An *in silico* mechanistic insight into HDAC8 activation facilitates the discovery of new small-molecule activators

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Supporting Information

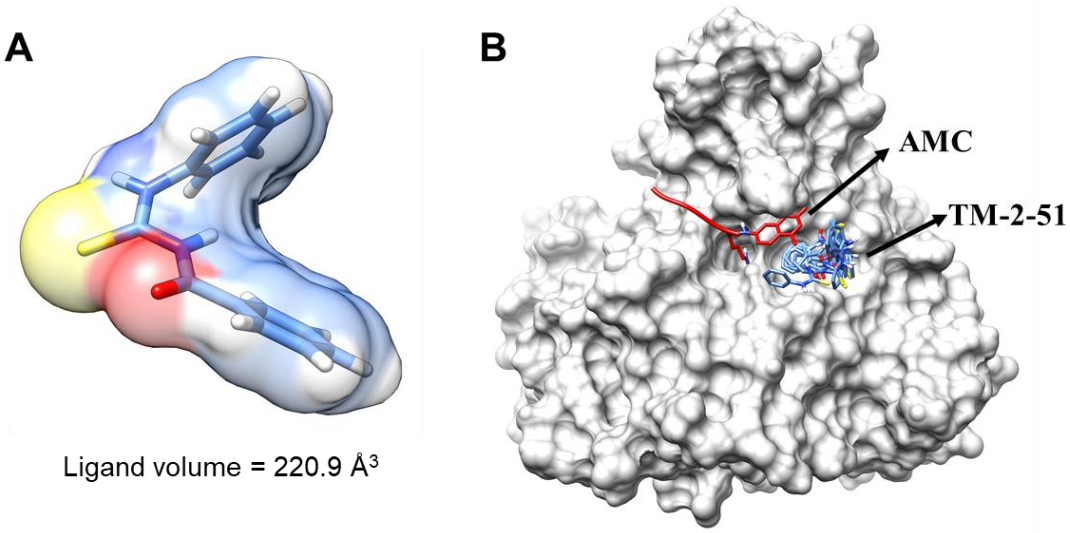

Fig. S1. (A) Calculated ligand volume of known HDAC8 activator **TM-2-51**. (B) Molecular docking results of **TM-2-51**. Briefly, **TM-2-51** was docked in the HDAC8-substrate crystal structure (PDB: 2V5W) using AutoDock Vina with the searching volume include the whole protein structure. Top 10 scored structure of **TM-2-51** were shown as stick models (colored in cornflower blue). The fluorescent substrate was presented as red ribbon with 7-Amino-4-methylcoumarin (AMC) group shown as red sticks.

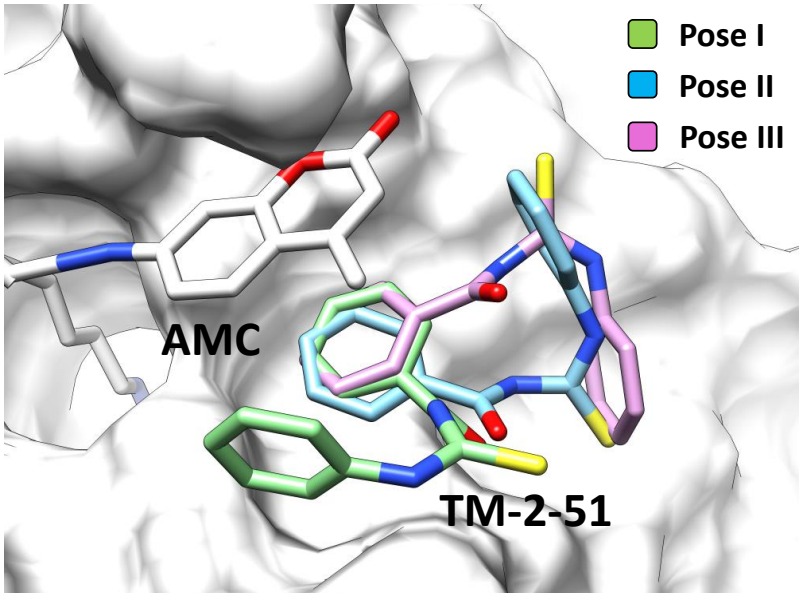

Fig. S2. Three representative top-scored docking poses of **TM-2-51**.

