

Supplementary material

A novel class of *Schistosoma mansoni* histone deacetylase 8 (HDAC8) inhibitors identified by structure-based virtual screening and in vitro testing

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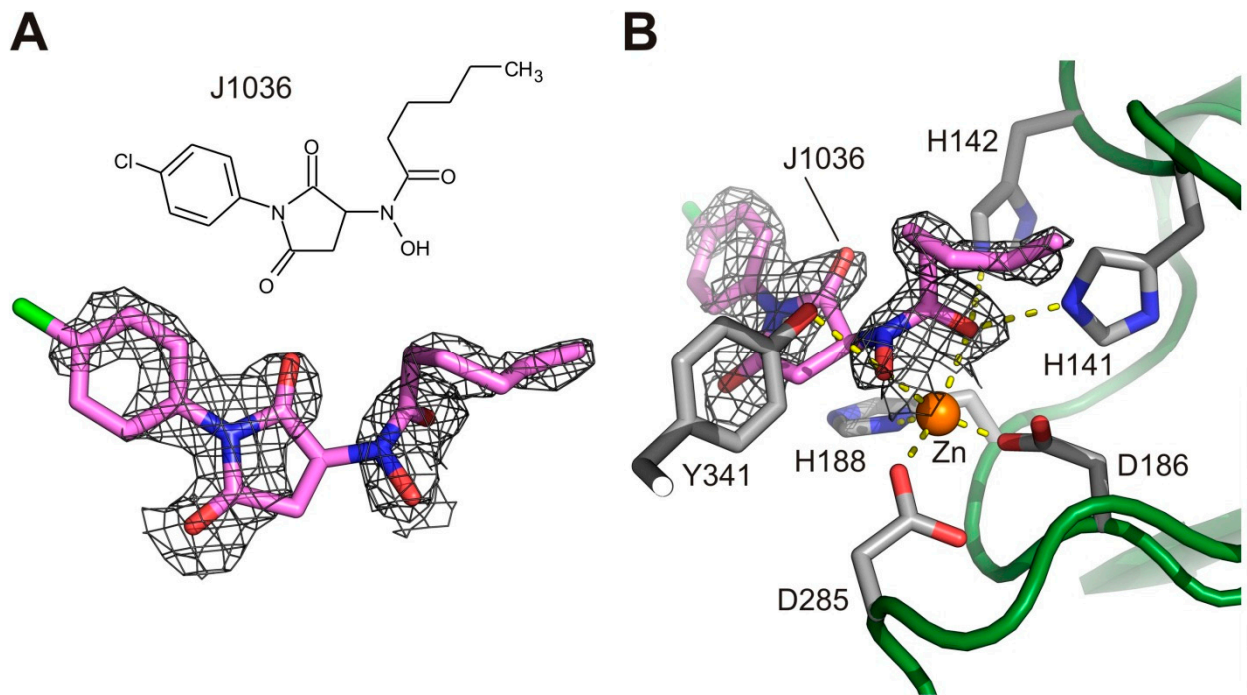


Figure S1. X-ray structure of smHDAC8/J1036 complex. A) Observed electron density (contour level 1σ) of the bound J1036 molecule B) smHDAC8/J1036 complex with electron density of bound J1036 (contour level 1σ). The inhibitor molecule is colored magenta, the zinc ion is colored gold.

