N-heterocyclization in gliotoxin biosynthesis is catalyzed by a distinct cytochrome P450 monooxygenase.

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Abstract

Gliotoxin and related epidithiodoketopiperazines (ETP) from diverse fungi feature highly functionalized hydroindole scaffolds with an array of medicinally and ecologically relevant activities. Mutational analysis, heterologous reconstitution, and biotransformation experiments revealed that a cytochrome P450 monooxygenase (GliF) from the human-pathogenic fungus Aspergillus fumigatus plays a key role in the formation of the complex heterocycle. In vitro assays using a biosynthetic precursor from a blocked mutant showed that GliF is specific to ETPs and catalyzes an unprecedented heterocyclization reaction that cannot be emulated with current synthetic methods. In silico analyses indicate that this rare biotransformation takes place in related ETP biosynthetic pathways.

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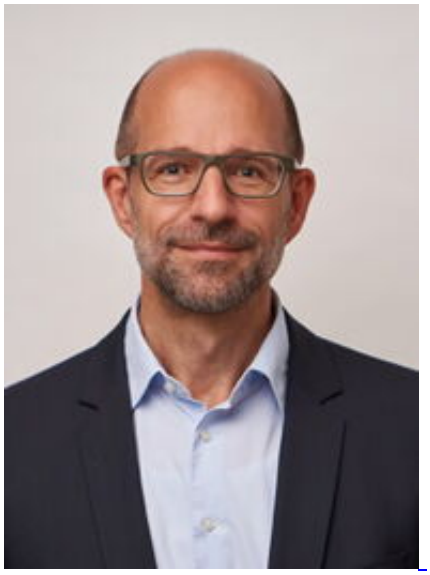
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