Design and synthesis of novel antibacterial oligourea foldamers

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Introduction

In recent years, the rapid spread of bacterial strains resistant to conventional antibiotics has become one of the most serious global health threats. This growing challenge highlights the urgent need to develop alternative antimicrobial strategies that are both effective and less prone to inducing resistance.

One of the most promising approaches involves antimicrobial peptides (AMPs), which are naturally occurring in living organisms and exhibit a broad spectrum of activity against various pathogens.[1] Natural AMPs are limited by enzymatic degradation and low stability. Peptidomimetics, particularly **oligourea foldamers**, overcome these limitations by mimicking AMP activity while providing enhanced stability and well-defined secondary structures.

This project focused on the design, synthesis, and biological evaluation of analogues of a compound with known antibacterial activity.[2] The analogues differed in the length of their basic side chains to investigate the influence of this structural modification on polarity, conformation and antibacterial properties.

Biological test and results

Five lipooligourea with antibacterial activity were successfully obtained. All compounds exhibited great activity against bacteria, indicating a distinct preference for Gram-positive bacterial cells. MBC assays confirmed that their activity is bactericidal, demonstrating that the compounds not only inhibit bacterial growth but also effectively eliminate bacterial cells.

CD spectroscopy indicated a well-defined helical structure. Concentration-dependent CD measurements showed that the value of molar ellipticity, which varies with concentration, indicates a strong tendency towards higher-order lipooligoureas assemblies in solution.[3]

Further studies will focus on aromatic derivatives and the effect of N-terminal chain length on biological activity.

Synthesis of building blocks

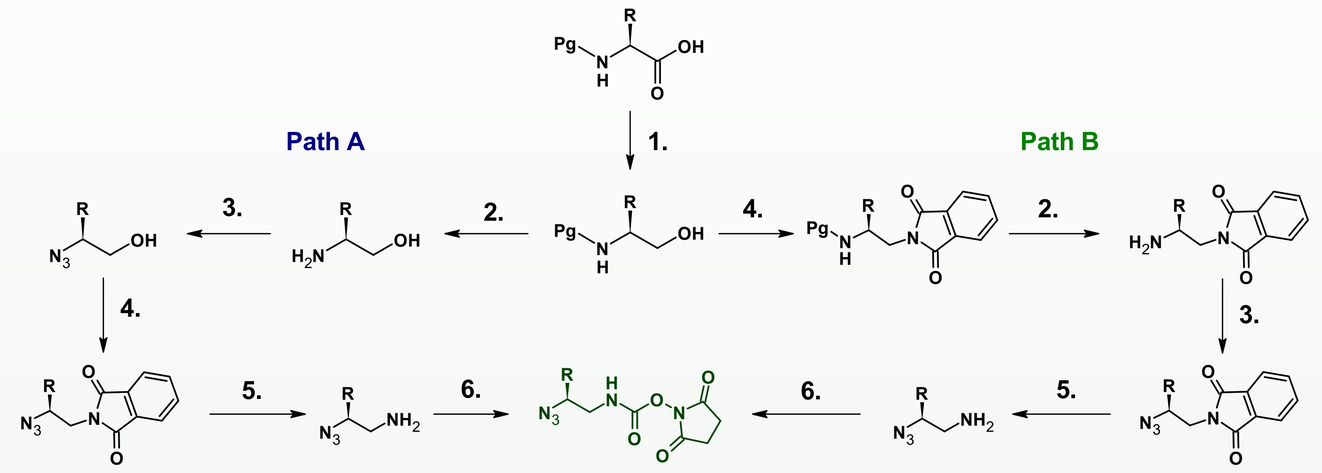


Fig. 1. Schematic diagram of building block synthesis.[4] Final building block structure is marked in **green**. Reagents used: **(1)** IBCF, NMM; $NaBH_4$; **(2)** PG-deprotection; **(3)** $ImSO_2N_3$. HCl, $CuSO_4$. $5H_2O$, K_2CO_3; **(4)** PhthNH, PPh_3, DIAD; **(5)** N_2H_4 . H_2O; **(6)** DSC;

