Supporting Information

Covalent Ligand Screening Uncovers a RNF4 E3 Ligase Recruiter for Targeted Protein Degradation Applications

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Supporting Methods

Synthesis and characterization of covalent ligands screened against RNF4 that have not been previously reported

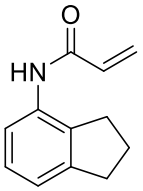
Chemicals and reagents were purchased from major commercial suppliers and used without further purification. Reactions were performed under a nitrogen atmosphere unless otherwise noted. Silica gel flash column chromatography was performed using EMD or Sigma Aldrich silica gel 60 (230-400 mesh). Proton and carbon nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) data was acquired on a Bruker AVB 400, AVQ 400, or AV 600 spectrometer at the University of California, Berkeley. High resolution mass spectrum were obtained from the QB3 mass spectrometry facility at the University of California, Berkeley using positive or negative electrospray ionization (+ESI or -ESI). Yields are reported as a single run.

General Procedure A

The amine (1 eq.) was dissolved in DCM (5 mL/mmol) and cooled to 0°C. To the solution was added acryloyl chloride (1.2 eq.) followed by triethylamine (1.2 eq.). The solution was warmed to room temperature and stirred overnight. The solution was then washed with brine and the crude product was purified by silica gel chromatography (and recrystallization if necessary) to afford the corresponding acrylamide.

General Procedure B

The amine (1 eq.) was dissolved in DCM (5 mL/mmol) and cooled to 0°C. To the solution was added chloroacetyl chloride (1.2 eq.) followed by triethylamine (1.2 eq.). The solution was warmed to room temperature and stirred overnight. The solution was then washed with brine and the crude product was purified by silica gel chromatography (and recrystallization if necessary) to afford the corresponding chloroacetamide.



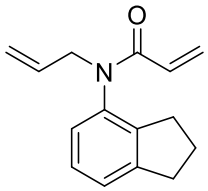
N-(2,3-dihydro-1H-inden-4-yl)acrylamide (DKM 2-84)

A solution of 4-aminoindan (402 mg, 3.0 mmol) in DCM (10 mL) was cooled to 0 °C. To the solution was added acryloyl chloride (379 mg, 4.2 mmol) followed by triethylamine (379 mg, 3.7 mmol). The solution was allowed to warm to room temperature and stirred overnight. The solution was washed with brine and the crude product was purified via silica gel chromatography (30% ethyl acetate in hexanes) to afford the product in 59% yield as a white solid (332 mg).

^{1}H NMR (400MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.5 Hz, 1H), 7.54 (s, 1H), 7.10 (t, *J* = 7.7 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.40-6.26 (m, 2H), 5.69 (dd, *J* = 1.9, 9.7 Hz, 1H), 2.91 (t, *J* = 7.4 Hz, 2H), 2.78 (t, *J* = 7.4 Hz, 2H), 2.05 (quint, *J* = 7.4 Hz, 2H).

^{13}C NMR (100MHz, $CDCl_3$): 163.5, 145.3, 134.4, 133.6, 131.2, 127.5, 127.2, 12.0, 19.2, 33.2, 30.1, 24.8.

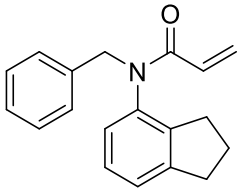
HRMS (+ESI): Calculated: 188.1070 ($C_{12}H_{14}NO$). Observed:188.1069



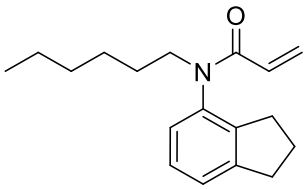
N-allyl-N-(2,3-dihydro-1H-inden-4-yl)acrylamide (IGA 1-12)

To a solution of sodium hydride (96 mg, 4.0 mmol) in tetrahydrofuran (8 mL) was added *N*-(2,3-dihydro-1H-inden-4-yl)acrylamide (187 mg, 1.0 mmol) in tetrahydrofuran (2 mL) under an atmosphere of nitrogen. The reaction mixture was cooled to 0°C and 3-bromoprop-1-ene (484 mg, 4.0 mmol) was and the mixture warmed to room temperature and stirred overnight. The reaction was quenched by the addition of water and extracted with ethyl acetate. The crude product was purified by silica gel chromatography (20% ethyl acetate in hexanes) to afford the product (151 mg, 67%) as a yellow crystalline solid.

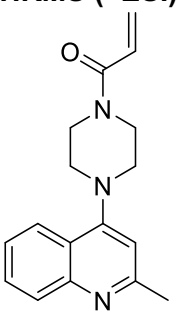
^{1}H NMR (400MHz, $CDCl_3$): δ 7.06-7.18 (m, 2H), 6.80-6.88 (m, 1H), 6.26-6.37 (dd, *J* = 16.8, 2.0 Hz, 1H), 5.76-5.96 (m, 2H), 5.38-5.48 (dd, *J* = 10.3, 2.1 Hz, 1H), 4.98-5.08 (m, 2H), 4.40-4.52 (ddt, *J* = 14.5, 6.3, 1.3 Hz, 1H), 4.00-4.11 (ddt, *J* = 14.5, 6.8, 1.2 Hz, 1H), 2.82-2.98 (m, 2H), 2.59-2.79 (m, 2H), 1.92-2.07 (m, 2H).
^{13}C NMR (100MHz, $CDCl_3$): δ 165.1, 146.5, 142.4, 137.9, 133.0, 128.4, 127.8, 127.48, 126.1, 124.3, 118.1, 51.6, 33.3, 30.9, 25.0.
HRMS (+ESI): Calculated: 228.13 ($C_{15}H_{17}NO$). Observed: 228.1381.



N-benzyl-N-(2,3-dihydro-1H-inden-4-yl)acrylamide (IGA 1-14)
To a solution of sodium hydride (96 mg, 4.0 mmol) in tetrahydrofuran (8 mL) was added *N*-(2,3-dihydro-1H-inden-4-yl)acrylamide (187 mg, 1.0 mmol) in tetrahydrofuran (2 mL) under an atmosphere of nitrogen. The solution was cooled to 0 °C and benzyl bromide (476 mg, 4.0 mmol) was added after which point the solution was warmed to room temperature and stirred overnight. The solution was quenched by the addition of water and extracted with ethyl acetate. The crude product was purified by silica gel chromatography (20% ethyl acetate in hexanes) to afford the product in 63% yield as an orange oil (173 mg).
^{1}H NMR (400MHz, $CDCl_3$): δ 7.10-7.35 (m, 7H), 6.74-6.85 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.40-6.55 (dd, *J* = 16.8, 2.1 Hz, 1H), 5.93-6.08 (dd, *J* = 16.8, 10.3 Hz, 1H), 5.49-5.62 (dd, *J* = 10.3, 2.1 Hz, 1H), 4.78-5.10 (m, 2H), 2.85-3.02 (m, 2H), 2.52-2.67 (m, 1H), 2.22-2.37 (m, 1H), 1.83-2.01 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 165.28, 146.40, 142.84, 137.71, 137.33, 129.29, 128.38, 128.30, 128.04, 127.53, 127.47, 126.00, 124.29, 52.33, 33.25, 30.64, 25.06.
HRMS (+ESI): Calculated: 278.15 ($C_{19}H_{19}NO$). Observed: 278.1538.

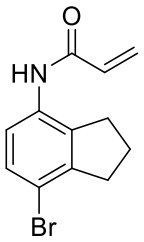


N-allyl-N-(2,3-dihydro-1H-inden-4-yl)acrylamide (IGA 1-15)
To a solution of sodium hydride (96 mg, 4.0 mmol) in tetrahydrofuran (8 mL) was added *N*-(2,3-dihydro-1H-inden-4-yl)acrylamide (187 mg, 1.0 mmol) in tetrahydrofuran (2 mL) under an atmosphere of nitrogen. The solution was cooled to 0°C and 1-bromohexane (660 mg, 4.0 mmol) was added after which point the solution was warmed to room temperature and stirred overnight. The solution was quenched with water and extracted with ethyl acetate. The crude product was purified via silica gel chromatography (20% ethyl acetate in hexanes) to afford the product in 34% yield as a yellow oil (92 mg).
^{1}H NMR (400MHz, $CDCl_3$): δ 7.11-7.25 (m, 2H), 6.86-6.96 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.30-6.40 (dd, *J* = 16.8, 2.1 Hz, 1H), 5.86-6.00 (m, 1H), 5.41-5.51 (dd, *J* = 10.3, 2.1 Hz, 1H), 3.82-3.96 (m, 1H), 3.42-3.56 (m, 1H), 2.90-3.04 (m, 2H), 2.65-2.85 (m, 2H), 1.98-2.16 (m, 2H), 1.47-1.63 (m, 2H), 1.20-1.36 (m, 6H), 0.80-0.90 (m, 3H).
^{13}C NMR (100MHz, $CDCl_3$): δ 165.2, 146.5, 142.4, 138.2, 128.6, 127.5, 127.4, 126.1, 124.1, 48.7, 33.3, 31.6, 30.9, 27.9, 26.7, 25.0, 22.6, 14.1.
HRMS (+ESI): Calculated: 272.19 ($C_{18}H_{25}NO$). Observed: 272.2007.



1-(4-(2-methylquinolin-4-yl)piperazin-1-yl)prop-2-en-1-one (IGA 1-26)
A solution of 2-methyl-4-(piperazin-1-yl)quinolone (455 mg, 2.0 mmol) in DCM (20 mL) was cooled to 0 °C. To the solution was added acryloyl chloride (217 mg, 2.4 mmol) followed by triethylamine (243 mg, 2.4 mmol). The

solution was allowed to warm to room temperature and stirred overnight. The solution was washed with brine and the crude product was purified via basic alumina chromatography (100% ethyl acetate) to afford the product in 26% yield as a yellow oil (145 mg).
^{1}H NMR (400MHz, $CDCl_3$): δ 7.90-8.05 (m, 2H), 7.58-7.70 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.40-7.50 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 6.68-6.76 (s, 1H), 6.56-6.67 (dd, *J* = 16.8, 10.5 Hz, 1H), 6.30-6.40 (dd, *J* = 16.8, 2.0 Hz, 1H), 5.70-5.80 (dd, *J* = 10.5, 2.0 Hz, 1H), 3.70-4.06 (d, *J* = 54.7 Hz, 4H), 3.10-3.30 (t, *J* = 5.0 Hz, 4H), 2.62-2.72 (s, 3H).
^{13}C NMR (100MHz, $CDCl_3$): δ 165.5, 159.4, 156.2, 149.2, 129.26, 129.24, 128.3, 127.3, 124.9, 123.0, 121.6, 109.8, 52.3, 51.9, 45.8, 42.0, 25.6.
HRMS (+ESI): Calculated: 282.17 ($C_{17}H_{19}N_3O$). Observed: 282.1597.

