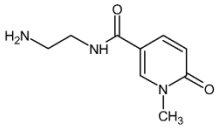
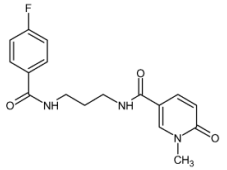
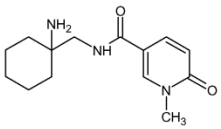
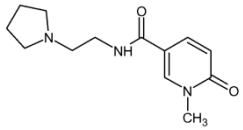
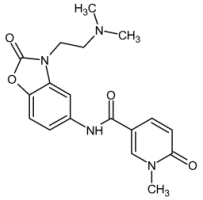
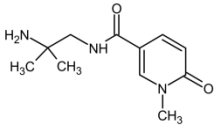
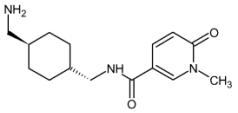
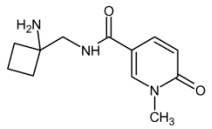
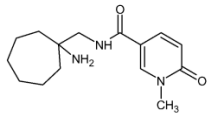
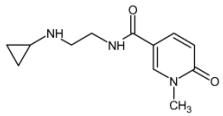
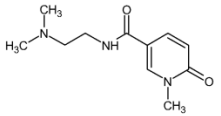
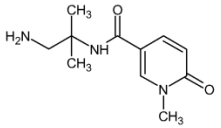
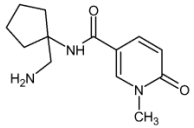
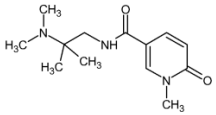
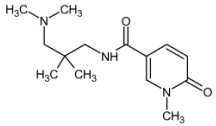
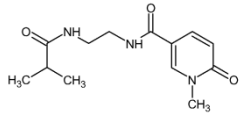
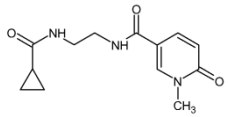
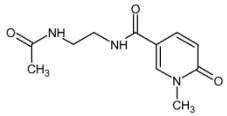
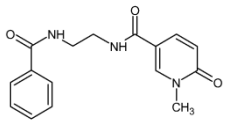
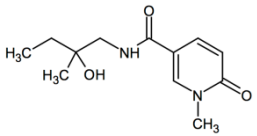
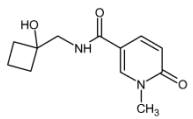
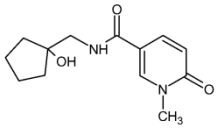
Table S1. Binding activity to BAZ2A for the 1-methylpyridinone compounds

Compound	Structure	% Ctrl[a]	K_D[b] (μM)
1		60	> 400
2		72	110
3		84	-
4		86	-
5		30	17
9		44	> 300
10		76	-

11		72	400
12		98	-
13		96	-
14		96	-
15		86	-
16		66	> 400
17		100	-
18		94	-

19		100	-
20		94	-
21		82	-
22		88	-
23		78	-
24		94	-
25		80	-

Dashes indicate data not acquired; [a]Residual binding of BAZ2A to the H3K(Ac)14 peptide at 0.5 mM compound concentration measured by AlphaScreen; [b] Determined by BROMOscan.

