"Novel Oncocin–Peptoid Hybrids Show Potent Antibacterial Activity Against Multidrug-Resistant *A. baumannii*"

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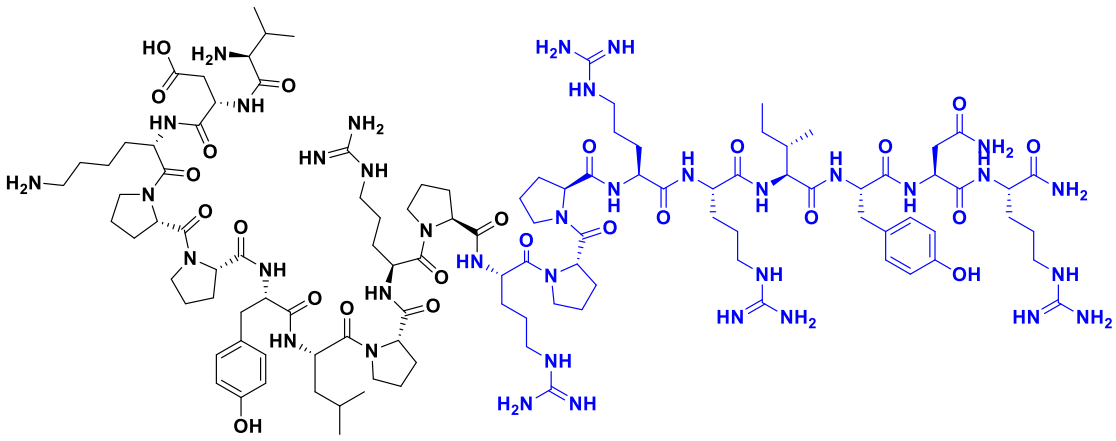
The escalating prevalence of multidrug-resistant Gram-negative bacterial infections necessitates the exploration of novel antimicrobial agents. Proline-rich antimicrobial peptides (PrAMPs) have emerged as promising candidates due to their unique mechanisms of action. Among them, Oncocin (VDKPPYLPRPRPPRRIYNR-NH_2), a synthetic derivative inspired by peptides from the milkweed bug Oncopeltus *fasciatus*, has demonstrated potent antibacterial activity against *K. pneumoniae* and *E. coli* by inhibiting bacterial ribosome (Figure 1).[1,2]

We have recently demonstrated that stereorandomization is compatible with target binding peptides to the C-terminal region of Oncocin. It preserved ribosome binding and antibacterial effects including activities against drug-resistant bacteria and protected against serum degradation.[3] Following up on this progress, we focus on the modification of the last 9 C-terminal residues by incorporating mixed peptide/peptoid chains, along with random chirality alterations. Preliminary biological assays reveal that some analogues exhibit broadened antimicrobial activity, including potent effect against *A. baumannii*, a strain against which Oncocin was inactive, while maintaining strong activity against *K. pneumoniae* and *E. coli*, and preserving the mechanism of action of the parent Oncocin peptide.



L-Oncocin: MIC *(A.baumannii): 64 µg/mL*
L-Oncocin-peptoid hybrid: MIC *(A.baumannii)*: *4 µg/mL*

Figure 1. Chemical structure of L-Oncocin.

[1] Seefeldt, A. C., *et al*. The proline-rich antimicrobial peptide Onc112 inhibits translation by blocking and destabilizing the initiation complex. *Nat. Struct. Mol. Biol.*, **2015**, *22*, 470–475.
[2] Roy, R. N., *et al*. The mechanism of inhibition of protein synthesis by the proline-rich peptide oncocin. *Nat. Struct. Mol. Biol.*, **2015**, *22*, 466–469.
[3] Gan, B. H., *et al*. Stereorandomized Oncocins with Preserved Ribosome Binding and Antibacterial Activity. *J. Med. Chem.* **2024**, *67*, 19448-19459.