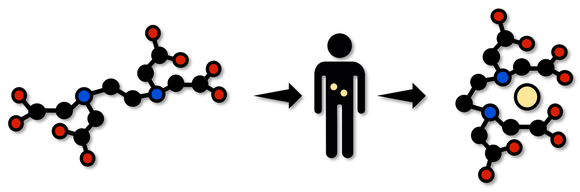
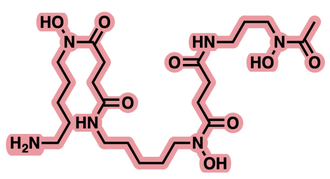
Synthesis of novel chiral peptoid-based metal chelators

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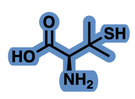
Introduction



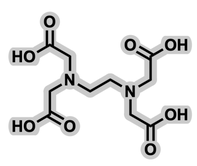
Chelation therapy involves administering a chemical agent, known as a **«chelator»**, to remove toxic exogenous metals from the body and reduce excess levels of essential metals in cases of overload disorders linked to various pathologies. The therapy works by binding metal ions into **high-affinity complexes**, which are then **excreted through the liver or kidneys** [1,2].



Desferal®
Iron chelator
Used for long-term iron chelation in beta-thalassemia



Pemine®
Copper chelator
Used for reduction of copper levels in Wilson's disease



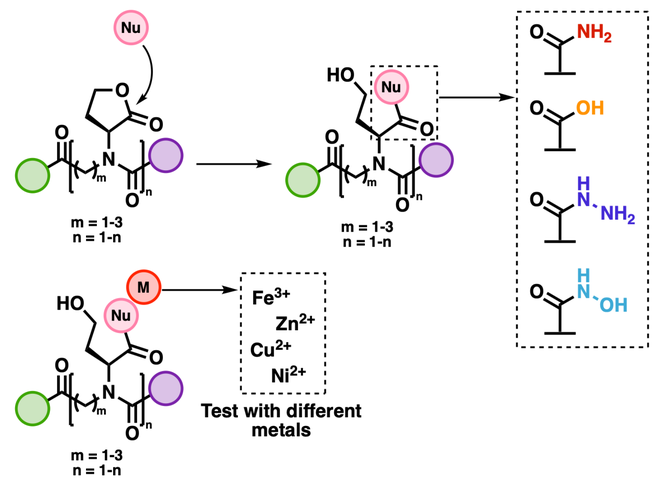
EDTA
Heavy metals chelator
Used for the treatment of acute heavy metal poisoning



✗ **Poor selectivity**, which leads to the depletion of essential metals
✗ The possible **biological activity** of the resulting metal complex

Aim of the work

Developing a class of peptoid-based chelators derived from L-homoserine lactone (L-HSL) with high selectivity for treating metal-related diseases

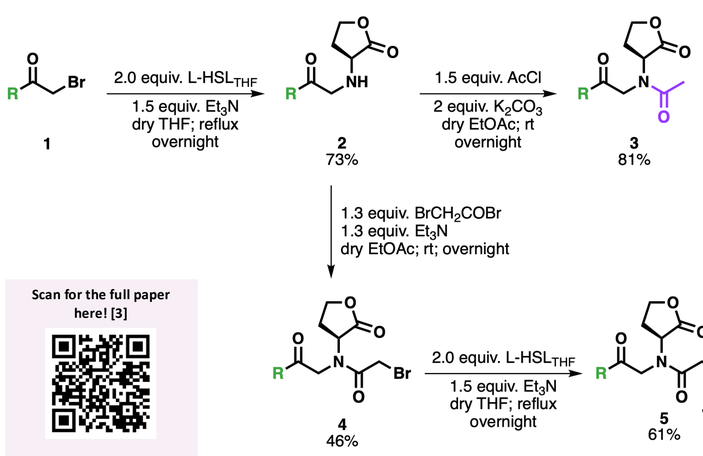


✔ Highly functionalizable peptoids
✔ Modular, divergent and side-chain protecting-group-free synthetic processes
✔ Promising biocompatible molecules
✔ Good bioavailability

The aim of this work is to optimize a solution-phase synthetic strategy for the preparation of chiral peptoid oligomers bearing L-homoserine lactone-derived side chains and their subsequent diversification via nucleophilic ring opening. Furthermore, this study evaluates the antibacterial activity of these potential chelating peptoids against antibiotic-resistant Gram-positive bacteria (*S. aureus)* and Gram-negative bacteria (*E. coli*).

