Vinylogous chain branching catalysed by a dedicated polyketide synthase module.

Bretschneider T, Heim JB, Heine D, Winkler R, Busch B, Kusebauch B, Stehle T, Zocher G, Hertweck C (2013) Vinylogous chain branching catalysed by a dedicated polyketide synthase module. *Nature* 502(7469), 124-128.

Abstract

Bacteria use modular polyketide synthases (PKSs) to assemble complex polyketides, many of which are leads for the development of clinical drugs, in particular anti-infectives and anti-tumoral agents. Because these multifarious compounds are notoriously difficult to synthesize, they are usually produced by microbial fermentation. During the past two decades, an impressive body of knowledge on modular PKSs has been gathered that not only provides detailed insight into the biosynthetic pathways but also allows the rational engineering of enzymatic processing lines to yield structural analogues. Notably, a hallmark of all PKS modules studied so far is the head-to-tail fusion of acyl and malonyl building blocks, which leads to linear backbones. Yet, structural diversity is limited by this uniform assembly mode. Here we demonstrate a new type of PKS module from the endofungal bacterium Burkholderia rhizoxinica that catalyses a Michael-type acetyl addition to generate a branch in the carbon chain. In vitro reconstitution of the entire PKS module, X-ray structures of a ketosynthase-branching didomain and mutagenesis experiments revealed a crucial role of the ketosynthase domain in branching the carbon chain. We present a

trapped intermediary state in which acyl carrier protein and ketosynthase are covalently linked by the branched polyketide and suggest a new mechanism for chain alkylation, which is functionally distinct from terpenoid-like β-branching. For the rice seedling blight toxin rhizoxin, one of the strongest known anti-mitotic agents, the non-canonical polyketide modification is indispensable for phytotoxic and anti-tumoral activities. We propose that the formation of related pharmacophoric groups follows the same general scheme and infer a unifying vinylogous branching reaction for PKS modules with a ketosynthase-branching-acyl-carrier-protein architecture. This study unveils the structure and function of a new PKS module that broadens the biosynthetic scope of polyketide biosynthesis and sets the stage for rationally creating structural diversity.

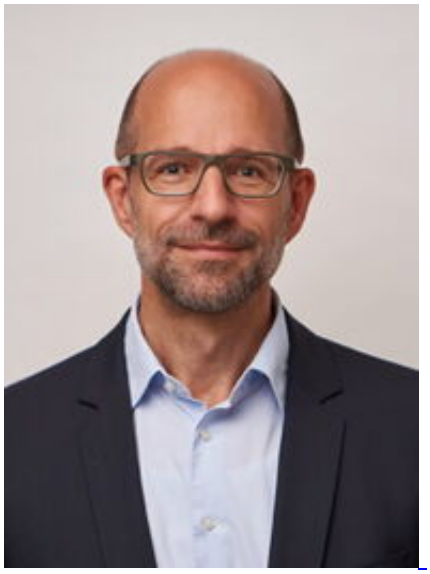
Involved units

Biomolecular Chemistry Christian Hertweck Read more

Leibniz-HKI-Authors

Daniel Heine

Details



Christian Hertweck

Details

Identifier

doi: 10.1038/nature12588

PMID: 24048471