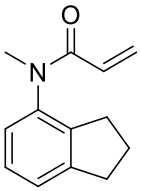


***N*-(7-bromo-2,3-dihydro-1*H*-inden-4-yl)acrylamide (TRH 1-65).**

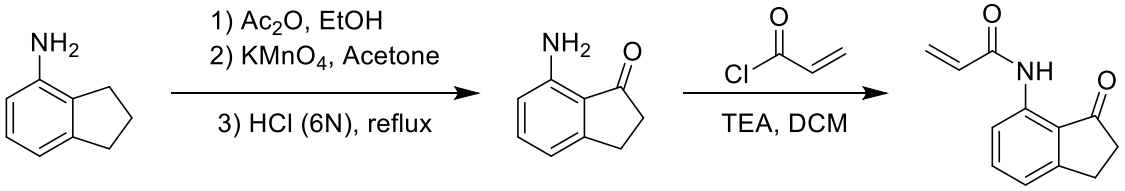
To a solution of *N*-(2,3-dihydro-1*H*-inden-4-yl)acrylamide (**DKM 2-84,** 469 mg, 2.5 mmol) in acetic acid (10 mL) was added ammonium bromide (305 mg, 3.1 mmol) followed by dropwise addition of hydrogen peroxide solution (50% in water, 1.90 mL). The reaction was stirred overnight, after which it was carefully neutralized with a solution of saturated sodium bicarbonate and extracted with ethyl acetate (3x20 mL). The combined organics were then evaporated and the resulting crude was purified via silica gel chromatography (20% ethyl acetate in hexanes) to give 621 mg of the product as a white solid (93%).

^{1}H NMR (400MHz, MeOD): δ 7.36 (d, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 6.49 (dd, *J* = 10.2, 17.0 Hz, 1H), 6.35 (dd, *J* = 1.8, 17.0 Hz, 1H), 5.77 (dd, *J* = 1.8, 10.2 Hz, 1H), 2.95 (q, *J* = 8.0 Hz, 4H), 2.08 (quint, *J* = 7.5 Hz, 2H).

^{13}C NMR (100MHz, MeOD): δ 146.5, 140.2, 134.2, 132.0, 130.8, 128.1, 124.3, 116.9, 101.4, 35.8, 32.9, 24.9.



N-methyl-N-(2,3-dihydro-1H-inden-4-yl)acrylamide (TRH 1-115)
To a solution of sodium hydride (60% dispersion in mineral oil, 167 mg, 4.0 mmol) in tetrahydrofuran (8 mL) under nitrogen atmosphere at 0 °C was added a solution N-(2,3-dihydro-1H-inden-4-yl)acrylamide (**DKM-2-84**, 188 mg, 1.0 mmol) in tetrahydrofuran (2 mL). After stirring for 30 minutes, methyl iodide (0.25 mL, 4.0 mmol) was added. The solution was allowed to warm to room temperature and stirred overnight. The solution was quenched with water and extracted with three times with ethyl acetate. The combined organics were washed with brine, dried with magnesium sulfate, filtered, and evaporated, and the resulting crude product was purified via silica gel chromatography (20% ethyl acetate in hexanes) to afford the product in 35% yield as a clear oil (71 mg).
^{1}H NMR (400MHz, $CDCl_3$): δ 7.19-7.13 (m, 2H), 6.90 (d, *J* = 7.4 Hz, 1H), 6.32 (dd, *J* = 2.0, 16.8 Hz, 1H), 5.96 (dd, *J* = 10.3, 16.8 Hz, 1H), 5.43 (dd, *J* = 2.0, 10.3 Hz, 1H), 3.24 (s, 3H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.81-2.66 (m, 2H), 2.08-2.00 (m, 2H).
^{13}C NMR (100MHz, $CDCl_3$): δ 165.6, 146.6, 141.7, 139.3, 128.2, 127.7, 127.4, 125.1, 124.2, 36.0, 33.2, 30.5, 24.9.
HRMS (+ESI): Calculated: 202.1226 ($C_{13}H_{16}NO$). Observed: 202.1224.



***N*-(3-oxo-2,3-dihydro-1*H*-inden-4-yl)acrylamide (TRH 1-129)**

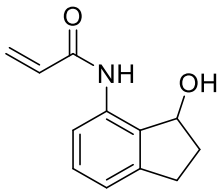
i. To a solution of 4-aminoindan (1.0 g, 7.5 mmol) in ethanol (20 mL) at 0 °C was added acetic anhydride (1.4 mL, 15.0 mmol). The solution was then warmed to room temperature and stirred overnight at which point the solvent was evaporated *in vacuo*. The residue was then dissolved in acetone (50 mL) and 15% aqueous magnesium sulfate (1.2 g in 6.75 mL of water) followed by potassium permanganate (3.4 g, 17.0 mmol) were added. The resulting solution was stirred for 24 hours and then filtered through a pad of celite, eluting with chloroform and then water. The eluent was separated, and the aqueous layer was extracted several times with additional chloroform. The combined organics were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was then dissolved in 6N HCl (20 mL) and heated to 90 °C. After stirring for 5 hours, the solution was cooled, neutralized with small portions of potassium carbonate, and extracted with ethyl acetate. The combined organics were dried with magnesium sulfate, filtered, and evaporated *in vacuo* to give the crude **7-aminoindan-1-one** (610 mg, 55% over 3 steps) which was used without further purification.

ii. To a solution of the crude 7-aminoindan-1-one in dichloromethane (15 mL) was added acryloyl chloride (0.39 mL, 4.8 mmol) followed by triethylamine (0.67 mL, 4.8 mmol) at 0˚C under an atmosphere of N_2. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was then washed with 1M HCl solution twice, brine, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (10% to 20% ethyl acetate in hexanes) to yield the product (390 mg, 47% yield, 26% combined yield over 4 steps) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ 10.64 (s, 1H), 8.45 (d, *J* = 8.2 Hz, 1H), 7.55 (t, *J* = 7.9 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.45 (dd, *J* = 1.0, 17.0 Hz, 1H), 6.33 (dd, *J* = 10.1, 17.0 Hz, 1H), 5.82 (dd, *J* = 1.0, 10.1 Hz, 1H), 3.11 (t, *J* = 11.5 Hz, 2H), 2.74-2.71 (m, 2H).

^{13}C NMR (100MHz, $CDCl_3$): δ 209.3, 164.4, 155.9, 138.7, 137.0, 131.7, 128.0, 123.1, 120.8, 116.9, 36.5, 25.5.

HRMS (+ESI): Calculated: 202.0863 ($C_{12}H_{12}NO_2$). Observed: 202.0860.



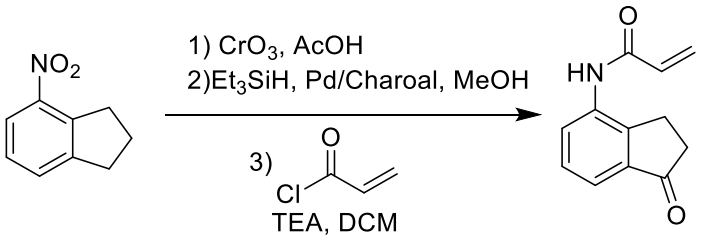
***N*-(3-hydroxy-2,3-dihydro-1*H*-inden-4-yl)acrylamide (TRH 1-133).**

To a solution of *N*-(3-oxo-2,3-dihydro-1*H*-inden-4-yl)acrylamide (**TRH 1-129**, 201 mg, 1.0 mmol) in anhydrous methanol (7 mL) under nitrogen atmosphere was added sodium borohydride (46.1 mg, 1.2 mmol). After 30 minutes of stirring, the reaction was quenched with saturated sodium bicarbonate solution and extracted three times with DCM. The combined organic layers were dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (30 to 50% ethyl acetate in hexanes) affording the product (190 mg, 94% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (s, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.29 (d, *J* = 16.8 Hz, 1H), 6.15 (dd, *J* = 10.2, 16.9 Hz, 1H), 5.66 (d, *J* = 10.2 Hz, 1H), 5.32 (q, *J* = 6.9 Hz, 1H), 3.60 (d, *J* = 6.7 Hz, 1H), 2.96 (ddd, *J* = 2.4, 9.0, 15.7 Hz), 2.73 (quint, *J* = 8.1 Hz, 1H), 2.56-2.48 (m, 1H), 1.96-1.86 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 143,7 ,135.6, 132.8, 131.6, 129.5, 127.3, 121.0, 118.5, 76.2, 36.0, 29.8.

HRMS (-ESI): Calculated: 202.0874 ($C_{12}H_{12}NO_2$). Observed: 202.0874.



***N*-(1-oxo-2,3-dihydro-1*H*-inden-4-yl)acrylamide (TRH 1-134).**

i. To a solution of 4-nitroindan (5.38 g, 33 mmol) in acetic acid (250 mL) was slowly added chromium trioxide (8.95 g, 90 mmol). After stirring for 24 hours, the reaction was neutralized with 2M NaOH and extracted five times with ethyl acetate. The combined organics were washed with a saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (10-20% ethyl acetate in hexanes) to give 1.26 g (ca. 7.1 mmol) of 4-nitroindanone as a white solid.

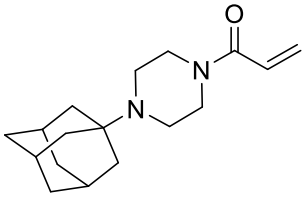
ii. This intermediate was then combined with palladium on activated charcoal (125 mg, 10 wt%) dissolved in anhydrous methanol (21 mL) under an atmosphere of a nitrogen. Triethylsilane (11.3 mL, 71 mmol) was slowly added by addition funnel over the course of 10 minutes to the reaction in a room temperature water bath. After an additional 20 minutes of stirring, the reaction mixture was filtered through a pad of celite and concentrated *in vacuo* to give 4-aminoindanone which was used without further purification.

iii. The aforementioned crude aminoindanone was dissolved in DCM (21 mL) under an atmosphere of nitrogen and cooled to 0 ˚C at which point acryloyl chloride (0.77 mL, 9.5 mmol) and triethylamine (1.19 mL, 8.5 mmol) were slowly added dropwise. The reaction mixture was warmed to room temperature, stirred overnight, washed twice with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (30-50% ethyl acetate in hexanes) to give the title compound (989 mg, 15% yield over 3 steps) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 5.8 Hz, 1H), 7.63 (s, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 6.48 (d, *J* = 16.7 Hz, 1H), 6.37 (dd, *J* = 10.0 Hz, 16.8 Hz, 1H), 5.83 (d, *J* = 10.1 Hz, 1H), 3.04 (t, *J* = 5.6 Hz, 2H), 2.70 (t, *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.3, 163.9, 146.0, 138.0, 135.4, 130.7, 128.8, 128.7, 127.6, 120.4, 36.1, 23.4.

HRMS (-ESI): Calculated: 200.0717 ($C_{12}H_{10}NO_2$). Observed: 200.0715.



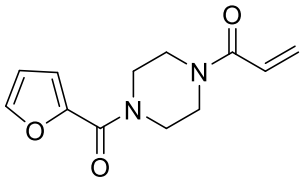
1-(4-((3*s*,5*s*,7*s*)-adamantan-1-yl)piperazin-1-yl)prop-2-en-1-one (TRH 1-143).

To a solution 1-(1-adamantyl)piperazine (441 mg, 2.0 mmol) in dichloromethane (10 mL) was added acryloyl chloride (0.20 mL, 2.4 mmol) followed by triethylamine (0.34 mL, 2.4 mmol) at 0˚ C under N_2 atmosphere. After stirring for 20 minutes, the reaction mixture was allowed to warm to room temperature and was stirred for 24 hours. The solution was washed twice with brine, dried with magnesium sulfate, and the resulting crude was purified by silica gel chromatography (0% to 5% methanol in DCM) to yield 131 mg of brown solid (24% yield).

