A SYNTHETIC APPROACH TO A LIBRARY OF ANTIMICROBIAL PPAP DERIVATIVES AND INSIGHTS INTO THEIR ANTIBIOTIC MECHANISM

Frank Kraus[a], Claudia Guttroff[a], Aslihan Baykal[a], Huanhuan Wang[b], Peter Popella[b], Nicole Biber[a], Sophia Krauss[b], Peter Sass[b], Friedrich Götz[b] and Bernd Plietker[a]

[a] Institute of Organic Chemistry, University of Stuttgart, 70569 Stuttgart, Germany
[b] Interfaculty Institute of Microbiology and Infection Medicine (IMIT), University of Tübingen, 72076 Tübingen, Germany

Polycyclic polyprenylated acylphloroglucinols (PPAPs) are versatile natural products of plantal origin isolated from shrubs, vines and trees of the *Clusiaceae* family.[1] Many of those compounds have had wide applications in traditional medicine due to their antifungal, antioxidant, antiprotozoal, antiviral, antidepressant and also antimicrobial properties.[1] The variability of the compounds is a result of permutations of $R^1 - R^4$ that are bound to a central bicyclo[3.3.1]nonane-2,4,9-trione core.[1]

The reported modular total synthesis approach leads to racemic *endo*-type B PPAPs in only 7 to 10 steps starting from acetylacetone.[2,3] Consequently, the antimicrobial activity of 8 natural and 15 non-natural PPAPs was investigated against methicillin-resistant (MRSA), as well as vancomycin-intermediate *Staphylococcus aureus* (VISA) and vancomycin-resistant *Enterococci* (VRE).[2] The most active candidates were furthermore screened for their cytotoxicity and four lead candidates were identified.[2] Investigation of the mode of action revealed that PPAP **23** preferentially inhibited Fe-S-cluster proteins, which was supported by X-ray analysis of an Fe-PPAP-complex. [4]

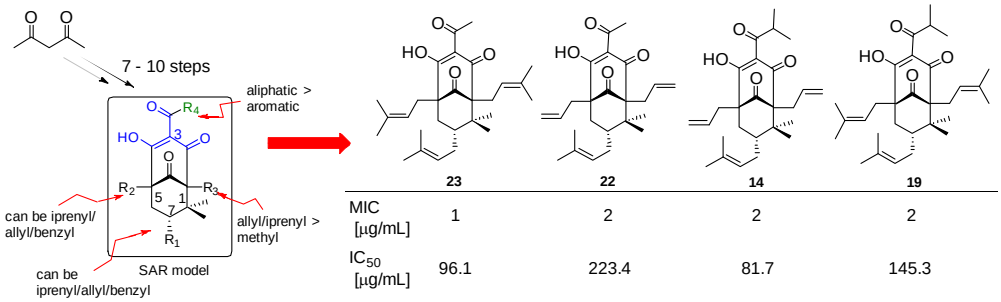

Figure 1: Antimicrobial activity of PPAPs against Staphylococcus aureus USA300 LAC and IC_{50}.[3]

[1] R. Ciochina, R.B. Grossman, *Chem. Rev.* **2006**, *106*, 3963.

[2] C. Guttroff, A. Baykal, H. Wang, P. Popella, F. Kraus, N. Biber, S. Krauss, F. Götz, B. Plietker, *Angew.Chem. Int. Ed.* **2017**, *56*, 15852–15856*; Angew.Chem.* **2017**, *129*, 16065–16070

[3] N. Biber, K. Möws, B. Plietker, *Nature Chemistry* **2011**, *3*, 938.

[4] H. Wang, F. Kraus, P. Popella, A. Baykal, C. Guttroff, P. Francois, P. Sass, B. Plietker, F. Götz, Front. Microbiol., **2019**, 10