Synthesis of Simplified Cyclomarin-Derivatives and Pharmacokinetic Studies in Zebrafish Larvae

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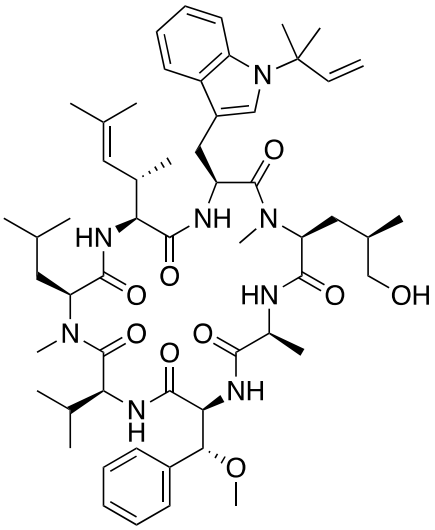
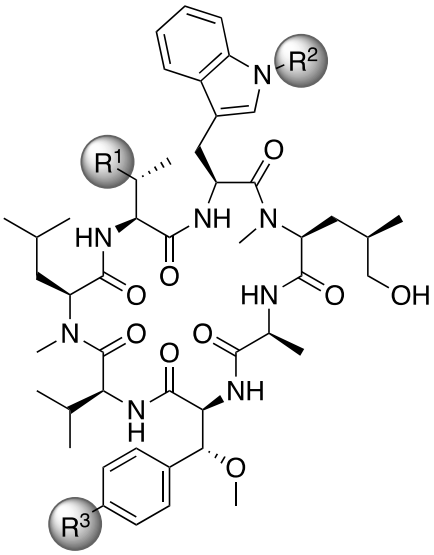
The cyclomarins are microbial, peptidic natural products, which show a remarkable antibacterial activity against *Mycobacterium tuberculosis* (*Mtb*) in both growing and non-replicating states.[1,2] Additionally, they show a strong inhibition of *Plasmodium falciparum*, based on a completely different cellular target compared to *Mtb*.[3]



Desoxycyclomarin C



possible derivatization points

Pharmacokinetic Studies

First metabolite identification studies in zebrafish larvae showed that desoxycyclomarin C is hydroxylated twice in a stepwise fashion in two different positions. The antimycobacterial activity of several cyclomarin derivatives was already confirmed. We will now test the *in vivo* efficacy of our frontrunner molecules in the zebrafish larvae model of *M. marinum* infection.

Synthesis of Derivatives

In previous synthetic studies, we found that the simplification of some amino acid residues does not impair the activity against *Mtb* significantly, some modifications even resulted in a slightly stronger inhibition.[4] Based on the insights from both

synthetic and pharmacokinetic studies, we now aimed to introduce substituents in specific positions in order to elucidate the exact locations of the oxidations. With this strategy, we aim to improve the metabolic stability of cyclomarins. The latest results regarding the synthesis as well as pharmakokinetic properties of the derivatives will be presented at the conference.

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[2] K. Weinhäupl, M. Brennich, U. Kazmaier, J. Lelievre, L. Ballell, A. Goldberg, P. Schanda, H. Fraga, *J. Biol. Chem.* **2018**, *293*, 8379–8393.

[3] N. Bürstner, S. Roggo, N. Ostermann, J. Blank, C. Delmas, F. Freuler, B. Gerhartz, A. Hinniger, D. Hoepfner, B. Liechty, *et al.*, *ChemBioChem* **2015**, *16*, 2433–2436.

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