Stereochemical Control of Cu(II) and Zn(II) Binding in Clavanin C Peptidomimetics

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Streszczenie

We redesign the histidine-rich antimicrobial peptide clavanin C through stereochemical inversion to generate proteolytically stable metallopeptidomimetics while preserving metal-binding functionality and antimicrobial activity. Two analogues were prepared: an all-d amino acid peptide and a *retro-inverso* variant. Remarkably, despite complete sequence reversal and inversion of chirality, both mimetics retain Cu^{2+} coordination through the N-terminal ATCUN motif, forming characteristic square-planar 4N complexes. Zn^{2+} binding is likewise preserved and involves a cluster of histidine residues located on one face of the amphipathic α-helix. This distinction reveals two complementary design principles: sequence-encoded metal binding in the case of Cu^{2+} versus topology-driven coordination for Zn^{2+}. Both stereochemical designs dramatically increase resistance to proteolytic degradation while maintaining the helical fold under membrane-mimicking conditions. In antimicrobial assays, the *retro-inverso* analogue and its metal complexes display particularly strong activity against methicillin-resistant *Staphylococcus aureus* (MRSA), with minimum inhibitory concentrations as low as 8 μg/mL and no detectable cytotoxicity toward mammalian cells. Taken together, our data show that both d-amino acid substitution and retro-inverso design can stabilize clavanin C while retaining its metal-binding ability and antimicrobial activity, providing a general strategy for the development of proteolytically stable antimicrobial metallopeptidomimetics.

Słowa kluczowe

Antimicrobial activity, Bacteria, Metals, Monomers, Peptides and proteins

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