doi:10.1038/nature12796

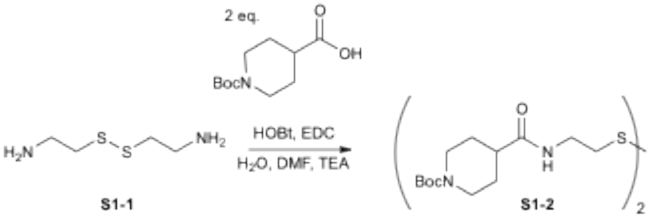
Crystallisation, data collection, and refinement. For X-ray crystallography 1 mM magnesium chloride and 40 µM GDP (final) were added to the freshly purified protein. After high-speed centrifugation hanging drop crystallization conditions were set up by mixing 1:1 protein and precipitation solutions. Common successful reservoir conditions were: 28-32% PEG3000, 200 mM NaCl, 100 mM Tris [pH 7.0]; 1.8-2.2 M 2:3 NaH_2PO_4:K_2HPO_4, 0.1 M NaAc; 28-32% PEG4000, 200 mM NH_4CH_3COO, 100 mM Na-citrate [pH 5.6]; 18-22% PEG8000, 100 mM $CaCl_2$, 100 mM Tris [pH 7.5]; 18-22% PEG3350, 0.2M $CaCl_2$ (see table below). After a varying amount of time, commonly several days, at 20^o C three-dimensional crystals were observed. If necessary, crystals were cryoprotected in the crystallization solution supplemented with glycerol, flash frozen and stored in liquid nitrogen prior to obtaining diffraction data at beamlines 8.2.1/8.2.2/8.3.1 (100 K nitrogen stream) at the Berkeley Lab Advanced Light Source. Data was initially processed with HKL2000 (HKL Research, Inc., scaling) and then solved by molecular replacement and refined to the indicated statistics using Phenix[31].

Crystal **(*PDB code*)**	**Growth condition**	**Beamline/ Wavelength (Å)**	**Ramachandran[*] (F/A/O)**	**Reflections used for R_{free} calculations (% of total)**
K-Ras(G12C) GDP (*4L9G*)	21% PEG3350, 0.2 M $CaCl_2$ (glycerol for cryo-prot.)	ALS 8.2.2./ 0.9999	98.7/1.3/0%	1941 (8.48)
K-Ras(G12C) - **6** (*4LUC*)	25% PEG8000, 100 mM $CaCl_2$, 100 mM Tris pH=7.5	ALS 8.2.2./ 1.0000	97.9/2.1/0%	1936 (2.83)
K-Ras(G12C) - **8** (*4LYF*)	31% PEG4000, 200 mM NH_4CH_3COO, 100 mM Na-citrate pH=5.6	ALS 8.2.2./ 0.9999	97.4/2.6/0%	2006 (3.17)
K-Ras(G12C) - **11** (*4M21*)	29% PEG4000, 200 mM NH_4CH_3COO, 100 mM Na-citrate pH=5.6	ALS 8.2.1./ 1.0700	97.8/2.2/0	2003 (5.87)
K-Ras(G12C) - **9** $P2_12_12_1$ (*4LYJ*)	30% PEG4000, 200 mM NH_4CH_3COO, 100 mM Na-citrate pH=5.6	ALS 8.2.2./ 1.0000	98.2/1.8/0%	1158 (10.01)
K-Ras(G12C) - **7** (*4M1O*)	31% PEG4000, 200 mM NH_4CH_3COO, 100 mM Na-citrate pH=5.6	ALS 8.2.2./ 0.9999	97.4/2.6/0%	1996 (3.16)
H-Ras(G12C) GMPPNP (*4L9W*)	19% PEG3350, 0.2M $CaCl_2$,	ALS 8.2.1./ 1.0000	97.6/2.4/0%	1494 (10.00)
H-Ras(G12C) GDP (*4L9S*)	17% PEG3350, 0.2M $CaCl_2$	ALS 8.3.1./ 1.1159	96.1/3.9/0	1933 (7.57)
K-Ras(WT) GDP (*4LPK*)	19% PEG3350, 0.2M $CaCl_2$	ALS 8.3.1./ 1.1159	96.8/3.2/0	1981 (3.91)
K-Ras(G12C) - **4** (*4LV6*)	22% PEG8000, 100 mM $CaCl_2$, 100 mM Tris pH=7.5	ALS 8.2.1./ 1.0000	99.4/0.6/0	1940 (4.34)
K-Ras(G12C) - **13** (*4M1S*)	32% PEG4000, 200 mM NH_4CH_3COO, 100 mM Na-citrate pH=5.6	ALS 8.2.2./ 0.9999	97.2/2.8/0	2002 (3.02)
K-Ras(G12C) - **14** (*4M1T*)	30% PEG4000, 200 mM NH_4CH_3COO, 100 mM Na-citrate, pH=5.6	ALS 8.2.2./ 1.0000	98.9/1.1/0	1962 (4.13)
K-Ras(G12C) - **15** (*4M1Y*)	31% PEG4000, 200 mM NH_4CH_3COO, 100 mM Na-citrate pH=5.6	ALS 8.2.2./ 1.0000	97.8/2.2/0	1999 (2.80)
K-Ras(G12C) - **16** (*4M22*)	31% PEG3000, 200 mM NaCl, 100 mM Tris pH=7	ALS 8.2.2./ 0.9999	98,3/1.7/0%	1989 (7.02)
K-Ras(G12C) - **9** *C2* (*4LYH*)	1.9M $(NH_4)_2SO_4$, 200 mM NaCl, 100 mM Na-cacodylate pH=6.5	ALS 8.2.2./ 1.0000	98.3/1.7/0	2007 (2.12)
K-Ras(G12C) - Cys-light, GDP (*4LRW*)	30% PEG4000, 200 mM $MgSO_4$, 100 mM Tris pH=8	ALS 8.2.1./ 0.9999	98.0/2.0/0	1639 (10.23)

[*] percentage of amino acids in regions of the Ramachandran plot (**F**avored, **A**llowed, **O**utliers) as determined by Molprobity[32]

Synthetic Methods

All reverse-phase high performance liquid chromatography (RP-HPLC) was carried out using a Varian ProStar solvent delivery system equipped with a Zorbax 300-SB C18 column. Separation was achieved using a gradient of 25-95% acetonitrile (ACN) in water with 0.1% TFA or formic acid monitoring by UV (λ=254 nm). ^{1}H NMR was recorded on a Varian Innova 400 MHz spectrometer. ^{1}H chemical shifts are reported in δ (ppm) as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet) or br (broad) and are referenced to the residual solvent peak. ^{13}C NMR was recorded on a Bruker DRX 500 MHz spectrometer. ^{13}C chemical shifts are reported in δ (ppm) and are referenced to the residual solvent peak. Mass spectrometry (ESI-MS) was carried out using a Waters Acquity UPLC/ESI-TQD with a 2.1 x 50 mm Acquity UPLC BEH C18 column.



Synthesis of di-tert-butyl 4,4'-(((dithiobis(ethane-2,1-diyl))bis(azanediyl))bis(carbonyl))bis(piperidine-1-carboxylate) (**S1-2**)

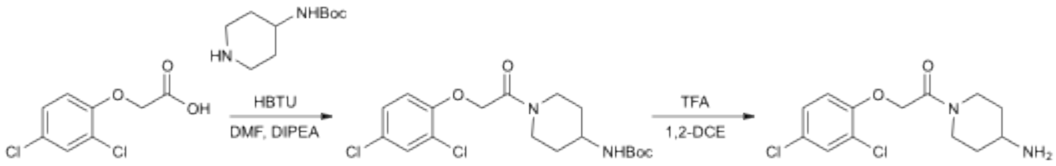
[S1-2] Cystamine dihydrochloride (980 mg, 4.36 mmol, 1 eq) was dissolved in a mixture of 17 mL DMF, 1 mL H_2O, and 1.21 mL triethylamine (8.7 mmol, 2 eq). Hydroxybenzotriazole hydrate (HOBt-H_2O) (1.87 g, 12.2 mmol, 2.8 eq) was added followed by boc-isonipecotic acid (2 g, 8.7 mmol, 2 eq). The solution was stirred at ambient temperature for 30 min followed by addition of N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC) (2.34 g, 12.2 mmol, 2.8 eq). The solution was stirred for 16 h at ambient temperature. The reaction was diluted into 300 mL EtOAc, washed with 50 mL H_2O. Aqueous layer was back extracted twice with 100 mL EtOAc. Cobined organic layers were washed three times with 50 mL saturated $NaHCO_3$, once with 50 mL brine, then dried over $MgSO_4$, filtered and solvent evaporated to dryness. Product was recrystallized from ethyl acetate to afford (**S1-2**) as a white solid (1.19 g, 48%).

S2-1

S2-2

Synthesis of *N*,*N*'-(dithiobis(ethane-2,1-diyl))bis(piperidine-4-carboxamide) (**S2-1**)

[S2-2] Trifluoroacetic acid (TFA) (5 mL) was added to a solution of (**S2-1**) (470 mg, 0.82 mmol) in 5 mL 1,2-dichloroethane and the reaction was stirred at ambient temperature for 2.5 h. The solvent and excess TFA were removed *in vacuo*. The product was washed twice with 5 mL 1,2-dichloroethane, evaporating to dryness each time. The crude product (**S2-2**) was used without further purification.



S3-1

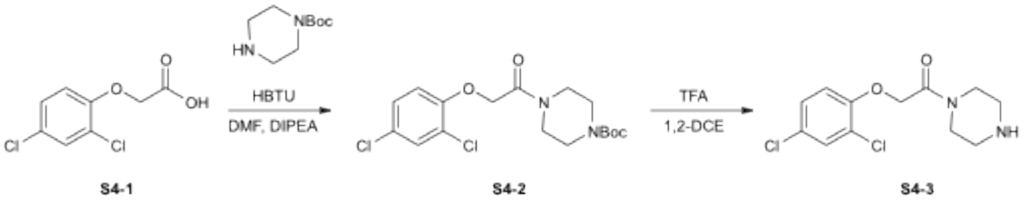
S3-2

S3-3

Synthesis of 1-(4-aminopiperidin-1-yl)-2-(2,4-dichlorophenoxy)ethanone (**S3-3**)

[S3-2] A flame-dried 4-mL vial was charged with 2,4-dichlorophenoxyacetic acid (22 mg, 0.1 mmol, 1 eq) and HBTU (53 mg, 0.14 mmol, 1.4 eq). Anhydrous DMF (300 μL) was added, followed by DIPEA (35 μL, 0.2 mmol, 2 eq). Precipitate formed rapidly, but dissolved upon addition of 4-(boc-amino)piperidine (20 mg, 0.1 mmol, 1 eq). The reaction was stirred at ambient temperature overnight. The mixture was diluted into 50 mL EtOAc, washed with 3x10 mL H_2O, 10 mL sat. $NaHCO_3$, then 10 mL brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness to afford (**S3-2**) as an off-white powder.

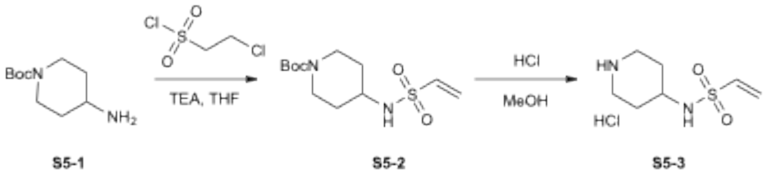
[S3-3] The (**S3-2**) was dissolved in 2 mL 1,2-dichloroethane and 2 mL TFA was added while stirring. After 2 h the solvent and excess TFA were removed *in vacuo* and the remaining orange oil was washed twice with 3 mL 1,2-dichloroethane evaporating to dryness each time. The crude product (**S3-3**) was used without further purification.



