Supporting Information

Novel K-Ras G12C Switch-II Covalent Binders Destabilize Ras and Accelerate Nucleotide Exchange

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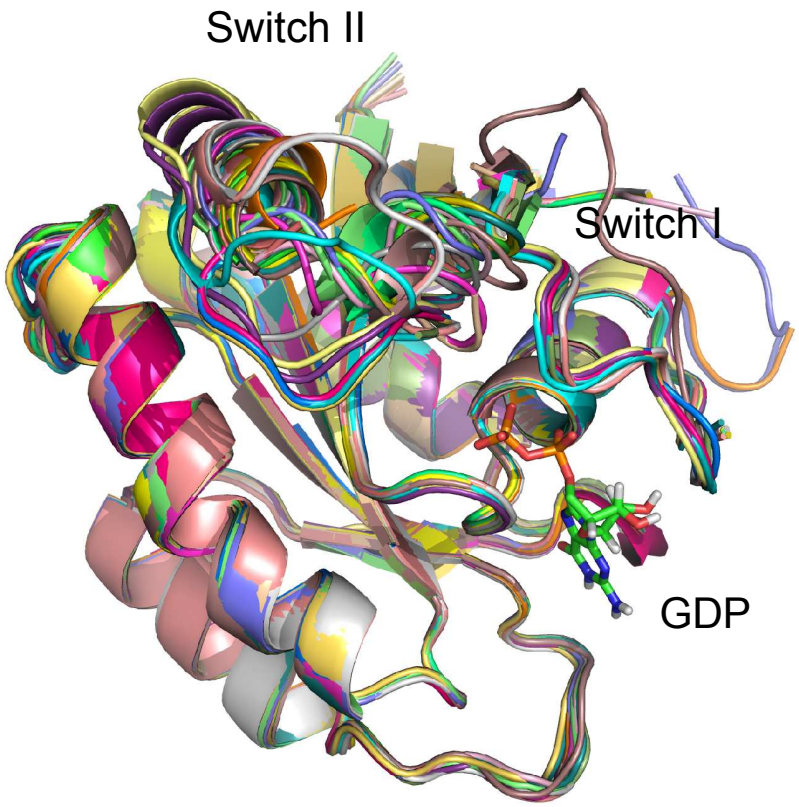


Figure S1. Structural alignment of 24 ligand-bound monomers of K-Ras^{G12C}.

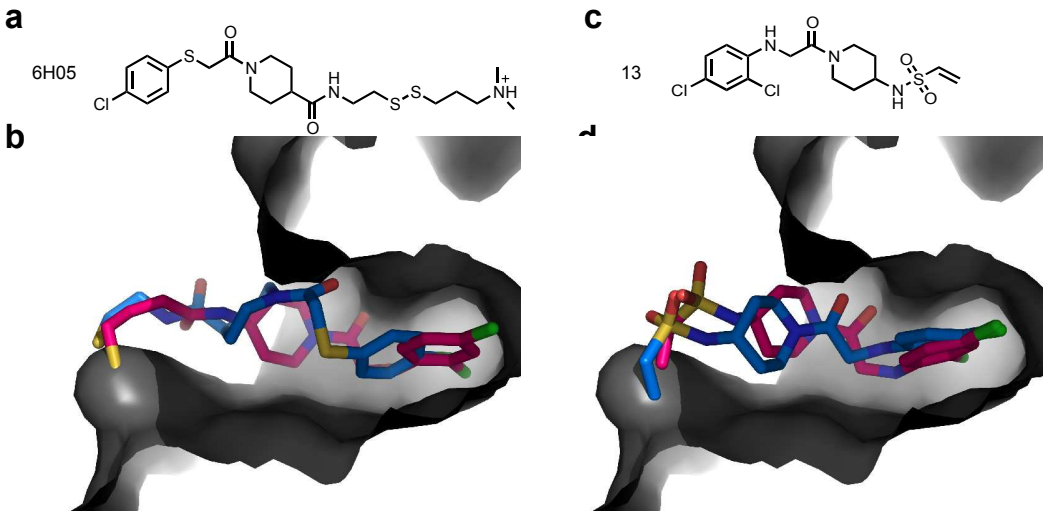


Figure S2. a. Structure of disulfide tethering hit, 6H05. **b.** Docking pose of 6H05 (blue) in docking model (PDB: 4M1S chain B) aligned to co-crystal structure of tethering analogue (magenta) (PDB: 4LUC). **c.** Structure of ligand 13. **d.** Docking pose of 13 (blue) aligned to co-crystal structure of 13 (magenta; PDB: 4M1S chain B).

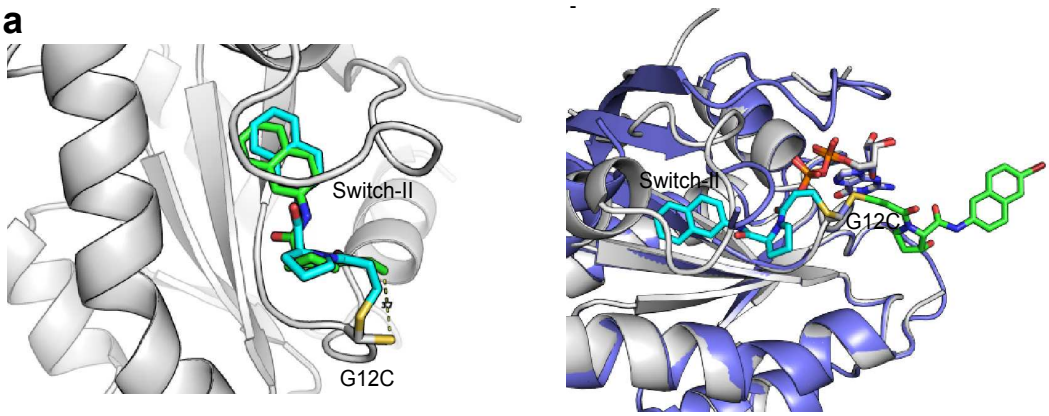


Figure S3. **a.** DOCK pose (green) and DOCKovalent pose (cyan) of compound 1 overlay closely with only a slight rotation of the amide bond in the pyrrolidine-2-carboxamide linker. **b.** Alignment of DOCKovalent pose of compound 1 (cyan; protein in slate) to crystal structure of K-Ras^{G12C} (white; PDB: 6ARK) in complex with compound 10 (green).

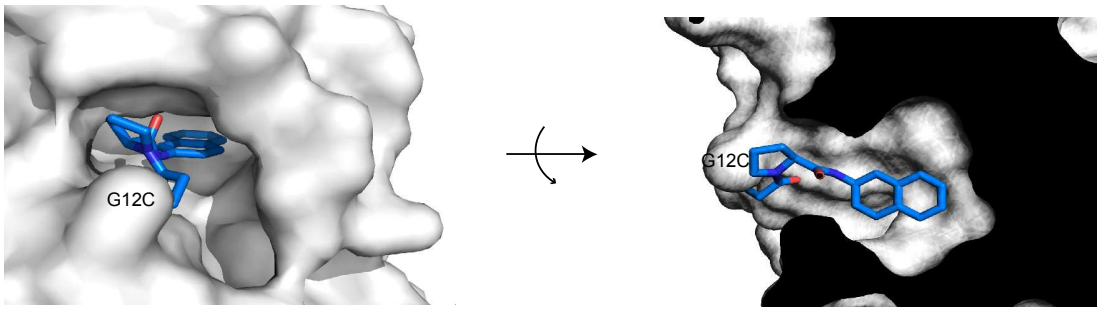
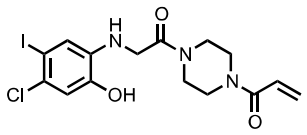
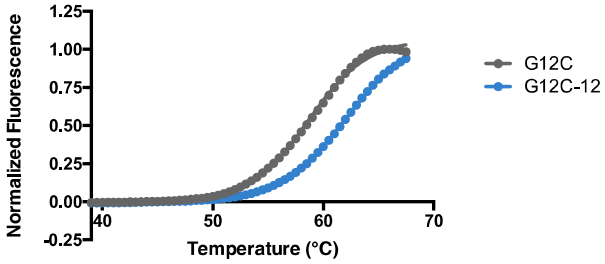


Figure S4. Surface representation of K-Ras^{G12C} with the docking pose of compound 1 depicting the interior of the S-IIP.

a



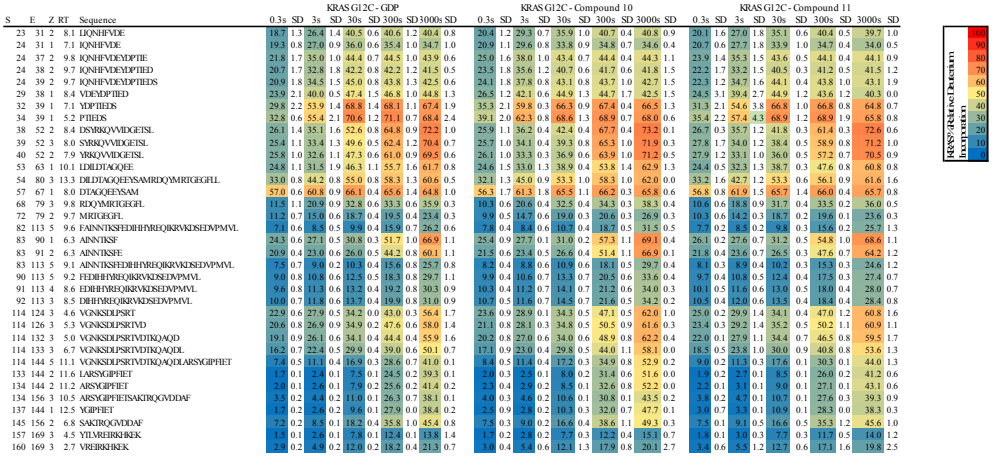
b



c

K-Ras^{G12C}	T_{50} (95% Confidence)
12	62.09°C (62.01 - 62.17°C)

Figure S5. a. Structure of compound 12. **b.** Thermal stability assay of K-Ras^{G12C} labeled with compound 12 and **c.** the T_{50} melting temperature.



