Stereochemistry vs Linker: Exploration of Ring C Analogues of Antimicrobial Peptide Nisin

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Introduction

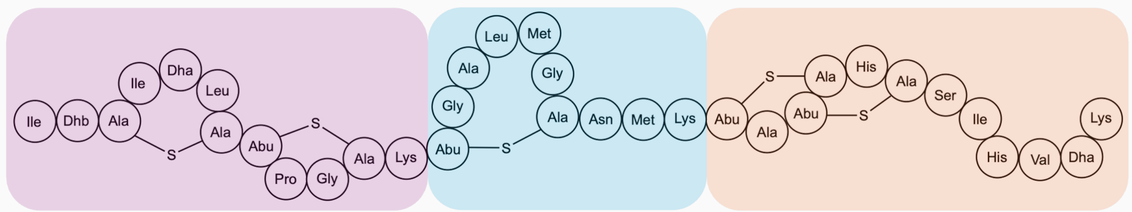
- Due to the rapidly increasing rate of resistance emerging against conventional antibiotics, which vastly exceeds the rate of novel therapeutic development, humanity is approaching a "post-antibiotic era".[1]
- Membrane-active macrocyclic peptides are a potential class of antimicrobial agents to address this gap in the antimicrobial development space.
- The lantibiotic nisin is a polycyclic peptide with broad-spectrum activity against Gram-positive bacteria, targeting lipid II to form stable pores composed of eight nisin and four lipid II molecules.[2]
- The complex structure of nisin is distinguished by five thioether-bridged rings, A–E, which are formed from the bis-amino acids lanthionine and methyllanthionine.

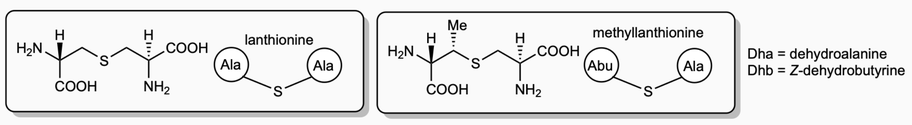
Aims

- Does ring C undergo a conformational change when entering the non-polar membrane environment?[4]
- Is the mode of action of nisin partly a function of the conformation(s) of ring C in the membrane?
- Do alterations of nisin's structure in the membrane environment facilitate its interaction with lipid II?