Synthesis of 2-(2,4-dichlorophenoxy)-1-(piperazin-1-yl)ethanone (**S4-3**)

[S4-2] A flame-dried 4-mL vial was charged with 2,4-dichlorophenoxyacetic acid (22 mg, 0.1 mmol, 1 eq) and HBTU (53 mg, 0.14 mmol, 1.4 eq). Anhydrous DMF (300 µL) was added, followed by DIPEA (35 µL, 0.2 mmol, 2 eq). Precipitate formed rapidly, but dissolved upon addition of 1-boc-piperazine (19 mg, 0.1 mmol, 1 eq). The reaction was stirred at ambient temperature overnight. The mixture was diluted into 50 mL EtOAc, washed with 3x10 mL H_2O, 10 mL sat. $NaHCO_3$, then 10 mL brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness to afford (**S4-2**) as an off-white powder.

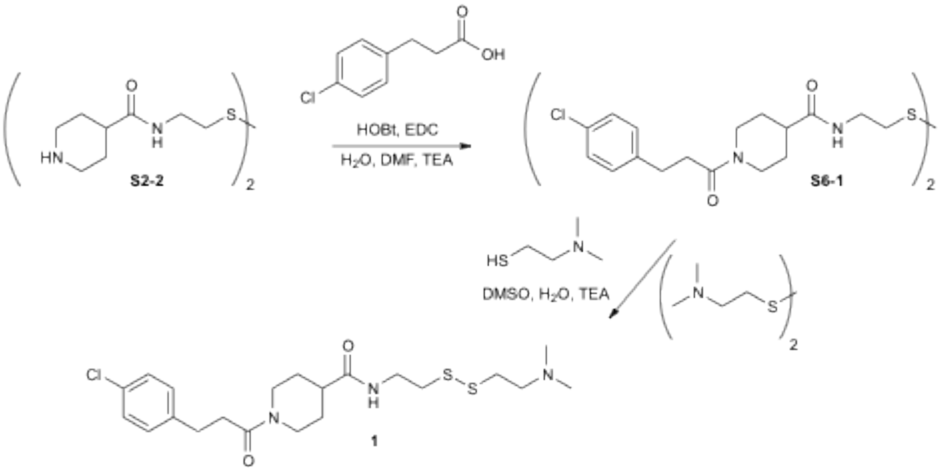
[S4-3] The (**S4-2**) was dissolved in 2 mL 1,2-dichloroethane and 2 mL TFA was added while stirring. After 2 h the solvent and excess TFA were removed *in vacuo* and the remaining orange oil was washed twice with 3 mL 1,2-dichloroethane evaporating to dryness each time. The crude product (**S4-3**) was used without further purification.



Synthesis of N-(piperidin-4-yl)ethenesulfonamide hydrochloride (**S5-3**)

[S5-2] TEA (20.2 g, 200 mmol, 2 eq) was added to the solution of tert-butyl 4-aminopiperidine-1-carboxylate (20 g, 100 mmol) in anhydrous THF (200 mL). Then 2-chloroethanesulfonyl chloride (16.3 g, 100 mmol, 1 eq) was added over 30 min while keeping the temperature between -5°C and 5°C. The resulting mixture was stirred overnight and poured into water (200 mL). The mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine, dried over Na2SO4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (5-50% ethyl acetate – petro ether) to afford the desired product (**S5-2**) (19.7 g, 68% yield) as a white solid.

[S5-3] The compound (**S5-2**) (8.7 g, 30 mmol) was dissolved in hydrogen chloride methanol solution (4N, 200 mL) and stirred at ambient temperature for 5 h then concentrated *in vacuo* to afford the desired product N-(piperidin-4-yl) ethenesulfonamide hydrochloride (**S5-3**) as a white solid (5.724 g, 90% yield).
^{1}H NMR (400 MHz, DMSO-*d6*) δ: 9.13 (br, 1H), 8.96 (br, 1H), 7.65 (d, J = 6.8 Hz, 1H), 6.77 (dd, J = 16.4, 10.0 Hz, 1H), 6.05(d, J = 16.4 Hz, 1H), 5.97 (d, J = 10.0 Hz, 1H), 3.32 (m, 1H), 3.18 (m, 2H), 2.89 (m, 2H), 1.94 (m, 2H), 1.67 (m, 2H).

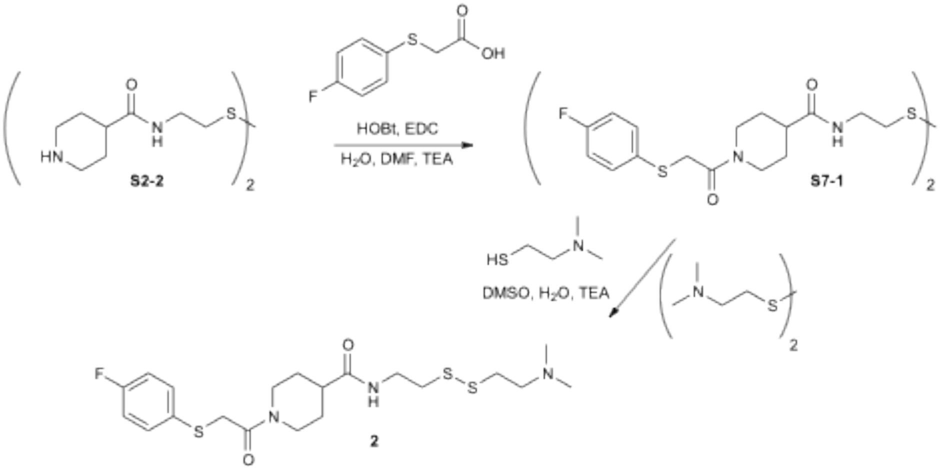


Synthesis of 1-(3-(4-chlorophenyl)propanoyl)-*N*-(2-((2-(dimethylamino)ethyl)disulfanyl)ethyl)piperidine-4-carboxamide (**1**)

[S6-1] HOBt-H_2O (4.5 mg, 0.03 mmol, 0.3 eq) was added to a solution of (**S2-2**) (20 mg, 0.05 mmol, 0.5 eq) in 320 µL DMF, 85 µL H_2O, and 28 µL triethylamine. 3-(4-chlorophenyl)propionic acid (20 mg, 0.1 mmol, 1 eq) was added followed by EDC-HCl (40 mg, 0.2 mmol, 2 eq). The reaction was stirred for 24 h at ambient temperature before addition of 4 eq more EDC-HCl (80 mg, 0.4 mmol). Reaction was stirred at ambient temperature for 24 h. Reaction was diluted into 50 mL EtOAc, washed with 3x10 mL H_2O, 10 mL sat. $NaHCO_3$, then 10 mL brine. Organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness to afford (**S6-1**) as an off-white powder.
[1] The crude product (**S6-1**) was dissolved in 300 µL DMF and added to a solution of 2,2'-dithiobis(*N*,*N*-dimethylethanamine) (75 mg, 0.27 mmol, 5 eq) and cysteamine hydrochloride (2 mg, 0.018 mmol, 0.2 eq) in 100 µL DMSO, 100 µL H_2O, 100 µL triethylamine. The reaction was stirred at ambient temperature for 16 h. The product was purified by RP-HPLC (H_2O:ACN:0.1%TFA) and lyophilized to afford the product as a TFA salt (9.9 mg, 33% over two steps). ESI-MS $[M+H]^+$ calc'd 458.17, found 458.30 *m/z*.

^{1}H NMR (400 MHz, CD_3OD) δ 7.23 (m, 4H), 4.49 (d, J = 13.1, 1H), 3.93 (d, J = 13.9, 1H), 3.48 (m, J = 14.8, 11.6, 7.3, 4H), 3.06 (m, 3H), 2.91 (s, 6H), 2.86 (m, 4H), 2.67 (m, 3H), 2.42 (m, J = 11.6, 3.9, 1H), 1.76 (m, 2H), 1.48 (m, 2H).

^{13}C NMR (126 MHz, CD_3OD) δ 177.47, 168.56, 158.46, 130.54, 127.53, 117.43, 67.95, 57.61, 45.75, 43.91, 43.79, 42.88, 39.46, 38.64, 32.70, 30.28, 29.75.



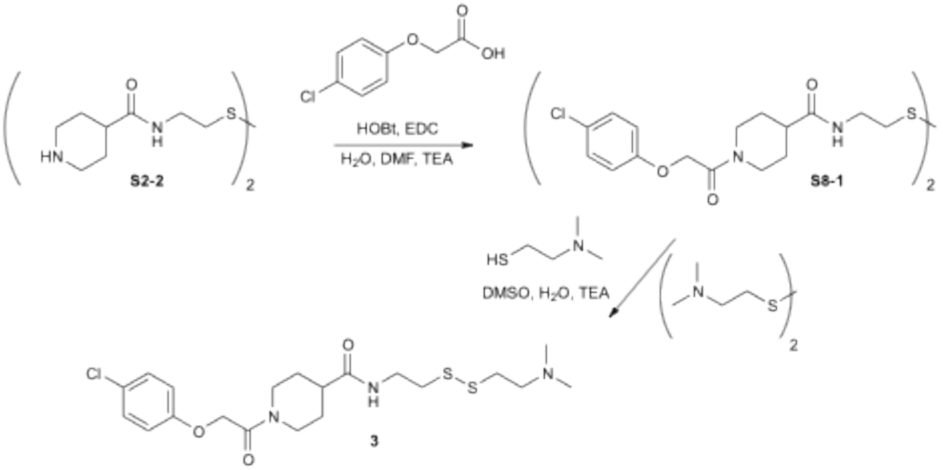
Synthesis of 1-(2-((4-fluorophenyl)thio)acetyl)-*N*-(2-((2-(dimethylamino)ethyl)disulfanyl)ethyl)piperidine-4-carboxamide (**2**)

[S7-1] HOBt-H_2O (4.5 mg, 0.03 mmol, 0.3 eq) was added to a solution of (**S2-2**) (20 mg, 0.05 mmol, 0.5 eq) in 320 µL DMF, 85 µL H_2O, and 28 µL triethylamine. (4-fluorophenylthio)acetic acid (20 mg, 0.1 mmol, 1 eq) was added followed by EDC-HCl (40 mg, 0.2 mmol, 2 eq). The reaction was stirred for 24 h at ambient temperature before addition of 4 eq more EDC-HCl (80 mg, 0.4 mmol). Reaction was stirred at ambient temperature for 24 h. Reaction was diluted into 50 mL EtOAc, washed with 3x10 mL H_2O, 10 mL sat. $NaHCO_3$, then 10 mL brine. Organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness to afford (**S7-1**) as a yellow film.

[2] The crude product (**S7-1**) was dissolved in 300 µL DMF and added to a solution of 2,2'-dithiobis(*N*,*N*-dimethylethanamine) (75 mg, 0.27 mmol, 5 eq) and cysteamine hydrochloride (2 mg, 0.018 mmol, 0.2 eq) in 100 µL DMSO, 100 µL H_2O, 100 µL triethylamine. The reaction was stirred at ambient temperature for 16 h. The product was purified by RP-HPLC (H_2O:ACN:0.1%TFA) and lyophilized to afford the product (**2**) as a TFA salt (16.5 mg, 54% over two steps). ESI-MS $[M+H]^+$ calc'd 460.16, found 460.28 *m/z*.

^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (m, 1H), 7.06 (m, 1H), 4.43 (d, *J* = 13.4, 1H), 3.97 (d, *J* = 13.5, 1H), 3.78 (q, *J* = 14.0, 2H), 3.49 (m, 4H), 3.09 (m, 4H), 2.92 (s, 6H), 2.86 (t, *J* = 6.6, 2H), 2.70 (m, 1H), 2.45 (m, 1H), 1.80 (br, 2H), 1.71 (m, 1H), 1.54 (m, 1H).

^{13}C NMR (126 MHz, CD_3OD) δ 177.49, 169.55, 135.26, 135.19, 117.34, 117.16, 57.61, 47.31, 43.83, 43.79, 42.92, 39.45, 38.64, 38.22, 32.70, 30.34, 29.78.