S	E	Z	RT	Sequence	KRAS G12C - GDP									KRAS G12C - Compound 10										KRAS G12C - Compound 11									
					0.3s	SD	3s	SD	30s	SD	300s	SD	3000s	SD	0.3s	SD	3s	SD	30s	SD	300s	SD	3000s	SD	0.3s	SD	3s	SD	30s	SD	300s	SD	3000s	SD
23	31	2	8.1	LIQNHFVDE	18.7	1.3	26.4	1.4	40.5	0.6	40.6	1.2	40.4	0.8	20.4	1.2	29.3	0.7	35.9	1.0	40.7	0.4	40.8	0.9	20.1	1.6	27.0	1.8	35.1	0.6	40.4	0.5	39.7	1.0
24	31	1	7.1	IQNHFVDE	19.3	0.8	27.0	0.9	36.0	0.6	35.4	1.0	34.7	1.0	20.9	1.1	29.6	0.8	33.8	0.9	34.8	0.7	34.6	0.4	20.7	0.6	27.7	1.8	33.9	1.0	34.7	0.4	34.0	0.5
24	37	2	9.8	IQNHFVDEYDPTIE	21.8	1.7	35.0	1.0	44.4	0.7	44.5	1.0	43.9	0.6	25.0	1.6	38.0	1.0	43.4	0.7	44.4	0.4	44.3	1.1	23.9	1.4	35.3	1.5	43.6	0.5	44.1	0.4	44.1	0.9
24	38	2	9.7	IQNHFVDEYDPTIED	20.7	1.7	32.8	1.8	42.2	0.8	42.2	1.2	41.5	0.5	23.5	1.8	35.6	1.2	40.7	0.6	41.7	0.6	41.8	1.5	22.2	1.7	33.2	1.5	40.5	0.3	41.2	0.5	41.5	1.2
24	39	2	9.7	IQNHFVDEYDPTIEDS	20.9	1.8	34.5	1.5	45.0	0.8	43.8	1.3	42.5	0.6	24.1	1.8	37.8	0.8	43.1	0.8	43.7	1.0	42.7	1.5	22.3	1.2	34.7	1.6	44.1	0.4	43.8	1.0	43.1	1.9
29	38	1	8.4	VDEYDPTIED	23.9	2.1	40.0	0.5	47.4	1.5	46.8	1.0	44.8	1.3	26.5	1.2	42.1	0.6	44.9	1.3	44.7	1.7	42.5	1.5	24.5	3.1	39.4	2.7	44.9	1.2	43.6	1.2	40.3	0.0
32	39	1	7.1	YDPTIEDS	29.8	2.2	53.9	1.4	68.8	1.4	68.1	1.1	67.4	1.9	35.3	2.1	59.8	0.3	66.3	0.9	67.4	0.4	66.5	1.3	31.3	2.1	54.6	3.8	66.8	1.0	66.8	0.8	64.8	0.7
34	39	1	5.2	PTIEDS	32.8	0.6	55.4	2.1	70.6	1.2	71.1	0.7	68.4	2.4	39.1	2.0	62.3	0.8	68.6	1.3	68.9	0.7	68.0	0.6	35.4	2.2	57.4	4.3	68.9	1.2	68.9	1.9	65.8	0.8
38	52	2	8.4	DSYRKQVVIDGETSL	26.1	1.4	35.1	1.6	52.6	0.8	64.8	0.9	72.2	1.0	25.9	1.1	36.2	0.4	42.4	0.4	67.7	0.4	73.2	0.1	26.7	0.3	35.7	1.2	41.8	0.3	61.4	0.3	72.6	0.6
39	52	3	8.0	SYRKQVVIDGETSL	25.4	1.1	33.4	1.3	49.6	0.5	62.4	1.2	70.4	0.7	25.7	1.0	34.1	0.4	39.3	0.8	65.3	1.0	71.9	0.3	27.8	1.7	34.0	1.2	38.4	0.5	58.9	0.8	71.2	1.0
40	52	2	7.9	YRKQVVIDGETSL	25.8	1.0	32.6	1.1	47.3	0.6	61.0	0.9	69.5	0.6	26.1	1.0	33.3	0.3	36.9	0.6	63.9	1.0	71.2	0.5	27.9	1.2	33.1	1.0	36.0	0.5	57.2	0.7	70.5	0.9
53	63	1	10.1	LDILDTAGQEE	24.8	1.1	31.5	1.9	46.3	1.1	55.7	1.6	61.7	0.8	24.6	1.5	33.0	1.3	38.9	0.4	53.8	1.4	62.9	1.3	24.4	0.5	32.3	1.3	38.7	0.3	47.6	0.8	60.8	0.8
54	80	3	13.3	DILDTAGQEEYSAMRDQYMRTGEGFL	33.0	0.8	44.2	0.8	55.0	0.8	58.3	1.3	60.6	0.5	32.1	1.3	45.0	0.9	53.3	1.0	58.3	1.0	62.0	0.0	33.2	1.6	42.7	1.2	53.3	0.6	56.1	0.9	61.6	1.6
57	67	1	8.0	DTAGQEEYSAM	57.0	0.6	60.8	0.9	66.1	0.4	65.6	1.4	64.8	1.0	56.3	1.7	61.3	1.8	65.5	1.1	66.2	0.3	65.8	0.6	56.8	0.8	61.9	1.5	65.7	1.4	66.0	0.4	65.7	0.8
68	79	3	9.8	RDQYMRTGEGFL	11.5	1.1	20.9	0.9	32.8	0.6	33.3	0.6	35.9	0.3	10.3	0.6	20.6	0.4	32.5	0.4	34.3	0.3	38.3	0.4	10.6	0.6	18.8	0.9	31.7	0.4	33.5	0.2	36.0	0.5
72	79	2	9.7	MRTGEGFL	11.2	0.7	15.0	0.6	18.7	0.4	19.5	0.4	23.4	0.3	9.9	0.5	14.7	0.6	19.0	0.3	20.6	0.3	26.9	0.3	10.3	0.6	14.2	0.3	18.7	0.2	19.6	0.1	23.6	0.3
82	113	5	9.6	FAINNTKSFEDIHHMREQIKRVKDSEDVPMVL	7.1	0.6	8.5	0.5	9.9	0.4	15.9	0.7	26.2	0.6	7.8	0.4	8.4	0.6	10.7	0.4	18.7	0.5	31.5	0.5	7.7	0.2	8.5	0.2	9.8	0.3	15.6	0.2	25.7	1.3
83	90	1	6.3	AINNTKSF	24.3	0.6	27.1	0.5	30.8	0.3	51.7	1.0	66.9	1.1	25.4	0.9	27.7	0.1	31.0	0.2	57.3	1.1	69.1	0.4	26.1	0.2	27.6	0.7	31.2	0.5	54.8	1.0	68.6	1.1
83	91	2	6.3	AINNTKSFE	20.9	0.4	23.0	0.6	26.0	0.5	44.2	0.8	60.1	1.1	21.5	0.6	23.4	0.5	26.6	0.4	51.4	1.1	66.9	0.1	21.8	0.4	23.6	0.7	26.5	0.3	47.6	0.7	64.2	1.2
83	113	5	9.1	AINNTKSFEDIHHYREQIKRVKDSEDVPMVL	7.5	0.7	9.0	0.2	10.3	0.4	15.6	0.8	25.7	0.8	8.2	0.4	8.8	0.6	10.9	0.6	18.1	0.5	29.7	0.4	8.1	0.3	8.9	0.4	10.2	0.3	15.3	0.3	24.6	1.2
90	113	5	9.2	FEDIHHYREQIKRVKDSEDVPMVL	9.0	0.8	10.8	0.6	12.5	0.5	18.3	0.8	29.7	1.1	9.9	0.4	10.6	0.7	13.3	0.7	20.5	0.6	33.6	0.4	9.7	0.4	10.8	0.5	12.4	0.4	17.5	0.3	27.4	0.7
91	113	4	8.6	EDIHHYREQIKRVKDSEDVPMVL	9.6	0.8	11.3	0.6	13.2	0.4	19.2	0.8	30.3	0.9	10.3	0.4	11.2	0.7	14.1	0.7	21.2	0.6	34.0	0.3	10.1	0.5	11.6	0.6	13.0	0.5	18.0	0.4	28.0	0.7
92	113	3	8.5	DIHHYREQIKRVKDSEDVPMVL	10.0	0.7	11.8	0.6	13.7	0.4	19.9	0.8	31.0	0.9	10.7	0.5	11.6	0.7	14.5	0.7	21.6	0.5	34.2	0.2	10.5	0.4	12.0	0.6	13.5	0.4	18.4	0.4	28.4	0.8
114	124	3	4.6	VGNKSDLPSRT	22.9	0.6	27.9	0.5	34.2	0.0	43.0	0.3	56.4	1.7	23.6	0.9	28.9	0.1	34.3	0.5	47.1	0.5	62.0	1.0	25.0	0.2	29.9	1.4	34.1	0.4	47.0	1.2	60.8	1.6
114	126	3	5.3	VGNKSDLPSRTVD	20.6	0.8	26.9	0.9	34.9	0.2	47.6	0.6	58.0	1.4	21.1	0.8	28.1	0.3	34.8	0.5	50.5	0.9	61.6	0.3	23.4	0.3	29.2	1.4	35.2	0.5	50.2	1.1	60.9	1.1
114	132	3	5.0	VGNKSDLPSRTVDTKQAQD	19.1	0.9	26.1	0.6	34.1	0.4	44.4	0.4	55.9	1.6	20.2	0.8	27.0	0.6	34.0	0.6	48.9	0.8	62.2	0.4	22.0	0.1	27.9	1.1	34.4	0.7	46.5	0.8	59.5	1.7
114	133	3	6.7	VGNKSDLPSRTVDTKQAQDL	16.2	0.7	22.4	0.5	29.9	0.4	39.0	0.6	50.1	0.7	17.1	0.9	23.0	0.4	29.8	0.5	44.0	1.1	58.1	0.0	18.5	0.5	23.8	1.0	30.0	0.9	40.8	0.8	53.6	1.3
114	144	5	11.1	VGNKSDLPSRTVDTKQAQDLARSVGIPFIET	7.4	0.5	11.1	0.4	16.9	0.3	28.6	0.7	41.0	0.1	8.4	0.5	11.4	0.4	17.2	0.3	34.9	0.8	52.9	0.2	9.0	0.2	11.3	0.3	17.6	0.1	30.3	0.1	44.0	1.3
133	144	2	11.6	LARSVGIPFIET	1.7	0.1	2.4	0.1	7.5	0.1	24.5	0.2	39.3	0.1	2.0	0.3	2.5	0.1	8.0	0.2	31.4	0.6	51.6	0.0	1.9	0.2	2.7	0.1	8.5	0.1	26.0	0.2	41.2	0.6
134	144	2	11.2	ARSVGIPFIET	2.0	0.1	2.6	0.1	7.9	0.2	25.6	0.2	41.4	0.2	2.3	0.4	2.9	0.2	8.5	0.1	32.6	0.8	52.2	0.0	2.2	0.1	3.1	0.1	9.0	0.1	27.1	0.1	43.1	0.6
134	156	3	10.5	ARSVGIPFIETSAKTRQGVDDAF	3.5	0.2	4.4	0.2	11.0	0.1	26.3	0.7	38.1	0.1	4.0	0.3	4.6	0.2	10.6	0.1	30.8	0.1	43.5	0.2	3.8	0.2	4.7	0.1	10.7	0.1	27.6	0.3	39.3	0.9
137	144	1	12.5	YGIPFIET	1.7	0.2	2.6	0.2	9.6	0.1	27.9	0.0	38.4	0.2	2.5	0.9	2.8	0.2	10.3	0.3	32.0	0.7	47.7	0.1	3.0	0.7	3.3	0.1	10.9	0.1	28.3	0.0	38.3	0.3
145	156	2	6.8	SAKTRQGVDDAF	7.2	0.2	8.5	0.1	18.2	0.4	35.8	1.0	45.4	0.8	7.5	0.3	9.0	0.2	16.6	0.4	38.6	1.1	49.3	0.3	7.5	0.1	9.1	0.5	16.6	0.5	35.3	1.2	45.6	1.0
157	169	3	4.5	YILVREIRKHKEK	1.5	0.1	2.6	0.1	7.8	0.1	12.4	0.1	13.8	1.4	1.7	0.2	2.8	0.2	7.7	0.3	12.2	0.4	15.1	0.7	1.8	0.1	3.0	0.3	7.7	0.3	11.7	0.5	14.0	1.2
160	169	3	2.7	VREIRKHKEK	2.9	0.2	4.9	0.2	12.0	0.2	18.2	0.4	21.3	0.7	3.0	0.4	5.4	0.6	12.1	1.3	17.9	0.8	20.1	2.7	3.4	0.6	5.5	1.2	12.7	0.6	17.1	1.6	19.8	2.5

Figure S6. Relative **%**deuterium incorporation in peptides of K-Ras^{G12C} with compounds 10 and 11 over time.

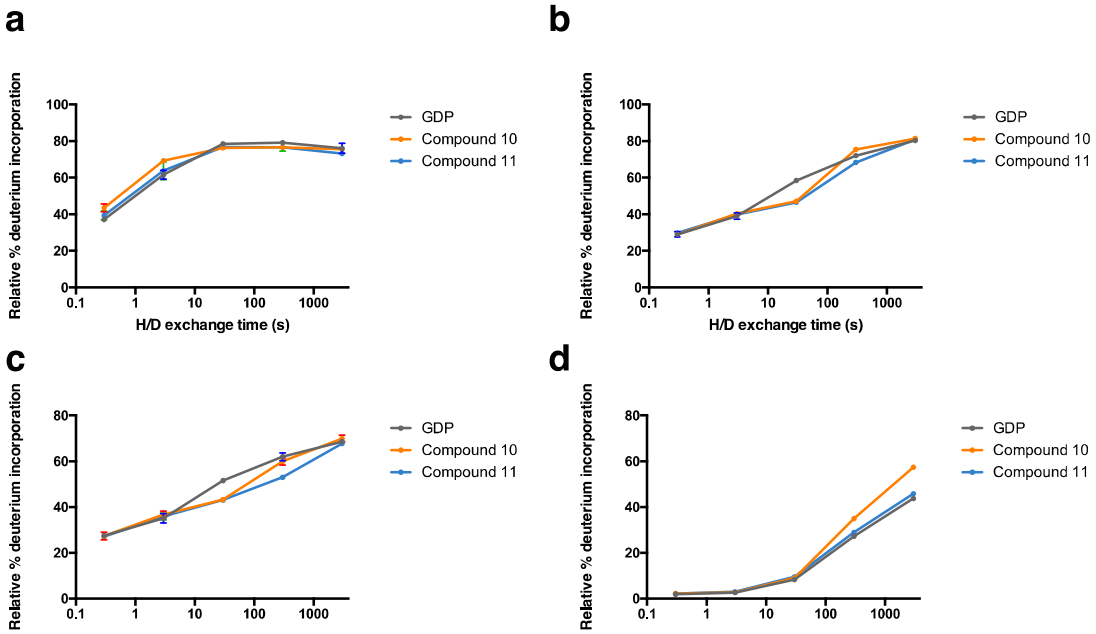


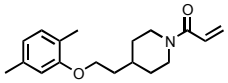
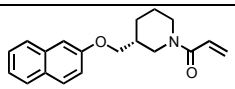
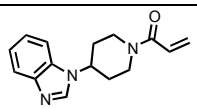
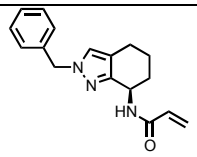
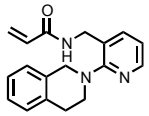
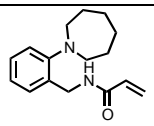
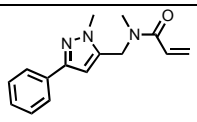
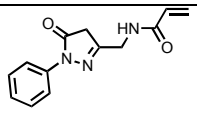
Figure S7. Relative %deuterium incorporation over time in **a.** peptides 34-39 (Switch-I region) **b.** peptides 38-52 **c.** peptides 53-63 (Switch-II region) and **d.** peptides 133-144. HDX curves are the average of three independent experiments (error bars represent SD).

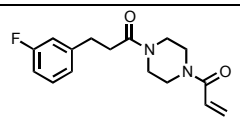
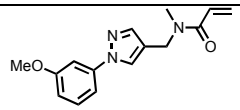
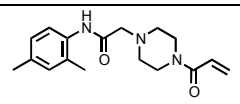
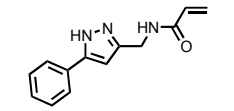
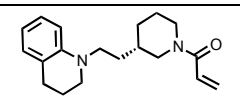
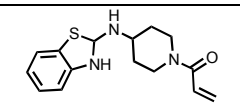
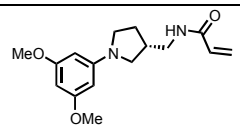
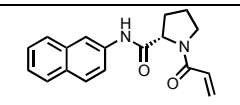
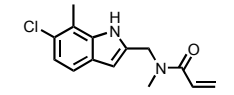
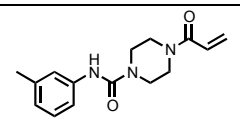
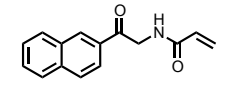
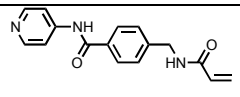
Table S1. Crystal structures used for docking.

Ligand-bound K-Ras monomers used for docking studies			
4M21 chain B	4M1S chain B	4M22 chain B	56A chain B*
4LYJ	4LUC chain A	4M22 chain C	56A chain C*
4LYH chain B	4LUC chain B	4M1T chain B	56A chain D*
4LYH chain C	4LV6 chain A	59 chain B*	56A chain E*
4LYF chain B	4LV6 chain B	59 chain C*	55_P1 chain A*
4M1Y chain B	4M1O chain B	56A chain A*	55_P1 chain B*

*Crystal structures are not deposited in the Protein Data Bank.

Table S2. Percent modification of cys-light K-Ras^{G12C} 1-169 and K-Ras^{WT} 1-189 by compounds in DOCKovalent Library

Compound Structure	Name	Mass	% Labeling of K-Ras^{G12C}	% Labeling of K-Ras^{WT} 1-189
	**S1-1**	287.40	0	0
	**S1-2**	295.38	0	0
	**S1-3**	255.31	0	0
	**S1-4**	281.35	0	0
	**S1-5**	293.36	0	61.7
	**S1-6**	258.36	0	0
	**S1-7**	255.31	0	24.2
	**S1-8**	243.26	0	0

	**S1-9**	290.33	0	0
	**S1-10**	271.31	0	0
	**S1-11**	301.38	0	0
	**S1-12**	227.26	0	0
	**S1-13**	298.42	0	0
	**2**	289.40	20	0
	**S1-14**	290.36	0	0
	**1**	294.35	41	43.5
	**S1-15**	262.73	0	0
	**S1-16**	273.33	0	23.6
	**S1-17**	239.27	0	0
	**S1-18**	281.31	0	0

