Supporting information

Discovery of Selective Histone Deacetylase 6 Inhibitors Using the Quinazolin as the Cap for the Treatment of Cancer

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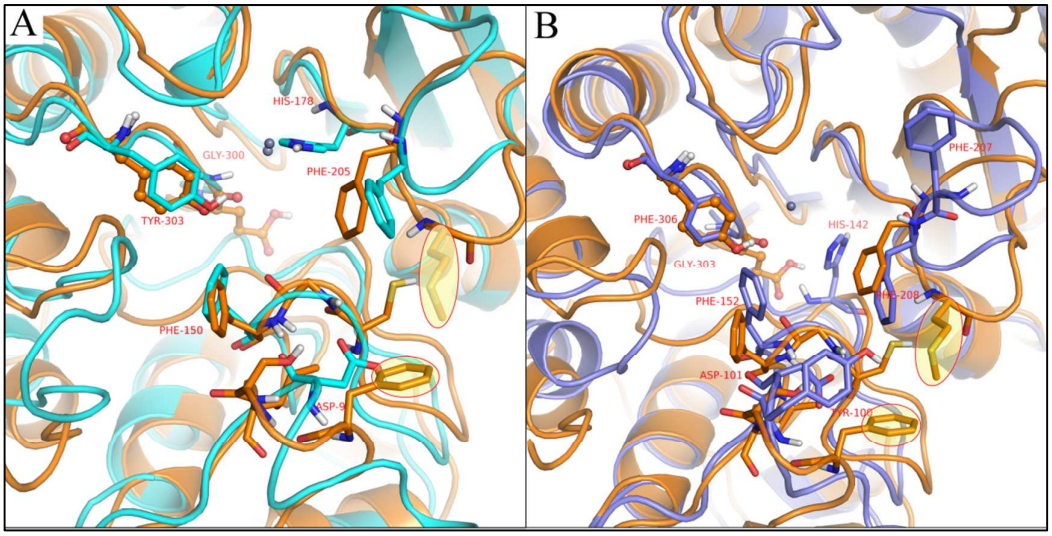
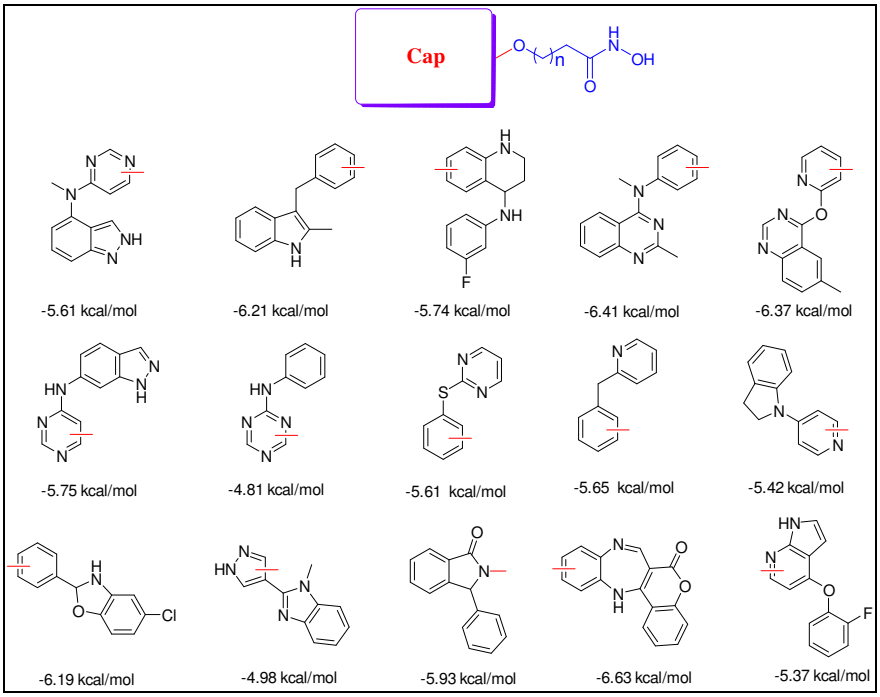
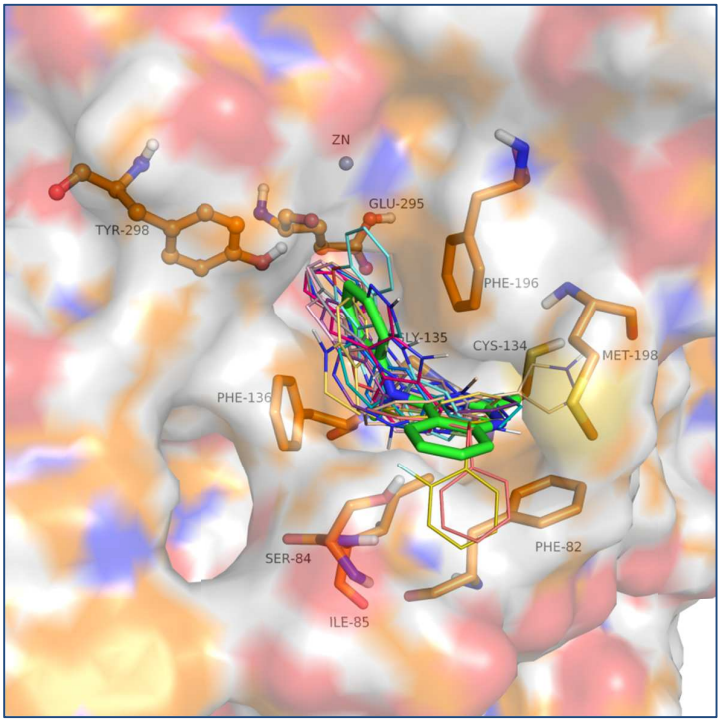