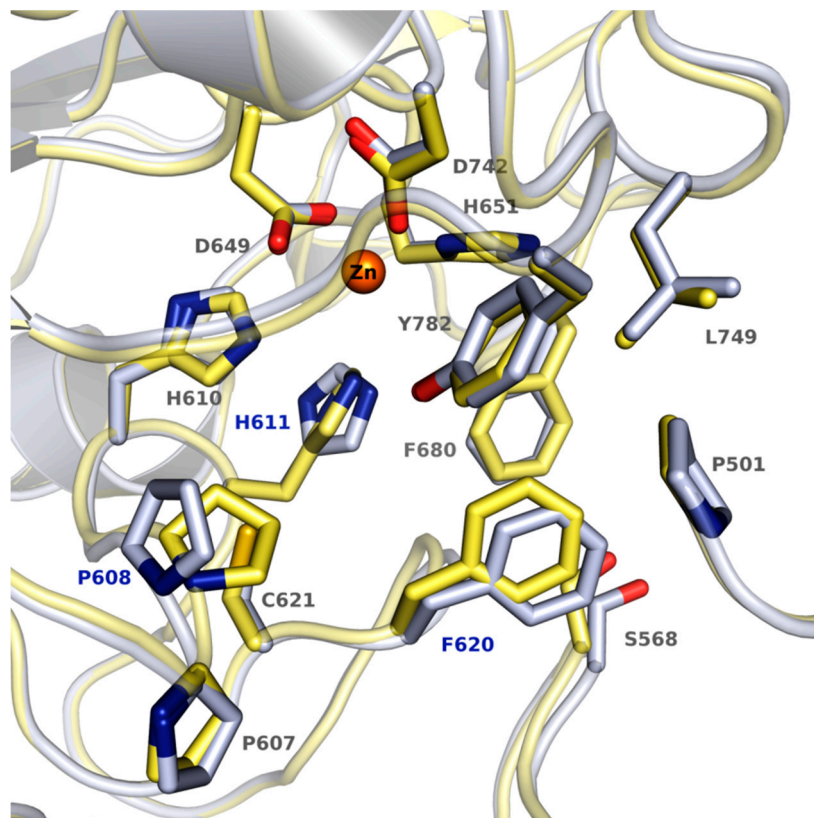


Figure S2. Superimposition of the CD2 of hsHDAC6 after minimization with J1036. Backbone of the original protein crystal structure (PDB ID: 5EDU) with closed pocket is shown as a yellow ribbon meanwhile the backbone of the open pocket structure after minimization with J1036 is shown as a white ribbon. Residues in the active site are shown in stick representation and colored respectively.

Table S1. Pre-filtered Interbioscreen database (80 compounds) considered for the docking study.