BB obtained* via path A and total yields	
N_3-Dap(Boc)-OSu	52 %
N_3-Dab(Boc)-OSu	50 %
N_3-Orn(Boc)-OSu	50 %
N_3-Lys(Boc)-OSu	23 %
N_3-Arg(Pbf)-OSu	48 %
BB obtained via path B and total yields**	
N_3-Leu-OSu	49 %
N_3-Phe-OSu	52 %

*obtained from Fmoc-AA(Pg)-OH
**obtained from Boc-AA-OH

Synthesis of oligoureas

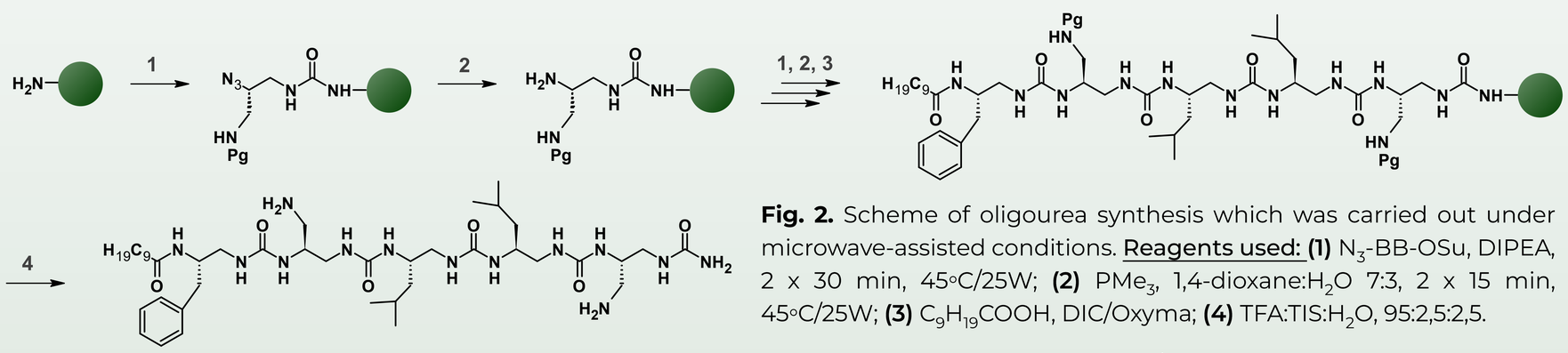


Fig. 2. Scheme of oligourea synthesis which was carried out under microwave-assisted conditions. Reagents used: **(1)** N_3-BB-OSu, DIPEA, 2 x 30 min, 45°C/25W; **(2)** PMe_3, 1,4-dioxane:H_2O 7:3, 2 x 15 min, 45°C/25W; **(3)** $C_9H_{19}COOH$, DIC/Oxyma; **(4)** TFA:TIS:H_2O, 95:2,5:2,5.

Total yields* of oligoureas synthesis		
1.	C_9H_{19}CO-Phe^{u}Dap^{u}Leu^{u}Leu^{u}Dap^u	10 %
2.	C_9H_{19}CO-Phe^{u}Dab^{u}Leu^{u}Leu^{u}Dab^u	16 %
3.	C_9H_{19}CO-Phe^{u}Orn^{u}Leu^{u}Leu^{u}Orn^u	34 %
4.	C_9H_{19}CO-Phe^{u}Lys^{u}Leu^{u}Leu^{u}Lys^u	28 %
5.	C_9H_{19}CO-Phe^{u}Arg^{u}Leu^{u}Leu^{u}Arg^u	38 %