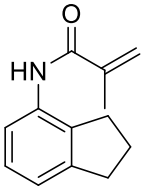
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.59 (dd, *J* = 10.5, 16.8 Hz, 1H), 6.31 (dd, *J* = 1.8, 16.8 Hz, 1H), 5.77 (dd, *J* = 5.77 Hz, 1H), 4.12 (s, 4H), 3.17 (s, 4H), 2.25 (s, 3H), 2.06 (s, 6H), 1.71 (q, *J* = 8.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 129.0, 126.4, 63.3, 44.6, 44.1, 42.9, 39.0, 36.4, 35.5, 29.3.

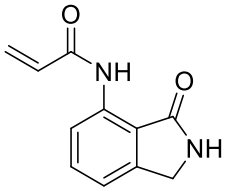
HRMS (+ESI): Calculated: 275.2118 ($C_{17}H_{27}N_2O$). Observed: 275.2113.



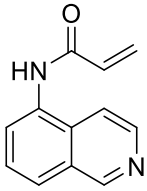
1-(4-(furan-2-carbonyl)piperazin-1-yl)prop-2-en-1-one (TRH 1-145).
To a solution 1-(2-furoyl)piperazine (362 mg, 2.0 mmol) in dichloromethane (10 mL) was added acryloyl chloride (0.20 mL, 2.4 mmol) followed by triethylamine (0.34 mL, 2.4 mmol) at 0˚C under an atmosphere of nitrogen. After stirring for 20 minutes, the reaction mixture was warmed to room temperature and was stirred an additional 24 hours. The reaction mixture was washed twice with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The resulting crude material was purified by silica gel chromatography (70% to 100% ethyl acetate in hexanes) to yield the product (446 mg, 95%) as a yellow solid.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (m, 1H), 7.06 (dd, *J* = 0.7, 3.5 Hz, 1H), 6.61 (dd, *J* = 10.5, 16.8 Hz, 1H), 6.52 (dd, *J* = 1.8, 3.5 Hz, 1H), 6.33 (dd, *J* = 1.9, 16.8 Hz, 1H), 5.75 (dd, *J* = 1.9, 10.5 Hz, 1H), 3.84-3.67 (m, 8H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 159.1, 147.5, 144.0, 128.5, 127.1, 117.0, 111.5, 45.6, 41.9.
HRMS (+ESI): Calculated: 235.1077 ($C_{12}H_{15}N_2O_3$). Observed: 235.1075.



***N*-(2,3-dihydro-1*H*-inden-4-yl)methacrylamide (TRH 1-149).**
To a solution 4-aminoindan (0.24 mL, 2.0 mmol) in dichloromethane (10 mL) was added methacryloyl chloride (0.23 mL, 2.4 mmol) followed by triethylamine (0.34 mL, 2.4 mmol) at 0˚C under an atmosphere of nitrogen. After stirring for 20 minutes, the reaction mixture was warmed to room temperature and stirred for an additional 3.5 hours. The reaction mixture was then washed twice with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The resulting crude material was purified by silica gel chromatography (35% to 40% ethyl acetate in hexanes) to yield the title compound (378 mg, 94%) as an off-white solid.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.55 (s, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 5.79 (s, 1H), 5.42 (s, 1H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.79 (t, *J* =7.4 Hz, 2H), 7.12-2.06 (m, 2H), 2.04 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 145.1, 140.6, 134.5, 133.7, 127.0, 120.7, 119.8, 118.9, 33.1, 29.9, 24.7, 18.6.
HRMS (+ESI): Calculated: 202.1226 ($C_{13}H_{16}NO$). Observed: 202.1224.



***N*-(3-oxoisoindolin-4-yl)acrylamide (TRH 1-152).**
To a solution of 7-aminoisoindolin-1-one (99 mg, 0.67 mmol) in dichloromethane (4 mL) was added acryloyl chloride (0.07 mL, 0.8 mmol) followed by triethylamine (0.11 mL, 0.8 mmol) at 0˚ C under N_2 atmosphere. After stirring for 20 minutes, the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was washed twice with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The resulting crude material was purified by silica gel chromatography (50 to 60% ethyl acetate in hexanes) to afford the title compound (58 mg, 43%) as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.50 (s, 1H), 8.58 (d, *J* = 8.2 Hz, 1H), 7.55 (t, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 6.82 (s, 1H), 6.46 (dd, *J* = 1.3, 17.0 Hz, 1H), 6.36 (dd, *J* = 10.0, 17.0 Hz, 1H), 5.81 (dd, *J* = 1.3, 10.0 Hz, 1H), 4.46 (s, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 164.2, 143.9, 138.2, 133.8, 131.8, 127.8, 118.0, 117.7, 117.6, 45.6.
HRMS (+ESI): Calculated: 203.0815 ($C_{11}H_{11}N_2O_2$). Observed: 203.0814.



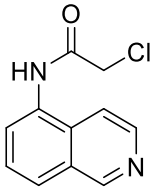
***N*-(isoquinolin-5-yl)acrylamide (TRH 1-162).**

To a solution of 5-aminoisoquinoline (287 mg, 2.0 mmol) in dichloromethane (10 mL) was added acryloyl chloride (0.20 mL, 2.4 mmol) followed by triethylamine (0.34 mL, 2.4 mmol) at 0˚ C under N_2 atmosphere. After stirring for 20 minutes, the reaction mixture was allowed to warm to room temperature and was stirred overnight. The solution was washed with brine, and the resulting aqueous layer was extracted with a 2:1 chloroform:methanol solution. The resulting crude was purified by chromatography on basic alumina (50% ethyl acetate in hexanes to 4% ethanol in ethyl acetate) to yield 43 mg of a yellow solid (11% yield).

^{1}H NMR (400 MHz, MeOD): δ 9.23 (s, 1H), 8.45 (d, *J* = 6.1 Hz, 1H), 8.03 (d, *J* = 7.5 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 6.1 Hz, 1H), 7.68 (t, *J* = 7.9 Hz, 1H), 6.66 (dd, *J* = 10.2, 17.0 Hz, 1H), 6.47 (dd, *J* = 1.5, 17.0 Hz, 1H), 5.88 (dd, *J* = 1.7, 10.2 Hz, 1H).

^{13}C NMR (100 MHz, MeOD): δ 167.1, 153.5, 143.0, 133.6, 132.4, 131.9, 130.6, 128.7, 127.9, 127.1, 117.2.

HRMS (+ESI): Calculated: 199.0866 ($C_{12}H_{11}N_2O$). Observed: 199.0863.



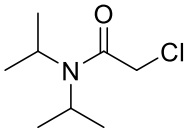
2-Chloro-*N*-(isoquinolin-5-yl)acetamide (TRH 1-163).

To a solution 5-aminoisoquinoline (289 mg, 2.0 mmol) in dichloromethane (10 mL) was added chloroacetyl chloride (0.19 mL, 2.4 mmol) followed by triethylamine (0.34 mL, 2.4 mmol) at 0˚ C under N_2 atmosphere. After stirring for 20 minutes, the reaction mixture was allowed to warm to room temperature and was stirred overnight. The solution was washed with saturated sodium bicarbonate solution and brine, dried with magnesium sulfate, and the resulting crude was purified by chromatography on basic alumina (30% ethyl acetate in hexanes to 4% ethanol in ethyl acetate) to yield 157 mg of yellow solid (36% yield).

^{1}H NMR (600 MHz, MeOD): δ 9.26 (s, 1H), 8.48 (d, *J* = 6.1 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 7.4 Hz, 1H), 7.91 (d, *J* = 6.1 Hz, 1H), 7.71 (t, *J* = 7.9 Hz, 1H), 4.39, (s, 2H).

^{13}C NMR (150 MHz, MeOD): δ 167.4, 152.1, 141.7, 131.8, 131.2, 129.2, 127.3, 127.0, 126.1, 115.7, 42.3.

HRMS (+ESI): Calculated: 221.0476 ($C_{11}H_{10}N_2O$). Observed: 221.0473.



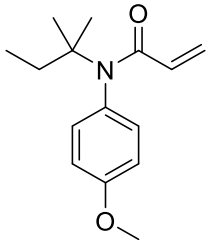
2-Chloro-*N,N*-diisopropylacetamide (TRH 1-168).

To a solution diisopropylamine (0.42 mL, 3.0 mmol) in dichloromethane (10 mL) was added chloroacetyl chloride (0.29 mL, 3.6 mmol) followed by triethylamine (0.50 mL, 3.6 mmol) at 0˚ C under N_2 atmosphere. After stirring for 20 minutes, the reaction mixture was allowed to warm to room temperature and was stirred overnight. The solution was washed with saturated sodium bicarbonate solution and brine, dried with magnesium sulfate, and the resulting crude was purified by silica gel chromatography (0 to 20% ethyl acetate in hexanes) to yield 376 mg of white solid (70% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (s, 2H), 3.88-3.82 (m, 1H), 3.38-3.31 (m, 1H), 1.29 (d, *J* = 6.5 Hz, 6H), 1.14 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 49.7, 46.1, 43.2, 20.7, 20.0.

HRMS (+ESI): Calculated: 200.0813 ($C_8H_{16}NOClNa$). Observed: 200.0811.



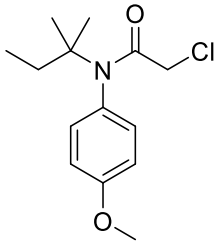
***N*-(4-methoxyphenyl)-*N*-(*tert*-pentyl)acrylamide (TRH 1-170).**

To a solution of 4-methoxy-*N*-(*tert*-pentyl)aniline (94 mg, 0.49 mmol) in dichloromethane (5 mL) was added acryloyl chloride (0.05 mL, 0.6 mmol) followed by triethylamine (0.09 mL, 0.6 mmol) at 0˚C under an atmosphere of nitrogen. After stirring for 15 minutes, the reaction mixture was warmed to room temperature and stirred an additional 18 hours. The reaction mixture was then washed with saturated aqueous sodium bicarbonate solution, brine, dried over magnesium sulfate, and concentrated *in vacuo*. The resulting crude material was purified by silica gel chromatography (0% to 20% ethyl acetate in hexanes) to yield the title compound (82 mg, 68%) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.17 (dd, *J* = 1.9, 16.7 Hz, 1H), 5.76 (dd, *J* = 10.3, 16.7 Hz, 1H), 5.28 (dd, *J* = 1.9, 10.3 Hz, 1H), 3.81 (s, 3H), 2.11 (q, *J* = 7.5 Hz, 2H), 1.20 (s, 6H), 0.91 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 159.0, 134.3, 131.49, 131.45, 125.6, 114.1, 61.7, 55.5, 32.0, 27.4, 9.4.

HRMS (+ESI): Calculated: 247.1572 ($C_{15}H_{21}NO_2$). Observed: 247.1577.



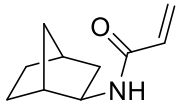
2-Chloro-*N*-(4-methoxyphenyl)-*N*-(*tert*-pentyl)acetamide (TRH 1-171).

To a solution 4-methoxy-*N*-(*tert*-pentyl)aniline (95 mg, 0.5 mmol) in dichloromethane (5 mL) was added chloroacetyl chloride (0.05 mL, 0.6 mmol) followed by triethylamine (0.085 mL, 0.6 mmol) at 0˚ C under N_2 atmosphere. After stirring for 15 minutes, the reaction mixture was allowed to warm to room temperature and was stirred overnight. The solution was washed with saturated sodium bicarbonate solution and brine, dried with magnesium sulfate, and the resulting crude was purified by silica gel chromatography (0 to 10% ethyl acetate in hexanes) to yield 99 mg of a yellow oil (74% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H), 3.63 (s, 2H), 2.05 (q, *J* = 7.4 Hz, 2H), 1.16 (s, 6H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 159.5, 133.2, 131.0, 114.5, 62.5, 55.5, 44.8, 31.8, 27.1, 9.3.

