Biosynthesis of Unusual Synthons in Natural Products

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Abstract

Natural products are small molecules known for their potent bioactivities and relevance in treating human health conditions. Unique functional groups like the isonitrile and azide often drive bioactivity and may serve as indicators of novel chemical logic and enzymatic machinery. Yet, the biosynthetic underpinnings of these groups remain only partially understood, constraining the opportunity to rationally engineer biomolecules with these functionalities for applications in pharmaceuticals, bioorthogonal chemistry, and other value-added chemical processes.

The isonitrile moiety is an electron-rich functionality that decorates various bioactive natural products isolated from diverse kingdoms of life. Isonitrile biosynthesis was restricted for over a decade to isonitrile synthases, a family of enzymes catalyzing a condensation reaction between ʟ-Trp/ʟ-Tyr and ribulose-5-phosphate. ScoE, a non-heme iron(II) dioxygenase, was recently shown to utilize an alternative pathway for isonitrile installation, yet the mechanistic steps for this transformation remain obscure. In this present work, we employed in vitro biochemistry, spectroscopy techniques, and computational simulations to propose a plausible molecular mechanism for isonitrile formation by ScoE.

Triacsins are an intriguing class of specialized metabolites possessing a conserved N-hydroxytriazene moiety not found in any other known natural products. Through extensive mutagenesis and biochemical studies, we here report all enzymes required to construct and install the N-hydroxytriazene pharmacophore of triacsins. Two distinct ATP-dependent enzymes were revealed to catalyze the two consecutive N–N bond formation reactions, including a glycine-utilizing, hydrazine-forming enzyme (Tri28) and a nitrite-utilizing, N-nitrosating enzyme (Tri17). By employing a retrobiosynthetic approach, we show that Tri17 plays the role of a promiscuous N-nitrosylase capable of synthesizing the coveted azide synthon.

Main Content

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