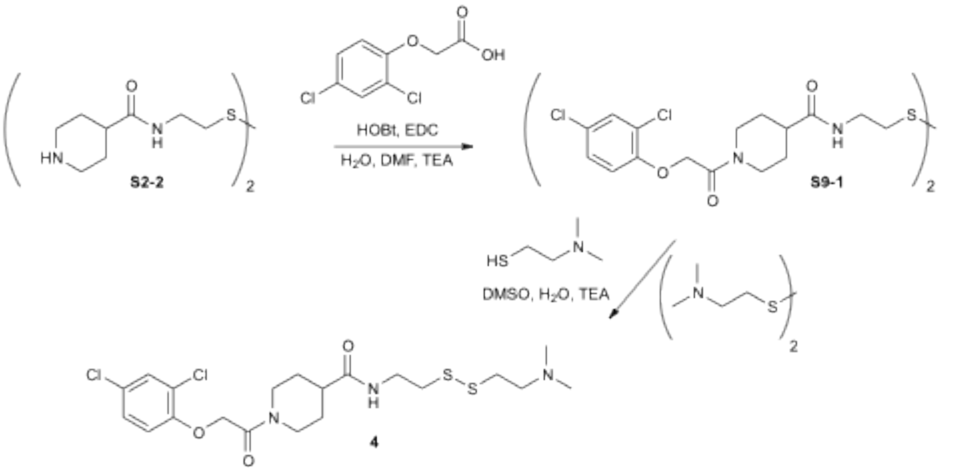
Synthesis of 1-(2-(4-chlorophenoxy)acetyl)-*N*-(2-((2-(dimethylamino)ethyl)disulfanyl)ethyl)piperidine-4-carboxamide (**3**)

[S8-1] HOBt-H_2O (4.5 mg, 0.03 mmol, 0.3 eq) was added to a solution of (**S2-2**) (20 mg, 0.05 mmol, 0.5 eq) in 320 µL DMF, 85 µL H_2O, and 28 µL triethylamine. 4-chlorophenoxyacetic acid (21 mg, 0.1 mmol, 1 eq) was added followed by EDC-HCl (40 mg, 0.2 mmol, 2 eq). The reaction was stirred for 24 h at ambient temperature before addition of 4 eq more EDC-HCl (80 mg, 0.4 mmol). Reaction was stirred at ambient temperature for 24 h. Reaction was diluted into 50 mL EtOAc, washed with 3x10 mL H_2O, 10 mL sat. $NaHCO_3$, then 10 mL brine. Organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness to afford (**S8-1**) as an off-white powder.

[3] To the crude product (**S8-1**) was added a solution of 2,2'-dithiobis(*N*,*N*-dimethylethanamine) (150 mg, 0.53 mmol, 10 eq) and cysteamine hydrochloride (2 mg, 0.018 mmol, 0.2 eq) in 100 µL DMSO, 100 µL H_2O, 100 µL triethylamine. The reaction was stirred at ambient temperature for 16 h. The reaction mixture was separated by RP-HPLC (H_2O:ACN:0.1%TFA) and lyophilized to afford the product (**3**) as a TFA salt (18.4 mg, 60% over two steps). ESI-MS $[M+H]^+$ calc'd 460.15, found 460.31 *m/z*.

^{1}H NMR (400 MHz, CD_3OD) δ 7.25 (d, *J* = 8.8, 2H), 6.93 (d, J = 8.8, 2H), 4.78 (dd, J = 26.2, 13.8, 2H), 4.48 (d, J = 13.2, 1H), 3.98 (d, J = 13.8, 1H), 3.49 (m, 4H), 3.15 (t, J = 12.1, 1H), 3.07 (t, J = 7.32, 2H), 2.92 (s, 6H), 2.86 (t, J = 6.7, 2H), 2.75 (t, J = 11.5, 1H), 2.48 (m, 1H), 1.83 (br, 2H), 1.69 (m, 1H), 1.57 (m, 1H).

^{13}C NMR (126 MHz, CD_3OD) δ 177.51, 172.96, 141.28, 133.13, 131.31, 129.65, 57.62, 46.57, 43.95, 43.80, 42.62, 39.47, 38.63, 35.54, 32.72, 32.00, 30.31, 29.75.

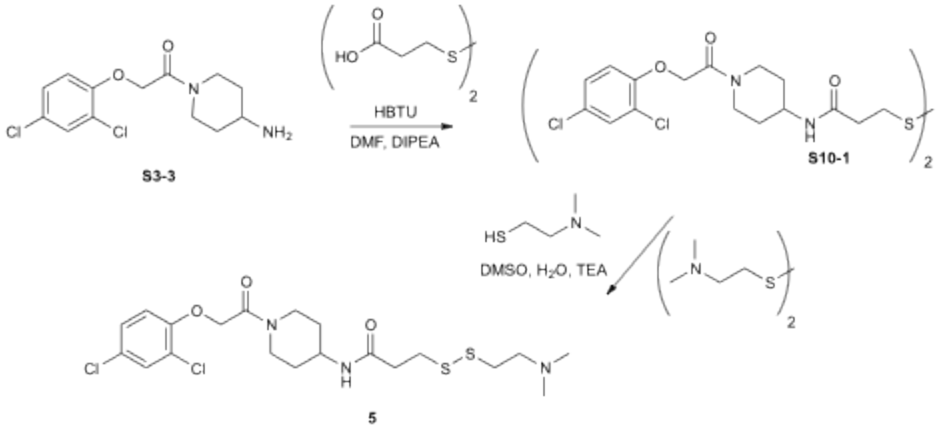


Synthesis of 1-(2-(2,4-dichlorophenoxy)acetyl)-*N*-(2-((2-(dimethylamino)ethyl)disulfanyl)ethyl)piperidine-4-carboxamide (**4**)

[S9-1] A flame-dried 4-mL vial was charged with 2,4-dichlorophenoxyacetic acid (24 mg, 0.11 mmol, 1 eq) and HBTU (56 mg, 0.15 mmol, 1.4 eq). Anhydrous DMF (300 μL) was added, followed by DIPEA (40 μL, 0.23 mmol, 2 eq). Precipitate formed but dissolved upon addition of (**S2-2**) (20 mg, 0.053 mmol, 0.5 eq). The reaction was stirred for 16 h at ambient temperature. Reaction was diluted into 50 mL EtOAc, washed with 3x10 mL H_2O, 10 mL sat. $NaHCO_3$, then 10 mL brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness to afford (**S9-1**) as an off-white powder.

[4] This crude product was dissolved in 300 μL DMF and added to a solution of 2,2'-dithiobis(*N*,*N*-dimethylethanamine) (150 mg, 0.53 mmol, 10 eq) and cysteamine hydrochloride (2 mg, 0.018 mmol, 0.2 eq) in 100 μL DMSO, 100 μL H_2O, 100 μL triethylamine. The reaction was stirred at ambient temperature for 16 h. The reaction mixture was separated by RP-HPLC (H_2O:ACN:0.1%TFA) and lyophilized to afford the product (**4**) as a TFA salt (13.5 mg, 42%). ESI-MS $[M+H]^+$ calc'd 494.22, found 494.11 *m/z*.

^{1}H NMR (400 MHz, CD_3OD) δ 7.41 (d, *J* = 2.6, 1H), 7.24 (dd, *J* = 8.9, 2.6, 1H), 7.00 (d, *J* = 8.9, 1H), 4.88 (dd, *J* = 33.6, 14.1, 2H), 4.46 (d, *J* = 13.3, 1H), 4.02 (d, *J* = 14.0, 1H), 3.49 (m, 4H), 3.17 (m, 1H), 3.07 (m, 2H), 2.92 (s, 6H), 2.86 (t, *J* = 6.6, 2H), 2.76 (m, 1H), 2.48 (tt, *J* = 11.6, 3.9, 1H), 1.83 (t, *J* = 11.4, 2H), 1.71 (m, 1H), 1.57 (m, 1H).

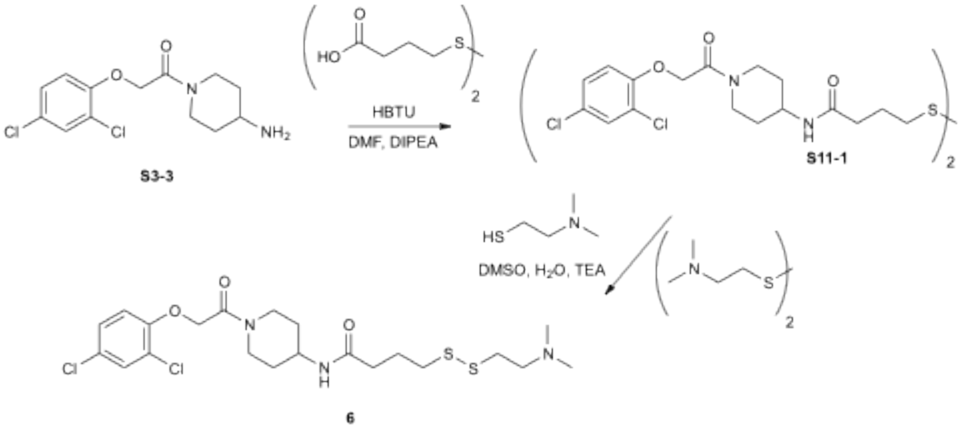


Synthesis of *N*-(1-(2-(2,4-dichlorophenoxy)acetyl)piperidin-4-yl)-3-((2-(dimethylamino)ethyl)disulfanyl)propanamide (**5**)

[S10-1] A flame-dried 4-mL vial was charged with 3,3′-Dithiodipropionic acid (10.5 mg, 0.05 mmol, 0.5 eq) and HBTU (53 mg, 0.14 mmol, 1.4 eq). Anhydrous DMF (300 μL) was added, followed by DIPEA (35 μL, 0.2 mmol, 2 eq). The reaction was stirred at ambient temperature for 30 min. In a separate vial, (**S3-3**) (crude, ~0.1 mmol, 1 eq) was dissolved in 200 μL anhydrous DMF and this solution was added to the reaction and stirring was continued overnight. The mixture was diluted into 50 mL EtOAc, washed with 3x10 mL H_2O, 10 mL sat. $NaHCO_3$, then 10 mL brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness to afford (**S10-**1) as a pale yellow solid.

[5] The crude product (**S10-1**) was dissolved in 300 μL DMF and added to a solution of 2,2'-dithiobis(*N*,*N*-dimethylethanamine) (190 mg, 0.5 mmol, 10 eq) and cysteamine hydrochloride (2 mg, 0.018 mmol, 0.2 eq) in 100 μL DMSO, 100 μL H_2O, 100 μL triethylamine. The reaction was stirred at ambient temperature for 16 h. The reaction mixture was separated by RP-HPLC (H_2O:ACN:0.1%TFA) and lyophilized to afford the product (**5**) as a TFA salt (12 mg, 20% over three steps). ESI-MS $[M+H]^+$ calc'd 494.22, found 494.22 *m/z*.

^1H NMR (400 MHz, CD_3OD) δ 7.45 (d, *J* = 2.5, 1H), 7.27 (dd, *J* = 8.9, 2.6, 1H), 7.04 (d, *J* = 8.9, 1H), 4.91 (dd, *J* = 43.3, 14.0, 2H), 4.39 (d, *J* = 14.8, 1H), 3.97 (m, 2H), 3.51 (m, 2H), 3.27 (m, 1H), 3.07 (m, 2H), 3.03 (t, *J* = 7.0, 2H), 2.96 (s, 6H), 2.92 (m, 2H), 2.63 (t, *J* = 6.9, 2H), 1.95 (m, 2H), 1.52 (m, 1H), 1.38 (m, 1H).

