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In Vitro and *In Silico* Evaluation of Novel *Ortho*-Substituted Phenols and Benzodiazepine Derivatives as Potent and Isoform-Specific Human and *Schistosoma mansoni* Lysine Deacetylase Inhibitors

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The study of epigenetics, or heritable changes in gene expression without genomic alterations, has been rapidly expanding due to the discovery of critical epigenetic contributions involved in human diseases. One such epigenetic mechanism is the reversible acetylation of lysine ε-amino groups, a post-translational modification that often occurs on histone tails to regulate transcription. Responsible for catalyzing acetyl group removal, the lysine deacetylase (KDAC) family of enzymes has been found to be linked with the development/progression of cancer, diabetes, and other critical disorders in humans when aberrant expression, activity, or mutations are present. KDACs also contribute to various parasitic diseases, including schistosomiasis, a disease concerning the infection of human intestinal and urogenital tracts by Schistosoma trematodes. Thus, development of potent KDAC inhibitors (KDACIs) against specific human and parasitic KDAC isoforms may lead to innovative therapies for many diseases.

In this study, we focus on the screening of novel KDACIs against four human KDAC isozymes (hKDAC1, 3, 6, and 8) and one *Schistosoma mansoni* KDAC isozyme (smKDAC8) using *in vitro* and *in silico* methods. Synthesized phenol and benzodiazepine derivatives were tested as inhibitors against each KDAC isozyme using electrophoretic mobility shift assays to measure relative half maximal inhibitory concentrations (IC_{50}s).

Experimental results revealed several KDACIs endowed with low nanomolar IC_{50}s and high selectivity against hKDAC6, as well as KDACIs with mid-range nanomolar IC_{50}s and selectivity against hKDAC3. Structure-activity relationships (SARs) were then rationalized through molecular docking simulations, further clarifying ligand-residue interactions relevant to inhibitory potency and isoform-selectivity against human and schistosome KDACs. The obtained data will be used to (1) refine a comprehensive pharmacophore model (recently published by the Marshall lab); (2) design and synthetize novel KDACIs with higher potency and selectivity; and (3) enhance structure-based 3D QSAR models as tools to predict the activity/selectivity of novel/untested compounds through virtual screening applications.