Coordination Chemistry in MMP Active Sites: Zinc Binding Group Properties and Inhibitory Activity

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Matrix metalloproteases (MMPs) constitute a subclass of the metzincins that comprises approximately 30 mammalian enzymes. They have as their substrates virtually all macromolecular components of the extracellular matrix. These enzymes play important roles in growth and development, tissue homeostasis, and intercellular signaling. Perhaps not surprisingly, dysfunction in one or more of these enzymes is implicated in a wide variety of tissue degenerative diseases, including cardiovascular disease, arthritis, cancers, and others. As such, the MMPs have been attractive targets for chemotherapeutic treatments with molecules that serve as MMP inhibitors. This approach to treatment of cancers has been plagued by short *in vivo* lifetimes and chemical toxicity of the drugs and/or their metabolites. The short *in vivo* lifetimes are attributed in part to lack of stability of hydroxamic acid functionalities, which are widely used as zinc chelating moieties (zinc binding groups or ZBGs) in clinical inhibitors. Hydroxamic acids, while good chelating agents for zinc, are not specific for it. This lack of specificity along with its lack of *in vivo* stability cries out for new approaches to blocking the active site zinc by coordination with ZBGs. To this end, we are designing, synthesizing, and investigating new ZBGs. The investigations include solid state and solution structural studies of ZBGs bound to synthetic complexes that mimic the MMP active sites, biological activity assays, and computational modeling. Results from all of these approaches to new ZBGs will be presented and discussed in the context of improving inhibitor stability and the stabilities of their MMP complexes.