Discovery and development of new biocatalysts to efficiently access bioactive targets

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Project description:
Using an interdisciplinary approach, our ultimate goal is to produce a multiplicity of high value biologically active compounds from simple feed-stocks by exploiting Nature's biosynthetic machinery. The modularity of the PKS/NRPS scaffold biosynthesis together with the plethora of post assembly modifications of tailoring enzymes offer prospects of creating novel compounds with optimized properties and production and the focus of this proposal is the discovery and exploitation of novel biocatalysts. Enzymes catalyze reactions with exquisite selectivity which, in general, simply cannot be emulated using standard chemical reactions. Whilst biotransformations are commonly used for simple resolutions (e.g. using acylases), reductions and more recently in aldol chemistry, there are a plethora of enzyme-catalyzed transformations which have yet to be exploited for the clean and efficient production of bioactive scaffolds. The project will begin by exploring the biocatalytic potential of enzymes which we have recently isolated with a view to exploiting their unique capabilities in industrially relevant processes. For example, using a combination of X-ray crystal structures, enzyme assays and molecular modeling, we have provided evidence for a Diels-Alderase (AbyU) in the biosynthesis of the antibiotic abyssomicin (J. Am. Chem. Soc., 2016). We will investigate both inter- and intramolecular DA reactions as well as the selectivity of AbyU using substrates with the potential of forming more than one ring (e.g. using analogues involved in the biosynthesis of the antibiotic tetrodecamycin). Further enzymes on the abyssomicin pathway have been characterized. The substrate specificities of these enzymes will also be explored and engineering of their active sites will be informed by molecular modeling leading to a series of non-natural linear tetronates with potential antibiotic activity. All new compounds will undergo screening for biological activity. Many bioactive compounds are assembled on oxygen heterocycles, 6-membered ring tetrahydropyrans (THPs) and 5-membered tetrahydrofurans (THFs). The selective creation of these rings via oxidation of un-activated methyl groups in complex linear substrates would be very difficult (arguably impossible) to achieve chemically. However exciting preliminary in vitro studies using oxygenases involved in the biosynthesis the antibiotic mupirocin have shown that enzymes can indeed be used to selectively generate either THFs of THPs. The mechanisms of these and other intriguing biotransformations will be elucidated and the substrate specificities explored. The project will include protein chemistry (including structural studies using X-ray crystallography, state-of the-art NMR and MS techniques), isolation and structure determination of novel compounds and molecular modeling.