In silico design of novel benzohydroxamate-based compounds as inhibitors for histone deacetylase 6 based on 3D-QSAR, molecular docking, and molecular dynamics simulations

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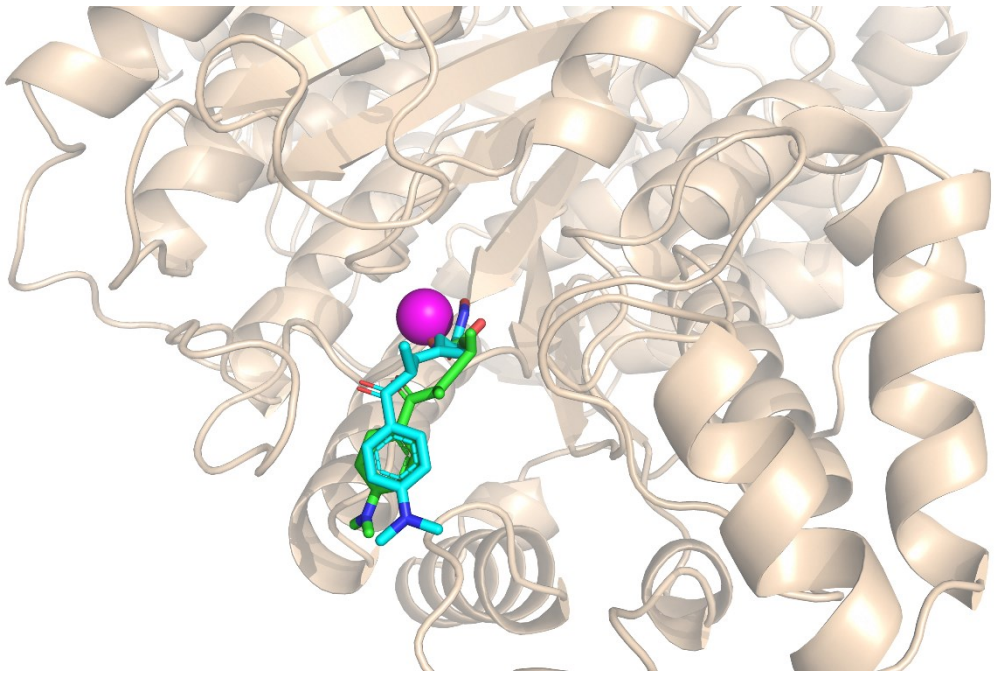


Figure S1. The re-docked result of theHDAC6 co-crystal ligand (TSN) in its binding site. The co-crystal conformation was shown as green sticks and the re-docked conformation was shown as blue sticks.

