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Photoaffinity Labeling of proteins by Photoreactive Probes in Live cells and Tissues

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Histone deacetylases (HDACs) constitute an epigenetic enzyme family that is implicated in cancer and a variety of other immunological, neurological, cardiac, and endocrine diseases. Development of novel HDAC isoform-selective inhibitors is necessary to improve their in vivo potency while reducing toxicity. The isoform selectivity of HDAC inhibitors is routinely measured in biochemical recombinant enzyme inhibition assays using synthetic substrates, which does not account for regulation of HDAC activity though post-translational modifications and multiprotien complex formation.
Photoaffinity labeling is a valuable tool to study ligand-target interactions within complex proteomes. A set of chemically diverse photoreactive probes (PRPs) were synthesized. The PRPs were tested for in vitro HDAC inhibitory activity in comparison to their parent compounds. Their ability to label HDACs within a complex proteome was studied in cell-based and tissue-based models.
The results showed that a subset of the PRPs retained HDAC isoform selectivity with respect to their parent compounds as demonstrated by their inhibitory profile against recombinant enzymes and labeling of HDAC isoforms in live cells. Other PRPs, however, while maintaining HDAC inhibition of recombinant enzymes, differed in selectivity with respect to their photolabeling of HDAC isoforms in live cells. This highlights the need for a cell-based approach during the early development stages of novel HDAC isoform-selective inhibitors. In addition, the physicochemical properties of four of the PRPs indicated they have drug-like character and could be used for in vivo studies of HDAC target engagement.

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