Rigidity vs Activity: Design of Gramicidin S Analogs against Multidrug-Resistant Bacteria Based on Molecular Engineering

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2025

Czasopismo

Journal of Medicinal Chemistry

Numer woluminu

68

Strony

20243-20263

DOI

10.1021/acs.jmedchem.5c01234

Kolekcja

Naukowa

Język

Angielski

Typ publikacji

Artykuł

Streszczenie

Antimicrobial peptides are a promising class of therapeutics to address antibiotic resistance; yet, their clinical use is limited by toxicity and narrow-spectrum activity. To better understand how conformational rigidity influences efficacy and safety, a series of β-sheet antimicrobial peptide analogs based on gramicidin S were designed and synthesized. Two stapled derivatives (GS_C-FB and GS_C-SS) and a flexible linear analog (GS-L) were prepared and evaluated. GS_C-FB retained potent activity against Gram-positive bacteria with a significantly reduced cytotoxicity. GS-L, characterized by increased conformational flexibility, showed broader-spectrum activity, including activity against Gram-negative strains, and similarly improved safety. Circular dichroism spectroscopy revealed that all analogs displayed structural perturbations relative to native gramicidin S. Molecular dynamics simulations indicated that only flexible or moderately rigid analogs effectively interact with membrane models. These findings demonstrate that conformational rigidity is a key parameter in the design of antimicrobial peptides, enabling the optimization of antimicrobial potency while mitigating toxicity.

Słowa kluczowe

Bacteria, Chemical structure, Cyclization, Membranes, Peptides and proteins

Adres publiczny

http://dx.doi.org/10.1021/acs.jmedchem.5c01234

Strona internetowa wydawcy

https://www.acs.org/content/acs/en.html