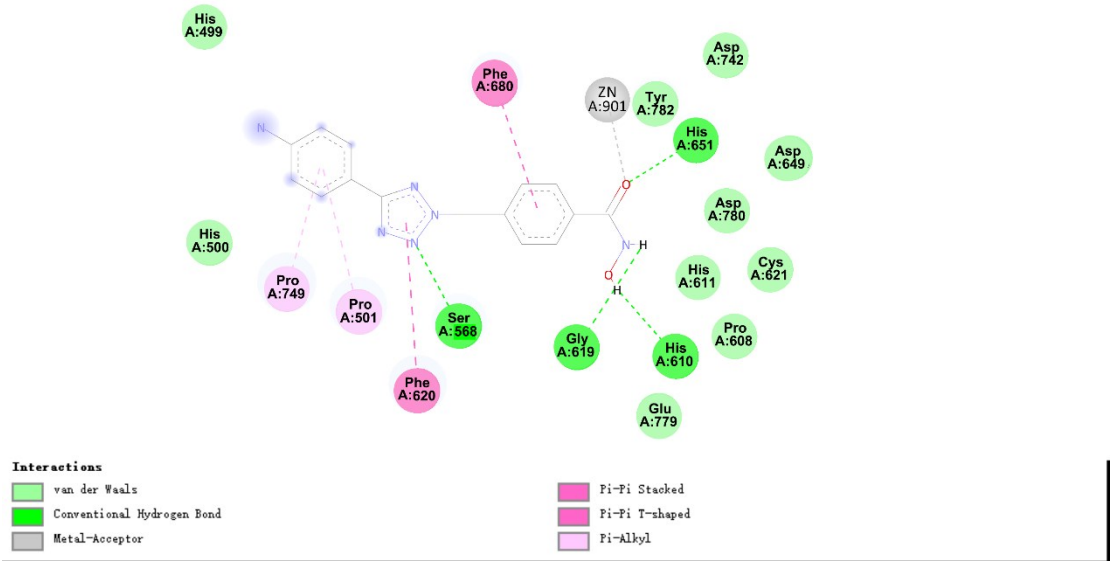
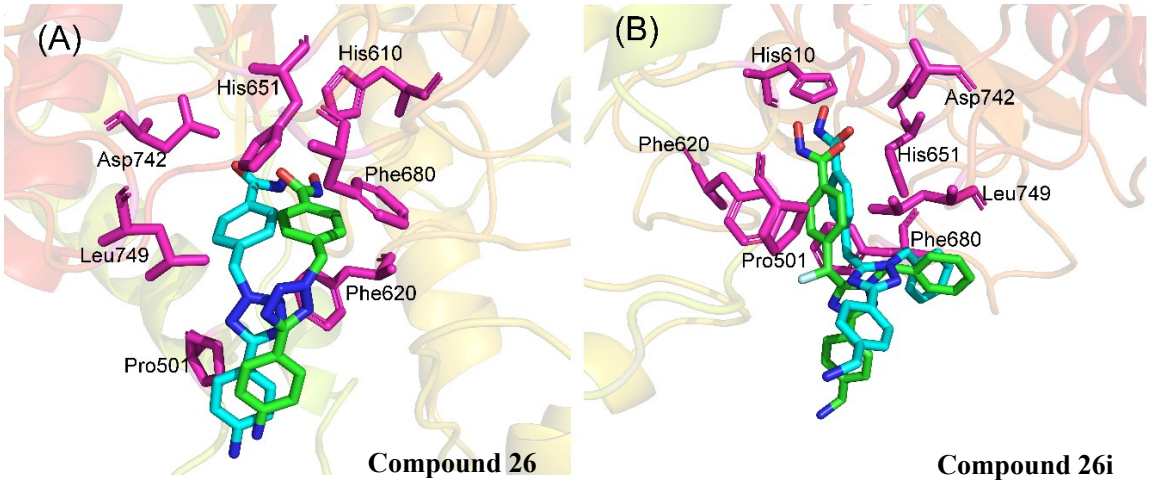
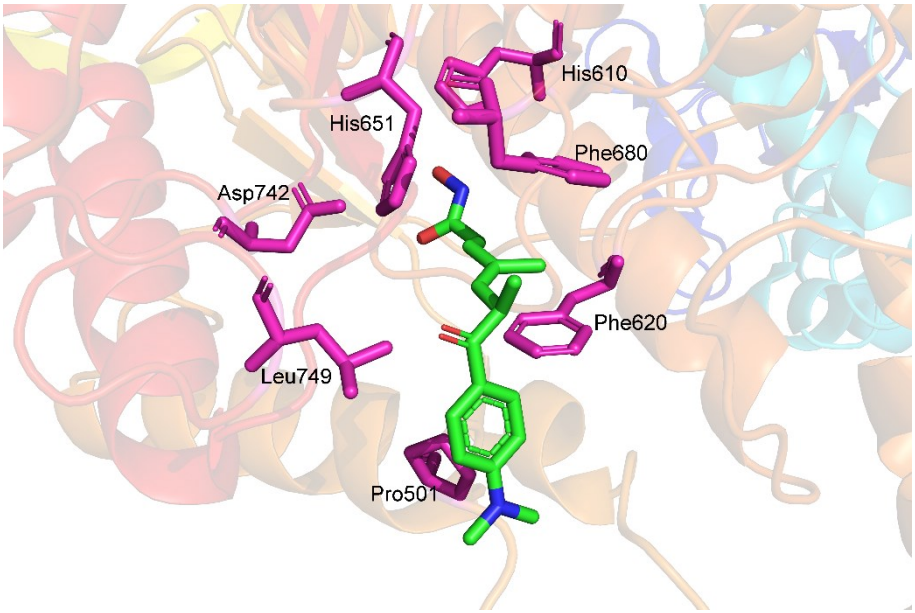


Figure S2. Docking model of HDAC6 with compound 26(2D).

