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Physicochemical characterization of MMP-14 active site-Zn(II)-peptide inhibitor ternary complexes: a strategy for matrix metalloproteinase inhibition in cancer progression

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Cancer metastasis remains the leading cause of cancer-related morbidity and mortality, highlighting the urgent need for novel therapeutic strategies. Matrix metalloproteinases (MMPs), *i.e.*, the membrane-bound **MMP-14**, play pivotal roles in tumor progression through extracellular matrix degradation and angiogenesis promotion. The catalytic activity of MMPs is critically dependent on Zn(II) coordination, making the zinc-binding site an attractive target for inhibitor design. This study investigates the thermodynamic properties of Zn(II) complexes with active site of **MMP-14** and selected four peptide-based inhibitors, focusing on inhibitors' potential to disrupt enzymatic activity by incorporating into the Zn(II) coordination sphere. The research utilized complementary analytical techniques including potentiometric titrations, mass spectrometry (MS), and nuclear magnetic resonance (NMR) spectroscopy to characterize the stoichiometry, donor atom preferences, and thermodynamic stability of binary Zn(II)-**MMP-14**/inhibitor, and ternary **MMP-14**-Zn(II)-inhibitor complexes. Density Functional Theory (DFT) calculations further elucidated coordination modes and structural properties of ternary complexes. Results showed that Zn(II) binding affinity depends on multiple factors beyond simply the number of histidine residues in the inhibitors, including their spatial arrangement and local environment. The most stable ternary **MMP-14**-Zn(II)-inhibitor complex was formed by inhibitor 1 (SDMAHSLPGHSH), which coordinates Zn(II) through aspartic acid, as confirmed by NMR spectroscopy and DFT. The formation of cooperative hydrogen bonding networks contributed significantly to the stability of the **MMP-14**-Zn(II)-**Inh1** complex, mirroring interactions observed in natural **MMP-14** inhibitors such as TIMP-2. This comprehensive analysis provides critical insights into the coordination chemistry of Zn(II) within the MMP active site and its interactions with potential inhibitors, establishing a molecular foundation for rational design of selective MMP inhibitors with therapeutic potential.

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