Synthesis and Structure-Activity Relationship Study of the Antimicrobial Lipopeptide Brevibacillin

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Antimicrobial resistance (AMR) has become a major challenge in the prevention and treatment of bacterial infections. Faced with this critical situation, the development of new antimicrobials with new modes of action has become a global priority. Antimicrobial peptides have been recognized as an interesting tool to fight AMR as they often show broad spectrum of activity and act via original modes of action. The cationic lipopeptide brevibacillin is particularly interesting because of its significant inhibitory activity against several clinically relevant bacteria, including multidrug-resistant strains. To better understand its mode of action and optimize its pharmacological properties, our objective was to develop a straightforward chemical synthesis and perform a structure-activity study.

In this study, brevibacillin and a series of analogues were produced by solid-phase peptide synthesis and their antimicrobial activity and cytotoxicity evaluated. Some analogues showed antimicrobial activity comparable to native brevibacillin against the tested bacteria. This structure-activity study identified key features of brevibacillin that allow modifications without affecting the inhibitory activity, while significantly reducing toxicity. The study highlights the great potential of brevibacillin, as well as opportunities for modifications to increase production yields, enhance stability, optimize activity, and reduce cytotoxicity for applications in the food, veterinary, and medical sectors.