Structural fine-tuning of a multifunctional cytochrome P450 monooxygenase.

Zocher G, Richter ME, Müller U, Hertweck C (2011) Structural fine-tuning of a multifunctional cytochrome P450 monooxygenase. *J Am Chem Soc* 133(7), 2292-2302.

Abstract

AurH is a unique cytochrome P450 monooxygenase catalyzing the stepwise formation of a homochiral oxygen heterocycle, a key structural and pharmacophoric component of the antibiotic aureothin. The exceptional enzymatic reaction involves a tandem oxygenation process including a regio- and stereospecific hydroxylation, followed by heterocyclization. For the structural and biochemical basis of this unparalleled sequence, four crystal structures of AurH variants in different conformational states and in complex with the P450 inhibitor ancymidol were solved, which represent the first structures of the CYP151A group. Structural data in conjunction with computational docking, site-directed mutagenesis, and chemical analyses unveiled a switch function when recognizing the two substrates, deoxyaureothin and the hydroxylated intermediate, thus allowing the second oxygenation-heterocyclization step. Furthermore, we were able to modify the chemo- and regioselectivity of AurH, yielding mutants that catalyze the regioselective six-electron transfer of a nonactivated methyl group to a carboxylic acid via hydroxyl and aldehyde intermediates.

Beteiligte Forschungseinheiten

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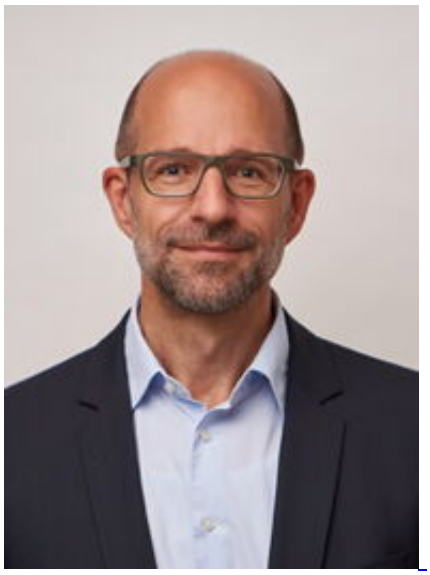

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Details

Identifier

doi: 10.1021/ja110146z

PMID: 21280577