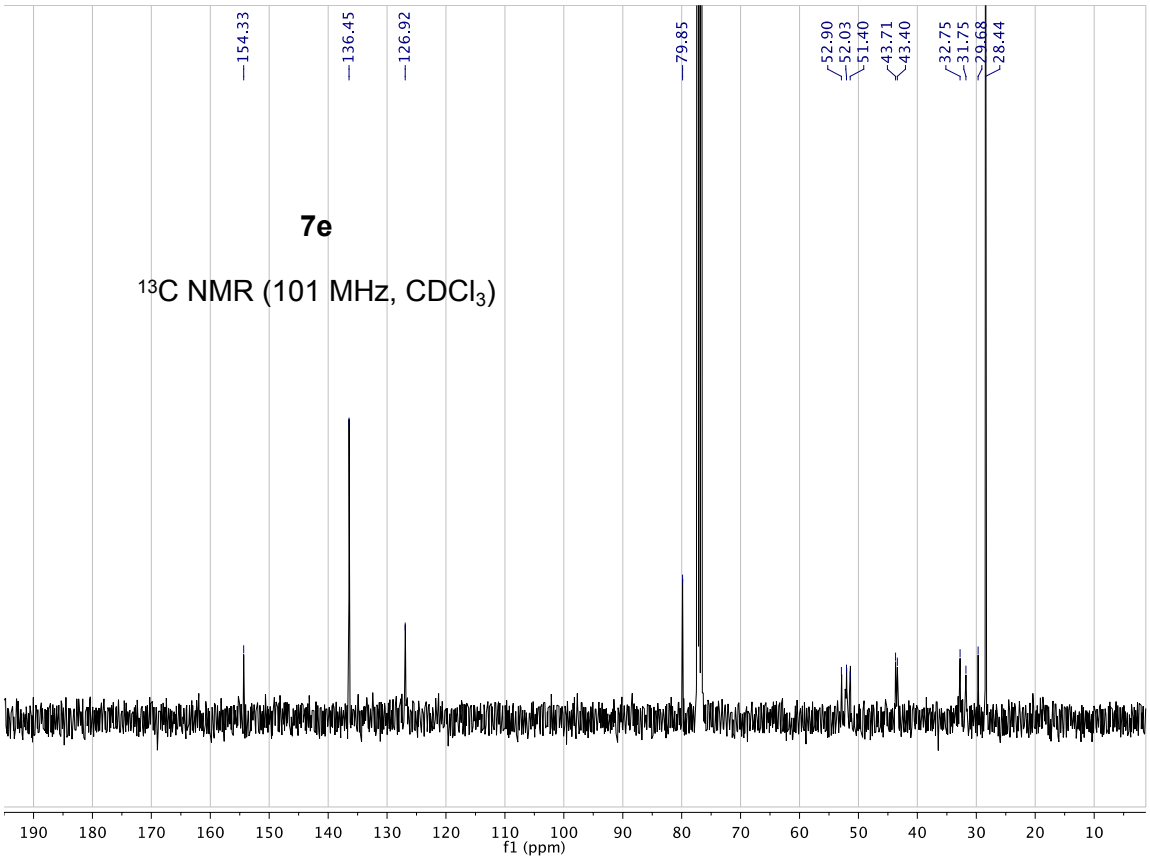
6e

^{13}C NMR (101 MHz, $CDCl_3$)



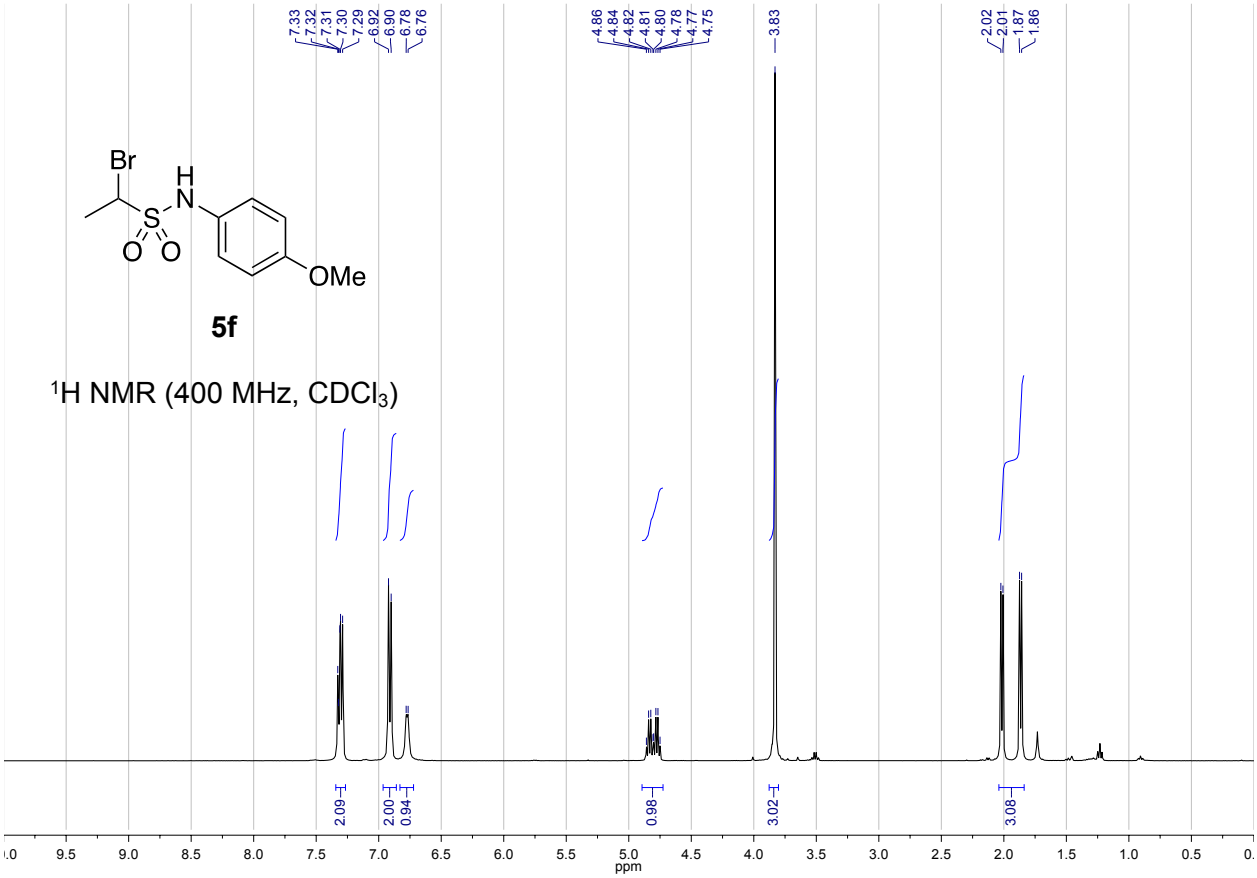
7e

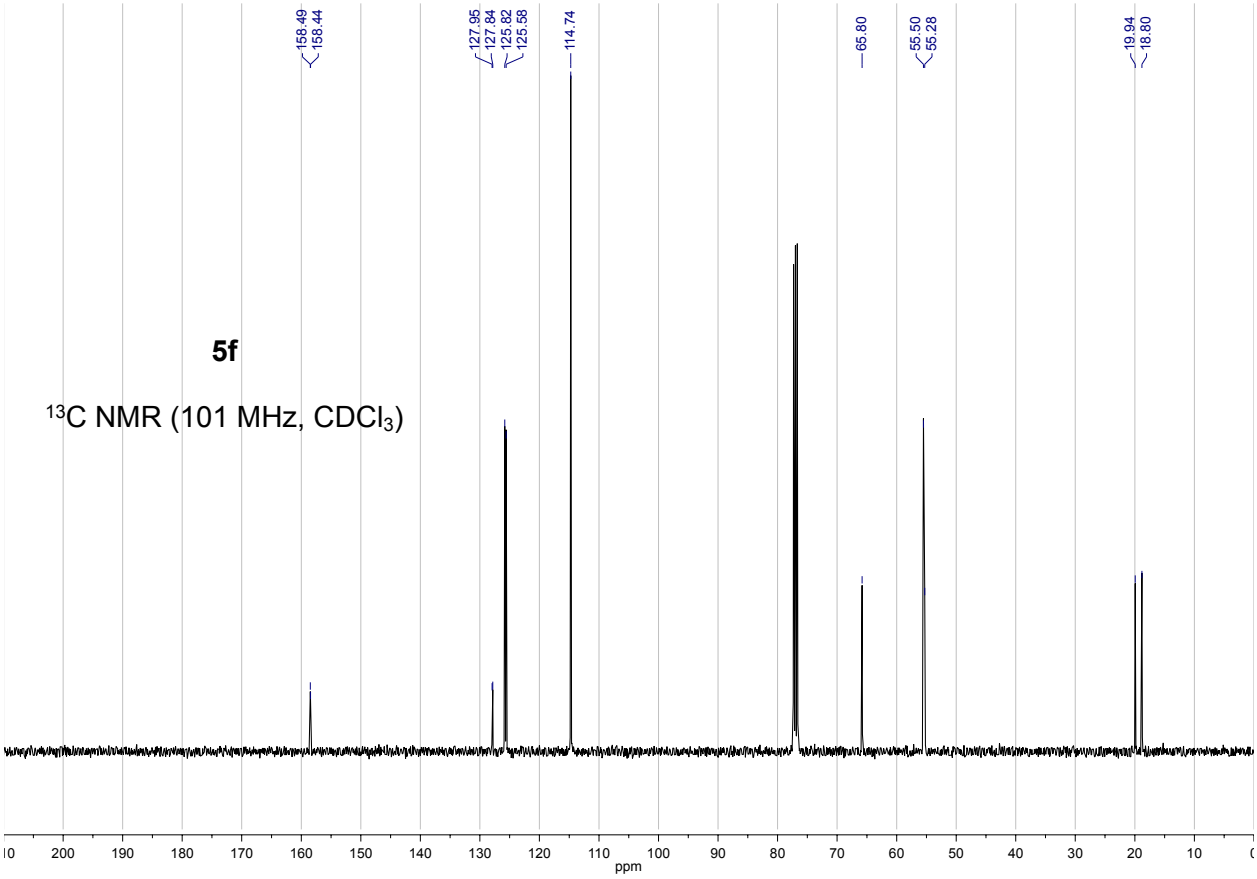
^{1}H NMR (400 MHz, $CDCl_3$)

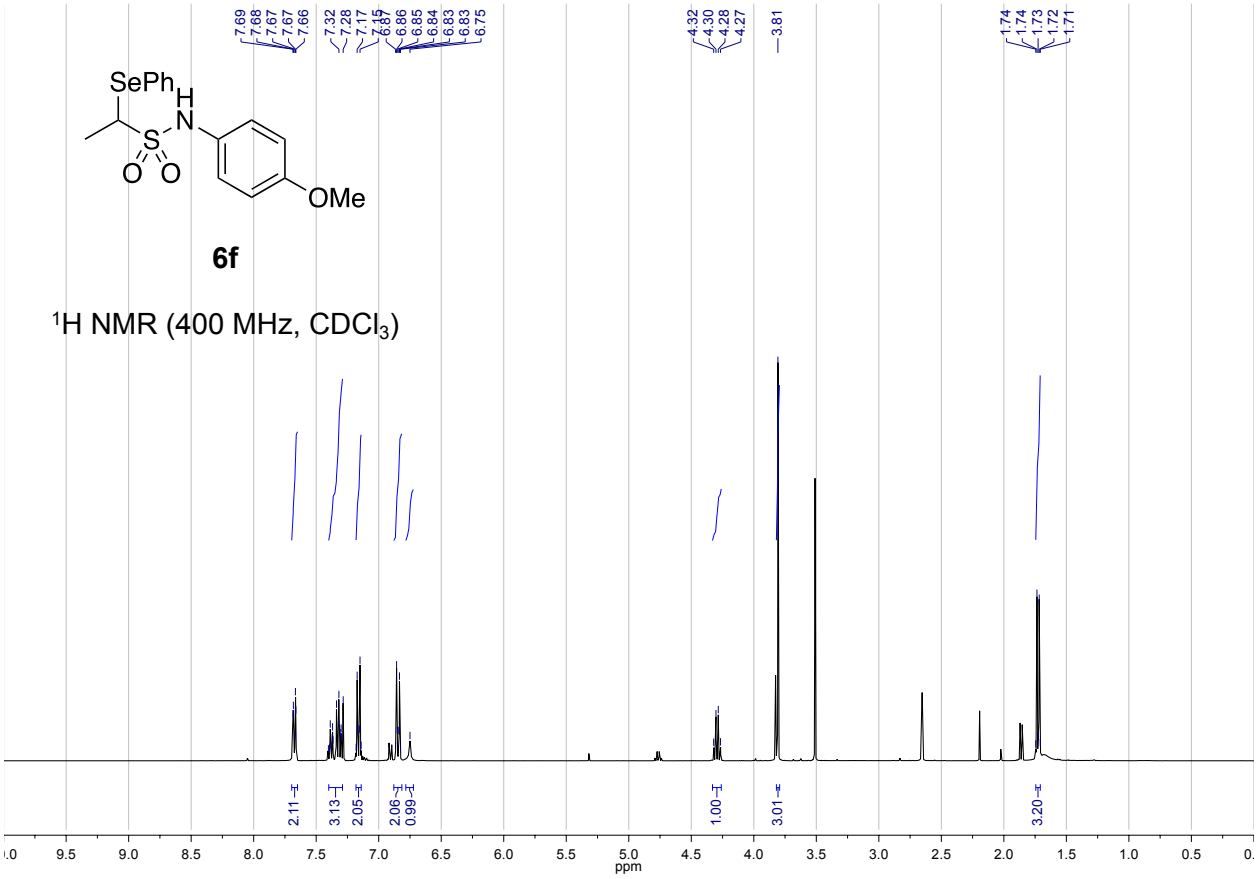


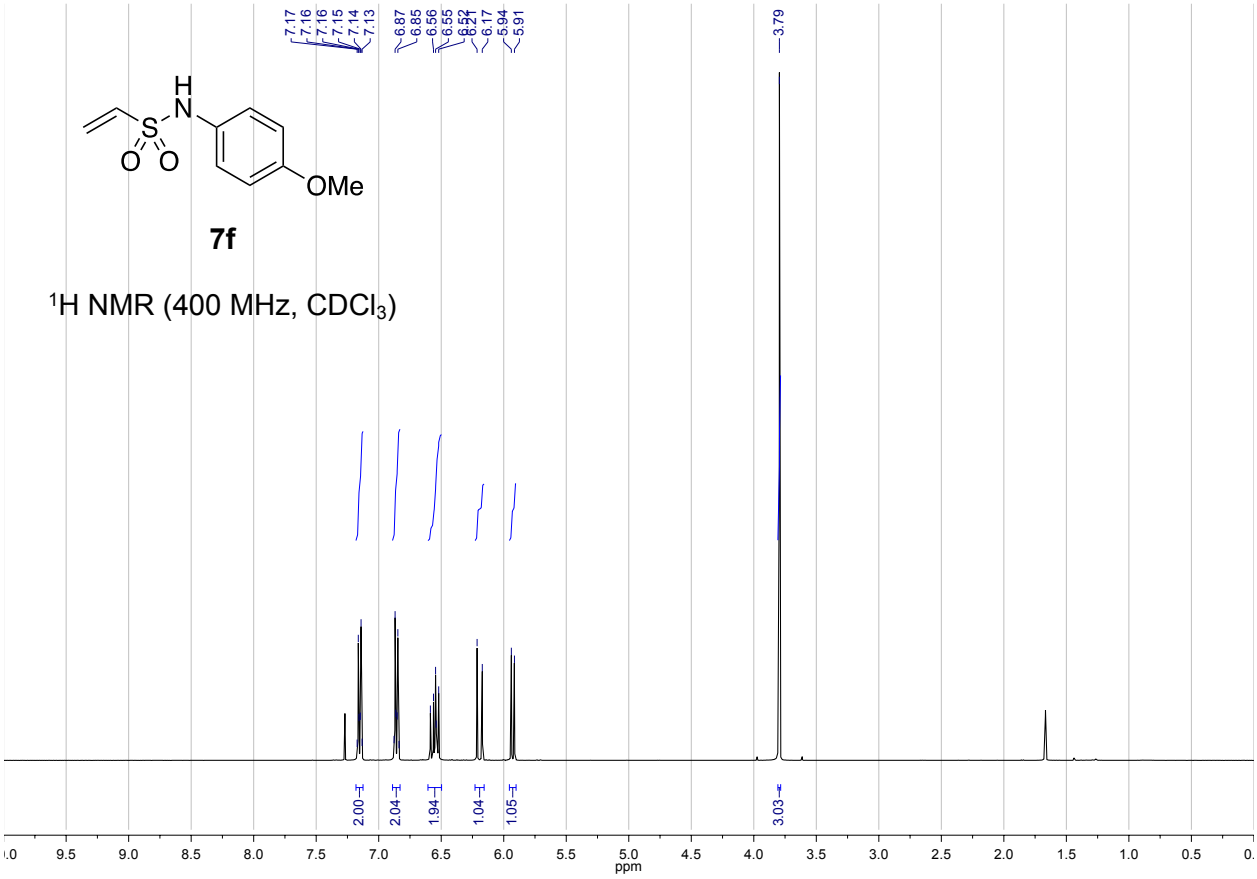
7e

^{13}C NMR (101 MHz, $CDCl_3$)


Br
H
N
S
O
O
OMe
5f
^{1}H NMR (400 MHz, $CDCl_3$)
7.33
7.32
7.31
7.30
7.29
6.92
6.90
6.78
6.76
4.86
4.84
4.82
4.81
4.80
4.78
4.77
4.75
3.83
2.02
2.01
1.87
1.86
2.09
2.00
0.94
0.98
3.02
3.08
ppm

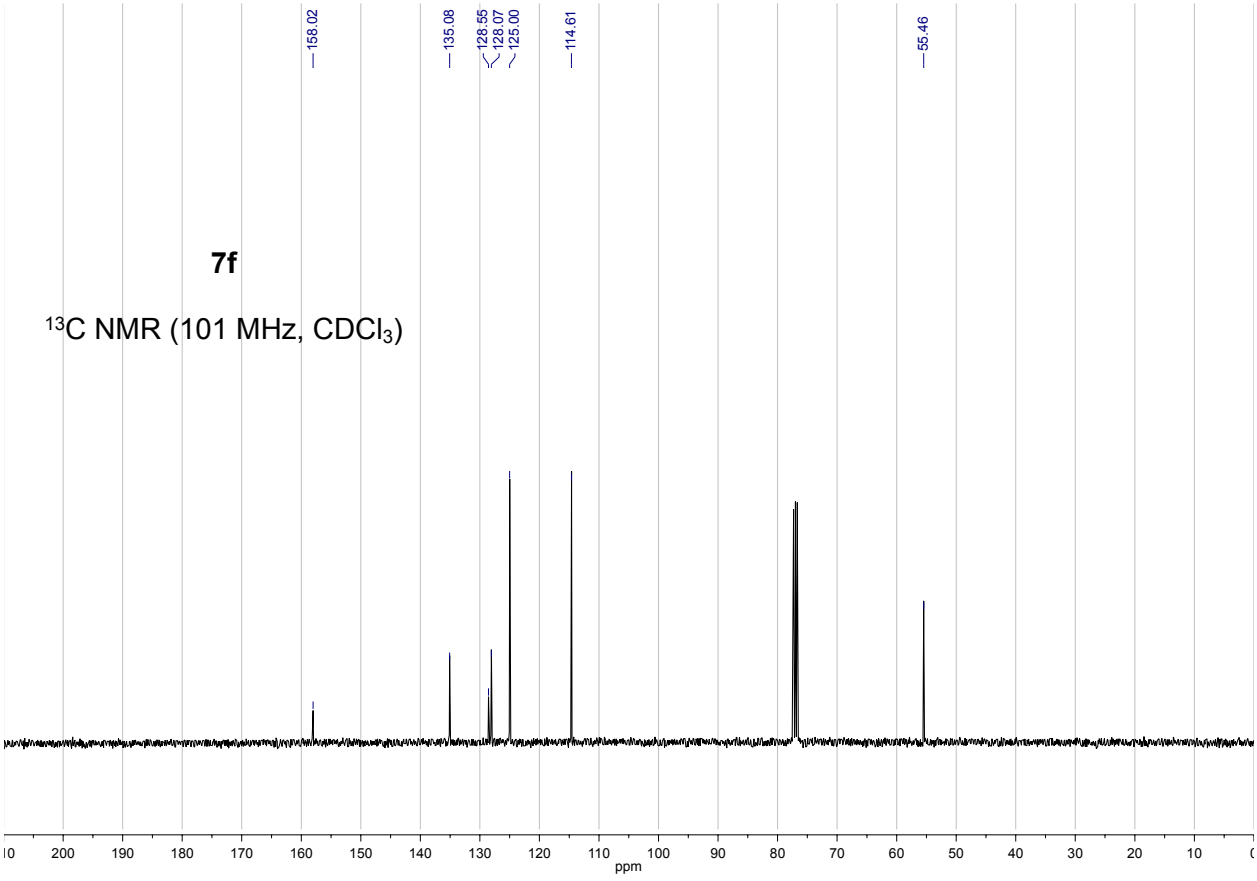

5f
^{13}C NMR (101 MHz, $CDCl_3$)
158.49
158.44
127.95
127.84
125.82
125.58
114.74
65.80
55.50
55.28
19.94
18.80
ppm


SePh
H
N
S
O
O
OMe
6f
^{1}H NMR (400 MHz, $CDCl_3$)
7.69
7.68
7.67
7.67
7.66
7.32
7.28
7.17
7.15
6.86
6.85
6.84
6.83
6.83
6.75
4.32
4.30
4.28
4.27
3.81
1.74
1.74
1.73
1.72
1.71
2.11
3.13
2.05
2.06
0.99
1.00
3.01
3.20
ppm



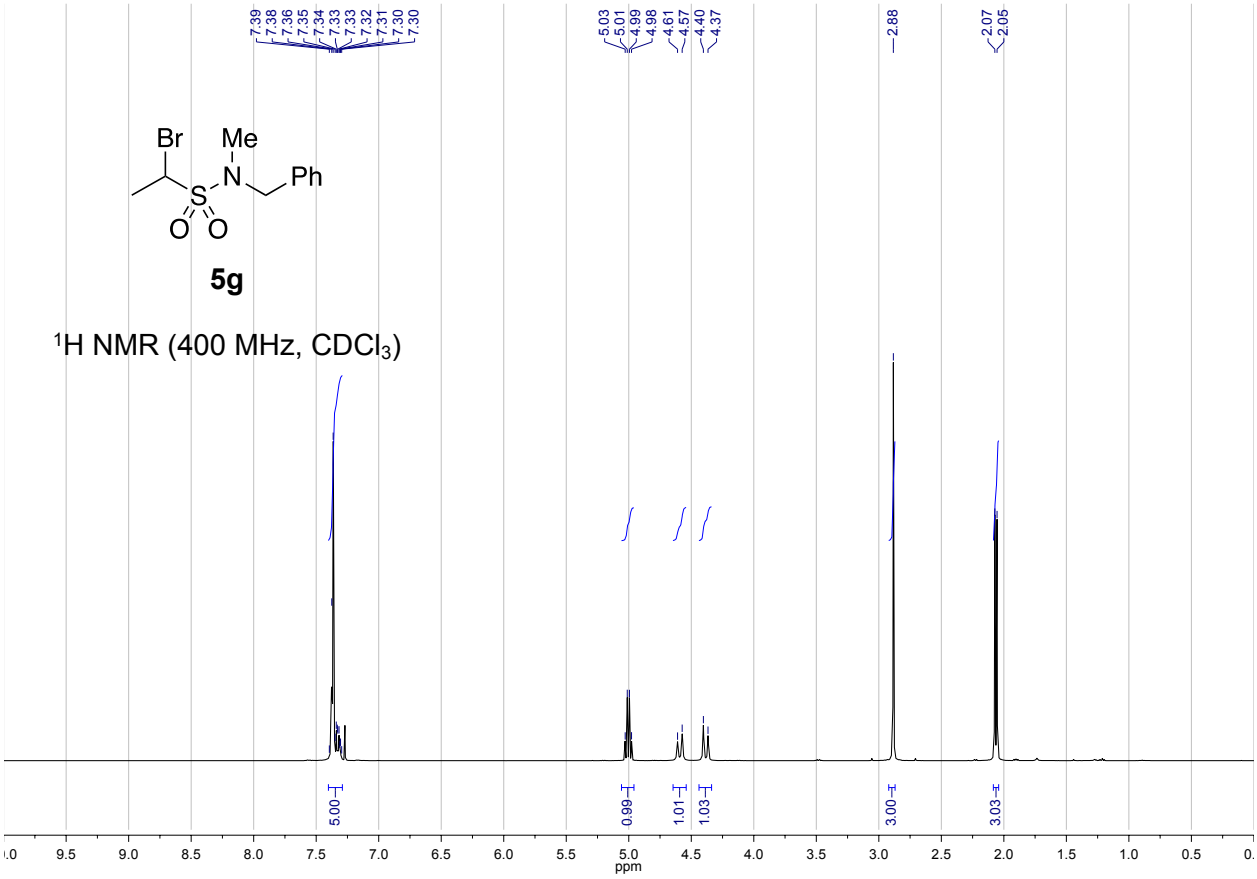
7f

^{1}H NMR (400 MHz, $CDCl_3$)



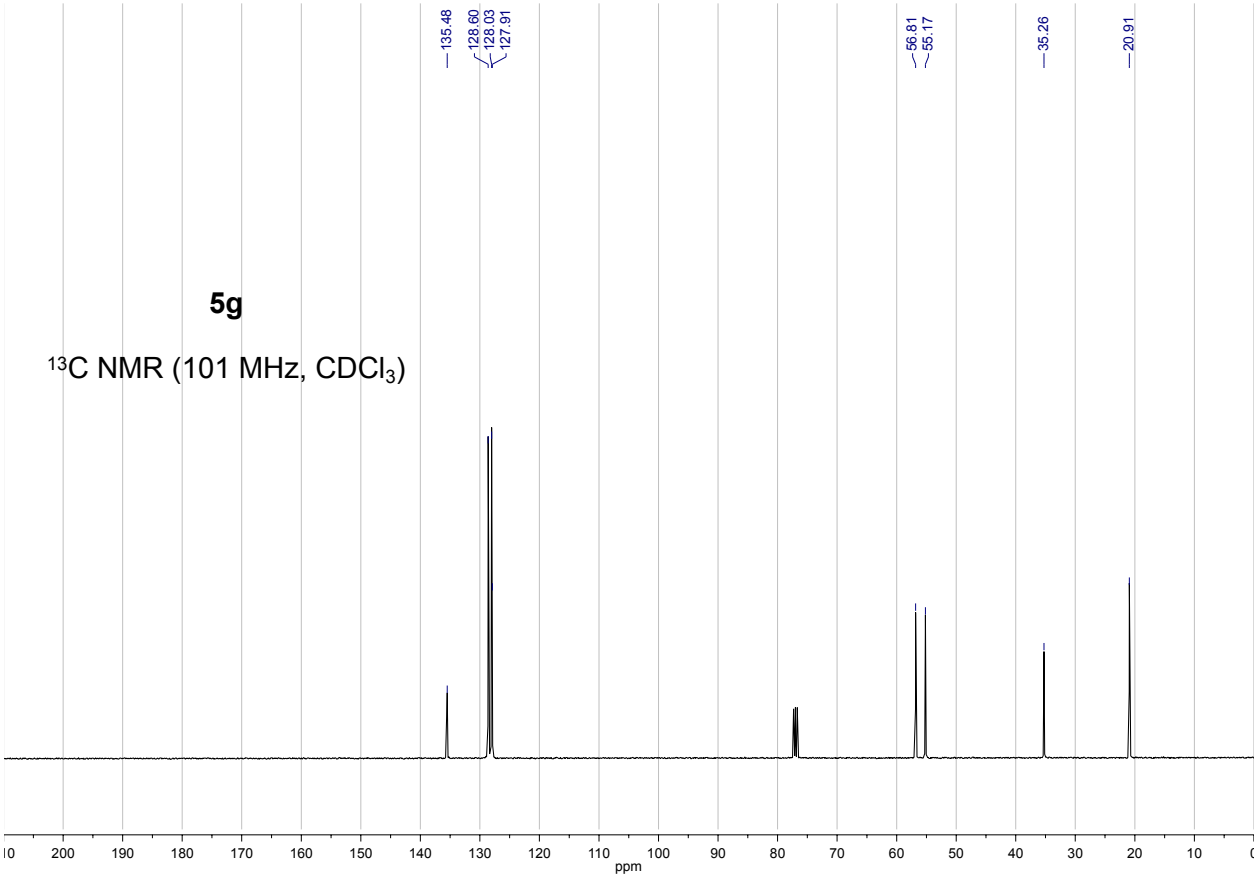
7f

^{13}C NMR (101 MHz, $CDCl_3$)