Optimization of the solution synthetic protocol

Peptoid synthesis via Zuckermann Submonomerich Approach



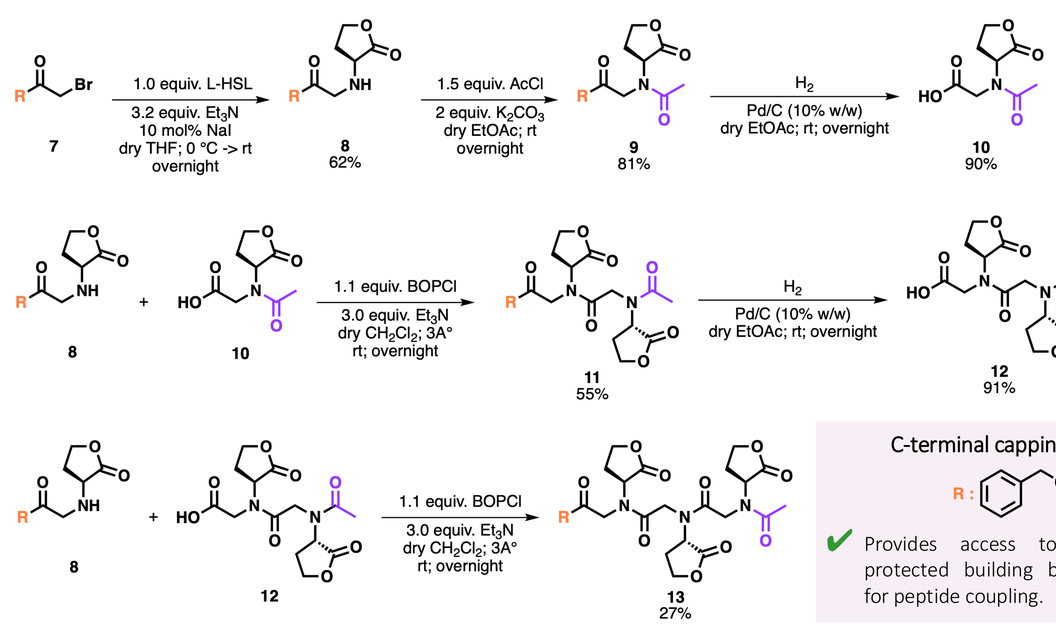
C-terminal capping group



✔ Simmetrical amide that simplifies NMR spectra interpretation
✔ It prevents the diketopiperazine formation

Scan for the full paper here! [3]

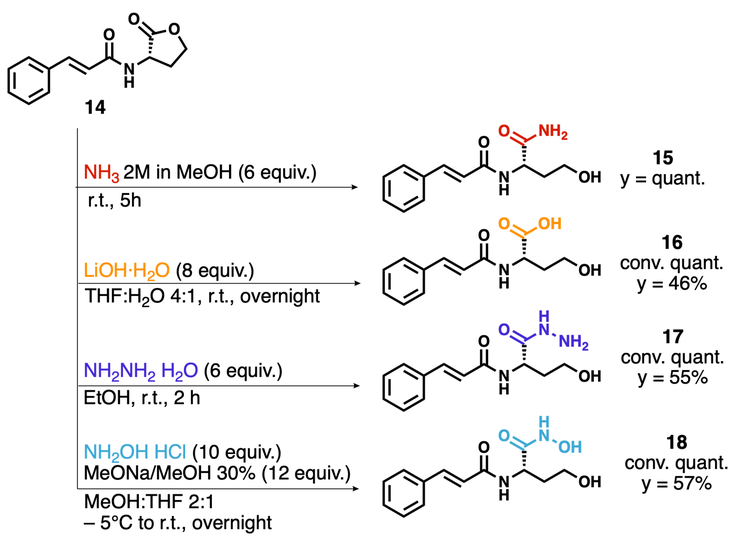
Peptoid synthesis via Peptide Coupling Approach



C-terminal capping group

✔ Provides access to orthogonally protected building blocks, suitable for peptide coupling.

