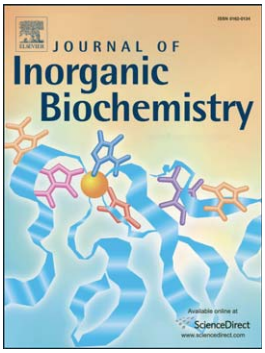

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Influence of metallocene substitution on the antibacterial activity of multivalent peptide conjugates

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Abstract

Peptide dendrimers and derivatisation of peptides with metallocenes showed promising results in the search for new antibacterial agents. The two concepts are combined in this work leading to multivalent, metallocene-containing peptide derivates. These new peptides were synthesised utilizing microwave assisted, copper(I) catalysed alkyne-azide cycloaddition (CuAAC, "click" chemistry). Twelve new peptide conjugates, containing either a ferrocenoyl group or a ruthenocenoyl group on so-called ultrashort (i.e. < 5 amino acids) peptides, and ranging from monovalent to trivalent conjugates, were synthesised and their antibacterial activity was investigated by minimal inhibitory concentration (MIC) assays on five different bacterial strains. The antibacterial activity was compared to the same peptide conjugates without metallocenes. The resulting MIC values showed a significant enhancement of the antibacterial activity of these peptide conjugates against Gram-positive bacteria by the metallocenoyl groups. Additionally, the compounds with two metallocenoyl groups presented the best antibacterial activities overall.

Introduction

With the discovery of antibiotics, the battle against bacteria was considered won, as previously deadly diseases could be cured in a matter of days.[1] However, the affinity of bacteria to adapt to their environment led to increasing resistance of bacteria against antibiotics.[2] Unlike any other drug antibiotics have a limited lifespan of utility.[3] At the same time, the pipeline of new antibiotics runs dry leading to major health problems again.[4] The world is therefore in dire need of new antibiotics, preferably with new modes of action.[5]

Antimicrobial peptides (AMPs) are considered possible candidates for new antibiotics as they show activity against a broad spectrum of microbes, including bacteria, fungi, and viruses.[6-8] Furthermore, these peptides target the bacterial membrane.[9] This offers the advantage of reduced resistance development.[10] However, natural AMPs show several disadvantages, including poor bioavailability, low metabolic stability, cytotoxicity to the host cell, and synthesis problems due to their size.[11] Therefore, research has turned towards the creation of synthetic AMPs (synAMPs). To enhance the activity of synAMPs, chemists have modified the peptide sequences in many ways. For example through lipidation of a *C*- or *N*-terminal lysine residue,[12] through an L- to D-substitution,[13] or through trivalency.[14] Another established way is the addition of metallocene substituents to the *N*-terminus of the peptide. As already shown, adding a metallocene group, like ferrocene,[15] on a linear peptide can modify and actually enhance the antibacterial activity.[16-18] In those cases, however, only one metallocene group was attached to the peptide. To investigate the influence of more than one metallocene group on the antibacterial activity, multivalent constructs were synthesised and thoroughly investigated.

Therefore, three benzene scaffolds with one, two, or three alkynes (Fig. 1) were chosen to obtain monovalent (**a**), divalent (**b**), and trivalent (**c**) peptide conjugates.

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