Late-stage diversification of natural products using aromatic prenyltransferases

Shanteri Singh, PhD
Institute for Natural Products Applications and Research Technologies, Department of Chemistry and Biochemistry, University of Oklahoma, 101 Stephenson Parkway Norman Oklahoma 73019, USA.

Natural products (NPs) harbor unique scaffolds not readily available through total synthesis, making them prime candidates for drug development. Prenylated NPs, in particular, display diverse biological activities, though little is known about how the prenyl substituents affect their activities. Furthermore, the alkylation of scaffolds with unnatural prenyl analogs opens previously unavailable chemical space ripe for drug development. However, the complex structures of NPs often prevent functionalization through traditional means, leading us to focus initially on developing a chemoenzymatic methodology to overcome this limitation. We began by investigating the aromatic prenyltransferases (PTs), which have a natural proficiency for such reactions and utilize prenyl pyrophosphates as alkyl donors. Using a library of synthetic alkyl pyrophosphates, we probed the substrate promiscuity of multiple PTs toward various alkyl groups, demonstrating the class's promiscuity towards donors even in the presence of non-natural acceptors. As a demonstration, this seminar will present the utility of PTs in the generation of daptomycin analogues, some of which displayed potency against daptomycin resistant strains of Gram-positive bacteria. The latter portion of the seminar will address our efforts to optimize a multienzyme platform, that addresses the hurdles associated with the chemical synthesis of alkyl pyrophosphates.