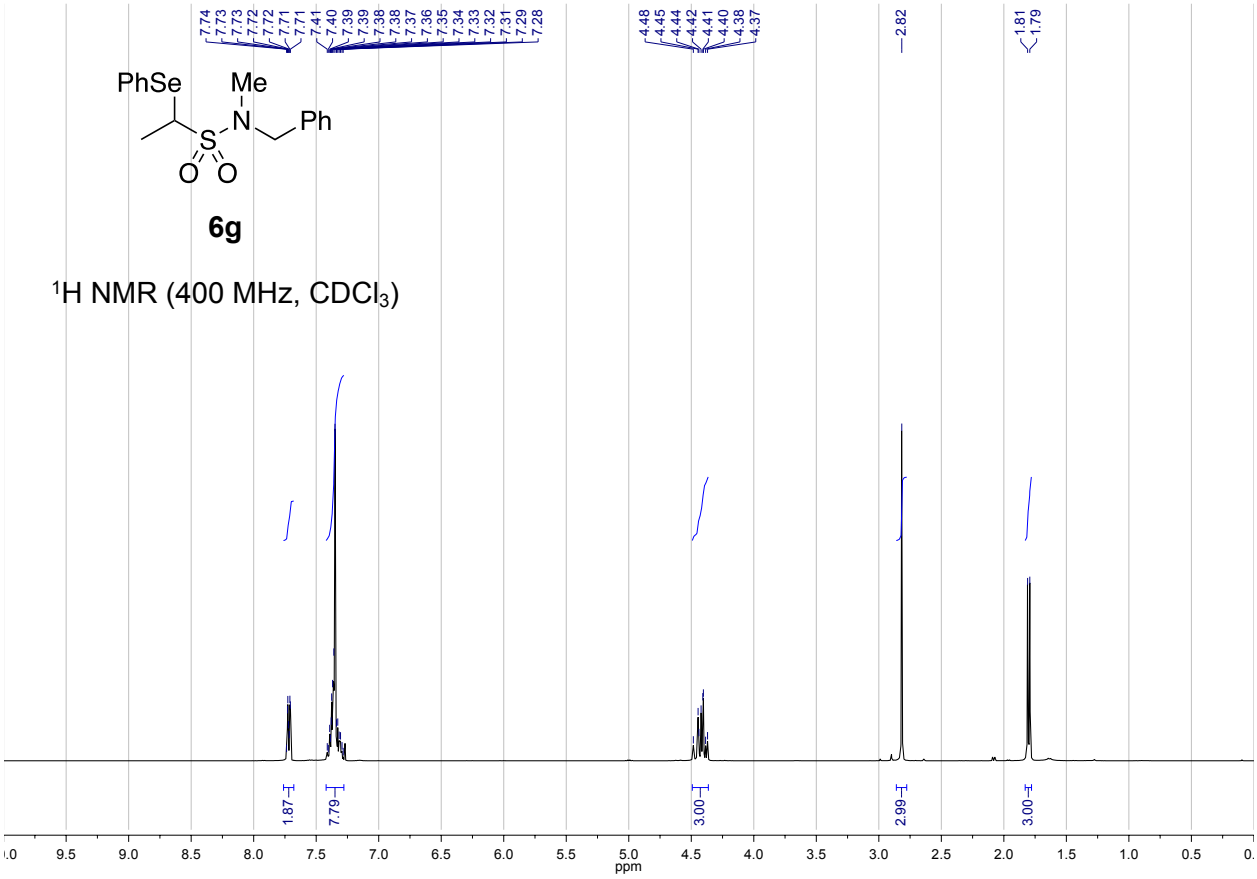
5g

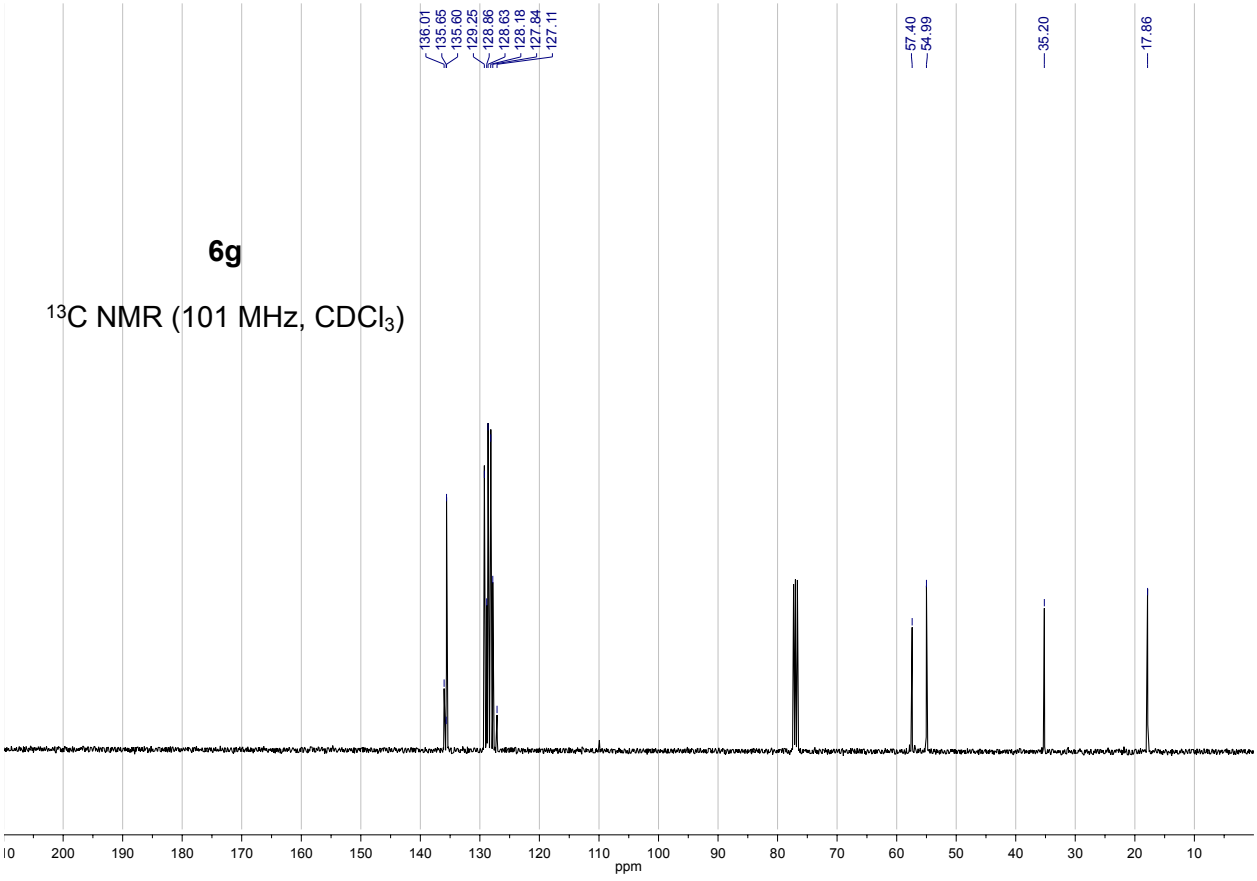
^{1}H NMR (400 MHz, $CDCl_3$)

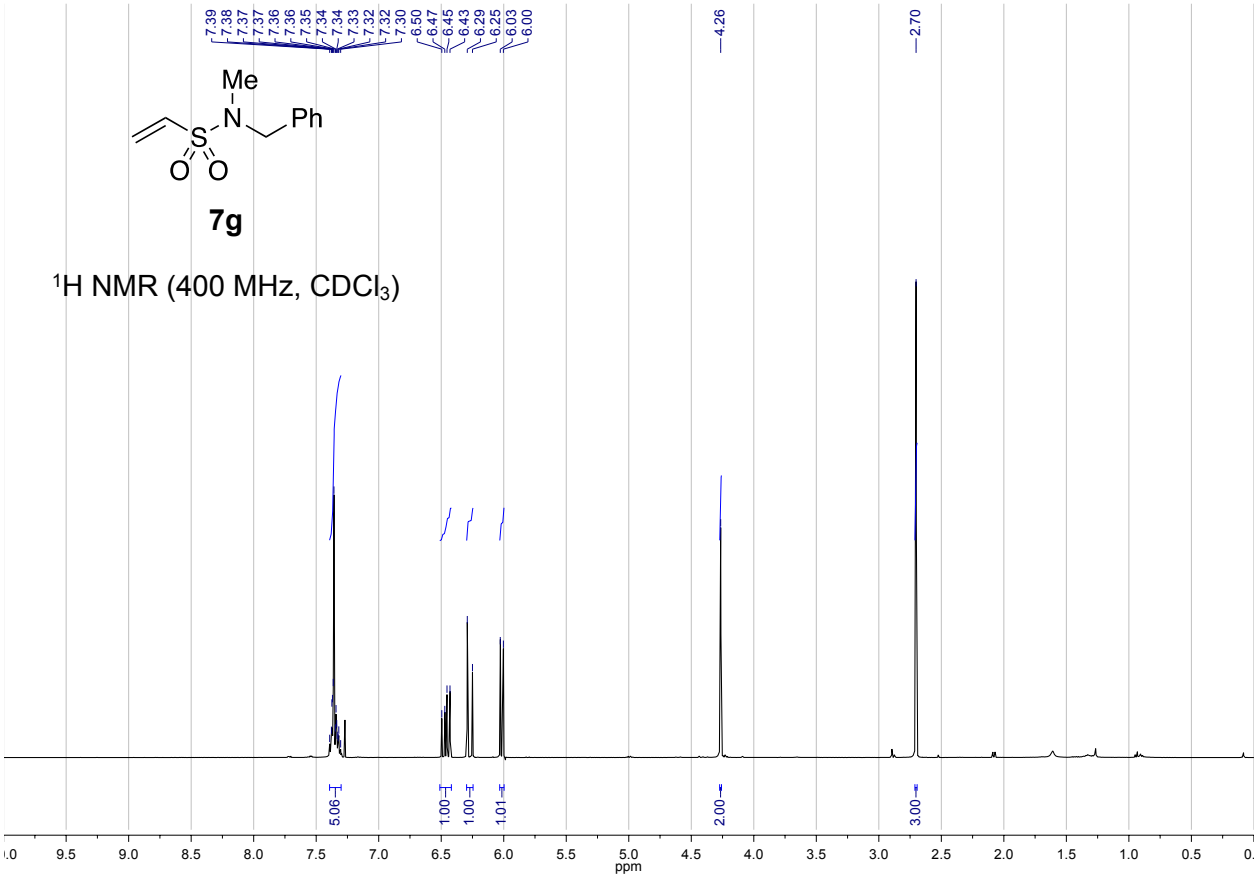


5g

^{13}C NMR (101 MHz, $CDCl_3$)

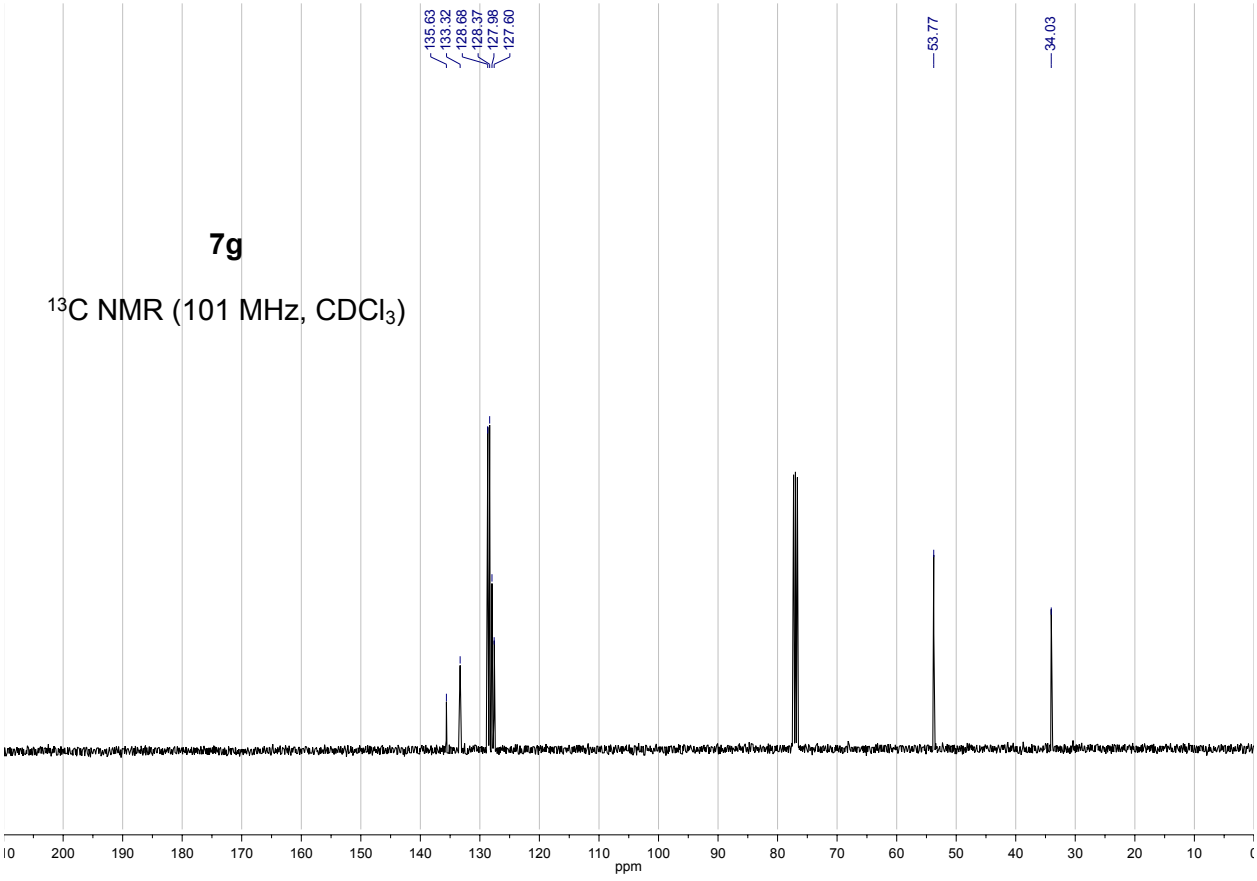

PhSe
Me
N
Ph
S
O
O
6g
^{1}H NMR (400 MHz, CDCl$_3$)
ppm


6g
^{13}C NMR (101 MHz, CDCl$_3$)
ppm



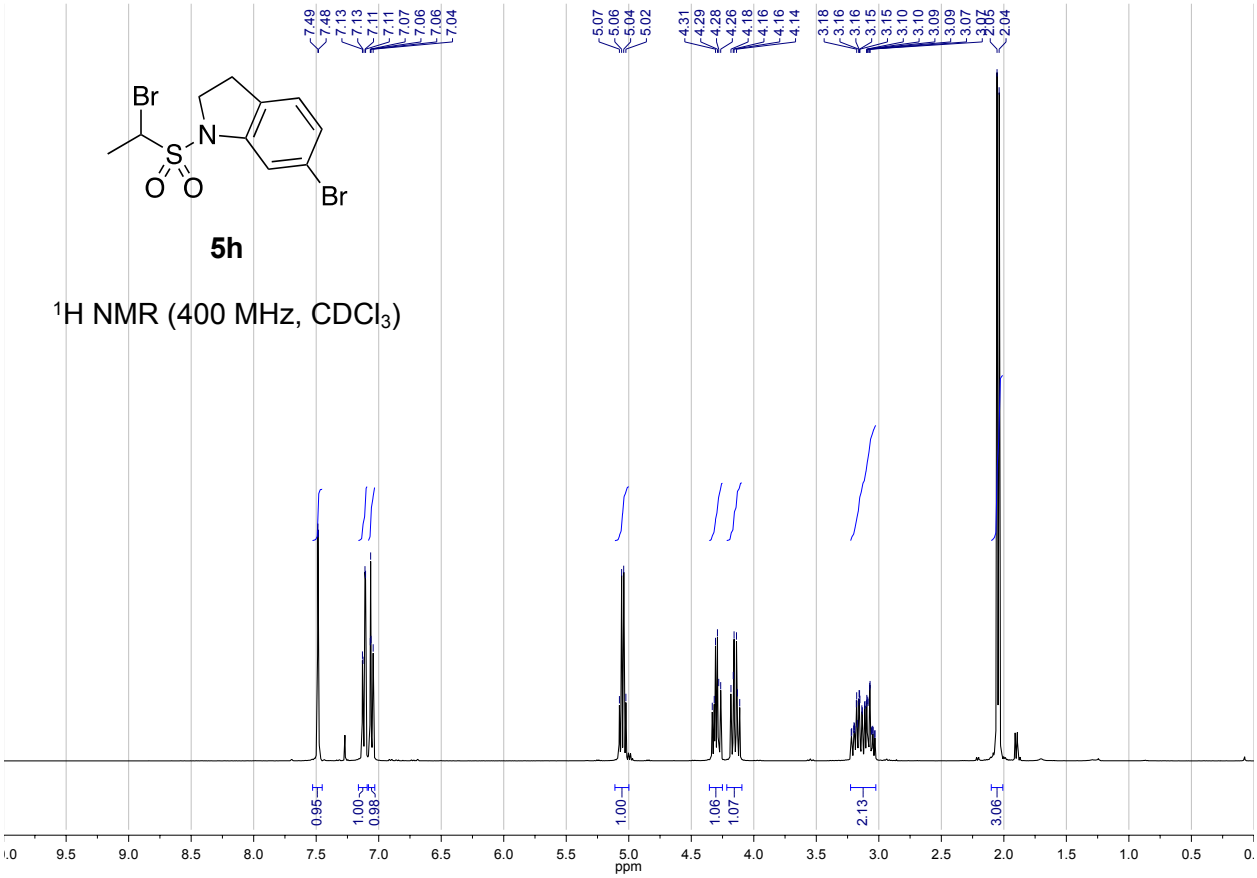
7g

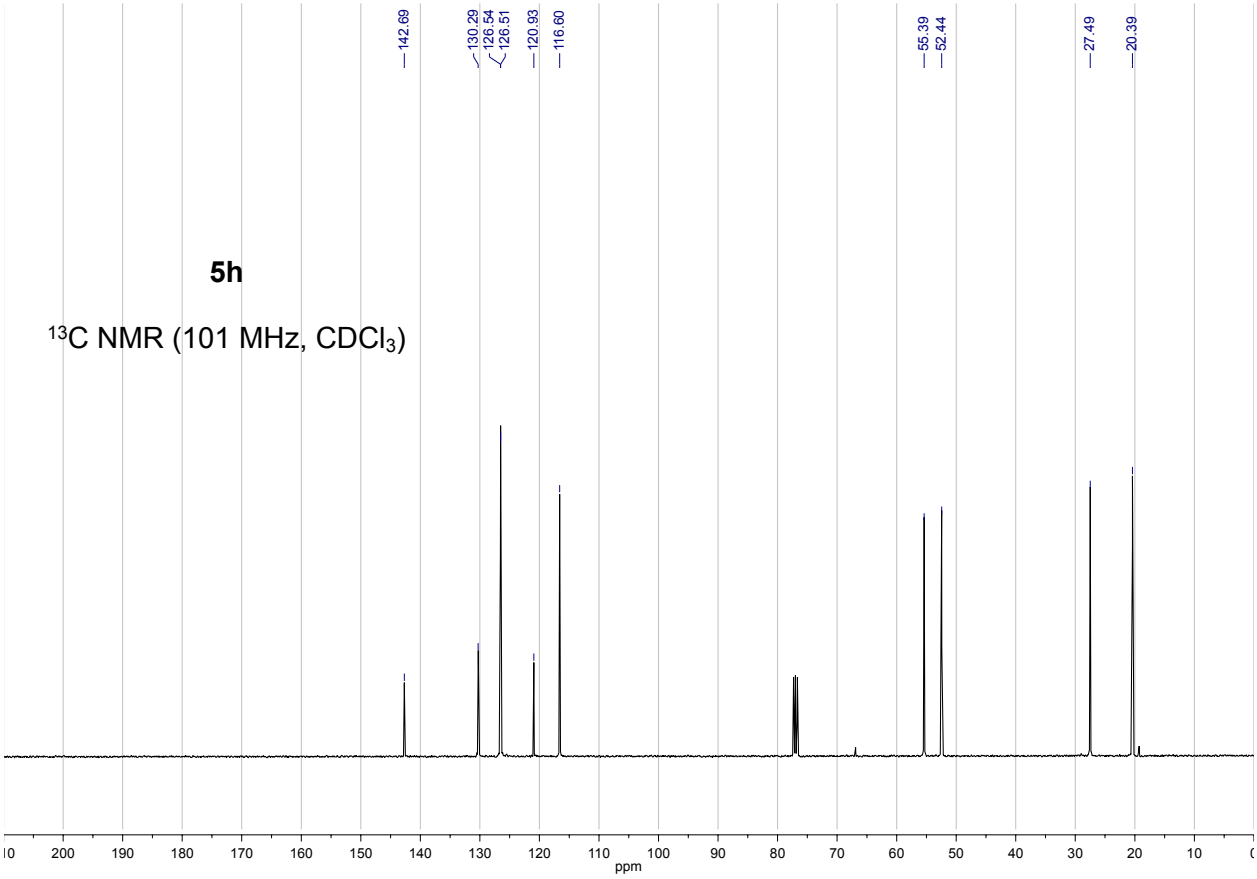
^{1}H NMR (400 MHz, $CDCl_3$)

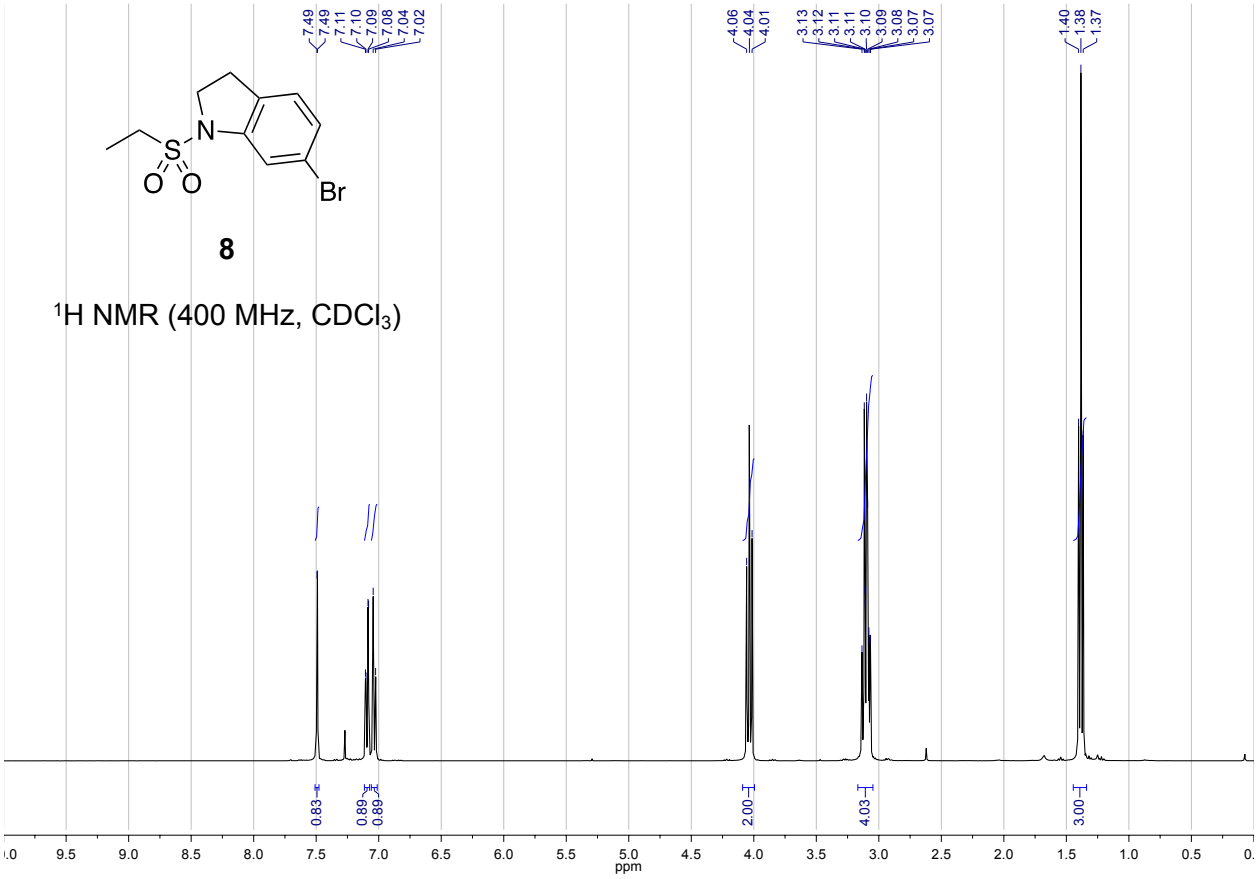


7g

^{13}C NMR (101 MHz, $CDCl_3$)

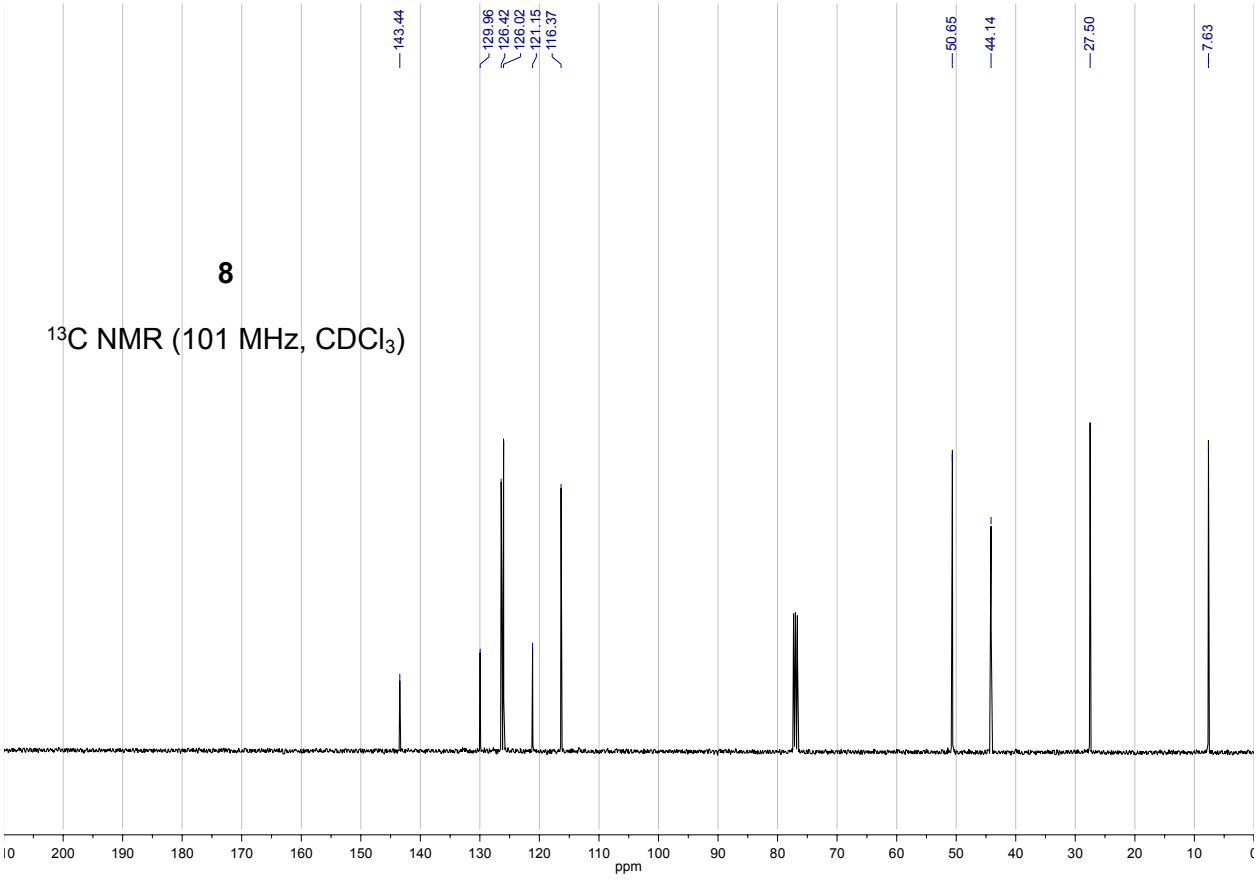

Br
S
N
O
O
Br
5h
1H NMR (400 MHz, CDCl3)
7.49
7.48
7.13
7.13
7.11
7.11
7.07
7.06
7.06
7.04
5.07
5.06
5.04
5.02
4.31
4.29
4.28
4.26
4.18
4.16
4.16
4.14
3.18
3.16
3.16
3.15
3.15
3.10
3.10
3.09
3.09
3.07
2.05
2.04
0.95
1.00
0.98
1.00
1.06
1.07
2.13
3.06
ppm


