SUPPORTING INFORMATION

Vinyl sulfonamide synthesis for irreversible tethering via a novel \( \alpha \)-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, CH₂Cl₂, 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 ¹H 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). ¹³C 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 (¹³CDCl₃: δ 77.0 ppm, ¹³CD₃OD: δ 49.0 ppm). ¹⁹F 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 ¹H and ¹³C 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 [α]₀. 
2. Synthetic Experimental Details and Characterisation Data

2.1. General Procedures

**General Procedure A: N-sulfonylation of amines**

1-Bromoethane-1-sulfonyl chloride \( \text{S–1} \) (1 equiv) was added dropwise to a solution of \( \text{NET}_3 \) (1.5 equiv) and amine (2.0 equiv) in \( \text{CH}_2\text{Cl}_2 \) (0.2 M wrt sulfonyl chloride \( \text{S–1} \)) 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 \( \times \) 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**

\( \text{NaBH}_4 \) (1.5 equiv) was added portionwise to a solution of \( \text{Ph}_2\text{Se}_2 \) (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\(_2\)O and CH\(_2\)Cl\(_2\) were added, and the phases were separated. The aqueous layer was further extracted with CH\(_2\)Cl\(_2\), the combined organic layers were dried over Na\(_2\)SO\(_4\), 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**

\( \text{NaIO}_4 \) (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. \( \text{NaHCO}_3 \) (10 mL) was added and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 \( \times \) 10 mL). The combined organic extracts were dried over Na\(_2\)SO\(_4\), 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\(_2\)Cl\(_2\)-catalysed amide bond formation**

A solution of carboxylic acid (1 equiv), amine (1.2 equiv) and \( \text{bis(cyclopentadienyl)zirconium(IV) dichloride} \) (5 mol%) in anhydrous toluene (0.05 M wrt carboxylic 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\(_2\)Cl\(_2\)) 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\(_2\)Cl\(_2\) (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 °C for 2 h and then cautiously poured into ice (30 g). After the ice had melted the aqueous phase was extracted with CH₂Cl₂ (3 × 40 mL). The organic layers were combined and successively washed with sat. aq. NaHCO₃ (10 mL), water (10 mL), and brine (10 mL). The solution was dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by serial vacuum distillation (42–46 °C at 1.5 mbar) to give 1-bromoethanesulfonyl chloride (5.19 g, 46%) as a colourless oil. 

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-aminomethyl-1-Boc-piperidine (312 mg, 1.56 mmol), NEt₃ (163 μL, 1.17 mmol) in CH₂Cl₂ (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. 

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

Prepared according to General Procedure B, using NaBH₄ (40.0 mg, 1.05 mmol), Ph₂Se₂ (109 mg, 0.35 mmol), bromoethanesulfonamide 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. 

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

Prepared according to General Procedure C, using seleno-sulfonamide 6a (23 mg, 0.05 mmol) and NaIO₄ (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. 

