**An integrated computational strategy to identify selective HDAC6 inhibitors against breast cancer**

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**Abstract**

Breast cancer is considered one of the leading causes of cancer-related mortality in women worldwide, with its progression often driven by aberrant estrogen receptor (ER) signaling and epigenetic dysregulation. Histone deacetylase 6 (HDAC6), a cytoplasmic class IIb enzyme, has emerged as a critical epigenetic regulator that modulates ER activity and promotes breast cancer development and metastasis. Despite the therapeutic potential of HDAC6 inhibition, currently available inhibitors have shown limited clinical efficacy due to poor selectivity, toxicity, and undesirable off-target effects. This study employed an integrated computational pipeline to identify novel, selective HDAC6 inhibitors with improved pharmacological profiles. A comprehensive virtual screening of 355,289 molecules was conducted, from which 2,107 virtual hits were shortlisted based on their initial binding potential. These hits underwent molecular docking experiments, leading to the top seven hit compounds prioritized based on their binding affinity to the HDAC6 catalytic domain. These selected compounds were further analyzed through 100 ns molecular dynamics simulations to evaluate their structural stability and interaction dynamics within the HDAC6 active site. Hit-1 emerged as a potent candidate as HDAC6 inhibitor, demonstrating a highly favorable MM/GBSA binding free energy of -131.12 kcal/mol, exceeding the binding performance of reference inhibitor Trichostatin A (-114.24 kcal/mol). Hit-1 demonstrated robust stability, minimal structural fluctuations, and maintained consistent interactions with key catalytic residues ASP649, HIS651, and ASP742 throughout the simulation period. *In-silico* ADMET profiling confirmed Hit-1 compounds' high oral bioavailability, non-mutagenic nature, low hepatotoxicity, and favorable metabolic stability. In conclusion, Hit-1 represents a potent and selective HDAC6 inhibitor with better binding and pharmacokinetic properties. This study demonstrates the efficacy of a multi-stage computational approach to accelerate drug discovery and supports further experimental validation for clinical development.

**Keywords**: Breast cancer, HDAC6 inhibitor, molecular docking, molecular dynamic simulation, MM/GBSA binding energy, *in-silico* ADMET