FigureS3. The docking conformation of CSF-1R with all compounds

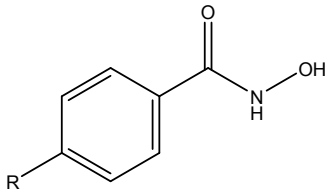


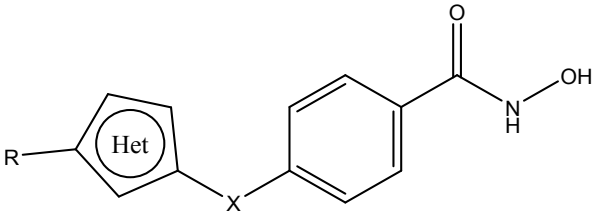
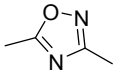
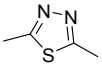
FigureS4. the initial and final complex structures of two (26/26i). The inital conformation was shown as green sticks and the final conformation was shown as blue sticks.

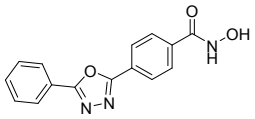
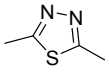
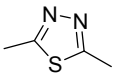


FigureS5. The co-crystal ligand TSN with HDAC6(5EDU)

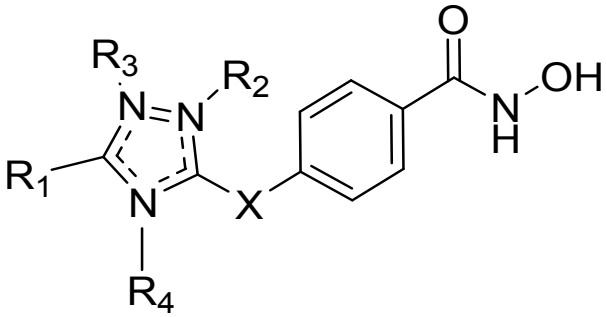
Table S1. Experimental and predicted activity (pIC_{50}) values of compounds

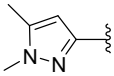
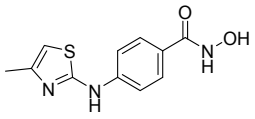
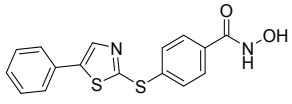
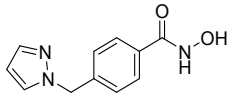
No.	R	R1	R2	R3	R4	Obs.	CoMFA	Err(%)	CoMSIA	Err(%)	Score
											
1	-H					5.63	5.62	0.18	5.70	1.24	5.11
2*	$-NH_2$					5.86	5.83	0.58	5.97	1.81	4.96
3						6.57	6.54	0.40	6.56	0.17	4.67
4						6.16	6.38	3.56	6.12	0.63	5.57
5						6.45	6.38	1.05	6.52	1.04	6.51
6						6.70	6.82	1.81	6.70	0.01	5.47

No.	Het	R	X	Obs.	CoMFA	Err(%)	CoMSIA	Err(%)	Score
									
7*			CH_2	8.30	7.71	7.17	7.38	11.07	8.14
8*			CH_2	8.40	7.86	6.48	8.45	0.61	7.42
9			CH_2	8.52	8.36	1.84	8.27	2.91	6.42
10			CH_2	7.28	7.22	0.82	7.31	0.36	7.43
11*			CH_2	8.22	7.95	3.24	7.71	6.19	6.95
12			CH_2	7.80	7.81	0.12	7.85	0.65	5.52

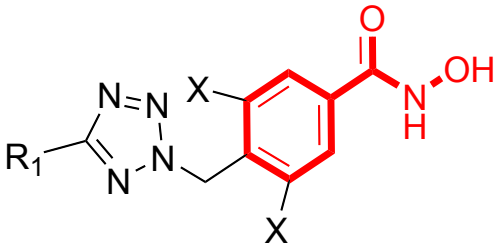
13						6.18	6.24	0.92	6.16	0.31	7.41
14			CH_2			7.77	7.76	0.15	7.75	0.28	6.78
15			S			8.22	8.15	0.89	8.16	0.71	6.37
16			S			8.22	8.14	0.99	8.15	0.85	6.54
17*			NH			7.18	7.04	1.95	7.15	0.47	5.52
18			NH			6.87	6.92	0.74	6.85	0.25	6.54

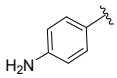
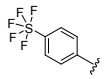
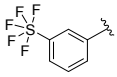
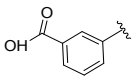
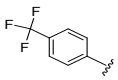
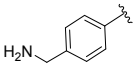
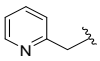
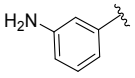
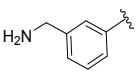
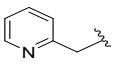
No.	R_1	R_2	R_3	R_4	X	Obs.	CoMFA	Err(%)	CoMSIA	Err(%)	Score