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

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. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2942, 2808, 2727, 2365, 1705, 1439, 1302, 1268, 1133, 1096, 990, 896, 761; $^1$H NMR (400 MHz, CD$_2$OD) $\delta$ 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$_2$OD) $\delta$ 136.7 (2 × C$_{\text{sp}}$), 130.3 (2 × C$_{\text{sp}}$), 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$_{27}$N$_2$O$_2$S$^{30}$Se$^{+}$ [M-Cl]$^+$ 349.0489; Found 349.0492 ($\Delta +0.9$ 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$_2$Cl$_2$ (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$_2$Cl$_2$ (3 × 10 mL). The combined organic extracts were dried over Na$_2$SO$_4$, 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); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3164, 2929, 1622, 1442, 1323, 1129, 907, 725; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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), 1.94–1.92 (m, 1 H), 1.80–1.72 (m, 1 H), 1.40–1.32 (m, 2 H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.9, 135.7, 135.6, 129.31, 129.27, 129.02, 128.99, 127.0, 58.33, 5.83, 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$_{13}$H$_{27}$N$_2$O$_2$S$^{30}$Se$^{+}$ [M+H]$^+$ 391.0595; Found 391.0587 ($\Delta -2.0$ 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 NaI$_4$ (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 °C (CHCl$_3$); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3169, 2923, 1607, 1460, 1312, 1260, 1152, 1132, 1090, 1054, 977, 914, 738, 674; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_9$H$_{17}$N$_2$O$_3$S$^{+}$ [M+H]$^+$ 233.0960; Found 233.0954 ($\Delta -0.6$ 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$_2$Cl$_2$ (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); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3294, 1441, 1340, 1311, 1142, 1068, 740; $^1$H NMR (400 MHz, MeOD) $\delta$ 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) $\delta$ 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$_9$H$_{16}$N$_2$O$_2$S$^{79}$Br$^{+}$ [M+NH$_4$]$^+$ 295.0116; Found 295.0121 ($\Delta +1.7$ ppm).
**N-Benzyl-1-(phenylselanyl)ethane-1-sulfonamide (6c)**

Prepared according to General Procedure B, using NaBH₄ (33.0 mg, 0.87 mmol), Ph₂Se₂ (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. Rₛ 0.29 (25% EtOAc/pentane); νₘₐₓ (film)/cm⁻¹ 3297, 3057, 1438, 1321, 1140, 1067, 742; ¹H 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); ³¹C NMR (101 MHz, MeOD) δ 139.5, 136.7 (2 × C), 130.2 (2 × C), 129.7, 129.6 (2 × C), 128.9, 128.6, 58.9, 48.4, 17.9; HRMS (ESI⁺) m/z Calulated for C₁₅H₁₈NO₂Se [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 NaIO₄ (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 (16.5 mg, 0.71 mmol) in ethyl acetate (3.55 mL). The crude material was purified by flash column chromatography (90% CH₂Cl₂/pentane grading to 50% EtOAc/pentane), followed by reversed-phase flash column chromatography (10% grading to 30% EtOAc/pentane), which gave the seleno-sulfonamide 5c (167 mg, 78%) as a colourless oil. Rₛ 0.33 (CH₂Cl₂); νₘₐₓ (film)/cm⁻¹ 3269, 1440, 1327, 1248, 1143, 1021, 911, 737; ¹H NMR (400 MHz, CDCl₃) 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 = 16.5 Hz, 1H), 4.54 (s, 1H), 4.22 (d, J = 5.9 Hz, 2H); ³¹C NMR (101 MHz, CDCl₃) δ 136.7, 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), NEt₃ (248 µL, 1.78 mmol) in CH₂Cl₂ (3.55 mL). The crude material was purified by flash column chromatography (90% CH₂Cl₂/pentane grading to CH₂Cl₂), which afforded the sulfonamide 5d (167 mg, 78%) as a colourless oil. Rₛ 0.33 (CH₂Cl₂); νₘₐₓ (film)/cm⁻¹ 3269, 1440, 1327, 1248, 1143, 1021, 911, 737; ¹H NMR (400 MHz, CDCl₃) 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), 3.73–3.69 (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); ³¹C NMR (101 MHz, CDCl₃) δ 172.7, 172.5, 161.8, 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 C₉H₁₈NO₂SeBr⁺ [M+Br⁺] 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 NaBH₄ (31 mg, 0.83 mmol), Ph₂Se₂ (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 (H₂O grading to MeOH, with 0.1% v/v HCO₂H additive), which gave the seleno-sulfonamide 6d (17 mg, 8%, 63:37 dr) as a colourless oil. Rₛ 0.37 (25% EtOAc/pentane); νₘₐₓ (film)/cm⁻¹ 2953, 1743, 1438, 1331, 1209, 1138, 1073, 1021, 742, 692; ¹H NMR (400 MHz, CDCl₃) 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); ³¹C NMR (101 MHz, CDCl₃) 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,
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 NaIO₄ (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\text{max} (film)/cm⁻¹: 2942, 1745, 1442, 1340, 1205, 1146, 1082, 1019, 732; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) δ: 172.8, 134.5, 127.0, 60.4, 52.4, 47.7, 31.0, 24.8; HRMS (ESI⁺ m/z) Calculated for C₈H₁₄NO₄S⁺ [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), NEt₃ (182 µL, 1.31 mmol) in CH₂Cl₂ (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. Rᵣ 0.35 (25% EtOAc/pentane); ν\text{max} (film)/cm⁻¹: 2979, 1669, 1412, 1334, 1151, 1125, 909, 727; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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, 28.3, 20.6; HRMS (ESI⁺ m/z) Calculated for C₁₁H₂₁N₂O₄NaS⁺ [M+Na⁺]⁺ 379.0303; Found 379.0318 (Δ +4.0 ppm).