Optimization of the ring-opening reaction on the model molecule 14



Highlights

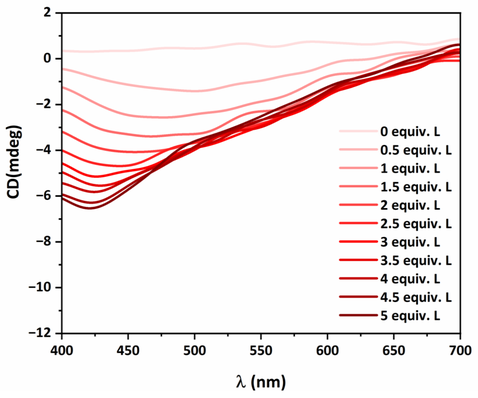
✔ Complete conversion under mild reaction conditions
✗ High product water-solubility limits purification yield
✔ Model molecule bearing a chromophoric moiety for ECD chelation studies

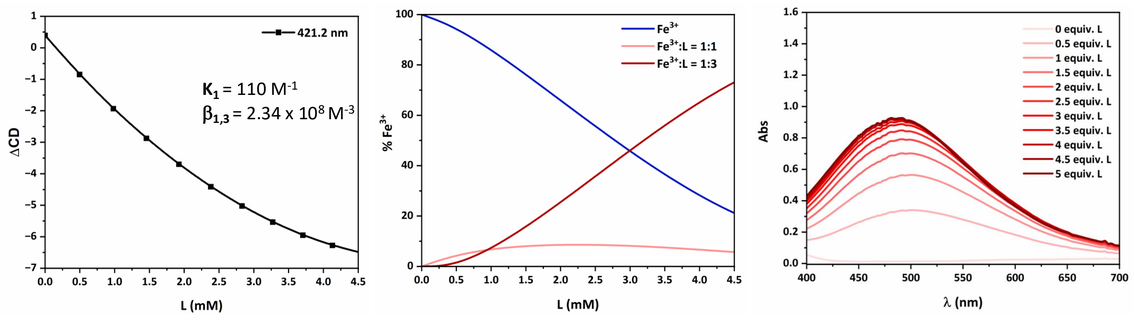
Conclusions

We have developed a **modular**, **side-chain protecting-group-free** strategy to access **chiral** peptoids bearing L-homoserine lactone-derived side chains, which can be easily functionalized via nucleophilic ring opening to yield **carboxylic acids**, **amides**, **hydrazides**, and **hydroxamic acids**. This late-stage diversification strategy expands peptoid chemical space, bypassing protecting-group manipulations that typically burden the synthesis of peptidomimetic systems containing natural chiral amino acid-derived motifs. Preliminary metal binding and antibacterial activity screening studies provide a strong basis for synthesizing novel derivatives with enhanced chelating properties and boosted biological efficacy.

