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## Total Synthesis of Largazole and Derivatives and Their Use as Prodrugs for the Selective Inhibition of Histone Deacetylases (HDACs) in Cancer Therapy

Drs. Robert Williams, Albert Bowers and James Bradner from Colorado State University Department of Chemistry have developed a histone deacetylases inhibitor (HDACi) that can induce terminal differentiation, cell cycle and growth arrest, cell death and/or inhibition of angiogenesis. Histone deacetylases (HDACs) are enzymes involved in the epigenetic regulation of gene expression are clinically relevant and are highly sought after as promising anticancer therapeutics.

Largazole exhibits a number of significant structural similarities to FK228, one of the most potent and isoform-selective HDAC inhibitors known. These results demonstrate the effectiveness of the largazole thioester as a new class of prodrug-HDAC inhibitor. Due to its exceptional bioavailability, combined with its selectivity for class I HDACs 1, 2, and 3 as opposed to class IIb HDAC 6 make it a valuable research tool and promising new anticancer therapeutic.

This invention provides the only extant total synthesis of largazole, its thiol, disulfide, and alternative acyl derivatives. Prior to this work there existed no proposed mode of action for largazoles potent and selective antiproliferative activity. This technology demonstrates a biochemical mechanism of activation of largazole and that largazole is in fact a pro-drug. This activity constitutes the most potent and selective inhibitory activity against class I HDACs to date.

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