Exploration of Novel Inhibitors for Class I Histone Deacetylase Isoforms by QSAR Modeling and Molecular Dynamics Simulation Assays

Zainab Noor, Noreen Afzal, Sajid Rashid*

Quaid-i-Azam University, Islamabad

***Email:** sajidrwp@yahoo.co.uk

Supplementary Material

Table A PDB ids of class 1 HDAC target proteins

Protein Name	PDB id	Resolutions	Date
HDAC1	4BKX	3.00 Å	2013
HDAC2	4LXZ	1.85 Å	2013
HDAC3	4A69	2.06 Å	2012
HDAC8	1T64	1.90 Å	2004

Table B IC_{50} values of 16 known class I HDAC inhibitors

Sr. No.	Compounds	IC_{50} values (nM)			
		HDAC1	**HDAC2**	**HDAC3**	**HDAC8**
1.	MS-275	120	250	120	>1000
2.	CI-994	900	900	1200	>2000
3.	LAQ-824	3.23	15.70	10.50	3.84
4.	LBH-589	6.8	<300	<300	<300
5.	Belinostat	18	-	46	-
6.	SK-7041	980	980	-	-
7.	SAHA	30	10	17	110
8.	Trichostatin A	5	18	2	25
9.	Oxamflatin	100	233.1	233.1	233.1
10.	Pyroxamide	200	200	200	200
11.	Valproic Acid	39000	62000	161000	103000
12.	Scriptaid	200	700	100	300
13.	Depsipeptide	36	1	-	-
14.	Phenyl Butyrate	65000	-	260000	9300
15.	Tubacin	1400	6270	1270	1270
16.	Mocetinostat	150	290	610	>1000

Table C IC50 (nM) values and SMILE codes for test set compounds. Test set compounds were labelled with the unique identifiers i.e. compound number- ChEMBL ID

ID	IC_{50}	SMILE code	ID	IC_{50}	SMILE code
1-16300	**9-20000**	ONC(=O)C1=CC=CC=C1	**19-487107**	**4.2-406**	ONC(=O)CCCCCCC(=O)NC1=CC=CC(=C1)C2=CN=N[N]2CC(O)C3=CC(=CC=C3)Br
2-55895	**600-4000**	ONC(=O)CCCC1=CC=CC=C1	**20-488747**	**18-433**	ONC(=O)CCCCCCC(=O)NC1=CC=CC(=C1)C2=CN=N[N]2CC3=CC=CC=C3
3-138626	**100000**	CC(=O)N(O)CCCCCCCC(=O)NC1=CC=CC=C1	**21-507592**	**17000-**	ONC(=O)C1=NOC(=C1)CCCCC(=O)NC2CCCC2
4-139193	**4000-11000**	ON(CCCCCCC(=O)NC1=CC=CC=C1)C=O	**22-511749**	**190-6000**	CC(C)(C)OC(=O)NC1=CC=C(C=C1)C2=CC(=NO2)C(=O)NCCCCCCC(=O)NO
5-141082	**6800-**	ON(CCCCCC(=O)NC1=CC=CC=C1)C=O	**23-551151**	**1700**	ONC(=O)CCC1=CC=C(C=C1)C2=CC=C(O)C=C2
6-146250	**1.6-57**	C\C=C1/NC(=O)C(CS)NC(=O)C(NC(=O)CC(OC(=O)C(NC1=O)C(C)C)\C=C\CCS)C(C)C	**24-564916**	**260-74000**	NC1=CC=CC=C1NC(=O)CCCCCC(C2=C[NH]C3=C2C=CC=C3)C4=C[NH]C5=C4C=CC=C5
7-152162	**2350-2720**	ONC(=O)CCC1=CC=CC=C1	**25-1076939**	**3.0-5.9**	COC1=C(F)C=CC(=C1)[N]2C=C(N=N2)C3=CC=CC(=C3)NC(=O)CCCCCCC(=O)NO
8-216641	**0.8-400**	COC1=CC2=C([NH]C(=C2CC(=O)NC(CCCCCC(=O)NO)C(=O)NCCC3=C([NH]C4=C3C=CC=C4)C5=CC=CC=C5)C)C=C1	**26-1083439**	**53-200**	ONC(=O)CCCCCNC(=O)NC(=O)C1=CC=CC=C1
9-217651	**55-3000**	CN1CCCCC1C(=O)NC(CCCCCC(C)=O)C(=O)NC2=NC(=CS2)C3=CC=CC=C3	**27-1088734**	**28-5000**	ONC(=O)CCCCCCC(=O)NC1=CC(=CC=C1)C2=C[N](N=N2)C3=CC=C(C=C3)C(F)(F)F
10-236060	**2000-20000**	NC1=CC=CC=C1NC(=O)C2=CC3=C(C=C2)N=CC=N3	**28-1093033**	**7.5-217**	CC(C)(C)C1=C(C2CCCN(C2)CC3=CC=C(\C=C\C(=O)NO)C=C3F)C4=C([NH]1)C=CC=C4
11-242533	**31-50**	ONC(=O)\C=C\C1=CC=CC(=C1)C(=O)C2=CC3=C([NH]2)C=CC=C3	**29-1093041**	**27-35**	CCC1=CC(=CC=C1)NC(=O)CCCCC(=O)NO
12-405072	**2400-50000**	NC1=C(NC(=O)C2=CC=CC=C2)C=CC=C1	**30-1094108**	**3100-7200**	CC1=CC=CC(=C1)C2=CC(=C(N)C=C2)NC(=O)C3=CC=CC=C3
13-440018	**1400-19000**	CN(C)C1=CC=C(C=C1)C(=O)NCCCCCCNC(=O)CS	**31-1096398**	**10000**	NC1=C(NC(=O)C2=CC=CC=C2)C=C(C=C1)C3=CC4=C(S3)C=CC=C4
14-466031	**30000**	OCC1=NOC(=C1)CCCCC(=O)NC2=NC(=CS2)C3=CC=CC=C3	**32-1096982**	**11000-23000**	OC(=O)CC\C=C/CC1NC(=O)C2CCCN2C(=O)C(CC3=CC=CC=C3)NC(=O)C(CC4=C[NH]C5=C4C=CC=C5)NC1=O
15-469134	**30-430**	ONC(=O)C1=NOC(=C1)CCCCC(=O)NC2=NC(=CS2)C3=CC=CC=C3	**33-1097744**	**21000**	NC1=C(NC(=O)C2=CC=CC=C2)C=C(C=C1)C3=CC(=CC=C3)[N+]([O-])=O
16-469275	**83-5000**	CC(C)(C)OC(=O)NC1=CC(=CC=C1)C2=CC(=NO2)C(=O)NCCCCC(=O)NO	**34-1630109**	**35-630**	ONC(=O)\C=C\C1=CC(=CC=C1)C2=CC=C3N=CN=C(NC4=CC(=C(OCC5=CC(=CC=C5)F)C=C4)Cl)C3=C2
17-470843	**127-13200**	Cl.ONC(=O)\C=C\C1=CC=C(C=C1)C2=NOC(=C2)CN3CCOCC3	**35-1631915**	**89-382**	COC1=CC2=CC(=C1)\C=C/COC(CCCCCC(=O)NO)C(=O)NC3=CC=CC=C3OC2
18-483693	**7.9-1900**	ONC(=O)CCCCCCC(=O)NC1=CC=CC(=C1)C2=C[N](CC3=CC=CC=C3)N=N2	**36-1631916**	**204-700**	COC1=CC2=CC(=C1)CCCOC(CCCCCC(=O)NO)C(=O)NC3=CC=CC=C3OC2