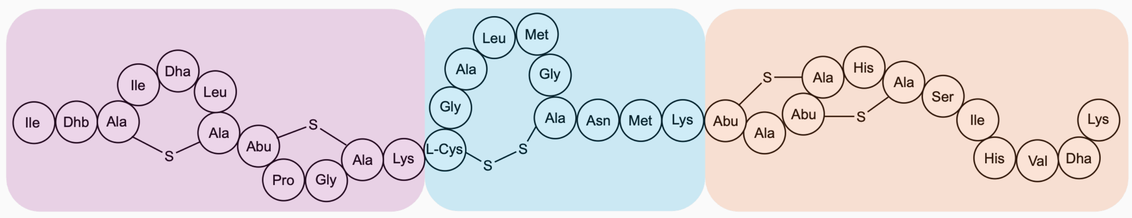
Analogues

Wild-type nisin

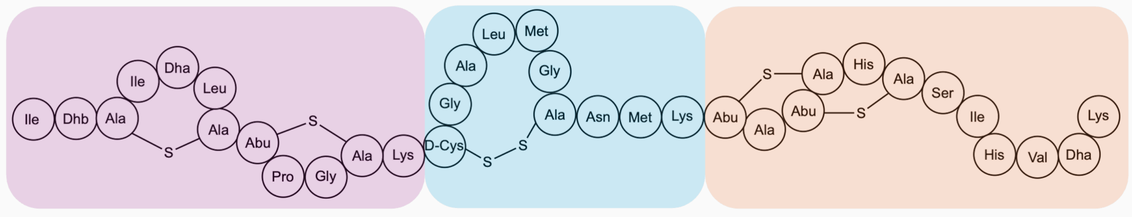


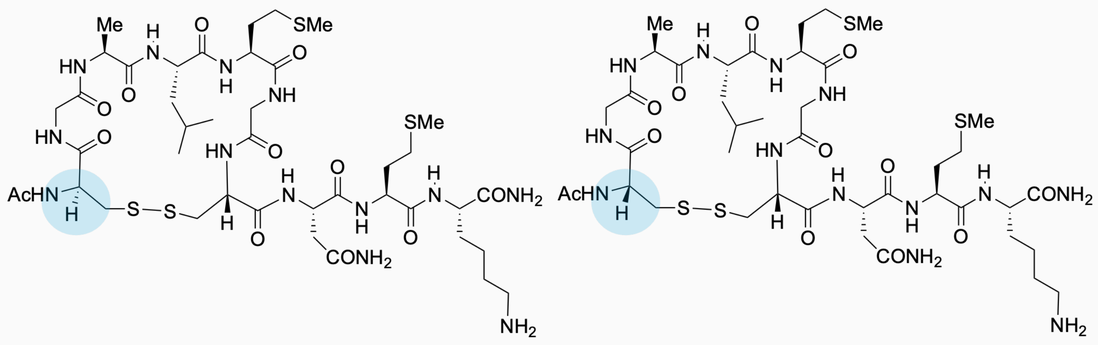


Disulfide mutant with inverted stereochemistry – inactive[3]



Disulfide mutant with native stereochemistry – active?