5h
13C NMR (101 MHz, CDCl3)
142.69
130.29
126.54
126.51
120.93
116.60
55.39
52.44
27.49
20.39
ppm



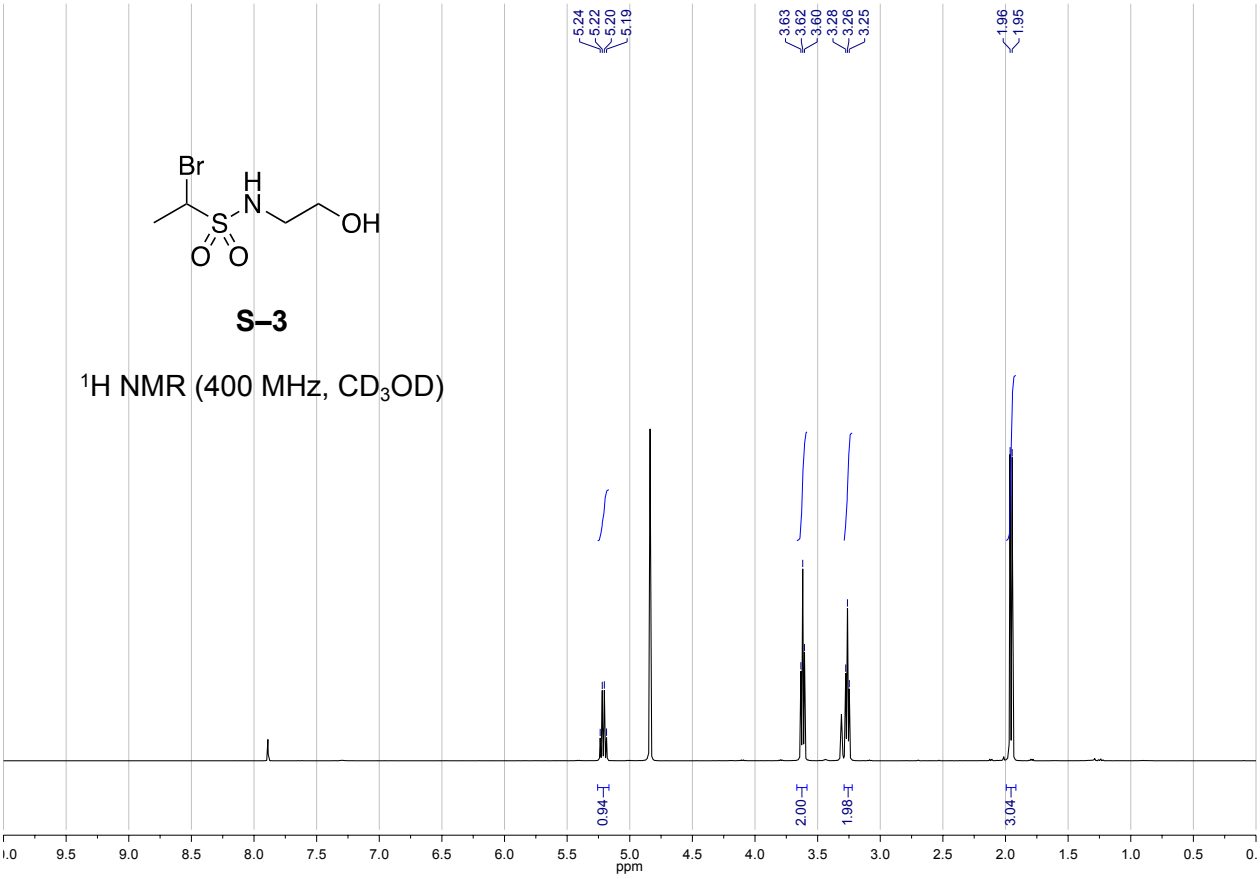
8

^{1}H NMR (400 MHz, $CDCl_3$)



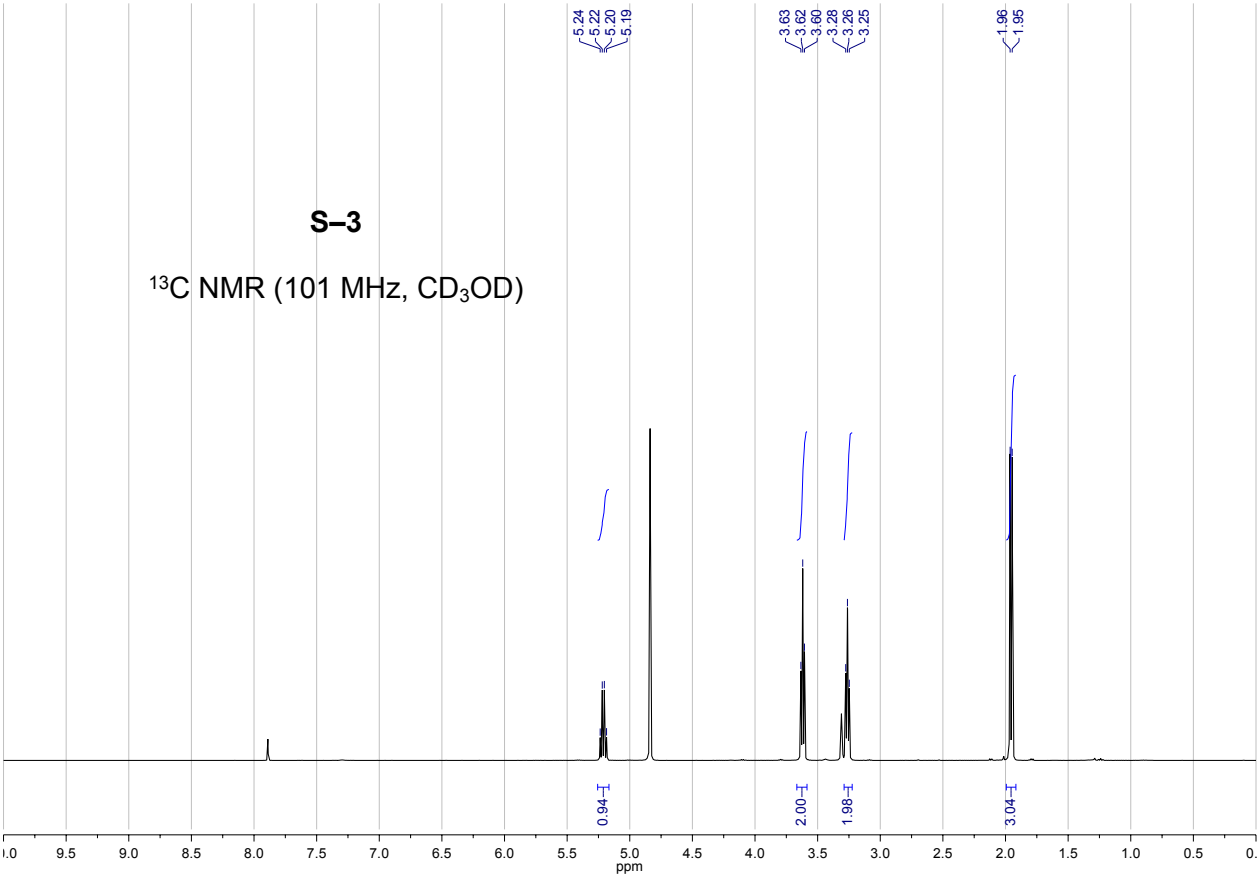
8

^{13}C NMR (101 MHz, $CDCl_3$)



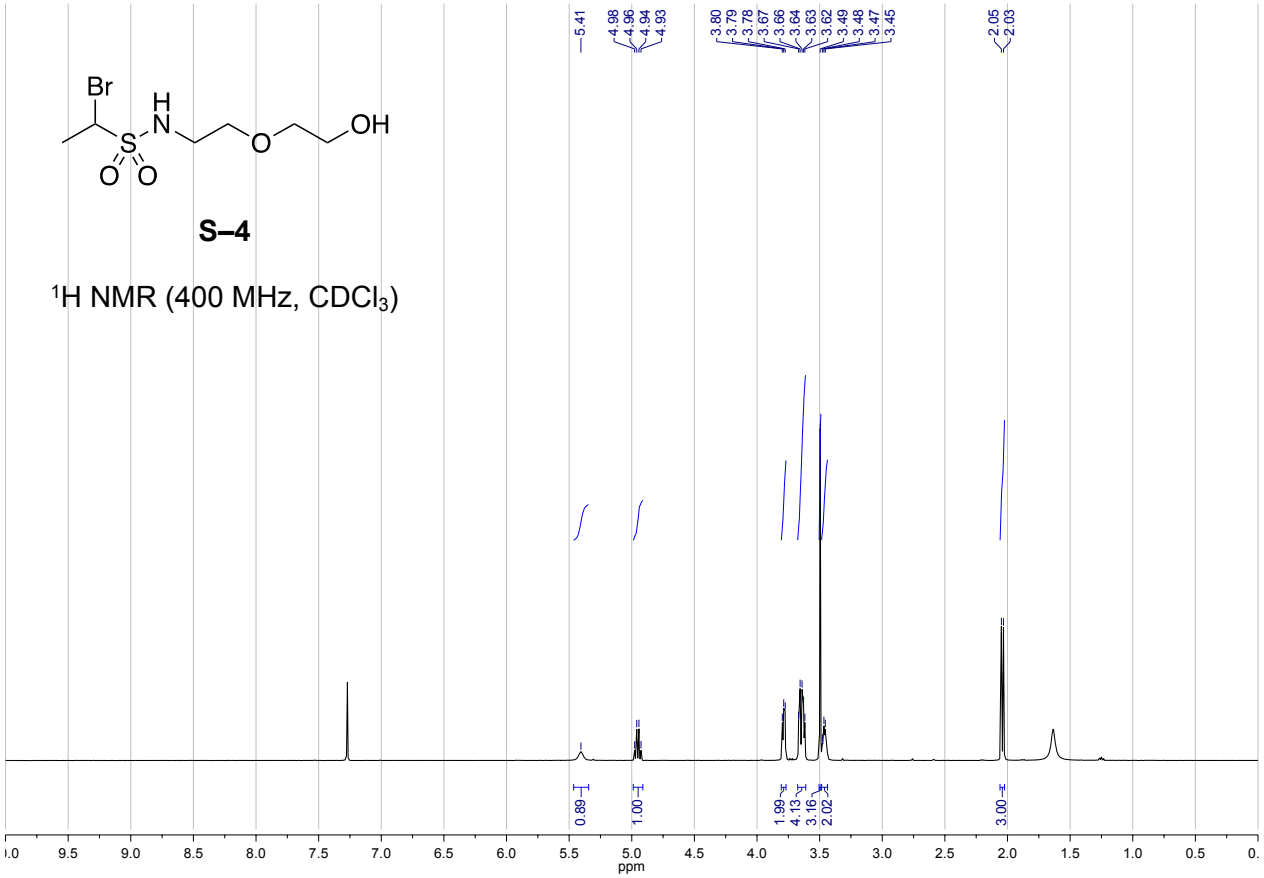
S–3

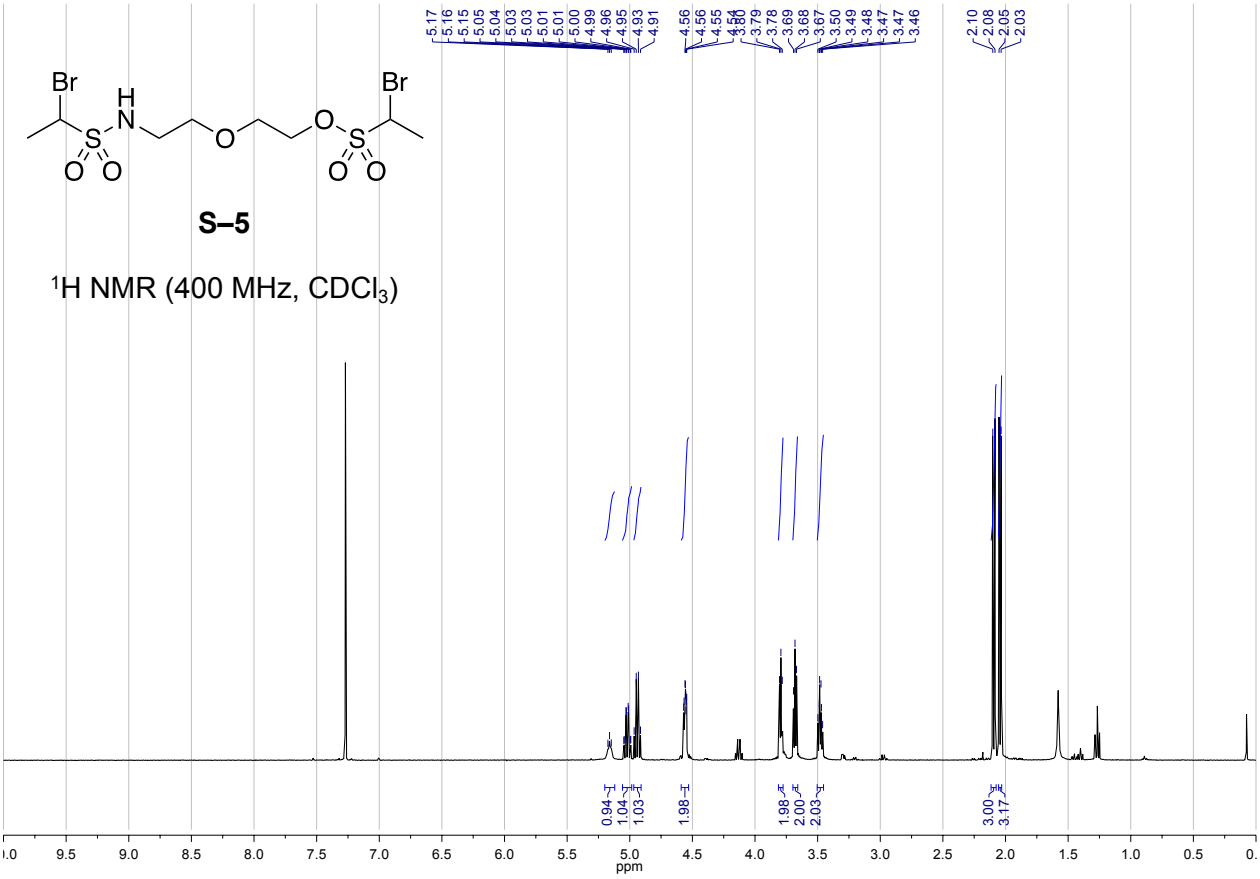
^{1}H NMR (400 MHz, CD_3OD)

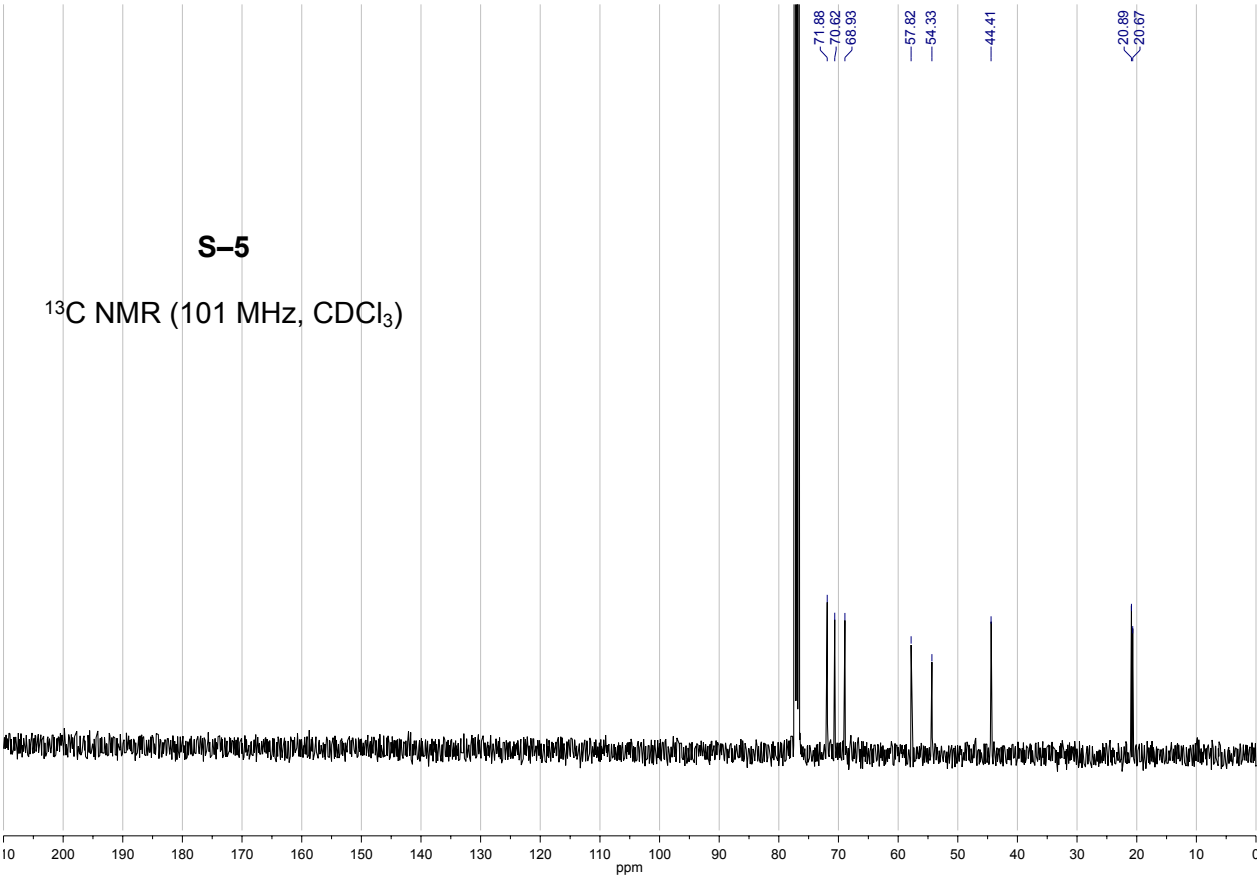


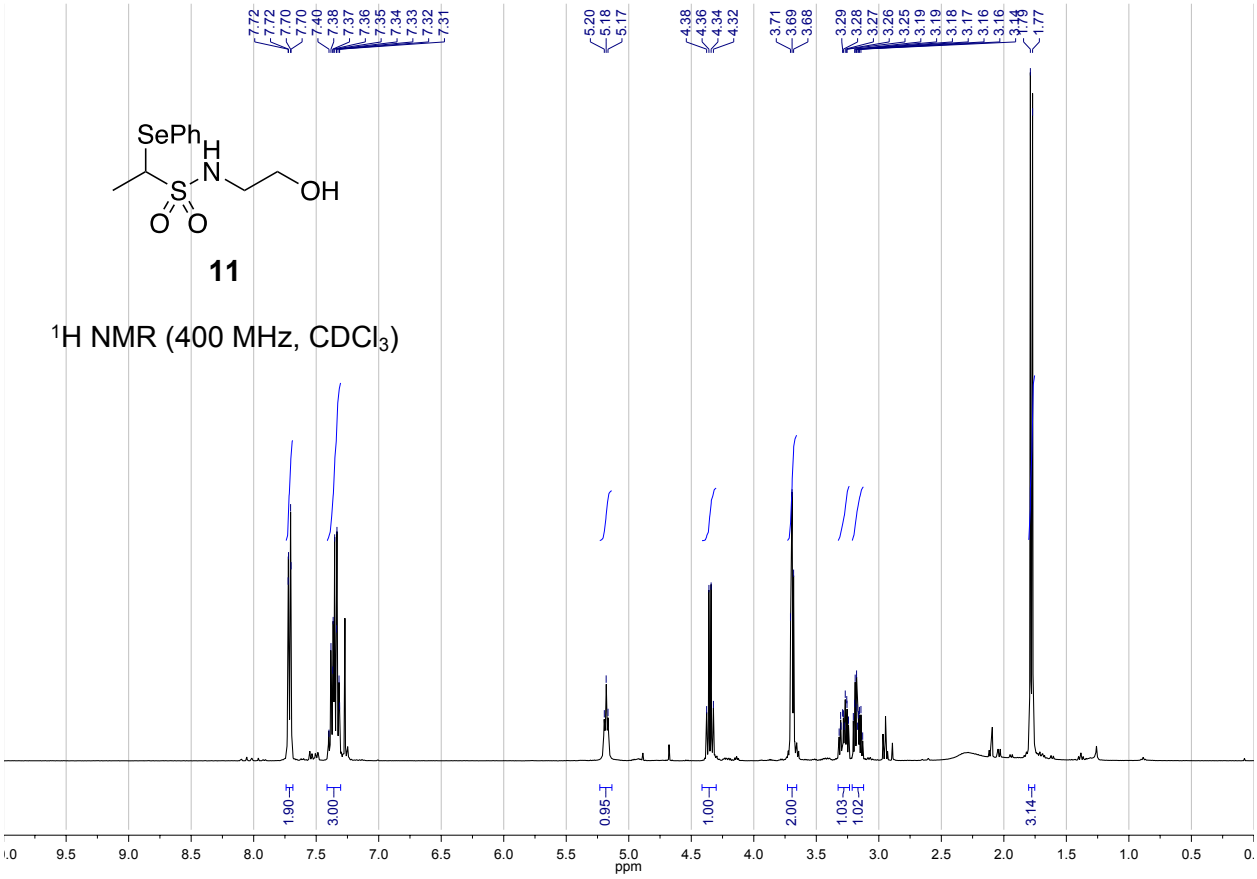
S–3

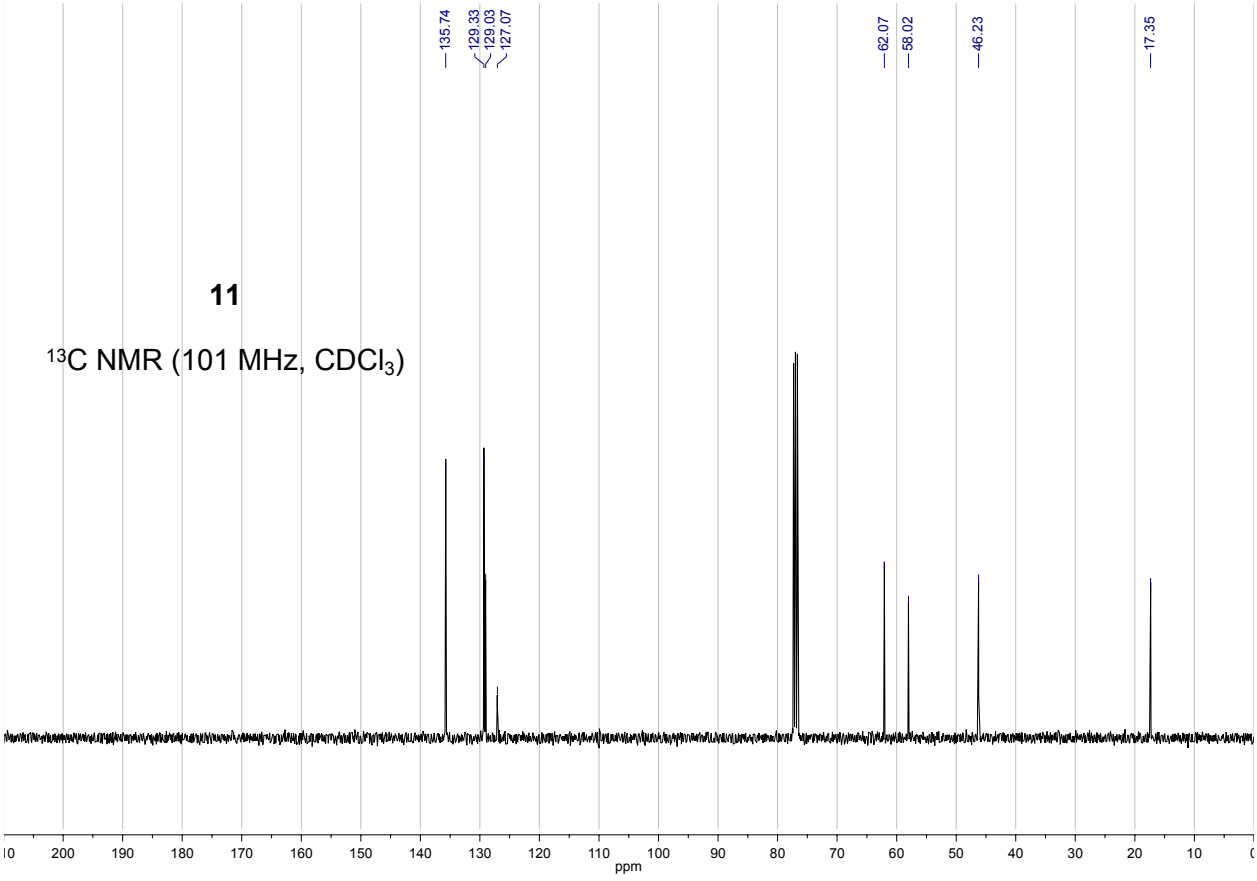
^{13}C NMR (101 MHz, CD_3OD)