Comp. ID	GLIDE SP Score	Classical Hydroxamate -C=O-NH-OH	PAINS	MW	R/S	SMILES
STOCK1S-00970	-5.89	x		297.29		O=C1N(CCCC(=O)N[O-])C(=O)c2c3c1cccc3ccc2
STOCK1S-05147	-8.73			173.24		O=C(N([O-])C(C)C)NC(C)C
STOCK1S-05630	-5.42	x		292.40		Oc1c(cc(cc1C(C)C)C)CCC(=O)N[O-]C(C)C
STOCK1S-13592	-6.78			199.62		Clc1cc(NC(=O)N([O-])C)ccc1
STOCK1S-14427	-6.82			286.72		Clc1ccc(NC(ON(CC)C(OCC)=O)=O)cc1
STOCK1S-44534	-5.20	x		150.58		ClCC(C(=O)N[O-])C(C)
STOCK1S-44885	-4.84			328.35		O(CCNC(=O)Nc1cccc1)C(=O)N([O-])c1ccc(cc1)C
STOCK1S-61698	-7.24	x		138.11		O=C(N[O-])c1nccnc1
STOCK1S-93629	-4.33	x		218.19		O=C(N[O-])c1[n+](O)c(nc2c1cccc2)C
STOCK2S-07694	-	x		235.05		Clc1cc(Cl)ccc1OCC(=O)N[O-]
STOCK2S-62642	-4.67	x		226.66		Clc1c2c(sc1C(=O)N[O-])cccc2
STOCK2S-83315	-7.01		x	243.20		o1cccc1C1=[N+](O)c2c(N([O-])C1=O)cccc2
STOCK2S-84963	-6.10	x		235.05		Clc1cc(Cl)ccc1OCC(=O)N[O-]
STOCK2S-87369	-5.34	x		263.10		Clc1cc(Cl)ccc1OCCCC(=O)N[O-]
STOCK2S-99347	-		x	287.68		Clc1ccc(cc1)C1=[N+](O)c2c(N([O-])C1=O)cccc2
STOCK3S-07818	-5.06	x		242.68		Clc1cc(C)c(OCCCC(=O)N[O-])cc1
STOCK3S-93087	-			317.33		O=C1N([O-])C(n2nc(cc2C)-c2cccc2)=Nc2c1cccc2
STOCK3S-95273	-7.53			295.28		Oc1cc(ccc1)\C=N/NC1=Nc2c(cccc2)C(=O)N1[O-]
STOCK4S-02282*	-3.60			351.81	S	Clc1ccc(N2C(=O)[C@H](N([O-])C(=O)CCCCC)CC2=O)cc1
STOCK4S-02282*	-3.92			351.81	R	Clc1ccc(N2C(=O)[C@H](N([O-])C(=O)CCCCC)CC2=O)cc1
STOCK4S-03815*	-4.31			331.39	S	O=C1N(Cc2cccc2)C(=O)C[C@H]1N([O-])C(=O)CCCCC
STOCK4S-03815*	-3.47			331.39	R	O=C1N(Cc2cccc2)C(=O)C[C@H]1N([O-])C(=O)CCCCC
STOCK4S-11028*	-3.81			335.35	R	Fc1ccc(N2C(=O)[C@H](N([O-])C(=O)CCCCC)CC2=O)cc1
STOCK4S-11028*	-4.47			335.35	S	Fc1ccc(N2C(=O)[C@H](N([O-])C(=O)CCCCC)CC2=O)cc1
STOCK4S-11661*	-3.82			396.26	S	Brc1ccc(N2C(=O)[C@H](N([O-])C(=O)CCCCC)CC2=O)cc1
STOCK4S-11661*	-3.82			396.26	R	Brc1ccc(N2C(=O)[C@H](N([O-])C(=O)CCCCC)CC2=O)cc1
STOCK4S-25147	-5.64			194.23	R	S1CC(=O)N([O-])[C@H]1c1cccc1
STOCK4S-25147	-6.95			194.23	S	S1CC(=O)N([O-])[C@H]1c1cccc1
STOCK4S-27444*	-3.73			317.36	R	O=C1N(C(=O)C[C@H]1N([O-])C(=O)CCCCC)c1cccc1
STOCK4S-27444*	-2.94			317.36	S	O=C1N(C(=O)C[C@H]1N([O-])C(=O)CCCCC)c1cccc1
STOCK4S-31959*	-5.13			331.39	S	O=C1N(C(=O)C[C@H]1N([O-])C(=O)CCCCC)c1ccc(cc1)C
STOCK4S-31959*	-4.49			331.39	R	O=C1N(C(=O)C[C@H]1N([O-])C(=O)CCCCC)c1ccc(cc1)C
STOCK4S-48892*	-5.64			289.31	S	O=C1N(C(=O)C[C@H]1N([O-])C(=O)CCCC)c1cccc1
STOCK4S-48892*	-6.60			289.31	R	O=C1N(C(=O)C[C@H]1N([O-])C(=O)CCCC)c1cccc1
STOCK4S-53643*	-5.13			337.78	S	Clc1ccc(N2C(=O)[C@H](N([O-])C(=O)CCCC)CC2=O)cc1
STOCK4S-53643*	-4.47			337.78	R	Clc1ccc(N2C(=O)[C@H](N([O-])C(=O)CCCC)CC2=O)cc1
STOCK4S-57300	-5.27	x		232.22	R	O(C)c1ccc(cc1)-c1[nH]nc(c1)C(=O)N[O-]
STOCK4S-57300	-6.63	x		232.22	S	O(C)c1ccc(cc1)-c1n[nH]c(c1)C(=O)N[O-]
STOCK4S-73929	-3.08			343.75	R	Clc1ccc(N2C(=O)[C@H](N([O-])C(=O)c3cccc3)CC2=O)cc1
STOCK4S-73929	-3.30			343.75	S	Clc1ccc(N2C(=O)[C@H](N([O-])C(=O)c3cccc3)CC2=O)cc1
STOCK4S-78560*	-3.46			303.34	S	O=C1N(C(=O)C[C@H]1N([O-])C(=O)CCCC)c1cccc1
STOCK4S-78560*	-5.99			303.34	R	O=C1N(C(=O)C[C@H]1N([O-])C(=O)CCCC)c1cccc1
STOCK4S-84022	-			255.26		O=C1N([O-])C(n2nc(cc2C)C)=Nc2c1cccc2
STOCK5S-04928	-6.87			193.21		S=C1Nc2c(cccc2)C(=O)N1[O-]
STOCK5S-12121	-			372.20		Brc1ccc(cc1)/C(=N/NC1=Nc2c(cccc2)C(=O)N1[O-])/C
STOCK5S-21668	-			358.17		Brc1ccc(cc1)\C=N\NC1=Nc2c(cccc2)C(=O)N1[O-]
STOCK5S-30259	-5.46			283.27		o1cccc1/C(=N\NC1=Nc2c(cccc2)C(=O)N1[O-])/C
STOCK5S-30523	-7.06		x	295.28		Oc1ccc(cc1)\C=N/NC1=Nc2c(cccc2)C(=O)N1[O-]
STOCK5S-31605	-6.23			339.33		O(C)c1cc(ccc1OC)\C=N/NC1=Nc2c(cccc2)C(=O)N1[O-]
STOCK5S-33544	-		x	345.34		Oc1ccc2c(cccc2)c1\C=N\NC1=Nc2c(cccc2)C(=O)N1[O-]

