-- Electronic Supplementary Information (ESI) --

Computational Insights in Repurposing Cardiovascular Drug for Alzheimer's Disease: The Role of Aromatic Amino Acids in Stabilizing the Drug through π-π Stacking Interaction

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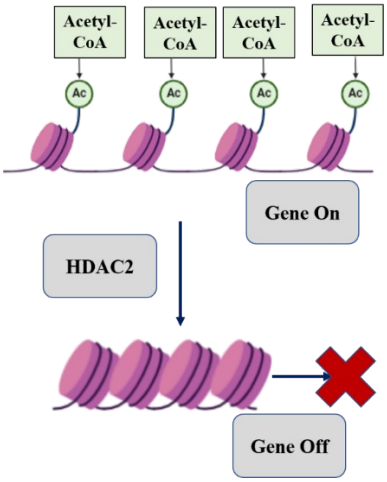


Fig. S1 Modification in histone protein to enhance gene expression and gene repression

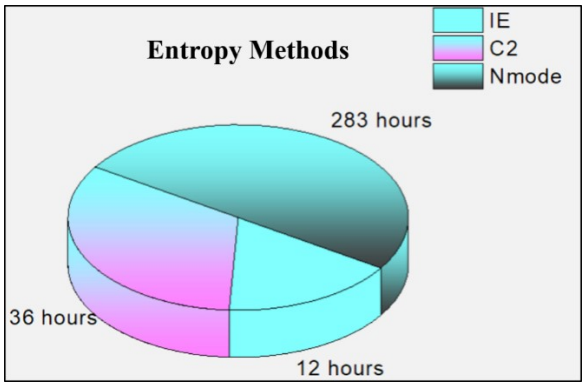


Fig. S2 Pie chart of time consumption for different entropy methods

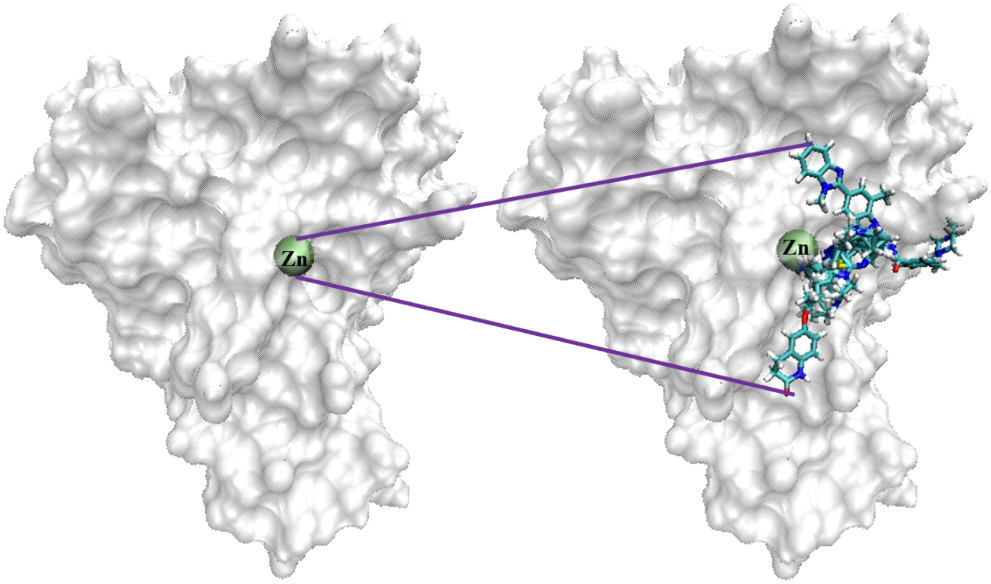
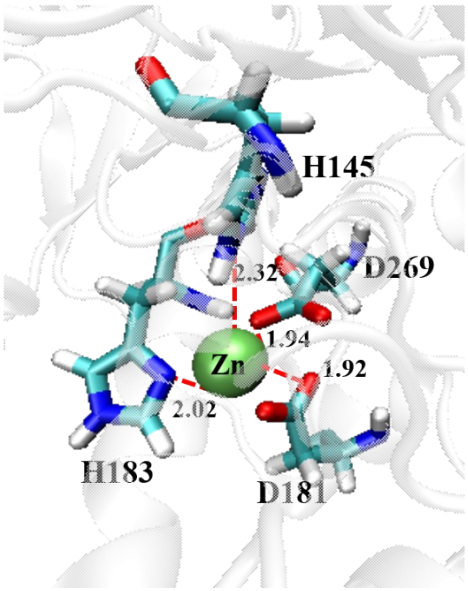


Fig. S3 Selected ligands (Drug1-5) were bound with the zinc-binding active site of the HDAC2 protein.



Bond	Bond Distance reported in ZAFF (Å)		Bond Distance (Å)
	Minimum distance (Å)	Maximum distance (Å)	
ZN-NE1	1.60	2.75	2.02
ZN-OD1	1.68	2.98	1.94
ZN-OD2	1.35	2.51	1.92
ZN-N1	1.82	2.56	2.32

Fig. S4 and **Table S1** show the bond parameters of the zinc-binding active site of the HDAC2 protein. The bond distance forcefield parameter value which was derived by our method lies in between the minimum and maximum bond values which are reported in ZAFF

