Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications.

The Applicability of QM/MM in Structure Based Design: An Investigation of Histone Deacetylase 8.

M. Paul Gleeson and Duangkamol Gleeson

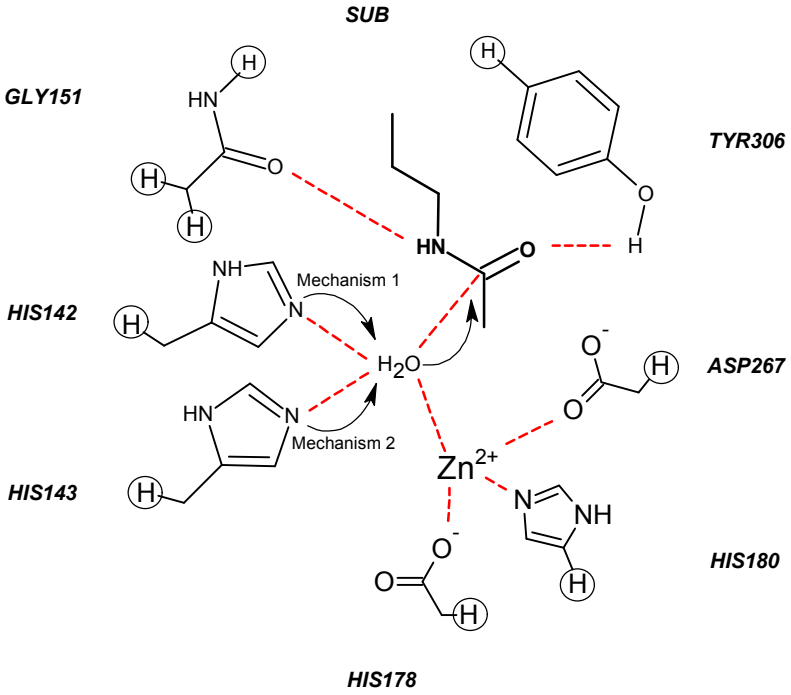

Figure S1 The QM model used for both the QM and QM/MM calculations.

ϕ HID Mechanism	HDAC8	H2O
REACT	0.0 (0.0) [0.0]	0.00 (0.00) [0.00]
M1-INT	14.9 (18.1) [16.3]	14.00 (9.29) [12.17]
M2-INT	10.8 (11.5) [12.2]	10.79 (6.93) [8.50]
M1-PROD	0.6 (1.9) [2.3]	3.57 (-1.92) [1.33]
M2-PROD	-2.2 (-4.5) [-1.7]	2.21 (-4.97) [-2.85]
M1-TS1	17.8 (19.2) [24.1]	21.11 (11.36) [17.93]
M2-TS1	17.9 (17.1) [17.5]	19.22 (15.99) [19.65]
M1-TS2	42.3 (40.3) [43.1]	42.12 (30.38) [37.96]
M2-TS2	12.1 (15.5) [15.2]	13.83 (6.87) [10.11]
TS3	8.9 (16.0) [16.8]	16.04 (9.84) [13.38]

HIP Mechanism	HDAC8	H2O
M3-REACT	0.0 (0.0) [0.0]	0.00 (0.00) [0.00]
M4 REACT	11.5 (6.3) [8.0]	6.41 (7.01) [8.18]
M3/4-INT	19.8 (23.3) [21.7]	16.90 (16.61) [16.89]
M3/4 PROD	-9.0 (-6.7) [-6.6]	3.27 (-0.16) [2.09]
TS0	10.6 (6.5) [14.7]	11.66 (9.64) [14.06]
M3-TS1	22.3 (24.8) [27.2]	25.43 (20.34) [26.35]
M4-TS1	-	21.33 (18.98) [21.35]
M3/4-TS2	29.9 (29.2) [30.9]	17.96 (23.97) [17.92]

Table 1 Relative energies in Kcal/mol for the QM/MM and QM solvent model structures. Reported are the M06/6-31G(d) for CH,C,N,O and M06/Lanl2DZ for transition metals. In brackets the single point energies for all atoms at the M06/6-31+G(d,p) level. The values in square brackets represent the free energy and single point energy corrected values.