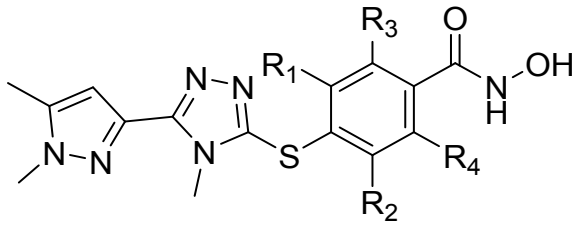
19		abs	abs		S	7.25	7.21	0.57	7.22	0.43	7.31
20		abs	abs	CH_3	S	8.10	8.07	0.33	7.90	2.49	6.51
21		abs	abs	CH_3	S	8.30	8.34	0.49	8.36	0.76	8.00
22			abs	abs	CH_2	6.48	6.43	0.71	6.53	0.76	7.74
23						6.86	6.95	1.31	6.86	0.04	5.45
24*						7.21	8.19	13.58	7.60	5.40	6.60
25						6.99	6.84	2.12	6.92	1.04	5.82

No.	R_1	X	Obs.	CoMFA	Err(%)	CoMSIA	Err(%)	Score



26		H			9.00	8.86	1.53	9.03	0.36	7.24
27		H			7.60	7.60	0.03	7.59	0.09	6.96
28		H			7.59	7.60	0.08	7.60	0.09	6.67
29*		H			7.92	8.53	7.70	8.30	4.76	6.44
30		H			7.96	7.92	0.49	7.96	0.04	7.14
31		H			8.70	8.84	1.61	8.76	0.69	6.09
32		H			8.05	7.94	1.37	7.99	0.76	5.93
33		H			8.15	8.14	0.13	8.10	0.61	6.30
34		H			7.70	7.60	1.25	7.74	0.52	7.18
35		H			7.60	7.54	0.84	7.70	1.34	6.41
36		F			8.15	8.27	1.48	8.05	1.28	6.57
37		F			8.30	8.38	0.96	8.25	0.57	5.71
38		F			8.52	8.42	1.20	8.58	0.66	6.69
39		F			8.40	8.40	0.04	8.45	0.60	7.93
40*		F			7.66	8.14	6.32	8.15	6.37	6.55
41		F			8.00	7.96	0.51	8.04	0.50	6.57

No.	R_1	R_2	R_3	R_4	Obs.	CoMFA	Err(%)	CoMSIA	Err(%)	Score



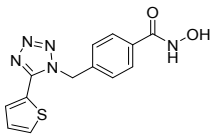
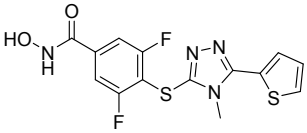
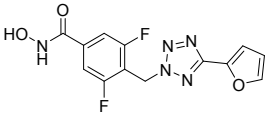
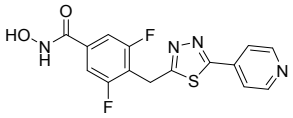
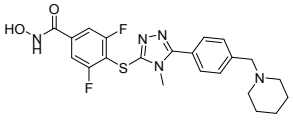
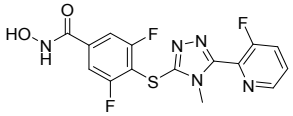
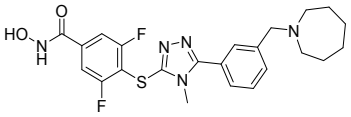
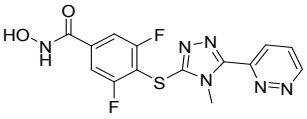
42	F	F	H	H	8.22	8.37	1.84	8.32	1.22	6.69
43	F	F	F	F	5.60	5.48	2.09	5.51	1.64	6.66
44	H	H	H	F	5.65	5.71	1.13	5.73	1.43	7.71
45					7.77	8.10	4.29	7.96	2.41	6.28
46*					8.05	8.08	0.32	7.80	3.09	5.77
47*					8.52	8.24	3.33	7.71	9.55	5.79
48					8.40	8.38	0.25	8.42	0.27	7.08
49					8.30	8.31	0.13	8.28	0.24	6.96
50					8.22	8.17	0.57	8.25	0.33	6.64
51					8.00	8.05	0.59	8.04	0.51	6.88
52*					7.89	8.18	3.64	8.07	2.33	5.65