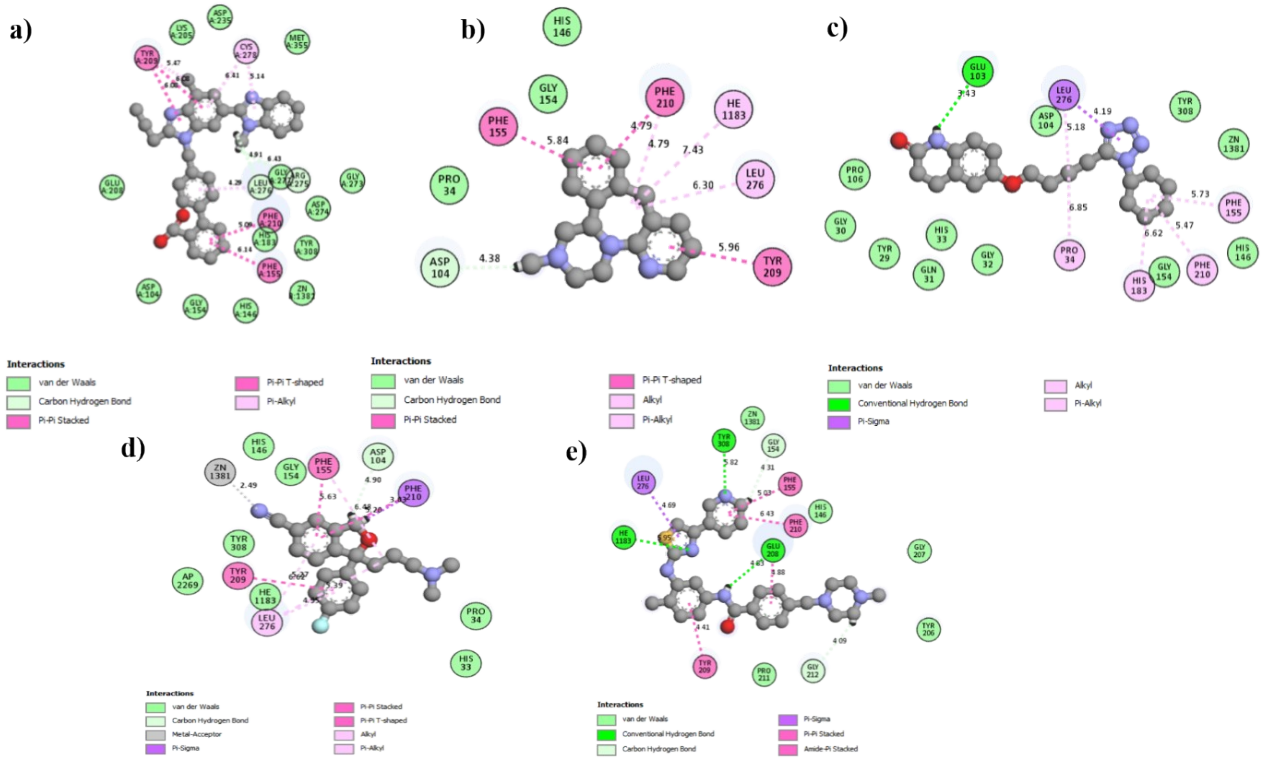


Fig. S5 2D interactions of protein-ligand complexes after docking.

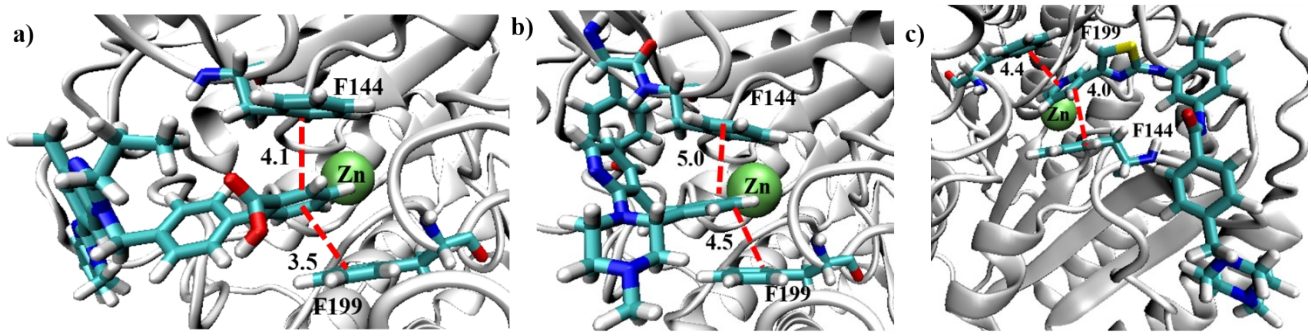


Fig. S6 pi-pi stacking interactions of HDAC2 with the compounds after docking **a)** Drug1, **b)** Drug2, and **c)** Drug5.

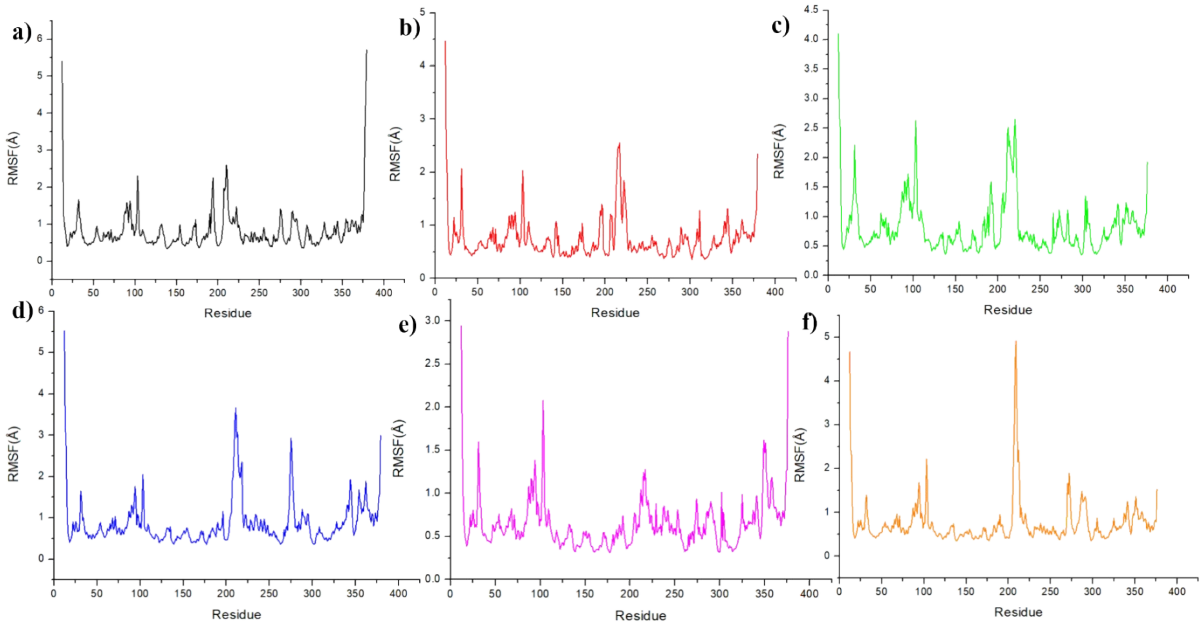


Fig. S7 RMSF plots for the apoprotein and complexes **a)** HDAC2, **b)** HDAC2-Drug1, **c)** HDAC2-Drug2, **d)** HDAC2-Drug3, **e)** HDAC2-Drug4 and **f)** HDAC2-Drug5.

