https://doi.org/10.17952/38EPS.2026.P183

“Antibacterial Activity of Novel Oncocin-Peptoid Hybrids”

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European Research Council
Established by the European Commission

Swiss National Science Foundation

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Introduction

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.

Structure Oncocin

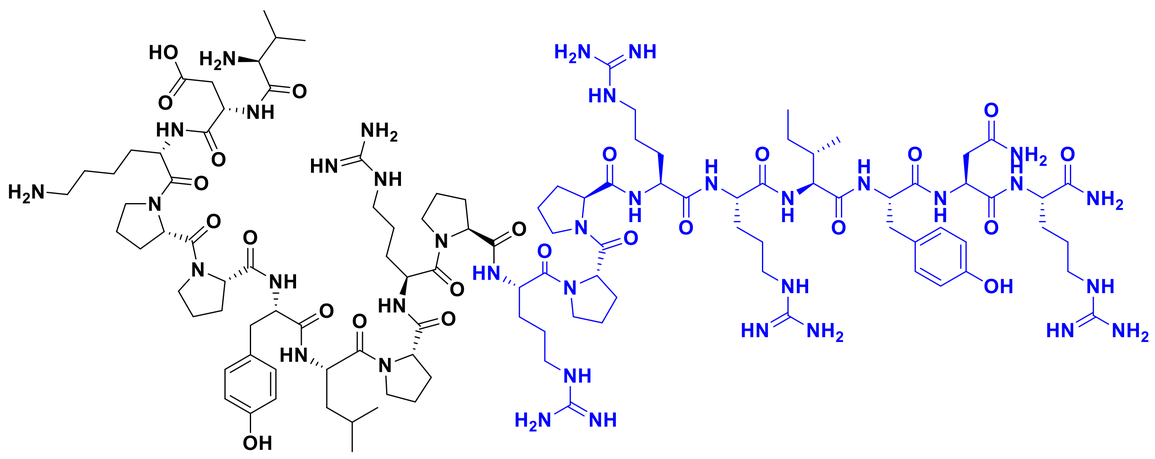


Figure 1. Chemical structure of L-Oncocin. The different parts are indicated through colours: BLACK - fixed part; BLUE – modifiable part.

Oncocin analogs visualization

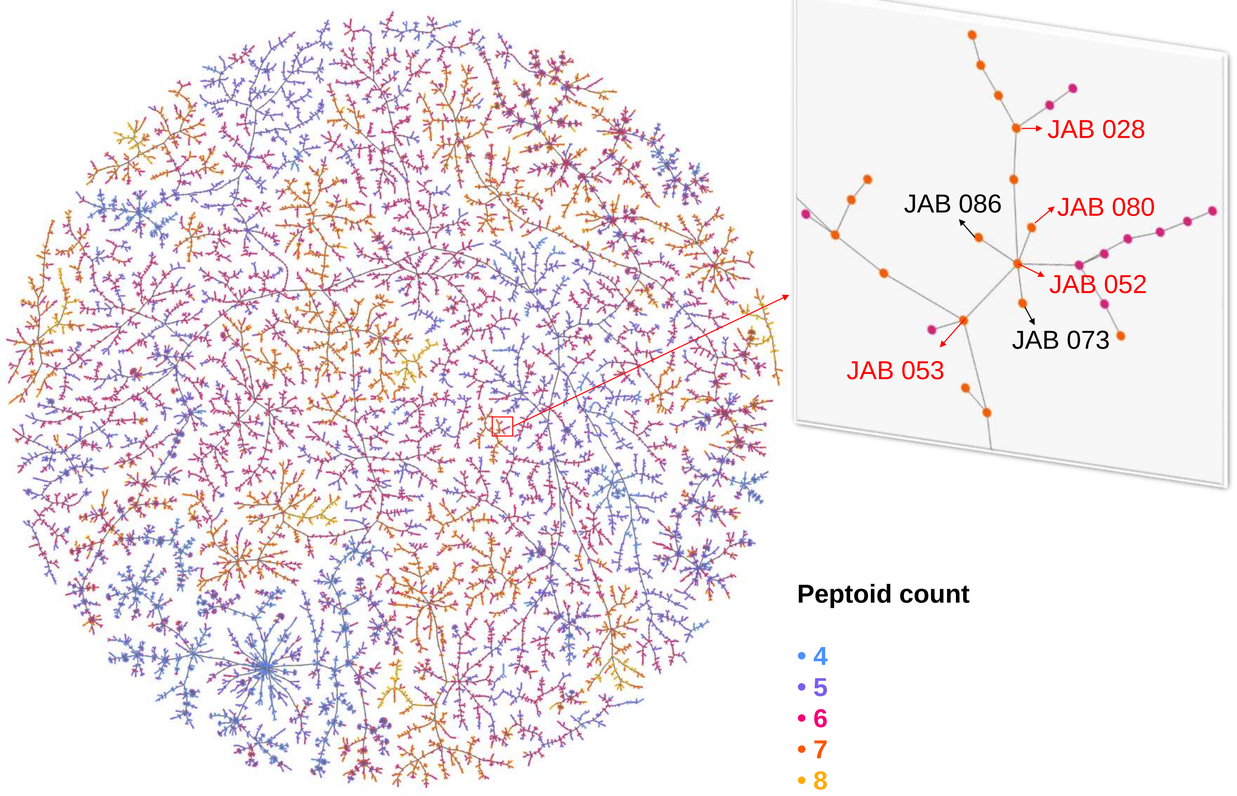
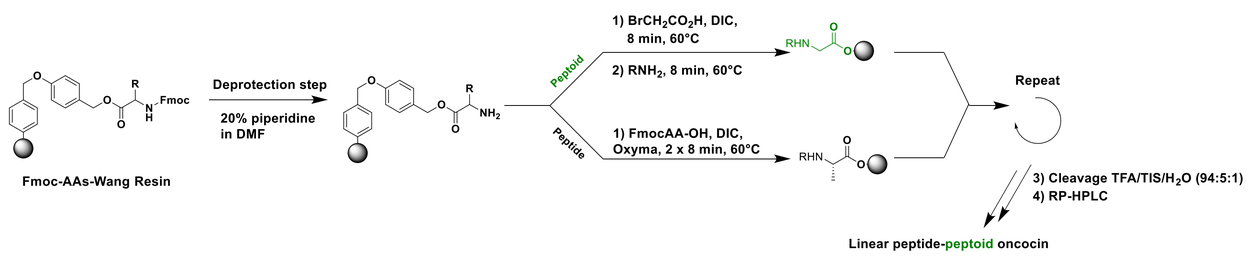