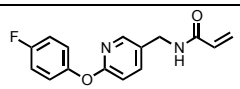
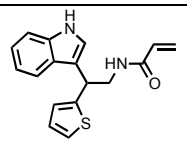
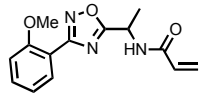
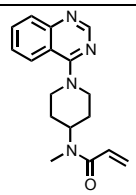
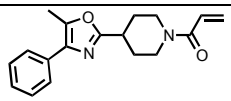
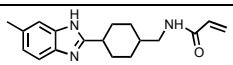
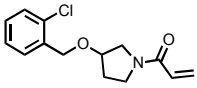
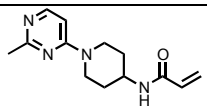
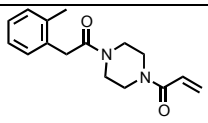
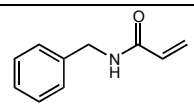
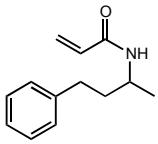
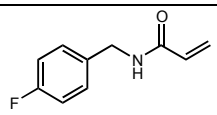
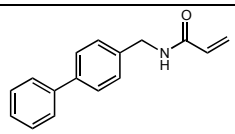
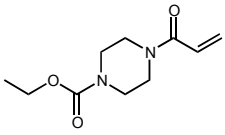
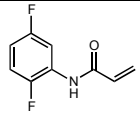
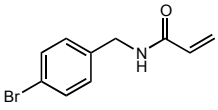
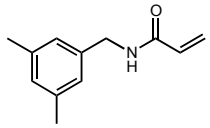
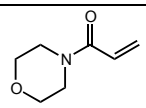
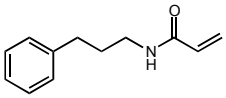
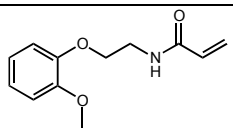
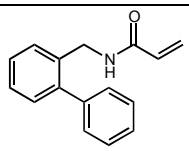
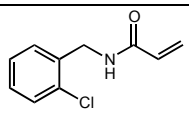
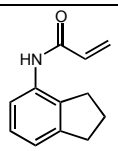
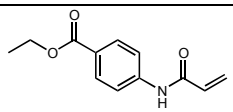
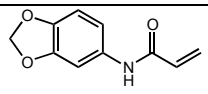
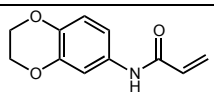
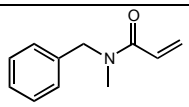
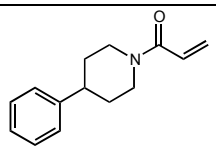
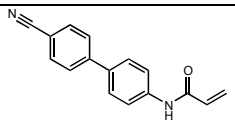
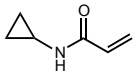
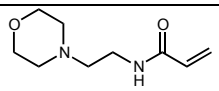
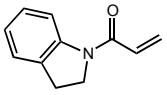
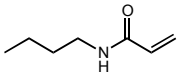
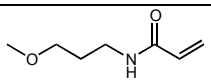
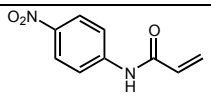
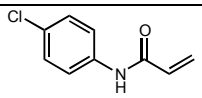
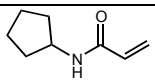
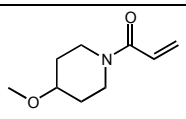
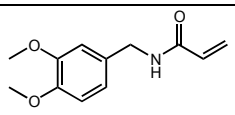
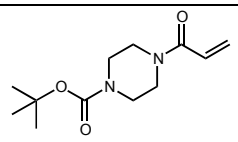
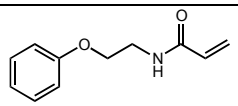
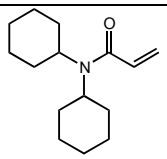
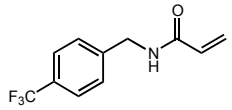
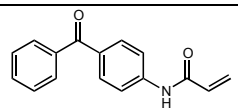
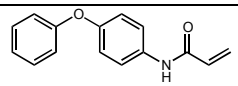
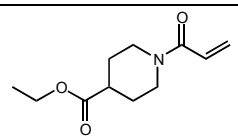
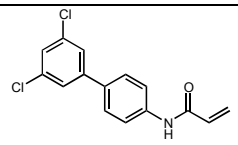
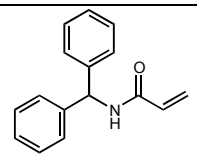
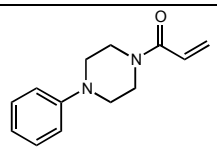
	**S1-19**	272.27	0	0
	**S1-20**	296.39	0	0
	**S1-21**	273.29	0	20.2
	**S1-22**	296.37	0	0
	**S1-23**	296.36	0	21.4
	**S1-24**	297.39	0	0
	**S1-25**	265.74	0	0
	**S1-26**	246.31	0	0
	**S1-27**	272.34	0	20

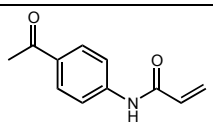
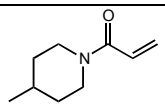
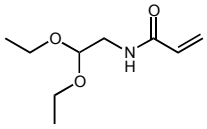
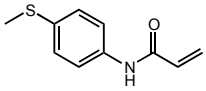
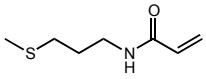
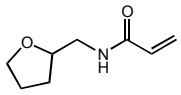
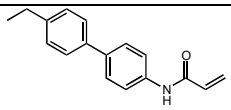
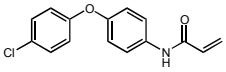
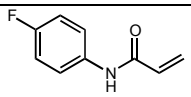
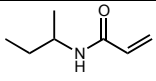
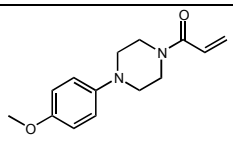
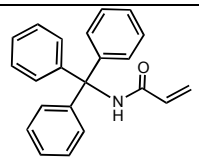
Table S3. Percent modification of cys-light K-Ras^{G12C} 1-169 and K-Ras^{WT} 1-189 by compounds in Acrylamide Library

Compound Structure	Name	Mass	% Labeling of K-Ras^{G12C}	% Labeling of K-Ras^{WT} 1-189
	**DKM-2-31**	161.20	0	0
	**DKM-2-32**	203.28	0	0
	**DKM-2-34**	179.19	0	0
	**DKM-2-37**	237.30	0	0
	**DKM-2-39**	212.25	0	18.2
	**DKM-2-40**	183.15	40.4	100
	**DKM-2-43**	240.10	0	0

	**DKM-2-47**	189.25	0	0
	**DKM-2-49**	141.17	0	22.4
	**DKM-2-50**	189.25	0	0
	**DKM-2-58**	221.25	0	0
	**DKM-2-59**	237.30	0	0
	**DKM-2-60**	195.65	0	0
	**DKM-2-84**	187.24	0	30.0
	**DKM-2-85**	219.24	56.5	100
	**DKM-2-86**	191.18	0	38.0
	**DKM-2-87**	205.21	0	40.0
	**DKM-2-95**	175.23	0	0

	**DKM-2-97**	215.29	0	0
	**DKM-2-98**	248.28	0	0
	**DKM-2-99**	111.14	0	0
	**DKM-2-100**	184.24	0	0
	**DKM-2-101**	173.21	41.7	100
	**DKM-2-102**	127.18	0	0
	**DKM-2-103**	143.18	0	0
	**DKM-2-104**	192.17	100	100
	**DKM-2-107**	181.62	0	31.0
	**DKM-2-108**	139.19	0	0
	**DKM-2-109**	169.22	0	0
	**DKM-2-110**	221.25	0	0

	**DKM-2-111**	240.30	0	0
	**DKM-2-113**	191.23	0	0
	**DKM-2-114**	235.37	0	0
	**DKM-2-116**	229.20	0	0
	**DKM-2-117**	251.28	100	100
	**DKM-2-119**	239.27	38.8	43
	**DKM-2-120**	211.26	0	0
	**DKM3-3**	292.16	16.3	0
	**DKM-3-4**	237.30	0	0
	**DKM-3-5**	216.28	0	15.7

	**DKM-3-7**	189.21	53	100
	**DKM-3-8**	153.22	0	0
	**DKM-3-9**	187.24	0	0
	**DKM-3-10**	193.27	0	62.5
	**DKM-3-12**	144.21	0	0
	**DKM-3-15**	155.19	0	0
	**DKM-3-16**	251.32	0	0
	**DKM3-30**	273.71	0	0
	**DKM3-31**	165.16	0	41.6
	**DKM-3-32**	127.18	0	0
	**DKM-3-36**	246.30	0	19.3
	**DKM-3-41**	313.39	0	0

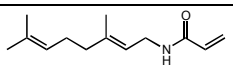
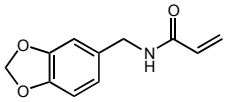
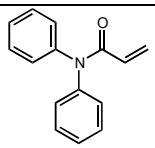
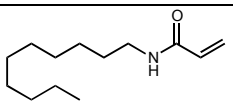
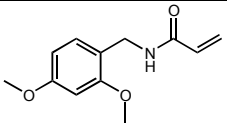
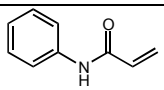
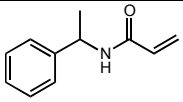
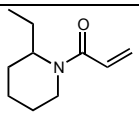
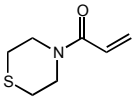
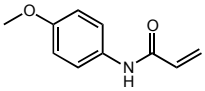
	**DKM-3-42**	207.31	0	0
	**DKM-3-43**	205.21	0	0
	**DKM3-70**	223.27	52	100
	**TRH-1-12**	211.34	0	0
	**TRH-1-13**	221.25	0	0
	**TRH-1-19**	147.17	0	28.2
	**TRH-1-20**	175.23	0	0
	**TRH-1-27**	167.25	0	0
	**TRH-1-30**	157.23	0	24.5
	**TRH-1-32**	177.20	0	20.9

Table S4. Data collection and refinement statistics for K-Ras^{G12C}-10 (PDB: 6ARK).

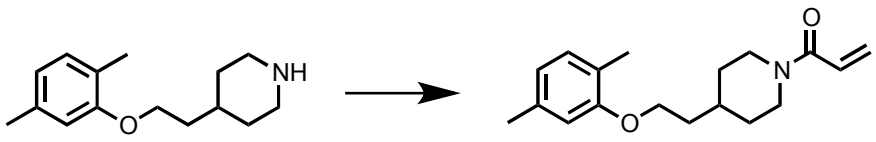
	K-Ras^{G12C}-10
Data Collection	
Space group	H 3 2
Cell Dimension	
a, *b*, *c* (Å)	94.2799, 94.2799, 119.55
α, β, γ (°)	90, 90, 120
Resolution range (Å)	30.43 - 1.75 (1.78 - 1.75)
R_{merge}	0.072 (0.996)
R_{pim}	0.033 (0.451)
Mean I/σI	13.60
CC1/2	0.999 (0.702)
Completeness (%)	100.00 (100.00)
Multiplicity	2.0 (2.0)
Refinement	
Resolution (Å)	29.88 - 1.75
Reflections used in refinement	39968
R_{work}/R_{free}	0.1937/0.2314
Number of atoms	1444
Protein	1323
Ligands/ions	65
Water	56
B-factors	52.59
Protein	53.04
Ligands/ions	52.11
Water	42.50
R.m.s. deviations	
Bonds (Å)	0.006

Angles (°)	0.98

*Statistics for the highest-resolution shell are shown in parentheses.

Synthetic Methods

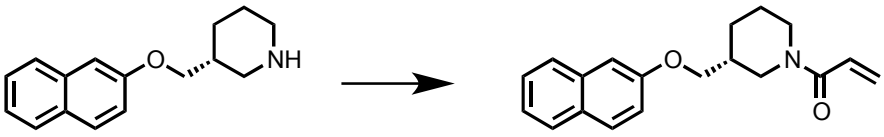
All commercial reagents were purchased and used without further purification. All reactions were done under argon in sealed vials with stirring. Silica gel chromatography was performed using a Combiflash Rf (Teledyne Isco) with pre-packed 4-24g silica columns and cartridges. All reverse-phase high performance liquid chromatography (RP-HPLC) was performed using a Waters 2545 solvent delivery system equipped with an XBridge prep C18 column. Separation was achieved using a gradient between 5-95% acetonitrile (ACN) in water with 0.1% formic acid by monitoring UV absorption (λ=254 nm). For most compounds, high-resolution mass spectrometry (HRMS) was performed using a high-resolution UPLC/TOF system (Synapt G2-S, Waters) equipped with ESI source. Compounds were analyzed in positive ionization mode. Separation was done on Acquity BEH C18 column using water-methanol-formic acid gradient for elution. Elemental composition was determined using Elemental Composition module of MassLynx v.4.1 software. Liquid chromatography traces and MS (for S1-14 and S1-20) were collected with a Waters Acquity UPLC Class I/XEVO G2-XS QToF with a 2.1 x 50 mm Acquity UPLC BEH C18 column. ^{1}H NMR were recorded on a Varian Innova 400 MHz or a Bruker DRX 500 MHz spectrometer. ^{1}H chemical shifts are reported in δ (ppm) as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), or m (multiplet) and are referenced to the residual solvent peak. Coupling constants (J) are reported as Hertz. ^{13}C NMR were recorded on a Bruker DRX 500 MHz spectrometer and the ^{13}C chemical shifts are reported in δ (ppm) and are referenced to the residual solvent peak.



S1-1

S1-1 1-(4-(2-(2,5-dimethylphenoxy)ethyl)piperidin-1-yl)prop-2-en-1-one:

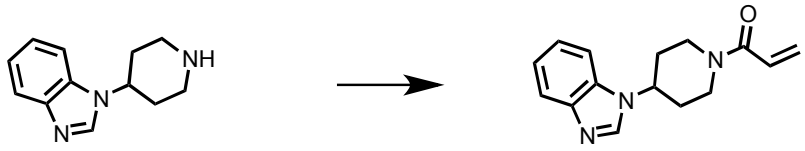
4-(2-(2,5-Dimethylphenoxy)ethyl)piperidine hydrochloride (50mg, 1 eq, 0.19 mmol) was dissolved in 2mL acetonitrile. TEA was added (150uL, 6 eq, 1.11mmol) at ambient temperature. The reaction was cooled to 0°C. Acryloyl chloride (16uL, 1.1 eq, 0.20mmol) was added and reaction was stirred for 30 minutes. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (0-15% dichloromethane: methanol gradient) and subsequently by RP-HPLC (45-95% gradient) to get the desired product the desired product (11.8mg, 22%yield) as a yellow oil. HRMS $C_{18}H_{26}NO_2$ $[M+H]^+$ expected mass: 288.1964; observed: 288.1972. ^1H NMR (400 MHz, $CDCl_3$) **δ** 7.01 (d, J=7.54, 1H), 6.67 (d, J=7.52, 1H), 6.62 (s, 1H), 6.59 (dd, J=16.96, 10.60, 1H), 6.26 (dd, J=16.86, 1.97, 1H) 5.66 (dd, J=10.59, 1.97, 1H), 4.66 (d, J=12.70, 1H), 4.00 (t, J=6.21, 2H), 3.98 (m, 1H) 3.06 (t, J=12.71, 1H), 2.65(t, J=12.63, 1H) 2.31 (s, 3H), 2.17 (s, 3H), 1.84 (m, 3H), 1.77 (q, J=6.23, 2H), 1.23 (m, 2H).



S1-2

S1-2 (*R*)-1-(3-((naphthalen-2-yloxy)methyl)piperidin-1-yl)prop-2-en-1-one:

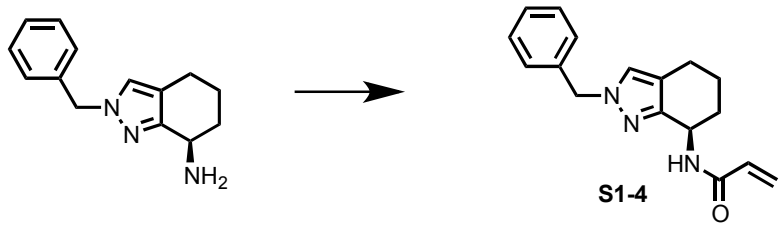
3-[(2-Naphthyloxy)methyl]piperidine (50mg, 1 eq, 0.18 mmol) was dissolved in 2mL acetonitrile. TEA was added (250uL, 5eq, 0.9mmol) at ambient temperature. The reaction was cooled to 0°C. Acryloyl chloride (30uL, 2 eq, 0.4mmol) was added and reaction was stirred for 30 minutes. The reaction was quenched with 5mL saturated NaHCO3. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (5-100% hexanes: ethyl acetate gradient) to get the desired product (25mg, 47%yield) as a yellow oil. HRMS $C_{19}H_{22}NO_2$ $[M+H]^+$ expected mass: 296.1651; observed: 296.1664. ^1H NMR (400 MHz, $CDCl_3$) **δ** 7.74 (m, 3H), 7.44 (m, 1H), 7.34 (m, 1H), 7.15 (d, J=8.92, 1H), 7.11 (s, 1H), 6.62 (m, 1H), 6.27 (t, J=16.37, 1H), 5.66 (dd, J=16.73, 10.79, 1H), 4.48 (dd, J=170.32, 13.47, 1H), 3.98 (m, 3H), 2.97 (m, 1H), 3.10 (m, 1H), 2.13 (m, 1H), 1.98 (m, 1H), 1.79 (m, 2H), 1.54 (m, 1H).