Table S2. Data Collection and Refinement Statistics for BAZ2A structures

	BAZ2A/cmp**1**	BAZ2A/cmp**2**	BAZ2A/cmp**3**	BAZ2A/cmp**4**	BAZ2A/cmp**5**	BAZ2A/cmp**6**	BAZ2A/cmp**7**	BAZ2A/cmp**8**
Data Collection								
Space group	$P3_121$	$P3_121$	$P3_121$	$P3_121$	$C222_1$	$P3_121$	$P3_121$	$P3_121$
Unit-cell parameters (Å)	a = 95.00 b = 95.00 c = 32.82	a = 95.34 b = 95.34 c = 32.55	a = 94.79 b = 94.79 c = 32.78	a = 94.83 b = 94.83 c = 32.74	a = 55.41 b = 62.57 c = 69.39	a = 95.28 b = 95.28 c = 33.04	a = 95.26 b = 95.26 c = 32.46	a = 95.18 b = 95.18 c = 33.13
Wavelength (Å)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Resolution (Å)	47.50-2.40 (2.49-2.40)	47.67-2.80 (2.95-2.80)	47.39-2.50 (2.60-2.50)	47.41-2.72 (2.86-2.72)	41.48-1.10 (1.12-1.10)	47.64-2.10 (2.16-2.10)	47.63-2.55 (2.66-2.55)	47.59-2.10 (2.16-2.10)
R_{merge} (%)	19.5 (129.4)	33.5 (108.1)	10.6 (135.4)	17.6 (139.4)	4.0 (37.5)	14.6 (120.8)	18.1 (124.8)	17.9 (106.0)
R_{meas} (%)	20.6 (136.1)	36.3 (117.7)	11.2 (143.5)	18.4 (146.2)	4.2 (40.0)	15.4 (127.0)	19.1 (131.6)	18.8 (110.9)
R_{pim} (%)	6.5 (42.0)	13.8 (45.7)	3.5 (47.0)	5.5 (43.6)	1.2 (13.6)	4.9 (39.0)	6.1 (41.6)	5.7 (32.5)
$\langle I/\sigma(I)\rangle$	10.0 (2.1)	4.9 (1.8)	15.8 (1.9)	11.4 (1.9)	30.5 (4.8)	13.2 (2.6)	9.8 (2.0)	12.5 (2.8)
$CC^{1/2}$	0.997 (0.859)	0.969 (0.588)	0.999 (0.875)	0.998 (0.853)	1.000 (0.953)	0.997 (0.783)	0.996 (0.736)	0.996 (0.769)
Completeness (%)	100.0 (100.0)	100.0 (100.0)	100.0 (100.0)	100.0 (100.0)	99.8 (96.3)	99.9 (100.0)	100.0 (100.0)	99.9 (100.0)
Multiplicity	9.9 (10.3)	6.7 (6.4)	10.1 (9.2)	11.1 (10.9)	12.3 (8.3)	9.8 (10.4)	9.7 (9.8)	10.9 (11.4)
Refinement								
Resolution (Å)	41.14-2.40	41.29-2.80	47.39-2.50	47.41-2.72	41.48-1.10	41.26-2.10	41.25-2.55	41.22-2.10
R_{work}/R_{free} (%)	21.8/24.6	21.9/25.6	22.8/26.6	22.2-25.3	14.7/15.5	18.9/21.5	21.1/24.1	19.1/22.4
R.m.s. deviations								
Bond lengths (Å)	0.003	0.003	0.005	0.002	0.007	0.006	0.003	0.007
Bond angles (°)	0.5	0.6	0.6	0.4	1.0	0.8	0.6	0.8
PDB entry	6FG6	6FGF	6FGV	6FGW	6FGG	6FGH	6FGI	6FGL

Values in parenthesis refer to the highest resolution shell

Table S3. Data Collection and Refinement Statistics for BAZ2B structures

	BAZ2B/cmp**1**	BAZ2B/cmp**2**	BAZ2B/cmp**3**	BAZ2B/cmp**4**
Data Collection				
Space group	$C222_1$	$C222_1$	$C222_1$	$C222_1$
Unit-cell parameters (Å)	a = 79.74, b = 96.00, c = 57.72	a = 79.57, b = 96.39, c = 57.95	a = 81.61, b = 95.97, c = 57.69	a = 82.63, b = 96.16, c = 57.85
Wavelength (Å)	1.00	1.00	1.00	1.00
Resolution (Å)	48.00-2.08 (2.15-2.08)	48.20-2.10 (2.16-2.10)	42.29-2.00 (2.05-2.00)	42.51-2.05 (2.11-2.05)
R_{merge} (%)	4.5 (46.1)	6.3 (39.1)	6.1 (42.0)	10.5 (82.1)
R_{meas} (%)	5.1 (49.6)	7.1 (43.9)	6.6 (45.1)	11.4 (88.7)
R_{pim} (%)	1.9 (17.5)	2.6 (15.6)	2.4 (16.2)	4.3 (33.2)
$\langle I/\sigma(I)\rangle$	20.7 (4.1)	15.2 (4.4)	17.2 (3.5)	11.6 (2.3)
$CC^{1/2}$	1.000 (0.966)	0.999 (0.958)	0.999 (0.983)	0.998 (0.915)
Completeness (%)	61.9 (33.5), spherical 94.8 (94.8), ellipsoidal	72.4 (42.5), spherical 95.1 (97.7), ellipsoidal	99.8 (100)	99.9 (99.9)
Multiplicity	7.4 (7.9)	7.3 (7.8)	7.0 (7.5)	6.9 (7.0)
Refinement				
Resolution (Å)	48.00-2.08	48.20-2.10	40.81-2.00	41.32-2.05
R_{work}/R_{free} (%)	21.0/24.6	19.7/23.3	21.4/23.9	21.5/24.8
R.m.s. deviations				
Bond lengths (Å)	0.003	0.007	0.006	0.007
Bond angles (°)	0.6	0.9	0.8	0.8
PDB entry	6FH6	6FH7	6FGT	6FGU