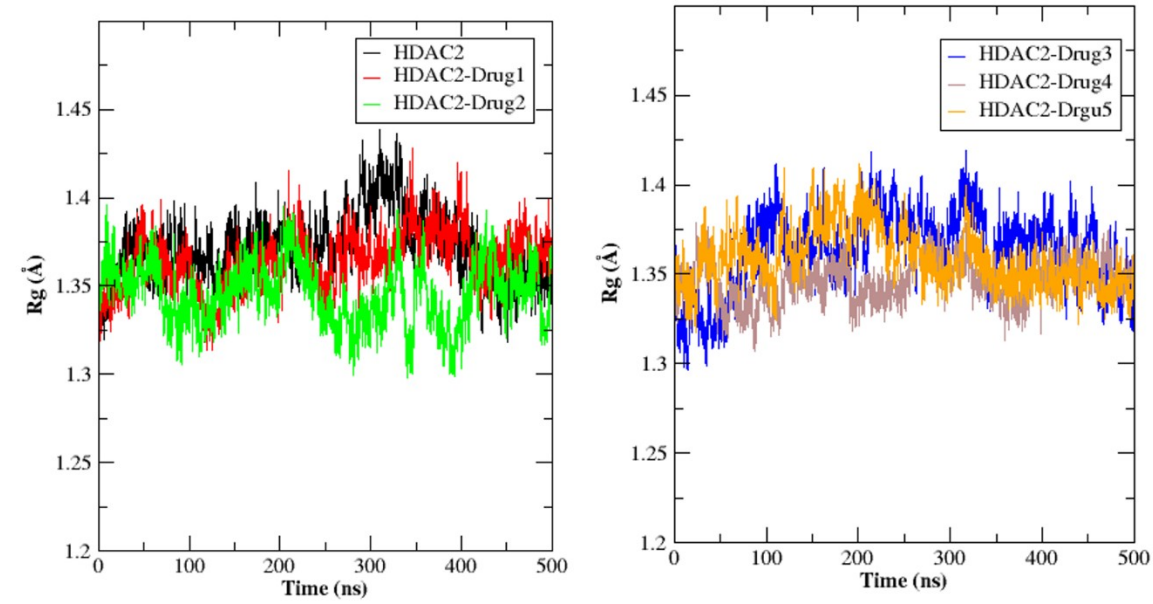


Fig. S8 Rg plots for the protein-ligand complexes.

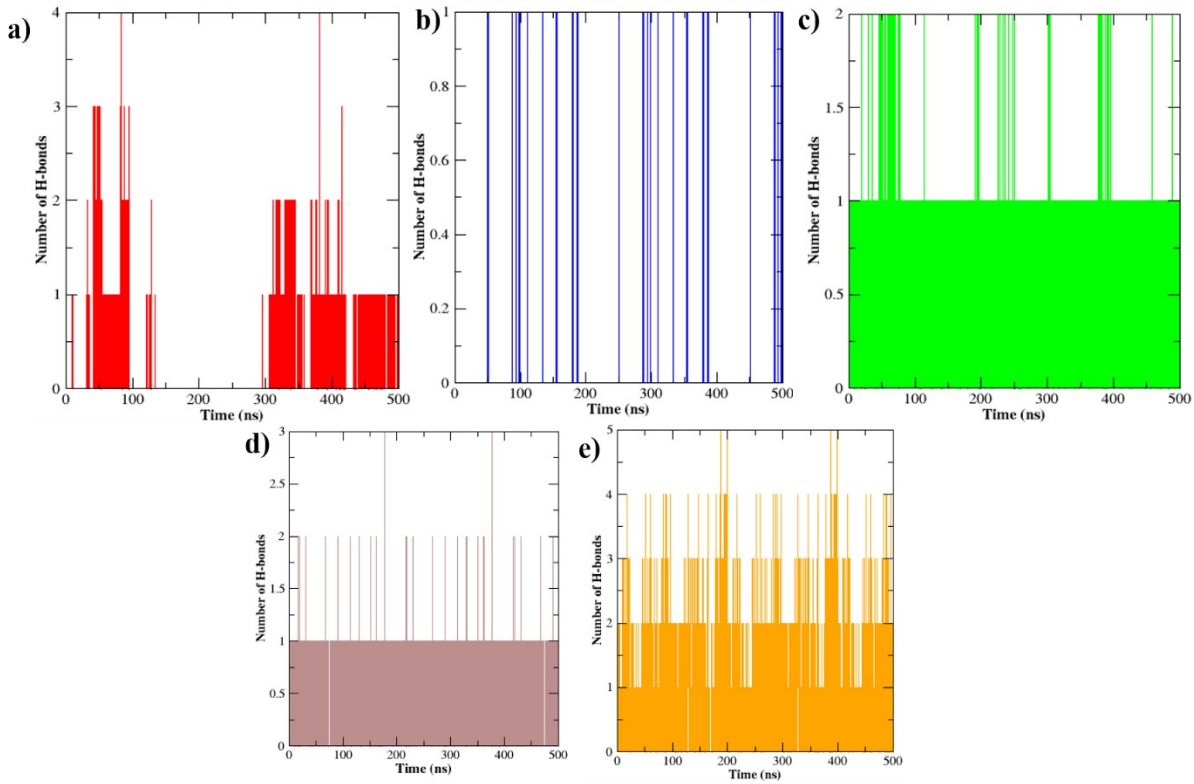


Fig. S9 H-bonding plots for the complexes **a)** HDAC2-Drug1, **b)** HDAC2-Drug2, **c)** HDAC2-Drug3, **d)** HDAC2-Drug4, and **e)** HDAC2-Drug5.

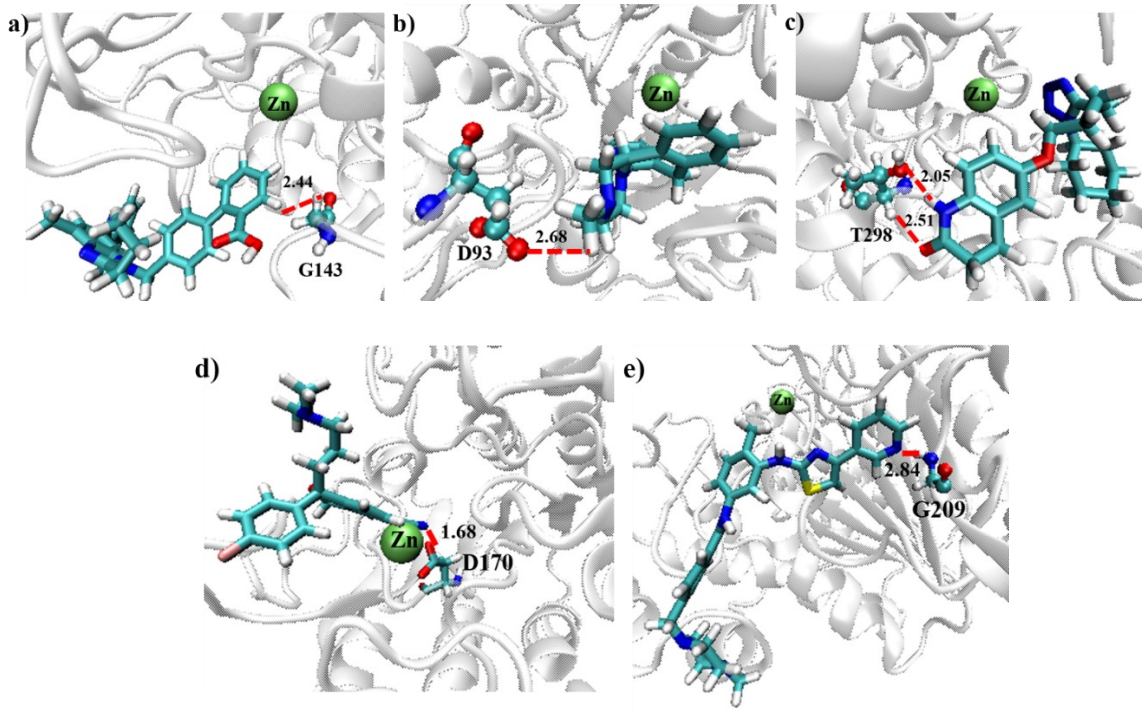


Fig. S10 Cluster analysis after MD simulations of HDAC2 with the compounds shows the H-bonding interaction **a)** Drug1, **b)** Drug2, **c)** Drug3, **d)** Drug4, and **e)** Drug5.