Supporting Figure S1. The protein structure alignment in the binding site, (A) HDAC6 (orange, homology model) and HDAC1 (cyans, PDB code: 4BKX), (B) HDAC6 (orange, homology model) and HDAC8 (blue, PDB code: 2V5W)

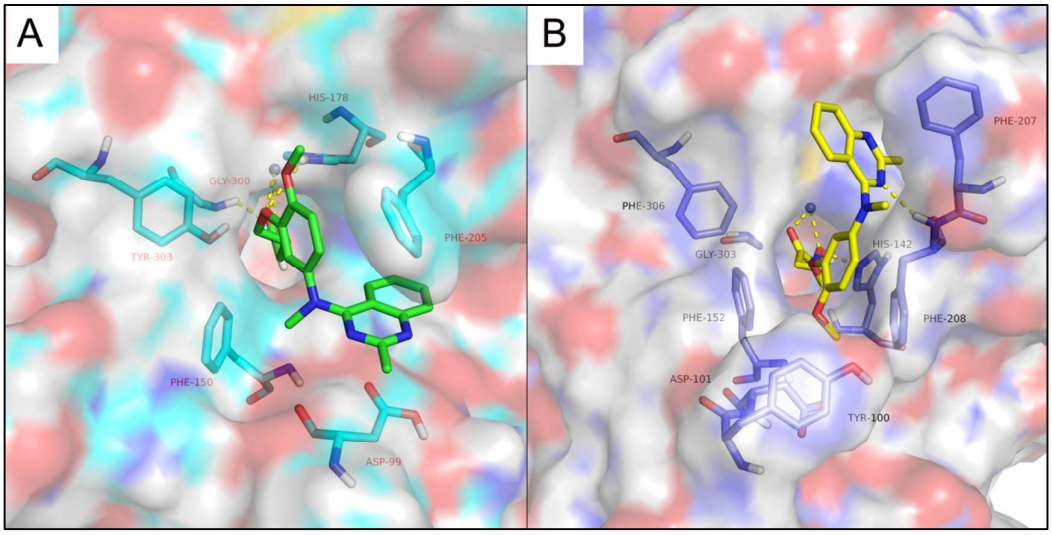


Supporting Figure S2. The binding energy of the comfortable fragments: The fragments were docked into the Cap region of HDAC6 homology model by

Autdock4.2, a grid centered on 57.046, 52.369, 74.766 was used with the spacing 0.375 Å, and the dimension of grid was set 32, 32, 30 so as to encompass the whole cap resgion.



Supporting Figure S3. The poses of the comfortable fragments. The green stick represents one of the most suitable fragments in our fragment library. In this fragment, 2-methylquinazoline could form π-π stacking interaction with residues of Phe-82. And the benzene of this fragment locates between Phe-136 and Phe-196 so as to form the robust stacking force.



Supporting Figure S4. Compounds **23bb** docked into HDAC1 (PDB code: 4BKX) and HDAC8 (PDB code: 2V5W): (A) HDAC1, (B) HDAC8

Supporting Table 1. The residues of binding pocket

Isoforms	ZN+Linker region
HDAC1	Tyr303, Gly300, His178, His141, His140, Leu139
HDAC6	Tyr298, Glu295, His167, His127, His126, Glu125
HDAC8	Phe306, Gly303, His180, His143, His142, Tyr141
Isoforms	Cap region
HDAC1	Leu271, Phe205, Gly207, Ser148, Asp99, Cys100, Pro101, Phe150
HDAC6	Leu265, Phe196, Met198, Cys134, Phe82, Ser84, Ile85, Phe136
HDAC8	Met272, Phe207, Pro209, Ser150, Gly99, Tyr100, Cys102, Phe152