Structure-based optimization of diastereomeric antimicrobial peptides

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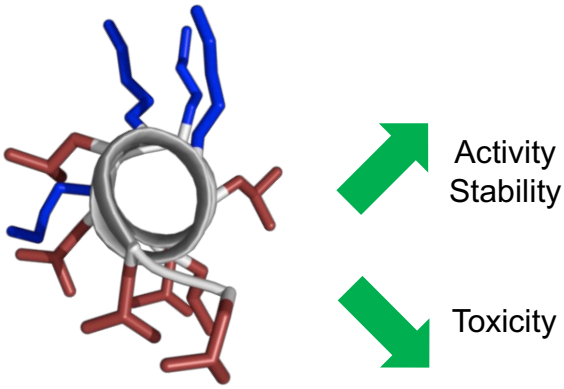
Antimicrobial peptides (AMPs) represent a promising opportunity to counter bacterial resistance due their non-specific membrane-disruptive mechanism of action. Although AMPs show high antibacterial activity, they are lacking of selectivity and are usually poorly stable against proteolysis. We recently showed that these issues can be overcome by partially switching chirality from L- to D- within the amino acids sequence, as exemplied with the 11-mer mixed-chirality AMP **In69** [1] while keeping intact the α-helical secondary structure. Based on these results, we further investigated 31 diastereomers of this sequence, and found new very potent peptides. Especially, **HP5** and **HP7** displayed better antimicrobial membrane-disruptive activity, similar stability, and reduced toxicity against HEK293 cells compared to **In69**. [2] Both **HP5** and **HP7** preserved α-helical folding as measured by circular dichroism, which was supported by the obtention of X-ray structures using co-crystallization with lectin LecB. This study highlighted a complex relationship between stereochemistry and biological properties of the diastereomers but revealed a pronounced connection between helicity and activity. These results emphasized the potential of diastereomers exploration to optimize AMPs properties.



HP7
kkLLKLLKLL**l**

[1] S. Baeriswyl, H. Personne, I. Di Bonaventura, T. Köhler, C. van Delden, A. Stocker, S. Javor and J.-L. Reymond, *RSC Chem. Biol.*, **2021**, 2, 1608-1617.
[2] H. Personne, T. Paschoud, S. Fulgencio, S. Baeriswyl, T. Köhler, C. van Delden, A. Stocker, S. Javor and J.-L. Reymond, *J. Med. Chem.*, **2023**, 66(11), 7570-7583.