Discovery of Novel Polyene Polyketide Natural Products using Bioinformatics and Reactivity-based Screening

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Natural products have been the source of a large portion of clinically used antimicrobial, antifungal, and anticancer compounds. Actinobacteria, which have produced many of these drug leads, have been shown by genome sequencing to harbor many more natural product biosynthetic gene clusters. We employ a combination of bioinformatics prioritization and reactivity-based screening toward both the discovery of novel natural products but also towards understanding their biosynthesis. Polyketides are one such class of natural products that has proven to be pharmaceutically prolific. Many of these polyketide natural products possess electron-rich alkenes, the biosynthesis of which can be bioinformatically traced to the presence of dehydratase domains on the polyketide synthase assembly line. While the electron-rich alkene motifs found on these molecules are often not the active pharmacophores, they are present on many pharmaceutically relevant natural product scaffolds. By using bioinformatics prioritization, bacterial strains with the potential to produce electron-rich alkene moieties can be selected. The active production of novel electron-rich alkene-containing natural products is then detected via differential mass spectrometry by an inverse electron-demand Diels-Alder reaction with a tetrazine-containing probe molecule. This workflow is being used to discover and bioinformatically characterize two families of polyene-containing polyketide natural products. The first, a proof of concept for the tetrazine-based probe, is the family of linear polyene aminopolyols. The second is the family of mycosamine-containing polyene macrolides.