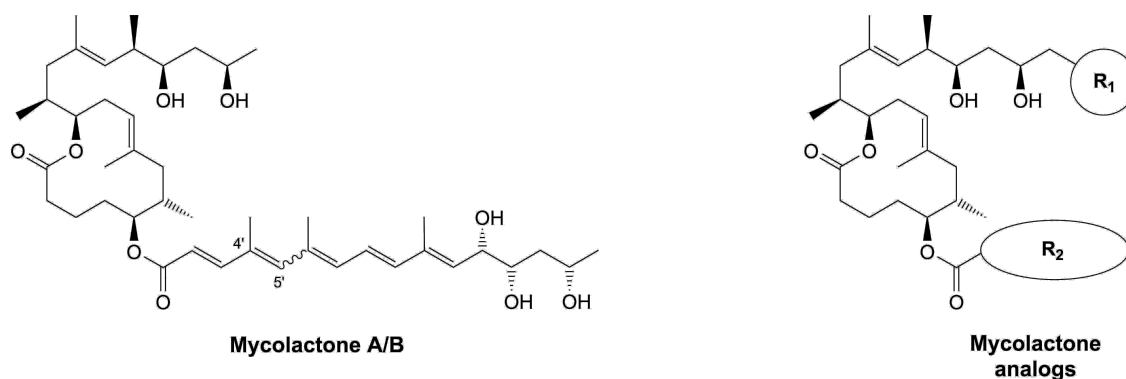


Total Synthesis, Target Evaluation and Structure-Activity Studies of Mycolactone and its Analogs

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Mycolactones are a group of macrolides which exhibit cytotoxic, immunosuppressive and analgesic properties. As the exotoxins of the human pathogen *Mycobacterium ulcerans*, mycolactones are central to the pathogenesis of the neglected disease Buruli ulcer, a severe and chronic medical condition characterized by necrotic skin ulcers. Despite extensive research in several academic laboratories, the molecular mechanism of action of mycolactones is still heavily debated and it is not even clear whether the *cis*- $\Delta^{4',5'}$ or the respective *trans*-derivative is the major contributor to bioactivity.



Driven by the desire to understand the action of mycolactones on a molecular level, we prepared a plethora of mycolactone analogs for SAR and target deconvolution studies. By using two distinct biotinylated mycolactone-derived probes in conjunction with real-time PCR, RNA interference and other techniques, we recently identified the mechanistic Target of Rapamycin (mTOR) signaling pathway as the key-driver of mycolactone-promoted apoptosis.[1] By interacting with the intracellular 12 kDa FK506-binding protein (FKBP12), mycolactone A/B inhibits the assembly of the mTORC2 multiprotein complex thereby blocking the phosphorylation of the downstream mediators Akt and FoxO3. The latter triggers the expression of the pro-apoptotic regulator Bim, which finally drives cells into apoptosis. Intriguingly, Bim knockout prevented the typical Buruli ulcer phenotype in *M. ulcerans*-infected mice thus confirming our results *in vivo*.

[1] Raphael Bieri, Nicole Scherr, Marie-Thérèse Ruf, Jean-Pierre Dangy, Philipp Gersbach, Matthias Gehringer,; Karl-Heinz Altmann, Gerd Pluschke, *ACS Chem. Biol.* **2017**, ASAP (March 15, 2017), DOI:10.1021/acscchembio.7b00053.