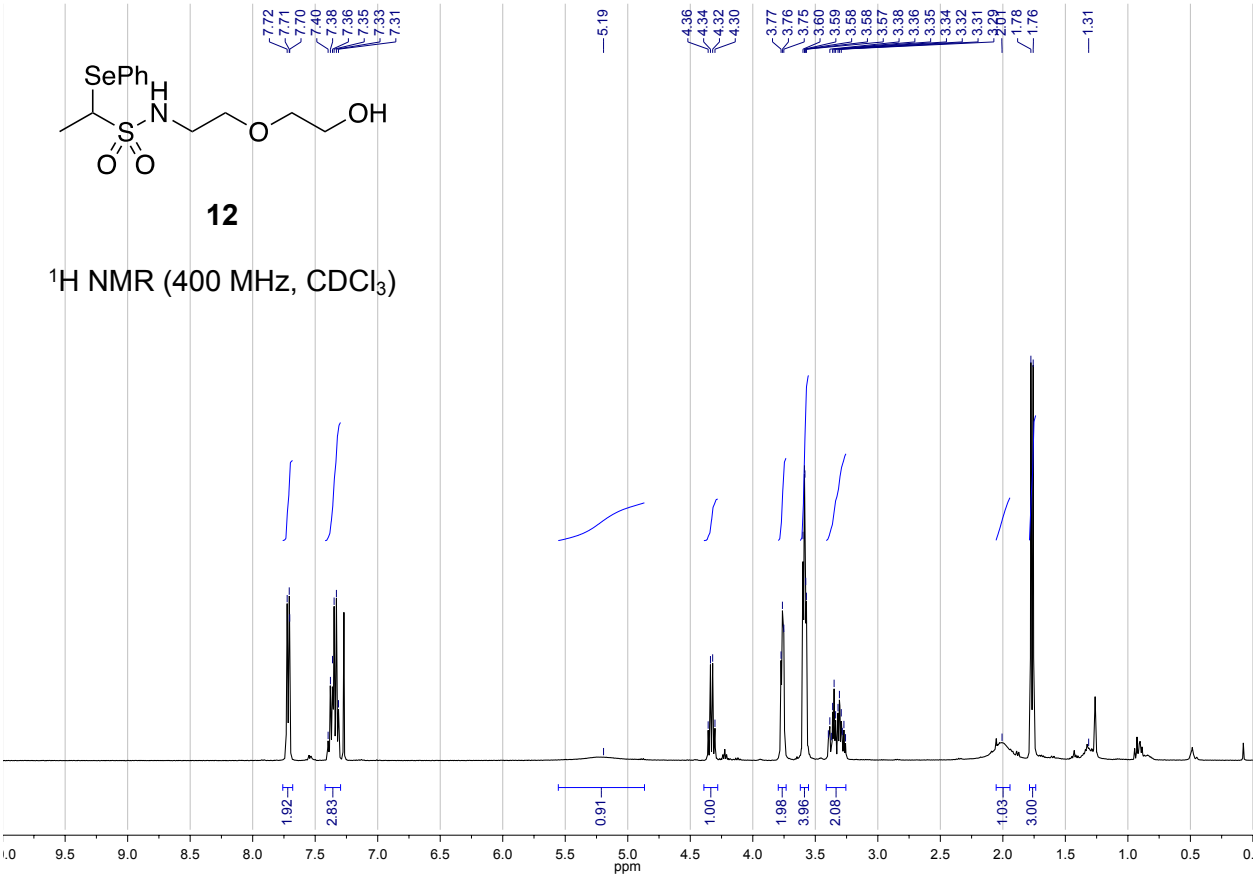

Br
H
N
S
O
O
O
OH
S–4
^{1}H NMR (400 MHz, CDCl$_3$)
5.41
4.98
4.96
4.94
4.93
3.80
3.79
3.78
3.67
3.66
3.64
3.63
3.62
3.49
3.48
3.47
3.45
2.05
2.03
0.89
1.00
1.99
4.13
3.16
2.02
3.00
ppm

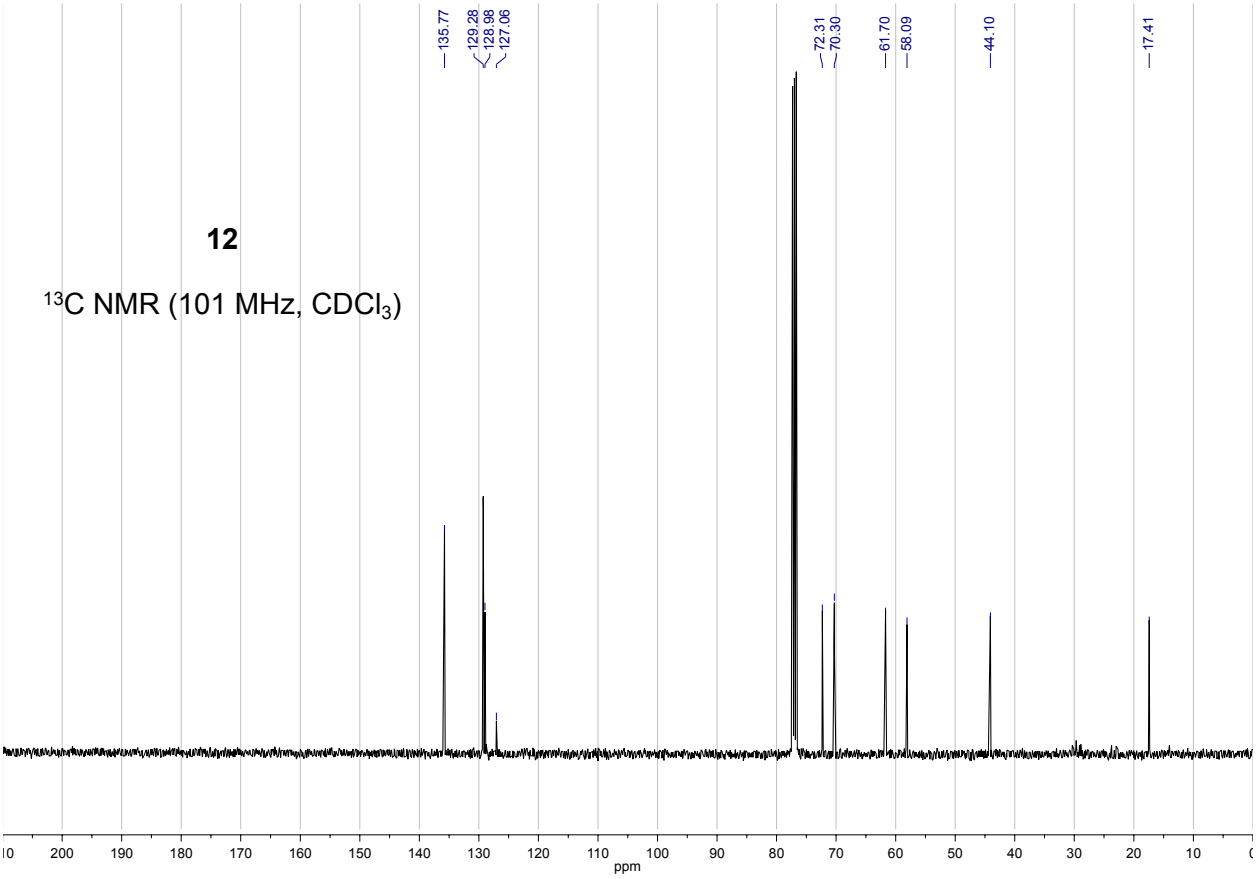

Br
H
N
Br
S
S
O
O
O
O
O
O
S–5
^{1}H NMR (400 MHz, $CDCl_3$)
5.17
5.16
5.15
5.05
5.04
5.03
5.03
5.01
5.01
5.00
4.99
4.96
4.95
4.93
4.91
4.56
4.56
4.55
3.80
3.79
3.78
3.69
3.68
3.67
3.50
3.49
3.48
3.47
3.47
3.46
2.10
2.08
2.05
2.03
0.94
1.04
1.03
1.98
1.98
2.00
2.03
3.00
3.17
ppm

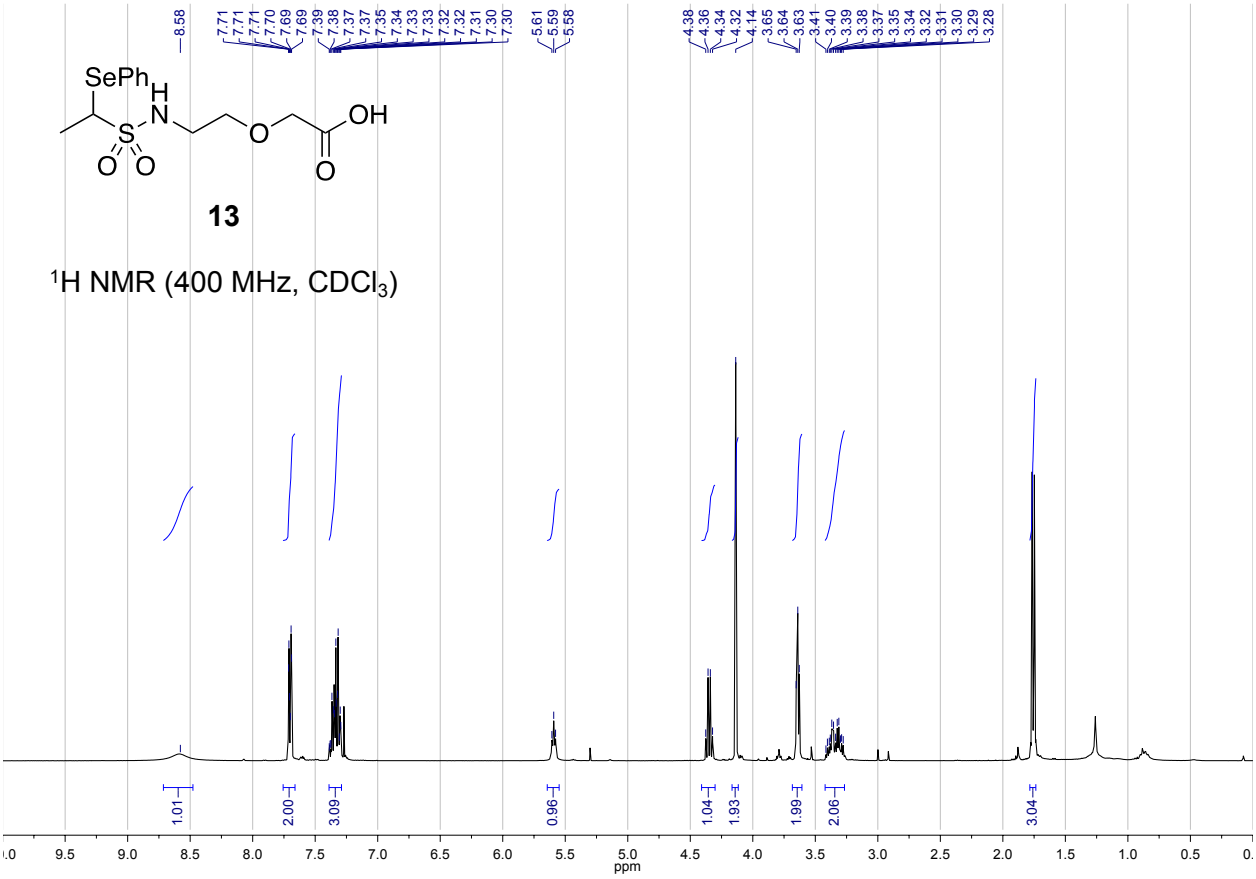

S–5
^{13}C NMR (101 MHz, $CDCl_3$)
71.88
70.62
68.93
57.82
54.33
44.41
20.89
20.67
ppm

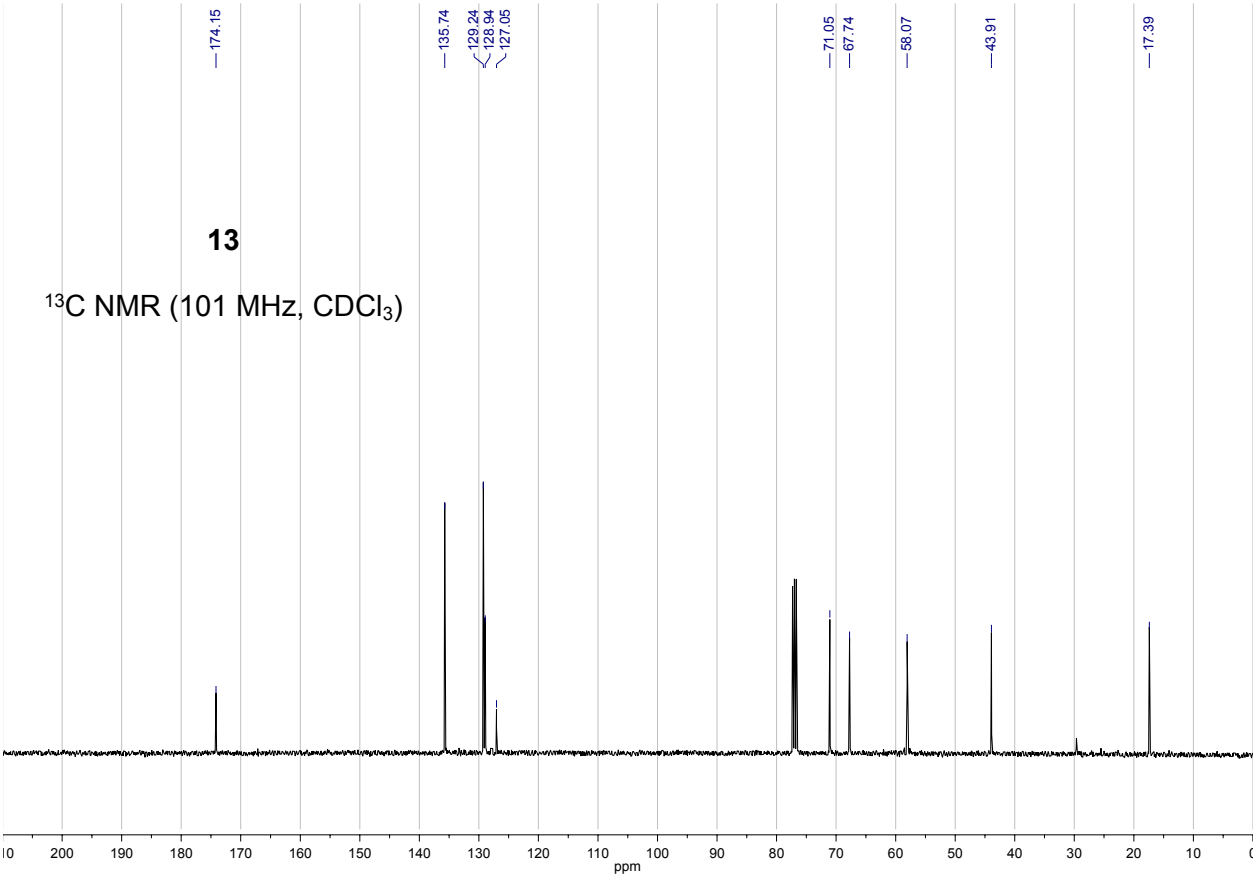

SePh
H
N
S
O O
OH
11
^{1}H NMR (400 MHz, CDCl$_3$)
7.72
7.72
7.70
7.70
7.40
7.38
7.37
7.36
7.35
7.34
7.33
7.32
7.31
5.20
5.18
5.17
4.38
4.36
4.34
4.32
3.71
3.69
3.68
3.29
3.28
3.27
3.26
3.25
3.19
3.19
3.18
3.17
3.16
3.16
3.14
3.13
1.77
1.90
3.00
0.95
1.00
2.00
1.03
1.02
3.14
ppm

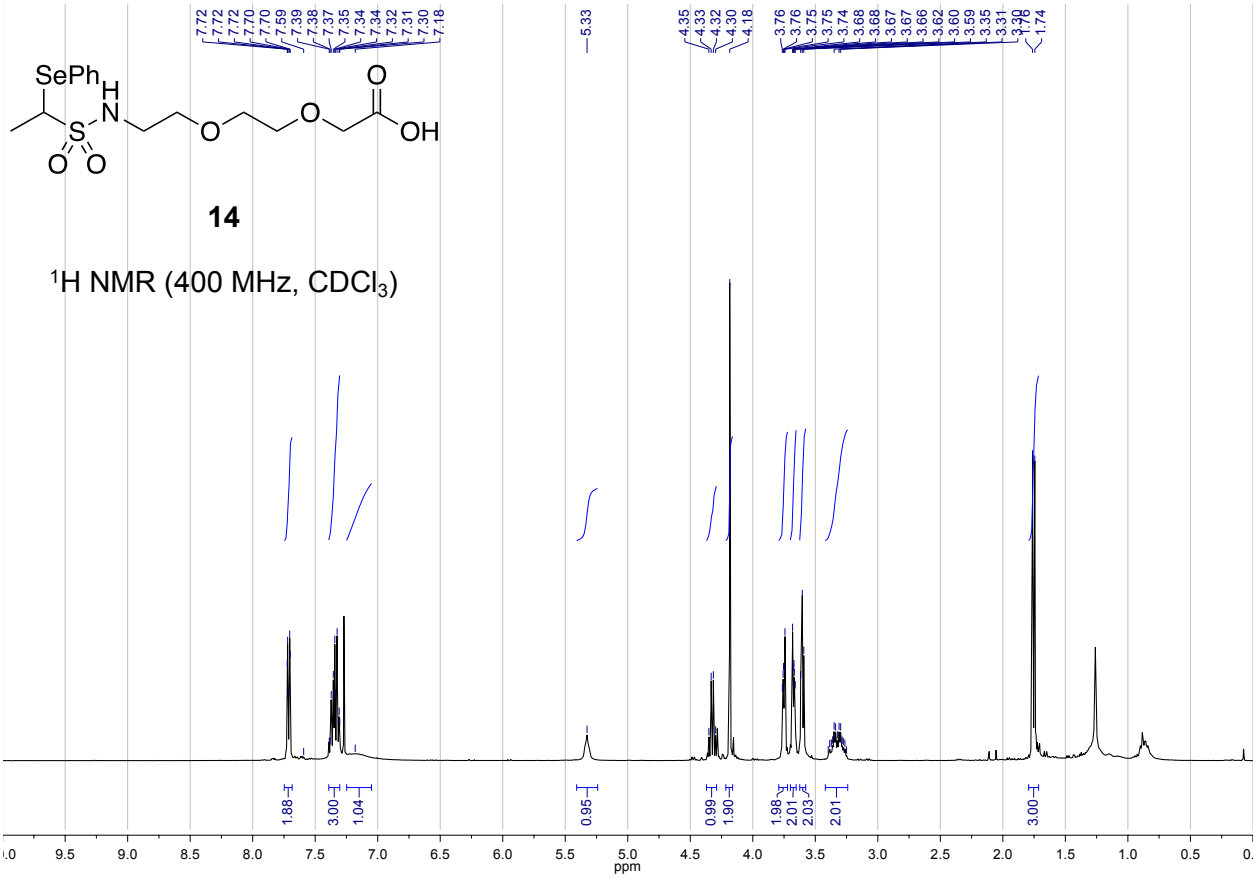

11
^{13}C NMR (101 MHz, CDCl$_3$)
135.74
129.33
129.03
127.07
62.07
58.02
46.23
17.35
ppm

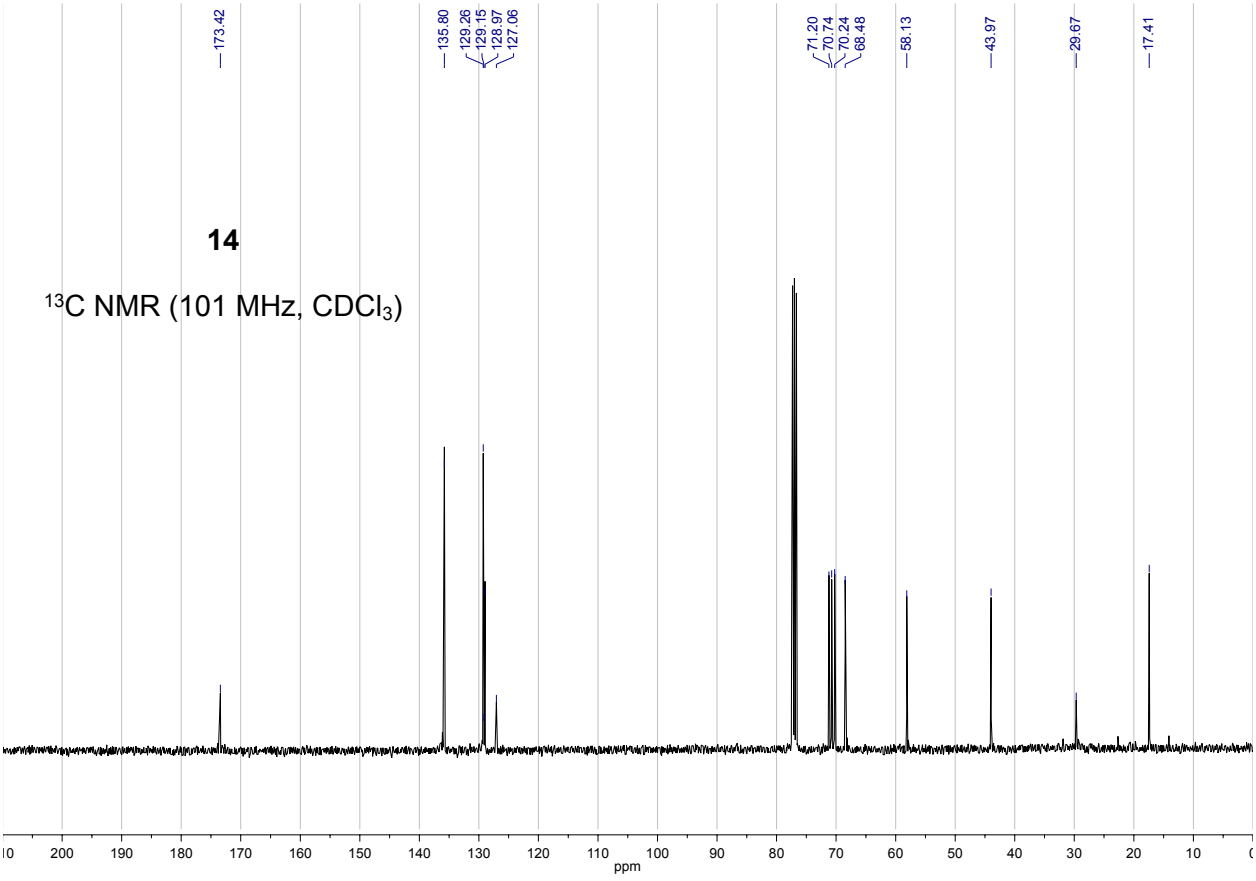

SePh
H
N
S
O
O
OH
12
^{1}H NMR (400 MHz, CDCl$_3$)
7.72
7.71
7.70
7.40
7.38
7.36
7.35
7.33
7.31
5.19
4.36
4.34
4.32
4.30
3.77
3.76
3.75
3.60
3.59
3.58
3.58
3.57
3.38
3.36
3.35
3.34
3.32
3.31
2.01
1.78
1.76
1.31
1.92
2.83
0.91
1.00
1.98
3.96
2.08
1.03
3.00
ppm

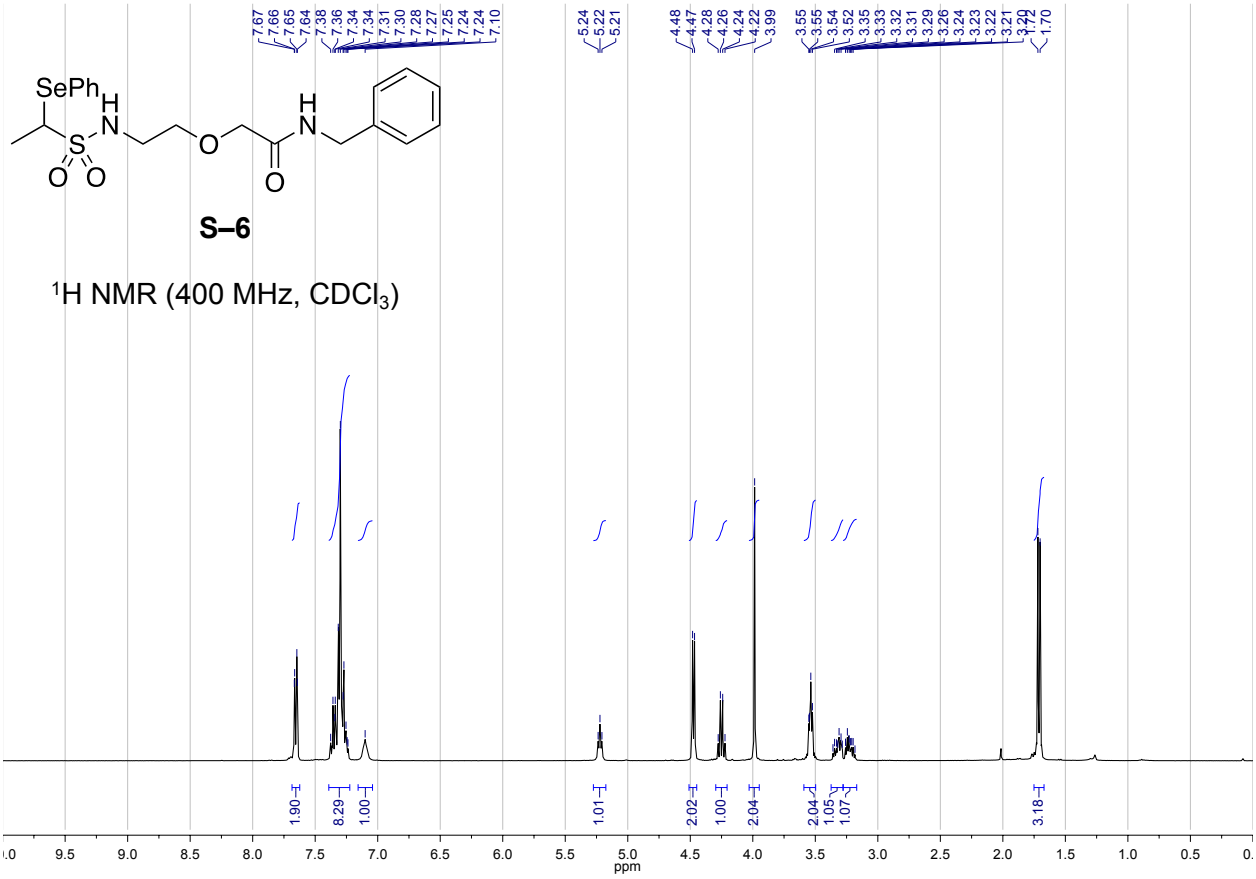

135.77
129.28
128.98
127.06
72.31
70.30
61.70
58.09
44.10
17.41
12
^{13}C NMR (101 MHz, CDCl$_3$)
ppm