Continued

ID	IC_{50}	SMILE code	ID	IC_{50}	SMILE code
37-1722433	**100000**	CC1=CC(=NC(=N1)SCC(=O)NCCC2=CC=CC=C2)O	**56-2170019**	**180-700**	CCC(=O)CCCCCC1NC(=O)C(CCCNC(N)=N)NC(=O)CCN(CC(C)C)C(=O)CN(CCC2=C[NH]C3=C2C=CC=C3)C1=O
38-1767030	**65000**	CNC(=O)\C(CCCCCCC(=O)NC1=CC2=CC=CC=C2C=C1)=N/O	**57-2323286**	**31-224**	CC(C)C1NC(=O)C[N]2N=NC(=N2)C3=CSC(=N3)CNC(=O)CC(OC1=O)\C=C\CCS
39-1767033	**10000**	CNC(=O)\C(CCCCCCC(=O)NC1=CC=C(C=C1)N(C)C)=N/O	**58-2323288**	**649-3270**	CC(C)C1NC(=O)C[N]2N=NN=C2C3=CSC(=N3)CNC(=O)CC(OC1=O)\C=C\CCS
40-1767038	**76000**	CNC(=O)\C(CCCCCCC(=O)NC1=CC(=CC=C1)C2=CN=CC=C2)=N/O	**59-2323289**	**14000-32000**	CCCCCCCC(=O)SCC\C=C\C1CC(=O)NCC2=NC(=CS2)C3=C[N](CC(=O)NC(C(C)C)C(=O)O1)N=N3
41-1767039	**1900-69000**	CNC(=O)\C(CCCCCCC(=O)NC1=CC(=CC=C1)C2=CN=C(Cl)C=C2)=N/O	**60-2333345**	**300-33000**	ONC(=O)C1CCCCC1
42-1767042	**5100-100000**	CNC(=O)\C(CCCCCCNC(=O)C1=NOC(=C1)C2=CC=C(NC(=O)OC(C)(C)C)C=C2)=N\O	**61-2347006**	**64-468**	CCC(C)C(=O)OC1CC(C)C=C2C=CC(C)C(CCC(O)CC(O)CC(=O)NO)C12
43-1800241	**15000-23000**	CC(=O)NC1=CC=C(C=C1)C(=O)CSC2=NC(=CC(=N2)C)O	**62-2381517**	**120-2300**	ONC(=O)C1=CC(=CC=C1)C(=O)NCCC2=CC=CC=C2
44-1800244	**100000**	CC(=O)NC1=CC=C(C=C1)C(=O)CSC2=NC(=CC(=N2)C)C	**63-2407721**	**410-12000**	NC1=CC=CC=C1NC(=O)C2=CC=C(CNC3=NC(CS3)CC4=CC=CC=C4)C=C2
45-1800247	**100000**	CC(=O)NC1=CC=C(C=C1)C(=O)COC2=CC(=CC(=N2)O)C	**64-2408778**	**230-2311**	NC1=C2C(=NC=N1)[N](N=C2C3=CC=C(Cl)C=C3)C4=CC=CC(=C4)C5=CN=N[N]5CCCCCC(=O)NO
46-1800248	**100000**	CC(=O)NC1=CC=C(CSC2=NC(=CC(=N2)O)C)C=C1	**65-2414098**	**6-282**	ONC(=O)CCCCCCC1=NC2=CC=C(Br)C=C2[NH]1
47-1800377	**100000**	CC1=CC(=NC(=N1)SCC(=O)C2=CC3=C(OCCO3)C=C2)O	**66-2417782**	**21-2580**	CC(C)(C)OC(=O)NC1=CC=CC(=C1)C2=CSC(=N2)NC(=O)CCCCCCC(=O)NO
48-1800379	**100000**	CC1=CC(=NC(=N1)SCC(=O)C2=CC=CS2)O	**67-2417783**	**5000-28000**	CC1=C(C(=O)NCCCCCNC(=O)CS)C(=NO1)C2=CC=CC=C2
49-1914702	**45-780**	ONC(=O)CCCCCCNC(=O)C1=NOC(=C1)C2=CC=C(NC(=O)C3=CC(=CC(=C3)N=[N+]=[N-])CN=[N+]=[N-])C=C2	**68-2425958**	**1700-6400**	CC1=NC2=CC(=CC=C2C(=O)N1CCC3=CC=CC=C3)\C=C\C(=O)NO
50-1938433	**65-1760**	ONC(=O)\C=C\C1=CC2=C(OC3(CCN(CC3)CC4=CC=CC=C4)CC2=O)C=C1	**69-2431906**	**1300-50000**	C[N]1C=CC=C1C(=O)N2CC3=C(C2)C=C(C=C3)C(=O)NO
51-2022829	**5.2-7.6**	O=C(NC(CCCCCCSSC1=CC=CC=N1)C(=O)OCC2C3=C(C=CC=C3)C4=C2C=CC=C4)OCC5=CC=CC=C5	**70-2436595**	**20-1200**	CC(C)C1NC(=O)C2(C)CSC(=N2)C3=COC(=N3)CNC(=O)CC(OC1=O)\C=C\CCS
52-2048749	**124-361**	COC1=CC=C(C=C1)[S](=O)(=O)[N]2C=CC3=C2C=CC(=C3)\C=C\C(=O)NO	**71-2442698**	**140-230**	COC1=CC(=CC(=C1O)OC)C2C3C(COC3=O)C(NC4=CC=C(NC(=O)CCCCCCC(=O)NO)C=C4)C5=CC6=C(OCO6)C=C25
53-2048750	**2.3-18**	COC1=C(OC)C=C(C=C1)[S](=O)(=O)[N]2C=CC3=C2C=CC(=C3)\C=C\C(=O)NO	**72-2448576**	**18-10000**	CCC(=O)CCCCCC(NC(=O)C1CN(C)C1)C2=NC=C([NH]2)C3=CC4=CC=CC=C4N=C3OC
54-2057821	**350-7000**	NC1=C(NC(=O)C2=CC=C(CNC(=O)OCC3=CC(=CC(=C3)N=[N+]=[N-])CN=[N+]=[N-	**73-3098695**	**34-89**	ONC(=O)CCCCCC(NC(=O)C1CC(=O)N1)C(=O)NC2=CC=CC=C2
55-2057828	**3000-1800**	NC1=C(NC(=O)C2=CC(=C(OCCN=[N+]=[N-])C=C2)N=[N+]=[N-])C=C(C=C1)C3=CC=CS3	**74-3098697**	**1400-5000**	ONC(=O)CCCCCC(NC(=O)C1CCCC(=O)N1)C(=O)NC2CCCC2