S1-3

S1-3 1-(4-(1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)prop-2-en-1-one:

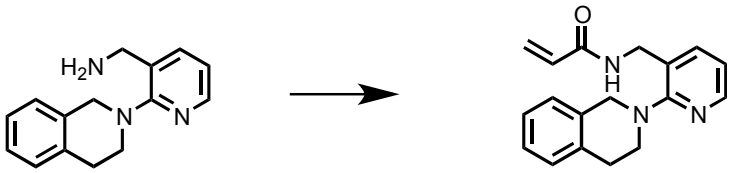
1-(piperidin-4-yl)-1H-1,3-benzodiazole hydrochloride (27mg, 1 eq, 0.13 mmol) was dissolved in 2mL acetonitrile. TEA was added (35uL, 1.9 eq, 0.247mmol) at ambient temperature. The reaction was cooled to 0°C. Acryloyl chloride (8uL, 0.8 eq, 0.1mmol) was added. The reaction was quenched with 5mL saturated NaHCO3. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (0-15% dichloromethane: methanol) to get the desired product (15.7mg, 50%yield) as a white solid. HRMS $C_{15}H_{18}N_3O$ $[M+H]^+$ expected mass: 256.145; observed: 256.145. ^1H NMR (400 MHz, CD_3OD) **δ** 8.28 (s, 1H), 7.71 (m, 2H), 7.30 (m, 2H), 6.84 (dd, J=16.56,10.64, 1H), 6.24 (dd, J=16.79, 2.02, 1H), 5.78 (dd, J=10.59, 2.02, 1H), 4.73 (m, 2H), 4.34 (d, J=13.41, 1H), 3.39 (t, J=13.41, 1H), 2.97 (t, J=13.41, 1H), 2.25 (d, J=12.49), 2.09 (m, 2H).



S1-4

S1-4 *N*-((2-(3,4-dihydroisoquinolin-2(1*H*)-yl)pyridin-3-yl)methyl)acrylamide:

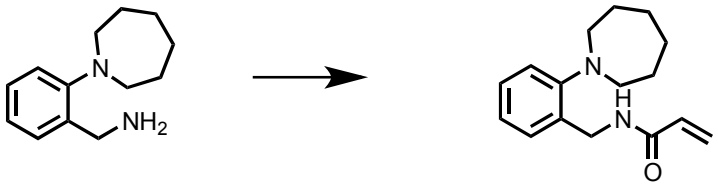
1-benzyl-4,5,6,7-tetrahydro-1H-indazol-4-amine (75mg, 1 eq, 0.33mmol) was dissolved in 2mL acetonitrile. TEA was added (90uL, 2 eq, 0.66mmol) at ambient temperature. The reaction was cooled to 0°C. Acryloyl chloride (30uL, 1.1 eq, 0.36mmol) was added. The reaction was quenched with 5mL saturated NaHCO3. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (5-100% hexanes: ethyl acetate) to get the desired product (7mg, 8%yield) as a yellow oil. HRMS $C_{17}H_{20}N_3O$ $[M+H]^+$ expected mass: 282.1606; observed: 282.1608. ^1H NMR (400 MHz, CD_3OD) **δ** 7.40 (s, 1H), 7.29 (m, 3H), 7.12 (d, J=7.25, 2H), 5.65 (dd, J=6.88, 5.00, 1H), 6.25 (m, 2H), 5.26 (s, 2H), 5.04 (t, J=4.91, 1H), 2.55 (m, 2H), 1.93 (m, 2H), 1.82 (m, 1H), 1.70 (m, 1H).



S1-5

S1-5 *N*-((2-(3,4-dihydroisoquinolin-2(1*H*)-yl)pyridin-3-yl)methyl)acrylamide:

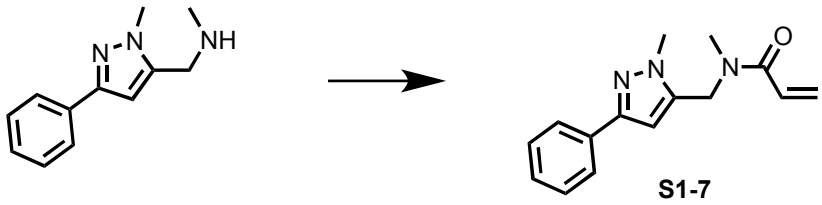
(2-(3,4-Dihydroisoquinolin-2(1H)-yl)pyridin-3-yl)methanamine (50mg, 1 eq, 0.208mmol) was dissolved in 2mL acetonitrile. TEA was added (58uL, 2 eq, 0.416mmol) at ambient temperature. The reaction was cooled to 0°C. Acryloyl chloride (19uL, 1.1 eq, 0.229mmol) was added. The reaction was quenched with 5mL saturated NaHCO3. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (5-100% hexanes: ethyl acetate) to get the desired product (8.2mg, 13%yield) as a white oily solid. HRMS $C_{18}H_{20}N_3O$ $[M+H]^+$ expected mass: 294.1606; observed: 294.1609. ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 8.29 (dd, J=4.87, 1.72, 1H), 7.59 (dd, J=7.49, 1.64, 1H), 7.19 (m, 3H), 7.15 (m, 1H), 6.99 (dd, J=4.92, 7.47, 1H), 6.42 (s, 1H), 6.26 (dd, J=16.98, 1.24, 1H), 6.05 (dd, J=17.00, 10.31, 1H), 5.63 (dd, J=10.31, 1.21, 1H), 4.64 (d, J=5.91, 2H), 4.39 (s, 2H), 3.40 (t, J=5.80, 2H), 3.07 (t, J=5.72, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) **δ** 165.78, 161.19, 147.05, 137.84, 134.91, 134.22, 130.71, 129.04, 127.01, 126.87, 126.55, 126.11, 125.41, 118.91, 77.39, 52.24, 49.62, 40.05, 29.84.



S1-6

S1-6 *N*-(2-(azepan-1-yl)benzyl)acrylamide:

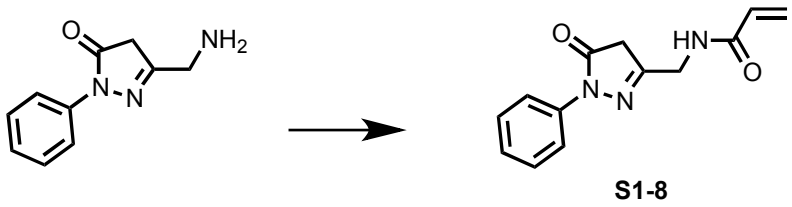
[2-(1-Azepanyl)phenyl]methanamine (61mg, 1 eq, 0.3mmol) was dissolved in 2mL acetonitrile. TEA (70uL, 2eq, 0.5mmol) was added at ambient temperature. The reaction was cooled to 0°C. Acryloyl chloride (22uL, 1.1 eq, 0.27mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (5-100% hexanes: ethyl acetate) to get the desired product (32.8mg, 42%yield) a white oily solid. HRMS $C_{16}H_{23}N_2O$ $[M+H]^+$ expected mass: 259.181; observed: 259.1819. ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.24 (m, 2H), 7.16 (d, J=8.13, 1H), 7.03 (t, J=7.04, 1H), 6.97 (s, 1H), 6.29 (dd, J=16.96, 1.25, 1H), 6.10 (dd, J=16.92, 10.25, 1H), 5.64 (dd, J=10.23, 1.24, 1H), 4.61 (d, J=5.51, 2H), 3.10 (t, J=5.31, 4H), 1.73 (m, 8H).



S1-7

S1-7 *N*-methyl-*N*-((1-methyl-3-phenyl-1*H*-pyrazol-5-yl)methyl)acrylamide:

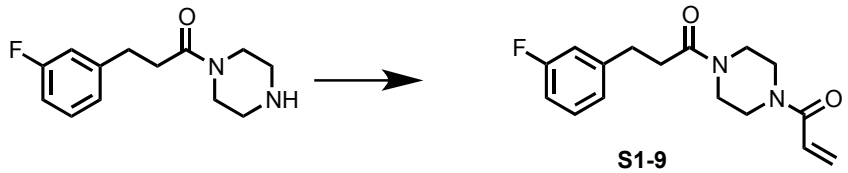
N-methyl-1-(1-methyl-3-phenyl-1*H*-pyrazol-5-yl)methanamine (25mg, 1 eq, 0.124mmol) was dissolved in 2mL acetonitrile. TEA (35uL, 2 eq, 0.25mmol) was added at ambient temperature. The reaction was cooled to 0°C. Acryloyl chloride (11uL, 1.1 eq, 0.136mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (5-100% hexanes: ethyl acetate) to get the desired product (17.6mg, 56% yield) as a white oily solid. HRMS $C_{15}H_{18}N_3O$ $[M+H]^+$ expected mass: 256.145; observed: 256.1458. ^1H NMR (400 MHz, $CDCl_3$) **δ** 7.76 (d, J=7.62, 2H), 7.38 (t, J=7.44, 2H), 7.30 (d, J=7.44, 1H), 6.61 (dd, J=10.40, 16.78, 1H), 6.50 (s, 1H) 6.40 (dd, J=16.78, 1.95, 1H), 5.77(d, J=10.69, 1H), 4.75 (s, 2H), 3.89 (s, 3H), 3.05 (s, 3H).



S1-8

S1-8 *N*-((5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)methyl)acrylamide:

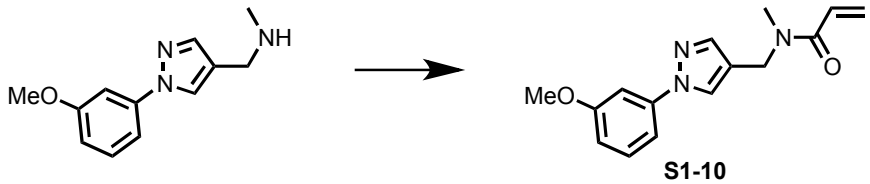
5-(Aminomethyl)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one dihydrochloride (25mg, 1 eq, 0.13mmol) was dissolved in 2mL acetonitrile. TEA (37uL, 2eq, 0.26mmol) was added at ambient temperature. The reaction was cooled to 0°C. Acryloyl chloride (12uL, 1.1 eq, 0.15mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (5-100% hexanes: ethyl acetate) to get the desired product (3mg, 9%yield) as a yellow oil. HRMS $C_{13}H_{14}N_3O_2$ $[M+H]^+$ expected mass: 244.1086; observed: 244.1089. ^1H NMR (400 MHz, MeOD) **δ** 7.66 (t, J=7.70, 2H), 7.44 (t, J=7.70, 2H), 7.29 (t, J=7.69, 1H), 6.29 (m, 2H), 5.69 (dd, J= 8.35, 3.65, 1H), 4.37 (s, 2H).



S1-9

S1-9 1-(4-(3-(3-fluorophenyl)propanoyl)piperazin-1-yl)prop-2-en-1-one:

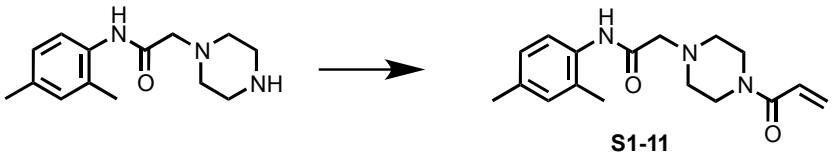
3-(3-Fluorophenyl)-1-(piperazin-1-yl)propan-1-one hydrochloride (25mg, 1 eq, 0.11mmol) was dissolved in 2mL acetonitrile. TEA (30uL, 2eq, 0.21mmol) was added at ambient temperature. The reaction was cooled to 0°C. Acryloyl chloride (10uL, 1.1 eq, 0.11mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (5-100% hexanes: ethyl acetate) to get the desired product (12.8mg, 40%yield) as a clear oil. HRMS $C_{16}H_{20}FN_2O_2$ $[M+H]^+$ expected mass: 291.1509; observed: 291.1509. ^1H NMR (400 MHz, $CDCl_3$) **δ** 7.25 (m, 1H), 7.00 (d, J =7.61, 1H), 6.90 (m, 2H), 6.53 (m, 1H), 6.32 (dd, J=16.97, 1.70, 1H), 5.74 (dd, J=10.56, 1.57, 1H), 3.55 (m, 8H), 2.99 (t, J= 7.40, 2H), 2.64 (t, J=7.40, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) **δ** 170.78, 165.74 + 164.02 (d, J=214.72), 162.06, 143.67, 130.19 + 130.12 (d, J=8.32), 129.00, 127.06, 124.28, 115.56 + 115.39 (d, J=21.09), 113.45 + 113.28 (d, J=21.09), 45.60, 45.25, 41.79, 41.44, 34.68, 31.13.



S1-10

S1-10 *N*-((1-(3-methoxyphenyl)-1*H*-pyrazol-4-yl)methyl)-*N*-methylacrylamide:

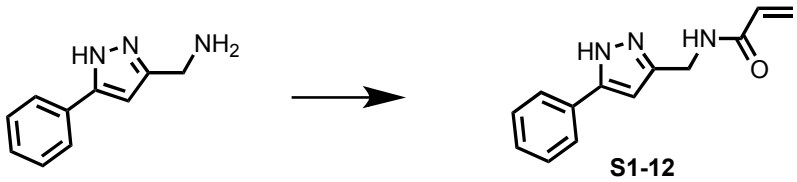
1-[1-(3-methoxyphenyl)-1H-pyrazol-4-yl]-N-methylmethanamine (57.6mg, 1 eq, 0.229mmol) was dissolved in 2mL acetonitrile. TEA (64uL, 2eq, 0.458mmol) was added at ambient temperature. The reaction was cooled to 0°C. Acryloyl chloride (20uL, 1.1 eq, 0.252mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (5-100% hexanes: ethyl acetate) to get the desired product (29.6mg, 48%yield) as a clear oil. HRMS $C_{15}H_{18}N_3O_2$ $[M+H]^+$ expected mass: 272.1399; observed: 272.1404. ^1H NMR (400 MHz, $CDCl_3$) **δ** 7.32 (t, J=8.06, 1H), 7.20 (d, J=8.06, 1H), 6.82 (d, J=8.06, 1H), 6.58 (dd, J=16.83, 10.27, 1H), 6.37 (dd, J=16.74, 1.78, 1H), 5.73 (dd, J=10.40, 1.68, 1H), 4.54 (s, 2H), 3.86 (s, 3H), 3.07 (s, 3H).



