Natural Product derived Polyazole and Lipidated Cyclodepsipeptide Collections

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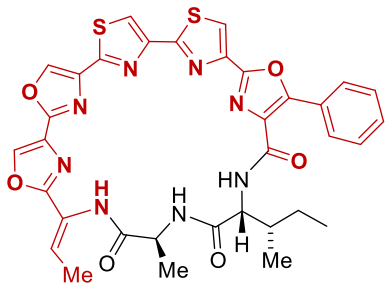
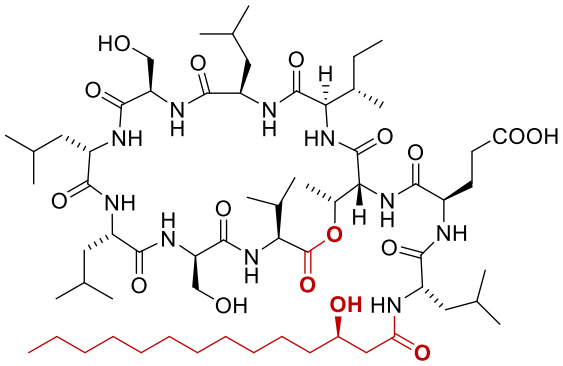
Cyclic peptides and peptidic secondary metabolites are a rich source of bioactive molecules[1] and are of high interest for drugging difficult novel targets.[2] Polyazole natural products are typically derived from posttranslational oxidative dehydration of precursor peptides by RiPP enzymes.[3] Synthesis methods for urukthapelstatin (**1**) and aurantizolicin have been developed in our laboratory.[4] We will report on the recent transfer of this chemistry to solid phase assembly, allowing the efficient synthesis of such cyclic polyazoles in 10-40% yield.[5] The compound collection accessed thereby was profiled for cellular toxicity and mode of action.[5] SAR data and a compound with improved activity will be discussed.[5]



1: urukthapelstatin A



2: orfamide A

Bacterial lipidated cyclodepsipeptides feature a wide spectrum of bioactivities.[6] We describe the synthesis of the 10mer orfamide A (**2**),[7] and of variants designed for SAR studies.[8] This methodology was recently completely transferred to solid phase and allowed an efficient total synthesis of the amoebicial lipodepsipeptide anikasin by employing a novel mild and orthogonal protecting group scheme.[9] Bioactivity studies of an orfamide collection led to a mode-of-action hypothesis in green alga,[8] as well as to insights into the bacterial ecosystem.[10] Notably, these compounds form left-handed α-helical substructures that have been systematically studied.[11]

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