Table D Binding energy values (kcal/mol) of training set compounds

Inhibitors	Binding energies			
	HDAC1	**HDAC2**	**HDAC3**	**HDAC4**
MS-275	-13.1	-13.9	-9.42	-9.4
LBH-589	-18.5	-29.58	-13.55	-20.21
LAQ-824	-12.48	-30.32	-13.2	-17.74
TSA	-13.57	-20.75	-9.1	-21.87
SAHA	-10.65	-21.64	-12.7	-13.34
Belinostat	-22.37	-24.83	-16.4	-23.92
Oxamflatin	-12.23	-20.34	-10.1	-21.22
Pyroxamide	-11.52	-21.69	-14.6	-14.61
Mocetinostat	-24.15	-21.8	-12.23	-
Scriptaid	-9.5	-17.85	-19.26	-12.47

Table E Molecular descriptors of training set compounds

Compounds	Mol. Weight	Mol. Polarizability	Huckel Analysis (pi energy)	Molar Refractivity	LogD	LogP	TPSA	HBD	HBA
MS-275	376	40.19	45.8	108.288	2	2.31	106.34	4	7
LBH-589	349	41.08	38.42	105.499	1	2.39	77.15	4	5
LAQ-824	379	43.6	42.6	111.936	1	3.18	88.59	4	5
TSA	274	29.44	30.57	80.511	1.4	2.41	92.42	4	5
Saha	264	28.1	25.62	73.805	1.67	2.46	78.43	3	5
Belinostat	318	32.39	39.69	83.47	1.5	1.81	95.5	3	6
Oxamflatin	344	35.82	42.23	93.798	2	2.73	95.5	3	6
Pyroxamide	265	27.23	26.23	71.648	1	1.396	91.32	3	6
Mocetinostat	396	44.93	47.6	120.316	2.6	2.93	105.82	4	7
Scriptaid	326	35.05	35.65	100.662	1	-3.9	92.47	2	6

Continued

SASA	Vander Wall's Volume	Weiner Index (W)	Platt Index	Randic Index	Balaban Index	Harary Index	Szeged Index
528.78	336.84	2622	78	13.61	1.18	98.96	3678
516.32	325.14	2128	74	12.67	1.27	89.6	2888
557.56	351.84	2462	86	14.53	1.27	100.51	3306
390.46	255.43	950	52	9.43	2.28	61.08	1142
422.78	253	954	44	9.22	1.8	53.35	1098
413.55	265.6	1160	62	10.51	1.65	72.9	1622
445.67	292.02	1667	66	11.51	1.55	79.64	2285
416.05	249.8	954	44	9.22	1.8	53.35	1098
546.41	351.37	3031	88	14.69	1.03	112.36	4662
452.79	288.37	1432	72	11.63	1.42	85.84	2428