*after purification, ^{u} means urea bond

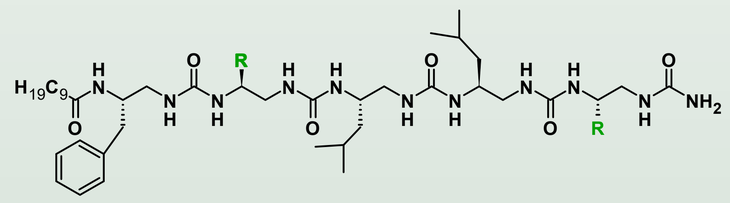
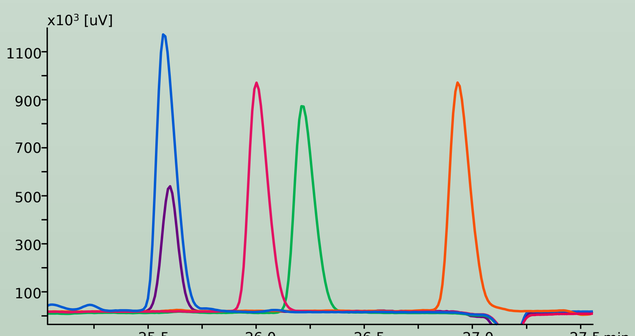


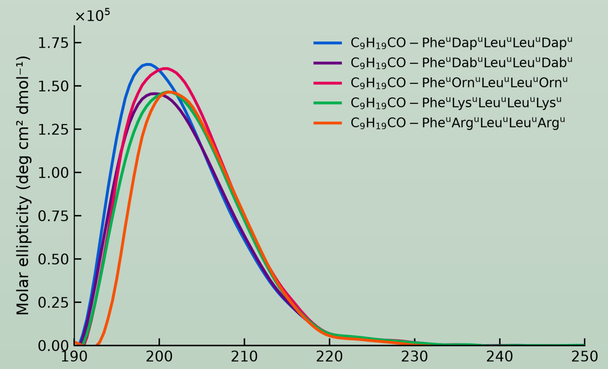
Fig. 3. The general sequence of oligoureas. **R** represents different basic residues showed in the table.

Analitycal characterisation of obtained compunds

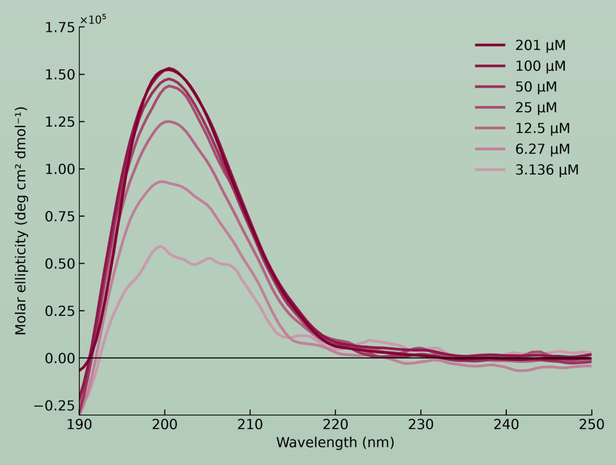
Fig. 4. HPLC chromatograms and CD spectra of oligoureas: **1.** C_9H_{19}CO-Phe^{u}Dap^{u}Leu^{u}Leu^{u}Dap^u, **2.** C_9H_{19}CO-Phe^{u}Dab^{u}Leu^{u}Leu^{u}Dab^u, **3.** C_9H_{19}CO-Phe^{u}Orn^{u}Leu^{u}Leu^{u}Orn^u, **4.** C_9H_{19}CO-Phe^{u}Lys^{u}Leu^{u}Leu^{u}Lys^u, **5.** C_9H_{19}CO-Phe^{u}Arg^{u}Leu^{u}Leu^{u}Arg^u. The synthesized compounds exhibit differences in polarity due to side chains length.