Table S2. 31 possible combinations of COMSIA molecular fields

CoMSIA	*LOO*		*PLS*			*Normalized Coefficients*				
	n	q^2	R^2	*SEE*	*F*	*S*	*E*	*H*	*D*	*A*
S	*2*	*0.254*	*0.596*	*0.589*	*27*	*1*				
E	*7*	*0.415*	*0.951*	*0.221*	*90*		*1*			
H	*3*	*0.409*	*0.702*	*0.512*	*29*			*1*		
D	*7*	*0.511*	*0.666*	*0.575*	*9*				*1*	
A	*3*	*0.128*	*0.564*	*0.620*	*15*					*1*
S+E	*10*	*0.741*	*0.993*	*0.085*	*448*	*0.413*	*0.587*			
S+H	*3*	*0.433*	*0.711*	*0.504*	*30*	*0.467*		*0.533*		
S+D	*10*	*0.551*	*0.978*	*0.156*	*130*	*0.771*			*0.229*	
S+A	*3*	*0.296*	*0.681*	*0.530*	*26*	*0.506*				*0.494*
E+H	*7*	*0.589*	*0.958*	*0.205*	*106*		*0.610*	*0.390*		
E+D	*4*	*0.570*	*0.822*	*0.401*	*41*		*0.631*		*0.369*	
E+A	*8*	*0.436*	*0.956*	*0.213*	*86*		*0.599*			*0.401*
H+D	*4*	*0.567*	*0.852*	*0.366*	*51*			*0.686*	*0.314*	
H+A	*4*	*0.428*	*0.781*	*0.446*	*32*			*0.529*		*0.471*
D+A	*4*	*0.497*	*0.854*	*0.364*	*52*				*0.384*	*0.616*
S+E+H	*10*	*0.673*	*0.996*	*0.069*	*676*	*0.306*	*0.456*	*0.238*		
S+E+D	*9*	*0.733*	*0.992*	*0.094*	*404*	*0.405*	*0.428*		*0.167*	
S+E+A	*8*	*0.653*	*0.979*	*0.147*	*185*	*0.343*	*0.432*			*0.225*
S+H+D	*10*	*0.632*	*0.993*	*0.087*	*427*	*0.446*		*0.375*	*0.180*	
S+H+A	*3*	*0.424*	*0.733*	*0.485*	*33*	*0.320*		*0.384*		*0.296*
S+D+A	*8*	*0.576*	*0.984*	*0.128*	*244*	*0.431*			*0.235*	*0.334*
E+H+D	*6*	*0.619*	*0.943*	*0.234*	*93*		*0.477*	*0.362*	*0.161*	
E+H+A	*8*	*0.604*	*0.977*	*0.154*	*167*		*0.426*	*0.304*		*0.270*
E+D+A	*6*	*0.541*	*0.919*	*0.278*	*64*		*0.376*		*0.256*	*0.368*
H+D+A	*4*	*0.570*	*0.871*	*0.342*	*60*			*0.356*	*0.257*	*0.387*
S+E+H+D	*10*	*0.688*	*0.996*	*0.066*	*744*	*0.301*	*0.348*	*0.219*	*0.130*	
S+E+H+A	*10*	*0.645*	*0.995*	*0.073*	*640*	*0.244*	*0.359*	*0.209*		*0.188*
S+E+D+A	*8*	*0.680*	*0.983*	*0.134*	*224*	*0.305*	*0.312*		*0.158*	*0.225*
S+H+D+A	*9*	*0.625*	*0.992*	*0.092*	*420*	*0.301*		*0.265*	*0.186*	*0.248*
E+H+D+A	*7*	*0.616*	*0.964*	*0.189*	*125*		*0.319*	*0.259*	*0.151*	*0.271*
S+E+H+D+A	*9*	*0.675*	*0.992*	*0.089*	*454*	*0.230*	*0.279*	*0.182*	*0.131*	*0.178*

