

Hydroxamic Acid as a Potent Metal-Binding Group for Inhibiting Tyrosinase

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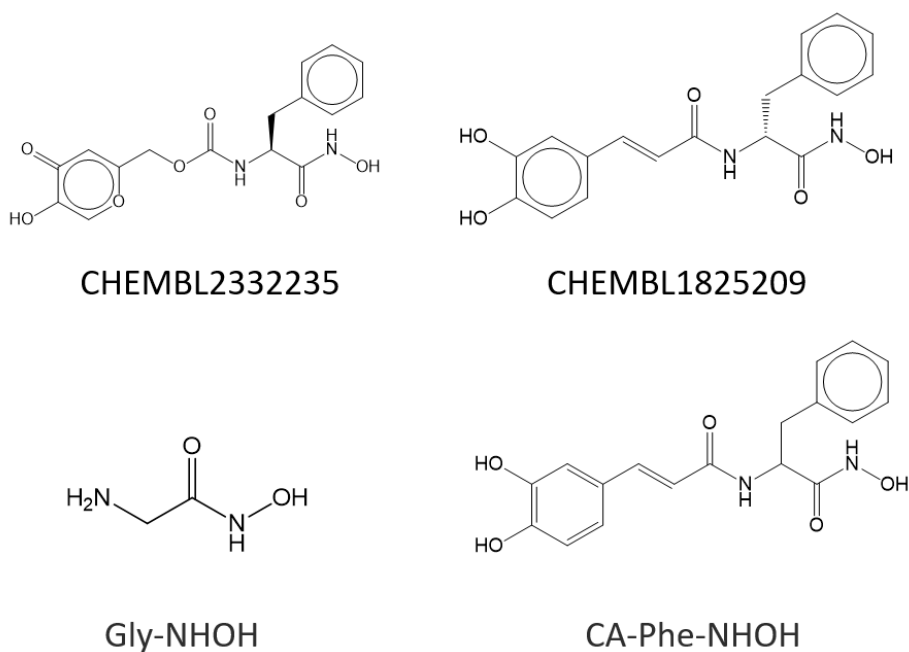


Figure S1. Known hydroxamate-containing tyrosinase inhibitors. ChEMBL database [1,2] includes CHEMBL2332235 and CHEMBL1825209. Gly-NHOH [3] and CA-Phe-NHOH [4,5] are inhibitors found by extensive publication survey.

