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Substrate-Mimicking Peptides as MMP-1 Inhibitors: Impact of Zinc-Binding Group Position on Ternary Complex Stability

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Cancer remains a leading cause of global mortality, with metastasis accounting for nearly 90% of related deaths. Matrix metalloproteinases (MMPs), and in particular MMP-1, play a pivotal role in tumor progression by degrading extracellular matrix components through a Zn(II)-dependent catalytic mechanism. Targeting the Zn(II) ion in the active site represents a potential approach for inhibitor design. In this study, we designed and investigated substrate-mimicking peptide inhibitors incorporating cysteine residues as zinc-binding groups (ZBGs) at distinct positions: CPQGLRG (Inh4, P4), PQGLCGR (Inh2′, P2′), and PQGLRGC (Inh4′, P4′). Using different techniques (potentiometry, mass spectrometry, NMR spectroscopy, and density functional theory calculations), we evaluated binary and ternary complexes formed between these peptides, Zn(II), and an MMP-1 active-site model. All inhibitors formed monomeric and bis(ligand) binary Zn(II)-complexes, with Inh4 demonstrating the highest thermodynamic stability. In ternary systems, the MMP-1 active site model served as the primary Zn(II) ligand coordinating through three histidine residues and reproducing the binding mode of the native enzyme. The inhibitors bound in the secondary step as the fourth coordination site, displacing the catalytic water. Ternary complexes of all inhibitors were predominant species formed above pH 6, coinciding with the optimal pH for MMP-1's activity. Among the peptides, Inh4, which stabilized ternary complexes most effectively, coordinates Zn(II) via its N-terminal amine. This binding mode is analogous to the strategy of tissue inhibitors of metalloproteinases. In contrast, Inh2′ and Inh4′ required structural rearrangements for Zn(II) coordination and formed less stable complexes due to steric constraints. The findings of this study identify N-terminal cysteine as the most effective ZBG placement for stabilizing Zn(II)-MMP-1 complexes, highlighting Inh4 as a promising lead for peptide-based MMP-1 inhibition. This work provides preliminary insights to guide the rational design of selective metalloproteinase inhibitors with therapeutic potential in cancer treatment.

Słowa kluczowe

Cancer, Inhibitors, Ligands, Monomers, Peptides and proteins

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