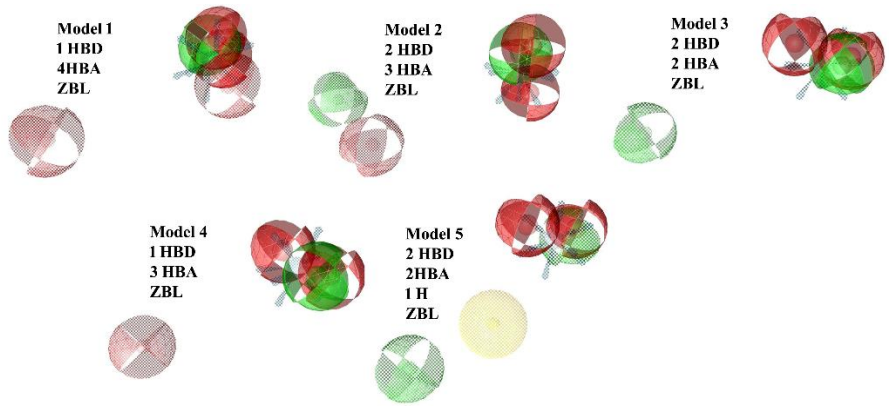

Fig A Top five pharmacophore models. HBD, Hydrogen Bond Donor (green); HBA, Hydrogen Bond Acceptor (red); H, Hydrophobic site (yellow); ZBL, Zinc Binding Location (blue)

Table F pIC_{50} and average pIC_{50} values of training set compounds

Compound	pIC_{50} values (nm)				Avg. pIC_{50}
	HDAC1	HDAC2	HDAC3	HDAC8	
MS-275	6.92	6.60	6.92	***	6.81
LBH-589	6.60	6.60	6.60	6.60	6.60
LAQ-824	8.49	7.80	7.97	8.41	8.16
TSA	8.30	7.74	8.69	7.60	8.07
SAHA	7.46	6.69	7	7	7.03
Belinostat	7.74	***	7.33	***	7.53
Oxamflatin	7	6.63	6.63	6.63	6.72
Pyroxamide	6.70	6.70	6.70	6.70	6.70
Mocetinostat	6.82	6.53	6.21	***	6.51
Scriptaid	6.69	6.15	7	6.52	6.58

Table G Screening results of pharmacophore models for validation

Model No.	True Positive (TP)	False Positive (FP)	True Negative (TN)	False Negative (FN)	Ha (active retrieved)	Ht (total retrieved)
Model-1	37	10	21	9	37	47
Model-2	24	10	20	8	24	34
Model-3	27	9	21	14	27	36
Model-4	22	14	16	19	22	36
Model-5	20	8	22	21	20	28

Formulas for sensitivity and specificity:

$$Sensitivity = \frac{TP}{TP+FN}$$
$$Specificity = \frac{TN}{TN+FP}$$

Whereas
$TP = True\ Positives$
$FN = False\ Negative$
$TN = True\ Negative$
$FP = False\ Positive$

Formulas for %Y, E.F and G.H:

$$\%Y = \left(\frac{Ha}{Ht}\right) * 100$$
$$E.F = \frac{(Ha/Ht)}{(A/D)}$$
$$GH = \frac{\{Ha\,(3A+Ht)\}}{(4*Ht*A)} * \ 1 - \frac{(Ht-Ha)}{(D-A)}$$

Whereas
$\%Y = Percent\ Yeild$
$Ha = Total\ actives\ retreived$
$Ht = Total\ hits\ retrieved$
$A = Total\ actives\ in\ dataset$
$D = Total\ decoys\ in\ dataset$

Formula for pIC_{50}:

$$pIC_{50} = -\log IC50\,(M)$$

Formula for Geometric Mean:

$$Geometric\ Mean = \ (\prod_{k=1}^{n} A_k)^{\frac{1}{n}} = \sqrt[n]{A_1 A_2 \ldots \ldots . A_n}$$

Where
$n = Total\ number\ of\ IC50\ values\ for\ each\ compound$
$A = Each\ IC_{50}\ value$

ANoVA represents hypothesis testing where the null and alternate hypothesis are:

$$H_{\circ}: \beta_i = 0 \quad for\ all\ i, i = 1, \ldots\ldots, n$$
$$H_1: \beta_i \neq 0 \quad for\ atleast\ 1\ coefficient$$

Where
$H_{\circ}$ = Null hypothesis
H_1 = Alternate hypothesis

Table H Binding energies of 16 novel hits compounds with class 1 HDACs

Inhibitors	Binding Energies (kcal/mol)			
	HDAC1	HDAC2	HDAC3	HDAC8
1	-14	-21.87	-10	-24
2	-10	-16	-6	-9
3	-13	-23.72	-18	-25
4	-10	-22.35	-14	-21.8
5	-10	-16	-10	-14
6	-11	-22	-13	-14.7
7	-10	-23.62	-17	-23.7
8	-17	-24	-14	-21.4
9	-21	-29.26	-22	-18
10	-16	-23.33	-16	-18.3
11	-16	-23	-16	-18
12	-11	-22	-16	-23.1
13	-20	-25.15	-22	-23.6
14	-20	-24.56	-21	-26
15	-15	-24	-10	-19.3
16	-14	-25.58	-13	-23.8

Table I Molecular descriptors for 10 selected lead-like compounds

	Mol. Weight	N	Mol. Polariza-bility	Huckel Analysis (pi energy)	Molar Refracti-vity	LogD	LogP	TPSA	(nOHNH)	(nON)	SASA	Vander Wall's Volume
C1	361.29	6	32.93	53.19	87.88	2.6	2.56	87.85	2	6	439.11	287.38
C2	385.36	7	38.46	50.97	100.8	1.29	1.63	106.31	2	8	528.36	329.62
C3	261.06	4	25.1	33.5	65.54	0.2	0.61	95.69	2	6	335.39	218.52
C4	377.29	5	32.25	53.54	89.73	1.8	1.9	110	2	8	463.5	294.9
C5	298.3	3	30.25	39.28	101.55	3.4	1.4	80.15	2	6	379.51	250.87
C6	274.7	3	27.8	33.77	75.02	2.8	3.3	61.69	2	4	346.05	227.67
C7	355.1	6	35.91	46.65	94.34	1.45	1.7	97.08	2	4	480.67	303.33
C8	360.4	5	36.8	43.98	91.985	1.2	1.8	111.63	3	7	485.46	298.5
C9	431.2	5	36.05	40.64	92.46	-0.2	-0.12	138.67	4	9	475.7	307.86
C10	309.3	4	32.77	38.09	84.65	2.2	2.9	78.62	2	5	417.63	270.02

