

Exploiting enzymatic promiscuity to engineer a focused library of highly selective antifungal and antiproliferative aureothin analogues.

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Abstract

Aureothin is a shikimate-polyketide hybrid metabolite from *Streptomyces thioluteus* with a rare nitroaryl moiety, a chiral tetrahydrofuran ring, and an O-methylated pyrone ring. The antimicrobial and antitumor activities of aureothin have caught our interest in modulating its structure as well as its bioactivity profile. In an integrated approach using mutasynthesis, biotransformation, and combinatorial biosynthesis, a defined library of aureothin analogues was generated. The promiscuity of the polyketide synthase assembly line toward different starter units and the plasticity of the pyrone and tetrahydrofuran ring formation were exploited. A selection of 15 new aureothin analogues with modifications at the aryl residue, the pyrone ring, and the oxygenated backbone was produced on a preparative scale and fully characterized. Remarkably, various new aureothin derivatives are less cytotoxic than aureothin but have improved antiproliferative activities.

Furthermore, we found that the THF ring is crucial for the remarkably selective activity of aureothin analogues against certain pathogenic fungi.

Beteiligte Forschungseinheiten

[Biomolekulare Chemie](#) [Christian Hertweck](#) [Mehr erfahren](#)

[Infektionsbiologie](#) [Peter F. Zipfel](#) [Mehr erfahren](#)

[Biotechnikum](#) [Miriam Agler-Rosenbaum](#) [Mehr erfahren](#)

Leibniz-HKI-Autor*innen



Hans-Martin Dahse

[Details](#)



Christian Hertweck

[Details](#)



Martin Roth

[Details](#)

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