

SUPPORTING INFORMATION

Fragment Hotspot Mapping to Identify Selectivity- Determining Regions between Related Proteins

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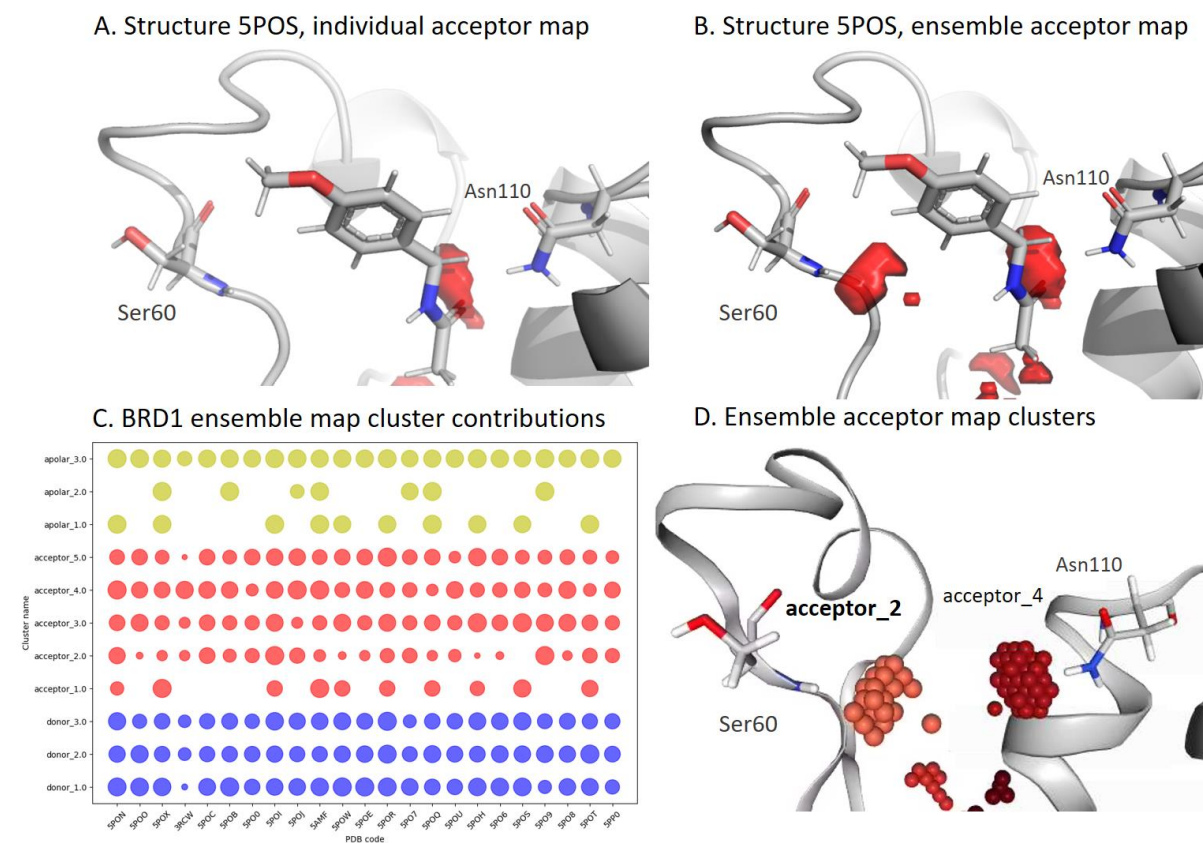


Figure S1: Ensemble maps identify binding site interactions that could be missed by focusing on a single structure. A. Shown as a red surface is the acceptor hotspot map for BRD1 structure 5PO1 at a threshold of 5 hotspot units. The ligand, Ser 60, and the bromodomain asparagine Asn110 are shown as sticks. This map identifies the acceptor hotspot arising from the asparagine, but not the additional selective hotspot that corresponds to the serine. B. The ensemble acceptor map (threshold 5) identifies the selective feature next to Ser60. C. To track which structures contribute to a particular feature, the ensemble maps were clustered using the HDBSCAN algorithm, as detailed in the Methods section. The number of points each hotspot map contributes to the ensemble clusters was then plotted as shown. Contributions are

represented by circles coloured by probe type. The radius of the circle is proportional to the number of grid points shared between the individual hotspot map and the ensemble map. D. Acceptor_2 corresponds to the Ser60 hotspot cluster. The plot in section C shows that structure 5POS does not contribute any points toward it, as expected.

