Mapping of the modular closthioamide architecture reveals crucial motifs of polythioamide antibiotics.

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Details

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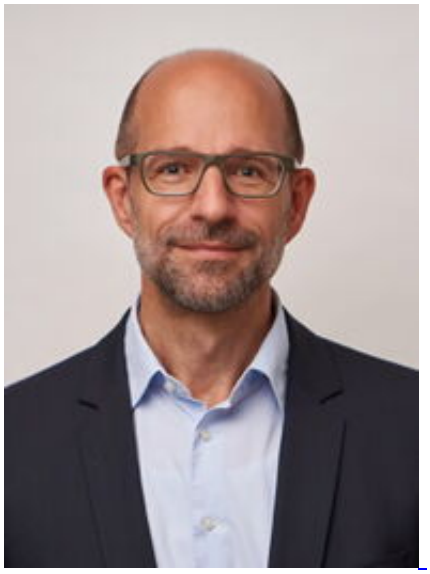
Abstract

Closthioamide, the first known secondary metabolite from an anaerobic microorganism (Clostridium cellulolyticum), represents a highly potent antibiotic that is active against methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus faecalis (VRE) at nanomolar concentrations. To unveil structure-activity relationships of the unusual polythioamide natural product we have designed a synthetic grid to access analogues with altered terminal aromatic moieties, diverse p-phenyl substituents, different types and sizes of aliphatic spacers, varying numbers of thioamide residues, and diverse sizes and symmetries of the poly-β-thioalanyl backbone. A library of 28 closthioamide analogues was tested against a panel of human pathogenic bacteria. We found that aromatic terminal groups, the defined length of the spacer groups, the presence of all six thioamide residues and the modular arrangement of the β-thioalanyl units play essential roles for the antibiotic activity of closthioamide, yet there is a degree of freedom in the symmetry of the molecule. This study yields the first insights into pivotal structural motifs and the structural space of this new family of antibiotics, a prerequisite for the development of these promising antibiotics.

Involved units

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