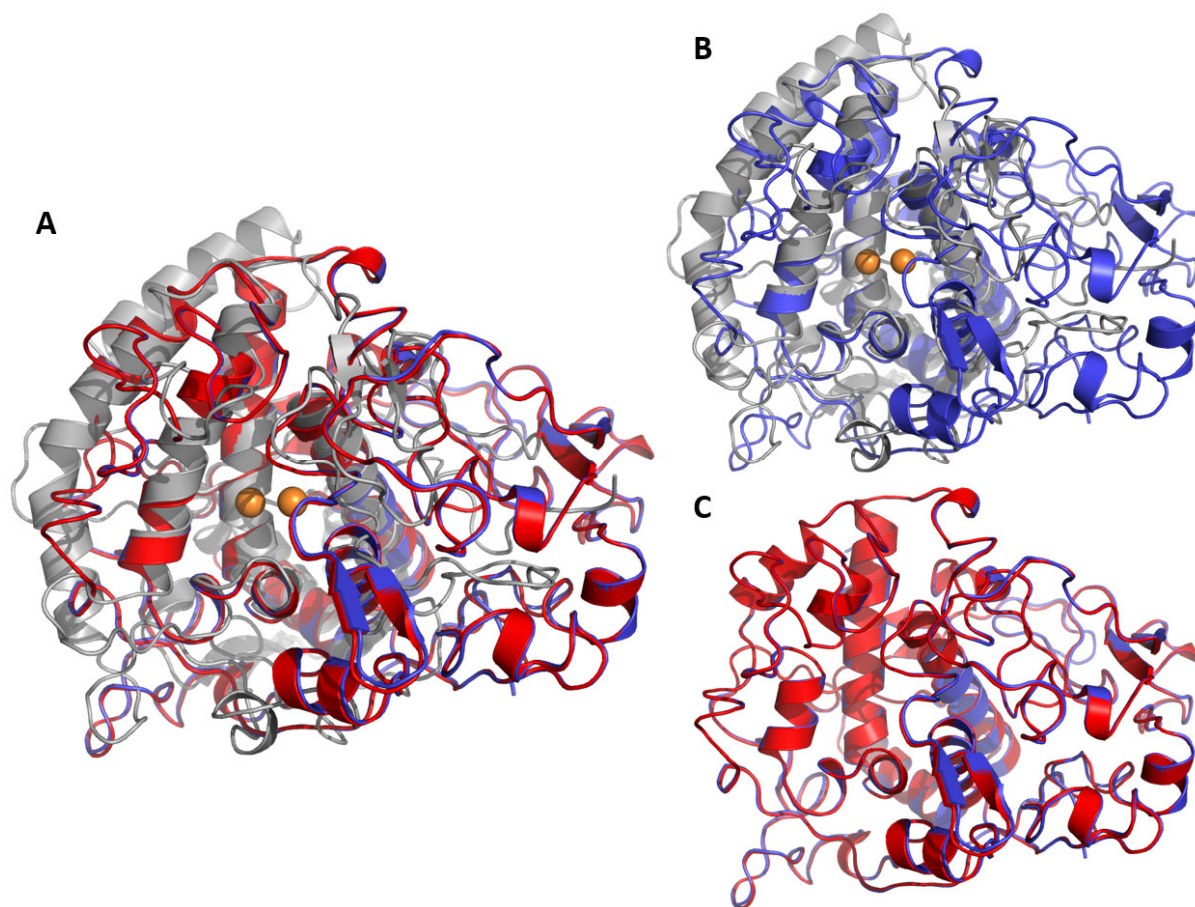


Figure S2. Comparison of mushroom, and AlphaFold-derived human and mouse tyrosinases. Mushroom tyrosinase (PDB ID: 2Y9X), and human (UniProt ID: P14679) and mouse (P11344) tyrosinase are extracted from PDB and AlphaFold databases. Gray, blue, and red colors indicate mushroom, human, and mouse tyrosinases, respectively. N- and C-terminal parts of human and mouse tyrosinases are omitted for clarity. (A) Overlay of three tyrosinase structures. (B) Overlay of mushroom and human tyrosinase structures. (C) Overlay of human and mouse tyrosinase structures.