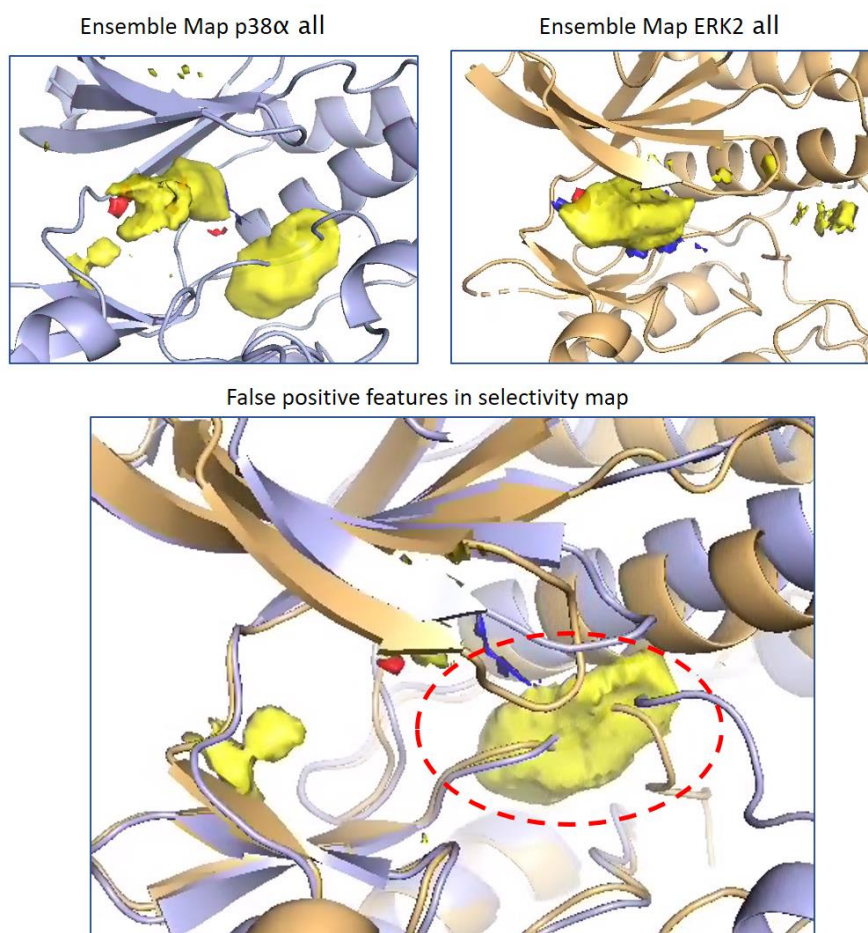


Figure S2: Rationale on not including mutually exclusive conformations in the ensemble maps. Shown above are ensemble maps calculated for the p38 α and ERK2 kinases without restricting the conformation of the DFG motif. In the case of p38 α , over 20 % of structures present an open conformation, whereas the ERK2 ensemble consisted almost exclusively of DFG-in structures. The resulting selectivity maps show an area of false positive propensity, resulting from the imbalance of classes in the two ensembles.

Table S1: SIENA Query parameters. All parameters not included were kept at their default values.

SIENA Parameter	Value
siteRadius	6.5
fragment_length	10
flexibility_sensitivity	0.6
fragment_distance	4
minimalSiteIdentity	1
resolution	2.5
complete_residues_only	True

Table S2: KLIFS query parameters

KLIFS parameter	Value
Species	Human
Resolution cutoff	2.5 Å
KLIFS quality cutoff	7.0
DFG conformation	IN
G-rich loop angle	All
αC-helix conformation	All