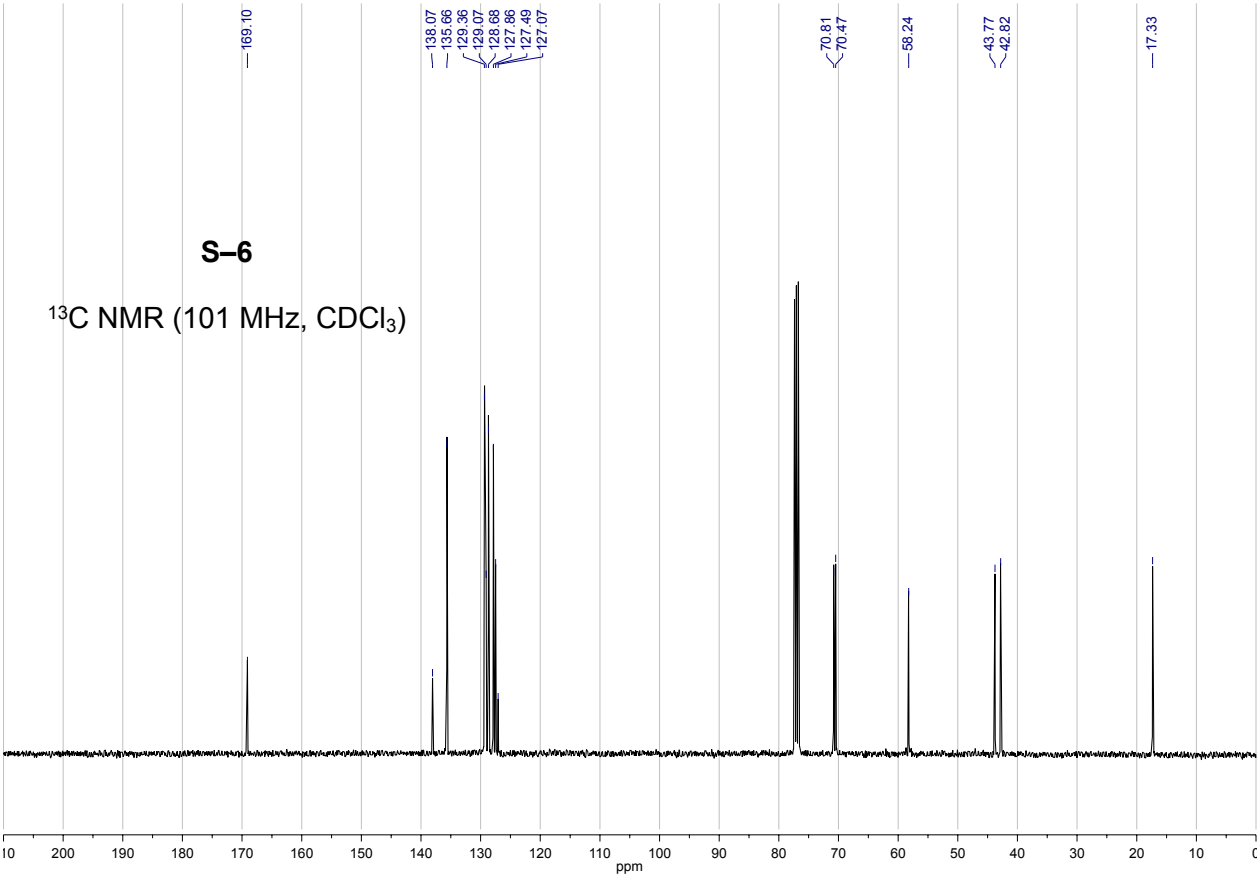

SePh
H
N
S
O
O
O
O
OH
13
1H NMR (400 MHz, CDCl3)
ppm

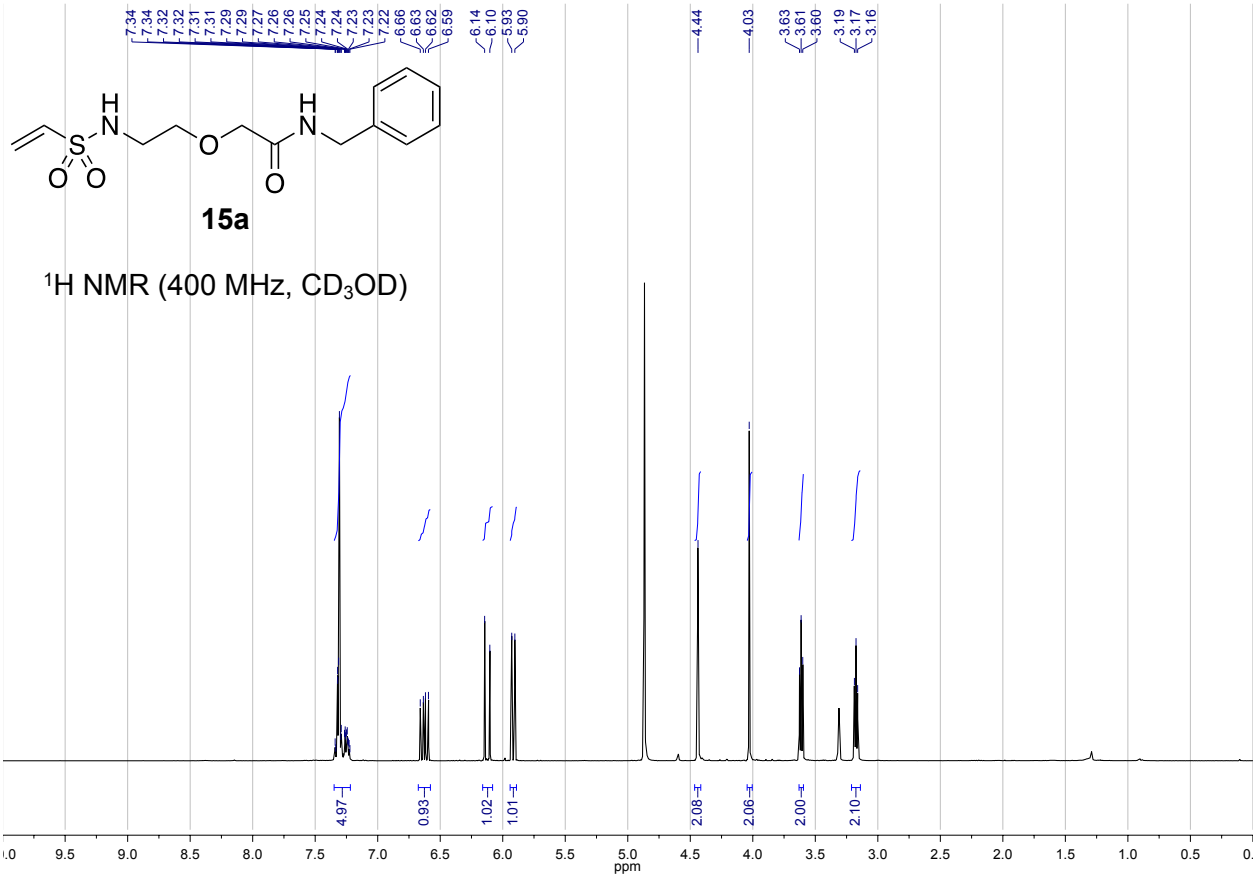

13
13C NMR (101 MHz, CDCl3)
ppm


SePh
H
N
S
O
O
O
O
O
OH
14
1H NMR (400 MHz, CDCl3)
ppm


14
13C NMR (101 MHz, CDCl3)
ppm

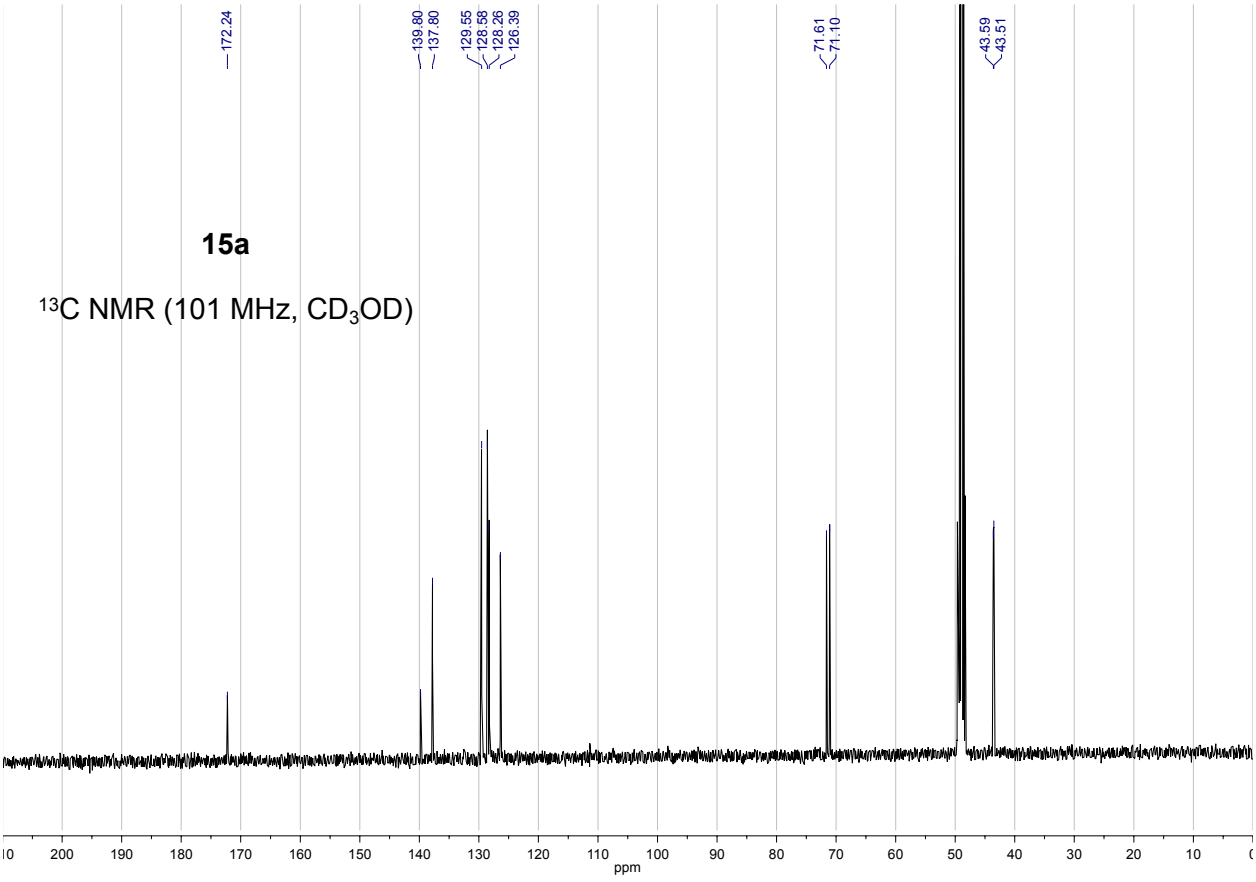

SePh
H
N
S
O
O
O
H
N
O
S–6
^{1}H NMR (400 MHz, CDCl$_3$)
ppm


S–6
^{13}C NMR (101 MHz, CDCl$_3$)
ppm



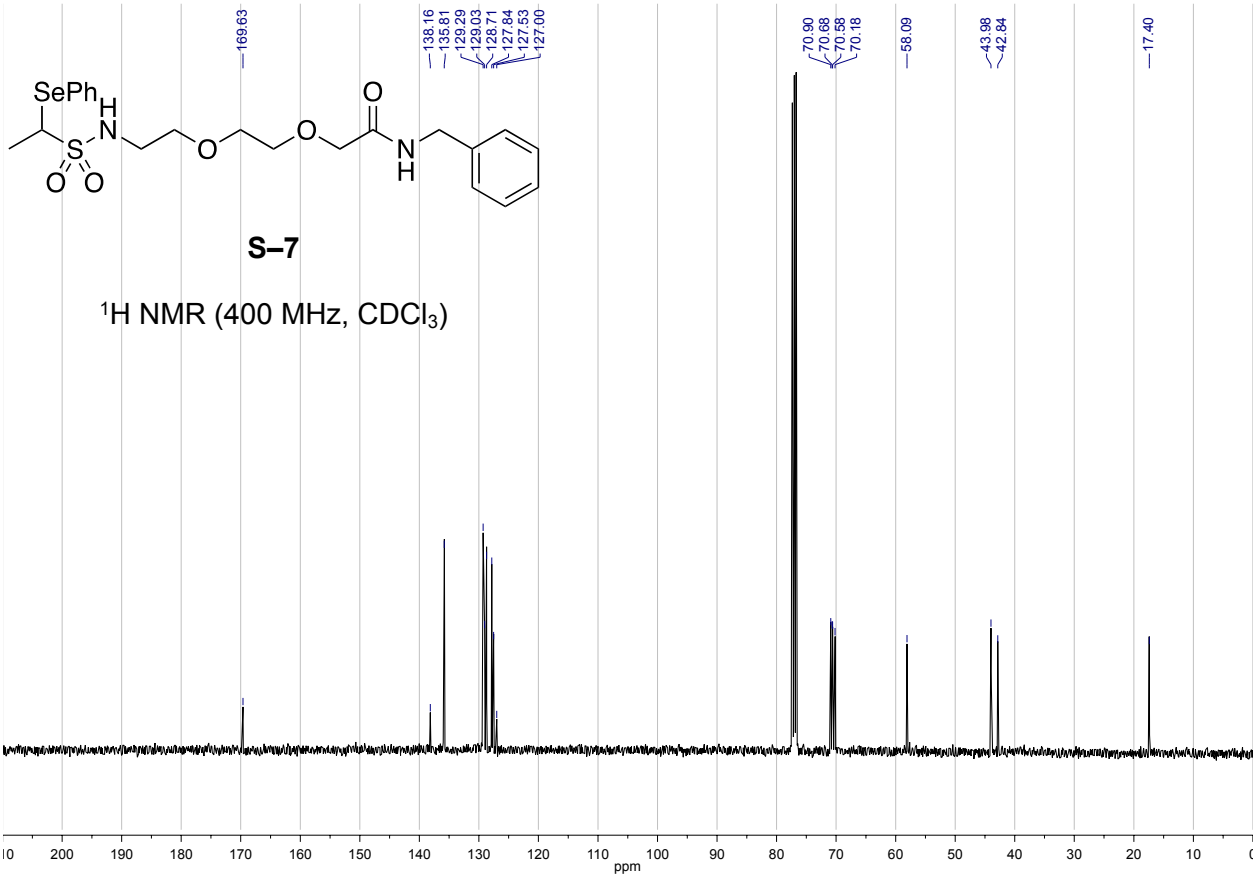
15a

^{1}H NMR (400 MHz, CD_3OD)



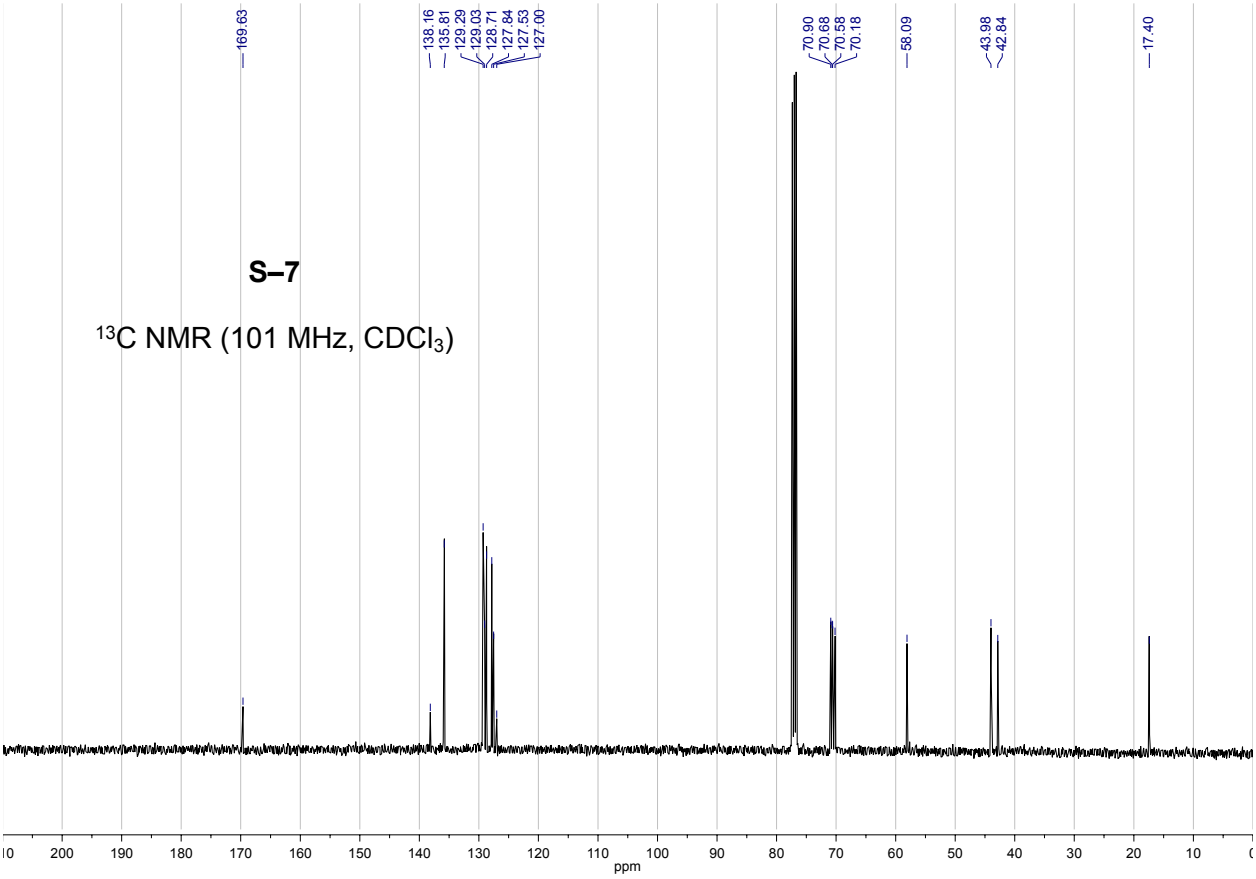
15a

^{13}C NMR (101 MHz, CD_3OD)



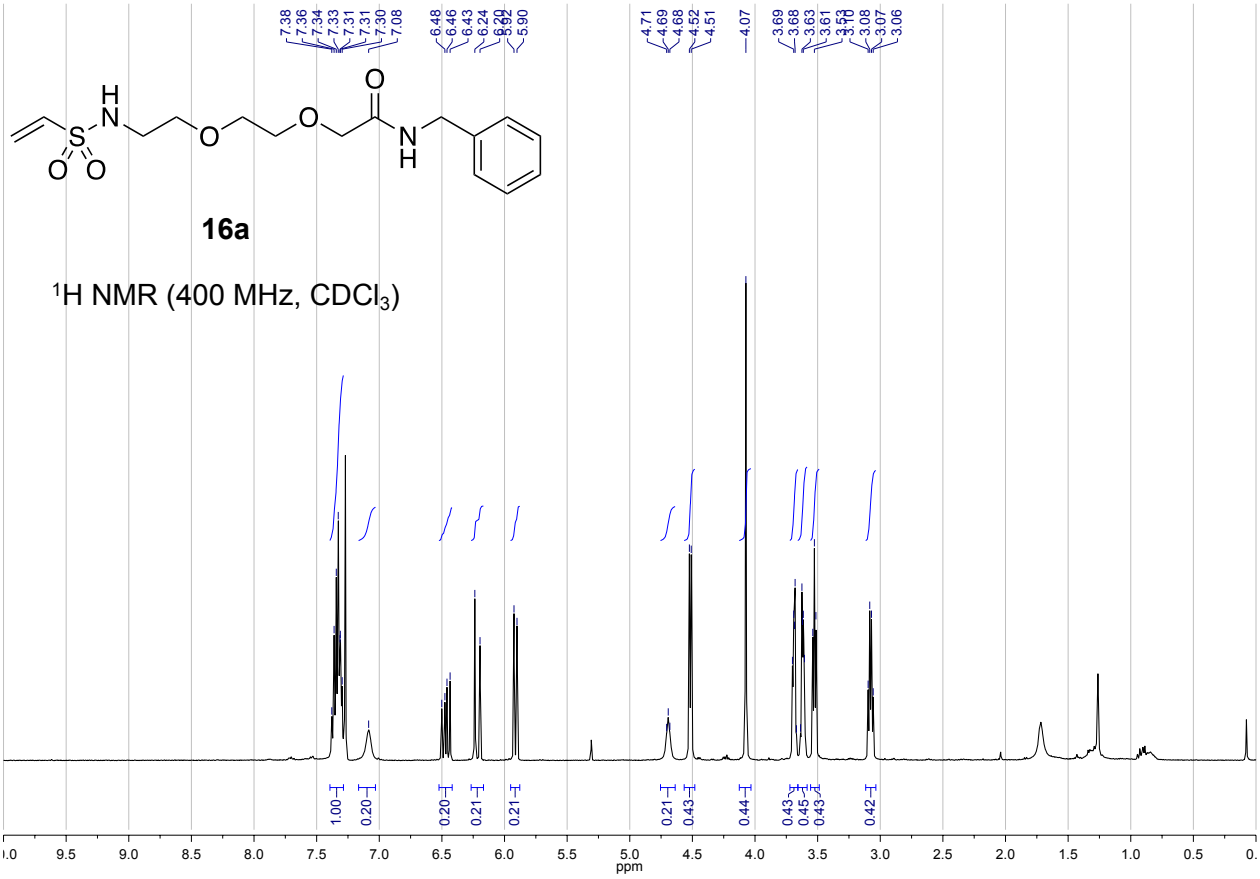
S–7

^{1}H NMR (400 MHz, $CDCl_3$)



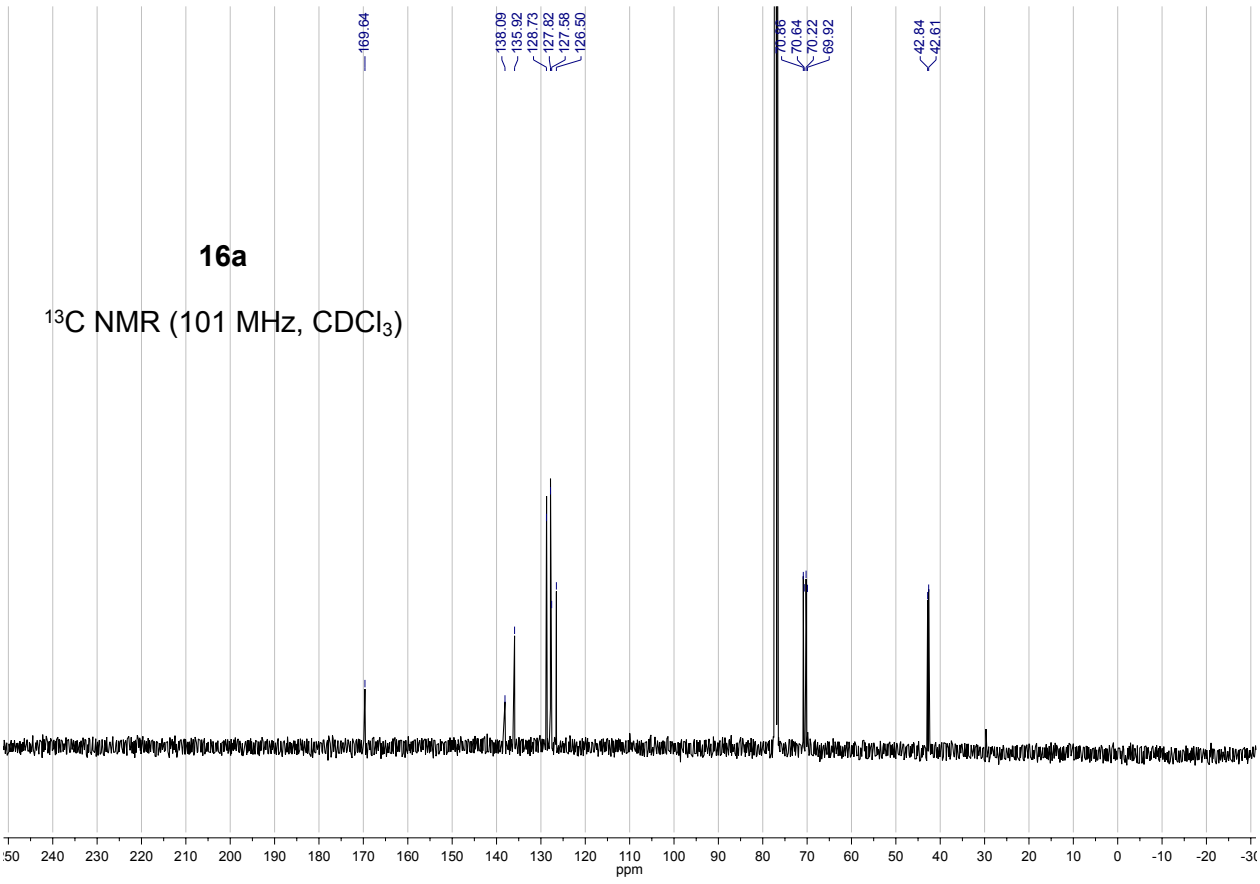
S–7

^{13}C NMR (101 MHz, $CDCl_3$)



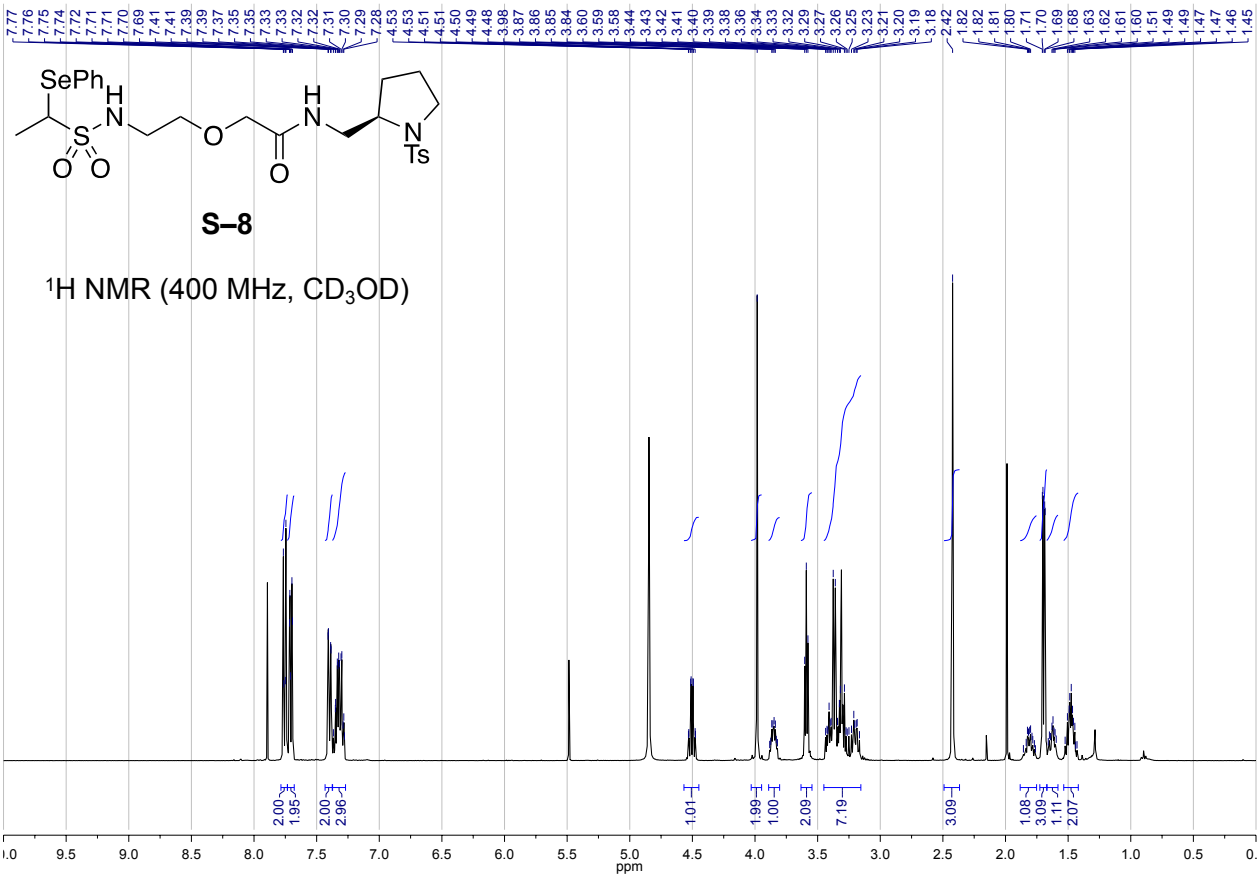
16a

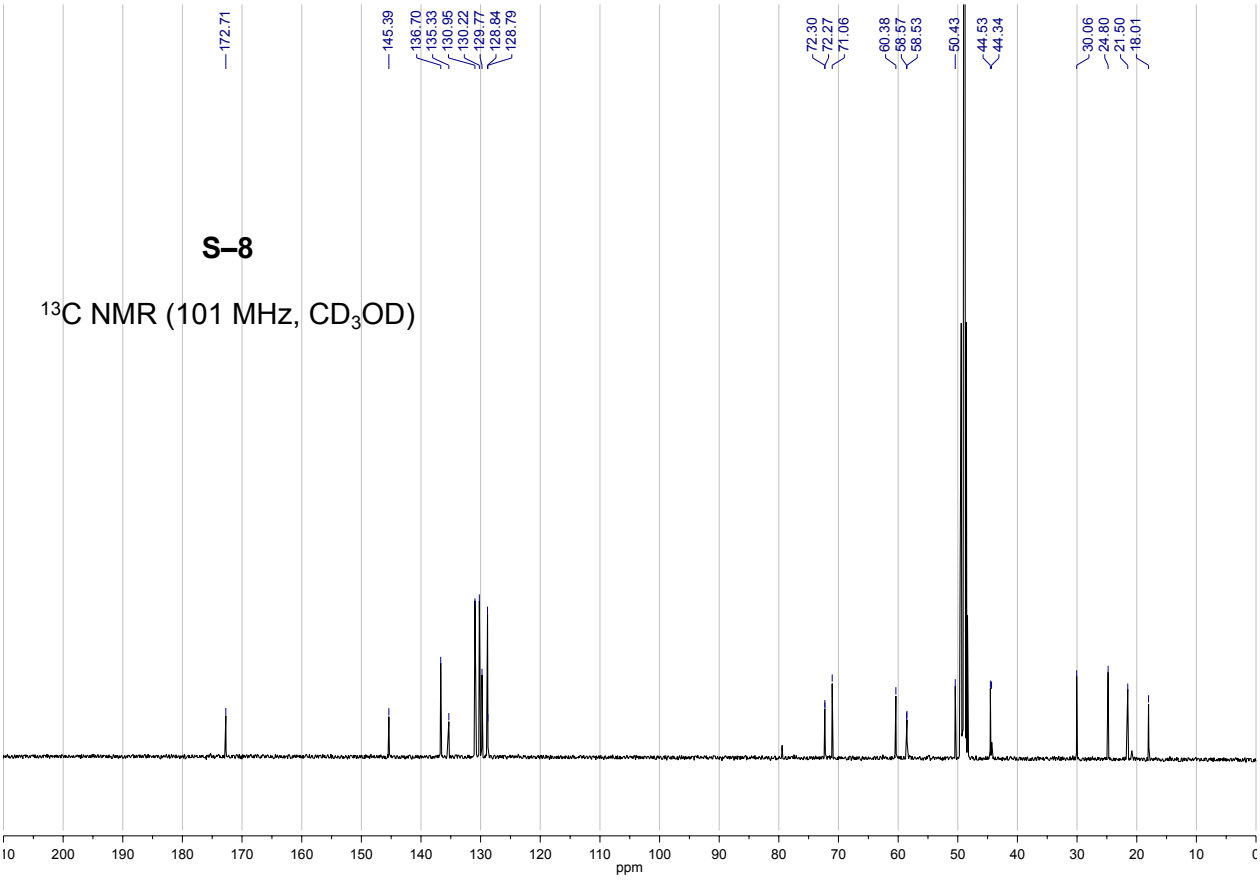
^{1}H NMR (400 MHz, $CDCl_3$)

