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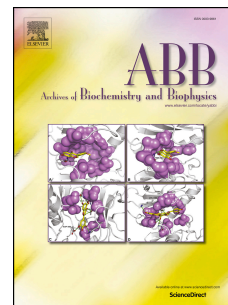
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# Flavin-catalyzed redox tailoring reactions in natural product biosynthesis

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Natural products are distinct and often highly complex organic molecules that constitute not only an important drug source, but have also pushed the field of organic chemistry by providing intricate targets for total synthesis. How the astonishing structural diversity of natural products is enzymatically generated in biosynthetic pathways remains a challenging research area, which requires detailed and sophisticated approaches to elucidate the underlying catalytic mechanisms. Commonly, the diversification of precursor molecules into distinct natural products relies on the action of pathway-specific tailoring enzymes that catalyze, e.g., acylations, glycosylations, or redox reactions. This review highlights a selection of tailoring enzymes that employ riboflavin (vitamin B2)-derived cofactors (FAD and FMN) to facilitate unusual redox catalysis and steer the formation of complex natural product pharmacophores. Remarkably, several such recently reported flavin-dependent tailoring enzymes expand the classical paradigms of flavin biochemistry leading, e.g., to the discovery of the flavin-N5-oxide - a novel flavin redox state and oxygenating species.

## Introduction

Primary metabolites are ubiquitous and found in all domains of life, whereas the production of the structurally more diverse secondary metabolites (natural products) is most common in bacteria, fungi, and plants. These specialized molecules are assumed to increase the organism's survivability, e.g., by serving as competitive weapons (toxins, antibiotics), signaling molecules (quorum sensing mediators, attractants, sexual hormones, effectors, etc.), protective pigments (melanin, carotenoids etc.) or metal binders (siderophores) [1]. The biological activity stems from the specific interaction of the natural products with proteins or other macromolecules. In many cases, however, the molecular target and the exact role of these metabolites are unknown. As a consequence of the diverse targets and activities, natural products exhibit an astounding structural diversity with currently over 270.000 compounds listed in the comprehensive Chapman & Hall/CRC chemical database.

But how is this staggering number of natural products synthesized? Many efforts have been made to elucidate the biosynthesis of different classes of natural products, such as terpenoids, polyketides or non-ribosomal peptides. In general, most secondary metabolic pathways depend on core enzymes like terpene synthases, polyketide synthases (PKS), or non-ribosomal peptide synthetases (NRPS) that condense monomeric building blocks (isopentenyl diphosphate, malonyl-CoA, or amino acids, respectively) in chain elongation reactions, thereby providing various natural product backbones [2]. Further structural diversification, however, may require additional tailoring enzymes that specifically modify the intermediates and often confer the biological activity, e.g., via glycosylation (C, O, or N), acylation, alkylation, halogenation, or by catalyzing redox reactions such as desaturation, hydroxylation, or epoxidation [2-5]. Occasionally, these tailoring reactions and in particular those involving redox catalysis substantially remodel the nascent natural product scaffolds in unforeseen ways, for example by triggering astonishing carbon-carbon rearrangement or

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