Table S3. Structures used in the case study examples

Target	Family	PDB code	Chain	Resolution (Å)	Ligand (Da)	MW
BRD1	Bromodomain	3RCW	C	2.21	99.13	
BRD1	Bromodomain	5AMF	A	1.75	194.23	
BRD1	Bromodomain	5PO0	A	1.46	164.16	
BRD1	Bromodomain	5PO6	A	1.61	238.08	
BRD1	Bromodomain	5PO7	A	1.50	236.23	
BRD1	Bromodomain	5PO8	A	1.50	176.21	
BRD1	Bromodomain	5PO9	A	2.12	241.21	
BRD1	Bromodomain	5POB	A	1.78	177.20	
BRD1	Bromodomain	5POC	A	1.48	283.08	
BRD1	Bromodomain	5POE	A	1.52	174.20	
BRD1	Bromodomain	5POH	A	1.61	178.23	
BRD1	Bromodomain	5POI	A	2.37	137.14	
BRD1	Bromodomain	5POJ	A	1.62	232.32	
BRD1	Bromodomain	5PON	A	1.52	205.26	
BRD1	Bromodomain	5POO	A	1.50	230.27	
BRD1	Bromodomain	5POQ	A	1.97	206.26	
BRD1	Bromodomain	5POR	A	1.58	142.16	
BRD1	Bromodomain	5POS	A	1.75	179.22	
BRD1	Bromodomain	5POT	A	1.63	183.63	
BRD1	Bromodomain	5POU	B	1.43	247.34	
BRD1	Bromodomain	5POW	A	1.77	150.18	
BRD1	Bromodomain	5POX	A	1.75	194.23	
BRD1	Bromodomain	5PP0	B	1.61	151.17	
BRPF1	Bromodomain	5C85	A	1.70	225.04	
BRPF1	Bromodomain	5C87	A	1.55	145.16	


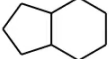
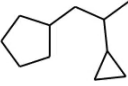
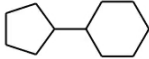
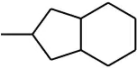


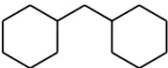




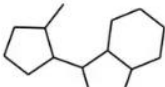
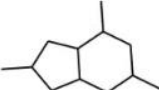



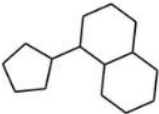

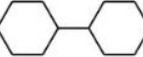
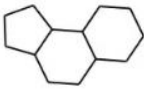
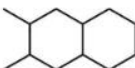
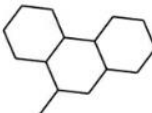
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BRPF1	Bromodomain	5DY7	A	1.69	216.16
BRPF1	Bromodomain	5DYA	A	1.65	220.22
BRPF1	Bromodomain	5DYC	A	1.65	225.04
BRPF1	Bromodomain	5E3D	A	1.71	200.24
BRPF1	Bromodomain	5E3G	A	1.65	184.18
BRPF1	Bromodomain	5EM3	A	1.40	145.16
BRPF1	Bromodomain	5EPR	A	1.65	162.19
BRPF1	Bromodomain	5EPS	A	1.47	160.17
BRPF1	Bromodomain	5EQ1	A	1.55	189.24
BRPF1	Bromodomain	5ETB	A	1.33	173.21
BRPF1	Bromodomain	5ETD	A	1.40	159.18
BRPF1	Bromodomain	5EV9	A	1.45	252.27
BRPF1	Bromodomain	5EVA	A	1.45	237.21
BRPF1	Bromodomain	5EWC	A	1.75	234.25
BRPF1	Bromodomain	5EWD	A	1.58	155.20
BRPF1	Bromodomain	5EWH	A	1.63	145.16
BRPF1	Bromodomain	5EWV	A	1.67	197.24
BRPF1	Bromodomain	5EWW	A	1.73	257.33
BRPF1	Bromodomain	5T4U	A	1.50	159.18
BRPF1	Bromodomain	5O4T	A	1.50	190.20
BRPF1	Bromodomain	5OWB	A	1.65	164.16
BRPF1	Bromodomain	5OWE	A	1.70	228.20
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ERK2	Kinase	6G91	A	1.80	213.66
ERK2	Kinase	5BUI	A	2.12	294.33
ERK2	Kinase	5BUJ	A	1.85	293.32


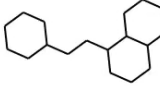
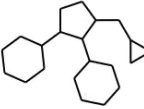
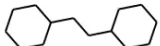
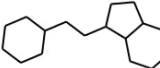
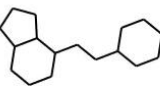
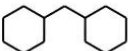
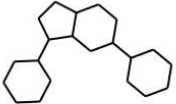
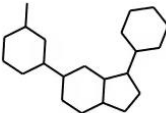
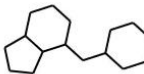
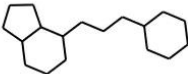