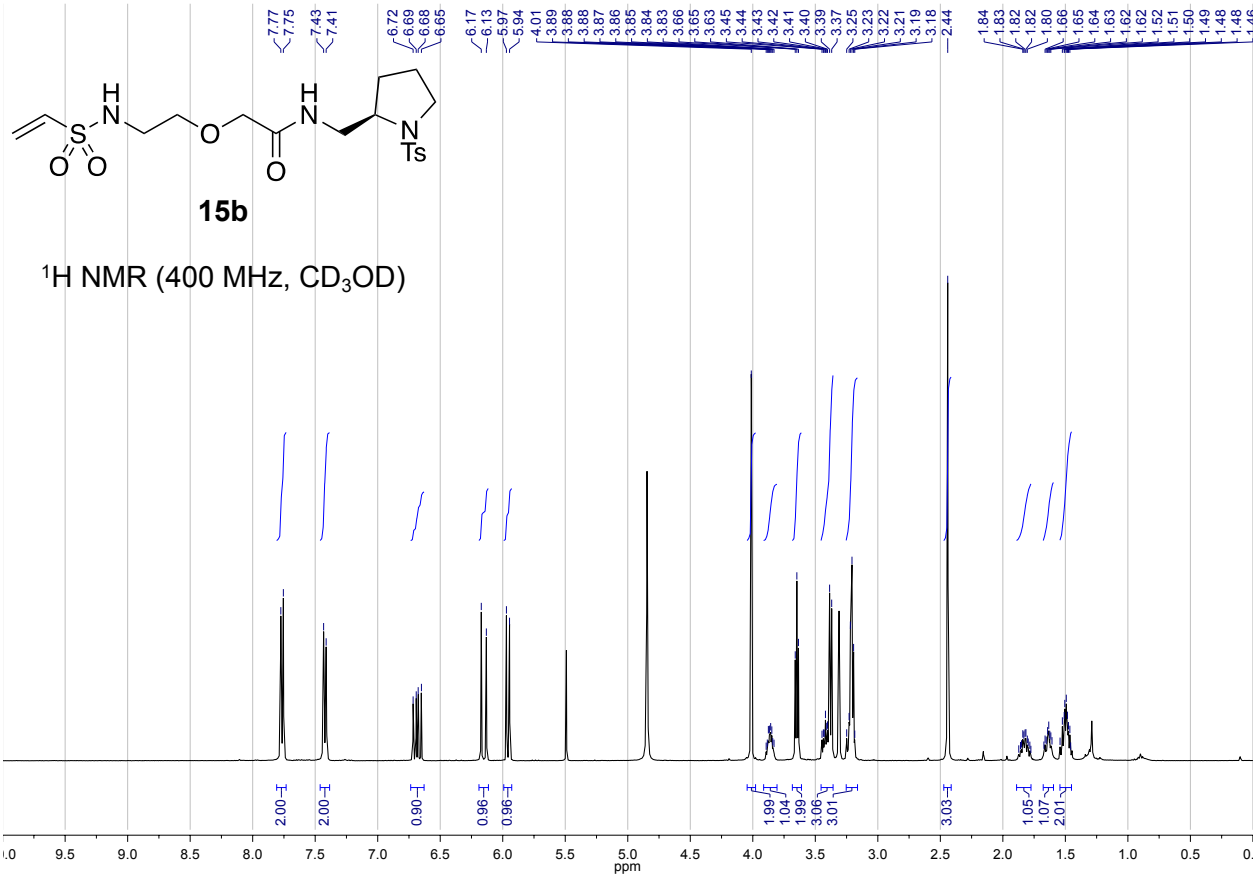


16a

^{13}C NMR (101 MHz, $CDCl_3$)

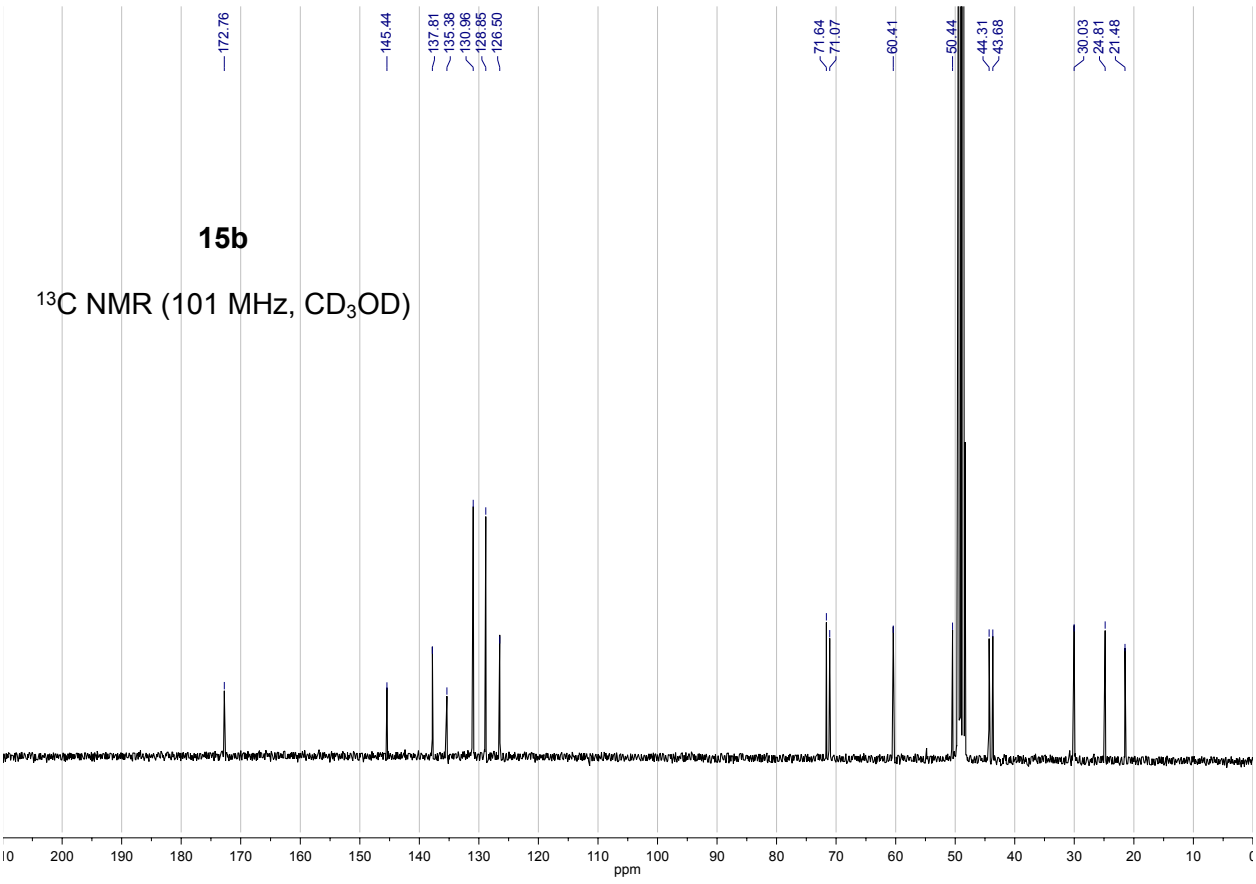

SePh
H
N
S
O
O
O
H
N
O
N
Ts
S–8
^{1}H NMR (400 MHz, CD_3OD)
ppm


S–8
^{13}C NMR (101 MHz, CD_3OD)
ppm



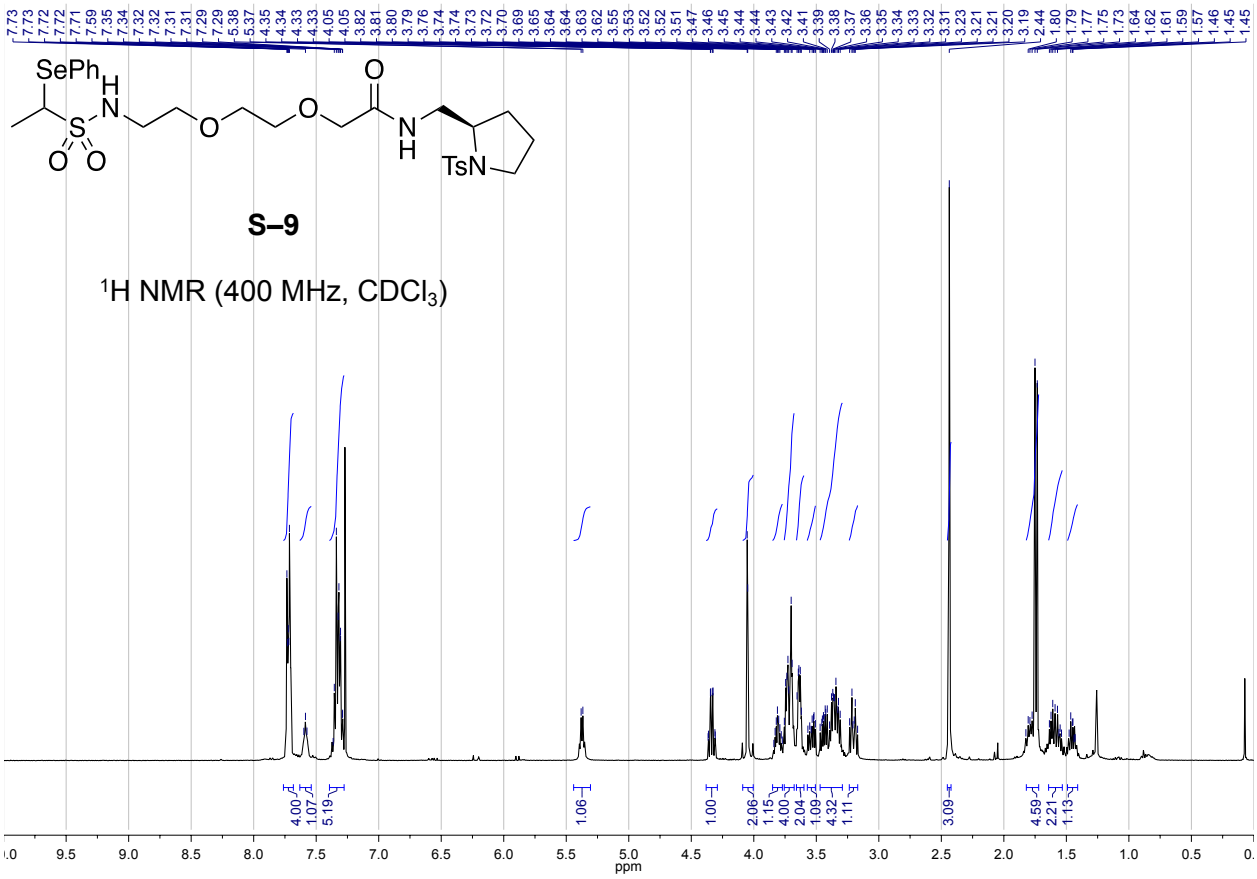
15b

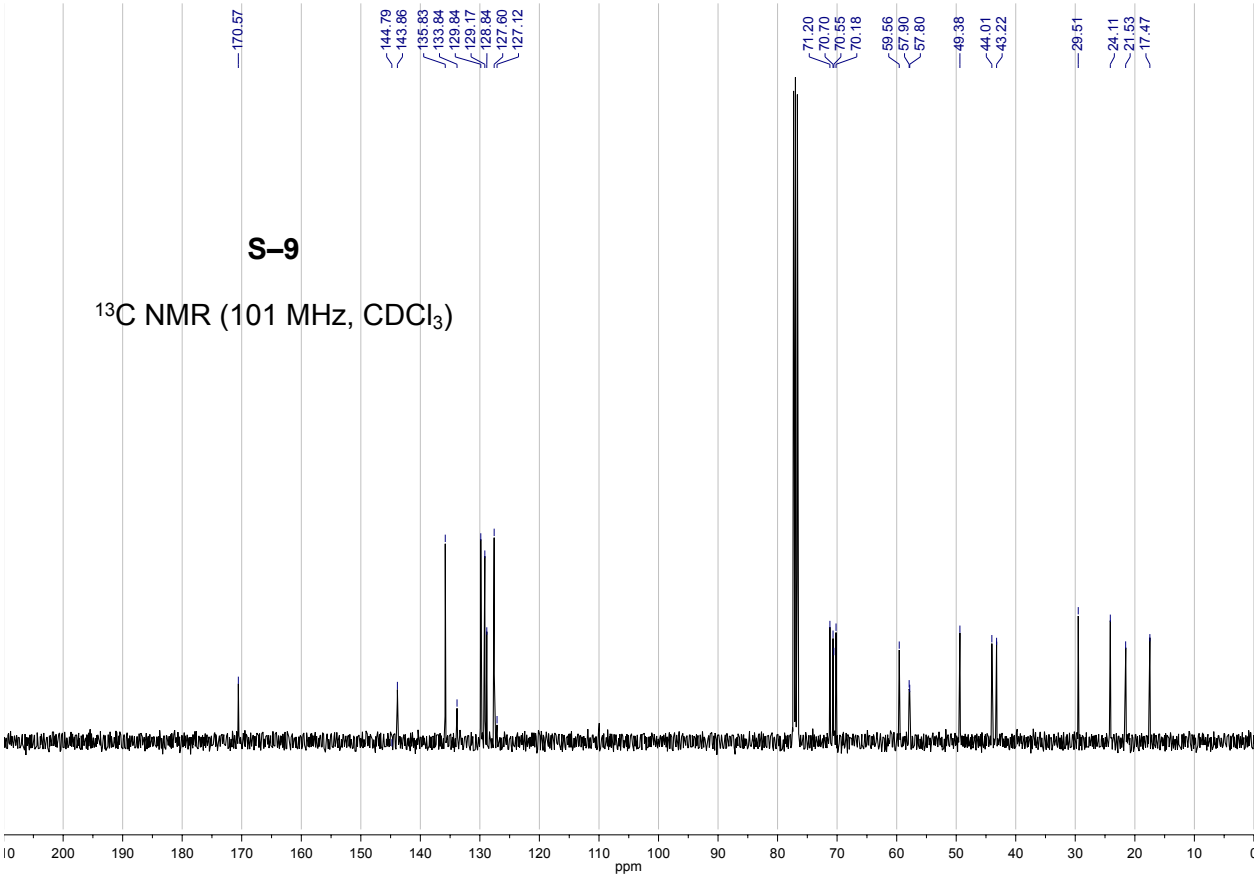
^{1}H NMR (400 MHz, CD_3OD)

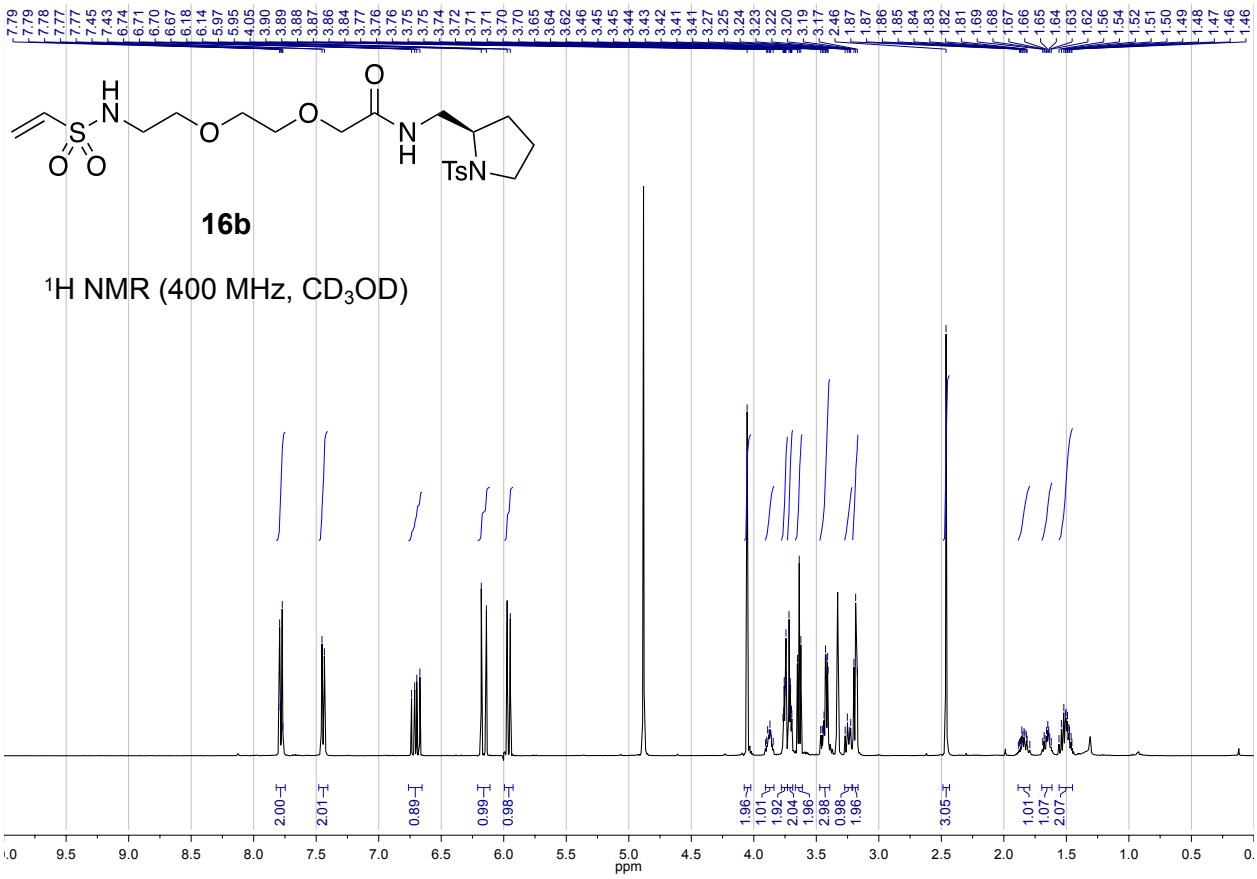


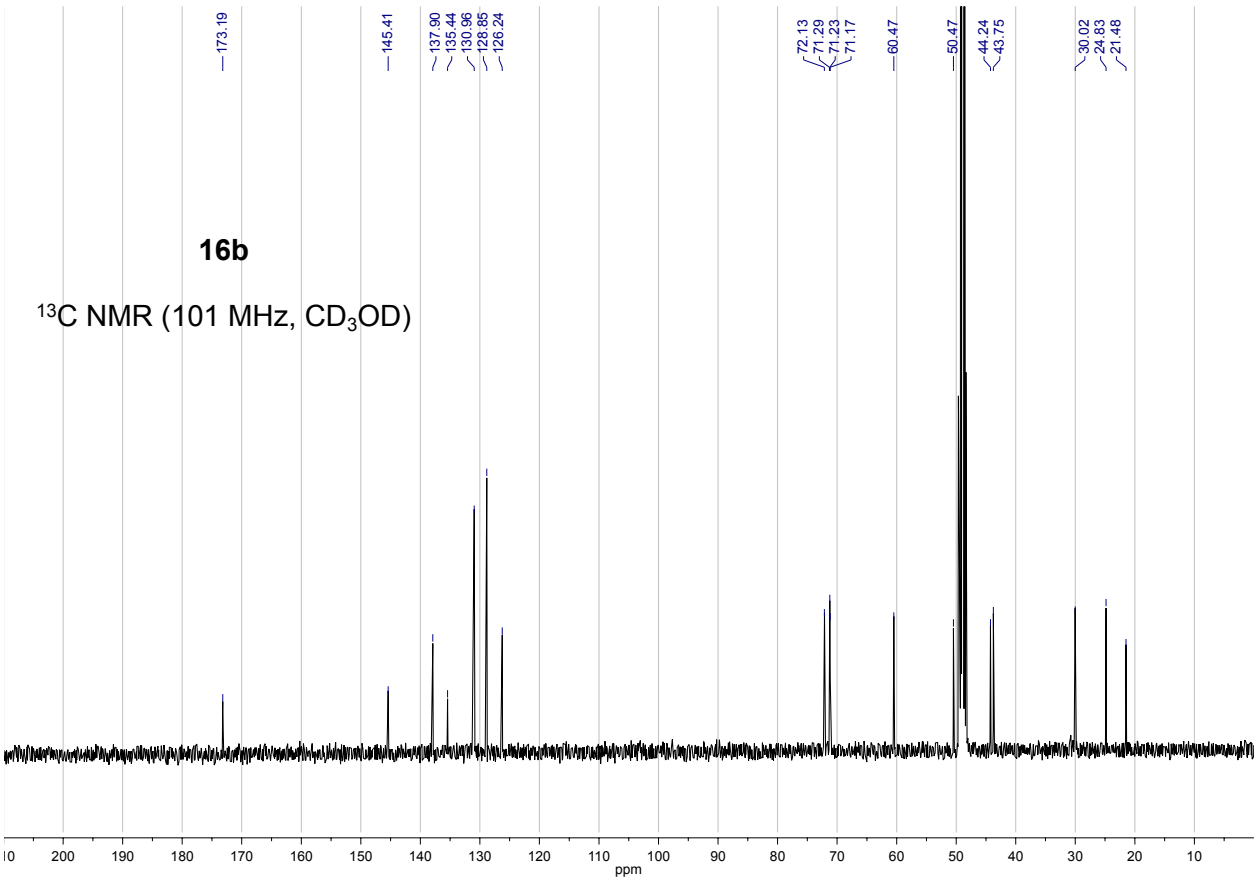
15b

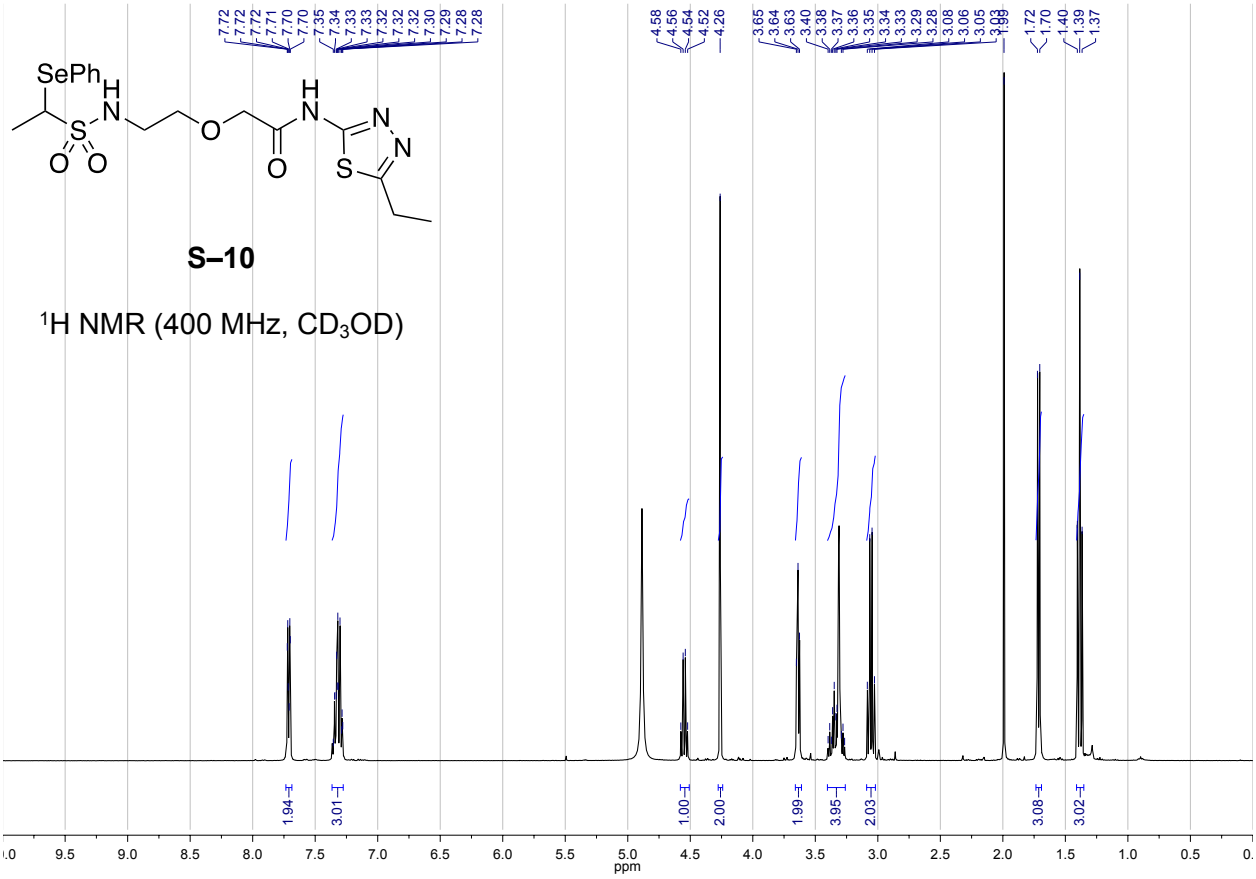
^{13}C NMR (101 MHz, CD_3OD)