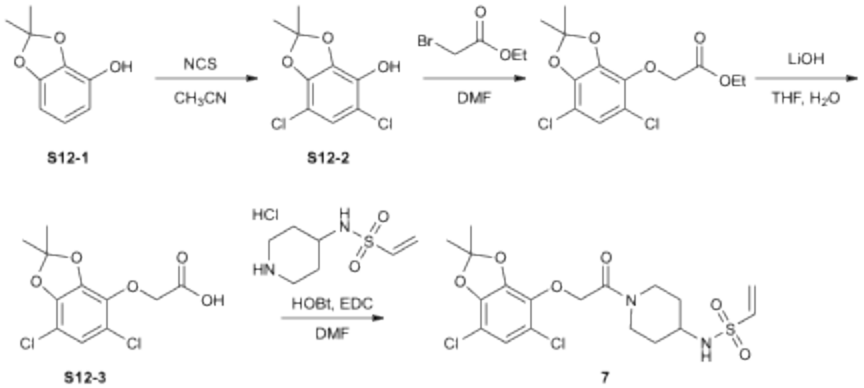


Synthesis of *N*-(1-(2-(2,4-dichlorophenoxy)acetyl)piperidin-4-yl)-3-((2-(dimethylamino)ethyl)disulfanyl)butanamide (**6**)

[S11-1] A flame-dried 4-mL vial was charged with 4,4′-Dithiodibutyric acid (12 mg, 0.05 mmol, 0.5 eq) and HBTU (53 mg, 0.14 mmol, 1.4 eq). Anhydrous DMF (300 µL) was added, followed by DIPEA (35 µL, 0.2 mmol, 2 eq). The reaction was stirred at ambient temperature for 30 min. In a separate vial, (**S3-3**) (crude, ~0.1 mmol, 1 eq) was dissolved in 200 µL anhydrous DMF and this solution was added to the reaction and stirring was continued overnight. The mixture was diluted into 50 mL EtOAc, washed with 3x10 mL H_2O, 10 mL sat. $NaHCO_3$, then 10 mL brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness to afford (**S11-1**) as a pale yellow solid.

[6] The crude product (**S11-1**) was dissolved in 300 µL DMF and added to a solution of 2,2'-dithiobis(*N*,*N*-dimethylethanamine) (190 mg, 0.5 mmol, 10 eq) and cysteamine hydrochloride (2 mg, 0.018 mmol, 0.2 eq) in 100 µL DMSO, 100 µL H_2O, 100 µL triethylamine. The reaction was stirred at ambient temperature for 16 h. The reaction mixture was separated by RP-HPLC (H_2O:ACN:0.1%TFA) and lyophilized to afford the final product (**6**) as a TFA salt (14.8 mg, 24% over three steps). ESI-MS $[M+H]^+$ calc'd 508.13, found 508.19 *m/z*.

^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (d, *J* = 2.5, 1H), 7.24 (dd, *J* = 8.9, 2.6, 1H), 7.00 (d, *J* = 8.9, 1H), 4.88 (dd, *J* = 43.5, 14.1, 2H), 4.37 (d, *J* = 15.0, 1H), 3.97 (d, *J* = 15.7, 1H), 3.91 (m, 1H), 3.47 (m, 2H), 3.23 (m, 1H), 3.03 (m, 2H), 2.92 (s, 6H), 2.87 (m, 1H), 2.77 (m, 2H), 2.29 (t, *J* = 7.3, 2H), 2.00 (m, 2H), 1.89 (m, 2H), 1.46 (m, 1H), 1.34 (m, 1H).



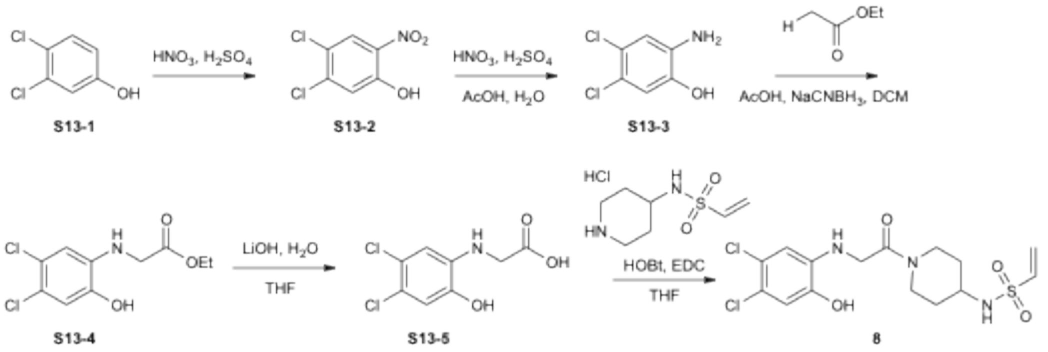
Synthesis of *N*-(1-(2-((5,7-dichloro-2,2-dimethylbenzo[*d*][1,3]dioxol-4-yl)oxy)acetyl)piperidin-4-yl)ethenesulfonamide (**7**)

[S12-2] To 2,2-dimethylbenzo[d][1,3]dioxol-4-ol (500 mg, 3 mmol, 1 eq) in 20 mL acetonitrile was added *N*-chlorosuccinimide (NCS) (801 mg, 6 mmol, 2 eq) and the reaction was brought to reflux. After stirring overnight, 150 mg more NCS was added and the reaction was stirred for an additional 6 h. The mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (0-20% ethyl acetate – hexanes) to afford the crude product (**S12-2**) as a light yellow oil.

[S12-3] To a solution of (**S12-2**) in 3 mL DMF at 0°C was added K_2CO_3. After 5 min, ethyl bromoacetate (315 μL, 2.85 mmol, 1.5 eq) was added and the reaction was allowed to warm to ambient temperature overnight. After 10 days, the reaction was diluted with 120 mL ice water and extracted with 3x40 mL EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was dissolved in 6 mL THF:H_2O (4:1), cooled to 0°C and LiOH hydrate (159 mg, 3.8 mmol, 2 eq) was added. The reaction was allowed to warm to ambient temperature over 4 h while stirring, then diluted into 50 mL water, acidified to pH 2 with 1N $KHSO_4$, and extracted with 2x40 mL EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford (**S12-3**) as a white powder.

[7] The acid (**S12-3**), HOBt-H_2O (18.1 mg, 0.134 mmol, 1 eq), EDC (38.5 mg, 0.2 mmol, 1.5 eq), and DIPEA (70.1 μL, 0.4 mmol, 3 eq) were all combined in 1 mL DMF, followed by addition of (**S5-3)** (30.3 mg, 0.134 mmol, 1 eq). The reaction was stirred overnight at ambient temperature. The reaction mix was concentrated *in vacuo* and the residue separated by RP-HPLC (H_2O:ACN:0.1% formic acid) and lyophilized to afford the final product (**7**) as a white powder (38.6 mg, 62%). ESI-MS $[M+H]^+$ calc'd 465.06, found 465.17 *m/z*.

^1H NMR (400 MHz, DMSO-*d6*) δ 7.51 (d, *J* = 6.7, 1H), 7.05 (s, 1H), 6.77 (dd, *J* = 9.9, 16.5, 1H), 6.05 (d, *J* = 16.5, 1H), 5.95 (d, *J* = 9.9, 1H), 5.02-4.91 (m, 2H), 4.12-4.07 (m, 1H), 3.68-3.63 (m, 1H), 3.29-3.25 (m, 1H), 3.12-3.05 (m, 1H), 2.81-2.74 (m, 1H), 1.85-1.77 (m, 2H), 1.67 (s, 6H), 1.42-1.23 (m, 2H).



Synthesis of N-(1-((4,5-dichloro-2-hydroxyphenyl)glycyl)piperidin-4-yl)ethenesulfonamide (**8**)

[S13-2] To a stirred mixture of 3,4-dichlorophenol (**3-1**) (30 g, 184.5 mmol, 1 eq) in DCM (300 mL) at -10 °C, H_2SO_4 (98%, 23.76 g, 270.75 mmol, 1.5 eq) and HNO_3 (65%, 18.84 g, 193.5 mmol, 1.05 eq) were added slowly. Then the mixture was stirred at RT for 2h and poured into ice water (500 mL). The mixture was extracted with ethyl acetate (300 mL x3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% ethyl acetate – petro ether) to afford the desired product, 4,5-dichloro-2-nitrophenol (**S13-2**) (18 g, 47.0 %yield) as a brown solid.

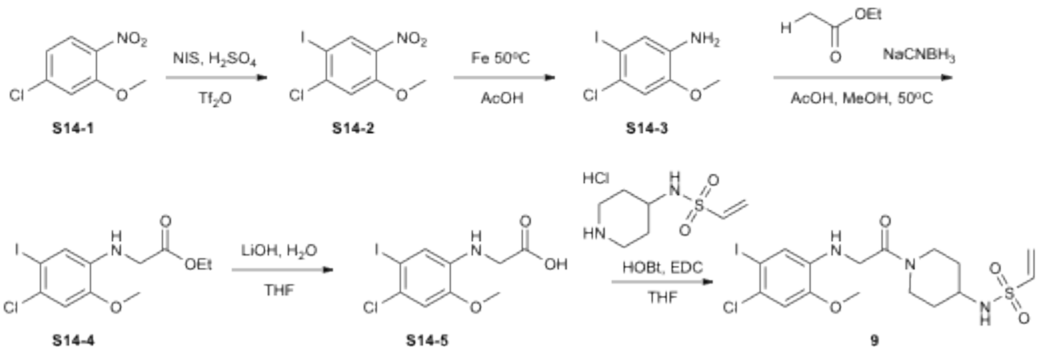
[S13-3] To a stirred mixture of 4,5-dichloro-2-nitrophenol (**S13-2**) (10 g, 48 mmol) in AcOH (100 mL) and H_2O (10 mL), Iron powder (10.3 g, 184 mmol, 4 eq) was added. The mixture was heated to 100 °C for 1h. Then this mixture was cooled to RT. The mixture was diluted with 250 mL of H_2O, extracted with ethyl acetate (70 mL x3). The combined organic layers were washed with brine (70 mL x3), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% ethyl acetate – petro ether) to afford the desired product, 2-amino-4,5-dichlorophenol (**S13-3**) (6.7 g, 78.4 % yield) as a brown solid.

[S13-4] The 2-amino-4,5-dichlorophenol (**S13-3**) (1.77 g, 10 mmol) and ethyl 2-oxoacetate (50% in toluene, 2.65 g, 13 mmol, 1.3 eq) was dissolved in MeOH (50 mL). To this mixture, AcOH (5 drops) was added. The resulting mixture was stirred at R.T. for 3 h and then $Na(CN)BH_3$ (1.26 g, 20 mmol, 2 eq) was added in portions. After stirring at RT for 10h, the reaction mixture was poured into water (200 mL). The mixture was extracted with ethyl acetate (100 mL x3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% MeOH-DCM) to afford the desired product, ethyl 2-(4,5-dichloro-2-hydroxyphenylamino)acetate (**S13-4**) (800 mg, 30.3 % yield) as a brown solid.

[S13-5] Ethyl 2-(4,5-dichloro-2-hydroxyphenylamino)acetate (**S13-4**) (528 mg, 2 mmol) was dissolved in H_2O (20 mL) and THF (10 mL). To this mixture, LiOH (252 mg, 6 mmol, 3 eq) was added. The resulting mixture was stirred at RT for 3 h, poured into water (200 mL) and neutralized with 1N HCl solution to adjust the pH value to 6-7 while keeping the temperature below 0 °C. The resulting mixture was stirred at RT for 30 min and then extracted with ethyl acetate (60 mL x3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the desired product, 2-(4,5-dichloro-2-hydroxyphenylamino)acetic acid (**S13-5**) as a yellow oil. The crude product was used directly in the next step.

[8] To a stirred mixture of 2-(4,5-dichloro-2-hydroxyphenylamino)acetic acid (**S13-5**) (2 mmol, 1 eq) in THF (30 mL) at RT, triethylamine (910 mg, 8 mmol, 4 eq) was added. Then HOBt (420 mg, 2.2 mmol, 1.1 eq) and EDC (298 mg, 2.2 mmol, 1.1 eq) were added sequentially. The resulting mixture was stirred at RT for 10 min, N-(piperidin-4-yl) ethenesulfonamide hydrochloride (**S5-3**) (252 mg, 2 mmol, 1 eq) was added. After stirring at RT for 10h, the reaction mixture was poured into water (50 mL). The mixture was extracted with ethyl acetate (30 mL x3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% MeOH - DCM) to afford the desired product, N-(1-((4,5-dichloro-2-hydroxyphenyl)glycyl)piperidin-4-yl)ethenesulfonamide (**8**) (28 mg, 3.1 % yield) as a white solid. ESI-MS $[M+H]^+$ found 408.05 *m/z*.

