UTILIZING BIOCATALYSIS AND SYNTHETIC CHEMISTRY TO ACCESS NEW NATURAL PRODUCTS

Elizabeth Parkinson[1,2]
[1]Department of Chemistry, [2]Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University

Natural products (NPs) are a bountiful source of bioactive molecules. Bioinformatics data suggest hundreds-of-thousands of novel NPs remain to be discovered. Unfortunately, many NPs are not produced under standard laboratory conditions. We are developing methods to access NPs from cryptic biosynthetic gene clusters (BGCs) utilizing a combination of bioinformatics, synthetic chemistry, and biocatalysis. Specifically, we are focused on the Actinomycetota quorum sensing molecules, the γ-butyrolactone (GBL) hormones. These molecules have previously been found to induce production of many bioactive NPs. Over half of Streptomyces strains are predicted to have GBL signaling pathways. Unfortunately, only a few GBLs and their cognate repressors are known because 1) GBLs are produced at very low quantities and 2) no rapid, efficient assays exist to identify them. We have used sequence similarity analysis to identify previously uncharacterized GBL receptors that we predict bind to known GBLs or close derivatives. We have developed synthetic and biocatalytic methods to access GBLs and derivatives in fewer steps and improved stereoselectivities. Finally, we have developed GFP-based assays that allow rapid identification of active hormones. This information will allow us to further explore the addition of exogenous hormones as a method to induce production of cryptic biosynthetic gene clusters.