Valiues in parenthesis refer to the highest resolution shell

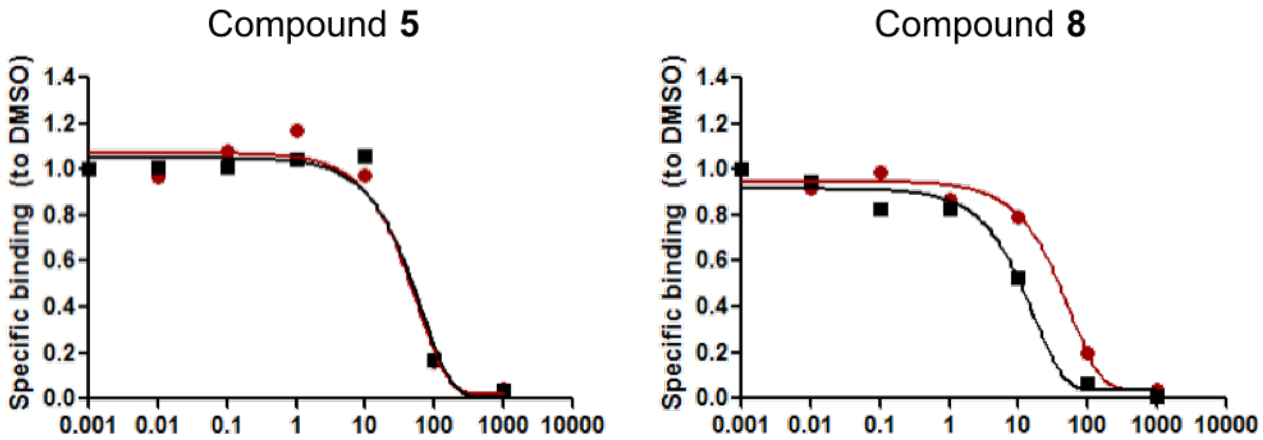


Figure S1. AlphaScreen competition binding assay for compounds **5** (left) and **8** (right). Data points and curves are shown in red for BAZ2A and black for BAZ2B. The specific binding to the acetylated peptide relative to the control DMSO (y-axis) is plotted against the corresponding compound concentration in μM in log10 scale (x-axis).

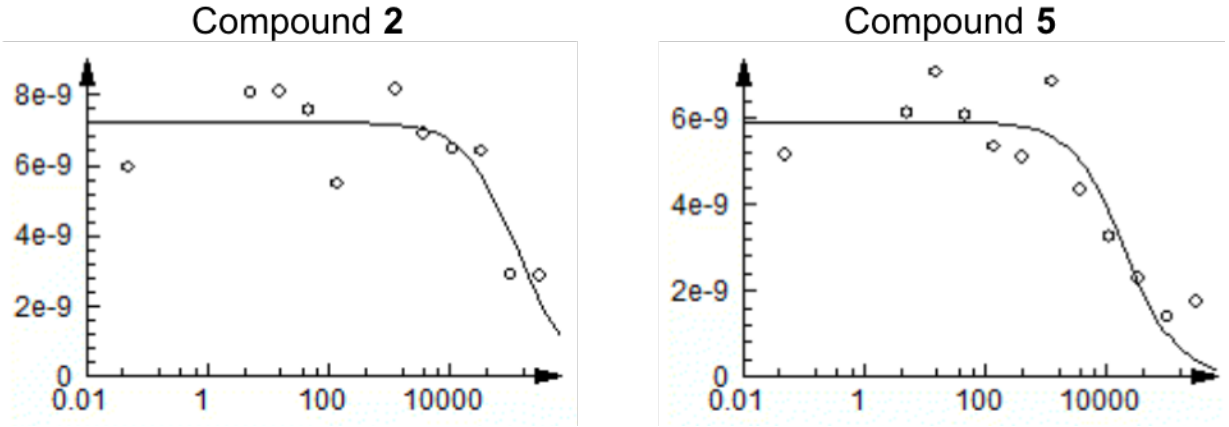


Figure S2. BromoScan competition assay for compounds **2** (left) and **5** (right) binding to BAZ2A, performed at DiscoverX. The amount of bromodomain measured by qPCR (Signal; y-axis) is plotted against the corresponding compound concentration in nM in log10 scale (x-axis).

