Optimization of a Benzothiazole Indolene Scaffold Targeting Bacterial Cell Wall Assembly.
Background: The bacterial cell envelope is comprised of the cell membrane and the cell wall. The bacterial cell wall provides structural integrity and protection from the environment. Essential cell wall precursors, such as Lipid II, are targets for antibiotic drug development. Many small molecule inhibitors that target bacterial cell wall assembly are abundant and many bind to the essential cell wall precursor molecule Lipid II.

Methods: We describe the structure-to-activity (SAR) relationship of an antimicrobial peptide-derived small molecule 7771-0701 and its derivatives, guided by Computer-Aided Drug Design and NMR. Derivatives were tested for antibacterial activity and Lipid II binding.

Results: Our results show that the N-alkyl moiety is subject to change without affecting functionality and further show the impact of the N-alkyl substituent on antibacterial activity and Lipid II binding. Incorporation of a bromide at the R3 position of the benzothiazole ring was found to enhance activity against the target bacteria and Lipid II affinity was achieved.

Conclusion: We identify optimized small molecule benzothiazole indolene scaffolds that bind to Lipid II for further development as antibacterial therapeutics.

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