

On-line polyketide cyclization into diverse medium-sized lactones by a specialized ketosynthase domain.

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Abstract

Ketosynthase (KS) domains of modular type I polyketide synthases (PKSs) typically catalyze the Claisen condensation of acyl and malonyl units to form linear chains. In stark contrast, the KS of the rhizoxin PKS branching module mediates a Michael addition, which sets the basis for a pharmacophoric δ -lactone moiety. The precise role of the KS was evaluated by site-directed mutagenesis, chemical probes, and biotransformations. Biochemical and kinetic analyses helped to dissect branching and lactonization reactions and unequivocally assign the entire sequence to the KS. Probing the range of accepted substrates with diverse synthetic surrogates in vitro, we found that the KS tolerates defined acyl chain lengths to produce five- to seven-membered lactones. These results show that the KS is multifunctional, as it catalyzes β -branching and lactonization. Information on the increased product portfolio of the unusual, TE-independent on-line cyclization is relevant for synthetic biology approaches.

Beteiligte Forschungseinheiten

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

Leibniz-HKI-Autor*innen



Ruth Bauer

[Details](#)



Daniel Heine

[Details](#)



Christian Hertweck

[Details](#)



Hak Joong Kim

[Details](#)



Srividhya Sundaram

[Details](#)



Tawatchai Thongkongkaew

[Details](#)

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