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

Prepared according to General Procedure B, using NaBH₄ (34 mg, 0.90 mmol), Ph₂Se₂ (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 (H₂O grading to MeOH, with 0.1% v/v HCO₂H additive), which gave the seleno-sulfonamide 6e (80 mg, 31%) as a colourless oil. ν\text{max} (film)/cm⁻¹: 3236, 2983, 2885, 1671, 1409, 1366, 1320, 1164, 1125, 911, 728; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) δ: 154.3, 135.7, 135.6, 129.3, 129.1, 126.9, 79.7, 57.9, 57.7, 54.3, 54.2, 53.6, 53.4, 43.8, 43.4, 33.2, 31.4, 31.8, 28.4, 17.5; HRMS (ESI⁺ m/z) Calculated for C₁₇H₁₂₇N₂O₄Sⁿ[Br]⁺ [M+H⁺]⁺ 435.0857; Found 435.0854 (Δ -0.7 ppm).

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

Prepared according to General Procedure C, using seleno-sulfonamide 6e (15 mg, 33 µmol) and NaIO₄ (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. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3220, 2929, 1669, 1408, 1331, 1148, 1121, 1017, 730; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$O$_4$S$^+$ [M+H]$^+$ 275.1066; Found 275.1070 ($\Delta +1.7$ 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 $\mu$L, 1.22 mmol) in CH$_2$Cl$_2$ (4.05 mL). The crude material was purified by flash chromatography (5% grading to 40% EtOAc/pentane), which afforded the sulfonamide 5f (157 mg, 66%) as a colourless oil.

$\nu_{\text{max}}$ (film)/cm$^{-1}$ 3261, 2965, 2840, 1508, 1443, 1333, 1248, 1151, 1030, 920; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 158.5, 158.4, 128.0, 127.8, 125.8, 125.6, 114.7, 65.8, 55.3, 19.9, 18.8; HRMS (ESI$^+$) $m/z$ Calculated for C$_9$H$_{13}$NO$_3$S$^+$ [M–H]$^-$ 293.9800; Found 293.9805 ($\Delta +1.7$ 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$_2$Se$_2$ (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$_3$/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$_3$) $\delta$ 7.70–7.65 (m, 2 H), 7.41–7.29 (m, 3 H), 7.18–7.13 (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 chromatography (10% EtOAc/pentane grading to Et$_2$O), which gave the vinyl sulfonamide 7f (19 mg, 80%) as a colourless oil. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3257, 1610, 1505, 1327, 1249, 1144, 1025, 913, 738; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_9$H$_{10}$N$_2$O$_3$S$^+$ [M–H]$^-$ 212.0381; Found 212.0376 ($\Delta -2.4$ 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 $\mu$L, 2.02 mmol), NEt$_3$ (211 $\mu$L, 1.52 mmol) in CH$_2$Cl$_2$ (5.00 mL). The crude material was purified by flash column chromatography (10% Et$_2$O/pentane grading to Et$_2$O), which afforded the sulfonamide 5g (252 mg, 85%) as a colourless oil. $R_f$ 0.69 (25% EtOAc/pentane); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2978, 2934, 1335, 1150, 989, 941, 910, 776, 737, 702; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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); 13C NMR (101 MHz, CDCl₃) 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 C₁₀H₁₅NO₂SeS¹⁷Br⁺ [M+H]⁺ 292.0007; Found 292.0014 (Δ +2.4 ppm).

