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 environmental stress. The assembly of the bacterial cell wall is a complex process that is tightly regulated and involves the modification of precursor molecules, such as Lipid II, to form the peptidoglycan layer. The peptidoglycan layer is a major target for antibacterial agents that inhibit cell wall assembly.

Methods: We describe the structure-to-activity (SAR) relationship of an antimicrobial peptide-derived small molecule 7771-0701 and its derivatives. We used Computer-Aided Drug Design and NMR spectroscopy to guide the optimization of the benzothiazole indolene scaffold. 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 importance of the benzothiazole indolene scaffold in the antibacterial activity. The incorporation of a bromide at the R3 position of the benzothiazole ring was found to increase the Lipid II affinity.

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