SePh
H
N
S
O
O
O
O
O
N
H
TsN
S–9
^{1}H NMR (400 MHz, $CDCl_3$)
ppm


S–9
^{13}C NMR (101 MHz, $CDCl_3$)
ppm

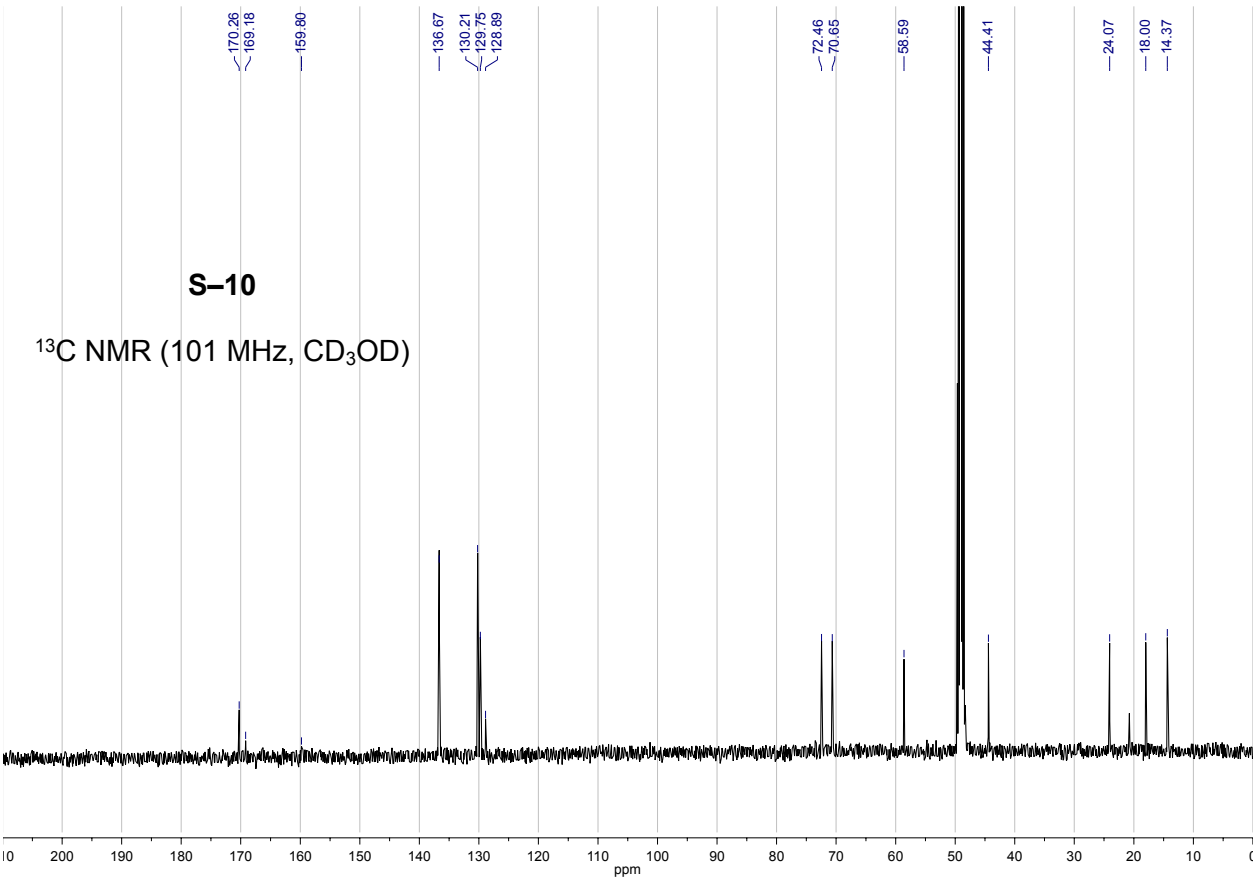

16b
1H NMR (400 MHz, CD3OD)
ppm


16b
13C NMR (101 MHz, CD3OD)
ppm



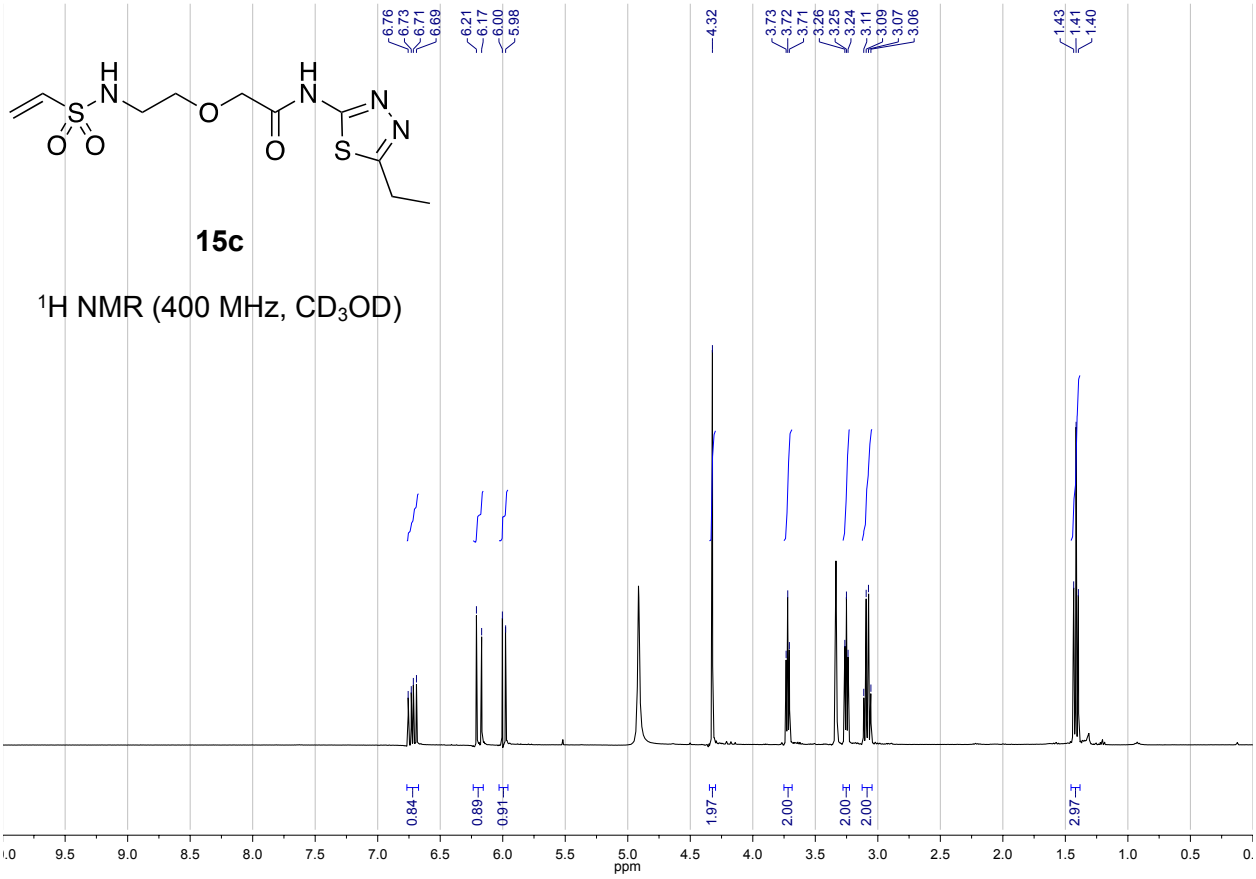
S–10

^{1}H NMR (400 MHz, CD_3OD)



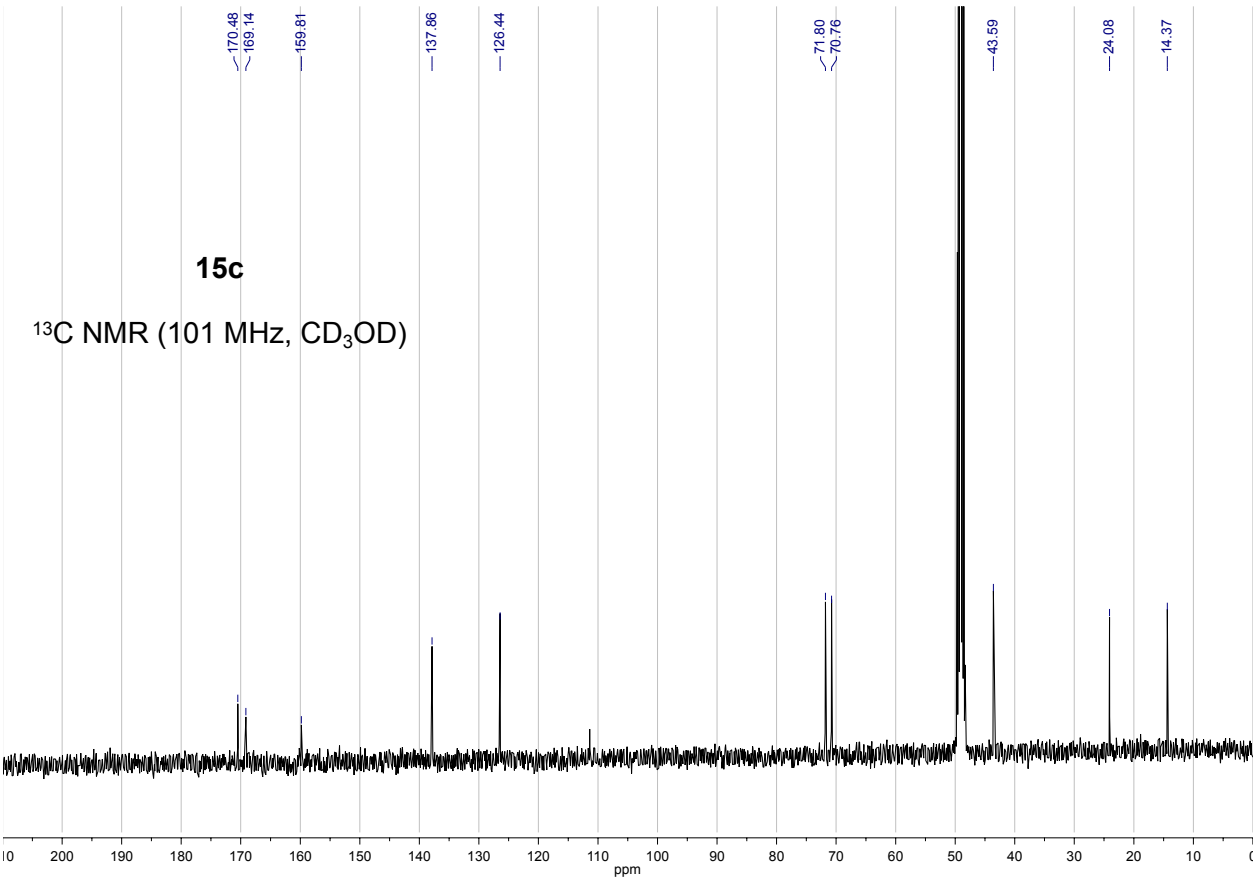
S–10

^{13}C NMR (101 MHz, CD_3OD)



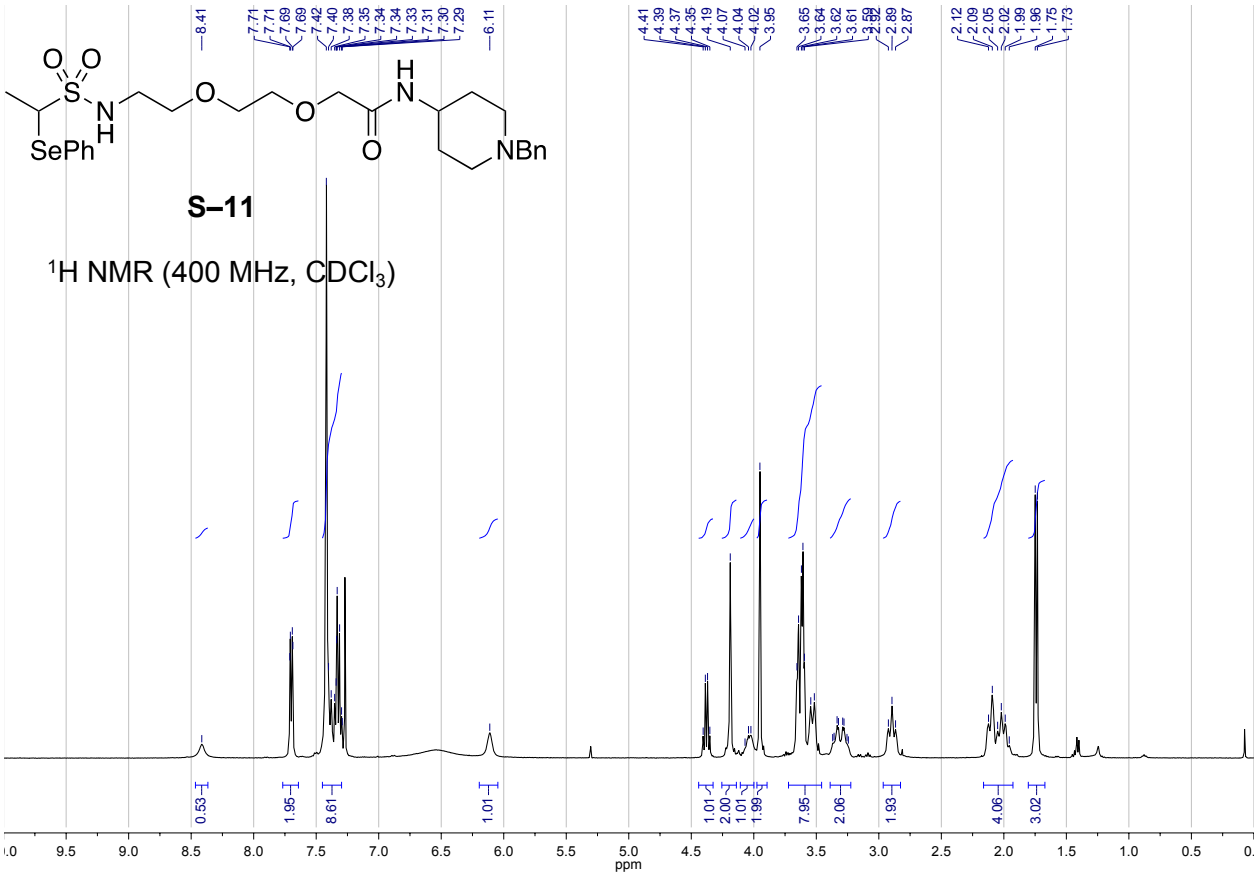
15c

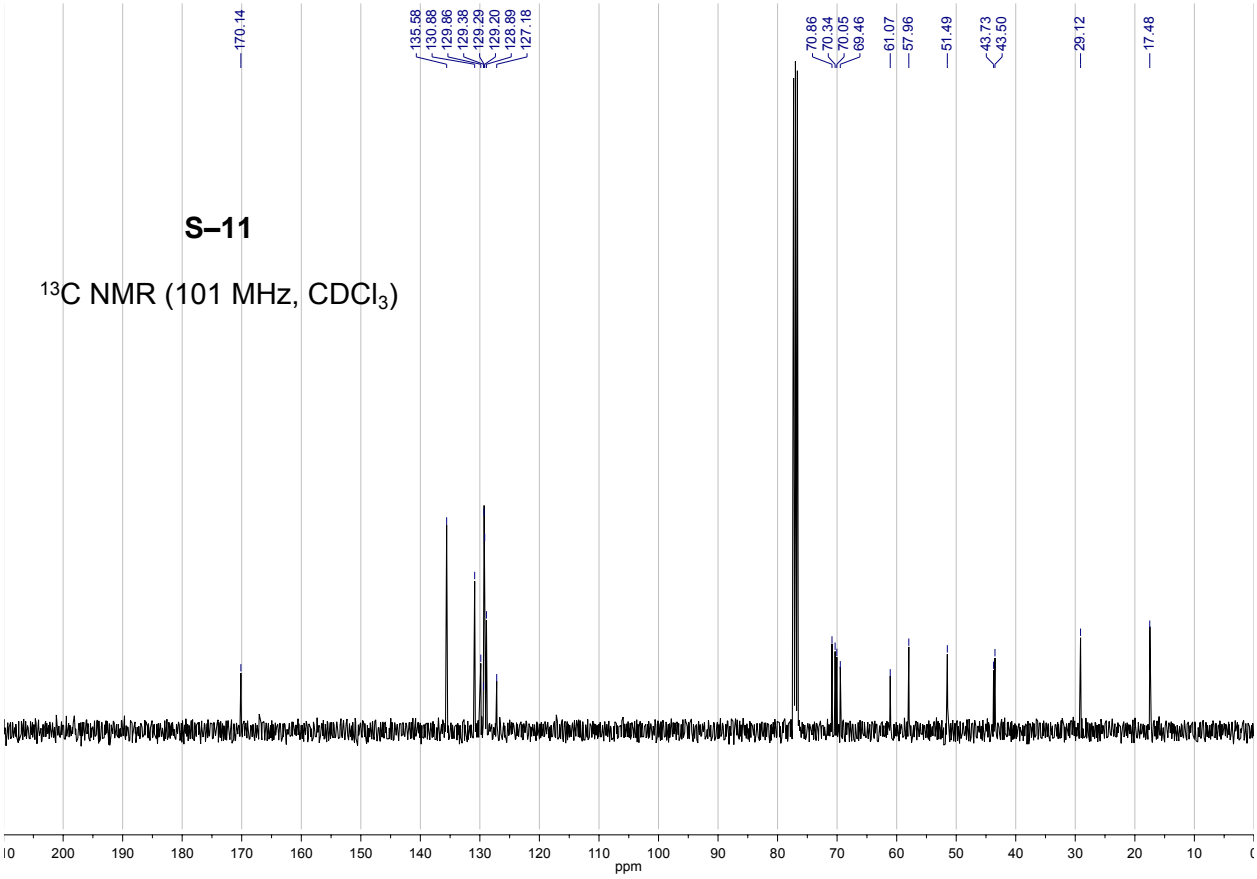
^{1}H NMR (400 MHz, CD_3OD)

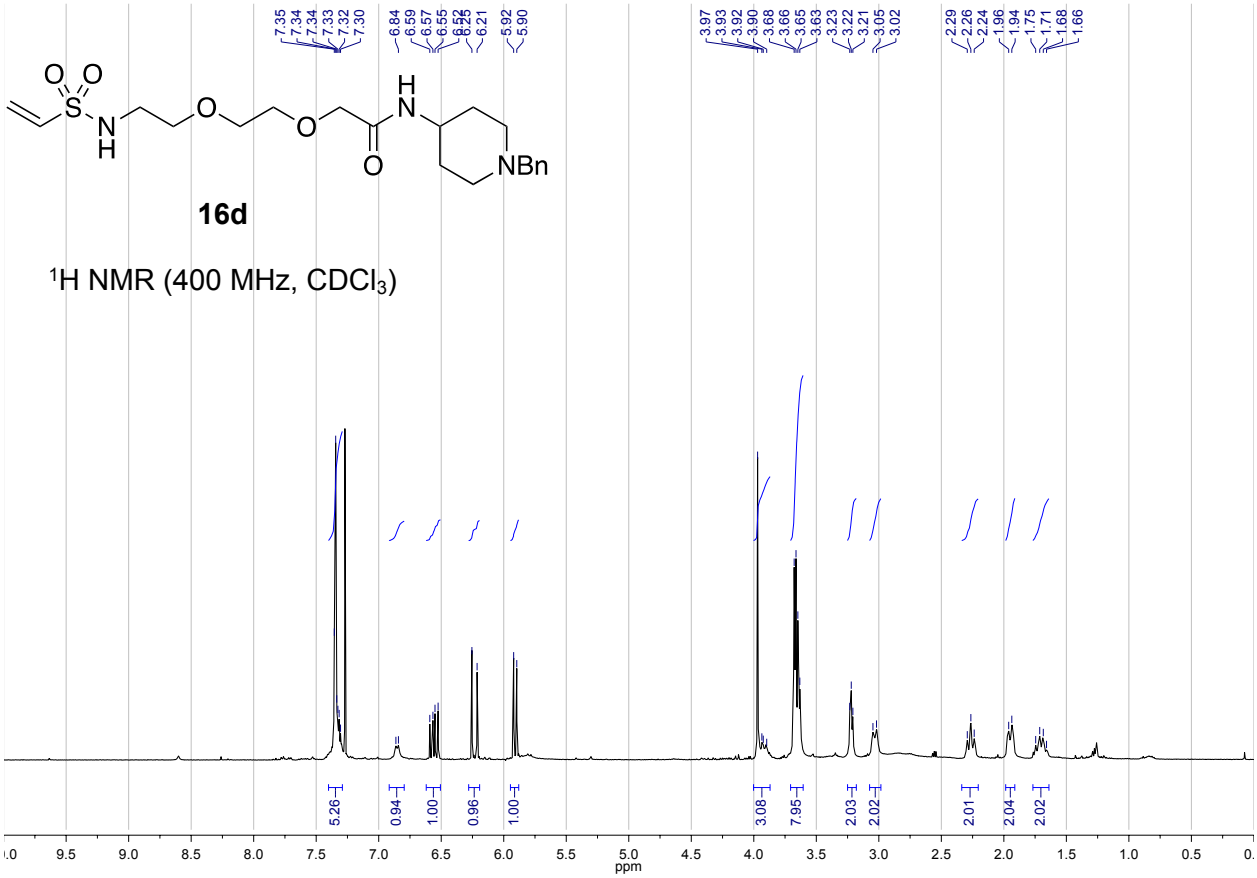


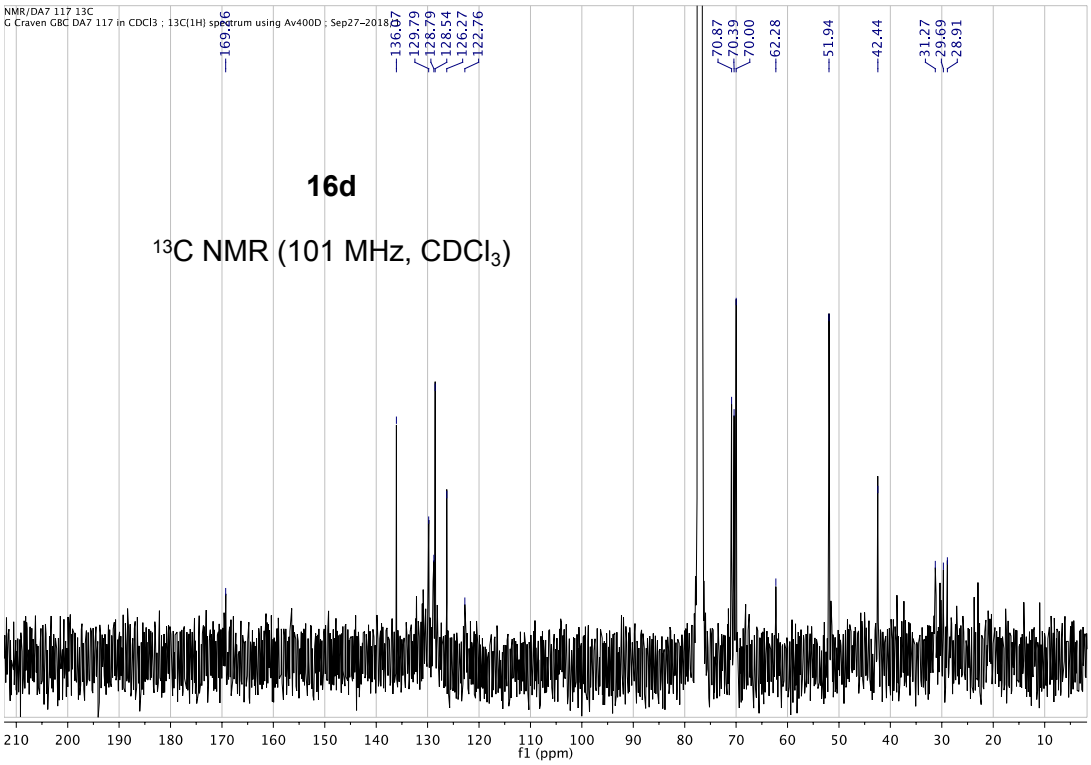
15c

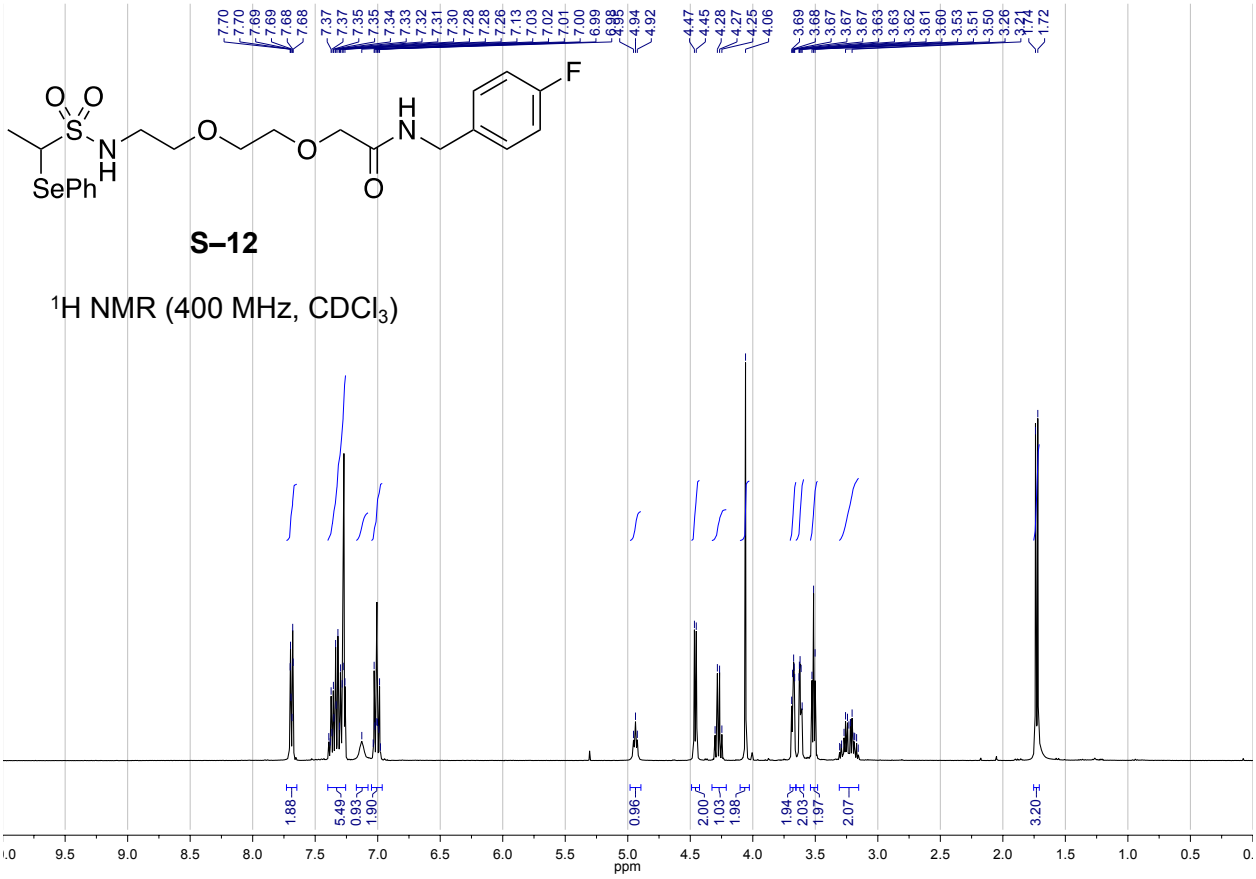
^{13}C NMR (101 MHz, CD_3OD)