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

![Structure](image)

Prepared according to General Procedure B, using NaBH₄ (49 mg, 1.29 mmol), Ph₂Se₂ (134 mg, 0.43 mmol), bromoethanesulfonamide 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 (H₂O grading to MeOH, with 0.1% v/v HCO₂H additive), which gave the seleno-sulfonamide 6g (44 mg, 14%) as a colourless oil. vmax (film)/cm⁻¹ 2921, 1439, 1324, 1148, 990, 941, 771, 736, 692; ¹H NMR (400 MHz, CDCl₃) 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); 13C NMR (101 MHz, CDCl₃) δ 135.6, 133.3, 128.7, 128.4, 128.0, 127.6, 53.8, 34.0; HRMS (ESI⁺) m/z Calculated for C₁₀H₁₄N₂O₂S⁺ [M+H]⁺ 212.0745; Found 212.0747 (Δ +0.9 ppm).

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

![Structure](image)

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), NEt₃ (167 μL, 1.20 mmol) in CH₂Cl₂ (2.0 mL). The crude material was purified by flash column chromatography (pentane grading to 15% EtOAc/pentane), which gave the dehalogenated sulfonamide 5h (226 mg, 77%) as a white solid. m.p. = 88–90 ºC (CHCl₃). vmax (film)/cm⁻¹ 2942, 1597, 1472, 1411, 1341, 1147, 1109, 1039, 970, 866, 776, 751, 710; ¹H NMR (400 MHz, CDCl₃) δ 7.49 (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); 13C NMR (101 MHz, CDCl₃) 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 Cl.

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

![Structure](image)

Prepared according to General Procedure B, using NaBH₄ (33 mg, 0.89 mmol), Ph₂Se₂ (92 mg, 0.30 mmol), bromoethanesulfonamide 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 (CH₂Cl₂); vmax (film)/cm⁻¹ 2942, 1597, 1472, 1411, 1341, 1147, 1109, 1039, 970, 866, 776, 751, 710; ¹H NMR (400 MHz, CDCl₃) 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); 13C NMR (101 MHz, CDCl₃) 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 C₁₀H₁₉NO₂S⁺ [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 NEt₃ (694 µL, 4.98 mmol) in CH₂Cl₂ (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; ¹H NMR (400 MHz, CDCl₃) δ 5.21 (q, J = 6.8 Hz, 1 H), 3.62 (t, J = 5.8 Hz, 2 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 = 6.9 Hz, 3 H); ¹³C NMR (101 MHz, CDCl₃) δ 72.0, 70.8, 68.9, 57.8, 54.3, 44.4, 21.0; HRMS: not found using ESI, EI or Cl.

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 NEt₃ (65 µL, 0.47 mmol) in CH₂Cl₂ (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-sulfonlated compound S–5 (5 mg, 5%) as a colourless oil. ν_max (film/cm⁻¹) 3405, 3311, 2978, 1444, 1332, 1151, 921; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) δ 72.0, 69.1, 58.0, 44.6, 21.0; HRMS (ESI⁺) m/z Calculated for C₂H₁₆NO₄S₇⁸BrNa⁺ [M+Na⁺] 253.9457; Found 253.9462 (Δ +3.9 ppm).

