Alternative Benzoxazole Assembly Discovered in Anaerobic Bacteria Provides Access to Privileged Heterocyclic Scaffold.

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Projects

Compounds from neglected bacteria and target analysis
Details

Investigation of new photochemical reactions
Details

Abstract

Benzoxazole scaffolds feature prominently in diverse synthetic and natural product-derived pharmaceuticals. Our understanding of their bacterial biosynthesis is, however, limited to ortho-substituted heterocycles from actinomycetes. We report an overlooked biosynthetic pathway in anaerobic bacteria (typified in Clostridium cavendishii) that expands the benzoxazole chemical space to meta-substituted heterocycles and heralds a distribution beyond Actinobacteria. The first benzoxazoles from the anaerobic realm (closoxazole A and B) were elucidated by NMR and chemical synthesis. By genome editing in the native producer, heterologous expression in Escherichia coli, and systematic pathway dissection we show that closoxazole biosynthesis invokes an unprecedented precursor usage (3-amino-4-hydroxybenzoate) and manner of assembly. Synthetic utility was demonstrated by the precursor-directed biosynthesis of a tafamidis analogue. A bioinformatic survey reveals the pervasiveness of related gene clusters in diverse bacterial phyla.

Identifier

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