

Beyond proteolysis: rational modification of mucin-derived peptidomimetics with enhanced metal-mediated antimicrobial activity

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Streszczenie

Mucin-derived peptides constitute attractive antimicrobial candidates, but their clinical application is restricted by limited stability and moderate efficacy. To address these limitations, we modified d-amino-acid-containing peptidomimetics and investigated their Cu(II) and Zn(II) complexes with respect to coordination chemistry, structure, proteolytic resistance, and antimicrobial activity. Potentiometric, spectroscopic, and DFT studies revealed that metal binding donor sets are analogous to those of the native peptide, producing only minor local conformational effects without significant global structural rearrangement, as confirmed by circular dichroism analysis. In contrast to the modest structural changes, biological activity was strongly influenced by chirality and metal coordination. The fully d-configured analogue displayed the highest antimicrobial potency, particularly at pH 5.5, and its Zn(II) and Cu(II) complexes showed enhanced antibacterial and antifungal effects relative to the native system. Proteolytic assays demonstrated rapid plasma degradation of the native peptide and the partially modified analogue, whereas the fully d-substituted peptidomimetic remained largely intact after 2 h. All compounds exhibited minimal hemolytic and cytotoxic effects. These findings demonstrate that d-amino-acid incorporation combined with metal coordination significantly improves both enzymatic stability and antimicrobial performance of mucin-derived peptides.

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