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

[(2-Hydroxyethyl)-1-(phenylselanyl)ethane-1-sulfonamide (11)]

NaBH₄ (301 mg, 7.93 mmol) was added portionwise to a solution of Ph₂Se₂ (1.34 g, 3.96 mmol) in THF (3.0 mL) and DMF (1.7 mL) at 0 °C, and the resulting solution was stirred for 10 min. The solution was then allowed to warm to rt for 2 h. A solution of 1-Bromo-(2-hydroxyethyl)ethane-1-sulfonamide (S–3) (50 mg, 0.22 mmol) in THF (2.0 mL) was then added dropwise. The solution was then heated to 40 °C for 15 h. H₂O and CH₂Cl₂ were added, and the phases were separated. The aqueous layer was further extracted with CH₂Cl₂, the combined organic layers were dried over Na₂SO₄, 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/CH₂Cl₂), which gave the seleno-sulfonamide 11 (196 mg, 32%) as a yellow oil. ν_max (film/cm⁻¹) 3289, 2910, 1432, 1320, 1125, 1065; ¹H NMR (400 MHz, CDCl₃) 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, 2 H), 3.21–3.12 (m, 1 H), 1.80–1.75 (m, 3 H); ¹³C NMR (101 MHz, CDCl₃) 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 C₁₀H₁₅NNaO₃S⁸⁰Se²⁺ [M+Na⁺] 331.9830; Found 331.9828 (Δ +3.1 ppm).

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

NaBH₄ (171 mg, 4.51 mmol) was added portionwise to a solution of Ph₂Se₂ (705 mg, 2.26 mmol) in THF (4.0 mL) and DMF (1.9 mL) at 0 °C, then the solution was allowed to warm to rt for 30 min. A solution of
bromoethanesulfonamide S–4 (310 mg, 1.13 mmol) in THF (5.4 mL) was then added dropwise. The solution was then heated to 40 °C for 8 h. H₂O and CH₂Cl₂ were added, and the phases were separated. The aqueous layer was further extracted with CH₂Cl₂, the combined organic layers were dried over Na₂SO₄, 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/CH₂Cl₂), which gave the seleno-sulfonamide 12 (113 mg, 25%) as a yellow oil. v_max (film)/cm⁻¹ 3282, 2929, 1438, 1319, 1129, 1065; ¹H NMR (400 MHz, CDCl₃) 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), 1.78–1.74 (m, 3 H); ¹³C NMR (101 MHz, CDCl₃) δ 135.8 (2 × C), 129.2 (2 × C), 128.9, 127.1, 127.0, 70.8, 70.5, 58.2, 43.8, 42.8, 17.3; HRMS (ESI⁺) m/z Calculated for C₁₂H₁₉NO₄NaS₈O₆Se⁺ [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 reflux for 1 h. The reaction was treated with H₂O (2 mL) and then extracted with Et₂O (10 mL). The aqueous layer was acidified with 1 M HCl (2 mL) and then extracted with CH₂Cl₂ (3 × 15 mL). The combined CH₂Cl₂ layers were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure, which afforded carboxylic acid 13 (137 mg, 99%) as a yellow oil. v_max (film)/cm⁻¹ 3274, 2925, 1729, 1438, 1315, 1133; ¹H NMR (400 MHz, CDCl₃) δ 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₁₂H₁₇NO₃NaS₈O₆Se⁺ [M+Na]⁺ 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 H₂O (2 mL) and then extracted with Et₂O (10 mL). The aqueous layer was acidified with 1 M HCl (2 mL) and then extracted with CH₂Cl₂ (3 × 15 mL). The combined CH₂Cl₂ layers were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure, which afforded carboxylic acid 14 (120 mg, 95%) as a yellow oil. v_max (film)/cm⁻¹ 3282, 2924, 1734, 1438, 1319, 1121; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₁₄H₂₄NO₆NaS₈O₆Se⁺ [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. Rf 0.30 (4% MeOH/CH₂Cl₂); v_max (film)/cm⁻¹ 3303, 2928, 1651, 1537, 1438, 1317, 1133; ¹H NMR (400 MHz, CDCl₃) 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), 3.66–3.51 (m, 3 H), 3.36–3.28 (m, 1 H), 3.26–3.17 (m, 1 H), 1.71 (d, J = 7.2 Hz, 3 H); ¹³C NMR (101 MHz, CDCl₃) 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 C₁₉H₂₅N₂O₃S₈O₆Se⁺ [M+H]⁺ 457.0700; Found 457.0706 (Δ +1.3 ppm).
N-Benzyl-2-(2-(vinylsulfonamido)ethoxy)acetamide (15a)