HRMS (+ESI): Calculated: 270.1255 ($C_{14}H_{21}NO_2Cl$). Observed: 270.1254.



+/-

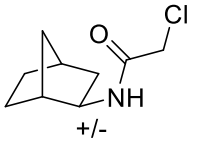
***N*-(*exo*-norborn-2-yl)acrylamide (TRH 1-176).**

To a solution of *exo*-2-aminonorbornane (0.24 mL, 2 mmol) in dichloromethane (10 mL) was added acryloyl chloride (0.20 mL, 2.4 mmol) followed by triethylamine (0.33 mL, 2.4 mmol) at 0˚C under an atmosphere of nitrogen. After stirring for 20 minutes, the reaction mixture was warmed to room temperature and stirred for an additional 18 hours. The reaction mixture was then washed with saturated aqueous sodium bicarbonate solution, brine, dried over magnesium sulfate, and concentrated *in vacuo*. The resulting crude material was purified by silica gel chromatography (30% ethyl acetate in hexanes) to yield the title compound (271 mg, 82%) as a white solid.

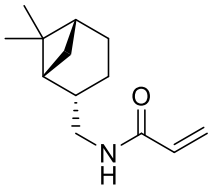
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (s, 1H), 6.25 (dd, *J* = 2.3, 17.0 Hz, 1H), 6.18 (dd, *J* = 9.5, 17.0 Hz, 1H), 5.58 (dd, *J* = 2.3, 9.5 Hz, 1H), 3.8-3.77 (m, 1H), 2.27-2.24 (m, 2H), 1.78 (ddd, *J* = 2.1, 8.1, 13.0 Hz, 1H), 1.55-1.38 (m, 3H), 1.30-1.10 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 131.4, 125.8, 52.9, 42.4, 40.0, 35.7, 35.6, 28.2, 26.6.

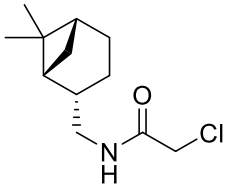
HRMS (+EI): Calculated:165.1154 ($C_{10}H_{15}NO$). Observed: 165.1155.



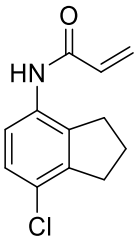
2-Chloro-*N*-(*exo*-norborn-2-yl)acetamide (TRH 1-177).
To a solution of *exo*-2-aminonorbornane (0.24 mL, 2 mmol) in dichloromethane (10 mL) was added chloroacetyl chloride (0.19 mL, 2.4 mmol) followed by triethylamine (0.33 mL, 2.4 mmol) at 0˚ C under N_2 atmosphere. After stirring for 20 minutes, the reaction mixture was allowed to warm to room temperature and was stirred overnight. The solution was washed with saturated sodium bicarbonate solution and brine, dried with magnesium sulfate, and the resulting crude was purified by silica gel chromatography (20 to 40% ethyl acetate in hexanes) to yield 345 mg of a white solid (91% yield).
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.48 (s, 1H), 3.93 (s, 2H), 3.67-3.63 (m, 1H), 2.24-2.22 (m, 1H), 2.16-2.15 (m, 1H), 1.74 (ddd, *J* = 1.9, 8.1, 13.0 Hz, 1H), 1.50-1.36 (m, 2H), 1.30-1.26 (m, 1H), 1.21-1.14 (m, 3H), 1.09-1.03 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 53.1, 42.6, 42.2, 40.0, 35.6, 35.5, 28.0, 26.3.
HRMS (+ESI): Calculated: 187.0764 ($C_9H_{14}NOCl$). Observed: 187.0765.



***N*-(((1*R*,2*S*,5*R*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)acrylamide (TRH 1-178).**
To a solution of (-)-*cis*-myrtanylamine (0.34 mL, 2 mmol) in dichloromethane (10 mL) was added acryloyl chloride (0.20 mL, 2.4 mmol) followed by triethylamine (0.33 mL, 2.4 mmol) at 0˚C under an atmosphere of nitrogen. After stirring for 20 minutes, the reaction mixture was warmed to room temperature and stirred for an additional 21 hours. The reaction mixture was then washed with saturated aqueous sodium bicarbonate solution, brine, dried over magnesium sulfate, and concentrated *in vacuo*. The resulting crude material was purified by silica gel chromatography (20 to 30% ethyl acetate in hexanes) to yield the title compound (369 mg, 89%) as a white solid.
^{1}H NMR (600 MHz, $CDCl_3$): δ 6.26 (dd, *J* = 1.5, 17.0 Hz, 1H), 6.11 (dd, *J* = 10.3, 17.0 Hz, 1H) 5.85 (s, 1H), 5.61 (dd, *J* = 1.5, 10.3 Hz, 1H), 3.39-3.29 (m, 2H), 2.38-2.34 (m, 1H), 2.26-2.21 (m, 1H), 1.98-1.90 (m, 4H), 1.88-1.83 (m, 1H), 1.53-1.47 (m, 1H), 1.19 (s, 3H), 1.04 (s, 3H), 0.89 (d, *J* = 9.6 Hz, 1H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 165.7, 131.2, 126.2, 45.3, 43.9, 41.5, 38.8, 33.3, 28.1, 26.1, 23.3, 19.9.
HRMS (-ESI): Calculated: 206.1550 ($C_{13}H_{20}NO$). Observed: 206.1551.



2-Chloro-*N*-(((1*R*,2*S*,5*R*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)acetamide (TRH 1-179).
To a solution of (-)-*cis*-myrtanylamine (0.34 mL, 2 mmol) in dichloromethane (10 mL) was added chloroacetyl chloride (0.19 mL, 2.4 mmol) followed by triethylamine (0.33 mL, 2.4 mmol) at 0˚ C under N_2 atmosphere. After stirring for 20 minutes, the reaction mixture was allowed to warm to room temperature and was stirred overnight. The solution was washed with saturated sodium bicarbonate solution and brine, dried with magnesium sulfate, and the resulting crude was purified by silica gel chromatography (0 to 20% ethyl acetate in hexanes) to yield 405 mg of an off-white solid (88% yield).
^{1}H NMR (600 MHz, $CDCl_3$): δ 6.61 (s, 1H), 4.05 (s, 2H), 3.33-3.30 (m, 2H), 2.40-2.36 (m, 1H), 2.27-2.21 (m, 1H), 1.99-1.83 (m, 5H), 1.53-1.46 (m, 1H), 1.20 (s, 3H), 1.05 (s, 3H), 0.90 (d, *J* = 9.7 Hz, 1H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 165.8, 45.5, 43.8, 42.9, 41.4, 41.2, 38.8, 33.3, 28.0, 26.0, 23.3, 19.8.
HRMS (-ESI): Calculated: 228.1161 ($C_{12}H_{19}NOCl$). Observed: 228.1162.



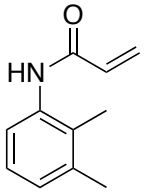
N-(7-chloro-2,3-dihydro-1H-inden-4-yl)acrylamide (YP 1-1)

A solution of *N*-(2,3-dihydro-1H-inden-4-yl)acrylamide (187 mg, 1.0 mmol) in PEG 400 (5.2 mL) was cooled to 0˚C and *N*-chlorosuccinimide (140 mg, 1.0 mmol) added. After 30 minutes, the mixture was warmed to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate, washed with brine twice, and dried over magnesium sulfate. The volatiles were removed *in vacuo* and the crude product purified by silica gel chromatography (30% ethyl acetate in hexanes). The obtained mixture of isomers were recrystallized to afford the title compound (47 mg, 22% yield) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.8 Hz, 1H), 7.15-7.11 (m, 2H), 6.42 (dd, *J* = 1.4, 16.8 Hz, 1H), 6.26 (dd, *J* = 10.2, 16.8 Hz, 1H), 5.77 (dd, *J* = 1.4, 10.2 Hz, 1H), 2.98 (t, *J* = 7.6 Hz, 2H), 2.87 (t, *J* = 7.5 Hz, 2H), 2.12 (quint, *J* = 7.5 Hz, 2 H).

^{13}C NMR (100MHz, $CDCl_3$): δ 163.4, 143.1, 136.1, 132.2, 131.0, 128.0, 127.2, 126.7, 120.9, 32.7, 31.1, 24.0.

HRMS (+ESI): Calculated: 220.0535 ($C_{12}H_{11}ClNO$). Observed: 220.0533.



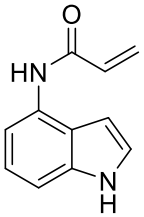
N-(2,3-dimethylphenyl)acrylamide (YP 1-18)

A solution of 2,3-dimethylaniline (121 mg, 1.0 mmol) in DCM (10 mL) was cooled to 0˚C and acryloyl chloride (109 mg, 1.2 mmol) and triethylamine (121 mg, 1.2 mmol) were added sequentially. The reaction mixture was maintained at this temperature for 30 minutes and then warmed to room temperature and stirred overnight. The reaction mixture was washed twice with brine and dried over magnesium sulfate. Volatiles were removed *in vacuo* and the crude material purified by silica gel chromatography (30% to 40% ethyl acetate in hexanes) to afford the product (154 mg, 88%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.9 Hz, 1H), 7.29 (s, 1H), 7.11-7.07 (m, 1H), 7.01 (d, *J* = 7.7, 1H) 6.40 (d, *J* = 17.1, 1H), 6.30 (dd, *J* = 7.3, 17.1 Hz, 1H), 5.74 (d, *J* = 10.1 Hz, 1H), 2.29 (s, 1H), 2.13 (s, 1H).

^{13}C NMR (100MHz, $CDCl_3$): δ 135.1, 131.2, 127.6, 127.3, 125.9, 122.3, 20.6, 13.9.

HRMS (+ESI): Calculated: 176.1070 ($C_{11}H_{14}NO$). Observed: 176.1068.



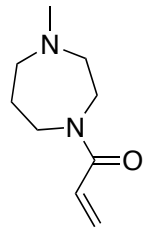
N-(1H-indol-4-yl)acrylamide (YP 1-19)

A solution of 4-aminoindole (132 mg, 1 mmol) in DCM/DMF (1:1 *v:v*, 10 mL) was cooled to 0˚C and acryloyl chloride (109 mg, 1.2 mmol) and triethylamine (121 mg, 1.2 mmol) added sequentially. The reaction mixture was stirred at this temperature for 26 minutes and then warmed to room temperature and stirred overnight. The reaction mixture was washed twice with brine and dried over magnesium sulfate. Volatiles were removed *in vacuo* and the crude product purified by basic alumina chromatography (60% to 75% ethyl acetate in hexanes) to afford the title compound (56mg, 30%) as a white-grey solid.

^{1}H NMR (600MHz, MeOD): δ 7.51 (d, *J* = 7.6 Hz, 1H), 7.24-7.22 (m, 2H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.64 (dd, *J* = 10.1, 16.7 Hz, 2H), 6.38 (dd, *J* = 1.7, 16.9 Hz, 1H), 5.78 (dd, *J* = 1.7, 10.3 Hz, 1H), 4.6 (s, 1H).

^{13}C NMR (150MHz, MeOD): δ 165.0, 137.2, 131.1, 129.2, 126.0, 123.8, 121.5, 120.9, 112.2, 108.4, 98.5.