S1-11

S1-11 2-(4-acryloylpiperazin-1-yl)-*N*-(2,4-dimethylphenyl)acetamide:

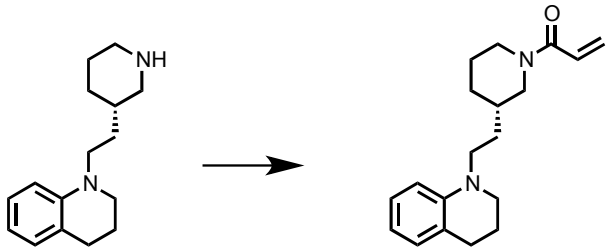
N-(2,4-dimethylphenyl)-2-piperazin-1-yl-acetamide (25mg, 1 eq, 0.10mmol) was dissolved in 2mL acetonitrile. TEA (28uL, 2eq, 0.20mmol) was added at ambient temperature. The reaction was cooled to 0°C. Acryloyl chloride (9uL, 1.1 eq, 0.11mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (0-15% dichloromethane: methanol) to get the desired product (9mg, 30% yield) a white solid. HRMS $C_{17}H_{24}N_3O_2$ $[M+H]^+$ expected mass: 302.1869; observed: 302.1874. ^1H NMR (400 MHz, $CDCl_3$) **δ** 9.06 (s, 1H) 7.94 (s, 1H), 7.06 (d, J=7.59, 1H), 6.88 (d, J=7.70, 1H), 6.56 (dd, J=17.09, 10.61, 1H), 6.31 (dd, J=17.05, 1.97, 1H), 5.73 (dd, J=10.68, 1.97, 1H), 3.76 (s, 2H), 3.65 (s, 2H), 3.22 (s, 2H), 2.68 (t, J=5.09, 4H), 2.33 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) **δ** 167.41, 165.65, 137.04, 135.43, 130.32, 128.66, 127.23, 125.49, 123.89, 121.77, 62.21, 53,73, 53.27, 46.04, 42.26, 21.39, 17.50



S1-12

S1-12 *N*-((5-phenyl-1*H*-pyrazol-3-yl)methyl)acrylamide:

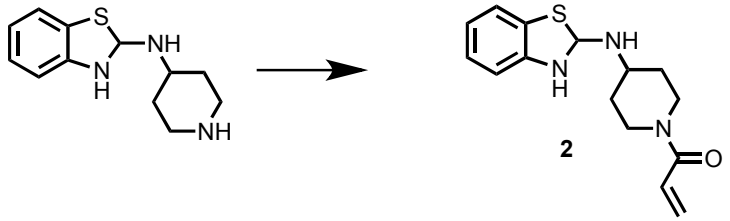
(3-phenyl-1*H*-pyrazol-5-yl)methanamine (50mg, 1eq, 0.287mmol) was dissolved in 2mL acetonitrile. TEA (80uL, 2eq, 0.574mmol) was added at ambient temperature. The reaction was cooled to 0°C. Acryloyl chloride (25uL, 1.1 eq, 0.316mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (0-15% dichloromethane: methanol) and RP-HPLC (35-70% gradient) to get the desired product (13mg, 20% yield) as a white powder. HRMS $C_{13}H_{14}N_3O$ $[M+H]^+$ expected mass: 228.1137; observed: 228.1145. ^1H NMR (400 MHz, MeOD) **δ** 7.69 (s, 2H), 7.41 (t, J=6.96, 2H), 7.32 (t, J=6.89, 1H), 6.57 (s, 1H), 6.28 (m, 2H), 5.69 (dd, J=7.84, 4.24, 1H), 4.50 (s, 2H).



S1-13

S1-13 (*S*)-1-(3-(2-(3,4-dihydroquinolin-1(2*H*)-yl)ethyl)piperidin-1-yl)prop-2-en-1-one:

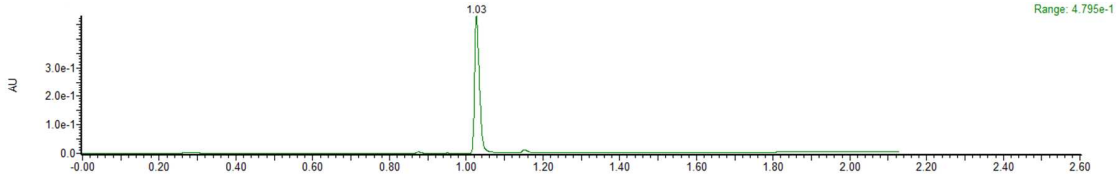
(*S*)-1-(2-(piperidin-3-yl)ethyl)-1,2,3,4-tetrahydroquinoline (63.8mg, 1 eq, 0.227mmol) was dissolved in 2mL acetonitrile. TEA (57uL, 2eq, 0.408mmol) was added at ambient temperature. The reaction was cooled to 0°C. Acryloyl chloride (18uL, 1 eq, 0.224 mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (5-95% hexanes: ethyl acetate), followed by RP-HPLC (45-95% gradient) to get the desired product (2.1mg, 3% yield) as an orange solid. HRMS $C_{19}H_{27}N_2O$ $[M+H]^+$ expected mass: 299.2123; observed: 299.2125. ^1H NMR (400 MHz, $CDCl_3$) **δ** 7.03 (m, 1H), 6.93 (m, 1H), 6.55 (m, 3H), 6.25 (d, J=16.94, 1H), 5.65 (t, J=9.53, 1H), 4.45 (dd, J=31.77, 12.64, 1H), 3.87 (d, J=12.64, 1H), 3.32 (t, J=6.24, 2H), 3.26 (m, 2H), 3.08 (t, J=12.11, 1H), 2.83 (t, J=12.96, 1H), 2.74 (t, J=6.24, 2H), 2.54 (t, J=10.80, 1H), 1.94 (m, 3H), 1.75 (d, J=13.57, 1H), 1.47 (m, 3H), 1.26 (m, 1H).



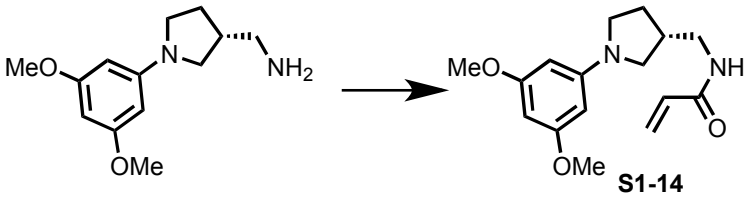
2

2 1-(4-(benzo[*d*]thiazol-2-ylamino)piperidin-1-yl)prop-2-en-1-one:

N-(piperidin-4-yl)benzo[*d*]thiazol-2-amine (58mg, 1 eq, 0.213 mmol) was dissolved in 2mL acetonitrile at ambient temperature. TEA (60uL, 2eq, 0.427mmol) was added at ambient temperature. The reaction was cooled to 0°C. Acryloyl chloride (19uL, 1.1 eq, 0.235mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (0-15% dichloromethane: methanol) to get the desired product (7mg, 11%yield) as a yellow oil.



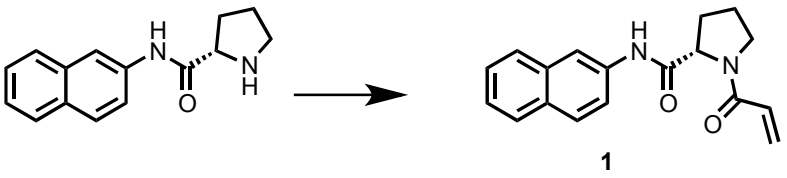
HRMS $C_{15}H_{18}N_3OS$ $[M+H]^+$ expected mass: 288.1171; observed: 288.1176. ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.58 (d, J=8.06, 1H), 7.54 (d, J=8.08, 1H), 7.30 (t, J=8.07, 1H), 7.10 (t, J=7.75, 1H), 5.17 (s, 1H), 4.58 (s, 1H), 4.00 (s, 2H), 3.27 (t, J=12.29, 1H), 2.97 (t, J=11.96, 1H), 2.23 (m, 2H), 1.63 (s, 2H), 1.49 (s, 2H)**.** ^{13}C NMR (500 MHz, $CDCl_3$) **δ** 165.63, 165.61, 152.44, 130.53, 128.25, 127.62, 126.16, 122.04, 120.94, 119.22, 52.16, 44.66, 41.02, 33.07, 32.08.



S1-14

S1-14 (*R*)-*N*-((1-(3,5-dimethoxyphenyl)pyrrolidin-3-yl)methyl)acrylamide:

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide(11mg, 1.4eq, 0.7mmol) was dissolved in 1mL dimethylformamide at ambient temperature. The reaction was cooled to 0°C. DIPEA (44uL, 5 eq, 0.25mmol), and then hydroxybenzotriazole (11mg, 1.4eq, 0.7mmol) was added. Acrylic acid (5uL, 1.4eq, 0.7mmol) was added to the reaction, and was stirred for 30 minutes. (R)-(1-(3,5-dimethoxyphenyl)pyrrolidin-3-yl)methanamine (12mg, 1 eq, 0.051mmol) was added at 0°C. The reaction was washed with 5mL saturated NaCl. The product was extracted with ethyl acetate (5mL x 3) and dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (5-100% hexanes: ethyl acetate) to get the desired product (2.3mg, 16% yield) as a yellow oil. MS $C_{16}H_{22}N_2O_3$ $[M+H]^+$ expected: 291.1703, observed: 291.1732. ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.30 (d, J=16.73, 1H), 6.09 (dd, J=16.54, 9.73, 1H), 5.89 (m, 1H), 5.74 (d, J=1.95, 2H), 5.67 (d, J=9.73, 1H), 3.78 (s, 6H), 3.40 (m, 4), 3.28 (m, 1H), 3.04 (m, 1H), 2.59 (m, 1H), 2.29 (m, 1H), 1.78 (m, 1H).

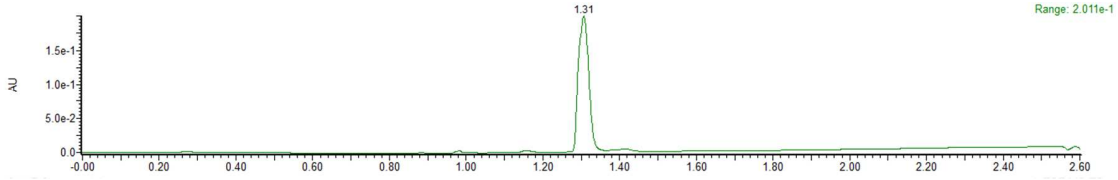


1

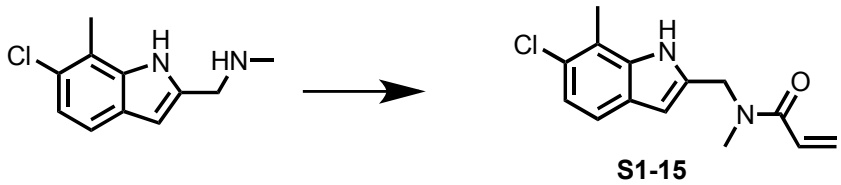
1 (1R)-2-acryloyl-*N*-(naphthalen-2-yl)cyclopentanecarboxamide:

L-Proline-2-naphthylamide hydrochloride (55.5mg, 1 eq, 0.20mmol) was dissolved in 2mL acetonitrile. TEA (58uL, 2eq, 0.414mmol) was added at ambient temperature. The reaction

was cooled to 0°C. Acryloyl chloride (19uL, 1.1 eq, 0.228mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (5-95% hexanes: ethyl acetate) to get the desired product (39.4mg, 67%yield) as a white, crystalline solid.



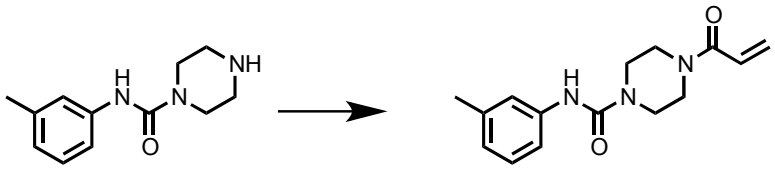
HRMS $C_{18}H_{18}N_2O_2Na$ $[M+Na]^+$ expected mass: 317.1266; observed: 317.1271. ^1H NMR (500MHz, $CDCl_3$) **δ** 10.02 (s, 1H), 8.23 (s, 1H), 7.73 (m, 3H), 7.45 (dd, J=8.82, 1.98, 1H), 7.41 (t, J=7.39, 1H), 7.35 (t, J=7.52, 1H), 6.52 (d, J=6.38, 2H), 5.82 (t, J=6.31, 1H), 4.94 (d, J=7.67, 1H), 3.72 (t, J=9.60, 1H), 3.57 (m, 1H), 2.66 (dd, J=12.48, 6.56, 1H), 2.22 (m, 1H), 2.09 (m, 1H), 1.88 (m, 1H). ^{13}C NMR (500MHz, $CDCl_3$) **δ** 169.06, 166.74, 135.92, 133.97, 130.57, 129.63, 128.62, 127.99, 127.74, 127.57, 126.37, 124.80, 120.21, 116.39, 60.99, 47.82, 26.54, 25.21.



S1-15

S1-15 *N*-((6-chloro-7-methyl-1*H*-indol-2-yl)methyl)-*N*-methylacrylamide:

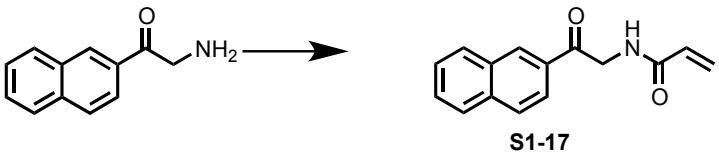
6-chloro-2-methyl-1H-indol-2-y methyl methylamine (50mg, 1eq, 0.24 mmol) was dissolved in 2mL acetonitrile. TEA was added (67uL, 2eq, 0.48mmol) was added at ambient temperature. The reaction was cooled to 0°C. Acryloyl chloride (21uL, 1.1 eq, 0.26mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (5-100% hexanes: ethyl acetate) to get the desired product (14.1mg, 22%yield), as an orange oil. HRMS $C_{14}H_{15}ClN_2ONa$ $[M+Na]^+$ expected mass: 285.0771; observed: 285.0776. ^1H NMR (400 MHz, $CDCl_3$) **δ** 7.31 (d, J=8.45, 1H) 7.08 (d, J=8.49, 1H) 6.57 (dd, J=16.73, 10.30, 1H), 6.41 (dd, J=16.73, 1.93, 1H), 6.38 (d, J = 2.11, 1H), 5.77 (dd, J=10.45, 1.83, 1H), 4.60 (s, 2H) 3.10 (s, 3H), 2.49 (s, 3H).



