

Novel Approaches to Inhibitors of Medically Relevant Metalloproteins

Seth M. Cohen, David T. Puerta, Jana A. Lewis, Faith E. Jacobsen, and Ba L. Tran

Department of Chemistry and Biochemistry, University of California, San Diego

Many metalloproteins including matrix metalloproteinases (MMPs), histone deacetylases (HDACs), and others are involved in the progression of various human diseases. New approaches to inhibiting these enzymes can be devised by examining the interactions between the active site metal ion and synthetic inhibitors.

This presentation will focus on MMPs, which are hydrolytic enzymes involved in the breakdown of connective tissue. MMP activity is correlated with a number of illnesses including arthritis, cancer, and cardiovascular disease. Compounds that can inhibit MMP activity may prove to be useful chemotherapeutics. The MMP active site contains a Zn(II) ion bound to three histidine ligands with open coordination sites for substrate binding. Novel MMP inhibitors will be described that were devised using a comprehensive approach that utilized model complexes of the MMP active site, augmented computational studies, and enzymatic screening. Lead compounds have been identified that are several orders of magnitude more potent than the hydroxamic acid ligands used in most clinically evaluated MMP inhibitors. Based on these lead compounds, we have prepared soluble, potent, and selective next-generation MMP inhibitors via facile synthetic methods. The utility of this overall strategy to metalloprotein inhibitor design will be discussed.