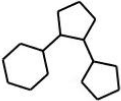
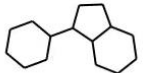
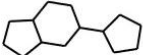

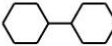

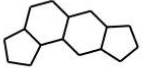
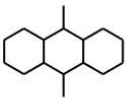
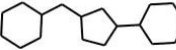
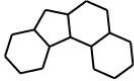

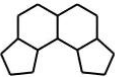
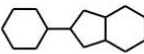
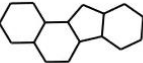
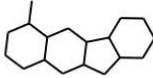
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ERK2	Kinase	4QP8	B	2.45	262.27
ERK2	Kinase	6QAG	A	2.07	138.13
ERK2	Kinase	2OJG	A	2.00	280.32
ERK2	Kinase	6QA3	A	1.57	136.15
ERK2	Kinase	4G6N	A	2.00	232.71
ERK2	Kinase	6Q7T	A	1.60	168.15
ERK2	Kinase	6Q7K	A	1.84	83.09
ERK2	Kinase	6QAW	A	1.84	232.30
ERK2	Kinase	4QP7	B	2.25	185.19
ERK2	Kinase	4QP2	A	2.23	168.58
p38a	Kinase	1WBO	A	2.16	128.56
p38a	Kinase	1WBW	A	2.41	250.29
p38a	Kinase	1BL6	A	2.50	293.34
p38a	Kinase	1W7H	A	2.21	200.24
p38a	Kinase	1W84	A	2.20	222.28
CK2a	Kinase	5CT0	B	2.01	276.78
CK2a	Kinase	6Q4Q	B	1.45	121.11
CK2a	Kinase	5MOH	A	1.38	181.17
CK2a	Kinase	6HOP	A	1.55	192.21
CK2a	Kinase	3MB6	A	1.75	294.22
CK2a	Kinase	3WAR	A	1.04	122.10
CK2a	Kinase	3Q9Y	A	1.80	272.21
CK2a	Kinase	6YPJ	A	1.64	295.34
CK2a	Kinase	5MO7	A	2.15	289.78
CK2a	Kinase	3AXW	A	2.50	220.23

CK2a	Kinase	3OWL	A	2.10	282.72
CK2a	Kinase	6HNW	A	2.00	268.22
CK2a	Kinase	3MB7	A	1.65	294.22
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CK2a	Kinase	5CSP	A	1.50	151.14
CK2a	Kinase	6QY7	A	2.10	271.24
CK2a	Kinase	6HOU	A	1.80	152.15
CK2a	Kinase	5MMF	A	1.99	260.78
CK2a	Kinase	5MOT	A	2.09	274.27
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CK2a	Kinase	5MOW	A	1.86	188.03
CK2a	Kinase	3OWK	A	1.80	282.72
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CK2a	Kinase	6HOT	A	1.50	178.18
CK2a	Kinase	3BQC	A	1.50	270.24
CK2a	Kinase	3WIK	A	2.00	264.26
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PIM1	Kinase	5KGD	A	1.98	195.22
PIM1	Kinase	5KGE	A	2.23	228.08
PIM1	Kinase	1YXX	A	2.00	238.24
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PIM1	Kinase	5N4N	A	2.09	204.25

PIM1	Kinase	5N5L	A	1.97	239.05
PIM1	Kinase	5N4Z	A	2.26	162.18
PIM1	Kinase	4LL5	A	2.00	297.35
PIM1	Kinase	5KGI	A	2.13	207.08
PIM1	Kinase	2XIZ	A	2.21	148.14
PIM1	Kinase	3C4E	D	1.98	209.25
PIM1	Kinase	3R00	A	2.10	240.03
PIM1	Kinase	3VBX	A	2.03	241.04
PIM1	Kinase	5DHJ	A	2.46	210.23
PIM1	Kinase	5KGG	A	1.95	195.67
PIM1	Kinase	5NDT	A	1.99	159.16
PIM1	Kinase	4MTA	A	2.20	201.20
PIM1	Kinase	5N50	A	1.92	216.69
PIM1	Kinase	5N4V	A	1.85	247.29
PIM1	Kinase	3UIX	A	2.20	295.36
PIM1	Kinase	3VBV	A	2.08	188.18
PIM1	Kinase	1YXV	A	2.00	191.18
PIM1	Kinase	3VC4	A	2.23	273.23
PIM1	Kinase	5N4U	A	2.20	232.26
PIM1	Kinase	2XIX	A	2.40	99.09
PIM1	Kinase	3VBY	A	2.27	211.22
PIM1	Kinase	3JYA	A	2.10	271.12