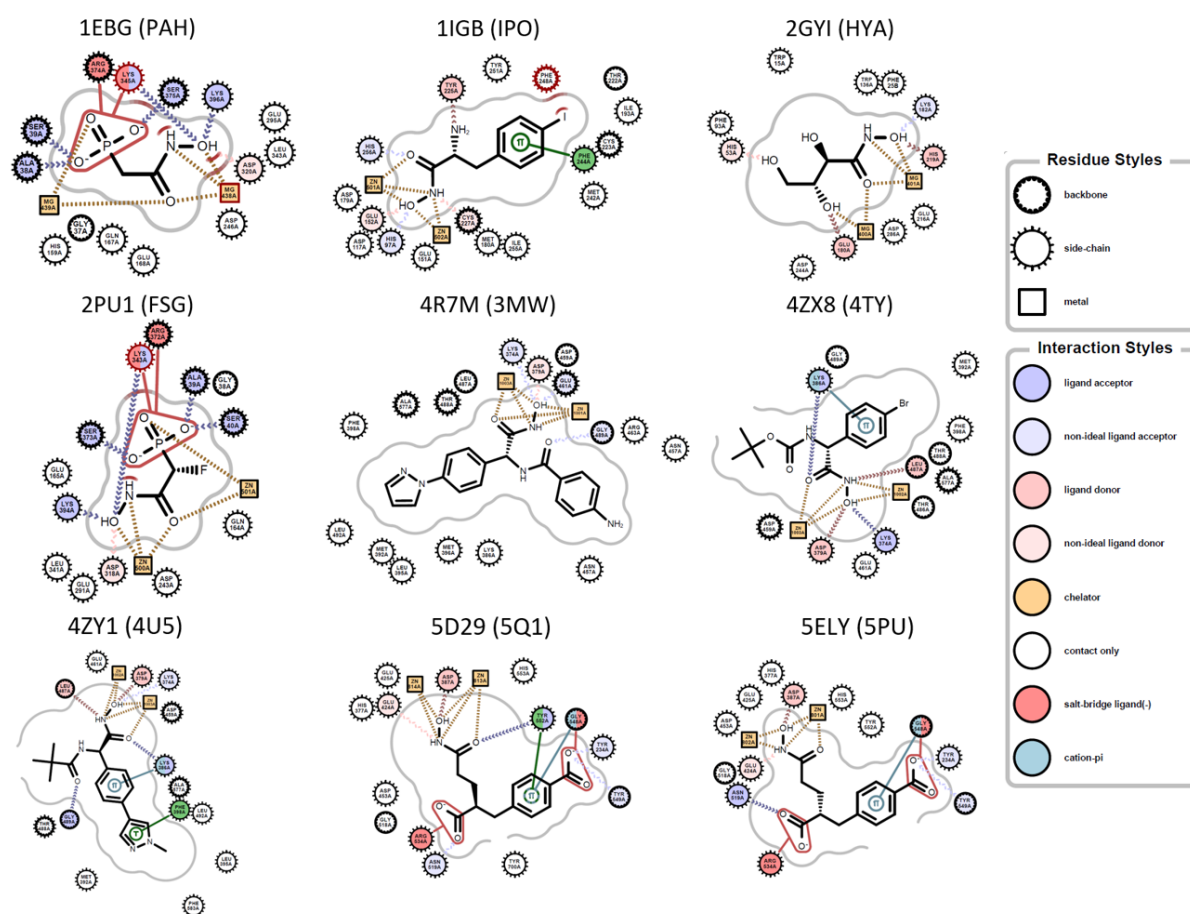


Figure S3. 2D diagrams for hydroxamate-containing inhibitors and di-metal metalloenzymes. PDBbind database [6] is employed to find nine hydroxamate-containing molecules complexed with the metalloenzymes having a di-metal catalytic center. The PDB IDs (code of hydroxamate-containing ligand) of them are 1EBG (PAH), 1IGB (IPO), 2GYI (HYA), 2PU1 (FSG), 4R7M (3MW), 4ZX8 (4TY), 4ZY1 (4U5), 5D29 (5Q1), and 5ELY (5PU). The OpenEye Grapheme package is employed to analyze and visualize the intermolecular interactions. Definition of the interactions is drawn on the right side.

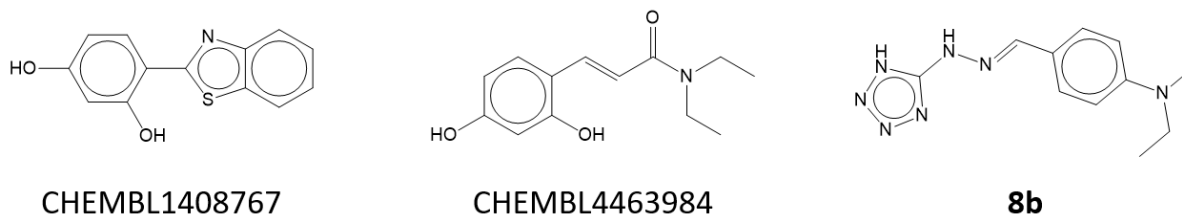


Figure S4. Known potent tyrosinase inhibitors. The reported IC_{50} values for CHEMBL1408767 [7] and CHEMBL4463984 [8] are 10 and 11 nM, respectively. The K_i value for **8b** is 11 nM [9].

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