NOVEL ENZYMES FROM THE BIOSYNTHETIC PATHWAYS OF ANTHRAQUINONE-FUSED ENEDIYNES

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Anthraquinone-fused enediynes (AQEs) are renowned for their distinctive molecular architecture and reactive enediyne warhead, which contribute to their potent antitumor and antibiotic activity. Despite the discovery of the first AQEs (i.e., dynemicins) three decades ago, the microbial biosynthetic pathway and enzymes responsible for constructing their nitrogen-containing carbon architecture remains largely mysterious. In our recent studies, we uncovered a degenerative AQE pathway named the sungeidine pathway, which contains the upstream enzymes involved in AQE biosynthesis. By integrating genes from the dynemicin pathway into the sungeidine pathway, we not only restored the biosynthesis of the AQE architecture but also generated a series of novel compounds as cycloaromatized derivatives of unstable biosynthetic intermediates. These studies have revealed previously unknown enzymes that catalyze a cascade of highly surprising biosynthetic steps, leading to the formation of the anthraquinone moiety, the characteristic C8-C9 linkage through alkyl-aryl cross-coupling, and the distinctive epoxide functionality.