Table S4. Number of unique Murcko scaffolds

Target	Number structures	Number unique scaffolds	Unique Murcko Scaffolds
BRD1	23	9	 3RCW  5AMF  5PO0  5PO6  5PO7  5PO8  5POH  5POJ  5POR
BRPF1	26	14	 5C85  5C87  5C89  5D7X  5E3D  5EM3  5EQ1  5ETB  5EV9  5EVA  5EWD  5EWW  5O4T  5OWE

p38 α	5	5	<div>  1W80  1WBW  1BL6  1W7H </div> <div>  1W84 </div>
ERK2	19	11	<div>  4QP1  6C9I  5BUI  5BUJ </div> <div>  4QP4  4QP3  6QAG  2OJG </div> <div>  4G6N  4QP7  4QP2 </div>
CK2 α	28	11	<div>  5CT0  6Q4Q  3MB6  3Q9Y </div> <div>  6YPJ  3OWL  6HNV  3MB7 </div> <div>  6QY7  3OWK  3OWJ </div>

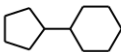
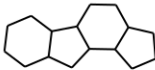
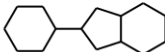
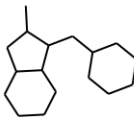
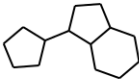


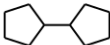
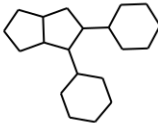
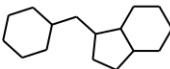
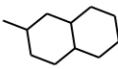
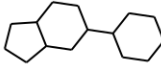
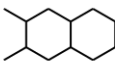
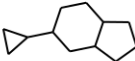
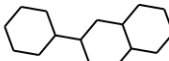
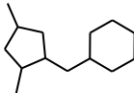
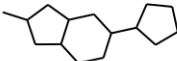
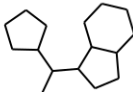
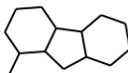
PIM1	32	19	<div>  3VBT </div> <div>  3JPV </div> <div>  5KGD </div> <div>  1YXX </div> <div>  4MBI </div> <div>  5N4R </div> <div>  5N4X </div> <div>  5N4N </div> <div>  4LL5 </div> <div>  3C4E </div> <div>  3VBX </div> <div>  5DHJ </div> <div>  5NDT </div> <div>  5N4V </div> <div>  3UIX </div> <div>  3VC4 </div> <div>  5N4U </div> <div>  3VBY </div> <div>  3JYA </div>
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Table S5. KLIFS DFG motif annotation of the p38 α and ERK2 structures in the Supplementary Figure 2 ensembles.

Target	In	Out	Out-like
p38 α	1W84, 1WBO, 1BL6, 1WBW, 1W7H, 2I0H, 1M7Q, 3ZYA, 3E92, 3S3I, 1OVE, 3U8W, 1YQJ, 1A9U, 1BL7, 4KIQ, 3RIN, 3GFE, 2YIX, 3BX5, 3ITZ, 2ZB0, 3GC7, 1OUK, 3NWW, 4KIP, 1ZZ2, 6ZQS, 1ZZL, 4KIN, 5XYY, 1BMK, 2BAL, 1OUY, 3FKL	6SFJ, 3UVR, 1WBT, 1W82, 1WBV, 1W83, 3HV5, 1WBN, 1WBS, 5MZ3, 3NNV, 3NNW, 3D83, 6SFI, 3NNU, 3KQ7, 3GCU	3QUD, 3OEF, 3BV2
ERK2	5BUE, 6GJD, 4FV7, 5NHL, 6QA3, 5LCK, 6G9D, 6G97, 2Y9Q, 4QP9, 4QP8, 6GDQ, 4FV5, 4ZZM, 6GE0, 6QAW, 5BUI, 4FV1, 6QAG, 6G93, 3I60, 4FV2, 4QP2, 4QP7, 5BVD, 5NHP, 4FV3, 5BVF, 4FUX, 6Q7T, 6G91, 5BUJ, 4ZZN, 6G9N, 4QTA, 6G92, 4FV6, 4QP4, 4FV8, 5V62, 4G6N, 6RQ4, 6G9M, 6Q7S, 4O6E, 1WZY, 5BVE, 2OJG, 5NHJ, 5NHO, 4QTE, 6G54, 3I5Z, 5K4I, 6SLG, 5NHF, 6GJB, 5LCJ, 5V60, 6G8X, 4ZZO, 6G9K, 6Q7K, 2OJJ, 6G9H, 6G9A, 4FV9, 5NHH, 5NHV	-	-