Prepared according to General Procedure D, using carboxylic acid (19 mg, 46 μmol) and benzylamine (5 μL, 46 μmol), which afforded amide (33 mg, 84%) as a colourless oil. \( \delta \) 7.72–7.66 (m, 2 H), 7.40–7.28 (m, 8 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\(_3\)) \( \delta \) 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\(_{18}\)H\(_{18}\)N\(_2\)O\(_3\)NaS\(_6\)Se\(^{80}\) [M+Na\(^{+}\)] 523.0782; Found 523.0779 (Δ +0.6 ppm).

N-Benzyl-2-(2-(2-((1-(phenylselanyl)ethyl)sulfonamido)ethoxy)ethoxy)ethoxy)acetamide (16a)

Prepared according to General Procedure C, using seleno-sulfonamide (19 mg, 28 μmol). The crude material was pure following the aqueous work up, which gave vinyl sulfonamide (38 mg, 79%) as a yellow oil. \( \delta \) 7.78–7.73 (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, CDCl\(_3\)) \( \delta \) 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\(_2\)O\(_3\)NaS\(_6\)Se\(^{80}\) [M+H\(^{+}\)] 626.0874; Found 626.0892 (Δ +2.9 ppm).

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

Prepared according to General Procedure C, using seleno-sulfonamide (19 mg, 28 μmol). The crude material was pure following the aqueous work up, which gave vinyl sulfonamide (18 mg, 79%) as a colourless oil. \( \delta \) 7.34–7.22 (m, 5 H), 7.08 (br s, 1 H), 6.47 (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, CDCl\(_3\)) \( \delta \) 169.6, 138.1, 135.9, 128.7 (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\(_{18}\)H\(_{18}\)N\(_2\)O\(_3\)NaS\(^{80}\) [M+Na\(^{+}\)] 523.0782; Found 523.0779 (Δ -0.6 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 \(\mu\)mol). 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, \text{CHCl}_3); \nu_{\text{max}}(\text{film})/\text{cm}^{-1} 3292, 2924, 1654, 1542, 1328, 1154; {^1}\text{H NMR (400 MHz, CD}_3\text{OD)} \delta 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}\text{C NMR (101 MHz, CD}_3\text{OD)} \delta 172.8, 145.4, 137.8, 135.4, 131.0 (2 \(\times\) C), 128.9 (2 \(\times\) 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\(_3\)O\(_6\)S\(_2^+\) [M+H\(^+\)] 446.1420; Found 446.1419 (\(\Delta -0.2\) 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 \(\mu\)mol) and \((R)\)-[1-(toluene-4-sulfonyl)-pyrrolidin-2-yl]-methylamine (14 mg, 56 \(\mu\)mol), which afforded amide S–9 (14 mg, 47%) as a white solid. 

\([\alpha]_D^{21} +0.22 \ (c 0.02, \text{CHCl}_3); \nu_{\text{max}}(\text{film})/\text{cm}^{-1} 3345, 2926, 2360, 1666, 1533, 1439, 1326, 1158; {^1}\text{H NMR (400 MHz, CDCl}_3) \delta 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}\text{C NMR (101 MHz, CDCl}_3) \delta 170.6, 143.9, 135.8 (2 \(\times\) C), 133.8, 129.8 (2 \(\times\) C), 129.2 (2 \(\times\) C), 128.8, 127.6 (2 \(\times\) C), 127.1, 71.2, 70.7, 70.2, 59.6, 57.9 (0.5 \(\times\) C), 57.8 (0.5 \(\times\) 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\(_3\)O\(_7\)NaS\(_2^+\) [M+Na\(^+\)] 648.1316; Found 648.1286 (\(\Delta -4.6\) ppm).