Table S3. SMILES notation for the designed molecules

No.	SMILES
26	[H]N([H])c1c([H])c([H])c(c([H])c1[H])C=2N=NN(N=2)C([H])([H])c3c([H])c([H])c(c([H])c3[H])C(=O)N([H])O[H]
26a	[H]N([H])c1c([H])c([H])c(c([H])c1[H])C2=NC(=NN2c3c([H])c([H])c([H])c([H])c3[H])C([H])([H])c4c([H])c([H])c(c([H])c4[H])C(=O)N([H])O[H]
26b	[H]N([H])c1c([H])c([H])c(c([H])c1[H])C2=NC(=NN2[S](=O)(=O)O[H])C([H])([H])c3c([H])c([H])c(c([H])c3[H])C(=O)N([H])O[H]
26c	[H]N([H])c1c([H])c([H])c(c([H])c1[H])C2=NC(=NN2C([H])([H])c3c([H])c([H])c([H])c([H])c3[H])C([H])([H])c4c([H])c([H])c(c([H])c4[H])C(=O)N([H])O[H]
26d	[H]N([H])c4c([H])c([H])c(/C1=N/N(C(=N1)C([H])([H])c2c([H])c([H])c(c([H])c2[H])C(=O)N([H])O[H])C([H])([H])c3c([H])c([H])c([H])c([H])c3[H])c([H])c4[H]
26e	[H]C([H])(c4c([H])c([H])c(/C1=N/N(C(=N1)C([H])([H])c2c([H])c([H])c(c([H])c2[H])C(=O)N([H])O[H])C([H])([H])c3c([H])c([H])c([H])c([H])c3[H])c([H])c4[H])N([H])[H]
26f	O=C(OC([H])([H])[H])c4c([H])c([H])c(/C1=N/N(C(=N1)C([H])([H])c2c([H])c([H])c(c([H])c2[H])C(=O)N([H])O[H])C([H])([H])c3c([H])c([H])c([H])c([H])c3[H])c([H])c4[H]
26g	O=C(c4c([H])c([H])c(/C1=N/N(C(=N1)C([H])([H])c2c([H])c([H])c(c([H])c2[H])C(=O)N([H])O[H])C([H])([H])c3c([H])c([H])c([H])c([H])c3[H])c([H])c4[H])N([H])[H]
26h	[H]C([H])(c4c([H])c([H])c(/C1=N/N(C(=N1)[C@@]([Cl])([H])c2c([H])c([H])c(c([H])c2[H])C(=O)N([H])O[H])C([H])([H])c3c([H])c([H])c([H])c([H])c3[H])c([H])c4[H])N([H])[H]
26i	[H]C([H])(c4c([H])c([H])c(/C1=N/N(C(=N1)[C@@]([F])([H])c2c([H])c([H])c(c([H])c2[H])C(=O)N([H])O[H])C([H])([H])c3c([H])c([H])c([H])c([H])c3[H])c([H])c4[H])N([H])[H]
26j	[H]N([H])c4c([H])c([H])c(/C1=N/N(C(=N1)[C@]([H])([F])c2c([H])c([H])c(c([H])c2[H])C(=O)N([H])O[H])C([H])([H])c3c([H])c([H])c([H])c([H])c3[H])c([H])c4[H]
26k	O=C(c4c([H])c([H])c(/C1=N/N(C(=N1)[C@@]([F])([H])c2c([H])c([H])c(c([H])c2[H])C(=O)N([H])O[H])C([H])([H])c3c([H])c([H])c([H])c([H])c3[H])c([H])c4[H])N([H])[H]

Table S4. Free energy decomposition for key residues of HDAC6 (MM/GBSA)

Residue	Van der Waals	Electrostatic	Polar Solvation	Non-Polar Solvation	Total
Compound 26 / HDAC6 system					
ASP742	-0.8974	-0.6166	-7.3693	-0.5377	-9.4211
HIS610	0.2695	-23.5513	16.5578	-0.3577	-7.0817
HIS651	-1.1668	-10.0554	8.936	-0.9265	-3.2128
GLY780	-0.3704	-3.5996	1.259	-0.3818	-3.0927
PRO501	-1.3662	-0.656	0.4124	-1.0383	-2.6482
LEU749	-1.2785	-0.0048	-0.0773	-1.1672	-2.5277
PHE620	-1.4119	-0.1114	0.1389	-1.0648	-2.4492
ASP497	-0.1254	-0.0238	-1.9976	-0.2729	-2.4198
TYR782	-1.6787	-0.3527	1.0094	-1.2591	-2.2811
HIS500	-1.0607	-0.2615	0.1152	-0.6806	-1.8876
PHE680	-0.5898	0.0146	-0.0662	-0.4595	-1.1008
Compound 26i / HDAC6 system					
ASP742	-0.5863	-0.1385	-7.6818	-0.2283	-8.635
HIS610	0.1328	-20.8476	14.3289	-0.289	-6.6749
HIS651	-2.2092	-13.0986	9.8401	-1.5016	-6.9693
GLY780	-0.4629	-1.8449	0.4733	-0.4287	-2.2632
PRO501	-1.0022	-0.4648	0.3371	-0.7664	-1.8964
LEU749	-1.6947	-0.4321	0.3443	-1.6044	-3.387
PHE620	-2.3709	-0.0733	0.2475	-1.6647	-3.8614
ASP497	-0.1733	3.6248	-4.2704	-0.195	-1.0141
TYR782	-0.7371	-0.8851	0.9103	-0.5963	-1.3083
HIS500	-0.6857	-0.2709	0.2099	-0.3981	-1.1448
PHE680	-2.2282	0.0841	-0.2666	-1.7116	-4.1223