Table S6. Ensemble PDB codes for the maps shown in Figure 6

Target	PDB
BRD1	5POJ, 5PO7, 5POO, 5PP0, 5POQ, 5POH, 3RCW, 5POW, 5PON, 5POT, 5POB, 5PO9, 5POR, 5PO6, 5POU, 5AMF, 5POE, 5PO8, 5PO0, 5POS, 5POC, 5POX, 5POI
BRPF1	5OWE, 5EQ1, 5ETD, 5OWB, 5EV9, 5D7X, 5ETB, 5C89, 5EPR, 5E3D, 5EWC, 5EWW, 5EPS, 5EWV, 5T4U, 5O4T, 5EWH, 5C85, 5DY7, 5EM3, 5DYC, 5DYA, 5E3G, ensemble, 5EWD, 5EVA, 5C87
BRD7	4XY8, 5MKY, 4UIV, 5F25, 6Y7J, 5EU1, 6V0S, 5E9V, 4UIT, 5F1L, 6YQW, 4Z6H, 6V0X, 4YYG, 4YYK, 5I7Y, 6HM0, 6Y7L, 5IGM, 4YYI, 6V1B, 5F1H, 6Y7H, 4UIW, 4YYJ, 6BQA, 5IGN, 4Z6I, 6Y7I, 5F2P, 6Y7K, 4YYH, 6V14, 4NQN, 4UIU
BRD2	7NQ8, 6E6J, 5EK9, 7NQJ, 5N2L, 4UYG, 5IG6, 6DBC, 5U6V, 6MOA, 7NQI, 6K04, 5DW1, 6VIY, 6DDJ, 6I81, 2DVV, 5UEW, 6FFE, 3ONI, 4MR5, 5XHK, 4J1P, 7JX7, 6FFF, 5BT5
BRD4	4LZS, 4HXS, 6G0H, 4ZW1, 5D3R, 5F63, 4QR4, 5WMA, 5COI, 5Z9K, 6FT4, 5KU3, 5Z5T, 6CJ2, 6VUF, 5M39, 5V67, 5EGU, 6DJC, 4X2I, 6LIH, 5EI4, 6LG5, 4XY9, 4CL9, 5XI4, 3U5K, 6CKR, 6FO5, 6VUB, 5Z1R, 6G0G, 6HOV, 4NUD, 5D25, 6S6K, 4C67, 5D26, 6SAH, 4UIZ, 6JJ5, 4BW4, 4E96, 6AJZ, 5YQX, 5AD3, 4A9L, 5LRQ, 3U5L, 4WHW, 6C7R, 6X7B, 4LYS, 5ACY, 4PCI, 6VIW, 5Z8Z, 3SVG, 4XYA, 5A85, 6XV7, 5TI3, 5D24, 5WUU, 4O70, 5MLI, 5Z5V, 5Y8Y, 5Z90, 6SA3, 5FBX, 3ZYU, 4BW2, 3SVF, 6KEJ, 5CS8, 5H21, 4HBY, 5Y1Y, 5KJ0, 6CD4, 5CFW, 5WMD, 6G0R, 5TI5, 4O75, 4QR5, 6G0P, 5TI4, 5Y8W, 6SAJ, 6V1K, 4MEN, 5CY9, 6FT3, 5D3S, 5OWM, 5Z1T, 6XVC, 6XUZ, 3MUK, 5DW2, 4MR4, 6DML, 5DLX, 4O7F, 4KV1, 5KDH, 6AJY, 6FSY, 6Q3Y, 5I80, 6UWX, 4QB3, 6VIZ, 5UVW, 4F3I, 4YH4, 5TI6, 6LG4, 6UWU, 6YIN, 7AJN, 5OVB, 6YQN, 5D3T, 3MXF, 4BW3, 5NND, 6AFR, 6X7D, 5N2M, 5CRZ, 4DON, 6CZV, 3P5O, 6YQO, 4PS5, 6LG6, 6DL2, 4NUE, 6E4A, 6HDQ, 4C66, 5Y8C, 5Y8Z, 4WIV, 5VOM, 4UYD, 6CZU, 6KEE, 6KEF, 5TI2, 5YOV, 4BW1, 4MEQ, 4O78, 5DX4, 5F62, 5KHM, 5VZS, 5YOU, 6RWJ, 5LJ2, 6KEG, 3UVX, 4HXX, 4O7B, 4QR3, 5A5S, 5D0C, 5D3H, 6P05, 4UIY, 4Z1S, 6DMJ, 4O71, 5WA5, 6I7X, 6MH1, 6LG8, 5E0R, 5EIS, 6MAU, 4NUC, 5D3P, 5WMG, 3JVK, 6V0U, 6S4B, 6XV3, 7KHL, 4LR6, 5HLS, 4IOO, 4LRG, 4GPJ, 5DLZ, 6I7Y, 4ZC9, 4NQM, 5D3N, 5CP5, 6FNX, 6Q3Z, 6LG7, 6JI4, 2YEL, 5ULA, 4O77, 5HQ5, 4O7A, 6YQZ, 4MEP, 6JJ6, 4HXP, 6SB8, 4BJX, 4MR3, 5BT4, 5LUU, 5XHY, 6KEI, 5IGK, 4PCE, 5HQ7, 4HBX, 4IOQ, 4HXM, 6KEH, 6CKS, 5D3J, 4YH3, 4O74, 5MKZ, 5HCL, 4HBV, 4J3I, 5F5Z, 5M3A, 4CFL, 5U28, 5W55, 4MEO, 4NR8, 5XI3, 6G0F, 4J0R, 6MH7, 6CIS, 6G0D, 6UVM, 4UIX, 6LG9, 5Y94, 6JI3, 6V1U, 6WGX, 5HM0, 5Z1S, 3U5J, 4LYW, 5CPE, 6WW8, 4O72, 5Z8G, 6CD5, 6JI5, 5TI7, 6PS9, 5Z5U, 6V1L, 6CIY, 4HBW, 6PRT, 6YQP, 5CRM, 6JJB, 4O7C, 6G0E, 4CLB, 5AD2, 5D3L, 5F60, 4HXL, 5I88, 5OWW, 5Y93, 6KEK, 6UVJ, 5U2E, 6KEC, 5O97, 6S25, 4HXN, 4HXR, 5CQT, 6VUC, 5LJ1, 6ULV, 3MUL, 6JJ3, 4HXO, 5F61, 6LIM, 5HQ6
BRD9	6V16, 5MQ1, 6V17, 6V1E, 6V1H, 6V0Q