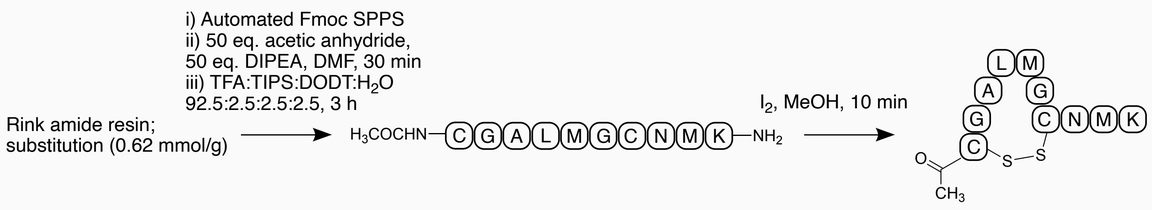




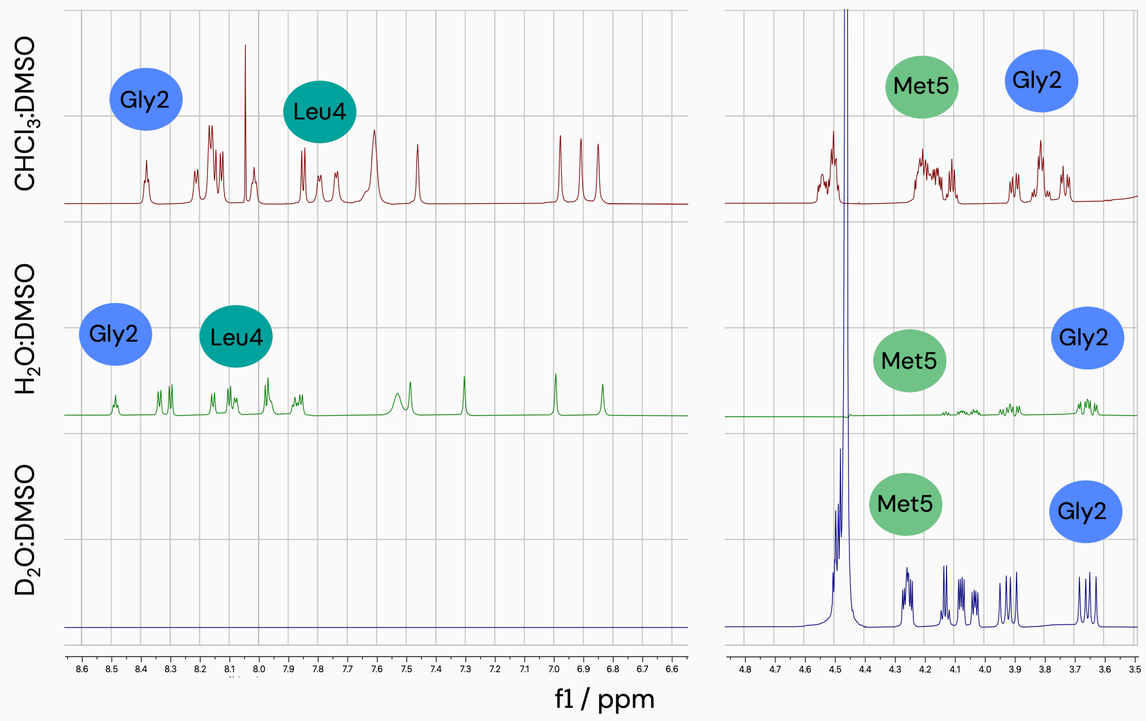
Analogue 1
(D,L)-Cys residues

Analogue 2
(L,L)-Cys residues

Synthesis of Analogues 1 and 2



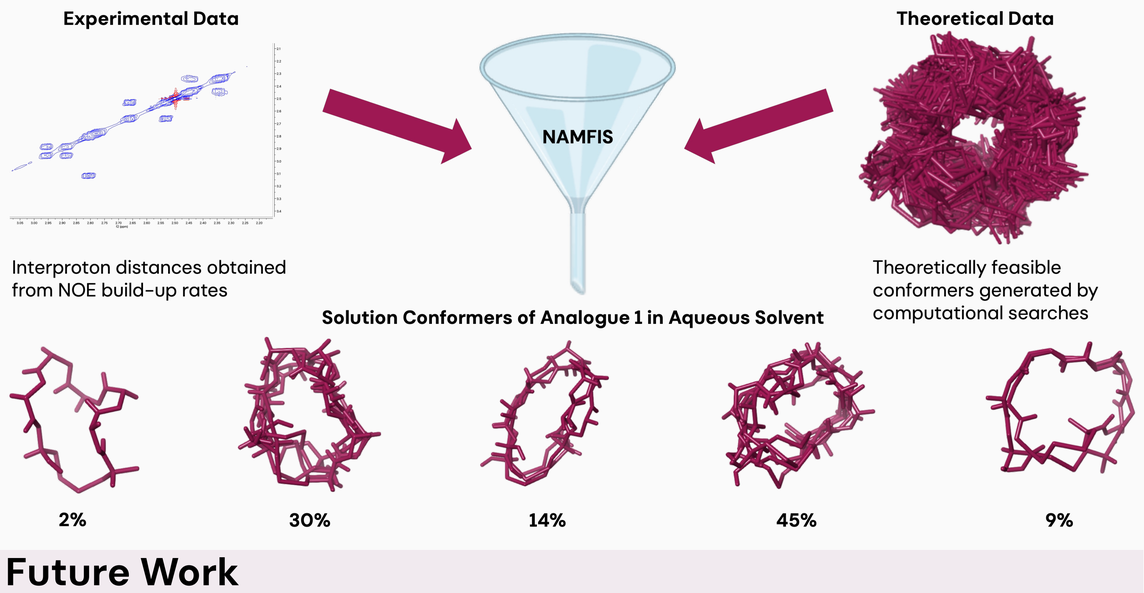
Chemical Shift Perturbations of Analogue 1 in Membrane-Like and Aqueous Solvents



Results

- Chemical shift perturbations in the 1D proton spectra between solvent systems indicate that Analogue 1 may be adopting different conformations depending on its environment.
- Solution ensembles determined by the NMR Analysis of Molecular Flexibility in Solution (NAMFIS)[5] algorithm suggest that Analogue 1 is a partial molecular chameleon.

NAMFIS Workflow



Future Work

- Develop semi-synthetic full-length hybrid nisin analogues to investigate if the disulfide mutants retain native activity levels against Gram-positive bacteria.
- Inform the development of subsequent analogues which retain the native, cyclic structure of the peptide family whilst increasing their antimicrobial activity.

1. World Health Organisation. Antimicrobial resistance: global report on surveillance. 2014. 2. E. Breukink and B. de Kruijff, *Nat. Rev. Drug. Discov.* 2006, 5, 321–323. 3. C. van Kraaij *et al. Eur. J. Biochem.* 2000, 267, 901–909. 4. J. Medeiros-Silva *et al. Nat. Commum.* 2018, 9, 3963. 5. L.H.E. Wieske *et al. Nat. Rev. Chem.* 2023, 7, 511–524.

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