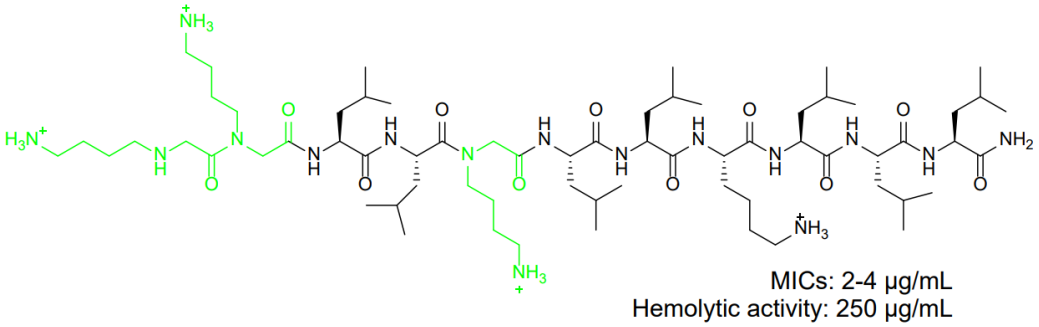
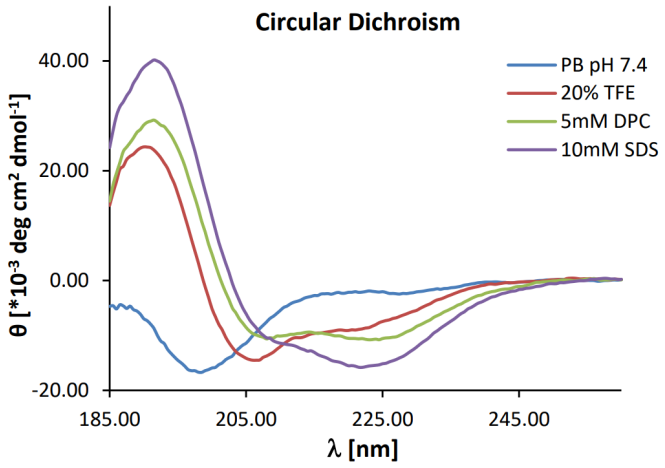
α-Helical mixed peptide-peptoid antimicrobial peptides to control multidrug resistant Gram-negative bacteria

Etienne Bonvin and Jean-Louis Reymond

Department of Chemistry, Biochemistry and Pharmaceutical Sciences, University of Bern, Freistrasse 3, CH-3012 Bern, Switzerland
etienne.bonvin@unibe.ch

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 investigate 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).





[1] N. Mookherjee, M. A. Anderson, H. P. Haagsman and D. J. Davidson, *Nat Rev Drug Discov*, **2020**, *19*, 311–332.
[2] C. J. Murray *et al.*, *The Lancet*, **2022**, *399*, 629–655.
[3] S. Baeriswyl, H. Personne, I. D. Bonaventura, T. Köhler, C. van Delden, A. Stocker, S. Javor and J.-L. Reymond, *RSC Chemical Biology*, **2021**, *2*, 1608–1617.
[4] T. Godballe, L. L. Nilsson, P. D. Petersen and H. Jenssen, *Chemical Biology & Drug Design*, **2011**, *77*, 107–116.