HRMS (+ESI): Calculated: 187.0866 ($C_{11}H_{11}N_2O$). Observed: 187.0865.



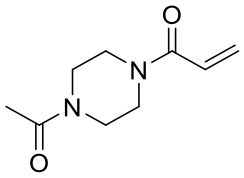
1-(4-methyl-1,4-diazepan-1-yl)prop-2-en-1-one (YP 1-23), mixture of rotamers

A solution of 1-methylhomopiperazine (114 mg, 1.0 mmol) in DCM (10 mL) was cooled to 0˚C and acryloyl chloride (109 mg, 1.2 mmol) and triethylamine (121 mg, 1.2 mmol) added sequentially. The solution was maintained at this temperature for 30 minutes and then warmed to room temperature and stirred overnight. The reaction mixture was washed twice with brine and dried over magnesium sulfate. After removal of the volatiles in *vacuo*, the crude product was purified via silica gel chromatography (1% to 10% methanol in DCM) affording the title compound (58 mg, 51%) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 6.61-6.53 (m, 1H), 6.35-6.29 (m, 1H), 5.70-5.66 (m, 1H), 3.74-3.72 (m, 1 H), 3.69 (t, *J* = 6.4 Hz, 1H), 3.65-3.61 (m, 2H), 2.66-2.63 (m, 2H), 2.59-2.54 (m, 2H), 2.37 (s, 3H), 1.94 (quint, *J* = 6.2 Hz, 2H).

^{13}C NMR (100MHz, $CDCl_3$): δ 166.4, 166.3, 128.0, 127.9, 127.8, 127.6, 59.1, 58.0, 57.1, 56.8, 47.4, 47.1, 46.7, 46.6, 45.3, 44.8, 28.1, 26.9.

HRMS (+ESI): Calculated: 169.1335 ($C_9H_{17}N_2O$). Observed: 169.1333.



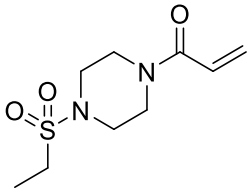
1-(4-acetylpiperazin-1-yl)prop-2-en-1-one (YP 1-24)

A solution of 1-acetylpiperazine (128 mg, 1.0 mmol) in DCM (10 mL) was cooled to 0˚C and acryloyl chloride (109 mg, 1.2 mmol) and triethylamine (121 mg, 1.2 mmol) added sequentially. The solution was stirred at this temperature for 23 minutes and then warmed to room temperature and stirred an additional two hours. The reaction mixture was washed twice with brine, dried over magnesium sulfate, and the volatiles removed *in vacuo*. The crude material was purified via silica gel chromatography (0% to 10% methanol in DCM) to afford the title compound (40 mg, 18%) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$): δ 6.57 (dd, *J* = 10.5, 16.8 Hz, 1H), 6.33 (dd, *J* = 1.8, 16.8 Hz, 1H), 5.75 (dd, *J* = 1.9, 10.5 Hz, 1H), 3.72 (s, 1H), 3.66-3.64 (m, 3H), 3.57 (s, 1H), 3.51-3.49 (m, 2H), 2.13 (s, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ 169.0, 165.6, 128.7, 127.0, 41.9, 41.4, 21.4.

HRMS (+ESI): Calculated: 183.1128 ($C_9H_{15}N_2O_2$). Observed: 183.1126.



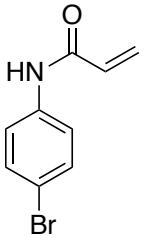
1-(4-(Ethylsulfonyl)piperazin-1-yl)prop-2-en-1-one (YP 1-25)

A solution of 1-(ethanesulfonyl)piperazine (178 mg, 1.0 mmol) in DCM (10 mL) was cooled to 0 ˚C and acryloyl chloride (109 mg, 1.2 mmol) and triethylamine (121 mg, 1.2 mmol) added sequentially. The solution was stirred at this temperature for 27 minutes and then warmed to room temperature and stirred for an additional two hours. The solution was washed twice with brine and dried over magnesium sulfate. The crude material was purified by silica gel chromatography (1% to 10% methanol in DCM) to afford the title compound (163 mg, 70%) as a white-yellow solid.

^{1}H NMR (400MHz, $CDCl_3$): δ 6.57 (dd, *J* = 10.5, 16.8 Hz, 1H), 6.32 (dd, *J* = 1.9, 16.8 Hz, 1H), 5.76 (dd, *J* = 1.8, 10.5 Hz, 1H), 3.77 (s, 2H), 3.67 (s, 2H), 3.32 (t, *J* = 5.2 Hz, 4H), 2.98 (q, *J* = 7.5 Hz, 2H), 1.37 (t, *J* = 7.4, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ 165.5, 128.8, 127.0, 77.4, 45.9, 45.6, 44.2, 41.9, 7.8.

HRMS (+ESI): Calculated: 233.0954 ($C_9H_{17}N_2O_3S_1$). Observed: 233.0953.



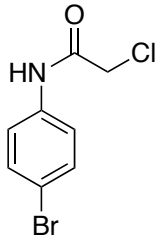
***N*-(4-bromophenyl)acrylamide (YP 1-36)**

Following **General Procedure A** starting from 4-bromoaniline (688 mg, 4.0 mmol), product was obtained after silica gel chromatography (30% to 60% ethyl acetate in hexanes) in 28% yield as a white solid (250 mg).

^{1}H NMR (400MHz, CD_3OD): δ 7.90 (s, 1H), 7.60-7.56 (m, 2H), 7.47-7.44 (m, 2H), 6.45-6.33 (m, 2H), 5.78 (dd, *J* = 2.8, 9.1 Hz, 1H).

^{13}C NMR (100MHz, CD_3OD): δ 164.7, 137.7, 131.4, 130.9, 126.7, 121.5, 116.3, 101.1, 78.1.

HRMS (+ESI): Calculated: 223.9716 (C_9H_7NOBr). Observed: 223.9719.



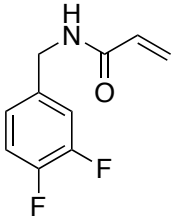
***N*-(4-bromophenyl)-2-chloroacetamide (YP 1-37)**

Following **General Procedure B** starting from 4-bromoaniline (688 mg, 4.0 mmol), product was obtained after silica gel chromatography (30% to 60% ethyl acetate in hexanes) in 49% yield as a white solid (491 mg).

^{1}H NMR (400MHz, CD_3OD): δ 7.9 (s, 1H), 7.57-7.53 (m, 2H), 7.50-7.47 (m, 2H), 4.17 (s, 2H).

^{13}C NMR (100MHz, CD_3OD): δ 166.0, 137.2, 131.5, 121.6, 116.7, 99.3, 78.1, 42.6.

HRMS (+ESI): Calculated: 245.9327 ($C_8H_6NOBrCl$). Observed: 245.9329.



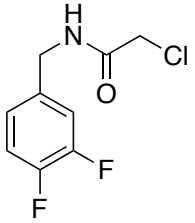
***N*-(3,4-difluorobenzyl)acrylamide (YP 1-38)**

Following **General Procedure A** starting from 3,4-difluorobenzylamine (286 mg, 2.0 mmol), product was obtained after silica gel chromatography (40% to 80% ethyl acetate in hexanes) in 61% yield as a white solid (239 mg).

^{1}H NMR (400MHz, $CDCl_3$): δ 7.56 (t, *J* = 6.2, 1H), 7.07-7.00 (m, 2H), 6.95-6.91 (m, 1H), 6.21-6.20 (m, 2H), 5.62-5.59 (m, 1H), 4.35 (d, *J* = 6.1, 2H).

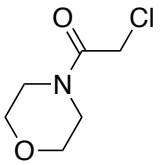
^{13}C NMR (100MHz, $CDCl_3$): δ 166.1, 151.4 (d), 150.7 (d), 148.9 (d), 148.2 (d), 135.5-135.4 (m), 130.5, 126.8, 123.5-123.4 (m), 117.2 (d), 116.3 (d), 42.4.

HRMS (+ESI): Calculated: 196.0579 ($C_{10}H_8NOF_2$). Observed: 196.0582.

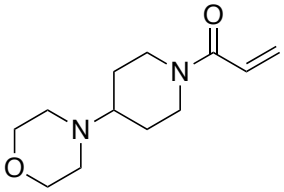


2-chloro-*N*-(3,4-difluorobenzyl)acetamide (YP 1-39)

Following **General Procedure B** starting from 3,4-difluorobenzylamine (286 mg, 2.0 mmol), product was obtained after silica gel chromatography (40% to 50% ethyl acetate in hexanes) in 82% yield as a white solid (359 mg).
^{1}H NMR (400MHz, $CDCl_3$): δ 7.23 (s, 1H), 7.15-7.08 (m, 2H), 7.03-7.6.99 (m, 1H), 4.42 (d, *J* = 6.1 Hz, 2H), 4.08 (s, 2H).
^{13}C NMR (100MHz, $CDCl_3$): δ 166.3, 151.5 (d), 151.0 (d), 149.1 (d), 148.5 (d), 134.7-134.6 (m), 123.7-123.6 (m), 117.5 (d), 116.6 (d), 42.6 (d).
HRMS (+ESI): Calculated: 218.0190 ($C_9H_7NOClF_2$). Observed: 218.0192



2-chloro-1-morpholinoethan-1-one (YP 1-40)
Following **General Procedure B** starting from morpholine (174 mg, 2.0 mmol), product was obtained after silica gel chromatography (85% ethyl acetate in hexanes) in 61% yield as a white solid (200 mg).
^{1}H NMR (400MHz, $CDCl_3$): δ 4.01 (s, 2H), 3.65-3.59 (m, 4H), 3.55-3.52 (m, 2H), 3.45 (t, *J* = 4.8 Hz, 2H).
^{13}C NMR (100MHz, $CDCl_3$): δ 165.1, 66.5 (d), 46.6, 42.4, 40.7.
HRMS (+ESI): Calculated: 186.0292 ($C_6H_{10}O_2NClNa$). Observed: 186.0292.



1-(4-morpholinopiperidin-1-yl)prop-2-en-1-one (YP 1-42)
Following **General Procedure A** using 4-morpholinopiperidine (336 mg, 2.0 mmol), the product was obtained after silica gel chromatography (1% methanol and 80% ethyl acetate in hexanes) as a colorless oil (259 mg, 58%).
^{1}H NMR (400MHz, $CDCl_3$): δ 6.42 (dd, *J* = 10.6, 16.8 Hz, 1H), 6.06 (dd, *J* = 2.0, 16.8 Hz, 1H), 5.49 (dd, *J* = 2.0, 10.6 Hz, 1H), 4.45 (d, *J* = 12.8 Hz, 1H), 3.86 (d, *J* = 12.8 Hz, 1H), 3.52 (t, *J* = 4.7 Hz, 4H), 2.90 (t, *J* = 12.8 Hz, 1H), 2.55-2.48 (m, 1H), 2.37-2.35 (m, 4H), 2.26 (tt, *J* = 3.7, 11.0 Hz, 1H), 1.72 (d, *J* = 12.8 Hz, 2H), 1.30-1.20 (m, 2H).
^{13}C NMR (100MHz, $CDCl_3$): δ 165.0, 127.7, 127.3, 67.1, 61.6, 49.6, 44.9, 41.1, 28.9, 27.8.
HRMS (+ESI): Calculated: 225.1598 ($C_{12}H_{21}N_2O_2$). Observed: 225.1595.

