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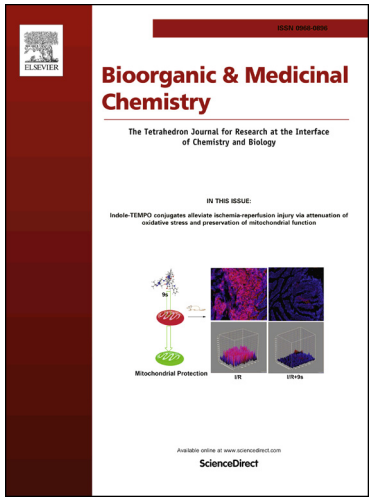

Synthesis and Biological Evaluation of Largazole Zinc-Binding Group Analogs

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Title: Synthesis and Biological Evaluation of Largazole Zinc-Binding Group Analogs

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ABSTRACT: Histone acetylation is an extensively investigated post-translational modification that plays an important role as an epigenetic regulator. It is controlled by histone acetyl transferases (HATs) and histone deacetylases (HDACs). The overexpression of HDACs and consequent hypoacetylation of histones have been observed in a variety of different diseases, leading to a recent focus of HDACs as attractive drug targets. The natural product largazole is one of the most potent natural HDAC inhibitors discovered so far and a number of largazole analogs have been prepared to define structural requirements for its HDAC inhibitory activity. However, previous structure–activity relationship studies have heavily investigated the macrocycle region of largazole, while there have been only limited efforts to probe the effect of various zinc-binding groups (ZBGs) on HDAC inhibition. Herein, we prepared a series of largazole analogs with various ZBGs and evaluated their HDAC inhibition and cytotoxicity. While none of the analogs tested were as potent or selective as largazole, the Zn^{2+}-binding affinity of each ZBG correlated with HDAC inhibition and cytotoxicity. We expect that our findings will aid in building a deeper understanding of the role of ZBGs in HDAC inhibition as well as provide an important basis for the future development of new largazole analogs with non-thiol ZBGs as novel therapeutics for cancer.