STOCK5S-36950	-		313.72	Clc1ccc(cc1)\C=N\NC1=Nc2c(cccc2)C(=O)N1[O-]
STOCK5S-38273	-		293.31	O=C1N([O-])C(=Nc2c1cccc2)N\N=C(/C)\c1cccc1
STOCK5S-40226	-2.39		295.27	R O=C(Nc1cc([N+](=O)[O-])ccc1)N([O-])[C@@H](C\C(=N/O)\C)C
STOCK5S-40226	-2.80		295.27	S O=C(Nc1cc([N+](=O)[O-])ccc1)N([O-])[C@H](C\C(=N/O)\C)C
STOCK5S-46144	-7.64	x	323.33	Oc1ccc(cc1)/C(=N\NC1=Nc2c(cccc2)C(=O)N1[O-])/CC
STOCK5S-46331	-8.10	x	309.30	Oc1ccc(cc1)/C(=N\NC1=Nc2c(cccc2)C(=O)N1[O-])/C
STOCK5S-46688	-4.48		284.72	Clc1ccc(NC(=O)N([O-])C\C(=N/O)\C)(C)Ccc1
STOCK5S-50748	-		293.31	O=C1N([O-])C(=Nc2c1cccc2)N\N=C\c1cccc1C
STOCK5S-52688	-		327.75	Clc1ccc(cc1)/C(=N\NC1=Nc2c(cccc2)C(=O)N1[O-])/C
STOCK5S-54734	-		313.72	Clc1cccc1\C=N\NC1=Nc2c(cccc2)C(=O)N1[O-]
STOCK5S-56064	-		307.33	O=C1N([O-])C(=Nc2c1cccc2)N\N=C\c1cc(ccc1)C
STOCK5S-58555	-3.79	x	295.28	Oc1cccc1\C=N\NC1=Nc2c(cccc2)C(=O)N1[O-]
STOCK5S-73318	-		285.33	O=C1N([O-])C(=Nc2c1cccc2)N\N=C/1\CCCCC\1
STOCK5S-81005	-5.18		280.27	O=C1N([O-])C(=Nc2c1cccc2)N\N=C/c1ccncc1
STOCK6S-00835	-5.95		273.13	R Brc1ccc(cc1)[C@H]1SCC(=O)N1[O-]
STOCK6S-00835	-6.69		273.13	S Brc1ccc(cc1)[C@@H]1SCC(=O)N1[O-]
STOCK6S-33232	-6.95		330.36	S1C[C@@H](N(C1)C(OC(C)(C)C)=O)C(ON1C(=O)CCC1=O)=O
STOCK6S-33232	-4.87		330.36	S1C[C@H](N(C1)C(OC(C)(C)C)=O)C(ON1C(=O)CCC1=O)=O
STOCK6S-38389	-5.85		295.29	O=C1N(OC(=O)c2ccc(cc2)-c2ccccc2)C(=O)CC1
STOCK7S-02226	-5.64		246.21	O=C1N([O-])C=CC=2n3nc(nc3N=CC1=2)COC
STOCK7S-02759	-5.83		201.16	O=C1N([O-])C=CC=2n3nccc3N=CC1=2
STOCK7S-16492	-5.83	x	161.53	Clc1[nH]nc(n1)C(=O)N[O-]
STOCK7S-16492	-5.19	x	161.53	Clc1[nH]c(nn1)C(=O)N[O-]
STOCK7S-16696	-6.48		235.22	O(C)c1cc2c(N=C(N([O-])C2=O)C)cc1OC
STOCK7S-26244	-5.70		202.15	O=C1N([O-])C=CC=2n3nccc3N=NC1=2
STOCK7S-43289	-7.59		142.11	O1N(C(=O)C)C(=O)C=C1N
STOCK7S-43543	-6.50		204.19	O1N(C(=O)c2ccccc2)C(=O)C=C1N
STOCK7S-45626	-7.73		170.17	O1N(C(=O)C(C)C)C(=O)C=C1N
STOCK7S-47746	-5.38		184.19	O1N(C(=O)CC(C)C)C(=O)C=C1N
STOCK7S-49196	-4.56		256.62	Clc1cc(ccc1F)C(=O)N1OC(N)=CC1=O