Continued

Weiner Index (W)	Platt Index	Randic Index	Balaban Index	Harary Index	Szeged Index
1808	132	17.72	1.53	94.77	2565
1651	76	11.94	1.33	89.34	2404
748	56	8.97	1.67	60.24	1268
2030	84	12.76	1.43	100.4	2740
1235	64	1.72	1.34	72.57	1930
838	52	9.15	1.43	57.32	1186
1847	78	12.51	1.5	94.43	2704
1719	78	11.88	1.25	88.67	2416
1710	76	11.57	1.62	87.73	2388
1200	70	11.06	1.56	81.88	2086

N= No. of rotatable bonds

TPSA= Topological Polar Surface Area

nOHNH= Hydrogen Bonds Donor

nON= Hydrogen Bond Acceptors

SASA= Solvent Accessible Surface Area

Table J IUPAC names and SMILE codes for compound C1-C10

Compound	IUPAC name	SMILE code
C1	2-{[(2Z)-2-{[2-(difluoromethoxy)phenyl]methylidene}-3-oxo-2,3-dihydro-1-benzofuran-6-yl]oxy}acetamide	NC(=O)COC1=CC=C2C(=O)\C(OC2=C1)=C\C3=C(OC(F)F)C=CC=C3
C2	(3-{[(2Z)-6-(carbamoylmethoxy)-3-oxo-2,3-dihydro-1-benzofuran-2-ylidene]methyl}phenyl)azinic acid	NC(=O)COC1=CC=C2C(=O)\C(OC2=C1)=C\C3=CC(=CC=C3)[NH+](O)[O-]
C3	2-[(3-acetyl-2-oxo-2H-chromen-7-yl)oxy]acetamide	CC(=O)C1=CC2=C(OC1=O)C=C(OCC(N)=O)C=C2
C4	({1,7-dimethyl-4-oxo-3H,4H-furo[3,4-d]pyridazin-5-yl}carbamoyl)methyl 3,5-difluorobenzoate	CC1=C2C(=NNC(=O)C2=C(NC(=O)COC(=O)C3=CC(=CC(=C3)F)F)O1)C
C5	N'-[(1E)-1,4-benzodioxin-6-ylmethylidene]-3-hydroxybenzohydrazide	OC1=CC=CC(=C1)C(=O)N\N=C\C2=CC3=C(O[CH2]=[CH2]O3)C=C2
C6	N'-[(1E)-(4-chlorophenyl)methylidene]-3-hydroxybenzohydrazide	OC1=CC=CC(=C1)C(=O)N\N=C\C2=CC=C(Cl)C=C2

C7	2-{[(2Z)-2-[(3,4-dimethoxyphenyl)methylidene]-3-oxo-2,3-dihydro-1-benzofuran-6-yl]oxy}acetamide	COC1=C(OC)C=C(C=C1)\C=C2/OC3=CC(=CC=C3C2=O)OCC(N)=O
C8	7-methoxy-N-[(4-sulfamoylphenyl)methyl]-1-benzofuran-2-carboxamide	COC1=C2OC(=CC2=CC=C1)C(=O)NCC3=CC=C(C=C3)[S](N)(=O)=O
C9	2-(5-bromo-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-N-[1-(4-sulfamoylphenyl)ethyl]acetamide	CC(NC(=O)CN1C=C(Br)C(=O)NC1=O)C2=CC=C(C=C2)[S](N)(=O)=O
C10	2-[(4-methyl-2-oxo-3-phenyl-2H-chromen-6-yl)oxy]acetamide	CC1=C(C(=O)OC2=C1C=C(OCC(N)=O)C=C2)C3=CC=CC=C3

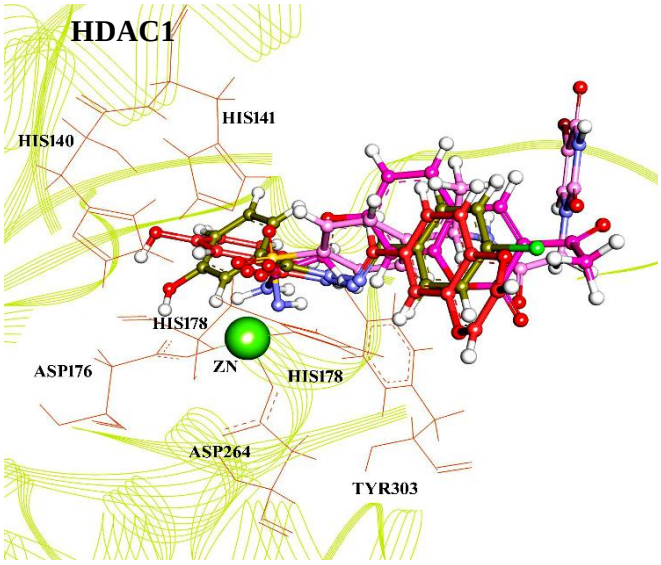

Fig B Binding view of selected compounds with HDAC1. A combined 3D binding view of C3, C5, C6 and C9 compounds with HDAC1. These compounds form hydrogen bonds with HIS140, HIS141, ASP176, HIS178, ASP264 and TYR303 and Zn+2 of HDAC1