Table S5. Results of Y-randomization test

No.	Method	LOO		PLS		
		n	q^2	r^2	*SEE*	*F*
1	CoMFA	1	-0.110	0.077	0.879	3.233
	CoMSIA	1	-0.071	0.171	0.833	8.020
2	CoMFA	2	-0.357	0.216	0.820	5.247
	CoMSIA	2	-0.433	0.336	0.755	9.624
3	CoMFA	2	-0.189	0.337	0.754	9.661
	CoMSIA	2	-0.140	0.356	0.743	10.512
4	CoMFA	1	-0.122	0.058	0.888	2.402
	CoMSIA	1	-0.196	0.166	0.835	7.762
5	CoMFA	1	0.017	0.157	0.840	7.239
	CoMSIA	1	-0.015	0.222	0.807	11.142
6	CoMFA	2	-0.254	0.345	0.750	9.992
	CoMSIA	2	-0.369	0.394	0.721	12.355
7	CoMFA	2	-0.333	0.232	0.812	5.749
	CoMSIA	2	-0.422	0.294	0.778	7.912
8	CoMFA	1	-0.052	0.067	0.883	2.796
	CoMSIA	1	-0.103	0.119	0.858	5.259
9	CoMFA	1	-0.067	0.059	0.887	2.445
	CoMSIA	1	-0.159	0.135	0.850	6.099
10	CoMFA	2	-0.236	0.294	0.779	7.898
	CoMSIA	2	-0.273	0.389	0.724	12.107
11	CoMFA	1	-0.300	0.050	0.891	2.049
	CoMSIA	1	-0.576	0.215	0.810	10.669
12	CoMFA	1	-0.095	0.041	0.896	1.650
	CoMSIA	1	-0.181	0.138	0.849	6.219
13	CoMFA	1	-0.047	0.058	0.887	2.417
	CoMSIA	1	-0.092	0.111	0.862	4.907
14	CoMFA	2	-0.105	0.317	0.766	8.815
	CoMSIA	1	-0.252	0.249	0.792	12.951
15	CoMFA	1	-0.314	0.058	0.888	2.387
	CoMSIA	1	-0.412	0.190	0.823	9.160
16	CoMFA	2	0.150	0.424	0.703	13.959
	CoMSIA	1	0.178	0.323	0.752	18.616
17	CoMFA	2	-0.294	0.296	0.778	7.973
	CoMSIA	1	-0.337	0.147	0.845	6.716
18	CoMFA	1	-0.126	0.039	0.896	1.598
	CoMSIA	1	-0.253	0.103	0.866	4.483
19	CoMFA	2	-0.208	0.263	0.795	6.786
	CoMSIA	2	-0.292	0.403	0.716	12.842
20	CoMFA	1	-0.129	0.074	0.880	3.103
	CoMSIA	1	-0.092	0.237	0.799	12.119