Table S7. Structural data for the compounds shown in Figure 6

PDB identifier	ChEMBL identifier	PDB structures	Smiles
5XE	CHEMBL3770173	5FG6, 5FG4	<chem>COc1cc2c(cc1NS(=O)(=O)c1ccc(Br)cc1C)n(C)c(=O)n2C</chem>
9F9	CHEMBL1522313	4UYE	<chem>COc1ccccc1C(=O)Nc1cc2c(cc1N1CCCC1)n(C)c(=O)n2C</chem>
8VI	CHEMBL3827932	5G4S	<chem>CCN(C(=O)c1ccccc1OC)c1cc2c(cc1N1CCNC[C@H]1C)n(C)c(=O)n2C</chem>
LF1	CHEMBL3828191	5G4R	<chem>COc1ccccc1C(=O)Nc1cc2c(cc1N1CCNC[C@H]1C)n(C)c(=O)n2C</chem>
LS8	CHEMBL3752151	5MYG	<chem>COc1cc(C#N)ccc1S(=O)(=O)Nc1ccc2c(c1)cc(C)c(=O)n2C</chem>
8LW	CHEMBL4098824	5N49	<chem>Cc1cc2c(cc1N1C(=O)c3cccc4cccc(c34)C1=O)n(C)c(=O)n2C</chem>
N48	CHEMBL4096095	5T4V	<chem>COc1cc2c(cc1NS(=O)(=O)c1ccc(C#N)cc1)c(C)cc(=O)n2C</chem>
5XF	CHEMBL3356143	5FG5	<chem>COc1ccccc1C(=O)Nc1cc2c(cc1N1CCCC1)n(C)c(=O)n2C</chem>