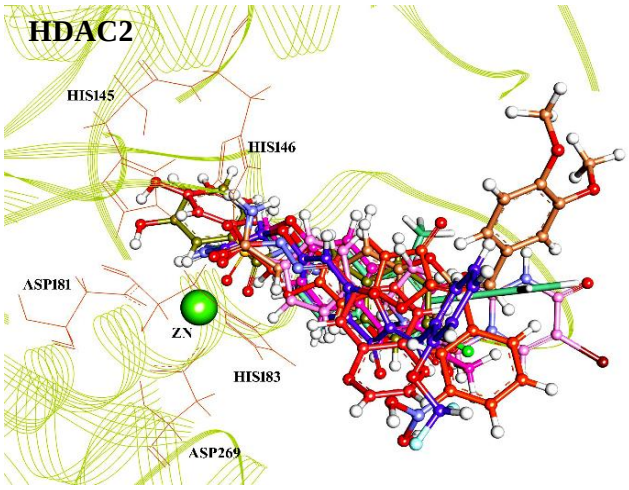

Fig C Combined 3D binding view of C1, C2, C3, C5, C6, C7, C9 and C10 compounds with HDAC2. These compounds formed hydrogen bonds with HIS145, HIS146, ASP181, HIS183, ASP269 and Zn+2 of HDAC2

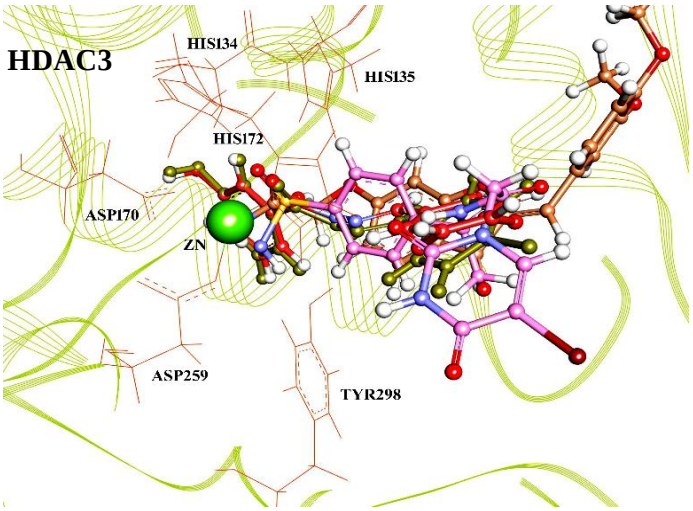

Fig D Binding view of selected compounds with HDAC3. Combined 3D binding view of C5, C6, C7 and C9 compounds with HDAC3. These compounds formed hydrogen bonds with HIS134, HIS135, ASP170, HIS172, ASP259, TYR298 and Zn+2 of HDAC3

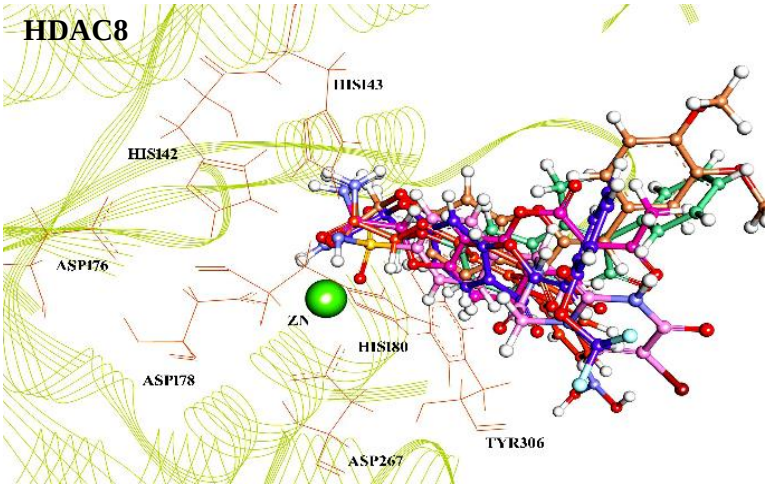

Fig E Binding view of selected compounds with HDAC8. Combined 3D binding view of compound C1, C2, C3, C7, C9 and C10 with HDAC8. These compounds formed hydrogen bonds with HIS142, HIS143, ASP178, HIS180, ASP267, TYR306 and Zn+2 of HDAC8.