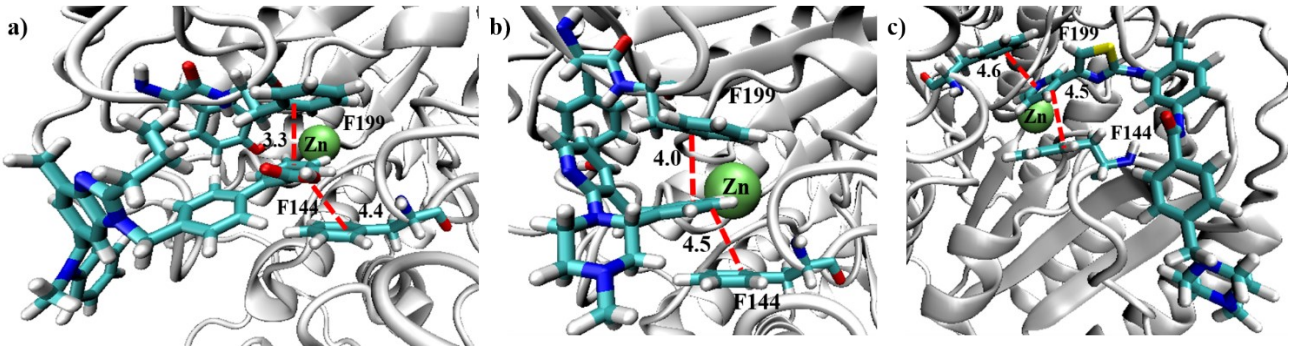


Fig. S11 Cluster analysis after MD simulations of HDAC2 with the compounds shows the pi-pi stacking interactions **a)** Drug1**, b)** Drug2**,** and **c)** Drug5**.**

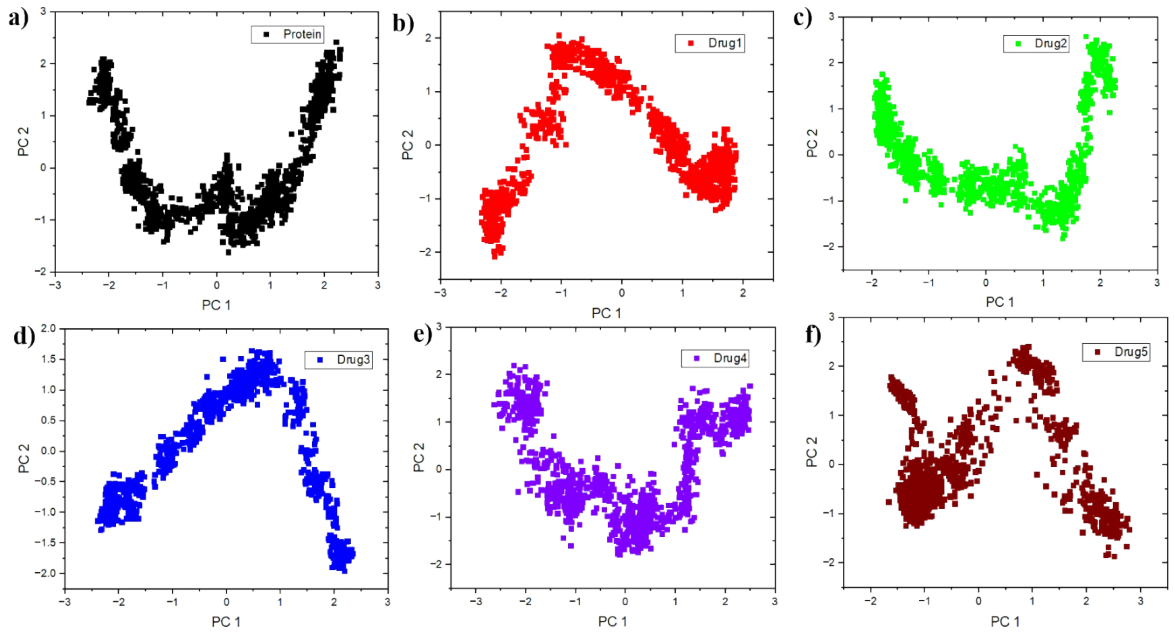


Fig. S12 PCA plots for the apoprotein and complexes **a)** HDAC2, **b)** HDAC2-Drug1, **c)** HDAC2-Drug2, **d)** HDAC2-Drug3, **e)** HDAC2-Drug4, and **f)** HDAC2-Drug5.