Figure 2. TMAP (Tree map) visualization of the virtual library of oncocin peptoid analogs, color-coded by the number of peptoid residues in the sequence. Each dot represents a different sequence; neighbouring dots are structurally related

Synthesis of mixed peptide-peptoid oncocin



Scheme 1. General procedure for the synthesis of linear peptide-peptoid oncocin analogs

Contact

SCAN ME

MIC and MHC

Compound	Sequence [a]	MHC [b]	MIC [c]		
			A. baumannii ATCC 19606	*K. pneumoniae NCTC 418*	*E. coli W 3110*
JAB 019	VDKPPYLPRP R p P r B_{75}I Y N R	>2000	8	32	32
JAB 020	VDKPPYLPRP R P p R R I B_{83}n R	>2000	8	64	>64
JAB 021	VDKPPYLPRP n p B_{73}R R V Y B_{57}R	>2000	8	32	32
JAB 022	VDKPPYLPRP R B_{57}P R R I y B_{52}R	>2000	8	16	32
JAB 028	VDKPPYLPRP R p P r B_{75}I Y n R	>2000	8	32	32
JAB 043	VDKPPYLPRP P p P B_{52}R V Y r R	>2000	4	32	32
JAB 051	VDKPPYLPRP R p B_{53}r R I y B_{73}R	>2000	8	8	32
JAB 052	VDKPPYLPRP R P P r B_{75}I y n R	>2000	4	16	8
JAB 053	VDKPPYLPRP R P P r B_{52}I y n R	>2000	8	32	16
JAB 055	VDKPPYLPRP n p P R R B_{61}Y B_{57}R	>2000	4	32	64
JAB 075	VDKPPYLPRP n p P R R B_{52}Y B_{57}R	>2000	4	16	32
JAB 080	VDKPPYLPRP R P P R B_{75}I y n R	>2000	4	16	8
JAB 089	VDKPPYLPRP R p P B_{63}R V Y r R	>2000	8	32	16
JAB 092	VDKPPYLPRP R p P r R B_{61}Y N R	>2000	>64	64	64
JAB 094	VDKPPYLPRP R p P r R I B_{86}n R	>2000	8	32	64
L-Onc	VDKPPYLPRP R P P R R I Y N R	>2000	64	16	16
Onc 112	VDKPPYLPRP R P P R r I Y N r	>2000	64	8	16

[a] One letter code for aminoacids. The L-amino acids are denoted with BLACK capital letters, D-amino acids with RED lower-case letters and N-substituted residues are indicated in GREEN in Italics; [b] Minimum hemolytic concentration (MHC) measured on human red blood cells (hRBC) in 10 mM phosphate buffer, 150 mM NaCl, pH 7.4, 25 °C, 4 h. [c] Minimum inhibitory concentration (MIC) in μg mL^{-1}, was determined on bacteria in Mueller-Hinton (MH) broth at pH 7.4 after incubation for 16-20 hours at 37 °C. Values two different duplicate MIC determinations.