S1-16

S1-16 4-acryloyl-*N*-(*m*-tolyl)piperazine-1-carboxamide:

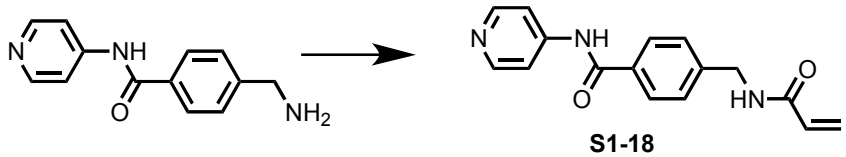
N-(*m*-tolyl)piperazine-1-carboxamide (35.6mg, 1 eq, 0.162 mmol) was dissolved in 2mL ACN. TEA was added (45uL, 2 eq, 0.324 mmol). The reaction was cooled to 0°C. Acryloyl chloride (13uL, 1 eq, 0.162 mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified twice by flash chromatography on silica gel (5-100% hexanes: ethyl acetate (to get the desired product (3.7mg, 8% yield) as a yellow powder. HRMS $C_{15}H_{20}N_3O_2$ $[M+H]^+$ expected mass: 274.1556; observed: 274.1563. ^{1}H NMR (500 MHz, $CDCl_3$) **δ** 7.21 (s, 1H), 7.18 (t, J=7.88, 1H), 7.11 (d, J=8.00, 1H), 6.88 (d, J=7.70, 1H), 6.57 (dd, J=16.79, 10.37, 1H), 6.35 (dd, J=16.85, 1.86), 6.34 (s, 1H), 5.76 (dd, J=10.53, 1.83, 1H), 3.64 (m, 8H), 2.33 (s, 3H)**.** ^{13}C NMR (500 MHz, $CDCl_3$) **δ** 167.72, 157.91, 140.58, 139.48, 129.47, 128.96, 128.76, 125.03, 122.82, 119.30, 46.70, 45.19, 44.93, 43.00, 21.55.



S1-17

S1-17 *N*-(2-(naphthalen-2-yl)-2-oxoethyl)acrylamide:

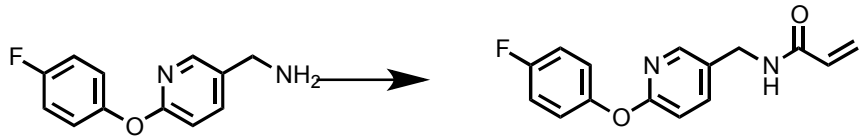
2-(naphthalen-2-yl)-2-oxoethanaminium chloride (25.3mg, 1 eq, 0.114 mmol) was dissolved in 2mL ACN. TEA was added (32uL, 2 eq, 0.228 mmol). The reaction was cooled to 0°C. Acryloyl chloride (9uL, 1 eq, 0.114 mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (5-100% hexanes: ethyl acetate), followed by RP-HPLC (25-90% gradient) to get the desired product (3.7mg, 14% yield) as a white solid. HRMS $C_{15}H_{14}NO_2$ $[M+H]^+$ expected mass: 240.1025; observed: 240.1029. ^{1}H NMR (500 MHz, $CDCl_3$) **δ** 8.80 (d, J=8.66, 1H), 8.08 (d, J=8.23, 1H), 8.04 (d, J=7.35, 1H), 7.90 (d, J=8.23, 1H), 7.65 (t, J=7.66, 1H), 7.58(t, J=7.58, 1H), 7.54 (d, J=7.66, 1H), 6.78 (s, 1H), 6.39 (dd, J=17.15,1.48, 1H), 6.29 (dd, J=17.02, 10.12, 1H), 5.75 (dd, J=10.18, 1.38, 1H). 4.91 (s, 2H).



S1-18

S1-18 4-(acrylamidomethyl)-*N*-(pyridin-4-yl)benzamide:

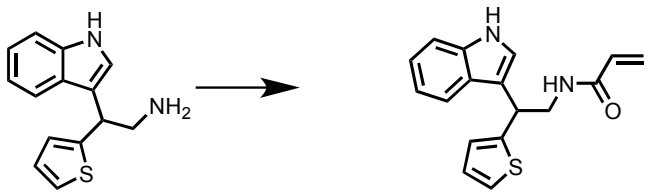
(4-(pyridin-4-ylcarbamoyl)phenyl)methanaminium chloride hydrochloride (25.6mg, 1 eq, 0.085 mmol) was dissolved in 2mL acetonitrile. TEA was added (75 uL, 6 eq, 0.51 mmol). The reaction was cooled to 0°C. Acryloyl chloride (7uL, 1 eq, 0.085mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (0-15% dichloromethane: methanol) followed by RP-HPLC with a gradient of 25-90% to get the desired product (1.1mg, 5% yield) as a white solid. HRMS $C_{16}H_{16}N_3O_2$ $[M+H]^+$ expected mass: 282.1243; observed: 282.1235. ^{1}H NMR (500MHz, CD_3OD) **δ** 8.44 (d, J = 6.3, 2H), 7.94(d, J=8.45, 2H), 7.84 (d, J=6.3, 2H), 6.32 (dd, J = 17.19, 9.16, 1H) 6.27 (dd, J = 17.19, 2.87, 1H), 5.71 (dd, J = 9.20, 2.83), 4.54 (s, 2H).



S1-19

S1-19 *N*-((6-(4-fluorophenoxy)pyridin-3-yl)methyl)acrylamide:

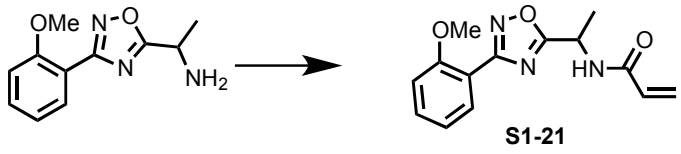
(6-(4-fluorophenoxy)pyridin-3-yl)methanamine hydrochloride (23.0mg, 1 eq, 0.105 mmol) was dissolved in 2mL ACN. TEA was added (29uL, 2 eq, 0.211 mmol). The reaction was cooled to 0°C. Acryloyl chloride (9uL, 1 eq, 0.105 mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (5-100% hexanes: ethyl acetate), followed by RP-HPLC (25-90% gradient) to get the desired product (0.8 mg, 3% yield), as an opaque oil. HRMS $C_{15}H_{14}FN_2O_2$ $[M+H]^+$ expected mass: 273.1039; observed: 273.1039. ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 8.09 (d, J=2.52, 1H), 7.69 (dd, J=8.47, 2.52, 1H), 6.89 (d, J=8.47), 7.08 (d, J=6.47, 4H), 6.33 (dd, J=16.99,1.20, 1H), 6.09 (dd, J=16.99, 10.26, 1H), 5.81 (s, 1H), 5.70 (dd, J=10.38, 1.21), 4.49 (s, 1H), 4.47 (s, 1H).



S1-20

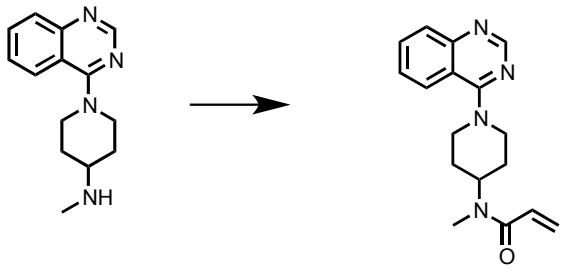
S1-20 *N*-(2-(1*H*-indol-3-yl)-2-(thiophen-2-yl)ethyl)acrylamide:

2-(1*H*-indol-3-yl)-2-(thiophen-2-yl)ethanamine (25.1mg, 1 eq, 0.104 mmol) was dissolved in 2mL ACN. TEA was added (30uL, 2 eq, 0.208 mmol). The reaction was cooled to 0°C. Acryloyl chloride (8uL, 1 eq, 0.104 mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (5-100% hexanes:EtOAC), followed by RP-HPLC (25-90% gradient) to get the desired product (4.7mg, 15**%** yield) as an opaque oil. HRMS $C_{17}H_{16}N_2OS$ $[M-H]^-$ expected mass: 295.0911, observed: 295.0901. ^1H NMR (500 MHz, $CDCl_3$) **δ** 7.57 (d, J=8, 1H), 7.38 (d, J=8.07, 1H), 7.21 (t, J=7.62, 1H), 7.18 (m, 1H), 7.13 (d, J=2.37, 1H), 7.09 (t, J=7.62, 1H), 6.96 (m, 2H), 4.77 (t, J= 7.22, 1H), 4.14 (m, 1H), 3.97 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) **δ** 165.63, 146.15, 136.59, 130.86, 126.95, 126.84, 126.53, 124.93, 124.22, 122.62, 122.04, 119.93, 119.57, 116.70, 111.43, 45.03, 38.29.



S1-21

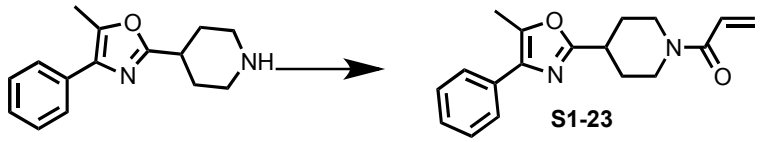
S1-21 *N*-(1-(3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-yl)ethyl)acrylamide:
1-[3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-yl]ethan-1-amine hydrochloride (26.8mg, 1 eq, 0.105 mmol) was dissolved in 2mL ACN. TEA was added (30uL, 2 eq, 0.21 mmol). The reaction was cooled to 0°C. Acryloyl chloride (9uL, 1 eq, 0.105 mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (5-100% hexanes:EtOAC), followed by RP-HPLC (25-90% gradient) to get the desired product (5.1mg, 20% yield), as an opaque oil. HRMS $C_{14}H_{16}N_3O_3$ $[M+H]^+$ expected mass: 274.1192; observed: 274.1198. ^1H NMR (500 MHz, $CDCl_3$) **δ** 7.97 (dd, J=7.68, 1.76, 1H), 7.49 (m, 1H), 7.07 (dd, 7.69, 14.81, 1H), 6.37 (dd, J=17.05, 1.05, 1H), 6.18 (dd, J=17.00, 10.38, 1H), 5.74 (J=10.35, 1.05, 1H), 5.59 (q, J=7.12, 1H), 3.97 (s, 3H), 1.68 (d, J=7.09, 3H).



S1-22

S1-22 *N*-methyl-*N*-(1-(quinazolin-4-yl)piperidin-4-yl)acrylamide:

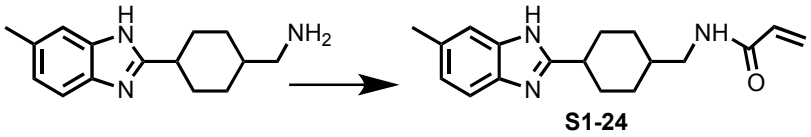
N-methyl-1-(quinazolin-4-yl)piperidin-4-amine (53.7mg, 1 eq, 0.222 mmol) was dissolved in 2mL ACN. TEA was added (62uL, 2 eq, 0.443 mmol). The reaction was cooled to 0°C. Acryloyl chloride (18uL, 1 eq, 0.222 mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (0-15% DCM:methanol), followed by RP-HPLC (25-55% gradient) to get the desired product (3.1mg, 5% yield), as an opaque oil. HRMS $C_{17}H_{21}N_4O$ $[M+H]^+$ expected mass: 297.1715; observed: 297.1717. ^1H NMR (500 MHz, MeOD) **δ** 8.59 (d, J=4.77, 1H), 8.48 (s, 1H), 8.06 (d, J=8.41, 1H), 7.82 (m, 1H), 7.57 (m, 1H), 6.90 (dd, 16.90, 10.90, 1H), 6.75 (dd, 16.88, 10.50, 1H), 6.23 (dd, J=16.91, 10.36, 1H), 5.76 (dd, 10.65, 19.7, 1H), 4.77 (m, 1H), 4.57 (m, 1H), 4.28 (m, 1H), 3.03 (s, 1H), 2.93 (s, 1H), 2.09 (m, 3H), 1.83 (m, 2H).



S1-23

S1-23 1-(4-(5-methyl-4-phenyloxazol-2-yl)piperidin-1-yl)prop-2-en-1-one:

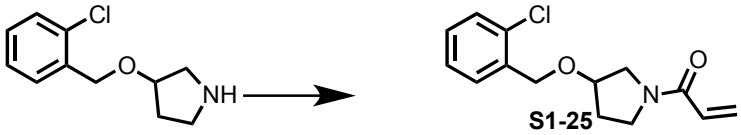
5-methyl-4-phenyl-2-(piperidin-4-yl)oxazole (27.0mg, 1eq, 0.111 mmol) was dissolved in 2mL CAN. TEA was added (31uL, 2eq, 0.223 mmol). The reaction was cooled to 0°C. Acryloyl chloride (9uL, 1 eq, 0.111 mmol) was added. The reaction was quenched with 5mL saturated $NaHCO_3$ and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), and dried over Na_2SO_4. The compound was purified by flash chromatography on silica gel (5-100% hexanes: ethyl acetate), followed by RP-HPLC (45-95% gradient) to get the desired product (3.1mg, 5% yield), as a white solid. HRMS $C_{18}H_{21}N_2O_2$ $[M+H]^+$ expected mass: 297.1603; observed: 297.1617. ^1H NMR (400 MHz, $CDCl_3$) **δ** 7.62 (d, J=8.06, 2H), 7.41 (t, J=7.52, 2H), 7.29 (t, J= 7.42, 1H), 6.60 (dd, J=16.87, 10.59, 1H), 6.28 (dd, J=16.82, 1.90, 1H), 5.70 (dd, J=10.56, 1.84, 1H), 3.12 (m, 1H), 3.08 (m, 2H), 2.50 (s, 3H), 2.13 (m, 2H), 1.89 (m, 2H), 1.65 (m, 2H).



S1-24

S1-24 *N*-((4-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)cyclohexyl)methyl)acrylamide:

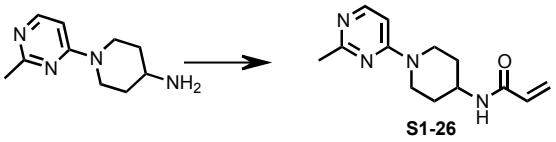
(4-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)cyclohexyl)methanamine (50.8mg, 1 eq, 0.209mmol) was dissolved in 2mL ACN. TEA was added (174uL, 6 eq, 1.254 mmol). The reaction was cooled to 0°C. Acryloyl chloride (17uL, 1 eq, 0.209 mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (0-15% hexanes:EtOAC), followed by RP-HPLC (5-95% gradient) to get the desired product (4.6mg, 7% yield), as a white solid. HRMS $C_{18}H_{24}N_3O$ $[M+H]^+$ expected mass: 298.1919; observed: 298.1925. ^1H NMR (500 MHz, MeOD) **δ** 7.39 (d, J=8.35, 1H), 7.31 (s, 1H), 7.07 (d, J=8.35, 1H), 6.27 (dd, J=17.05, 9.41, 1H), 6.22 (dd, J = 17.05, 2.68, 1H), 5.66 (dd, J=9.41, 2.64, 1H), 3.18 (d, J=6.80, 2H), 2.89 (m, 1H), 2.45 (s, 3H), 2.16 (d, J=13.01, 2H), 1.76 (d, J=13.01, 2H), 1.69 (m, 2H), 1.66 (m, 1H), 1.19 (d, 2H).



S1-25

S1-25 1-(3-((2-chlorobenzyl)oxy)pyrrolidin-1-yl)prop-2-en-1-one:

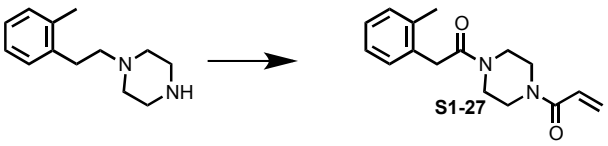
3[(2-chlorobenzyl)oxy]pyrrolidine hydrochloride (50.3mg, 1 eq, 0.203mmol) was dissolved in 2mL ACN. TEA was added (57uL, 2 eq, 0.405 mmol). The reaction was cooled to 0°C. Acryloyl chloride (16uL, 1 eq, 0.203 mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (5-100% hexanes:EtOAc), followed by RP-HPLC (45-95% gradient) to get the desired product (1.5mg, 3% yield), as an opaque oil. HRMS $C_{14}H_{17}ClNO_2$ $[M+H]^+$ expected mass: 266.0948; observed: 266.0959. ^1H NMR (500 MHz, MeOD, 1:1 rotamers) **δ** 7.48 (m, 1H), 7.38 (m, 1H), 7.29 (m, 2H), (6.63 + 6.58) (rotamers dd, J=16.83, 10.51, 1H), (6.27+6.26) (dd, rotamers, J=16.86, 1.88, 1H), (5.75+5.73) (rotamers, dd, J=10.46, 1.89, 1H), 4.65 (m, 2H), 4.32 (m, 1H), 3.75 (m, 2H), 3.68 (m, 1H), 3.56 (m, 1H), 2.14 (m, 2H).