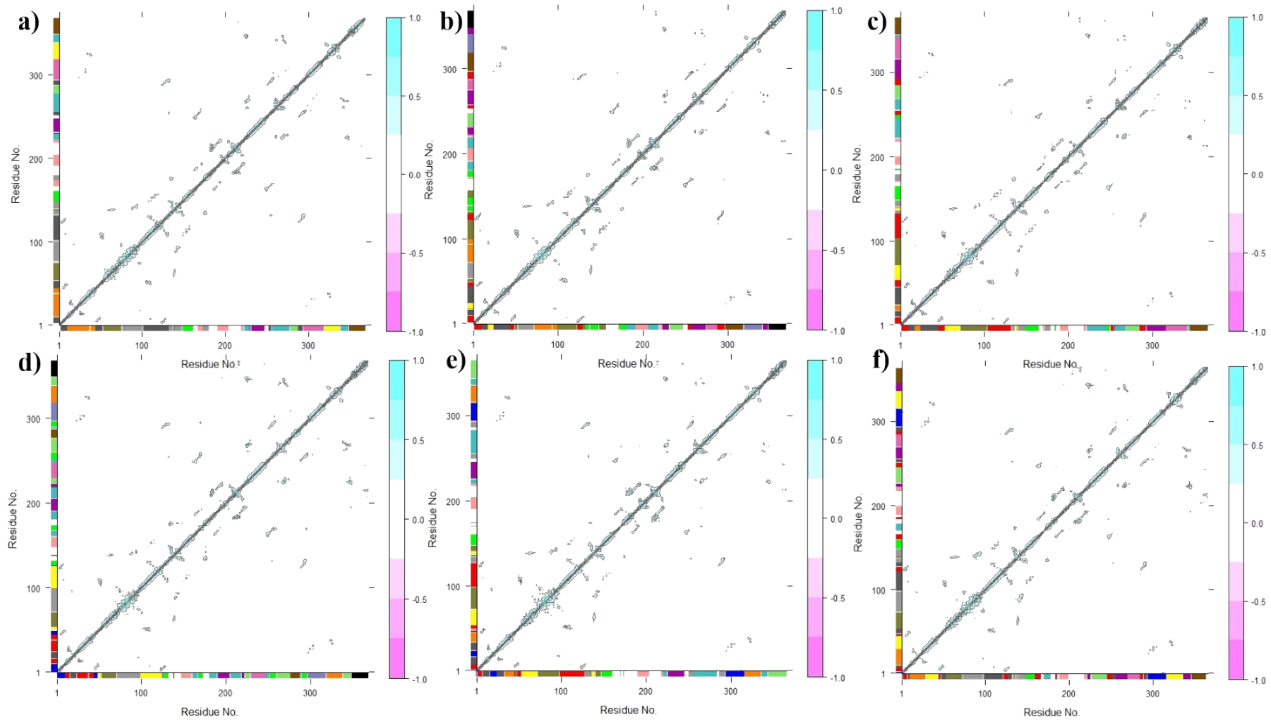


Fig. S13 DCCM plots for the apoprotein and complexes **a)** HDAC2, **b)** HDAC2-Drug1, **c)** HDAC2-Drug2, **d)** HDAC2-Drug3, **e)** HDAC2-Drug4, and **f)** HDAC2-Drug5.

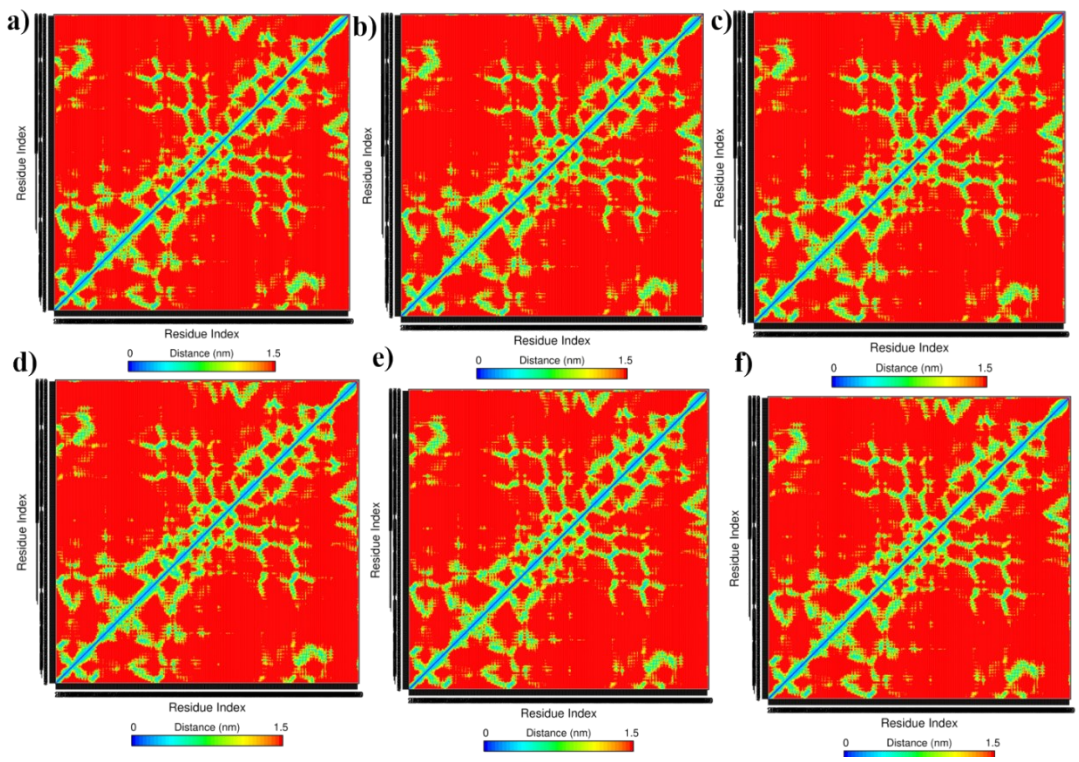


Fig. S14 Contact map plots for the apoprotein and complexes **a)** HDAC2, **b)** HDAC2-Drug1, **c)** HDAC2-Drug2, **d)** HDAC2-Drug3, **e)** HDAC2-Drug4, and **f)** HDAC2-Drug5.

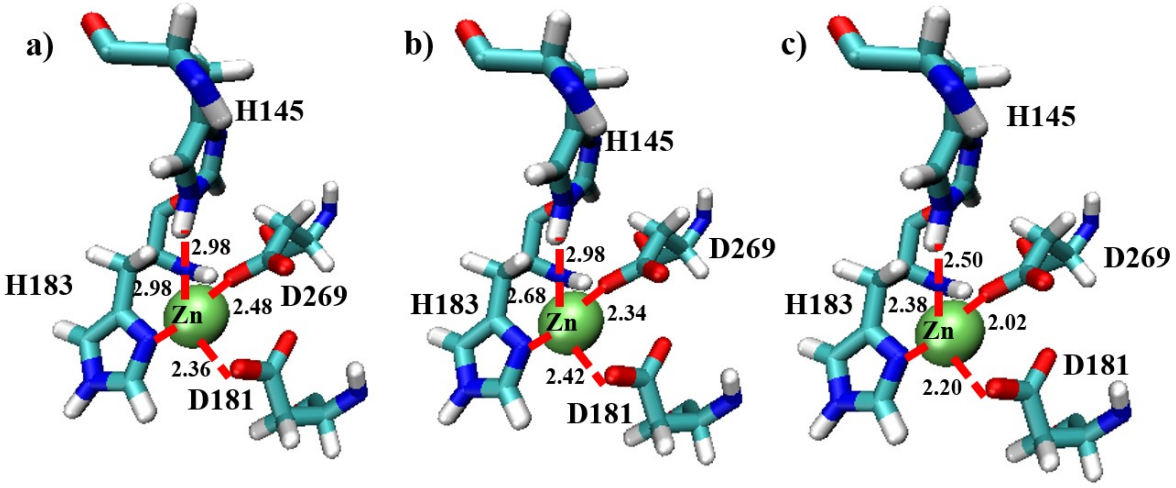


Fig. S15 Conformational analysis of the zinc with its active site **a)** Apo-protein **b)** After docking and **c)** After cluster analysis.