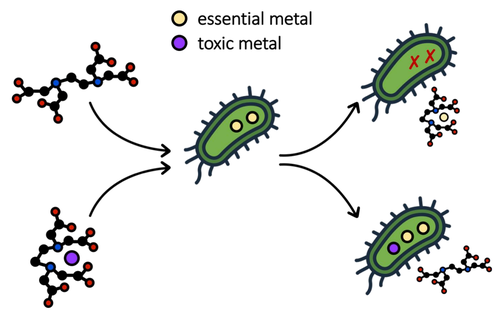
Metal binding pre-screening studies

A competition ECD titration was carried out on a multi-element mixture (Fe^{3+}, Ca^{2+}, Mg^{2+}, Mn^{2+}, Zn^{2+}, Cu^{2+} at 1 mM) in HCl/KCl (pH=2) with **hydroxamic acid** 18 (up to 5 equiv.). The induced ECD band supports the formation of a new ferric complex, while the spectral evolution suggests the involvement of two species. The best fit was obtained by considering a 1:1 transient complex followed by the formation of a more stable 1:3 complex. This complex retains a high affinity ($\beta_{1,3}$ = 2.34 x 10^8 M^{-3}) despite competition, compared to the single-metal Fe^{3+} titration ($\beta_{1,3}$ = 1.84 x 10^{10} M^{-3}), confirming high Fe^{3+} selectivity over competing metal ions.



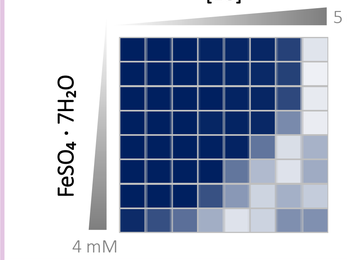


Antibacterial activity evaluation

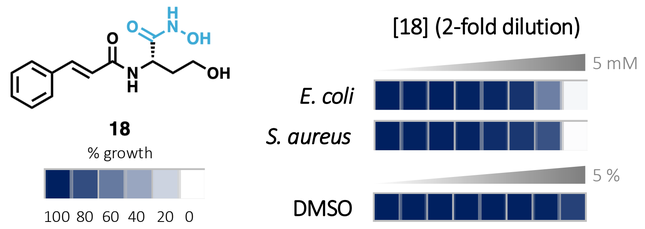


Targeting **bacterial metal homeostasis** [4,5] offers several biological advantages over conventional antibiotics. Antibacterial activity can occur through two main mechanisms of action:
→Sequestering essential metal ions
→Causing a metal overload from either intrinsically toxic metals or an excess of essential metals

Chequerboard assay: 18-Fe combination against *S.aureus* [18]

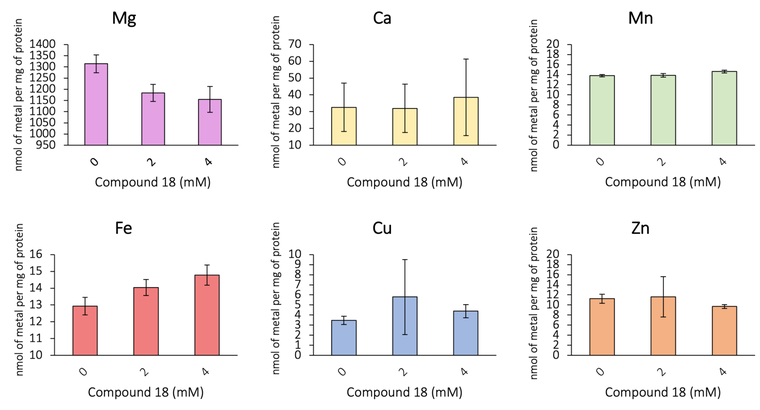


MIC determination of 18 against E. coli and S. aureus using the broth microdilution method [4,6]



Hydroxamic acid 18 showed a MIC of 5 mM against both *E. coli* and *S. aureus,* regardless of their distinct biological barriers. An increase in cellular Fe levels was observed only in S. aureus upon treatment with 18. Coupled with the observed synergistic effect with Fe, it suggests that the compound may facilitate cellular iron uptake, leading to iron overload and subsequent toxicity.

Cellular metal content of *S. aureus* after the treatment with 18 using ICP-MS



References

[1] K. Franz, *Curr. Opin. Chem. Biol.* **17**, 143–149 (2013). **[2]** E. Vigna et al. *Eur J Haematol.* **110,** 490–497 (2023). **[3]** L. Dei et al. *Org, Biomol. Chem* 10.1039.D6OB00951D (2026) **[4]** C. C. Murdoch et al. *Nat. Rev. Microbiol.* **20**, 657–670 (2022). **[5]** J. R. Paterson et al. *J. Appl. Microbiol.* **136**, lxaf258 (2025).