STOCK7S-49604	-7.96		220.02	BrC=1C(=O)N(OC=1C)C(=O)C
STOCK7S-50104	-5.85		258.16	Fc1c(F)c(F)ccc1C(=O)N1OC(N)=CC1=O
STOCK7S-50249	-4.71		172.14	O1N(C(OCC)=O)C(=O)C=C1N
STOCK7S-51469	-6.07		210.23	O1N(C(=O)C2CCCC2)C(=O)C=C1N
STOCK7S-52645	-7.04		282.09	BrC=1C(=O)N(OC=1C)C(=O)c1cccc1
STOCK7S-53377	-7.17		274.06	Clc1nc(Cl)ccc1C(=O)N1OC(N)=CC1=O
STOCK7S-53722	-6.24		283.63	Clc1ccc([N+](=O)[O-])cc1C(=O)N1OC(N)=CC1=O
STOCK7S-54511	-7.05		240.16	Fc1ccc(F)c1C(=O)N1OC(N)=CC1=O
STOCK7S-54658	-7.14		240.16	Fc1ccc(F)cc1C(=O)N1OC(N)=CC1=O
STOCK7S-54794	-7.62		288.18	FC(F)(F)Oc1ccc(cc1)C(=O)N1OC(N)=CC1=O
STOCK7S-55112	-6.18		273.07	Clc1cc(cc(Cl)c1)C(=O)N1OC(N)=CC1=O
STOCK7S-55612	-6.84		239.62	Clc1ncc(cc1)C(=O)N1OC(N)=CC1=O
STOCK7S-56364	-6.61		284.07	Brc1cc(cnc1)C(=O)N1OC(N)=CC1=O
STOCK7S-59574	-		312.37	O=C1N(OC)C(n2nc(cc2CC(C)C)C)=Nc2c1cccc2
STOCK7S-64837	-		297.34	O=C1N([O-])C(n2nc(cc2CC(C)C)C)=Nc2c1cccc2
STOCK7S-69412	-		316.13	Brc1cccc1C1=Nc2c(cccc2)C(=O)N1[O-]

*Compounds that were selected for biological testing (highlighted in green); - = Compounds for which no docking pose was generated since they failed to correctly coordinate to the zinc ion; MW = Molecular weight; For chiral compounds both R/S stereoisomers were considered.

Table S2. smHDAC8/inhibitor X-ray structure. Data collection and refinement statistics.

Data collection	smHDAC8-J1036
Space group	P1
Cell dimensions	
a, b, c (Å)	70.71 70.69 99.19
α , β , γ (°)	75.33 77.78 84.8
Resolution (Å)*	41.21 - 1.55 (1.59 - 1.55)
Rmerge (%)	6.3 (74.7)
I / σ I	11.87 (1.94)
Completeness (%)	95.6 (87.8)
Redundancy	3.5 (2.9)
CC(1/2)	99.4 (60)
Refinement	
Resolution (Å)	41.96-1.55
No. reflections	253034
Rwork / Rfree (%)	19.94/22.27
No. atoms	
Protein	1628
Ligand/ion	90
Water	599
B-factors	
Protein	29.01
Ligand/ion	43.84
Water	34.93
R.m.s deviations	
Bond lengths (Å)	0.007
Bond angles (°)	0.86
*Values in parentheses are for highest-resolution shell.	