HID Mechanism	HIS 142	HIS 143	ASP 178	HIS 180	ASP 267	TYR 306	ZN	SUB
REACT	0.10	0.57	-0.69	0.14	-0.68	-0.06	0.86	0.22
M1-INT	0.09	0.88	-0.69	0.14	-0.68	-0.08	0.82	-0.50
M2-INT	0.55	0.45	-0.69	0.14	-0.68	-0.08	0.82	-0.48
M1-PROD	0.04	0.88	-0.68	0.14	-0.68	-0.06	0.83	-0.24
M2-PROD	0.55	0.10	-0.69	0.14	-0.68	-0.06	0.86	-0.48
M1-TS1	0.11	0.73	-0.69	0.14	-0.67	-0.06	0.85	-0.44
M2-TS1	0.88	0.06	-0.71	0.15	-0.69	-0.08	0.82	-0.41
M1-TS2	0.11	0.78	-0.70	0.14	-0.69	-0.08	0.84	-0.39
M2-TS2	0.58	0.24	-0.69	0.14	-0.67	-0.06	0.85	-0.41
TS3	0.02	0.15	-0.67	0.16	-0.66	-0.04	0.86	0.17
HIP Mechanism	**HIS 142**	**HIS 143**	**ASP 178**	**HIS 180**	**ASP 267**	**TYR 306**	**ZN**	**SUB**
M3-REACT	0.70	0.16	-0.67	0.16	-0.64	-0.04	0.87	0.44
M4 REACT	0.14	0.75	-0.67	0.16	-0.63	-0.04	0.86	0.43
M3/4-INT	0.69	0.56	-0.67	0.17	-0.63	-0.04	0.80	0.12
M3/4 PROD	0.69	0.39	-0.66	0.16	-0.64	-0.04	0.84	0.26
TS0	0.65	0.48	-0.68	0.16	-0.65	-0.04	0.86	0.23
M3-TS1	0.63	0.54	-0.67	0.15	-0.62	-0.05	0.83	0.20
M4-TS1	-	-	-	-	-	-	-	-
M3/4-TS2	0.66	0.27	-0.67	0.16	-0.62	-0.05	0.84	0.41

Table 2 The sum of the Mulliken charges on the atoms associated with each residues for all QM/MM optimized structures.

HID Mechanism	HIS 142	HIS 143	ASP 178	HIS 180	ASP 267	TYR 306	ZN	SUB
REACT	0.08	0.10	-0.63	0.16	-0.65	-0.06	0.82	0.19
M1-INT	0.09	0.84	-0.63	0.17	-0.66	-0.09	0.75	-0.47
M2-INT	0.91	0.10	-0.62	0.16	-0.66	-0.10	0.75	-0.54
M1-PROD	-0.04	0.39	-0.60	0.18	-0.65	-0.06	0.79	0.00
M2-PROD	0.89	0.05	-0.62	0.17	-0.64	-0.06	0.75	-0.53
M1-TS1	0.08	0.82	-0.63	0.15	-0.66	-0.08	0.78	-0.47
M2-TS1	0.11	0.71	-0.62	0.18	-0.65	-0.07	0.77	-0.43
M1-TS2	0.84	0.09	-0.63	0.15	-0.66	-0.09	0.80	-0.51
M2-TS2	0.84	0.06	-0.59	0.14	-0.66	-0.08	0.77	-0.47
TS3	0.04	0.09	-0.59	0.18	-0.63	-0.04	0.79	0.17
HIP Mechanism	**HIS 142**	**HIS 143**	**ASP 178**	**HIS 180**	**ASP 267**	**TYR 306**	**ZN**	**SUB**
M3-REACT	0.90	0.14	-0.61	0.17	-0.64	-0.05	0.80	0.30
M4 REACT	0.10	0.92	-0.63	0.18	-0.62	-0.06	0.83	0.28
M3/4-INT	0.91	0.88	-0.58	0.18	-0.65	-0.08	0.78	-0.43
M3/4 PROD	0.92	0.91	-0.61	0.17	-0.65	-0.07	0.80	-0.47
TS0	0.74	0.85	-0.62	0.17	-0.65	-0.05	0.79	-0.23
M3-TS1	0.94	0.85	-0.58	0.18	-0.66	-0.09	0.81	-0.45
M4-TS1	0.87	0.92	-0.62	0.16	-0.66	-0.07	0.82	-0.42
M3/4-TS2	0.91	0.80	-0.58	0.17	-0.65	-0.08	0.79	-0.37

Table 3 The sum of the Mulliken charges on the atoms associated with each residues for all QM optimized structures.