S1-26

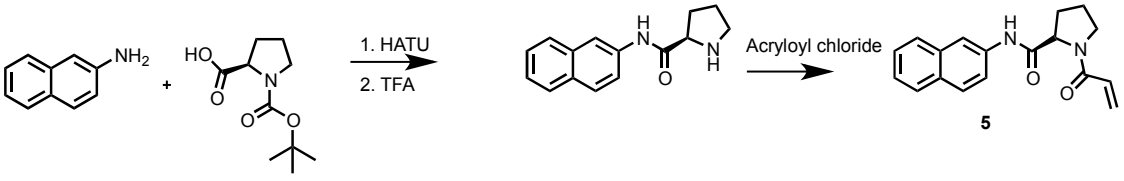
S1-26 *N*-(1-(2-methylpyrimidin-4-yl)piperidin-4-yl)acrylamide:

1-(2-methylpyrimidin-4-yl)piperidin-4-amine (34.1mg, 1 eq, 0.177mmol) was dissolved in 2mL ACN. TEA was added (50uL, 2 eq, 0.355 mmol). The reaction was cooled to 0°C. Acryloyl chloride (14uL, 1 eq, 0.177 mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by flash chromatography on silica gel (0-15% DCM:methanol), followed by RP-HPLC (20-55% gradient) to get the desired product (5.1mg, 12% yield), as a white solid. HRMS $C_{13}H_{19}N_4O$ $[M+H]^+$ expected mass: 247.1559; observed: 247.1561.^{1}H NMR (500 MHz, MeOD) **δ** 8.32 (s, 1H), 8.04 (d, J=7.15, 1H), 6.83 (d, J=7.14, 1H), 6.58 (dd, J=6.58, 5.52, 1H), 6.24 (m, 2H), 4.10 (m, 1H), 3.26 (m, 2H), 2.50 (s, 3H), 2.04 (m, 2H), 1.51 (m, 2H).



S1-27 1-(4-(2-(*o*-tolyl)acetyl)piperazin-1-yl)prop-2-en-1-one:

1-(piperazin-1-yl)-2-(*o*-tolyl)ethanone (67mg, 1 eq, 0.307mmol) was dissolved in 2mL ACN. TEA was added (86uL, 2 eq, 0.614 mmol). The reaction was cooled to 0°C. Acryloyl chloride (25uL, 1 eq, 0.307 mmol) was added. The reaction was quenched with 5mL saturated NaHCO3 and left stirring for 15 minutes at ambient temperature. The reaction was extracted with ethyl acetate (5mL x 3), dried over Na_2SO4. The compound was purified by RP-HPLC (5-95% gradient) to get the desired product 8.4mg, 10% yield), as an opaque oil. HRMS $C_{16}H_{21}N_2O_2$ $[M+H]^+$ expected mass: 273.1603; observed: 273.1608.^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.15 (m, 4H), 6.53 (m, 1H), 6.31 (d, J=16.75, 1H), 5.73 (d, J=9.76, 1H), 3.71 (s, 4H), 3.57 (s, 2H), 3.43 (s, 2H), 2.29 (s, 3H).

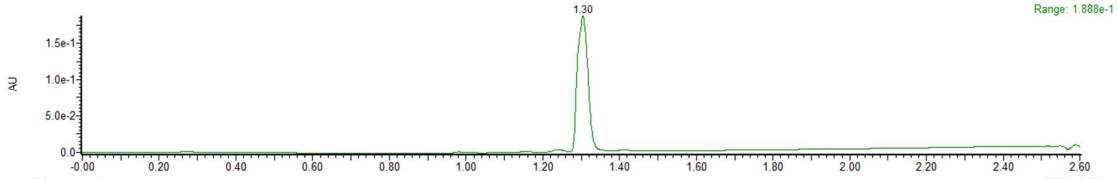


5 (*R*)-1-acryloyl-*N*-(naphthalen-2-yl)pyrrolidine-2-carboxamide:

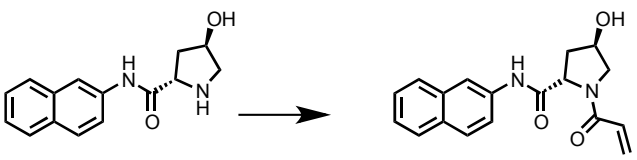
N-Boc-L-proline (100mg, 0.465 mmol, 1 eq) was dissolved in 1mL DMF and DIPEA (324uL, 4 eq, 1.86 mmol). The solution was cooled to 0°C and HATU (194mg, 0.511 mmol, 1.1 eq) was added. The reaction was stirred for 20 minutes followed by an addition of 2-amino-naphthalene (73mg, 0.511 mmol, 1.1eq). After 2-5 hours, the solution was diluted with 10mL brine and extracted with EtOAc (3x10mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The residue was purified by flash chromatography on silica gel (5-100%) EtoAC:hexanes to afford the desired product, (*R*)-*tert*-butyl 2-(naphthalen-2-ylcarbamoyl)pyrrolidine-1-carboxylate.

The product was dissolved in 2mL DCM. The mixture was cooled to 0°C and 1mL TFA was added. When the reaction was complete, the mixture was quenched using 5mL NaHCO3 and the product was extracted with 3x3mL DCM. The crude product, (*R*)-*N*-(naphthalen-2-yl)pyrrolidine-2-carboxamide, was used without further purification.

(*R*)-*N*-(naphthalen-2-yl)pyrrolidine-2-carboxamide (38.6 mg, 0.161 mmol, 1 eq) was dissolved in 2mL ACN to which TEA (45uL, 0.321 mmol, 2 eq) was added. The solution was cooled to 0°C upon which acryloyl chloride (14uL, 0.177 mmol, 1.1 eq) was added. After 30 minutes, the reaction was quenched with 5mL NaHCO3. The solution was left to stir for 15 minutes. The mixture was extracted with ethyl acetate (3x5mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (5-100%) hexanes: ethyl acetate to get the desired product (*R*)-1-acryloyl-*N*-(naphthalen-2-yl)pyrrolidine-2-carboxamide (14.6mg, 31% yield), as an opaque oil.



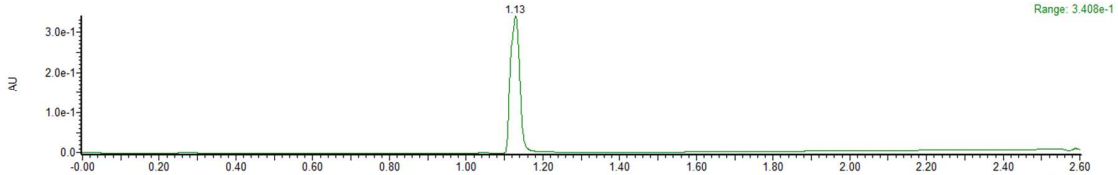
HRMS $C_{18}H_{18}N_2O_2Na$ $[M+Na]^+$ expected mass: 317.1266; observed: 317.1267. ^1H NMR (400 MHz, $CDCl_3$) **δ** 9.99 (s, 1H), 8.23 (s, 1H), 7.74 (m, 3H), 7.47 (dd, J=8.84, 2.12, 1H), 7.42 (t, J=6.82, 1H), 7.36 (t, J=7.44, 1H). 6.52 (J=6.10, 2H), 5.82 (t, J=6.10, 1H), 4.94 (d, J=7.82, 1H), 3.72 (m, 1H), 3.58 (m, 1H), 2.68 (dd, J=12.62, 6.50, 1H), 2.21 (m, 1H), 2.09 (m, 1H), 1.86 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) **δ** 169.01, 166.81, 135.92, 134.00, 130.60, 129.68, 128.66, 127.98, 127.76, 127.60, 126.42, 124.84, 120.24, 116.42, 60.99, 47.84, 26.46, 25.23.



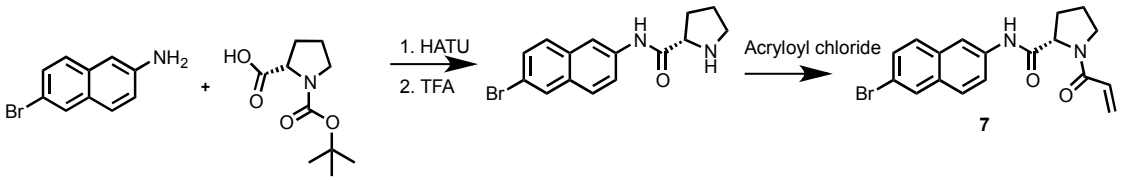
6

6 (2*S*,4*R*)-1-acryloyl-4-hydroxy-*N*-(naphthalen-2-yl)pyrrolidine-2-carboxamide:

4-hydroxy-*N*-(naphthalen-2-yl)pyrrolidine-2-carboxamide (50mg, 1 eq, 0.195 mmol) was dissolved in 4mL mixture of 1:1 ACN:DMF. TEA (164uL, 1.170 mmol, 6 eq) was added. The solution was cooled to 0°C upon which acryloyl chloride (17uL, 0.215 mmol, 1.1 eq) was added. After 30 minutes, the reaction was quenched with 5mL NaHCO3. The solution was left to stir for 15 minutes. The mixture was extracted with ethyl acetate (3x5mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (5-100%) hexanes: ethyl acetate to get the desired product (2*S*,4*R*)-1-acryloyl-4-hydroxy-*N*-(naphthalen-2-yl)pyrrolidine-2-carboxamide (10.5mg, 17% yield), as a white solid. MS



HRMS $C_{18}H_{18}N_2O_3Na$ $[M+Na]^+$ expected mass: 333.1215; observed: 333.1219. ^1H NMR (400 MHz, $(CD_3)_2SO$, 9:1 rotamers) **δ** (10.28+10.41) (s, 1H), 8.29 (s, 1H), 7.83 (m, 3H), 7.59 (d, J=8.85, 1H), 7.46 (t, J=6.76, 1H), 7.39 (t, 6.90, 1H), (6.63 + 6.36) (dd, J=16.67, 10.05, 1H), 6.13 (J=16.62, 2.08, 1H), (5.71 + 5.64) (J=10.15, 2.28, 1H), 5.20 (d, J=3.56, 1H), (4.62 + 4.76) (t, J=7.93, 1H), (4.43 + 4.35) (s, 1H), 3.76 (dd, J=10.69, 4.49, 1H), 3.58 (d, J=10.69, 1H), 2.16 (m, 1H), 1.99 (m, 1H). ^{13}C NMR (500 MHz, MeOD) **δ** 172.94, 167.25, 137.18, 135.21, 132.19, 129.87, 129.52, 128.88, 128.59, 127.46, 126.05, 121.29, 121.13, 118.06, 71.22, 61.38, 56.94, 39.18.

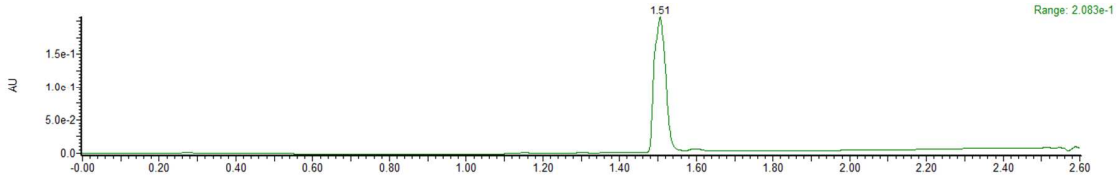


7 (*S*)-1-acryloyl-*N*-(6-bromonaphthalen-2-yl)pyrrolidine-2-carboxamide:

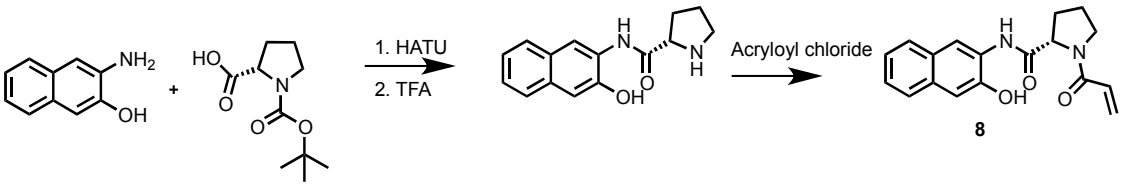
N-Boc-L-proline (100mg, 0.465 mmol, 1 eq) was dissolved in 1mL DMF. The solution was cooled to 0°C and HATU (582mg, 1.533 mmol, 3.3 eq) was added. The reaction was stirred for 15 minutes followed by an addition of 2-amino-6-bromo-naphthalene (114mg, 0.511 mmol, 1.1eq). After 6 hours, the solution was diluted with 10mL brine and extracted with EtOAc (3x10mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The residue was purified by flash chromatography on silica gel (5-100%) EtoAC:hexanes to afford the desired product, (2*S*,4*R*)-*tert*-butyl-2-((6-bromonaphthalen-2-yl)carbamoyl)-4-hydroxypyrrolidine-1-carboxylate, (217mg, yield quantitative).

The product was dissolved in 2mL DCM. The mixture was cooled to 0°C and 1mL TFA was added. When the reaction was complete, the mixture was quenched using 5mL NaHCO3 and the product was extracted with 3x3mL DCM. The crude product, (*S*)-*N*-(6-bromonaphthalen-2-yl)pyrrolidine-2-carboxamide was used without further purification.

(*S*)-*N*-(6-bromonaphthalen-2-yl)pyrrolidine-2-carboxamide (83.8 mg, 0.263 mmol, 1 eq) was dissolved in 2mL ACN to which TEA (73uL, 0.525 mmol, 2 eq) was added. The solution was cooled to 0°C upon which acryloyl chloride (8uL, 0.104 mmol, 1.1 eq) was added. After 30 minutes, the reaction was quenched with 5mL NaHCO3. The solution was left to stir for 15 minutes. The mixture was extracted with ethyl acetate (3x5mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (5-100%) hexanes: ethyl acetate, followed by RP-HPLC gradient of 5-95% to afford the desired product (*S*)-1-acryloyl-*N*-(6-bromonaphthalen-2-yl)pyrrolidine-2-carboxamide (14.2mg, 14%yield), as an opaque oil.



^{1}H NMR (400 MHz, $CDCl_3$). HRMS $C_{18}H_{18}BrN_2O_2$ $[M+H]^+$ expected mass: 373.0552; observed: 373.0553. **δ** 10.10 (s, 1H), 8.20 (s, 1H), 7.86 (s, 1H), 7.61 (d, J=8.78, 1H), 7.56 (d, J=8.78, 1H), 7.44 (m, 2H), 6.52 (dd, J=6.03, 1.41, 2H), 5.83 (dd, J=6.71, 5.44, 1H), 4.94 (d, J=7.68, 1H), 3.73 (m, 1H), 3.60 (m, 1H), 2.64 (m, 1H), 2.23 (m, 1H), 2.10 (m, 1H), 1.90 (m, 1H) ^{13}C NMR (400 MHz, $CDCl_3$) **δ** 169.23, 166.75, 136.38, 132.42, 131.52, 129.74, 129.70, 129.59, 129.38, 127.97, 127.70, 121.18, 118.54, 116.22, 61.04, 47.89, 26.64, 25.24.