Synthesis and characterization of TRH 1-23 Analogs and CCW 28-3 Degrader
General synthetic methods
Chemicals and reagents were purchased from major commercial suppliers and used without further purification. Reactions were performed under a nitrogen atmosphere unless otherwise noted. Silica gel flash column chromatography was performed using EMD or Sigma Aldrich silica gel 60 (230-400 mesh). Proton and carbon nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) data was acquired on a Bruker AVB 400, AVQ 400, or AV 600 spectrometer at the University of California, Berkeley. High resolution mass spectrum were obtained from the QB3 mass spectrometry facility at the University of California, Berkeley using positive or negative electrospray ionization (+ESI or -ESI). Yields are reported as a single run.

General method for chloroacetamide synthesis
The amine (1 eq.) was dissolved in anhydrous DCM (2-10 mL) in a 20 mL scintillation vial. To the solution was added 2-chloroacetyl chloride (Sigma, 1.2 eq.) followed by triethylamine (Sigma, 1.2 eq.). The solution was stirred overnight under nitrogen. The reaction was monitored by TLC with ninhydrin staining. Upon reaction completion, the solvent was removed with rotary evaporation and the crude applied directly to a silica gel column for flash chromatography which gave the corresponding chloroacetamide.

2-chloro-N-(4-(4-(trifluoromethyl)phenoxy)phenyl)acetamide (CCW 1)

To a solution of 4-(4-(trifluoromethyl)phenoxy)aniline (AK Scientific, 63 mg, 0.25 mmol) in DCM 2-chloroacetyl chloride (Sigma, 34 mg, 0.30 mmol) and triethylamine (Sigma, 30.4 mg, 0.30 mmol) were added and the reaction stirred overnight. Upon reaction completion the crude was purified by silica gel chromatography (10-40% EtOAc/hexanes) to yield 65 mg (78%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.63 – 7.51 (m, 4H), 7.12 – 6.99 (m, 4H), 4.22 (s, 2H).
HRMS: (-ESI): calcd. for: $C_{15}H_{10}O_2NF_3Cl$ = 328.0358, found: 327.0356

2-chloro-N-(4-(3-fluorophenoxy)phenyl)acetamide (CCW 2)
To a solution of 4-(3-fluorophenoxy)aniline (AK Scientific, 63 mg, 0.31 mmol) in DCM 2-chloroacetyl chloride (Sigma, 42 mg, 0.37 mmol) and triethylamine (Sigma, 38 mg, 0.37 mmol) were added and the reaction stirred overnight. Upon reaction completion the crude was purified by silica gel chromatography (10-40% EtOAc/hexanes) to yield 53 mg (61%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.55 (dq, *J* = 10.0, 3.5, 2.4 Hz, 2H), 7.33 – 7.23 (m, 1H), 7.05 (dq, *J* = 10.1, 3.5, 2.6 Hz, 2H), 6.85 – 6.74 (m, 2H), 6.69 (dq, *J* = 10.2, 2.3 Hz, 1H), 4.21 (s, 2H).
^{13}C NMR (151 MHz, $CDCl_3$): δ 164.29, 163.75, 162.66, 158.85, 158.78, 153.31, 132.67, 130.51, 130.45, 121.95, 120.13, 113.71, 113.69, 109.98, 109.84, 105.92, 105.75, 77.19, 76.97, 76.76, 42.79.
HRMS: (-ESI): calcd. for: $C_{14}H_{10}O_2NFCl$ = 278.0390, found: 278.0389

2-chloro-N-(3-chloro-4-(4-chlorophenoxy)phenyl)acetamide (CCW 3)
To a solution of 3-chloro-4-(4-chlorophenoxy)aniline (Sigma, 64 mg, 0.25 mmol) in DCM 2-chloroacetyl chloride (Sigma, 34 mg, 0.30 mmol) and triethylamine (Sigma, 30.4 mg, 0.30 mmol) were added and the reaction stirred overnight. Upon reaction completion the crude was purified by silica gel chromatography (10-40% EtOAc/hexanes) to yield 69 mg (83%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.83 (d, *J* = 2.6 Hz, 1H), 7.44 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.36 – 7.28 (m, 3H), 7.05 (d, *J* = 8.8 Hz, 1H), 6.95 – 6.89 (m, 2H), 4.25 (s, 2H).
^{13}C NMR (151 MHz, $CDCl_3$): δ 163.85, 155.67, 148.97, 133.57, 129.72, 128.30, 126.60, 122.59, 121.48, 119.87, 118.65, 77.20, 76.98, 76.77, 42.73.
HRMS: (-ESI): calcd. for: $C_{14}H_9O_2NCl$ = 327.9704, found: 327.9702

2-chloro-N-(4-(4-methoxyphenoxy)phenyl)acetamide (CCW 5)
To a solution of 4-(4-methoxyphenoxy)aniline HCl (Astatech, 63 mg, 0.25 mmol) in DCM 2-chloroacetyl chloride (Sigma, 34 mg, 0.30 mmol) and triethylamine (Sigma, 60.8 mg, 0.60 mmol) were added and the reaction stirred overnight. Upon reaction completion the crude was purified by silica gel chromatography (10-40% EtOAc/hexanes) to yield 69 mg (95%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.49 – 7.42 (m, 2H), 7.00 – 6.84 (m, 6H), 4.19 (s, 2H), 3.80 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ 163.67, 155.92, 155.72, 150.11, 131.22, 121.95, 120.57, 118.14, 114.87, 77.18, 76.97, 76.76, 55.63, 42.79.
HRMS: (-ESI): calcd. for: $C_{15}H_{13}O_3NCl$ = 290.0589, found: 290.0587

2-chloro-N-(4-(4-nitrophenoxy)phenyl)acetamide (CCW 6)
To a solution of 4-(4-nitrophenoxy)aniline (Sigma, 50 mg, 0.22 mmol) in DCM 2-chloroacetyl chloride (Sigma, 29 mg, 0.26 mmol) and triethylamine (Sigma, 26 mg, 0.26 mmol) were added and the reaction stirred overnight. Upon reaction completion the crude was purified by silica gel chromatography (10-40% EtOAc/hexanes) to yield 62.5 mg (93%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H), 8.25 – 8.16 (m, 2H), 7.67 – 7.59 (m, 2H), 7.14 – 7.07 (m, 2H), 7.05 – 6.96 (m, 2H), 4.22 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 163.93, 163.27, 151.63, 142.77, 133.98, 126.01, 122.18, 121.26, 117.01, 77.36, 77.04, 76.73, 42.85.
HRMS: (+ESI): calcd. for: $C_{14}H_{10}O_4N_2Cl$ = 305.0335, found: 305.0332

2-chloro-N-(4-(naphthalen-2-yloxy)phenyl)acetamide (CCW 7)
To a solution of 2-(4-Aminophenoxy)naphthalene (TCI, 118 mg, 0.50 mmol) in DCM 2-chloroacetyl chloride (Sigma, 67.8 mg, 0.60 mmol) and triethylamine (Sigma, 60.8 mg, 0.60 mmol) were added and the reaction

stirred overnight. Upon reaction completion the crude was purified by silica gel chromatography (10-40% EtOAc/hexanes) to yield 111 mg (71%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.83 (dt, *J* = 7.8, 3.3 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.49 – 7.37 (m, 2H), 7.31 – 7.22 (m, 2H), 7.12 – 7.03 (m, 2H), 4.21 (s, 2H), .
^{13}C NMR (101 MHz, $CDCl_3$): δ 163.86, 155.13, 154.31, 134.30, 132.22, 130.19, 129.99, 127.77, 127.14, 126.63, 124.80, 122.10, 119.84, 119.76, 113.84, 77.39, 77.07, 76.75, 42.89.
HRMS: (+ESI): calcd. for: $C_{18}H_{15}O_2NCl$ = 312.0786, found: 312.0785

2-chloro-N-(4-(3,5-dimethylphenoxy)phenyl)acetamide (CCW 8)
To a solution of 4-(3,5-dimethylphenoxy)aniline (Enamine, 107 mg, 0.50 mmol) in DCM 2-chloroacetyl chloride (Sigma, 67.8 mg, 0.60 mmol) and triethylamine (Sigma, 60.8 mg, 0.60 mmol) were added and the reaction stirred overnight. Upon reaction completion the crude was purified by silica gel chromatography (10-40% EtOAc/hexanes) to yield 60 mg (41%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.53 – 7.46 (m, 2H), 7.03 – 6.96 (m, 2H), 6.74 (s, 1H), 6.61 (s, 2H), 4.20 (s, 2H), 2.28 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 163.80, 157.21, 154.61, 139.67, 131.79, 125.09, 121.98, 119.55, 116.36, 77.37, 77.06, 76.74, 42.87, 21.33.
HRMS: (+ESI): calcd. for: $C_{18\backslash 6}H_{17}O_2NCl$ = 290.0942, found: 290.0941

N-benzyl-4-(4-methoxyphenoxy)aniline (CCW 14)
4-(4-methoxyphenoxy)aniline (Astatech, 108 mg, 0.50 mmol) was dissolved in anhydrous DCM (5 mL) in a 20 mL scintillation vial. Benzaldehyde (Alfa Aesar, 53 mg, 0.50 mmol) was added and the solution stirred for 2 h under nitrogen. Sodium triacetoxyborohydride (Sigma, 159 mg, 0.75 mmol) was added in small aliquots and the reaction stirred overnight. TLC (20% EtOAc/hexanes) showed full conversion of starting materials. The solution was washed with saturated sodium bicarbonate and, followed by brine. The aqueous fractions were combined, extracted with 3x5 mL EtOAc and all organic fractions combined, concentrated and purified on a silica gel column (10-40% EtOAc/hexanes) to give 89.7 mg (58.8%)
1H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.33 (m, 4H), 7.32 – 7.27 (m, 1H), 6.94 – 6.81 (m, 6H), 6.64 – 6.59 (m, 2H), 4.31 (s, 2H), 3.79 (s, 3H).
HRMS: (+ESI): calcd. for: $C_{20}H_{20}O_2N_1$ = 306.1489, found: 307.1481.