^1H NMR (400 MHz, DMSO-*d6*) δ: 10.16 (s, 1H), 7.48 (d, *J* = 7.2 Hz, 1H), 6.78 (s, 1H), 6.77 (m, 1H), 6.72 (s, 1H), 6.06 (d, *J* = 16.4 Hz, 1H), 5.96 (d, *J* = 10 Hz, 1H), 5.31 (m, 1H), 4.17 (m, 1H), 3.88 (m, 3H), 3.28 (m, 1H), 3.14 (m, 1H), 2.86 (m, 1H), 1.84 (m, 2H), 1.34 (m, 2H).



Synthesis of N-(1-((4-chloro-5-iodo-2-methoxyphenyl)glycyl)piperidin-4-yl)ethenesulfonamide (**9**)

[S14-2] To a stirred mixture of H_2SO_4 (90%, 45 mL) and triflic anhydride Tf_2O (22.57 g, 80.0 mmol, 3 eq), NIS (12.0 g, 53.34 mmol, 2 eq) was added. The mixture was stirred at RT for 1h. To the mixture, 4-chloro-2-methoxy-1-nitrobenzene (**S14-1**) (5.0 g, 26.67 mmol, 1 eq) was added in portions. The resulting mixture was stirred at RT for 16 h and poured into ice water (250 mL). The mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% ethyl; acetate / petro ether to afford the desired product, 1-chloro-2-iodo-5-methoxy-4-nitrobenzene (**S14-2**) (2.4 g, 28.7% yield) as a yellow solid.

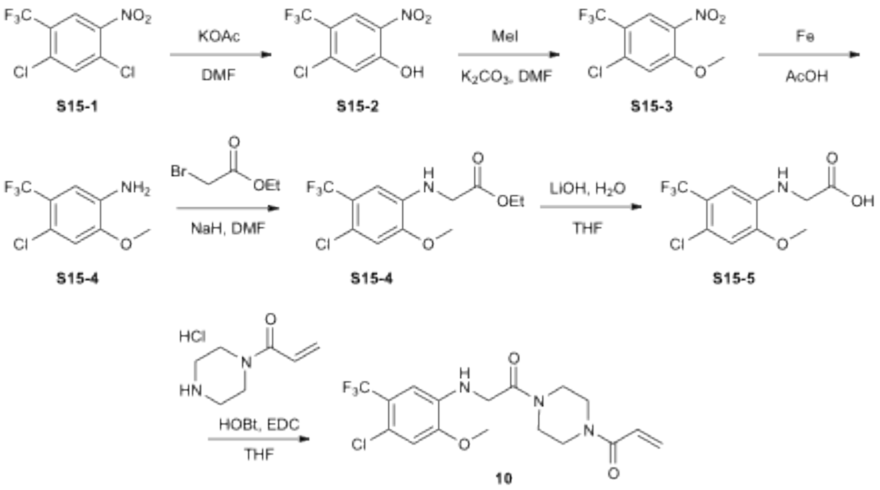
[S14-3] To a stirred mixture of 1-chloro-2-iodo-5-methoxy-4-nitrobenzene (**S14-2**) (1.5 g, 4.785 mmol) in AcOH (25 mL), Iron powder (1.61 g, 28.7 mmol, 6 eq) was added. The mixture was heated to 40 – 50 ^oC for 1h. To this mixture, H_2O (25 ml) was added over 1 h while keeping the temperature at 40 – 50 ^oC. The mixture was diluted with H_2O (250 mL), extracted with ethyl acetate (70 mL x 3). The combined organic layers were washed with NaOH solution (2%, 70 mL x 3), brine (70 mL x 3), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the desired product 4-chloro-5-iodo-2-methoxyaniline (**S14-3**) (1.30 g, 95% yield) as a brown solid

[S14-4] The 4-chloro-5-iodo-2-methoxyaniline (**S14-3**) (400 mg, 1.41 mmol) was combined with ethyl 2-oxoacetate (50% in toluene, 374 mg, 1.83 mmol, 1.3 eq), then was diluted with MeOH (10 mL). To this mixture, AcOH (5 drops) was added. After the mixture was stirred at RT for 3 h, $Na(CN)BH_3$ (178 mg, 2,82 mmol, 2 eq) was added in portions. After stirring at RT for 10 h, the reaction mixture was poured into water (50 mL). The mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-20% ethyl acetate / petro ether) to afford the desired product, ethyl 2-(4-chloro-5-iodo-2-methoxyphenylamino)acetate (458 mg, 88.0% yield) as a brown solid.

[14-5] ethyl 2-(4-chloro-5-iodo-2-methoxyphenylamino)acetate (**S14-4**) (370 mg, 1 mmol) was dissolved in H_2O (8 mL) and THF (2 mL). To this mixture, LiOH (126 mg, 3 mmol, 3 eq) was added. The resulting mixture was stirred at RT for 3h, poured into water (200 mL) and neutralized with 1N HCl solution to adjust the pH value to 6-7 while keeping the temperature below 0^oC. The resulting mixture was stirred at RT for 30 min and then extracted with ethyl acetate (60 mL x3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the desired product, 2-(4-chloro-5-iodo-2-methoxyphenylamino)acetic acid (**S14-5**) as a red solid. The crude product was used directly in the next step. ESI-MS *m/z* : 341.95 $[M+H]^+$.

[9] To a stirred mixture of 2-(4-chloro-5-iodo-2-methoxyphenylamino)acetic acid (**S14-5**) (1 mmol, 1 eq) in THF (20 mL) at RT, triethylamine (405 mg, 4 mmol, 4 eq) was added. Then HOBt (210 mg, 1.1 mmol, 1.1 eq) and EDC (149 mg, 1.1 mmol, 1.1 eq) were added sequentially. The resulting mixture was stirred at RT for 10 min, N-(piperidin-4-yl) ethenesulfonamide hydrochloride (**S5-3**) (226 mg, 1 mmol, 1 eq) was added. After stirring at RT for 10 h, the reaction mixture was poured into water (50 mL). The mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% MeOH - DCM) to afford the desired product, N-(1-((4-chloro-5-iodo-2-methoxyphenyl)glycyl)piperidin-4-yl)ethenesulfonamide (**9**) (28 mg, 5.4% yield) as a white solid. ESI-MS $[M+H]^+$ found 514.05 *m/z*.

^1H NMR (400 MHz, DMSO-*d6*) δ: 7.49 (d, *J* = 7.2 Hz, 1H), 7.02 (s, 1H), 6.99 (s, 1H), 6.79 (dd, *J* = 10.0, 16.4 Hz, 1H), 6.06 (d, *J* = 16.4 Hz, 1H), 5.96 (d, *J* = 10 Hz, 1H), 5.34 (m, 1H), 4.18 (m, 1H), 4.02 (m, 1H), 3.86 (m, 2H), 3.82 (s, 3H), 3.27 (m, 1H), 3.06 (m, 1H), 2.85 (m, 1H), 1.84 (m, 2H), 1.40 (m, 2H).
^{13}C NMR (126 MHz, DMSO-*d6*) δ 166.71, 147.19, 138.07, 137.43, 124.82, 123.18, 118.91, 110.55, 87.82, 55.99, 49.74, 44.05, 42.13, 32.97, 32.30.



Synthesis of 1-(4-((4-chloro-2-methoxy-5-(trifluoromethyl)phenyl)glycyl)piperazin-1-yl)prop-2-en-1-one (**10**)

[S15-2] The 1,5-dichloro-2-(trifluoromethyl)-4-nitrobenzene (**S15-1**) (5 g, 19 mmol) was dissolved in anhydrous DMF (50 mL), KOAc (4.6 g, 47 mmol, 2.4 eq) was added in portions and the resulting mixture was heated to 80 °C for 4 h. Then this mixture was cooled to RT. The mixture was diluted with H_2O (250 mL), extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (70 mL x 3), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% ethyl acetate / petro ether) to afford the desired product, 5-chloro-4-(trifluoromethyl)-2-nitrophenol (**S15-2**) (2.7 g, 58.9 % yield) as a white solid. ESI-MS *m/z* : 241.30 $[M+H]^+$.
[S15-3] The 5-chloro-4-(trifluoromethyl)-2-nitrophenol (**S15-2**) (2.2 g, 9.1 mmol) and K_2CO_3 (3 g, 21 mmol, 2.4 eq) were dissolved in anhydrous DMF (50 mL), MeI (1.55 g, 11 mmol, 1.2 eq) was added in portions and the resulting mixture was stirred at RT for 8 h. The resulting mixture was poured into water (60 mL). The mixture was extracted with ethyl acetate (60 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% ethyl acetate / petro ether) to afford the desired product, 1-chloro-2-(trifluoromethyl)-5-methoxy-4-nitrobenzene (**S15-3**) (950 mg, 40.9% yield) as a brown solid.

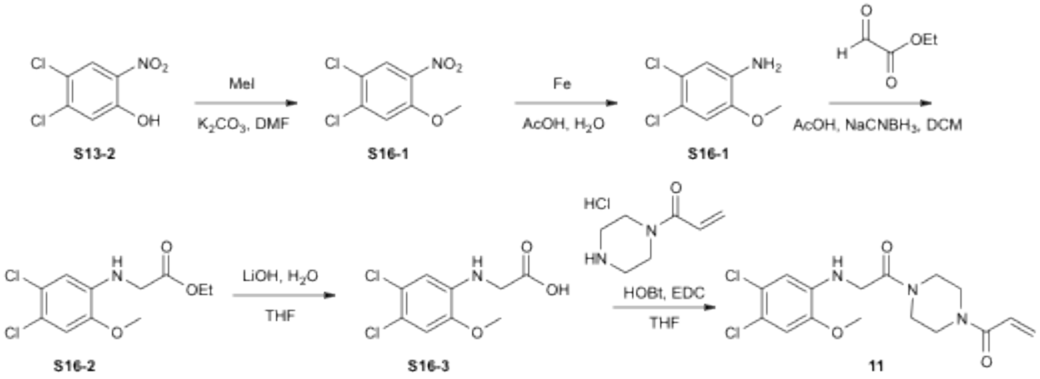
[S15-4] To a stirred mixture of 1-chloro-2-(trifluoromethyl)-5-methoxy-4-nitrobenzene (**S15-3**) (950 mg, 3.72 mmol) in AcOH (40 mL) and H_2O (10 mL), Iron powder (1.5 g, 26.8 mmol, 7 eq) was added. The mixture was heated to 100 ^{o}C for 1 h. Then this mixture was cooled to RT. The mixture was diluted with 50 mL of H_2O, extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-50% ethyl acetate / petro ether) to afford the desired product, 4-chloro-5-(trifluoromethyl)-2-methoxybenzenamine (**S15-4**) (800 mg, 95.5 % yield) as a brown solid.

[S15-5] The 4-chloro-5-(trifluoromethyl)-2-methoxybenzenamine (**S15-4**) (800 mg, 3.56 mmol) was dissolved in anhydrous DMF (20 mL), NaH (60% in mineral oil, 300 mg, 7.5 mmol, 2.1 eq) was added in portions and the resulting mixture was stirred at RT for 0.5 h. To this mixture, ethyl 2-bromoacetate (1.1 g, 6.5 mmol, 1.8 eq) was added. The resulting mixture was stirred overnight and poured into water (30 mL). The mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% ethyl acetate / petro ether) to afford the desired product, ethyl 2-(4-chloro-5-(trifluoromethyl)-2-methoxyphenylamino)acetate (**S15-5**) (600 mg, 54.2% yield) as a brown solid. ESI-MS *m/z* : 311.10 $[M+H]^+$.