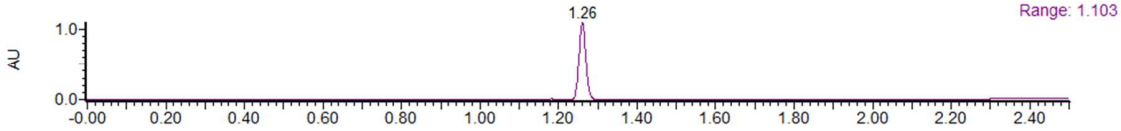
8

8 ((*S*)-1-acryloyl-*N*-(3-hydroxynaphthalen-2-yl)pyrrolidine-2-carboxamide:

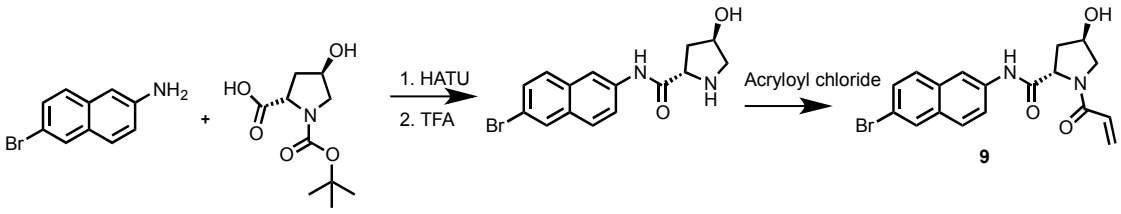
N-Boc-L-proline (100mg, 0.465 mmol, 1 eq) was dissolved in 1mL DMF. The solution was cooled to 0°C and HATU (194mg, 0.511 mmol, 1.1 eq) was added. The reaction was stirred for 15 minutes followed by an addition of 3-amino-2-naphthol (81mg, 0.511 mmol, 1.1eq). After 12-18 hours, the solution was diluted with 10mL brine and extracted with EtOAc (3x10mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The residue was purified by flash chromatography on silica gel (5-100%) hexanes: ethyl acetate to afford the desired product, (*S*)-*tert*-butyl 2-((3-hydroxynaphthalen-2-yl)carbamoyl)pyrrolidine-1-carboxylate, (27.3mg, 19% yield).

The product was dissolved in 2mL DCM. The mixture was cooled to 0°C and 1mL TFA was added. When the reaction was complete, the mixture was quenched using 5mL NaHCO3 and the product was extracted with 3x3mL DCM. The crude product, ((*S*)-*N*-(3-hydroxynaphthalen-2-yl)pyrrolidine-2-carboxamide, was used without further purification.

(*S*)-*N*-(3-hydroxynaphthalen-2-yl)pyrrolidine-2-carboxamide (24.3 mg, 0.095 mmol, 1 eq) was dissolved in 3mL ACN to which TEA (80uL, 0.570 mmol, 6 eq) was added. The solution was cooled to 0°C upon which acryloyl chloride (8uL, 0.104 mmol, 1.1 eq) was added. After 30 minutes, the reaction was quenched with 5mL NaHCO3. The solution was left to stir for 15 minutes. The mixture was extracted with ethyl acetate (3x5mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (5-100%) hexanes: ethyl acetate, followed by RP-HPLC gradient of 5-95% to afford the desired product ((*S*)-1-acryloyl-*N*-(3-hydroxynaphthalen-2-yl)pyrrolidine-2-carboxamide (1.7mg, 6% yield), as a white powder.



HRMS $C_{18}H_{18}N_2O_3Na$ $[M+Na]^+$ expected mass: 333.1215; observed: 333.1223. ^1H NMR (400 MHz, $CDCl_3$) **δ** 10.21 (s, 1H), 7.83 (s, 1H), 7.65 (d, J=7.99, 1H), 7.63 (d, J=7.99, 1H), 7.32 (m, 3H), 6.54 (d, J=5.93, 2H), 5.85 (t, J=5.92, 1H), 5.02 (d, J=7.51, 1H), 3.76 (t, J=9.13, 1H), 3.63 (q, J=9.06, 1H), 2.66 (q, J=6.21, 1H), 2.24 (m, 1H), 2.13 (m, 1H), 1.95 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) **δ** 170.47, 167.06, 147.27, 132.54, 130.28, 128.60, 127.75, 127.72, 127.29, 126.17, 125.14, 124.06, 119.90, 113.32, 60.72, 47.92, 26.77, 25.28.

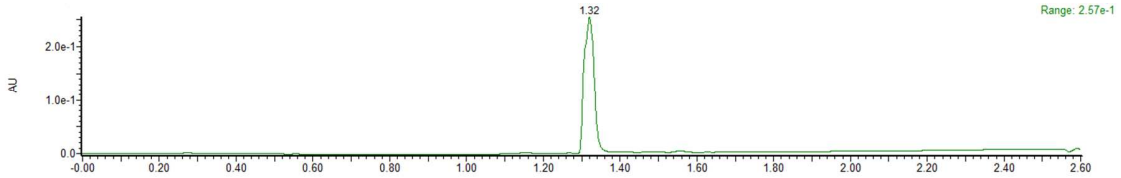


9 (2*S*,4*R*)-1-acryloyl-*N*-(6-bromonaphthalen-2-yl)-4-hydroxypyrrolidine-2-carboxamide:

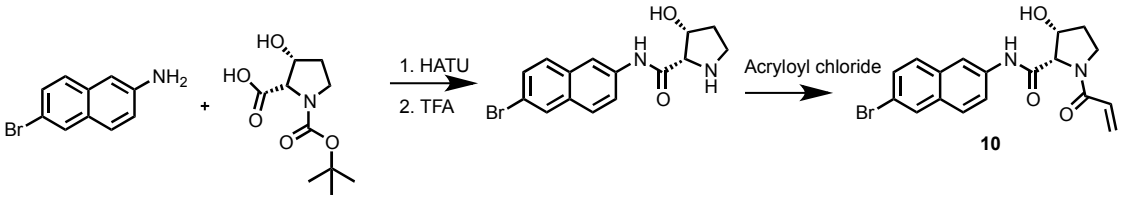
Trans-N-(tert-Butoxycarbonyl)-4-hydroxy-L-proline (100mg, 0.433 mmol, 1 eq) was dissolved in 1mL DMF. The solution was cooled to 0°C and HATU (329mg, 0.865mmol, 2 eq) was added. The reaction was stirred for 15 minutes followed by an addition of 2-amino-6-bromo-naphthalene (106mg, 0.476 mmol, 1.1eq). DMAP (5mg, 0.0433mmol, 0.1 eq) was added. After heating the solution to 50°C for 6 hours, the solution was diluted with 10mL brine and extracted with ethyl acetate (3x10mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The residue was purified by flash chromatography on silica gel (5-100%) hexanes: ethyl acetate to afford the desired product, (2*S*,4*R*)-*tert*-butyl 2-((6-bromonaphthalen-2-yl)carbamoyl)-4-hydroxypyrrolidine-1-carboxylate (199.8mg, yield quantitative).

The product was dissolved in 2mL DCM. The mixture was cooled to 0°C and 1mL TFA was added. After 5 hours, the solvent and excess TFA was removed *in vacuo* with 3x 5mL toluene. The crude product, (2*S*,4*R*)-*tert*-butyl 2-((6-bromonaphthalen-2-yl)carbamoyl)-4-hydroxypyrrolidine-1-carboxylate, was used without further purification.

(2*S*,4*R*)-*tert*-butyl 2-((6-bromonaphthalen-2-yl)carbamoyl)-4-hydroxypyrrolidine-1-carboxylate (37.3 mg, 0.086 mmol, 1 eq) was dissolved in 2mL ACN to which TEA (24uL, 0.172 mmol, 2 eq) was added. The solution was cooled to 0°C upon which acryloyl chloride (8uL, 0.094 mmol, 1.1 eq) was added. After 30 minutes, the reaction was quenched with 5mL NaHCO3. The solution was left to stir for 15 minutes. The mixture was extracted with ethyl acetate (3x5mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (5-90%) hexanes: ethyl acetate to afford the desired product (2*S*,4*R*)-1-acryloyl-*N*-(6-bromonaphthalen-2-yl)-4-hydroxypyrrolidine-2-carboxamide (8.7mg, 26% yield), as a white powder.



HRMS $C_{18}H_{17}BrN_2O_3Na$ $[M+Na]^+$ expected mass: 411.032; observed: 411.0333. ^1H NMR (400 MHz, $(CD_3)_2SO$, 4:1 rotamers) δ (10.36+10.48) (s, 1H), 8.32 (s, 1H), 8.12 (s, 1H), 7.86 (d, J=8.77, 1H), 7.77 (d, J=8.77, 1H), 7.63 (dd, J=8.86, 2.05, 1H), 7.57 (dd, J=8.81, 1.98, 1H), (6.63+6.35) (dd, J=16.73,10.30, 1H), 6.13 (dd, J=16.77, 2.05, 1H), (5.71 + 5.64) (dd, J=10.38, 2.16, 1H), (5.20 + 5.14) (d, J=3.38, 1H), (4.61+4.78) (t, J=7.94, 1H), (4.43 + 4.34) (s, 1H), 3.76 (dd, J=10.77, 4.23, 1H), 3.58 (d, J=10.94, 1H), 2.15 (m, 1H), 1.99 (m, 1H). ^{13}C NMR (500 MHz, $(CD_3)_2SO$) **δ** 170.87, 163.66, 137.25, 136.70, 131.95, 130.80, 129.52, 129.41, 129.32, 127.65, 127.38, 120.99, 117.24, 115.06, 68.92, 59.45, 55.40, 37.99.



10

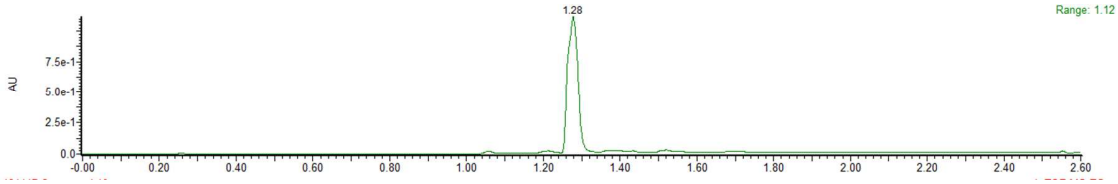
10 (2*S*,3*R*)-1-acryloyl-*N*-(6-bromonaphthalen-2-yl)-3-hydroxypyrrolidine-2-carboxamide:

N-boc-cis-3-hydroxy-L-proline (57mg, 0.248 mmol, 1.1eq) was dissolved in 2mL pyridine. The solution was cooled to 0°C and HATU (171mg, 2 eq, 0.450mmol) was added. The reaction was stirred for 15 minutes followed by an addition of 2-amino-6-bromo-naphthalene (50mg, 0.225 mmol, 1eq). After heating the solution to 70°C in a reflux condenser for 2.5 hours, the solution was diluted with 10mL brine and extracted with ethyl acetate (3x10mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The residue was purified by flash chromatography on silica

gel (5-100%) hexanes: ethyl acetate to afford the desired product(2*S*,3*R*)-*tert*-butyl 2-((6-bromonaphthalen-2-yl)carbamoyl)-3-hydroxypyrrolidine- 1-carboxylate (60.5mg, 62% yield).

The product was dissolved in 2mL DCM. The mixture was cooled to 0°C and 1mL TFA was added. After 5 hours, the solvent and excess TFA was removed *in vacuo* with 3x 5mL toluene. The crude product, (2*S*,3*R*)-*N*-(6-bromonaphthalen-2-yl)-3-hydroxypyrrolidine-2-carboxamide, was used without further purification.

(2*S*,3*R*)-*N*-(6-bromonaphthalen-2-yl)-3-hydroxypyrrolidine-2-carboxamide (53.2 mg, 0.159 mmol, 1 eq) was dissolved in 2mL ACN to which TEA (44uL, 0.318 mmol, 2 eq) was added. The solution was cooled to 0°C upon which acryloyl chloride (13uL, 0.159 mmol, 1 eq) was added. After 30 minutes, the reaction was quenched with 5mL NaHCO3. The solution was left to stir for 15 minutes. The mixture was extracted with EtOAc (3x5mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (5-100%) EtoAC:hexanes, followed by (0-15%) dichloromethane: methanol, to afford the desired product, (2*S*,3*R*)-1-acryloyl-*N*-(6-bromonaphthalen-2-yl)-3-hydroxypyrrolidine-2-carboxamide (6.6mg, 11% yield), as a white powder.



HRMS $C_{18}H_{17}BrN_2O_3Na$ $[M+Na]^+$ expected mass: 411.032; observed: 411.0328. ^{1}H NMR (400 MHz, MeOD, 75:25 rotamers) **δ** 8.25 (s, 1H), 7.99 (s, 1H), 7.76 (dd, J=9.85, 9.10, 1H), 7.69 (d, J=8.55, 1H), 7.65 (dd, J=8.55, 2.01, 1H), 7.53 (m, 1H), (6.68+6.43) (dd, J=16.93, 10.49, 1H), 6.28 (J=16.84,1.90, 1H), (5.78+5.71) (dd, J=10.51, 1.90, 1H), 4.70 (m, 1H), 4.67 (m, 1H), 3.96 (m, 1H), 3.74 (m, 2H), 2.21 (m, 1H). ^{13}C NMR (500 MHz, MeOD, 75:25 rotamers) **δ** 170.00, 167.25, 137.93, 133.70, 133.04, (130.70+130.64), (130.60+130.58), (130.45+130.50), 129.47, 128.80, 128.59, (122.64+122.46), 119.40, 117.90, (71.88+73.55), (66.03+66.21), (46.47+45.57), (34.04+31.83).

11 and **12** were synthesized and characterized as described in Ostrem *et al.*[4]

Acrylamide library (N=62) synthesis is described in Bateman *et al* and Roberts *et al*.[39,40]

References

(39) Bateman, L. A.; Nguyen, T. B.; Roberts, A. M.; Miyamoto, D. K.; Ku, W.-M.; Huffman, T. R.; Petri, Y.; Heslin, M. J.; Contreras, C. M.; Skibola, C. F.; Olzmann, J. A.; Nomura, D. K. Chemoproteomics-Enabled Covalent Ligand Screen Reveals a Cysteine Hotspot in Reticulon 4 That Impairs ER Morphology and Cancer Pathogenicity. *Chem. Commun. (Camb.)* **2017**.

(40) Roberts, A. M.; Miyamoto, D. K.; Huffman, T. R.; Bateman, L. A.; Ives, A. N.; Akopian, D.; Heslin, M. J.; Contreras, C. M.; Rape, M.; Skibola, C. F.; Nomura, D. K. Chemoproteomic Screening of Covalent Ligands Reveals UBA5 as a Novel Pancreatic Cancer Target. *ACS Chem. Biol.* **2017**, *12* (4), 899–904.