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

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

Prepared according to General Procedure C, using seleno-sulfonamide S–9 (19 mg, 33 \(\mu\)mol). 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, \text{CHCl}_3); \nu_{\text{max}}(\text{film})/\text{cm}^{-1} 3292, 2924, 1654, 1542, 1328, 1154; {^1}\text{H NMR (400 MHz, CD}_3\text{OD)} \delta 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}\text{C NMR (101 MHz, CD}_3\text{OD)} \delta 173.2, 145.4, 137.9, 135.4, 131.0 (2 \(\times\) C), 128.9 (2 \(\times\) 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\(_{38}\)N\(_3\)O\(_6\)S\(_2^+\) [M+H\(^+\)] 512.1501; Found 512.1503 (\(\Delta +0.4\) ppm).

\(N-(5-Ethyl-1,3,4-thiadiazol-2-yl)-2-(2-((1-(phenylselanyl)ethyl)sulfonamido)ethoxy)acetamide (S–10)\)
**N-(5-Ethyl-1,3,4-thiadiazol-2-yl)-2-(2-(vinylsulfonamido)ethoxy)acetamide (15c)**

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. $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3280, 2931, 1701, 1530, 1438, 1307, 1137; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 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$_3$OD) $\delta$ 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)$_q$; HRMS (ESI$^+$) m/z Calculated for C$_{16}$H$_{23}$N$_{2}$O$_5$S$_2$[M+H]$^+$ 479.0326; Found 479.0334 ($\Delta$ +1.7 ppm).

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

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 °C (CH$_3$Cl$_2$); $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3263, 2937, 1698, 1530, 1432, 1325, 1143, 1095; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 6.72 (dd, $J$ = 16.6, 10.0 Hz, 1 H), 6.19 (br s, 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$_3$OD) $\delta$ 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$_4$O$_4$S$_2$$^{\delta}$[M+H]$^+$ 321.0691; Found 321.0688 ($\Delta$ -0.9 ppm).

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

Prepared according to General Procedure C, using carboxylic acid 14 (20 mg, 49 µmol). The crude material was purified by reversed-phase flash column chromatography (H$_2$O grading to MeOH, with 0.1% v/v HCO$_2$H additive), which gave the amide S–11 (19 mg, 65%) as a colourless oil. R$_t$ 0.50 (10% MeOH/CH$_3$Cl$_2$); $\nu_{\text{max}}$ (film)/cm$^{-1}$: 1663, 1539, 1439, 1318, 1143, 839, 734, 703; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 170.1, 135.6, 130.9, 129.9, 129.4, 129.3, 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$_{28}$H$_{38}$N$_3$O$_5$S$^{\delta}$[M+H]$^+$ 584.1697; Found 584.1702 ($\Delta$ +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$_2$O grading to MeOH, with 0.1% v/v HCO$_2$H additive), which gave the vinyl sulfonamide 16d (5 mg, 38%) as a colourless oil. $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2929, 1666, 1535, 1453, 1327, 1148, 734; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_{29}$H$_{32}$N$_3$O$_5$S$^{\delta}$[M+H]$^+$ 426.2063; Found 426.2077 ($\Delta$ +3.3 ppm).
N-(4-Fluorobenzyl)-2-(2-((1-phenylselanyl)ethyl)sulfonamido)ethoxy)ethoxy)acetamide (S–12)

Prepared according to General Procedure E, using seleno-sulfonamide 16e (9.1 mg, 81%) as a colourless oil. 

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

Prepared according to General Procedure E, using seleno-sulfonamide 16f (22 mg, 31 µmol) and NaIO₄ (13 mg, 62 µmol) in EtOH (0.31 mL). The crude material was pure following the aqueous work up, which gave the vinyl sulfonamide 16f (16 mg, 31%). 