[S15-6] Ethyl 2-(4-chloro-5-(trifluoromethyl)-2-methoxyphenylamino)acetate (**S15-5**) (400 mg, 1.29 mmol) was dissolved in H_2O (10 mL) and THF (10 mL). To this mixture, LiOH (400 mg, 9.5 mmol, 7.4 eq) was added. The resulting mixture was stirred at RT for 3 h, poured into water (50 mL) and neutralized with 1N HCl solution to adjust the pH value to 6-7 while keeping the temperature below 0 ^{o}C. The resulting mixture was stirred at RT for 30 min and then extracted with ethyl acetate (60 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*to afford the desired product, 2-(4-chloro-5-(trifluoromethyl)-2-methoxyphenylamino)acetic acid (**S15-6**) (150 mg) as a yellow oil. The crude product was used directly in the next step.

[10] To a stirred mixture of 2-(4-chloro-5-(trifluoromethyl)-2-methoxyphenylamino)acetic acid (**S15-6**) (73 mg, 0.25 mmol, 1 eq) in THF (10 mL) at RT, triethylamine (100 mg, 1 mmol, 4 eq) was added. Then HOBt (53mg, 0.28 mmol, 1.1 eq) and EDC (38 mg, 0.28 mmol, 1.1 eq) were added sequentially. The resulting mixture was stirred at RT for 10 min, 1-(piperazin-1-yl)prop-2-en-1-one hydrochloride (44 mg, 0.25 mmol, 1 eq) was added. After stirring at RT for 10h, the reaction mixture was poured into water (50 mL). The mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% MeOH-DCM) to afford the desired product, 1-(4-((4-chloro-2-methoxy-5-(trifluoromethyl)phenyl)glycyl)piperazin-1-yl)prop-2-en-1-one (**10**) (15 mg, 14.8% yield) as a white solid. ESI-MS $[M-H]^-$ found 404.15 *m/z*.

^{1}H NMR (400 MHz, DMSO-*d6*) δ: 7.10 (s, 1H), 6.91 (s, 1H), 6.82 (m, 1H), 6.15 (d, *J* = 16.8 Hz, 1H), 5.74 (d, *J* = 9.6 Hz, 1H), 5.57 (t, *J* = 4.4 Hz, 1H), 4.05 (d, *J* = 4.0 Hz, 2H), 3.59 (m, 8H).



Synthesis of 1-(4-((4,5-dichloro-2-methoxyphenyl)glycyl)piperazin-1-yl)prop-2-en-1-one (**11**)

[S16-1] The 4,5-dichloro-2-nitrophenol (**S13-2**) (17.9 g, 86.5 mmol) and K_2CO_3 (19.1 g, 130 mmol, 1.5 eq) were dissolved in anhydrous DMF (150 mL). To this mixture, MeI (20.5 g, 144 mmol, 1.5 eq) was added in portions and the resulting mixture was stirred at RT for 8 h. The resulting mixture was poured into water (500 mL). The mixture was extracted with ethyl acetate (300 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% ethyl acetate / petro ether) to afford the desired product, 1,2-dichloro-4-methoxy-5-nitrobenzene (18.4 g, 95.8% yield) as a brown solid.

[S16-2] To a stirred mixture of 1,2-dichloro-4-methoxy-5-nitrobenzene (**S16-1**) (18.4 g, 83 mmol) in AcOH (300 mL) and H_2O (50 mL), Iron powder (18.6 g, 332 mmol, 4 eq) was added. The mixture was heated to 100 ^{o}C for 1 h. Then this mixture was cooled to RT. The mixture was diluted with 500 mL of H_2O, extracted with ethyl acetate (300 mL x 3). The combined organic layers were washed with brine (300 mL x 3), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% ethyl acetate – petro ether) to afford the desired product, 4,5-dichloro-2-methoxybenzenamine (**S16-2**) (13.3 g, 83.4 % yield) as a brown solid.

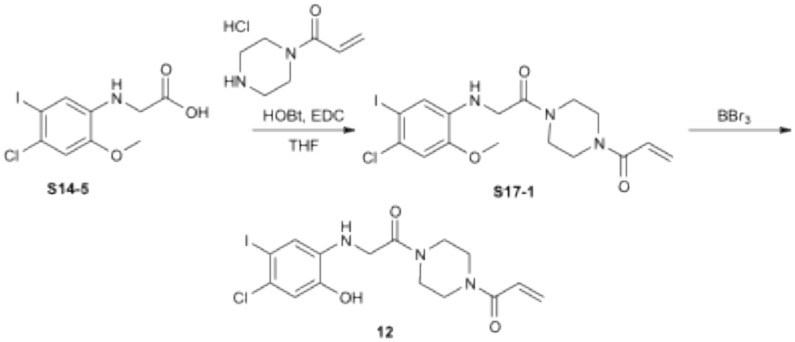
[S16-3] The 4,5-dichloro-2-methoxybenzenamine (**S16-2**) (13.3 g, 70 mmol) was combined with ethyl 2-oxoacetate (50% in toluene, 18.55 g, 91 mmol, 1.3 eq), then was diluted with MeOH (200 mL). To the mixture AcOH (5 drops) was added. The mixture was stirred at R.T. for 3 h and $Na(CN)BH_3$ (8.82 g, 140 mmol, 2 eq) was added in portions. After stirring at RT for 10 h, the reaction mixture was poured into water (300 mL). The mixture was extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% MeOH-DCM) to afford the desired product, ethyl 2-(4,5-dichloro-2-methoxyphenylamino)acetate (**S16-3**) (10.6 g, 54.4 % yield) as a brown solid.

[S16-4] Ethyl 2-(4,5-dichloro-2-methoxyphenylamino)acetate (**S16-3**) (900 mg, 3.3 mmol) was dissolved in H_2O (20 mL) and THF (10 mL). To this mixture, LiOH (454 mg, 10.0 mmol, 3 eq) was added. The resulting mixture was stirred at RT for 3 h, poured into water (50 mL) and neutralized with 1N HCl solution to adjust the pH value to 6-7 while keeping the temperature below 0 °C. The resulting mixture was stirred at RT for 30 min. and then extracted with ethyl acetate (60 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*to afford the desired product, 2-(4,5-dichloro-2-methoxyphenylamino)acetic acid (**S16-4**) as a yellow oil. The crude product was used directly in the next step.

[11] To a stirred mixture of 2-(4,5-dichloro-2-methoxyphenylamino)acetic acid (**S16-4**) (200 mg, 0.8 mmol, 1 eq) in THF (30 mL) at RT, triethylamine (728 mg, 3.2 mmol, 4 eq) was added. Then HOBt (168 mg, 0.88 mmol, 1.1 eq) and EDC (120 mg, 0.88 mmol, 1.1 eq) was added sequentially. The resulting mixture was stirred at RT for 10 min, 1-(piperazin-1-yl)prop-2-en-1-one hydrochloride (140 mg, 0.8 mmol, 1 eq) was added. After stirring at RT for 10 h, the reaction mixture was poured into water (50 mL). The mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% MeOH-DCM) to afford the desired product, 1-(4-((4,5-dichloro-2-methoxyphenyl)glycyl)piperazin-1-yl)prop-2-en-1-one (**11**) (58 mg, 19.5% yield) as a white solid. ESI-MS $[M-H]^-$ found 372.10 *m/z*.

^1H NMR (400 MHz, DMSO-*d6*) δ: 7.01 (s, 1H), 6.84 (m, 1H), 6.78 (s, 1H), 6.15 (dd, J_1 = 16.4 Hz, J_2 = 2 Hz, 1H), 5.72 (dd, J_1 = 10 Hz, J_2 = 2 Hz, 1H), 5.44 (t, J_2 = 4.4 Hz, 1H), 4.00 (d, J = 4.4 Hz, 1H), 3.55 (m, 8H).

^{13}C NMR (126 MHz, DMSO-*d6*) δ 167.49, 164.44, 145.26, 137.29, 127.68, 122.85, 119.28, 113.39, 85.46, 44.30.



Synthesis of 1-(4-((4-chloro-2-hydroxy-5-iodophenyl)glycyl)piperazin-1-yl)prop-2-en-1-one (**12**)

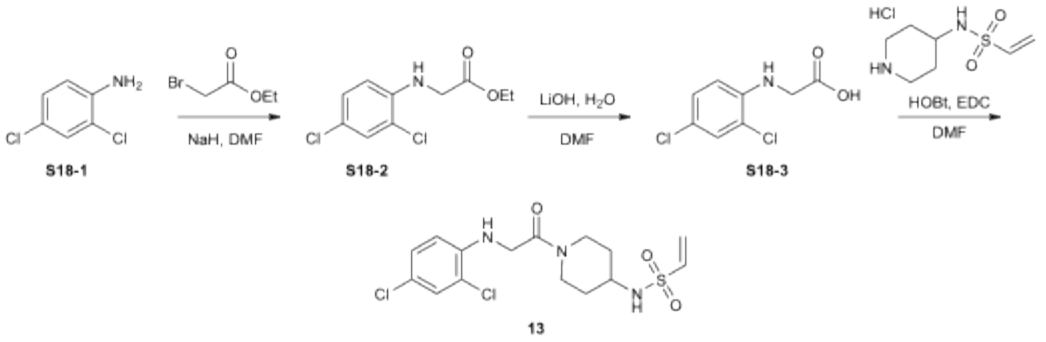
[S17-1] To a stirred mixture of 2-(4-chloro-5-iodo-2-methoxyphenylamino)acetic acid (**S14-5**) (237 mg, 0.69 mmol, 1 eq) in DCM (20 mL) at RT, triethylamine (419 mg, 4.14 mmol, 6 eq) was added. Then HOBt (112 mg, 0.83 mmol, 1.2 eq) and EDC (198 mg, 1.03 mmol, 1.5 eq) was added sequentially. The resulting mixture was stirred at RT for 10 min, 1-(piperazin-1-yl)prop-2-en-1-one hydrochloride (500 mg, 2.08

mmol, 3eq) was added. After stirring at RT for 10 h, the reaction mixture was poured into water (50 mL). The mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% MeOH-DCM) to afford the desired product, 1-(4-(2-(4-chloro-5-iodo-2-methoxyphenylamino) acetyl)piperazin-1-yl)prop-2-en-1-one (**S17-1**) (155 mg, 48.5% yield) as a white solid. ESI-MS $[M+H]^+$ found 464.00 *m/z*.

[12] The 1-(4-(2-(4-chloro-5-iodo-2-methoxyphenylamino)acetyl)piperazin-1-yl) prop-2-en-1-one (**S17-1**) (140 mg, 0.3 mmol) was dissolved in anhydrous DCM (10 mL). The mixture was cooled to -78°C and BBr_3 (0.35 ml, 3.7 mmol, 1.3 eq) was added. The resulting mixture was stirred overnight at RT and poured into water (50 mL). The mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with aqueous solution $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% MeOH-DCM) to afford the desired product, 1-(4-((4-chloro-2-hydroxy-5-iodophenyl)glycyl)piperazin-1-yl)prop-2-en-1-one (**12**) (25 mg, 18.5% yield) as a white solid. ESI-MS $[M-H]^-$ found 450.00 *m/z*.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.19 (s, 1H), 6.97 (s, 1H), 6.81 (m, 2H), 6.15 (d, *J* = 16.8 Hz, 1H), 5.72 (d, *J* = 10.4 Hz, 1H), 5.24 (m, 1H), 3.94 (d, *J* = 3.6 Hz, 2H), 3.55 (m, 8H).

^{13}C NMR (126 MHz, DMSO-*d6*) δ 167.49, 164.44, 145.26, 137.29, 127.68, 122.85, 119.28, 113.39, 85.46, 44.30.