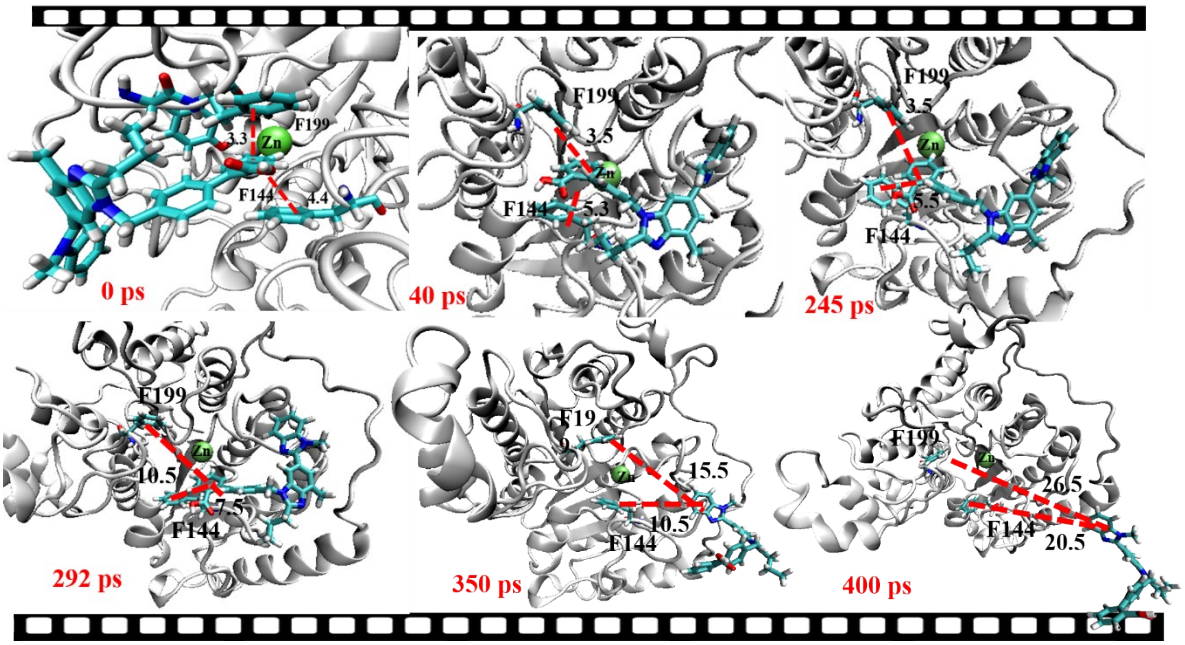


Fig. S16 Unbinding mechanism of the ligand from the zinc-binding site with the time frame and distance.

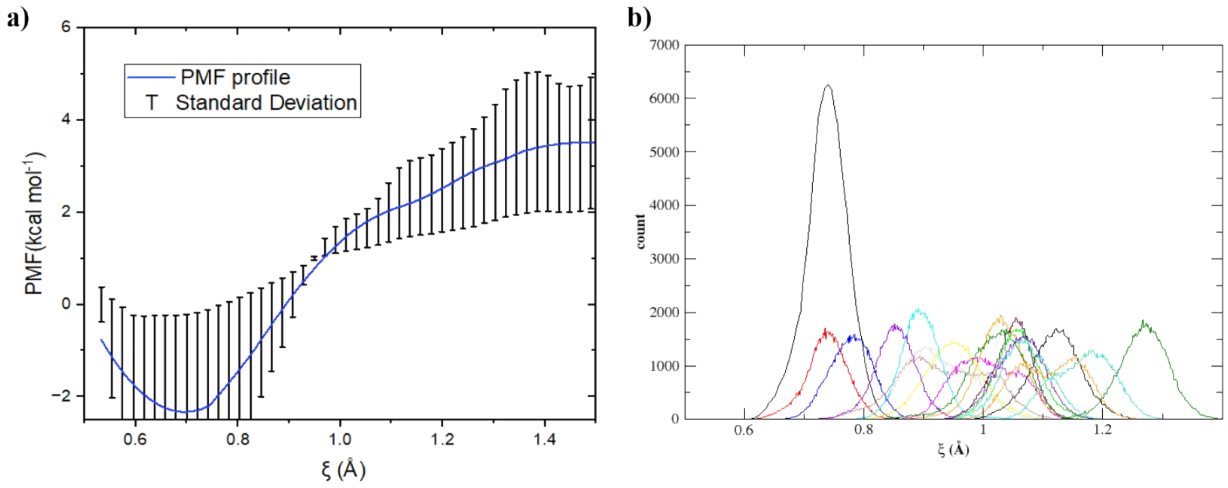


Fig. S17 The energy profiles of HDAC2-Drug1 after SMD a) PMF energy profile of HDAC2-Drug1 b) Histograms of 50 best configurations.

Table S2. Docking binding scores of 58 compounds against HDAC2.

S.No	Drugs	Docking Scores
1	Aciclovir	-5.4
2	Allopregnanolone	-6.2
3	Amlodipine	-5.2
4	Atorvastatin	-7.2
5	Allopurinol	-5.2
6	Bdpp	-6.3
7	Benfotiamine	-6.2
8	Bromocriptine	-7.6
9	Bupropion	-5.9
10	Candesartan	-7.2
11	Cannabidiol	-5.9
12	**Cilostazol**	**-8.7**
13	Cromolyn	-7.1
14	Dabigatran	-7.0
15	Dapagliflozin	-7.6
16	Deferiprone	-4.8
17	Donepezil	-7.2
18	Dronabinol	-6.5
19	Efavirenz	-7.0
20	Empagliflozin	-7.3
21	**Escitalopram**	**-8.7**
22	Fasudil	-6.3
23	Foscarnet	-4.5
24	Galatamine	-5.5
25	Guanfacine	-5.5
26	Icosapent-Ethyl	-4.9
27	Levetiracetam	-4.8
28	Levodopa	-5.9
29	Losartan	-6.3
30	**Mastinib**	**-8.6**
31	Metformin	-4.6
32	Methylphenidate	-6.1
33	**Mirtazapine**	**-8.8**
34	Montelukast	-8.0
35	Nicotinamide	-5.4
36	Nicotine	-5.3
37	Nilotinib	-7.4
38	Penciclovir	-5.6
39	Perindopril	-4.6
40	Phenserine	-7.2
41	Prazosin	-7.3
42	Raloxifene	-7.1
43	Riluzole	-6.4
44	Rivastigmine	-4.6
45	Rosigitazone	-6.0
46	Rotigotine	-6.2

47	Salsalte	-6.7
48	Sodium-Phenyl butyrate	-6.0
49	**Telmisartan**	**-9.4**
50	Thalidomide	-7.4
51	Thiethylperazine	-6.3
52	Valaciclovir	-5.6
53	Valacyclovir	-5.7
54	Venlafaxine	-6.2
55	Vorinostat	-6.3
56	Zidovudine	-5.5
57	Zolpidem	-6.3
58	Zopiclone	-6.4

Table S3. Bond and angle parameters of Drug 1 with the HDAC2 zinc-binding site.

