Mode of action of gyrase poisoning by the peptide antibiotic albicidin

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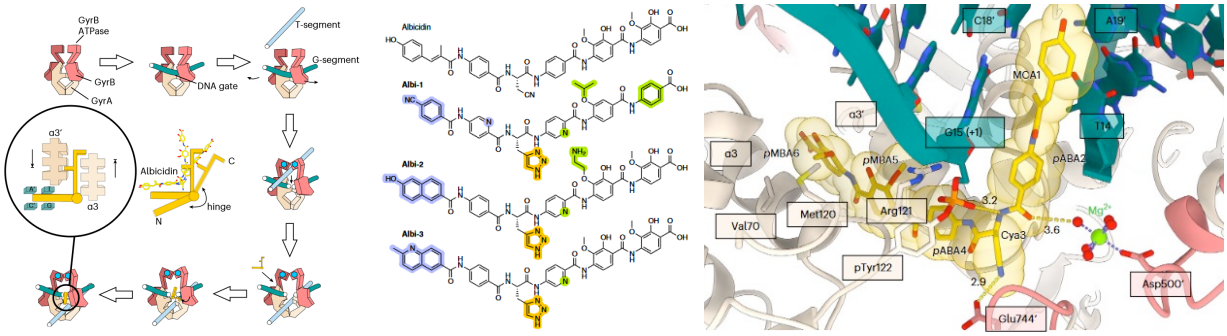
The natural product albicidin exhibits potent bactericidal activity in the low-nanomolar range against Gram-negative pathogens that are resistant to fluoroquinolones. This makes it an excellent candidate for the development into a drug candidate to combat the emerging antibiotic resistance crisis. Its unique structure consists of four substituted and unsubstituted para-aminobenzoic acids (PABA), a central β-cyano-L-alanine (Cya) and at the N-terminus a methyl coumaric acid (MCA).[1]
Despite the peptide antibiotic was identified as novel bacterial topoisomerase inhibitor, the exact mechanism of action remains elusive.[2] To shed light on the binding mode, the structure of the complex of albicidin and DNA Gyrase was determined using cryoelectron microscopy. As a result, a ternary complex consisting of *E. coli* DNA gyrase, a 217 bp double-stranded DNA fragment and albicidin was elucidated. The C-terminal part of the peptide obstructs the gyrase dimer interface, while the N-terminal part intercalates into the gyrase bound DNA indicating a unique dual binding mechanism. The most relevant interactions involve hydrophobic interactions of the methoxy groups on the substituted PABA units with a hydrophobic pocket on the gyrase dimer interface, hydrogen bonding of Cya with Glu744 and the amide backbone with a conserved Mg^{2+}-ion and π-π-stacking interactions of the MCA with the gyrase bound DNA. Consequently, albicidin effectively blocks DNA gyrase, preventing it from reconnecting the DNA strand and completing its catalytic cycle This results in irreversible DNA damage, which triggers an SOS response of the bacterial cell, which leads to cell apoptosis.
Additionally, three synthetic albicidin analogues with improved physicochemical properties where synthesized and their antibacterial effect characterized. The structure of the complex of DNA gyrase with these novel bacterial topoisomerase inhibitors was determined, showing slightly different binding modes of these analogues.[3]



The elucidated inhibition complex enables rational design of novel albicidin derivatives with further improved antibacterial and physicochemical properties. The exceptional promiscuity of albicidins' DNA-intercalating region, along with its outstanding performance against fluoroquinolone-resistant bacteria, holds tremendous potential for the development of a last-resort antibiotic.

References

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[3] E. Michalczyk, *et al.*, *Nat. Catal.* **2023**, *6*, 52–67.