Synthesis of N-(1-((2,4-dichlorophenyl)glycyl)piperidin-4-yl)ethenesulfonamide (**13**)

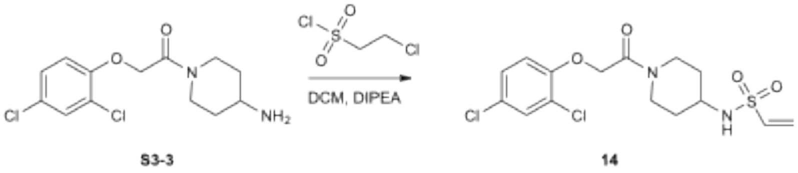
[S18-2] The 2,4-dichlorobenzenamine (1.61 g, 10 mmol) was dissolved in anhydrous DMF (50 mL), NaH (60% in mineral oil, 400 mg, 10 mmol, 1.0 eq) was added in portions and the resulting mixture was stirred at RT for 0.5 h. To this mixture, ethyl 2-bromoacetate (1.68 g, 10 mmol, 1.0 eq) was added. The resulting mixture was stirred overnight and poured into water (100 mL). The mixture was extracted with ethyl acetate (100 mL x3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-

10% ethyl acetate – petro ether) to afford the desired product, ethyl 2-(2,4-dichlorophenylamino) acetate (**S18-2**) (800 mg, 32.2% yield) as a brown solid.

[S18-3] Ethyl 2-(2,4-dichlorophenylamino)acetate (**S18-2**) (248 mg, 1 mmol) was dissolved in H_2O (8 mL) and THF (2 mL). To this mixture, LiOH (126 mg, 3 mmol, 3 eq) was added. The resulting mixture was stirred at RT for 3h, then poured into water (200 mL) and neutralized with 1N HCl solution to adjust the pH value to 6-7 while keeping the temperature below 0 ^oC. The resulting mixture was stirred at RT for 30 min and then extracted with ethyl acetate (60 mL x3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the desired product, 2-(2,4-dichlorophenylamino)acetic acid (**S18-3**) as a yellow oil. The crude product was used directly in the next step.

[13] To a stirred mixture of 2-(2,4-dichlorophenylamino)acetic acid (**S18-3**) (1 mmol, 1 eq) in THF (20 mL), triethylamine (405 mg, 4 mmol, 4 eq) was added at RT. Then HOBt (210 mg, 1.1 mmol, 1.1 eq) and EDC (149 mg, 1.1 mmol, 1.1 eq) was added sequentially. The resulting mixture was stirred at RT for 10 min, N-(piperidin-4-yl) ethenesulfonamide hydrochloride (**S5-3**) (226 mg, 1 mmol, 1 eq) was added. After stirring at RT for 10 h, the reaction mixture was poured into water (50 mL). The mixture was extracted with ethyl acetate (30 mL x3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1 - 10% MeOH - DCM) to afford the desired product, N-(1-((2,4-dichlorophenyl)glycyl)piperidin-4-yl)ethenesulfonamide (**13**) (80 mg, 20.4% yield) as a white solid.

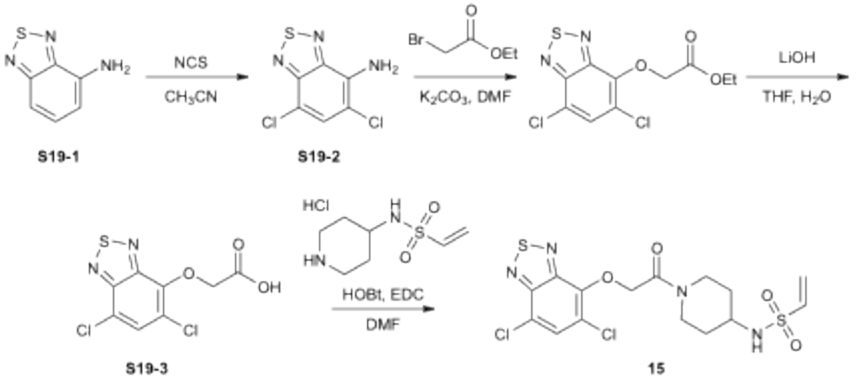
^1H NMR (400 MHz, DMSO-*d6*) δ 7.48 (d, *J* = 7.2 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.21 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.77 (m, 2H), 6.06 (d, *J* = 16.8 Hz, 1H), 5.96 (d, *J* = 10 Hz, 1H), 5.64 (m, 1H), 4.17 (m, 1H), 4.00 (m, 2H), 3.82 (m, 1H), 3.32 (m, 1H), 3.12 (m, 1H), 2.87 (m, 1H), 1.84 (m, 2H), 1.44 (m, 2H).



Synthesis of *N*-(1-(2-(2,4-dichlorophenoxy)acetyl)piperidin-4-yl)ethenesulfonamide (**14**)

[14] DIPEA (175 µL, 1.0 mmol, 10 eq) to a solution of (**S3-3**) (crude, ~0.1 mmol, 1 eq) in anhydrous DCM (5 mL) on ice. 2-chloroethane sulfonyl chloride (16 µL, 0.1 mmol, 1 eq) diluted in anhydrous DCM (5 mL) was added dropwise. The reaction was allowed to warm to RT overnight, then concentrated *in vacuo*, dissolved in 70%ACN/H_2O, separated by RP-HPLC (H_2O:ACN:0.1%TFA) and lyophilized to afford the final product (12 mg, 31%). ESI-MS $[M+H]^+$ calc'd 393.04, found 393.19 *m/z.*

^{1}H NMR (400 MHz, CD_3OD) δ: 7.41 (d, *J* = 2.5, 1H), 7.23 (dd, *J* = 8.9, 2.6, 2H), 6.98 (d, *J* = 8.9, 2H), 6.67 (dd, *J* = 16.5, 9.9, 2H), 6.14 (d, *J* = 16.5, 2H), 5.92 (d, *J* = 9.9, 3H), 4.87 (q, *J* = 14.1, 13H), 4.25 (d, *J* = 13.5, 3H), 3.90 (d, *J* = 14.0, 3H), 3.36 (m, 2H), 3.33 (m, 6H), 3.22 (m, 3H), 2.92 (m, 3H), 1.95 (m, 6H), 1.55 (m, 3H), 1.41 (m, 3H).



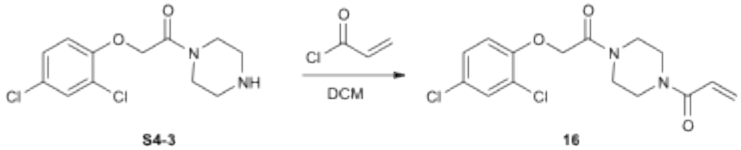
Synthesis of *N*-(1-(2-((5,7-dichlorobenzo[*c*][1,2,5]thiadiazol-4-yl)amino)acetyl)piperidin-4-yl)ethenesulfonamide (**15**)

[S19-2] 1.24 g (9.26 mM, 2 eq.) of N-chlorosuccinimide were added at once to 700 mg (4.6 mM, 1 eq) of benzo[c][1,2,5]thiadiazol-4-amine in 25 mL acetonitrile. After heating under reflux for 12 h, the mixture was cooled down, concentrated *in vacuo*, and dry-loaded onto 5 g of silica gel. The residue was purified by flash column chromatography on silica gel (1-18% ethyl acetate – hexanes) to afford 400 mg (1.82 mM, 40% yield) of the desired dichlorinated product (**S19-2**) as orange powder.

[S19-3] To a solution of 315 mg (1.43 mM, 1 eq) of (**S19-2**) in 8 mL DMF at 0°C, 396 mg (2.86 mM, 2 eq) of K_2CO_3 were added followed after 5 min by ethyl bromoacetate (206 μL, 1.86 mmol, 1.3 eq). The reaction mix allowed to warm to ambient temperature and stirred overnight. Then the mixture was warmed to 50 ^{o}C and stirred for an additional day, followed by addition of an equivalent of ethyl bromoacetate. The reaction was concentrated in vacuo, taken up in 100 mL water, and extracted with 3x40 mL of EtOAc. After washing with brine, drying over $MgSO_4$, and concentration *in vacuo* a reddish solid was obtained. The crude residue was dissolved in 10 mL THF:H_2O (4:1), cooled to 0°C and LiOH hydrate (120 mg, 2.9 mmol, 2 eq) was added. The reaction was allowed to warm to ambient temperature over 3 h while stirring, then diluted into 100 mL water,and acidified with 10% citric acid solution. The aqueous mix was extracted with 4x40 mL EtOAc, the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% methanol – dichlormethane) to afford 102 mg (0.37 mM, 26% yield) of impure (**S19-3**)

[15] The acid (**S19-3**) (25 mg, 90 μM, 1eq), HOBt-H_2O (12.1 mg, 90 μM, 1 eq), EDC (25.8 mg, 0.14 mmol, 1.5 eq), and DIPEA (47 μL, 0.27 mmol, 3 eq) were all combined in 1 mL DMF, followed by addition of **S5-3** (30.3 mg, 0.134 mmol, 1 eq). The reaction was stirred overnight at ambient temperature. The reaction mix was concentrated *in vacuo* and the residue separated by RP-HPLC (H_2O:ACN:0.1% formic acid) and lyophilized to afford the final product (**15**) as an orange powder (12 mg, 27 μM, 30%). ESI-MS $[M+H]^+$ calc'd 450.01, found 450.11 *m/z*.

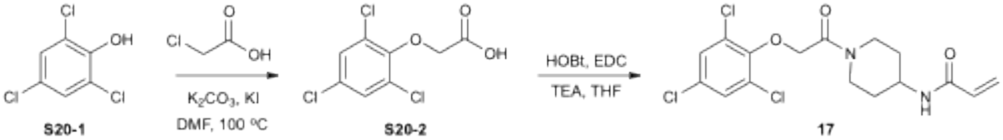
^1H NMR (400 MHz, DMSO-*d6*) δ 7.82 (s, 1H), 7.52 (d, *J* = 7.1, 1H), 6.76 (dd, *J* = 9.9, 16.4, 1H), 6.54 (t, *J* = 5.7, 1H), 6.06 (d, *J* = 16.5, 1H), 5.96 (d, *J* = 9.9, 1H), 4.86-4.67 (m, 2H), 4.13-4.07 (m, 1H), 3.80-3.76 (m, 1H), 3.21-3.13 (m, 1H), 2.84-2.78 (m, 1H), 1.82-1.75 (m, 2H), 1.56-1.48 (m, 1H), 1.33-1.23 (m, 1H).



Synthesis of 1-(4-(2-(2,4-dichlorophenoxy)acetyl)piperazin-1-yl)prop-2-en-1-one (**16**)

[16] Acryloyl chloride (25 μL, 0.3 mmol, 3 eq) was added to a solution of (**S4-3**) (crude, ~0.1 mmol, 1 eq) in 1,2-dichloroethane (5 mL) and the resulting mixture was stirred at ambient temperature. After 25 min, DIPEA (55 μL, 0.3 mmol, 3 eq) was added and stirring was continued at ambient temperature for an additional 15 min. Product formation was confirmed by LC/ESI-MS and the reaction mixture was separated by RP-HPLC (H_2O:ACN:0.1%TFA) and lyophilized to afford the final product (16 mg, 45%). ESI-MS $[M+H]^+$ calc'd 343.06, found 343.22 *m/z.*

^1H NMR (400 MHz, DMSO) δ 7.54 (d, *J* = 2.6, 0H), 7.31 (dd, *J* = 8.9, 2.6, 1H), 7.04 (d, *J* = 9.0, 1H), 6.79 (br, 1H), 6.11 (dd, *J* = 16.7, 2.3, 1H), 5.68 (dd, *J* = 10.4, 2.4, 1H), 5.01 (s, 2H), 3.52 (m, 8H).



Synthesis of N-(1-(2-(2,4,6-trichlorophenoxy)acetyl)piperidin-4-yl)acrylamide (**17**)

[20-2] The 2,4,6-trichlorophenol (**S20-1**) (1.97 g, 10 mmol) was dissolved in anhydrous DMF (100 mL), K_2CO_3 (4.145 g, 30 mmol, 3 eq) and KI (0.166 g, 1 mmol, 0.1 eq) were added and the resulting mixture was heated to 100 °C for 0.5 h. To this mixture, 2-chloroacetic acid (0.9449 g, 10 mmol, 1 eq) was added over 0.5 h. The resulting mixture was heated to 100 ^{o}C and stirred for 1.5 h. Then the reaction mixture was cooled to room temperature and poured into water (300 mL). The mixture was extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% MeOH - DCM) to afford the desired product, 2-(2,4,6-trichlorophenoxy)acetic acid (**S20-2**) (500 mg, 20 % yield) as a gray solid.