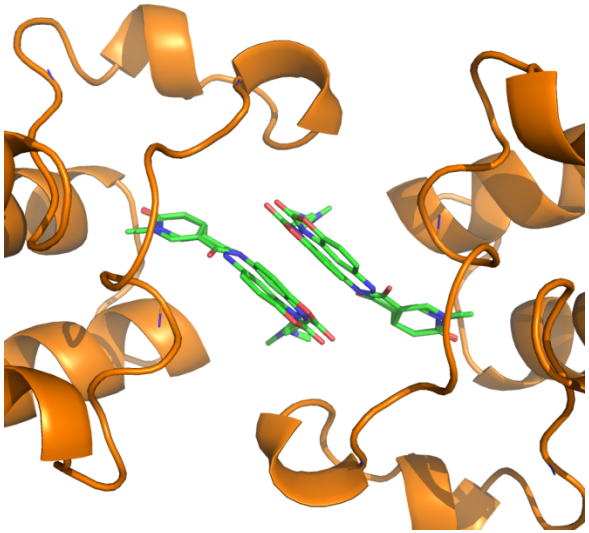


Figure S3. Orthorhombic crystallographic packing in BAZ2A (orange) induced by stacking of compound **5** (green) from neighboring protein chains.

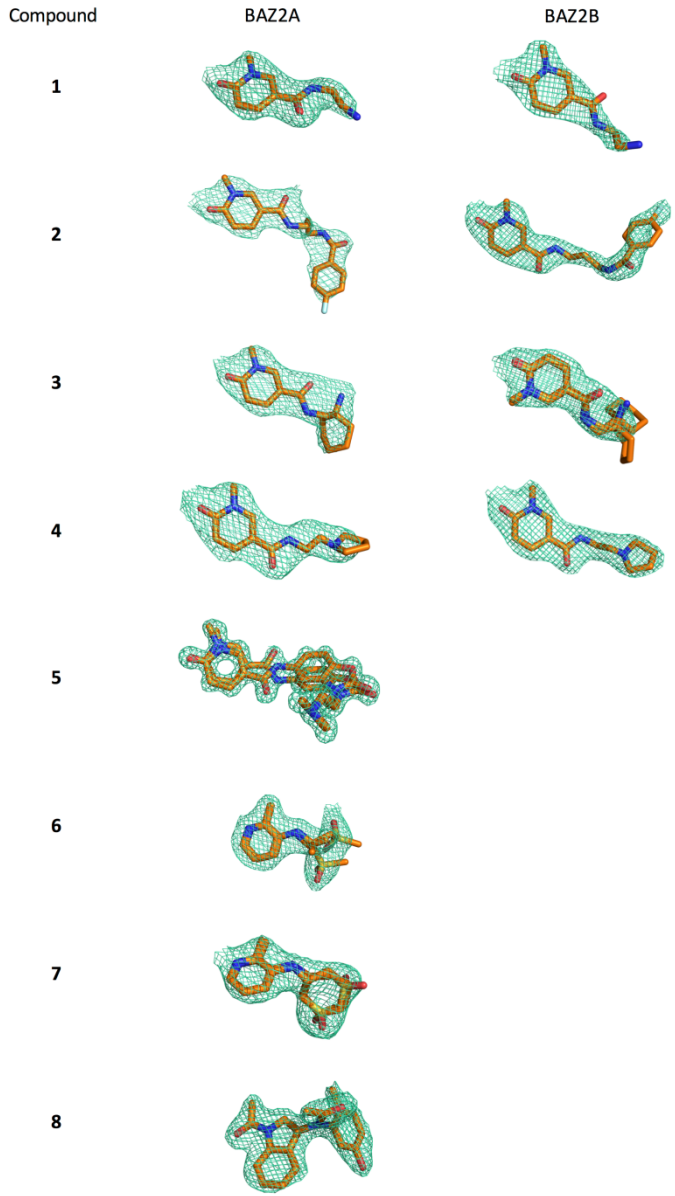


Figure S4. Electron density for compounds **1-8** in their complexes with BAZ2A and BAZ2B bromodomains. $2F_o$-F_c is contoured at 1σ.