Preliminary ribosome foot-printing assay

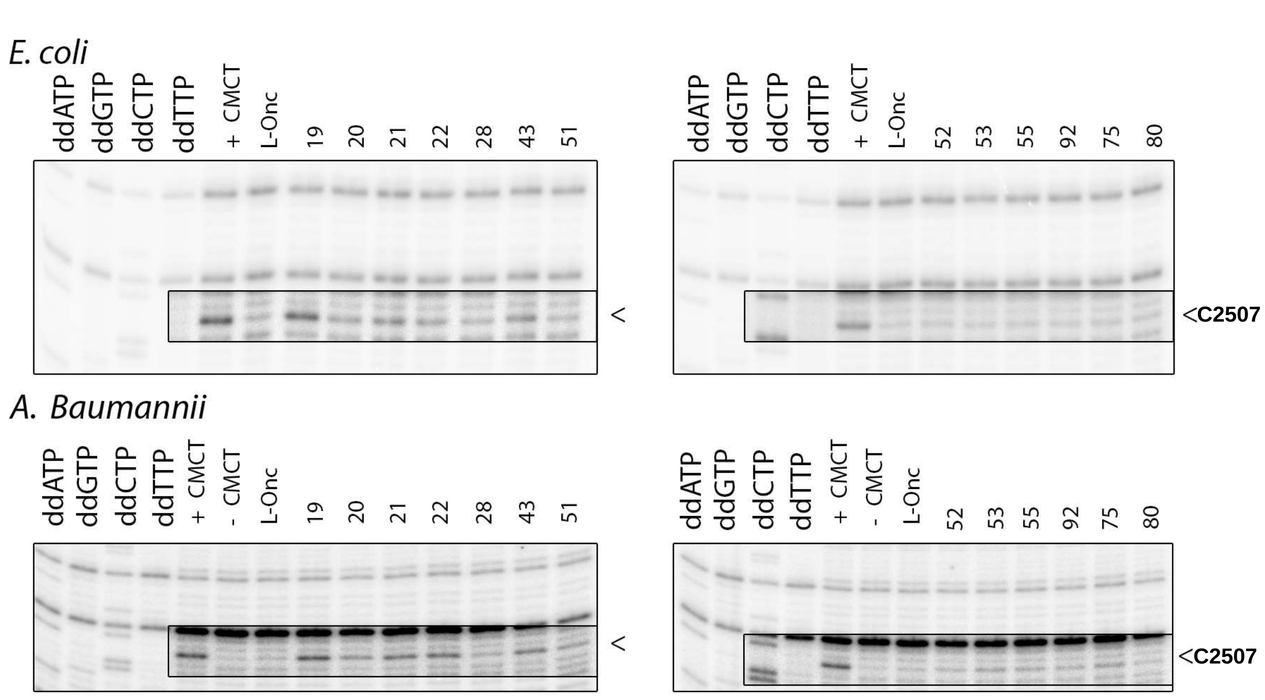


Figure 3. Ribosome foot printing experiment: The arrows indicate the position C2507 on the sequencing gel of the 23S Ribosomal RNA (*E. coli* W 3110 and *A. Baumannii ATCC 19606*). The more intense bands result from the U2506 CMCT modification in absence of peptide binding. The CMCT modifies U2506 and produces a visible band at the position C2507, in absence of CMCT there is no modification of U2506. No bands are observable with **L-Onc**, **JAB 020**, **028**, **051**, **052**, **053**, **055**, **075**, **080** and **092** compared to background (*A. Baumannii ATCC 19606)*; revealing the interaction of the peptide with U2506. [3]

Conclusion and Outlook

Our research started from the idea of modifying the last 9 C-terminal residues to create a mixed peptide-peptoid oncocin derivatives. This approach led to an increase in antibacterial activity, as shown by the MIC values of the tested compounds. Notably, **JAB 055** and **JAB 094** appear to be selectively active against *A. baumannii* and inactive against *K. pneumoniae* and *E. coli* in preliminary analyses.

These promising initial results prompted us to further investigate whether the new oncocin derivatives retain the same ribosomal binding site, and to explore the role of bacterial membrane uptake in enhancing antibacterial activity and selectivity.

Acknowledgement

This work was supported by the Swiss National Science Foundation and the European Research Council .

References

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(3) Gan, B. H., *et al. Stereorandomized Oncocins with Preserved Ribosome Binding and Antibacterial Activity. J. Med. Chem.* ***2024****, 67, 19448-19459.*