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The search for potential isoform-selective histone deacetylase inhibitors via structure-based virtual screening

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Histone deacetylases (HDACs) have gained increased attention as targets for anticancer drug design and development. HDAC inhibitors have proven to be effective for reversing the malignant phenotype in HDAC-dependent cancer cases. However, lack of selectivity of the many HDAC inhibitors in clinical use and trials is causes adverse effect. It is believed that, the continued identification of isoform-selective inhibitors will eliminate these undesirable adverse effects — a task that remains a major challenge due to high structural similarity around the HDACs active site. The present work attempted to identify isoform-selective inhibitors of individual members of class I HDACs by screening a large compound library containing ~ 200,000 compounds retrieved from Otava database. We identified a total of 40 compounds with high isoform selectivity and these compounds passed drug-likeness and absorption, distribution, metabolism, elimination and toxicity prediction tests. Furthermore, to study the stability of ligand binding modes, 10 ns-molecular dynamics (MD) simulations of the free HDAC isoforms and their complexes with respective best-ranked ligands were performed using nanoscale molecular dynamics (NAMD) software. The inhibitors remained bound to their respective targets over time of the simulation and the overall potential energy, root-mean-square deviation, root-mean-square fluctuation profiles suggested that the predicted inhibitors may be potential isoform-selective inhibitors or serve as promising lead compounds for further optimization.

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