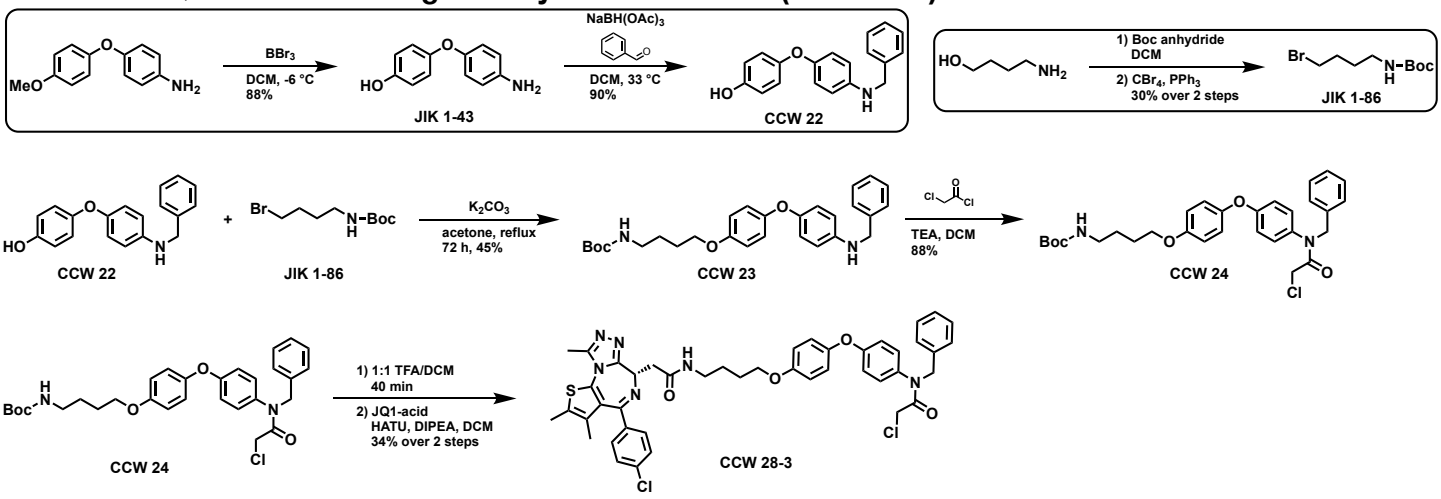
N-benzyl-2-chloro-N-(4-(4-methoxyphenoxy)phenyl)acetamide (CCW 16)
To a solution of N-benzyl-4-(4-methoxyphenoxy)aniline **(CCW 14)** (25 mg, 0.081 mmol) in DCM 2-chloroacetyl chloride (Sigma, 11 mg, 0.097 mmol) and triethylamine (Sigma, 9.8 mg, 0.097 mmol) were added and the reaction stirred overnight. Upon reaction completion the crude was purified by silica gel chromatography (10-40% EtOAc/hexanes) to yield 26 mg (84%)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 3H), 7.20 (dd, *J* = 7.3, 2.3 Hz, 2H), 7.01 – 6.96 (m, 2H), 6.93 – 6.82 (m, 6H), 4.86 (s, 2H), 3.87 (s, 2H), 3.81 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 166.45, 158.95, 156.54, 148.89, 136.63, 134.71, 129.54, 129.03, 128.51, 127.71, 121.47, 117.82, 115.07, 77.36, 77.25, 77.05, 76.73, 55.69, 53.85, 42.09.
HRMS: (+ESI): calcd. for: $C_{22}H_{21}O_3NCl$ = 382.1204, found: 307.1199.

2-chloro-N-(4-(4-(hydroxymethyl)phenoxy)phenyl)acetamide (JIK 1-36)
To a solution of (4-(4-aminophenoxy)phenyl)methanol (Sigma, 54.8 mg, 0.25 mmol) in DCM 2-choloracetyl chloride (Sigma, 34 mg, 0.30 mmol) and triethylamine (Sigma, 30.4 mg, 0.30 mmol) were added and the reaction stirred overnight. Upon reaction completion the crude was purified by silica gel chromatography (10-40% EtOAc/hexanes) to yield 55 mg (74%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.55 – 7.48 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.05 – 6.96 (m, 4H), 4.67 (s, 2H), 4.20 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.70, 156.77, 154.32, 135.82, 132.01, 128.68, 121.93, 119.46, 118.71, 64.85, 42.79.
HRMS: (-ESI): calc'd for $C_{15}H_{10}ClF_3NO_2$ = 328.0352; found 328.0358.

2-chloro-N-(4-(3-(trifluoromethyl)phenoxy)phenyl)acetamide (JIK 1-37)

To a solution of (4-(3-trifluoromethyl)phenyl)aniline (Sigma, 64.5 mg, 0.25 mmol) in DCM 2-choloracetyl chloride (Sigma, 34 mg, 0.30 mmol) and triethylamine (Sigma, 30.4 mg, 0.30 mmol) were added and the reaction stirred overnight. Upon reaction completion the crude was purified by silica gel chromatography (10-40% EtOAc/hexanes) to yield 80 mg (95%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.22 (s, 1H), 7.15 (d, *J* = 8.1 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 4.21 (s, 2H).^{13}C NMR (151 MHz, $CDCl_3$) δ 163.76, 157.81, 153.12, 132.85, 130.30, 124.51, 122.71, 122.04, 121.31, 120.10, 119.69, 115.02, 42.78.
HRMS: (-ESI): calc'd for $C_{15}H_{13}ClNO_3$ = 290.0585; found 290.0589.

CCW-16 + JQ1 bifunctional degrader synthesis scheme (CCW 28-3)



***tert*-butyl (4-bromobutyl)carbamate (JIK 1-86)**
4-amino-1-butanol (TCI; 5.0 g, 56.0 mmol) was dissolved in dry DCM (22mL). To the solution di-tert-butyl dicarbonate (Chem-Impex Int'l Inc.; 17.3 g, 79.4 mmol) was added. The reaction was stirred at room temperature for 3 hours and was monitored by TLC (developed in 100% EtOAc, visualized by ninhydrin). Upon completion, the solvent was removed by rotary evaporation. The crude was partially purified by silica gel chromatography (55 to 100% EtOAc in hexanes) to remove baseline impurity; eluent from column was carried forward to next reaction. DCM (22 mL, dry) was added to column eluent and the solution was cooled to 0°C. To the solution carbon tetrabromide (Aldrich; 23.9 g, 72.0 mmol) was added and dissolved, followed by triphenylphosphine (Sigma Aldrich; 22.3 g, 84.9 mmol). Reaction was stirred for 1hr, then allowed to warm to room temperature and run overnight. After 24 hours, solvent was removed by rotary evaporation. The crude was purified by silica gel chromatography (2-15% EtOAc in hexanes) to afford 4.1 g of product as a pale yellow oil (29.6% yield over two reactions).
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.55 (s, 1H), 3.42 (t, *J* = 6.7 Hz, 2H), 3.15 (q, *J* = 6.8 Hz, 2H), 1.93 – 1.83 (m, 2H), 1.63 (m, 1H), 1.43 (s, 10H).

4-(4-aminophenoxy)phenol (JIK 1-43)
4-(4-methoxyphenoxy)aniline (AstaTech; 2.5g, 11.6 mmol) was dissolved in DCM (40 mL) at -6°C. Boron tribromide (Acros; 34.8 mL, 1M in DCM, 34.8 mmol) was added dropwise over the course of 3 hours, monitored by TLC (40% EtOAc/Hex, $KMnO_4$). Upon completion, solution was quenched with 1 volume of sodium bicarbonate. Biphasic mixture was refrigerated overnight and product crystallized out and was removed by filtration. The aqueous layer was neutralized with NaOH, and back extracted with 3x25mL EtOAc. The combined organic layers were dried with $MgSO_4$ and condensed. Yielded 2.33 g (88%) product as a tan solid which required no further purification.
^{1}H NMR (400 MHz, Methanol-*d*$_4$): δ 5.22 – 5.09 (m, 8H), 1.73 (p, *J* = 1.6 Hz, 3H).
HRMS: (+ESI): calc'd for $C_{12}H_{12}NO_2$ = 202.0863; found 202.0860.

4-(4-(benzylamino)phenoxy)phenol (CCW 22)
4-(4-aminophenoxy)phenol **(JIK 1-43)** (604 mg, 3.0 mmol) was dissolved in anhydrous DCM (50mL) at 33 C to aid solubility, benzaldehyde (Alfa Aesar, 240 mg, 3.0 mmol) was added and the reaction stirred for two hours

under nitrogen. Sodium triacetoxyborohydride (Sigma, 952 mg, 4.5 mmol) was added and the reaction stirred overnight. The mixture was concentrated and applied directly to a silica column for flash chromatography, yielding 787 mg (90%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.24 (m, 5H), 6.89 – 6.80 (m, 4H), 6.78 – 6.71 (m, 2H), 6.65 – 6.58 (m, 2H), 4.31 (s, 2H).

tert-butyl (4-(4-(4-(benzylamino)phenoxy)phenoxy)butyl)carbamate (CCW 23)
4-(4-(benzylamino)phenoxy)phenol **(CCW 22)** (450 mg, 1.55 mmol) and *tert*-butyl (4-bromobutyl)carbamate **(JIK 1-86)** (585 mg, 2.32 mmol) were dissolved in acetone (20 mL). Potassium carbonate (642 mg, 4.65 mmol) was added and the solution brought to reflux and stirred for 72 h. The mixture was concentrated and applied directly to a silica column for flash chromatography (10-30 % EtOAc/hexanes), yielding 325 mg (45.3%)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (m, 5H), 6.91 – 6.77 (m, 6H), 6.60 (d, J = 8.8 Hz, 2H), 4.62 (s, 1H), 4.30 (s, 2H), 3.93 (t, J = 6.2 Hz, 2H), 3.19 (q, J = 6.4 Hz, 2H), 1.83 – 1.74 (m, 2H), 1.66 (p, J = 7.1 Hz, 2H), 1.44 (s, 9H).
HRMS: (+ESI): calc'd for $C_{28}H_{35}O_4N_2$ = 463.2591; found 462.2583.

tert-butyl (4-(4-(4-(N-benzyl-2-chloroacetamido)phenoxy)phenoxy)butyl)carbamate (CCW 24)
To a solution of **CCW 23** (200 mg, 0.43 mmol) in DCM (10 mL). 2-choloracetyl chloride (Sigma, 59 mg, 0.52 mmol) and triethylamine (Sigma, 53 mg, 0.52 mmol) were added and the reaction stirred overnight. Upon reaction completion the crude was purified by silica gel chromatography (20-60% EtOAc/hexanes) to yield 232 mg (87.6%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 4.8 Hz, 2H), 7.20 (dd, *J* = 7.2, 2.2 Hz, 3H), 6.97 (d, *J* = 9.0 Hz, 2H), 6.93 – 6.83 (m, 6H), 4.86 (s, 2H), 4.61 (s, 1H), 3.96 (t, *J* = 6.2 Hz, 2H), 3.87 (s, 2H), 3.20 (q, *J* = 6.4 Hz, 2H), 1.87 – 1.77 (m, 2H), 1.68 (p, *J* = 7.1 Hz, 2H), 1.45 (s, 9H).

(S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (JQ1-acid)
tert-butyl (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate (**JQ1**) was prepared based on previous procedures [1]. JQ1 (eNovation Chemicals, 204 mg, 0.446 mmol) was dissolved in formic acid (3mL) and stirred at 45 °C overnight. The mixture was diluted with DCM and solvent removed *in vacuo.* The resulting yellow oil was redissolved in 3 mL DCL and evaporated to dryness repeated until the process gave a fine yellow-brown solid: 178 mg (99.8%). No further purification was necessary.
1H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.40 (m, 2H), 7.34 (d, J = 8.7 Hz, 2H), 4.59 (t, J = 6.8 Hz, 1H), 3.75 – 3.55 (m, 2H), 2.68 (s, 3H), 2.41 (s, 3H), 1.74 – 1.65 (m, 3H).
HRMS: (-ESI): calcd. for $C_{19}H_{16}O_2N_4ClS$ = 399.0688; found 399.0683.