21	CoMFA	1	-0.038	□	0.081	0.877	3.440
	CoMSIA	1	-0.076	□	0.152	0.842	6.989
22	CoMFA	1	-0.147	□	0.082	0.876	3.480
	CoMSIA	1	-0.245	□	0.140	0.848	6.327
23	CoMFA	1	-0.321	□	0.047	0.893	1.911
	CoMSIA	2	-0.688	□	0.393	0.722	12.310
24	CoMFA	2	-0.094	□	0.380	0.730	11.637
	CoMSIA	1	-0.125	□	0.152	0.842	7.004
25	CoMFA	1	-0.119	□	0.065	0.884	2.698
	CoMSIA	1	-0.177	□	0.184	0.826	8.796
26	CoMFA	1	-0.081	□	0.049	0.892	2.015
	CoMSIA	1	-0.143	□	0.098	0.868	4.250
27	CoMFA	2	-0.146	□	0.269	0.792	6.982
	CoMSIA	2	-0.220	□	0.303	0.773	8.265
28	CoMFA	2	-0.410	□	0.265	0.794	6.868
	CoMSIA	2	-0.393	□	0.329	0.759	9.314
29	CoMFA	1	-0.086	□	0.064	0.855	2.680
	CoMSIA	1	-0.143	□	0.108	0.864	4.714
30	CoMFA	1	-0.097	□	0.042	0.895	1.704
	CoMSIA	1	-0.154	□	0.102	0.867	4.408
31	CoMFA	1	0.110	□	0.192	0.822	9.262
	CoMSIA	1	0.082	□	0.247	0.794	12.782
32	CoMFA	2	-0.089	□	0.283	0.785	7.482
	CoMSIA	1	-0.046	□	0.248	0.793	12.868
33	CoMFA	1	-0.114	□	0.078	0.878	3.282
	CoMSIA	1	-0.173	□	0.172	0.832	8.100
34	CoMFA	2	-0.383	□	0.262	0.796	6.757
	CoMSIA	2	-0.395	□	0.295	0.778	7.950
35	CoMFA	1	0.021	□	0.133	0.851	5.990
	CoMSIA	1	0.011	□	0.195	0.820	9.467
36	CoMFA	1	-0.102	□	0.060	0.887	2.500
	CoMSIA	1	-0.117	□	0.140	0.848	6.357
37	CoMFA	2	-0.281	□	0.353	0.745	10.385
	CoMSIA	2	-0.332	□	0.401	0.717	12.719
38	CoMFA	2	-0.379	□	0.310	0.770	8.533
	CoMSIA	2	-0.311	□	0.336	0.743	10.526
39	CoMFA	1	-0.019	□	0.110	0.863	4.796
	CoMSIA	1	-0.041	□	0.194	0.821	9.360
40	CoMFA	1	-0.109	□	0.067	0.884	2.780
	CoMSIA	1	-0.184	□	0.112	0.862	4.898
41	CoMFA	1	-0.152	□	0.065	0.884	2.705
	CoMSIA	1	-0.224	□	0.190	0.823	9.165
42	CoMFA	1	-0.108	□	0.072	0.881	3.024
	CoMSIA	2	-0.025	□	0.381	0.729	11.074

43	CoMFA	2	-0.439	0.278	0.787	7.307
	CoMSIA	2	-0.425	0.328	0.759	9.279
44	CoMFA	1	-0.083	0.070	0.882	2.933
	CoMSIA	1	-0.071	0.163	0.837	7.592
45	CoMFA	1	-0.150	0.058	0.887	2.423
	CoMSIA	1	-0.213	0.194	0.821	9.336
46	CoMFA	1	-0.342	0.045	0.894	1.824
	CoMSIA	1	-0.399	0.157	0.840	7.266
47	CoMFA	1	-0.140	0.143	0.895	1.756
	CoMSIA	1	-0.182	0.107	0.864	4.687
48	CoMFA	1	-0.104	0.053	0.890	2.185
	CoMSIA	1	-0.114	0.149	0.844	6.814
49	CoMFA	1	-0.402	0.038	0.897	1.535
	CoMSIA	1	-0.394	0.112	0.862	4.911
50	CoMFA	1	-0.066	0.169	0.834	7.936
	CoMSIA	1	-0.109	0.169	0.834	7.936
51	CoMFA	2	-0.348	0.304	0.773	8.302
	CoMSIA	2	-0.298	0.396	0.720	12.439
52	CoMFA	2	-0.078	0.356	0.744	10.494
	CoMSIA	1	-0.083	0.190	0.823	9.178
53	CoMFA	1	-0.110	0.066	0.884	2.767
	CoMSIA	1	-0.109	0.162	0.837	7.530
54	CoMFA	2	-0.286	0.334	0.756	9.151
	CoMSIA	2	-0.411	0.306	0.772	8.359
55	CoMFA	1	-0.039	0.069	0.882	2.893
	CoMSIA	1	-0.110	0.131	0.853	5.871

Table S6. Summary of some other 3D-QSAR results

No.	Method	LOO		PLS			Contribution of force fields				
		n	q^2	r^2	SEE	*F*	S	E	H	D	A
Alignment Ⅰ	CoMFA	2	0.315	0.622	0.547	40	-	-	-	-	-
	CoMSIA	3	0.305	0.747	0452	47	0.218	0.136	0.228	0.226	0.192

Note: Alignment Ⅰ: 3D-QSAR model based on docking-aligned ligands on the receptor. The training set and test set are consistent with the QSAR model in the article.