

Comparative coordination chemistry of MMP-14 peptide inhibitors: histamine-like coordination and poly-glycine effect in Cu(II) complexes

Autorzy

Martyna Zawada

Paulina Potok

Robert Wieczorek

Sławomir Potocki

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Streszczenie

The rational design of matrix metalloproteinase (MMP) inhibitors, such as those targeted for **MMP-14**, prioritizes the native Zn(II) cofactor. The elevated levels of Cu(II), which are characteristic of the tumor microenvironment, are often overlooked. In this study, we investigated the Cu(II) coordination chemistry of selected **MMP-14** inhibitors using potentiometric titrations, UV-Vis spectroscopy, circular dichroism, and density functional theory. Our findings reveal a striking inversion of metal selectivity in comparison with previously studied Zn(II) complexes. While Inhibitor 1 (**Inh1**) retains high specificity for the native Zn(II) active site, Inhibitor 4 (**Inh4**) exhibits exceptional thermodynamic stability with Cu(II) ($pK_d = 11.87$). **Inh4** favors copper over zinc by more than six orders of magnitude. This remarkable stability comes from a highly pre-organized, histamine-like mixed N/O donor environment and an extended poly-glycine tail. This tail adopts a 3_{10} -helical conformation that additionally stabilizes the coordination site and minimizes the entropic penalty of complexation. These results demonstrate that while **Inh1** remains a highly specific candidate for targeted **MMP-14** inhibition, the pronounced selectivity gap of **Inh4** transforms it into a highly specific Cu(II) scavenger. This study highlights the critical risk of off-target metal sequestration in the tumor microenvironment while simultaneously opening the door to the potential repurposing of **Inh4** as a targeted, copper-depleting agent in anti-angiogenic therapies.

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