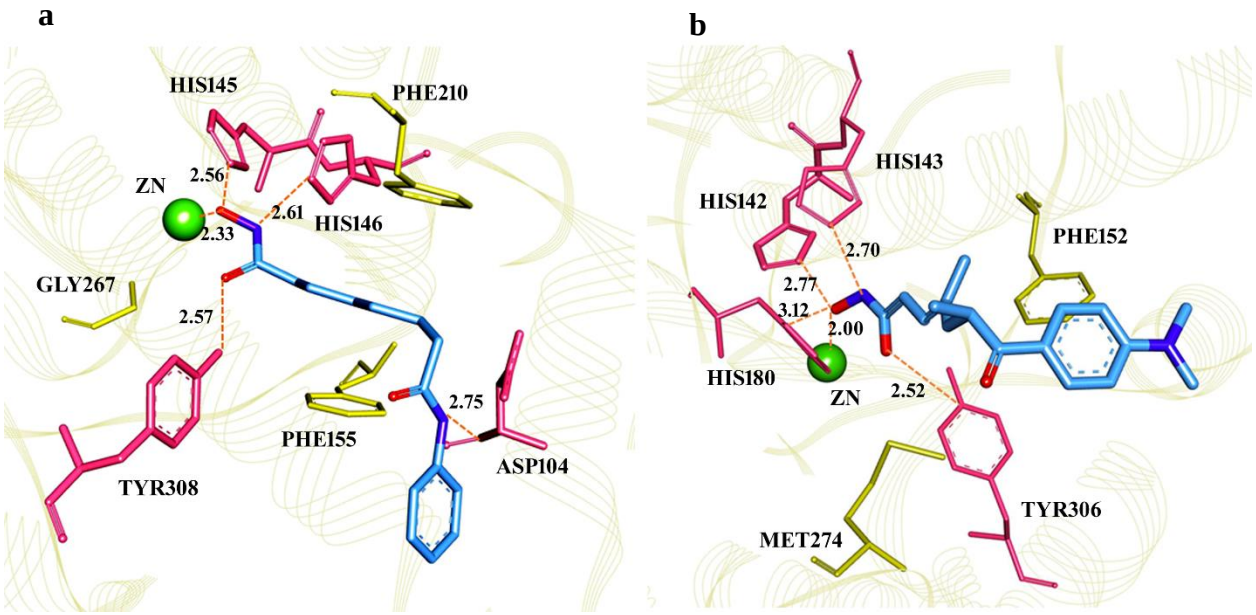

Fig F Experimental 3D binding view of **(a)** compound SAHA with HDAC2 and **(b)** compound Trichostatin A with HDAC8. Residues shown in pink formed hydrogen bonds with inhibitors. Hydrophobic residues and Zn^{+2} are shown in yellow and green, respectively.

HDAC2

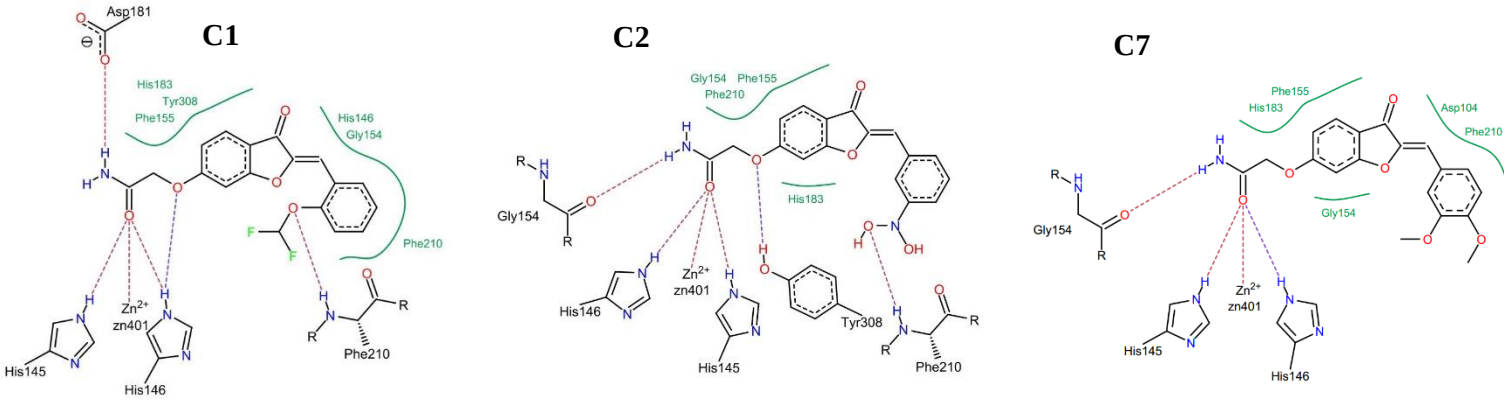

Fig G 2D binding view of C1, C2 and C7 with HDAC2.

HDAC8

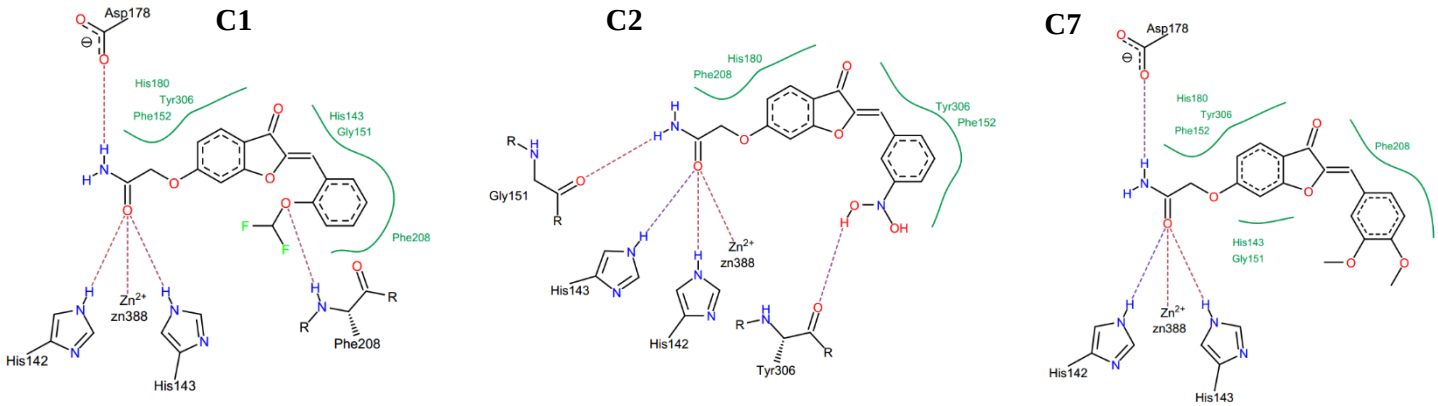

Fig H 2D binding view of C1, C2 and C7 with HDAC8.