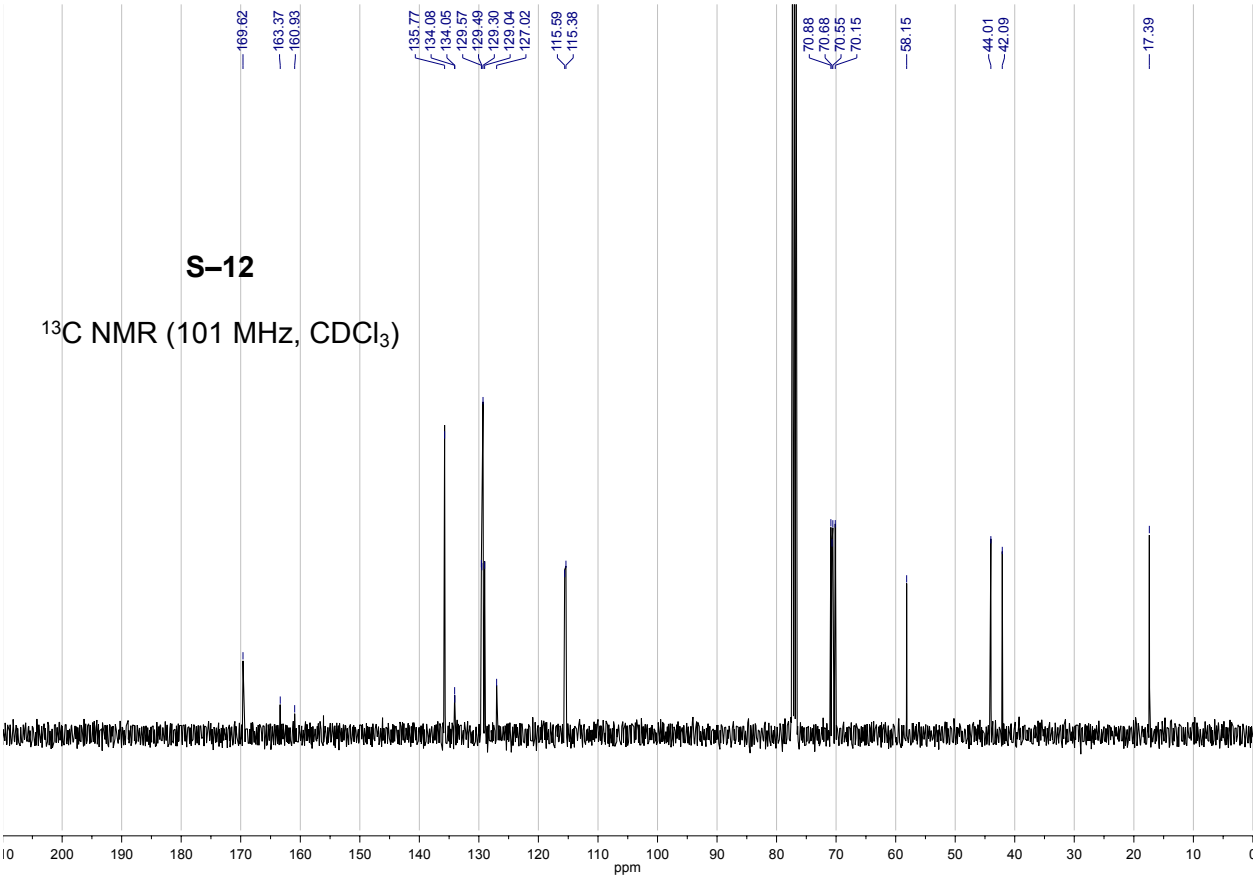

S–11
^{1}H NMR (400 MHz, $CDCl_3$)
ppm

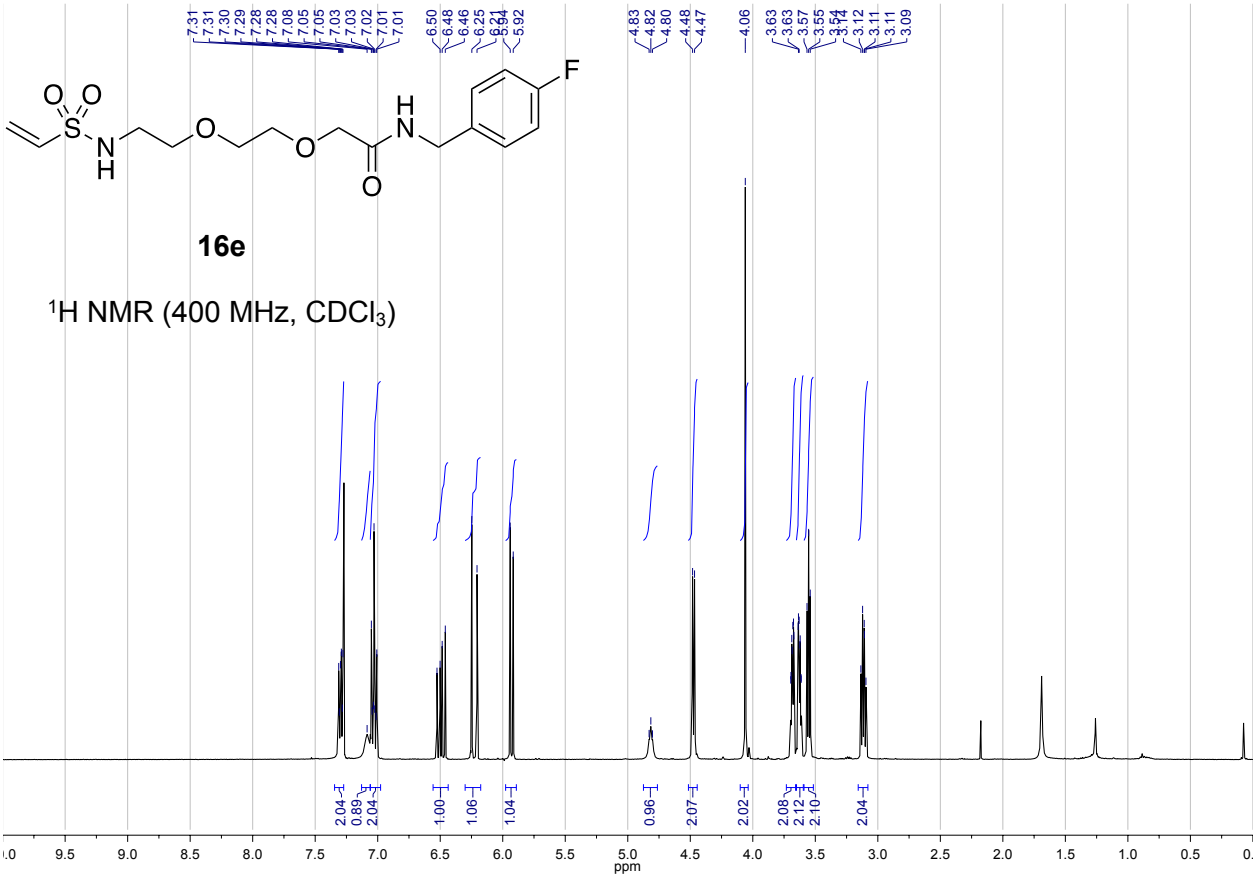

S–11
^{13}C NMR (101 MHz, $CDCl_3$)
ppm

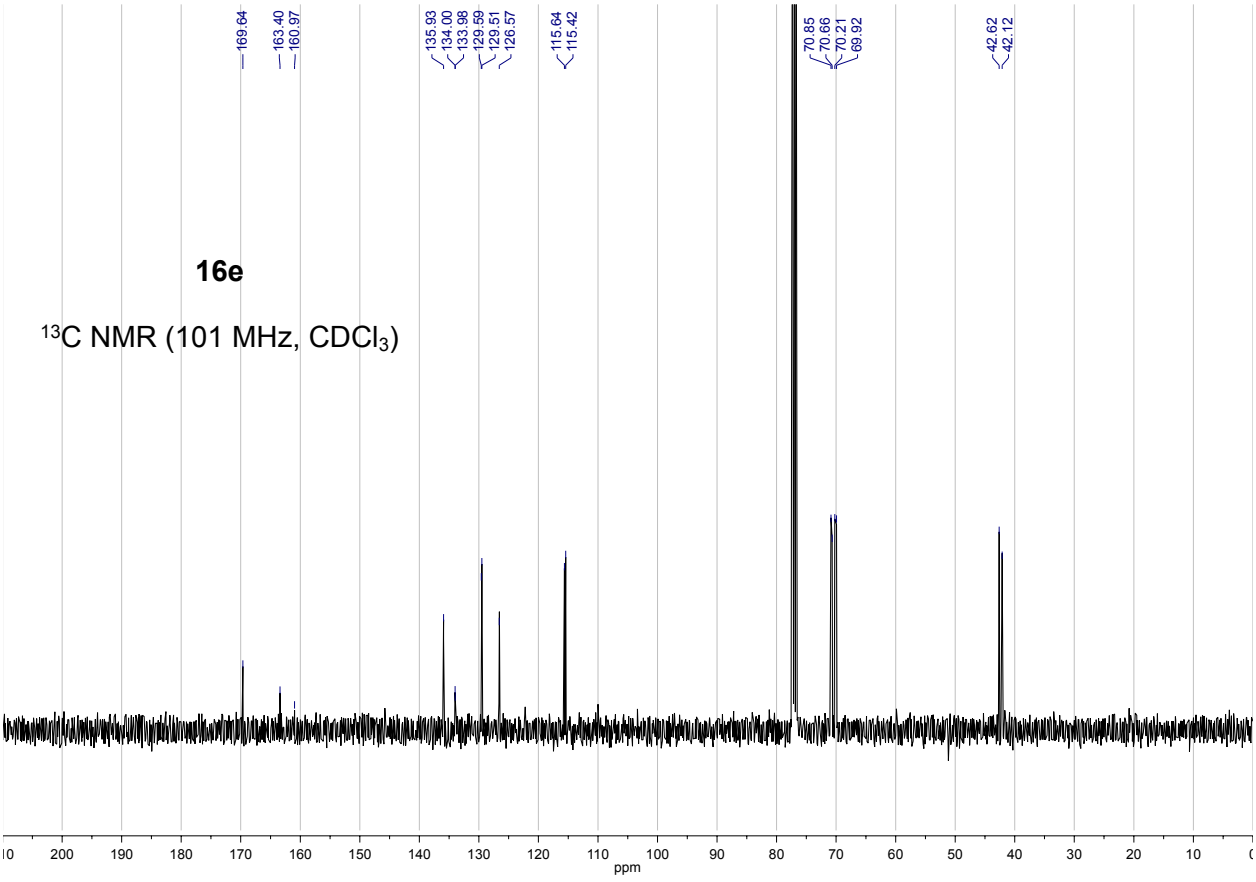

16d
^{1}H NMR (400 MHz, $CDCl_3$)
ppm

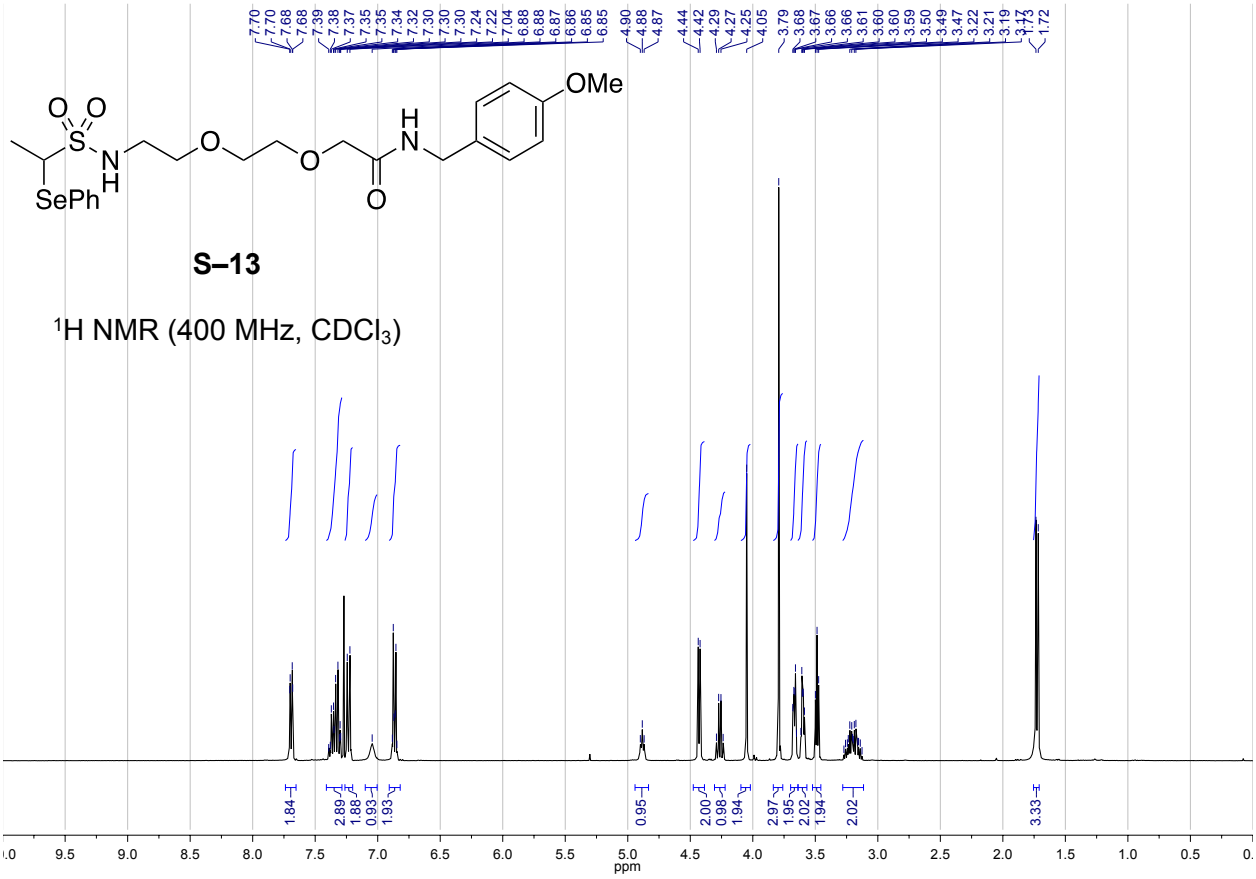

16d
^{13}C NMR (101 MHz, $CDCl_3$)
f1 (ppm)


S–12
^{1}H NMR (400 MHz, $CDCl_3$)
ppm


S–12
^{13}C NMR (101 MHz, $CDCl_3$)
ppm


16e
^{1}H NMR (400 MHz, CDCl$_3$)
ppm


16e
^{13}C NMR (101 MHz, CDCl$_3$)
ppm


OMe
SePh
S–13
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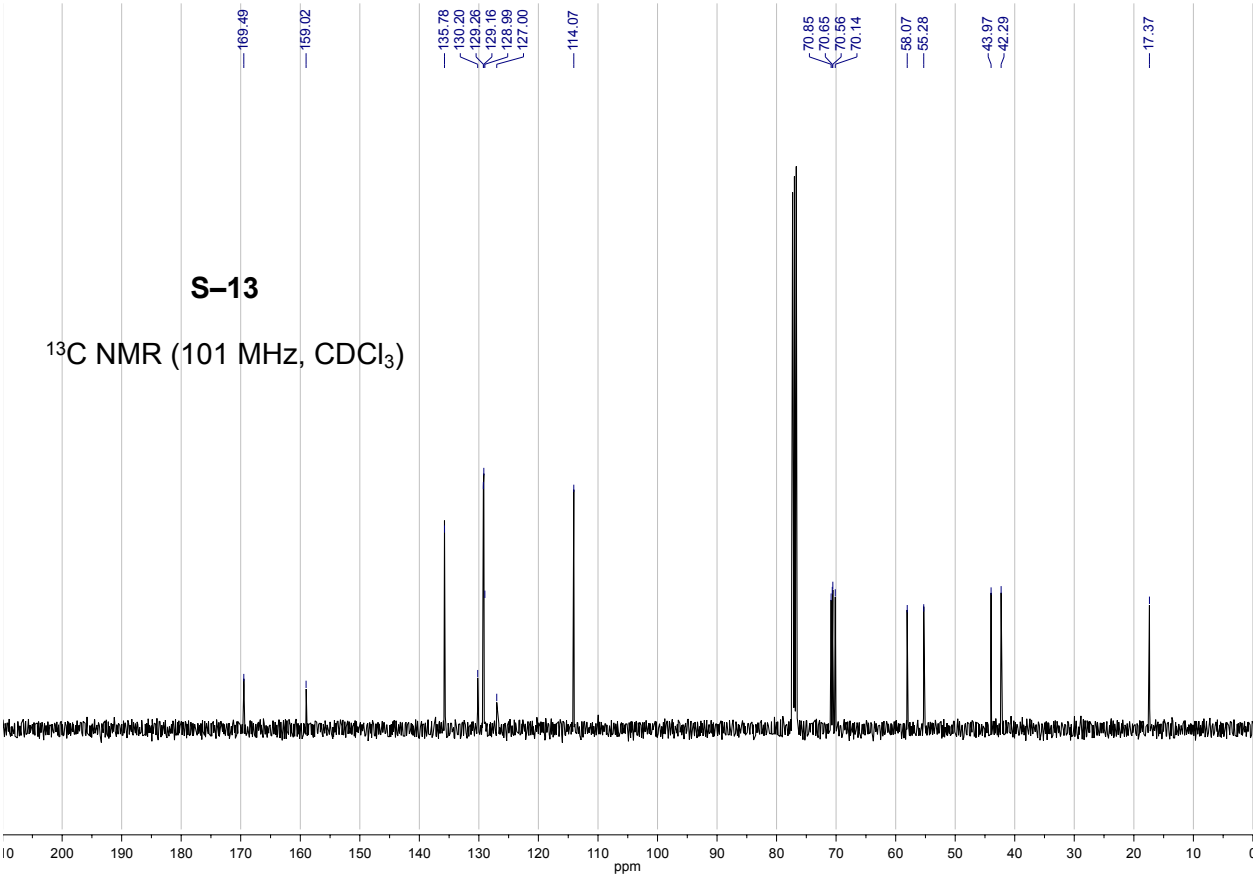
ppm


S–13
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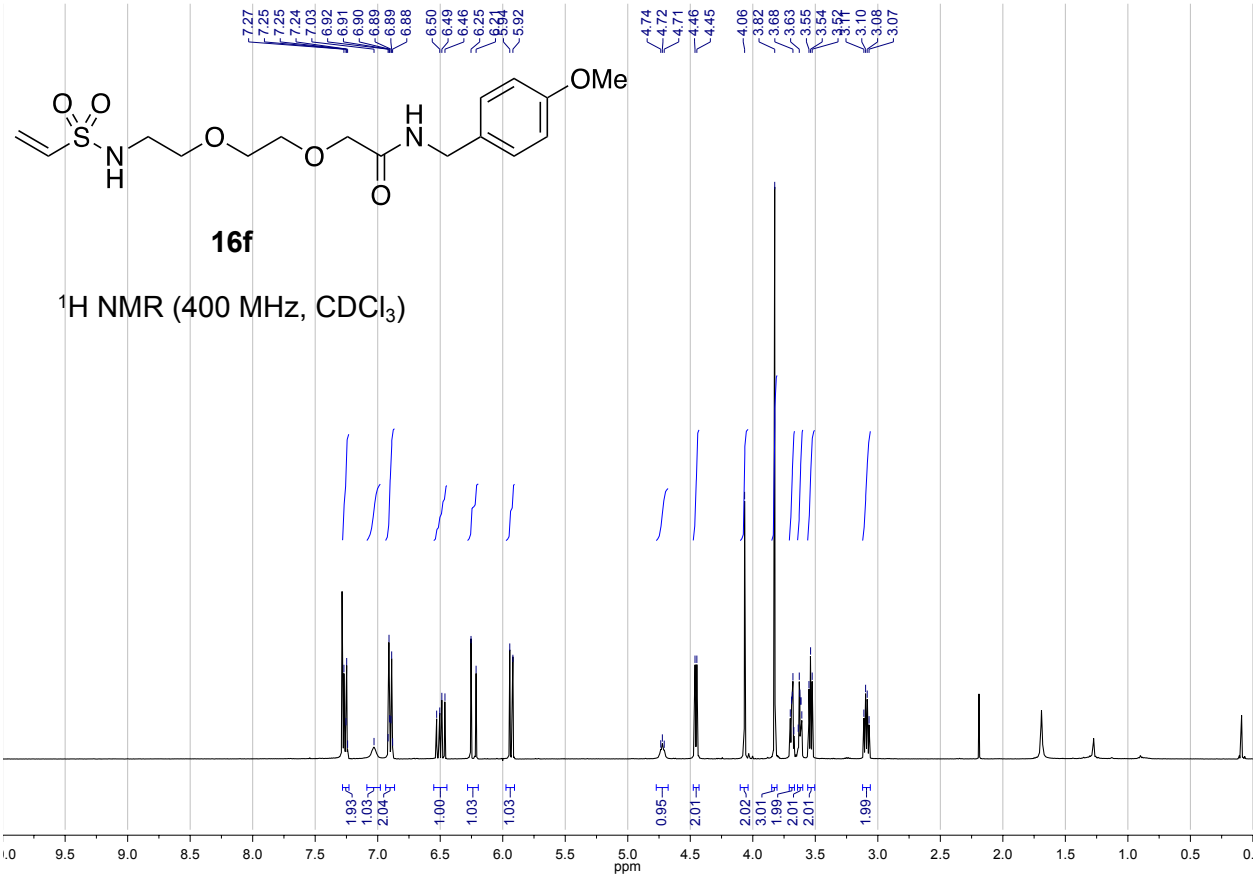
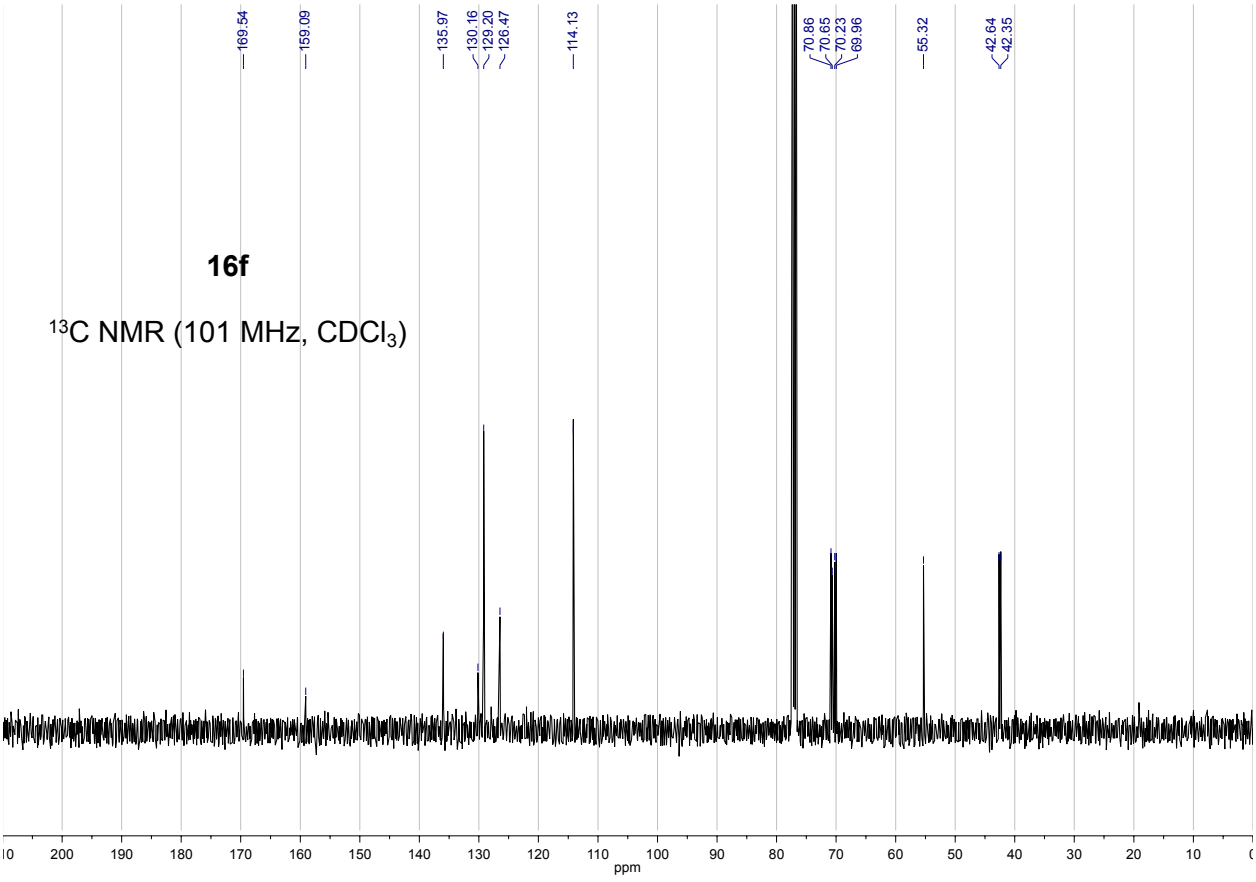
ppm


OMe
16f
^{1}H NMR (400 MHz, $CDCl_3$)
ppm


16f
^{13}C NMR (101 MHz, $CDCl_3$)
ppm

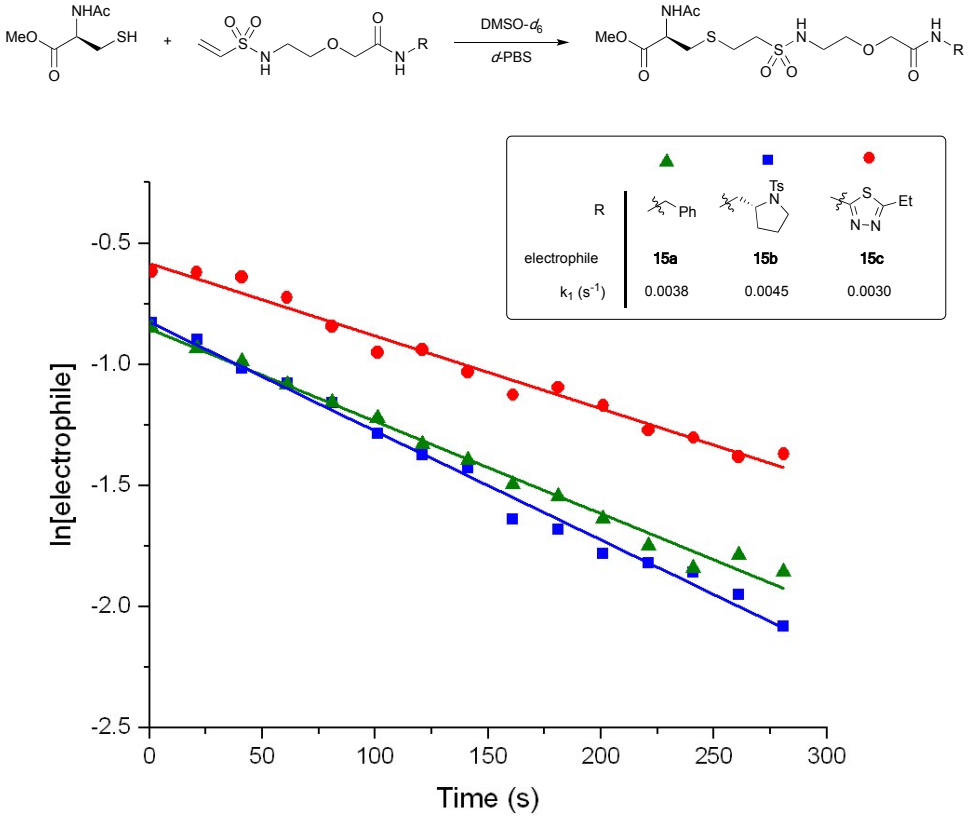
4. Biochemical and Biophysical Protocols

4.1. Thymidylate synthase expression and purification.

E. coli BL21 cells were transformed by electroporation with pET21a containing the catalytic domain of TS. Colonies were grown overnight at 37°C in 10 mL LB supplemented with ampicillin. This was scaled up to 400 mL and incubated at 37°C overnight, and finally to 2000 mL and incubated for a further 1 hour at 37°C. Then protein expression was induced by the addition of 1 mM IPTG. The cells were shaken overnight at 37 °C, and pelleted by centrifugation (5000 rpm, 5 min, 4°C). The pellet was washed twice with 10 mM TRIS-HCl (pH 7.5), 10 mM $MgCl_2$, and the cells stored at -80 °C until required.

The pellet was resuspended in 20 mM TRIS-HCl (pH 7.5), 10 mM $MgCl_2$, 5 mM DTT (100 mL) and sonicated for 4 minutes (2 seconds on, 2 seconds off) at 50% amplitude, with cooling on ice. The solution was centrifuged (9000 rpm, 20 min, 4 °C) and the supernatant collected. 5 % streptomycin sulfate (15 mL/100 mL of the supernatant fraction) (*v/v*) was added. After stirring for 10 minutes at 4 °C, the resulting nucleic acid precipitate was removed by centrifugation (9000 rpm, 30 minutes, 4 °C). Solid ammonium sulfate was added portionwise with stirring to the resulting supernatant fraction to reach 50 % saturation at 4 °C. After 10 minutes the resulting precipitate was collected by centrifugation (9000 rpm, 20 minutes, 4 °C) and discarded. Further solid ammonium sulfate was added to the supernatant fraction to reach final saturation of 80 %. After stirring at 4 °C for 10 minutes the resulting precipitate was collected by centrifugation (9000 rpm, 4 °C, 20 minutes) and stored at -80 °C prior to further purification. The ammonium sulfate pellet was thawed, dissolved in 20 mM TRIS-HCl pH 7.5, 1 mM DTT (40 mL) and loaded onto DE-52 beads pre-equilibrated with 20 mM TRIS-HCl pH 7.5, 1 mM DTT. The protein mixture was spun with the beads at 4 °C overnight. Elution of the TS was achieved by passing 20 mM TRIS-HCl pH 7.5, 1 mM DTT (20 mL) through the beads, followed by 20 mL portions of the same buffer containing an increasing concentration of NaCl from 0.13 to 0.39 M and fractions of 2-3 mL were collected. Fractions containing TS were combined and ammonium sulfate added to 80 % saturation with stirring for 10 min at 4 °C to precipitate the protein. The protein was collected by centrifugation (5000 rpm, 4°C, 60 minutes) and stored at -80 °C until required.

5. Supplemetary Figures



Supplementary figure 1. NMR rate study. Electrophiles (10 mM) were reacted with *N*-acetyl cysteine methyl ester (78 mM) and the reaction monitored by ^{1}H NMR spectroscopy. The natural logarithm of the electrophile concentration is plotted over time. Linear trends were fitted to the data and the pseudo-first-order rate constants (k_1) were determined from the gradients.

6. Supplementary References

1 Carpino, L. A.; McAdams, L. V.; Rynbrandt, R. H.; Spiewak, J. W. J. Am. Chem. Soc. 1971, **93**, 476

2 H. Chen, R. Huang, Z. Li, W. Zhu, J. Chen, Y. Zhan and B. Jiang, Org. Biomol. Chem., 2017, **15**, 7339–7345.