Bond Type	**Bond stretch force constant (Kcal/(mol*Å^2)**	**Bond length (Å)**
ZN-E1	68.53	2.028
ZN-D1	73.98	1.945
ZN-D2	93.42	1.929
ZN-O	42.69	2.018
C -O2	656.00	1.250
C -D1	656.00	1.250
C -D2	656.00	1.250
CR-E1	488.00	1.335
CC-E1	410.00	1.394
OH-ZN	78.64	1.951
N1-ZN	60.82	1.993
O2-ZN	37.89	2.093
NB-ZN	84.50	1.992
O2-ZN	52.32	2.051
Angle Type	**Angle bend force constant [Kcal/(mol*rad^2)]**	**Angle [degree]**
O -ZN-E1	23.313	117.307
O -ZN-D1	35.887	110.838
O -ZN-D2	44.443	100.046
E1-ZN-D1	29.398	109.410
E1-ZN-D2	34.849	115.434
D1-ZN-D2	42.090	102.624
C -O -ZN	27.898	138.471
C -D1-ZN	39.878	134.618
C -D2-ZN	54.049	114.941
CR-E1-ZN	63.840	118.961
CC-E1-ZN	68.556	133.570
CW-CC-E1	70.000	120.000
H5-CR-E1	35.000	120.000

NA-CR-E1	70.000	120.000
CC-E1-CR	70.000	117.000
CT-CC-E1	70.000	120.000
CT-C -D1	70.000	117.000
CT-C -D2	70.000	117.000
CT-C -O2	70.000	117.000
O2-C -D1	126.557	121.174
O2-C -D2	126.557	121.174
D1-ZN-OH	28.321	81.560
E1-ZN-OH	231.671	98.119
D2-ZN-OH	27.440	98.008
HO-OH-ZN	52.287	78.808
N -OH-ZN	71.024	108.152
D1-ZN-N1	126.122	28.798
E1-ZN-N1	109.70	39.800
D2-ZN-N1	114.003	41.808
CZ-N1-ZN	147.253	22.662
O2-ZN-NB	125.352	42.029
O2-ZN-O2	110.640	39.595
CO-O2-ZN	88.343	91.355
CR-NB-ZN	133.855	61.171
NB-ZN-O2	125.685	32.215
CC-NB-ZN	118.776	58.056
CO-O2-ZN	92.675	96.664

Table S4. Bond and angle parameters of Drug 2 with the HDAC2 zinc-binding site.

Bond Type	**Bond stretch force constant (Kcal/(mol*Å^2)**	**Bond length (Å)**
ZN-E1	68.53	2.028
ZN-D1	73.98	1.945
ZN-D2	93.42	1.929
ZN-O	42.69	2.018
C -O2	656.00	1.250
C -D1	656.00	1.250
C -D2	656.00	1.250
CR-E1	488.00	1.335
CC-E1	410.00	1.394
OH-ZN	78.64	1.951
N1-ZN	60.82	1.993
Angle Type	**Angle bend force constant [Kcal/(mol*rad^2)]**	**Angle [degree]**
O -ZN-E1	23.313	117.307
O -ZN-D1	35.887	110.838
O -ZN-D2	44.443	100.046
E1-ZN-D1	29.398	109.410
E1-ZN-D2	34.849	115.434
D1-ZN-D2	42.090	102.624

C -O -ZN	27.898	138.471
C -D1-ZN	39.878	134.618
C -D2-ZN	54.049	114.941
CR-E1-ZN	63.840	118.961
CC-E1-ZN	68.556	133.570
CW-CC-E1	70.000	120.000
H5-CR-E1	35.000	120.000
NA-CR-E1	70.000	120.000
CC-E1-CR	70.000	117.000
CT-CC-E1	70.000	120.000
CT-C -D1	70.000	117.000
CT-C -D2	70.000	117.000
CT-C -O2	70.000	117.000
O2-C -D1	126.557	121.174
O2-C -D2	126.557	121.174
D1-ZN-OH	28.321	81.560
E1-ZN-OH	231.671	98.119
D2-ZN-OH	27.440	98.008
HO-OH-ZN	52.287	78.808
N -OH-ZN	71.024	108.152
D1-ZN-N1	126.122	28.798
E1-ZN-N1	109.70	39.800
D2-ZN-N1	114.003	41.808
CZ-N1-ZN	147.253	22.662

Table S5. Bond and angle parameters of Drug 3 with the HDAC2 zinc-binding site.

Bond Type	**Bond stretch force constant (Kcal/(mol*Å^2)**	**Bond length (Å)**
ZN-E1	68.53	2.028
ZN-D1	73.98	1.945
ZN-D2	93.42	1.929
ZN-O	42.69	2.018
C -O2	656.00	1.250
C -D1	656.00	1.250
C -D2	656.00	1.250
CR-E1	488.00	1.335
CC-E1	410.00	1.394
OH-ZN	78.64	1.951
N1-ZN	60.82	1.993
O2-ZN	37.89	2.093
NB-ZN	84.50	1.992
O2-ZN	52.32	2.051
Angle Type	**Angle bend force constant [Kcal/(mol*rad^2)]**	**Angle [degree]**
O -ZN-E1	23.313	117.307
O -ZN-D1	35.887	110.838
O -ZN-D2	44.443	100.046

E1-ZN-D1	29.398	109.410
E1-ZN-D2	34.849	115.434
D1-ZN-D2	42.090	102.624
C -O -ZN	27.898	138.471
C -D1-ZN	39.878	134.618
C -D2-ZN	54.049	114.941
CR-E1-ZN	63.840	118.961
CC-E1-ZN	68.556	133.570
CW-CC-E1	70.000	120.000
H5-CR-E1	35.000	120.000
NA-CR-E1	70.000	120.000
CC-E1-CR	70.000	117.000
CT-CC-E1	70.000	120.000
CT-C -D1	70.000	117.000
CT-C -D2	70.000	117.000
CT-C -O2	70.000	117.000
O2-C -D1	126.557	121.174
O2-C -D2	126.557	121.174
D1-ZN-OH	28.321	81.560
E1-ZN-OH	231.671	98.119
D2-ZN-OH	27.440	98.008
HO-OH-ZN	52.287	78.808
N -OH-ZN	71.024	108.152
D1-ZN-N1	126.122	28.798
E1-ZN-N1	109.70	39.800
D2-ZN-N1	114.003	41.808
CZ-N1-ZN	147.253	22.662
O2-ZN-NB	125.352	42.029
O2-ZN-O2	110.640	39.595
CO-O2-ZN	88.343	91.355
CR-NB-ZN	133.855	61.171
NB-ZN-O2	125.685	32.215
CC-NB-ZN	118.776	58.056
CO-O2-ZN	92.675	96.664

Table S6. Bond and angle parameters of Drug 4 with the HDAC2 zinc-binding site.