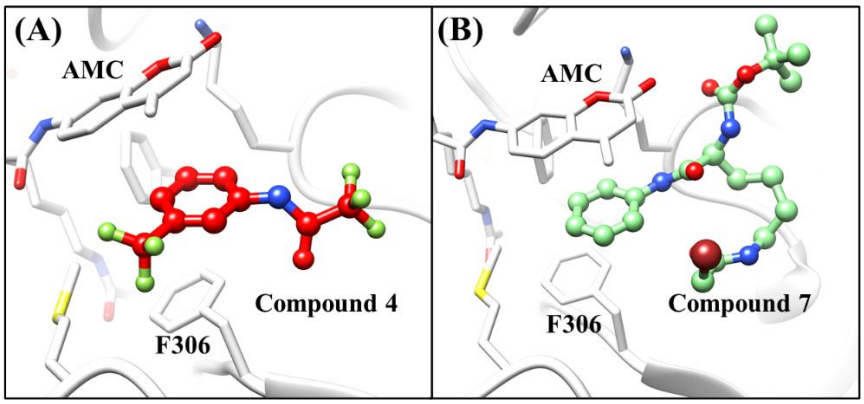

Fig. S3. Predicted binding mode of known HDAC8 activators compound **4** (A) and compound **7** (B) with HDAC8-fluorescent substrate complex.

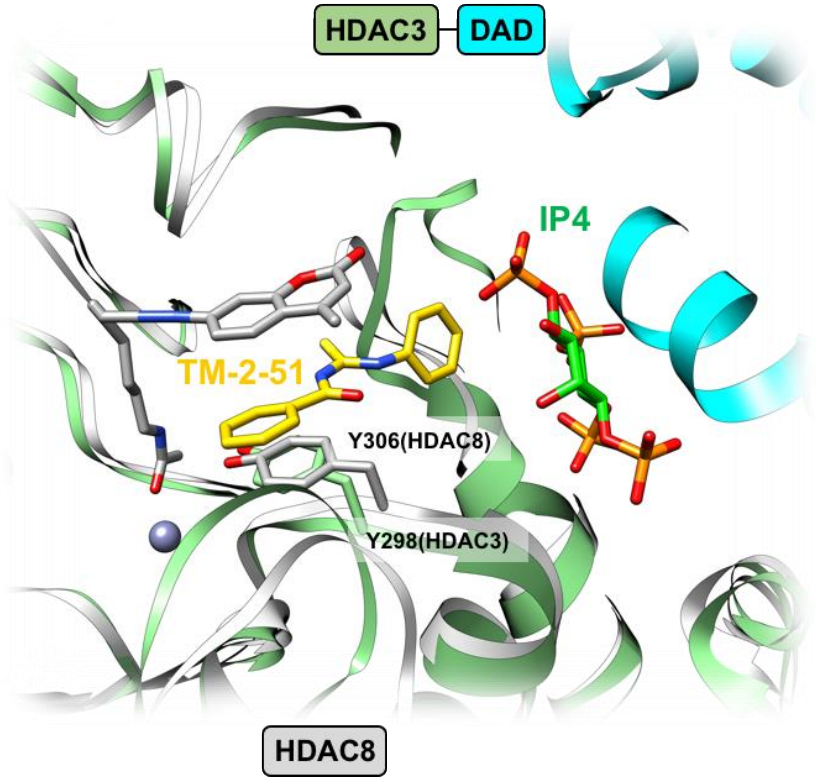

Fig. S4. Comparison of HDAC3-DAD-IP4 complex (PDB: 4A69) and HDAC8-p53AMC-activator complex (Representative snapshot from MD simulation).

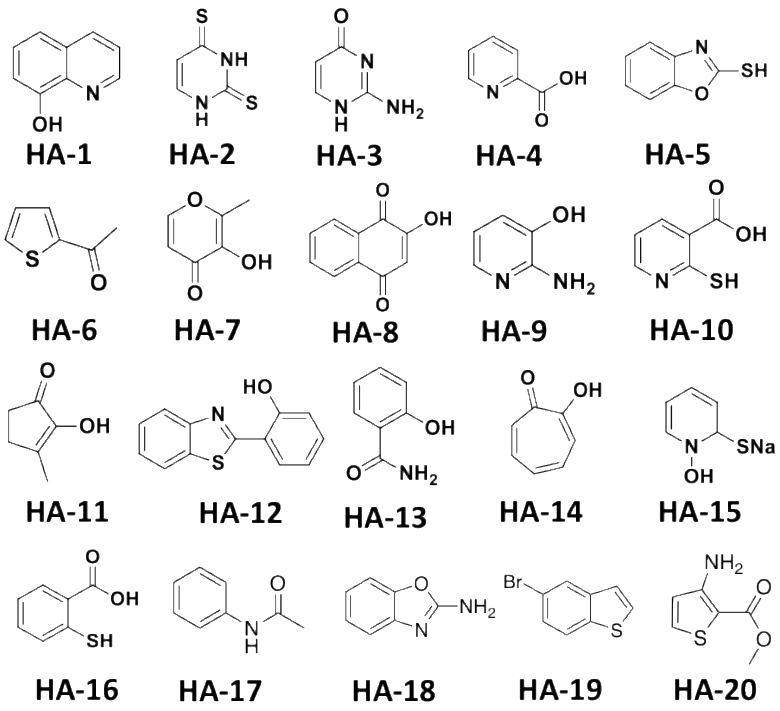

Fig. S5. Twenty low-molecular weight fragments from virtual screening.