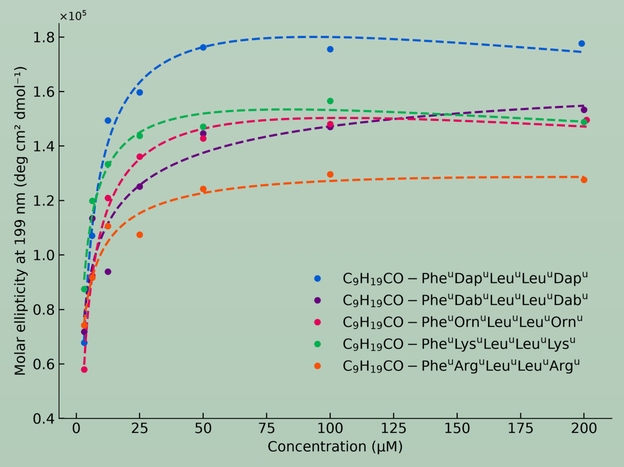
RP-HPLC: Jupiter Proteo (C12) 250 x 4,6 mm. Eluents: (A): 0.1 % TFA in H_2O and (B): 0.1 % TFA in acetonitrile; gradient 10-97 % B for 2.5-33 min. with flow 1 ml/min, λ = 200 nm.



CD: CD spectra of the compounds in Milli-Q water at 200 µM, showing a band characteristic for the helix around 200–203 nm.



Representative **concentration-dependent CD** spectra of compound 3. with ornithine side chain.



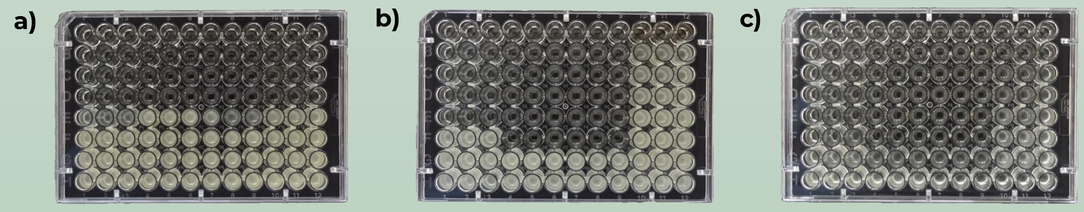
Concentration dependence of molar ellipticity at λ = 199 nm for all investigated compounds.

Biological studies

Fig. 5. Minimum inhibitory concentrations (MIC) were determined by the broth microdilution method using 96-well plates in LB medium. The compounds were tested against Gram-negative bacteria (e.g. *E. coli, K. pneumoniae, P. aeruginosa*), Gram-positive bacteria (e.g. *S. aureus, S. epidermidis*), and the yeast *C. albicans*.

MIC assay for **a)** *S. aureus* (5-0.5 µg/ml); **b)** *K. pneumoniae* (50-5 µg/ml); **c)** *C. albicans* (50-5 µg/ml).
First row (A) – negative control; last row (H) – positive control; columns 1–3, 4–6, and 7–9 correspond to oligourea **4. Lys**, **1. Dap** and **2. Dab**, respectively; columns 10-12 correspond to daptomycin (5-0.5 µg/ml).

MBC assay for *S. epidermidis* at **d)** 3 µg/ml and **e)** 2 µg/ml. At concentration 2 µg/ml bacteria growth was observed. In contrast, no bacterial growth was observed at concentration 3 µg/ml, indicating the absence of viable bacteria.



	MBC/MFC value		
Oligourea:	1. Dap	2. Dab	4. Lys
E.coli	20	20	20
S. epidermidis	3	4	-
C. albicans	10	10	30

Oligourea	1. Dap	2. Dab	3. Orn	4. Lys	5. Arg
Gram-negative bacteria (MIC values in µg/ml)					
E. coli	20	20	20	20	n.d.
K. pneumoniae	10	10	10	20	n.d.
P. aeruginosa	10	10	20	20	n.d.
Gram-positive bacteria (MIC values in µg/ml)					
S. aureus	3	3	2	3	2
S. epidermidis	2	3	1	2	3
L. plantarum	20	20	20	30	5
Yeast (MIC values in µg/ml)					
C. albicans	10	10	10	20	n.d.

References

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[3] Collie, G., Pulka-Ziach, K., Lombardo, C. et al. Nature Chem 7, 871–878, **2015**
[4] Douat-Casassus, Céline et al. Organic letters vol. 14, No. 12; 3130-3133 **2012**

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