[17] To a stirred mixture of 2-(2,4,6-trichlorophenoxy)acetic acid (**S20-2**) (255 mg, 1 mmol, 1 eq) in THF (20 mL), triethylamine (910 mg, 4 mmol, 4 eq) was added at room temperature. Then HOBt (210 mg, 1.1 mmol, 1.1 eq) and EDCI (149 mg, 1.1 mmol, 1.1 eq) was added sequentially. The resulting mixture was stirred at RT for 10 min, N-(piperidin-4-yl)acrylamide hydrochloride (190 mg, 1 mmol, 1 eq) was added. After stirring at room temperature for 10 h, the reaction mixture was poured into water (50 mL). The mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1-10% MeOH-DCM) to afford the final product (**17**) (110 mg, 28.2 % yield) as a white solid. ESI-MS $[M-H]^-$ found 389.00 *m/z*.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.10 (d, J = 8.4 Hz, 1H), 7.74 (s, 2H), 6.22 (dd, J_1 = 16.8 Hz, J_2 = 10.0 Hz, 1H), 6.10 (dd, J_1 = 16.8 Hz, J_2 = 2.0 Hz, 1H), 5.60 (dd, J_1 = 10.0 Hz, J_2 = 2.0 Hz, 1H), 4.73 (m, 2H), 4.21 (m, 1H), 3.85 (m, 2H), 3.18 (m, 1H), 2.85 (m, 1H), 1.81 (m, 2H), 1.37 (m, 2H)

^{13}C NMR (126 MHz, DMSO-*d6*) δ 164.35, 163.75, 149.63, 131.77, 129.15, 128.96, 125.20, 71.03, 45.57, 43.28, 43.27, 31.82, 31.05.

References

31. Adams, P. D. *et al.* PHENIX: a comprehensive Python-based system for macromolecular structure solution. *Acta Crystallogr D Biol Crystallogr* **66,** 213–221 (2010).
32. Chen, V. B. *et al.* MolProbity: all-atom structure validation for macromolecular crystallography. *Acta Crystallogr D Biol Crystallogr* **66,** 12–21 (2010).

Supplementary Table 1 Data collection and refinement statistics (**Molecular replacement**)[†], (1/3)

	K-Ras(WT) GDP	K-Ras(G12C) GDP	H-Ras(G12C) GDP	H-Ras(G12C) GMPPNP	K-Ras(G12C) cys-light, GDP	K-Ras(G12C) - **4**
Data collection						
Space group	$P3$	$P6_3$	$H3_2$	$H3_2$	$P3$	$P1$
Cell dimensions						
a, b, c (Å)	84.3, 84.3, 41.3	82.1, 82.1, 39.5	92.7, 92.7, 121.9	89.1, 89.1, 136.3	82.9, 82.9, 38.4	33.1, 39.3, 62.8
α, β, γ (°)	90, 90, 120	90, 90, 120	90, 90, 120	90, 90, 120	90, 90,120	77.3, 81.2, 77.4
Resolution (Å)	25 – 1.50	20-1.52	25 – 1.61	20 – 1.95	25 – 2.15	20 – 1.50
	(1.53 – 1.50) *	(1.55-1.52) *	(1.64 – 1.61) *	(1.98 – 1.95)*	(2.19 – 2.15) *	(1.53 – 1.50) *
R_{sym}	0.050 (0.289)	0.042 (0.349)	0.050 (0.384)	0.060 (0.371)	0.128 (0.354)	0.068 (0.319)
$I/\sigma I$	19.9 (2.7)	38.9 (5.0)	28.3 (4.6)	34.0 (7.2)	12.9 (5.5)	14.7 (3.6)
Completeness (%)	98.3 (92.4)	99.9 (100.0)	99.7 (100.0)	100.0 (100.0)	100.0(100.0)	96.3 (92.8)
Redundancy	3.0 (2.3)	6.7 (6.2)	6.5 (6.4)	10.9 (11.0)	5.7 (5.7)	3.9 (3.6)
Refinement						
Resolution (Å)	25 – 1.50	20 – 1.52	25 – 1.61	20 – 1.95	25 – 2.15	20-1.50
	(1.54 – 1.50)	(1.56-1.52)	(1.65 – 1.61)	(2.01 - 1.95)	(2.22 – 2.15)	(1.55 – 1.50)
No. reflections	51602 (3499)	23540 (1623)	26375 (1822)	15376 (1367)	16022 (1332)	46242 (4366)
$R_{\mathrm{work}}/ R_{\mathrm{free}}$	0.1578 (0.2684)/ 0.1916 (0.2981)	0.1484(0.1879)/ 0.1804(0.2324)	0.1547 (0.1883)/ 0.1729 (0.2089)	0.1560 (0.2024)/ 0.1890 (0.2846)	0.1797 (0.2348)/ 0.2043 (0.2569)	0.1566 (0.2068)/ 0.1868 (0.2366)
No. atoms						
Protein	2560	1252	1270	1322	2458	2669
Ligand/ion	60	30	33	35	60	108
Water	389	127	167	144	49	247
B-factors						
Protein	27.6	28.8	30.8	36.0	28.6	24.4
Ligand/ion	29.0	14.8	24.4	24.5	16.9	21.5
Water	42.5	36.0	39.2	42.0	21.6	28.9
R.m.s deviations						
Bond lengths (Å)	0.003	0.019	0.010	0.008	0.002	0.009
Bond angles (º)	0.69	1.87	1.30	1.14	0.56	1.25

*Highest resolution shell is shown in parenthesis.

†All compound bound K-Ras(G12C) structures were obtained with the Cys-light construct (C51S/C80L/C118S)

Data collection and refinement statistics (**Molecular replacement**)[†], continued (2/3)

	K-Ras(G12C) - **6**	K-Ras(G12C) - **7**	K-Ras(G12C) - **8**	K-Ras(G12C) - **9** ***C*2**	K-Ras(G12C) - **9** $\boldsymbol{P2_12_12_1}$
Data collection					
Space group	*P*1	*C*2	*C*2	*C*2	$P2_12_12_1$
Cell dimensions					
a, *b*, *c* (Å)	32.8, 39.1, 62.5	68.3, 84.2, 86.4	68.3, 83.8, 86.2	68.0, 83.5, 87.0	38.8, 43.2, 87.5
α, β, γ (°)	77.9, 82, 77.6	90, 111, 90	90, 111, 90	90, 111, 90	90, 90, 90
Resolution (Å)	20-1.29 (1.31-1.29) *	25 – 1.57 (1.60 – 1.57) *	25 – 1.57 (1.60 – 1.57) *	20 – 1.37 (1.39 – 1.37) *	25 – 1.93 (1.96 – 1.93)*
R_{sym} or R_{merge}	0.065 (0.279)	0.062 (0.370)	0.053 (0.368)	0.051 (0.363)	0.170 (0.382)
$I/\sigma I$	13.1 (4.4)	15.2 (3.4)	21.2 (3.5)	21.5 (3.7)	10.2 (4.7)
Completeness (%)	95.2 (91.3)	99.6 (99.9)	99.9 (100.0)	99.9 (100.0)	100.0 (100.0)
Redundancy	3.8 (3.5)	3.7(3.6)	3.7 (3.7)	3.9 (3.8)	7.0 (7.1)
Refinement					
Resolution (Å)	20 – 1.29 (1.32-1.29)	25 – 1.57 (1.61 – 1.57)	25 – 1.57 (1.61 – 1.57)	20 – 1.37 (1.41 – 1.37)	25 – 1.93 (2.01 – 1.93)
No. reflections	70527 (4764)	63257 (4453)	63330 (4453)	94646 (6657)	11569 (1361)
$R_{\mathrm{work}/}$ R_{free}	0.1517 (0.2115)/ 0.1694 (0.2300)	0.1834 (0.2465)/ 0.2017 (0.2899)	0.1693 (0.2163)/ 0.1922 (0.2338)	0.1648 (0.2212)/ 0.1882 (0.2684)	0.1793 (0.1828)/ 0.2069 (0.2356)
No. atoms					
Protein	2713	3682	3704	3860	1315
Ligand/ion	110	113	109	146	55
Water	329	182	197	389	78
B-factors					
Protein	18.9	39.8	35.0	24.6	28.0
Ligand/ion	16.5	30.6	25.2	22.9	19.6
Water	25.8	39.1	37.3	34.4	31.4
R.m.s deviations					
Bond lengths (Å)	0.021	0.010	0.009	0.023	0.007
Bond angles (º)	1.94	1.23	1.19	1.93	1.50

*Highest resolution shell is shown in parenthesis.

†All compound bound K-Ras(G12C) structures were obtained with the Cys-light construct (C51S/C80L/C118S)

Data collection and refinement statistics (**Molecular replacement**) [†], continued (3/3)

	K-Ras(G12C) - **11**	K-Ras(G12C) – **13**	K-Ras(G12C) - **14**	K-Ras(G12C) - **15**	K-Ras(G12C) - **16**
Data collection					
Space group	*C*2	*C*2	*C*2	*C*2	*C*2
Cell dimensions					
a, b, c (Å)	68.6, 83.9, 87.1	68.5, 84.8, 86.8	68.2, 83.5, 85.7	68.1, 83.5, 86.2	70.9, 83.5, 86.9
α, β, γ (°)	90,111,90	90, 111, 90	90, 111, 90	90, 111, 90	90, 109, 90
Resolution (Å)	25 – 1.94	25 – 1.55	25 – 1.70	25 – 1.49	25 – 2.09
	(1.97 – 1.94) *	(1.58 – 1.55) *	(1.73 – 1.70) *	(1.52 – 1.49) *	(2.13 – 2.09) *
R_{sym} or R_{merge}	0.064 (0.407)	0.036 (0.392)	0.041 (0.443)	0.031 (0.381)	0.080 (0.311)
$I/\sigma I$	17.6 (3.5)	28.6 (2.9)	27.4 (3.1)	31.2 (3.7)	16.8 (5.3)
Completeness (%)	99.9 (100.0)	99.4 (99.3)	100.0 (99.8)	97.6 (96.2)	99.9 (100.0)
Redundancy	4.1 (4.1)	3.6 (3.5)	3.7 (3.7)	3.8 (3.8)	3.8 (3.7)
Refinement					
Resolution (Å)	25 – 1.94	25 – 1.55	25 – 1.70	25 – 1.49	25 – 2.09
	(1.99 – 1.94)	(1.59 – 1.55)	(1.75 – 1.70)	(1.53 – 1.49)	(2.14 – 2.09)
No. reflections	34101 (2346)	66325 (4607)	48940 (3331)	71402 (4855)	28329 (1915)
R_{work}/ R_{free}	0.1902 (0.2421)/	0.1797 (0.2362)/	0.1700 (0.2366)/	0.1668 (0.2179)/	0.1790(0.2072)/
	0.2258 (0.2470)	0.1968 (0.2332)	0.2024 (0.2894)	0.1908 (0.2366)	0.2156 (0.2540)
No. atoms					
Protein	3554	3635	3773	3743	3748
Ligand/ion	108	108	108	111	131
Water	87	201	163	314	154
B-factors					
Protein	53.5	41.7	35.9	36.5	38.6
Ligand/ion	50.9	31.9	28.5	25.7	31.4
Water	45.1	40.5	35.3	41.2	33.6
R.m.s deviations					
Bond lengths (Å)	0.006	0.009	0.006	0.011	0.009
Bond angles (º)	1.02	1.16	1.00	1.24	1.16

*Highest resolution shell is shown in parenthesis.

[†] All compound bound K-Ras(G12C) structures were obtained with the Cys-light construct (C51S/C80L/C118S)