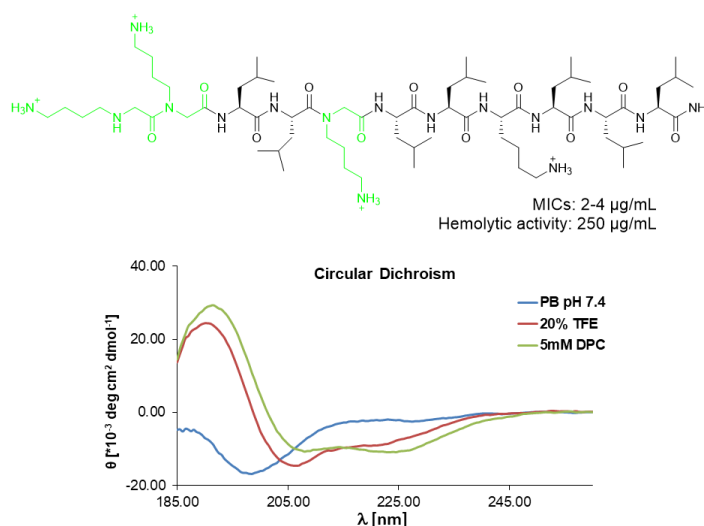


Antimicrobial peptide-peptoid hybrids to control multidrug resistant Gram-negative bacteria

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Membrane disruptive antimicrobial peptides (AMPs) such as polymyxin B offer an opportunity to control multidrug resistant (MDR) Gram-negative bacteria,¹ which are a leading cause of death in hospitals.² Recently we discovered that inverting the chirality of lysine amino acids in an 11-residues α -helical AMP with strong activity against these bacteria preserved its α -helical folding and activity while abolishing its hemolytic properties and serum instability.³ Inspired by several reports of using peptoid building blocks to tune AMP activity,⁴ we investigated if our AMP activity might also be tolerant to peptoid substitutions. Our investigations revealed several peptide-peptoid hybrids with preserved α -helical folding and antibacterial activity, but increased serum stability and reduced hemolysis compared to the parent all-L AMP sequence (Figure). Additionally, even if helicity was lacking, several hybrids including the full peptoid displayed strong antibacterial effect under dilute medium conditions, typically used for proline-rich antimicrobial peptides,⁵ suggesting a transition from membrane disruption to intracellular targets.



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