Bond Type	Bond stretch force constant (Kcal/(mol*Å^2)	Bond length (Å)
ZN-E1	68.53	2.028
ZN-D1	73.98	1.945
ZN-D2	93.42	1.929
ZN-O	42.69	2.018
C -O2	656.00	1.250
C -D1	656.00	1.250
C -D2	656.00	1.250
CR-E1	488.00	1.335
CC-E1	410.00	1.394
OH-ZN	78.64	1.951
Angle Type	**Angle bend force constant [Kcal/(mol*rad^2)]**	**Angle [degree]**
O -ZN-E1	23.313	117.307
O -ZN-D1	35.887	110.838
O -ZN-D2	44.443	100.046
E1-ZN-D1	29.398	109.410
E1-ZN-D2	34.849	115.434
D1-ZN-D2	42.090	102.624
C -O -ZN	27.898	138.471
C -D1-ZN	39.878	134.618
C -D2-ZN	54.049	114.941
CR-E1-ZN	63.840	118.961
CC-E1-ZN	68.556	133.570
CW-CC-E1	70.000	120.000
H5-CR-E1	35.000	120.000
NA-CR-E1	70.000	120.000
CC-E1-CR	70.000	117.000
CT-CC-E1	70.000	120.000
CT-C -D1	70.000	117.000
CT-C -D2	70.000	117.000
CT-C -O2	70.000	117.000
O2-C -D1	126.557	121.174
O2-C -D2	126.557	121.174
D1-ZN-OH	28.321	81.560
E1-ZN-OH	231.671	98.119
D2-ZN-OH	27.440	98.008
HO-OH-ZN	52.287	78.808
N -OH-ZN	71.024	108.152

Table S7. Bond and angle parameters of Drug 5 with the HDAC2 zinc-binding site.

Bond Type	**Bond stretch force constant (Kcal/(mol*Å^2)**	**Bond length (Å)**
ZN-E1	68.53	2.028
ZN-D1	73.98	1.945
ZN-D2	93.42	1.929
ZN-O	42.69	2.018
C -O2	656.00	1.250
C -D1	656.00	1.250
C -D2	656.00	1.250
CR-E1	488.00	1.335
CC-E1	410.00	1.394
OH-ZN	78.64	1.951
Angle Type	**Angle bend force constant [Kcal/(mol*rad^2)]**	**Angle [degree]**
O -ZN-E1	23.313	117.307
O -ZN-D1	35.887	110.838
O -ZN-D2	44.443	100.046
E1-ZN-D1	29.398	109.410
E1-ZN-D2	34.849	115.434
D1-ZN-D2	42.090	102.624
C -O -ZN	27.898	138.471
C -D1-ZN	39.878	134.618
C -D2-ZN	54.049	114.941
CR-E1-ZN	63.840	118.961
CC-E1-ZN	68.556	133.570
CW-CC-E1	70.000	120.000
H5-CR-E1	35.000	120.000
NA-CR-E1	70.000	120.000
CC-E1-CR	70.000	117.000
CT-CC-E1	70.000	120.000
CT-C -D1	70.000	117.000
CT-C -D2	70.000	117.000
CT-C -O2	70.000	117.000
O2-C -D1	126.557	121.174
O2-C -D2	126.557	121.174
D1-ZN-OH	28.321	81.560
E1-ZN-OH	231.671	98.119
D2-ZN-OH	27.440	98.008
HO-OH-ZN	52.287	78.808
N -OH-ZN	71.024	108.152

Table S8. The average values of RMSD, RMSF, and Rg analysis of protein-ligand complexes.

Compounds	RMSD (Å)	RMSF (Å)	Rg (Å)
Protein	1.72	0.85	1.69
Drug-1	1.33	0.78	1.64
Drug-2	1.43	0.83	1.67
Drug-3	1.57	0.88	1.69
Drug-4	1.45	0.74	1.68
Drug-5	1.50	0.78	1.64

Table S9. The average values of H-bond analysis of protein-ligand complexes.

Compounds	The average no. of H-bonds
Drug-1	1
Drug-2	1
Drug-3	1
Drug-4	1
Drug-5	1

Table S10. Binding energy values for protein-ligand complexes in Interaction Entropy (IE) method

Compounds	Enthalpy (ΔH) kcal mol^{-1}	Entropy (TΔS) kcal mol^{-1}	Total Binding Free Energy (ΔG_{bind}) kcal mol^{-1}
Drug-1	-34.40 ± 2.28	-8.70 ± 2.18	-25.70 ± 2.23
Drug-2	-30.49 ± 1.12	-15.80 ± 1.19	-14.69 ±1.15
Drug-3	-15.52 ± 1.22	-7.21 ± 1.87	-8.31 ± 1.04
Drug-4	-11.12 ± 1.98	-7.60 ± 1.66	-3.52 ± 1.82
Drug-5	-15.97 ± 2.69	-12.60 ± 2.89	-3.37 ± 2.79
Romidepsin	-15.54 ± 3.66	-8.50 ± 1.98	-7.04 ± 0.82

Table S11. Binding energy values for protein-ligand complexes in the C2 method.

Compounds	Enthalpy (ΔH) kcal mol^{-1}	Entropy (TΔS) kcal mol^{-1}	Total Binding Free Energy (ΔG_{bind}) kcal mol^{-1}
Drug-1	-20.08 ± 1.28	-10.97 ± 1.26	-9.11 ± 1.14
Drug-2	-19.08 ± 2.10	-11.01 ± 3.14	-8.07± 2.25
Drug-3	-25.09 ± 2.24	-18.27 ± 1.13	-6.82 ± 1.16
Drug-4	-18.97 ± 3.12	-12.19 ± 2.14	-6.78 ± 2.14
Drug-5	-16.09 ± 1.13	-10.01± 2.15	-5.99 ± 1.13
Romidepsin	-15.24 ± 3.15	-11.01 ± 1.13	-4.23 ± 2.14

Table S12. Binding energy values for protein-ligand complexes in normal mode method.

Compounds	Enthalpy (ΔH) kcal mol^{-1}	Entropy (TΔS) kcal mol^{-1}	Total Binding Free Energy (ΔG_{bind}) kcal mol^{-1}
Drug-1	-24.14 ± 1.12	-8.15 ± 2.12	-15.98 ± 2.10
Drug-2	-18.20 ± 2.44	-16.93 ± 2. 65	-1.27 ± 2.14
Drug-3	-12.42 ± 3.24	-7.58 ± 2.23	-4.84 ± 3.62
Drug-4	-11.12 ± 4.12	-7.60 ± 2.25	-3.52 ± 1.14
Drug-5	-10.22 ± 1.24	-4.60 ± 2.54	-5.62 ± 3.12
Romidepsin	-10.12 ± 3.23	-5.60 ± 2.45	-4.52 ± 3.12

Table S13. Per-residue decomposition analysis for protein-ligand complexes.

Amino acid residues	Drug-1 (kcal mol^{-1})	Drug-2 (kcal mol^{-1})	Drug-3 (kcal mol^{-1})	Drug-4 (kcal mol^{-1})	Drug-5 (kcal mol^{-1})
Pro 23	-1.44	-1.46	-2.30	-0.21	-0.23
Phe144	**-2.48**	**-1.61**	**-2.28**	**-0.42**	**-2.06**
Phe199	**-2.77**	**-1.00**	**-0.57**	**-1.09**	**-1.33**
Leu265	-3.05	-2.22	-1.42	-1.46	-0.02
Tyr198	**-1.79**	**-0.47**	**-1.26**	**-3.12**	**-0.28**