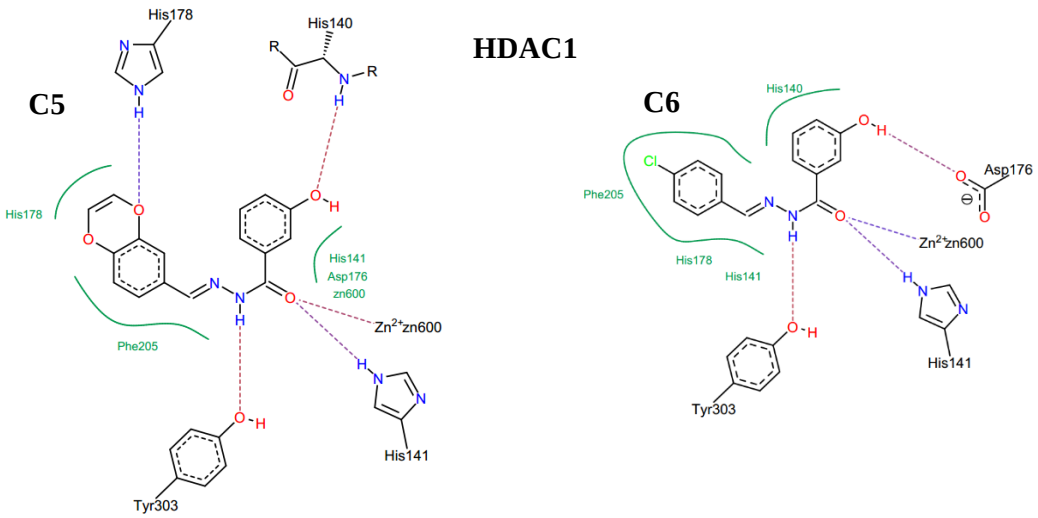

Fig I 2D binding view of C5 and C6 with HDAC1.

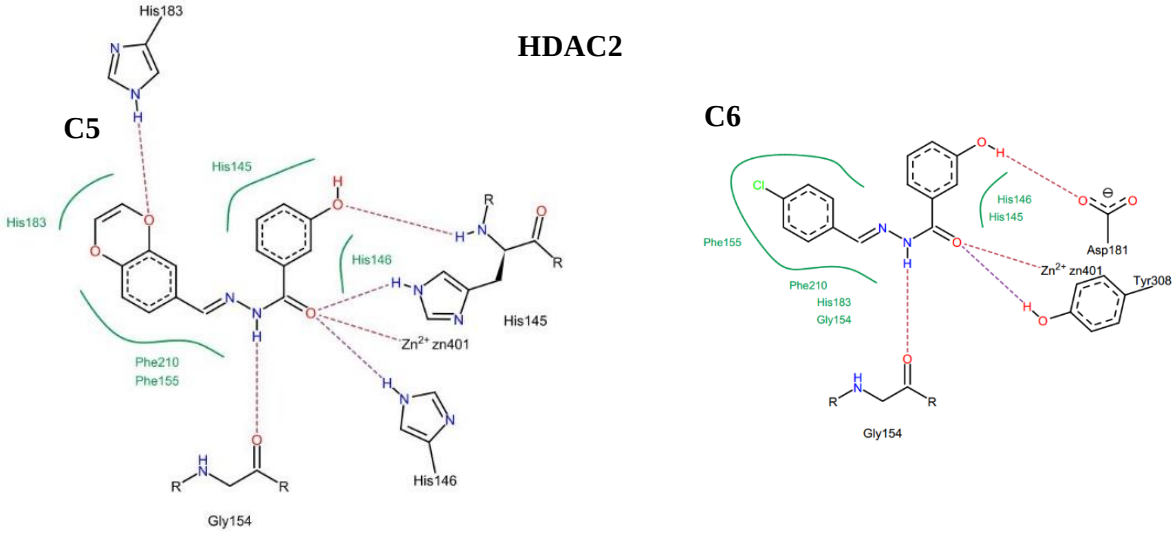

Fig J 2D binding view of C5 and C6 with HDAC2.

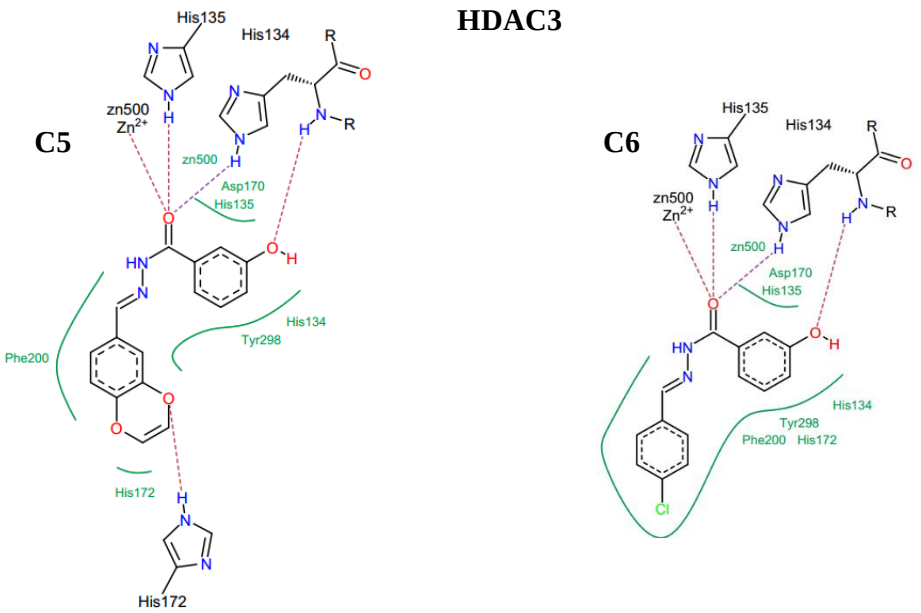

Fig K 2D binding view of C5 and C6 with HDAC3.