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Abstract

In Search of Selectivity: Design, Synthesis, and Biological Evaluation of New Classes of HDAC Inhibitors †

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Abstract: Epigenetic regulation of gene expression without changing DNA sequences is a promising strategy in developing therapeutic agents for human diseases, especially cancer. Histone deacetylases (HDACs) are a family of enzymes involved in epigenetic modulation of gene expression by chromatin remodeling. Deacetylation of the lysine side chains of histones by HDAC proteins renders DNA transcriptionally inactive, resulting in the inhibition of expression of tumor suppressor genes, leading to tumorigenesis and tumor progression. Therefore, inhibiting HDAC enzymes has become an attractive strategy to modulate gene expression as a strategy for developing anticancer drugs. There are currently four FDA-approved cancer drugs in clinical use, and many more are in different stages of clinical trials. However, their clinical utility is limited due to undesirable side effects, mainly attributed to their lack of selectivity and the presence of a hydroxamic acid moiety as the metal-binding group. There are eighteen different isoforms of HDACs belonging to four classes that have been identified in humans. A major challenge in HDAC inhibitor development is how to make them selective for these HDAC isoforms and classes. We report the design and synthesis of new classes of HDAC inhibitors and the evaluation of their anticancer activity and selectivity.

Keywords: anticancer agents; epigenetics; HDAC inhibitors