(S)-N-benzyl-2-chloro-N-(4-(4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butoxy)phenoxy)phenyl)acetamide (CCW-28-3)
CCW 24 (175 mg, 0.325 mmol) was deprotected in 1:1 DCM/TFA (5mL) by adding trifluoroacetic acid (Sigma-Aldrich) slowly over 20 min followed by stirring for an additional 20 min. TLC showed full conversion to amine and the solvent was removed *in vacuo,* and chases three times with 3mL DCM to remove excess TFA. The deprotected crude was used without further purification for amide coupling.
The resulting TFA salt was dissolved in 8 mL DCM, **JQ1-acid** (180 mg, 0.390 mmol), 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) (Small Molecules Inc., 201.5 mg, 0.530 mmol), and N,N-Diisopropylethylamine (DIPEA) (Sigma-Aldrich, 168 mg, 1.30 mmol). Stirred overnight and monitored by TLC (5% MeOH in DCM, 100% EtOAc). Crude concentrated and applied direct to a silica column for flash chromatography (1-5% MeOH/DCM). The eluted fractions were insufficiently pure and those containing product were combined, concentrated and purified again by flash silica chromatography (100-0% EtOAc/DCM followed by 0-5% MeOH/DCM) to afford 91.4 mg (34.2%).
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 (dd, *J* = 50.3, 8.3 Hz, 4H), 7.26 (s, 2H), 7.22 – 7.18 (m, 2H), 6.99 – 6.95 (m, 2H), 6.92 – 6.83 (m, 6H), 6.59 (d, *J* = 6.1 Hz, 1H), 4.86 (s, 2H), 4.62 (dd, *J* = 7.9, 6.1 Hz, 1H), 3.96 (t, *J* = 6.2 Hz, 2H), 3.87 (s, 2H), 3.57 (dd, *J* = 14.1, 7.9 Hz, 1H), 3.42 (dq, *J* = 13.3, 6.7 Hz, 1H), 3.32 (ddd, *J* = 13.2, 11.4, 6.2 Hz, 2H), 2.67 (s, 3H), 2.40 (s, 3H), 1.82 (td, *J* = 13.8, 13.2, 6.9 Hz, 2H), 1.74 (p, *J* = 6.8 Hz, 2H), 1.67 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.46, 166.38, 163.87, 158.90, 155.84, 155.63, 149.84, 148.82, 136.79, 136.58, 136.56, 134.65, 132.10, 130.87, 130.82, 130.42, 129.76, 129.46, 128.97, 128.69, 128.44, 127.63, 121.39, 117.78, 115.64, 67.84, 54.53, 53.78, 42.01, 39.60, 39.20, 29.65, 26.59, 26.26, 14.32, 13.04, 11.78.
HRMS: (+ESI): calcd. for $C_{44}H_{43}Cl_2N_6O_4S$ = 821.2438; found 821.2426.

Supporting References

(1) Zengerle, M.; Chan, K.-H.; Ciulli, A. Selective Small Molecule Induced Degradation of the BET Bromodomain Protein BRD4. *ACS Chem. Biol.* **2015**, *10* (8), 1770–1777.

Supporting Table Legend

Table S1. Structures of covalent ligands screened against RNF4

Table S2. isoTOP-ABPP analysis of CCW 28-3 in 231MFP breast cancer cells *in situ*. 231MFP cells were treated with DMSO vehicle or CCW 28-3 (10 μM) *in situ* for 1 h prior to labeling of proteomes *in vitro* with IA-alkyne (100 μM) for 1h. Isotopically light (for DMSO-treated) or heavy (for compound-treated) TEV protease-cleavable biotin-azide tag were appended by CuAAC for isoTOP-ABPP analysis. Only probe-modified peptides that were present in two out of three biological replicates were interpreted. For those ratios >3, we only interpreted those peptides that were present in all biological replicates where all replicate ratios were >3. For those ratios >4, we only interpreted those peptides that were present in all biological replicates where all replicate ratios were >4. MS1 peak shape qualities were manually curated to confirm good peak quality for all replicates. Data in table shows probe-modified peptide identified, the site of modification, the light to heavy probe-modified peptide ratio, and the protein identification. Data is from 3 biological replicates.

Supporting Figures

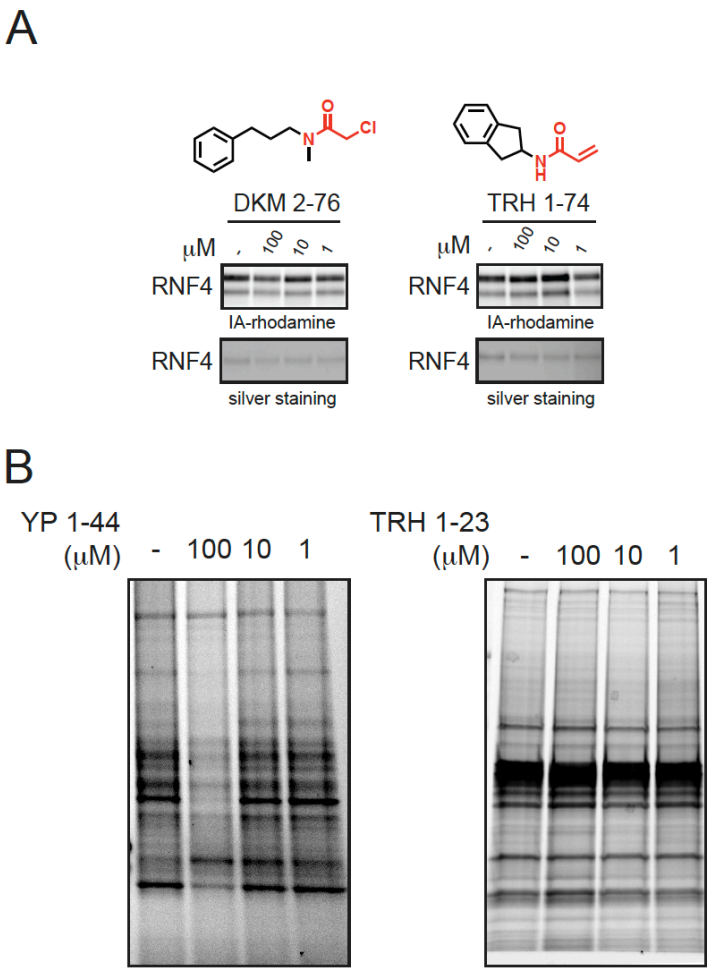


Figure S1. Non-reproducible hits against RNF4 and general assessment of proteome-wide selectivity of RNF4 hits by gel-based ABPP. (A) Gel-based ABPP analysis of DKM 2-76 and TRH 1-74 against IA-rhodamine labeling of RNF4. Covalent ligands were pre-incubated with pure RNF4 protein for 30 min prior to IA-rhodamine labeling (250 nM) for 1 h. Proteins were subjected to SDS/PAGE and visualized by in-gel fluorescence. **(B)** Gel-based ABPP screen of RNF4 hits YP 1-44 and TRH 1-23 against IA-rhodamine labeling in 231MFP breast cancer cell proteomes. YP 1-44 and TRH 1-23 were pre-incubated with proteome for 30 min prior to IA-rhodamine labeling (250 nM) for 1 h. Proteins were subjected to SDS/PAGE and visualized by in-gel fluorescence.

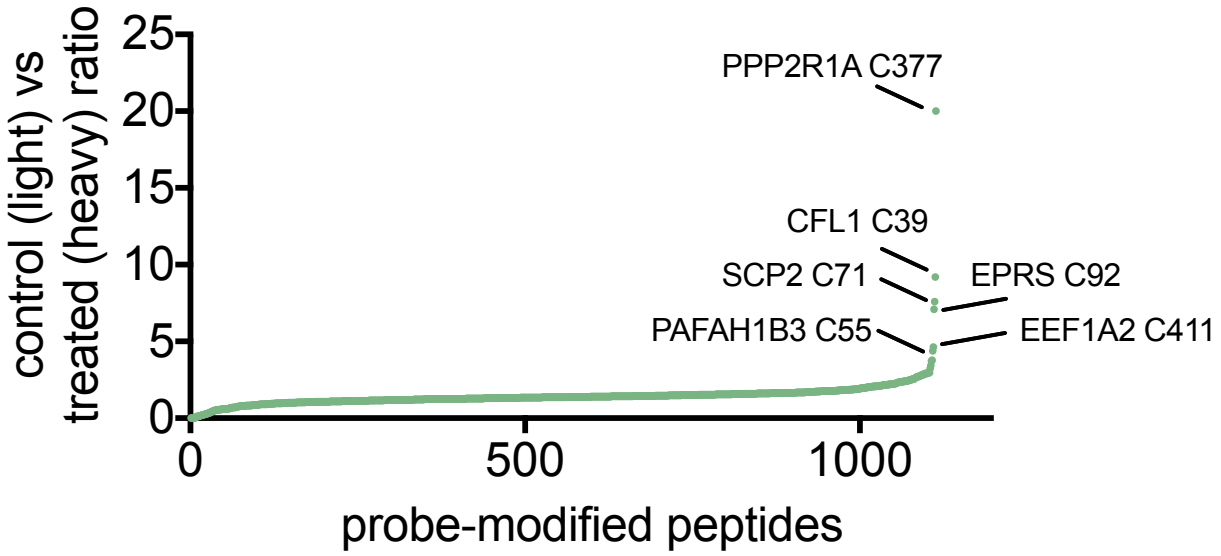


Figure S2. isoTOP-ABPP analysis of CCW 28-3 in 231MFP breast cancer cells *in situ*. 231MFP cells were treated with DMSO vehicle or CCW 28-3 (10 μM) *in situ* for 1 h prior to labeling of proteomes *in vitro* with IA-alkyne (100 μM) for 1h. Isotopically light (for DMSO-treated) or heavy (for compound-treated) TEV protease-cleavable biotin-azide tag were appended by CuAAC for isoTOP-ABPP analysis. Data is for three biological replicates. Raw proteomic data is in Table S2.

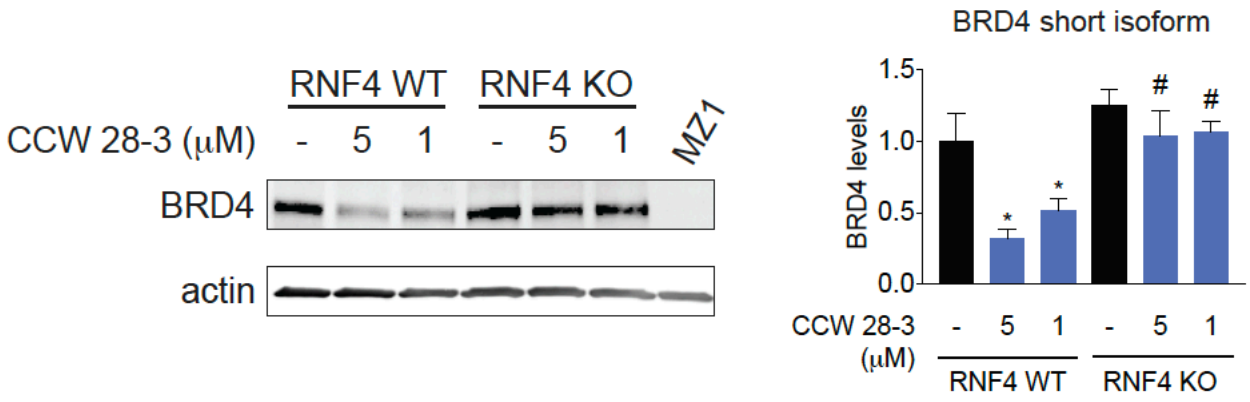


Figure S3. CCW 28-3 tested at lower concentrations in RNF4 wild-type and knockout Hela cells. RNF4 wild-type and knockout Hela cells were treated with DMSO vehicle or CCW 28-3 (5 or 1 μM) for 5 h and subjected to SDS/PAGE and Western blotting for BRD4 and GAPDH. Blots were quantified by densitometry. Data in are from representative gels from n=3. Bar graphs are average ± sem, n=3/group. Significance is expressed as *p<0.05 compared to vehicle-treated controls and #p<0.05 compared to CCW 28-3 treated wild-type cells.