Novel Macrocyclic Antibiotic Structure Targeting Bama Against Gram-Negative Pathogens

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Discovery of antibiotics against Gram-negative species is uniquely challenging due to their restrictive penetration barrier. BamA, which assists in folding and insertion of proteins into the outer membrane, is an attractive target because of its surface location, exposed to the extracellular environment. In this study, we identify dynobactin A, a novel peptide antibiotic from *Photorhabdus australis* which targets BamA, and unveil two unique unlinked rings by cryogenic electron microscopy.[a] The novel compound is the first natural product antibiotic of unknown structure solved *de novo* by this approach (PDB 7T3H). It is a decapeptide of sequence $W^1N^2S^3N^4V^5H^6S^7Y^8R^9F^{10}$, which has two closed rings: 1) a carbon-carbon bond formed between the Trp^1 C_6 and the β-carbon of Asn^4 (green box) and 2) an unusual nitrogen-carbon linkage between the His^6 imidazole $N\varepsilon_2$ and the β-carbon of Tyr^8 (orange box). These connections create unfused 4- and 3-constituent rings respectively, resulting in a flexible peptide, contrasting the fused rings of darobactins. Dynobactin A is one example of natural-product antibiotics acting against the outer membrane protein of Gram-negative bacteria. This study demonstrates how electron microscope accelerates antibiotic discovery by providing unambiguous structures from submicron-sized crystals.

[a]Miller, R.D., Iinishi, A., Modaresi, S.M., Yoo, B.-K. et al. Computational identification of a systemic antibiotic for Gram-negative bacteria. Nat Microbiol 7, 1661–1672 (2022)

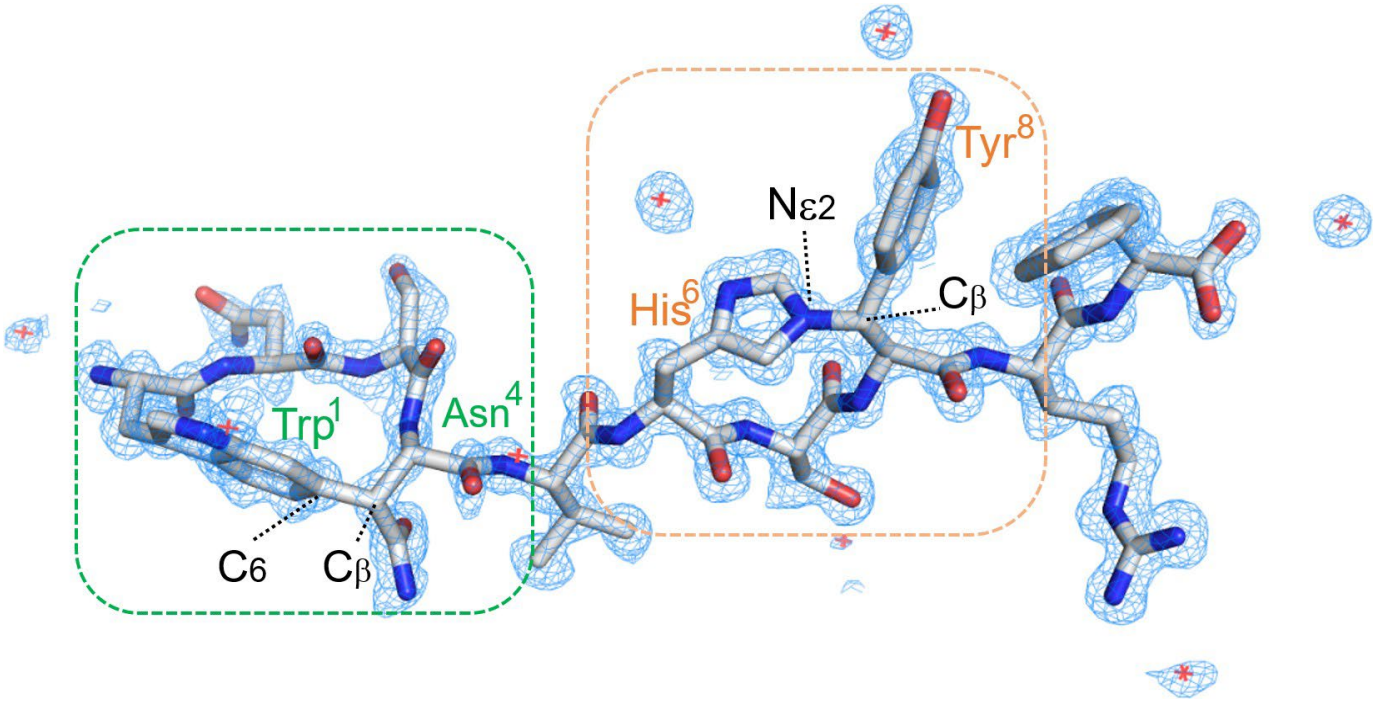

Figure 1