N-(4-Methoxybenzyl)-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 (H₂O grading to MeOH, with 0.1% v/v HCO₂H additive), which gave the amide S–13 (16 mg, 62%) as a colourless oil.

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

Prepared according to General Procedure C, using vinylsulfonamide S–12 (16 mg, 31 µmol) and NaIO₄ (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.

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

Prepared according to General Procedure C, using seleno-sulfonamide S–13 (16 mg, 30 µmol) and NaIO₄ (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. $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3286, 2906, 1658, 1513, 1445,
1325, 1246, 1146, 1109, 1030, 965, 812, 733; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$O$_6$S$^+$ [M+H]$^+$ 373.1433; Found 373.1440 ($\Delta$ +1.9 ppm).
3. \(^1\text{H}\) and \(^{13}\text{C}\) NMR Spectra of Selected Compounds
\[5a\]

$^1$H NMR (400 MHz, CDCl$_3$)

$^1$C NMR (101 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CD$_3$OD)

$^{13}$C NMR (101 MHz, CD$_3$OD)
1H NMR (400 MHz, CDCl₃)

13C NMR (101 MHz, CDCl₃)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, MeOD)

$^{13}$C NMR (101 MHz, MeOD)
6c

$^1$H NMR (400 MHz, MeOD)

$^{13}$C NMR (101 MHz, MeOD)
$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, MeOD)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$\text{H NMR} \ (400 \text{ MHz, CDCl}_3)$

$\text{C NMR} \ (101 \text{ MHz, CDCl}_3)$
$^1$H NMR (400 MHz, CDCl$_3$)

$^1$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^1$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^1$C NMR (101 MHz, CDCl$_3$)
H NMR (400 MHz, CDCl₃)

13C NMR (101 MHz, CDCl₃)
$^1$H NMR (400 MHz, CDCl$_3$)

$^1$H NMR (400 MHz, CDCl$_3$)

$^1$C NMR (101 MHz, CDCl$_3$)

$^1$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl₃)

$^1$H NMR (400 MHz, CDCl₃)

$^1$C NMR (101 MHz, CDCl₃)

$^1$C NMR (101 MHz, CDCl₃)
$^1$H NMR (400 MHz, CDCl$_3$)

$^1^3$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CD$_3$OD)

$^{13}$C NMR (101 MHz, CD$_3$OD)
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1H NMR (400 MHz, CDCl₃)
S–5

$^1$H NMR (400 MHz, CDCl$_3$)

S–5

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}C$ NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
1H NMR (400 MHz, CD$_3$OD)

13C NMR (101 MHz, CD$_3$OD)
$^1$H NMR (400 MHz, CDCl$_3$)

$^1^3$C NMR (101 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CD$_3$OD)

$^{13}$C NMR (101 MHz, CD$_3$OD)
H NMR (400 MHz, CDCl₃)

^1^H NMR (400 MHz, CDCl₃)

S–9

S–9

^1^C NMR (101 MHz, CDCl₃)
$^{1}H$ NMR (400 MHz, CD$_{3}$OD)

$^{13}C$ NMR (101 MHz, CD$_{3}$OD)
$S\text{–}10$

$^1\text{H NMR (400 MHz, CD}_2\text{OD)}$

$S\text{–}10$

$^{13}\text{C NMR (101 MHz, CD}_2\text{OD)}$
$^{1}$H NMR (400 MHz, CD$_3$OD)

$^{13}$C NMR (101 MHz, CD$_3$OD)
S–13

$^1$H NMR (400 MHz, CDCl$_3$)

S–13

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}C$ NMR (101 MHz, CDCl$_3$)
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 MgCl₂, and the cells stored at -80°C until required.

The pellet was resuspended in 20 mM TRIS-HCl (pH 7.5), 10 mM MgCl₂, 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. Supplementary 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