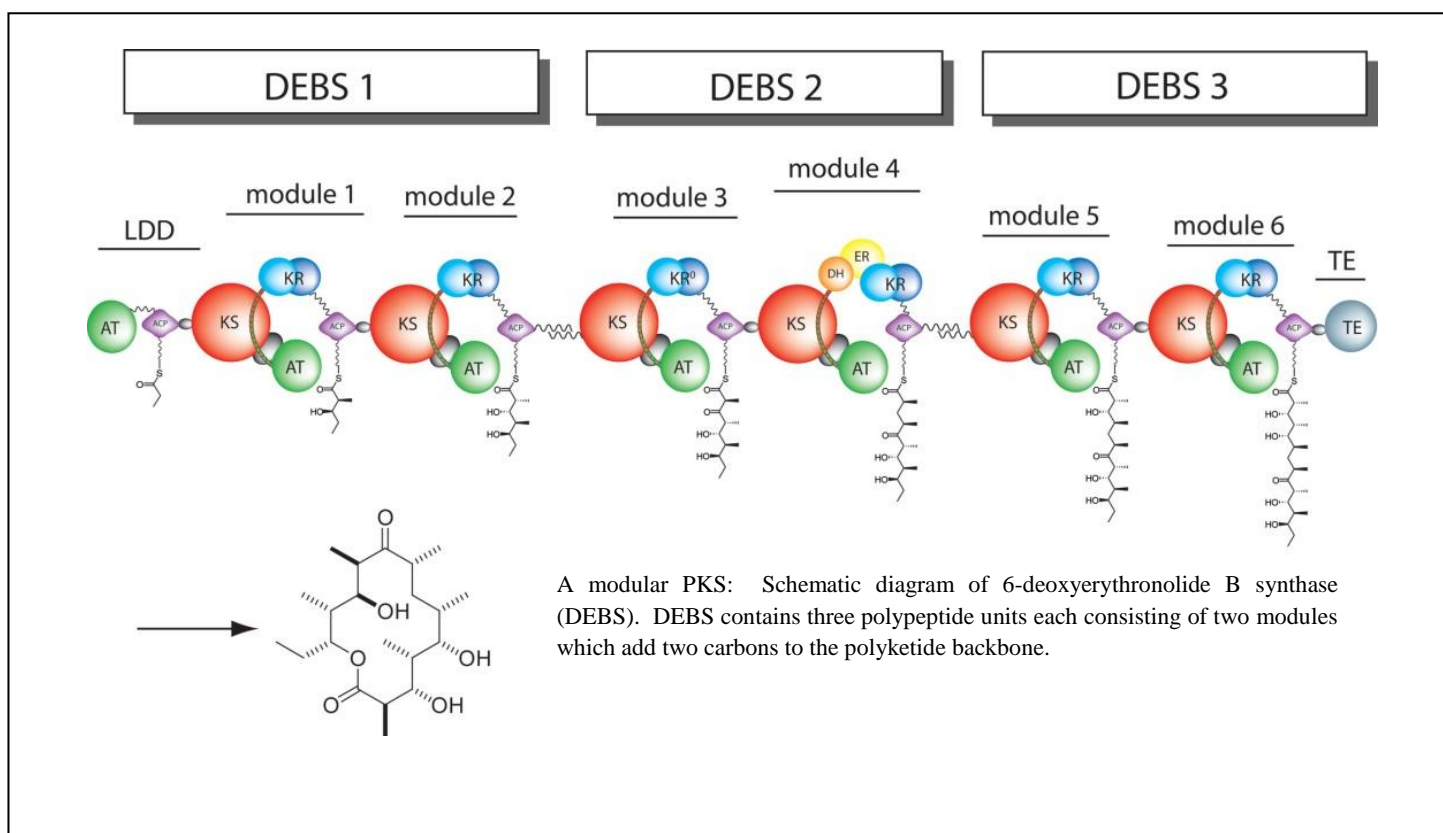


## Developing Heterocycle Probes to Investigate Polyketide Synthases (PKSs)



Polyketide-derived natural products are an enormously valuable source of biologically active compounds assembled via dedicated protein assemblies known as polyketide synthases. Our lab is interested in developing new molecular tools to study polyketide biosynthesis and improve polyketide engineering. The Acyl carrier protein (ACP) is a critical component in the polyketide biosynthesis responsible for transporting intermediates between active sites. Along with the ketosynthase domain, it serves as a primary point of attachment for all small molecule intermediates. We have successfully designed thiol-reactive small molecules such as  $\beta$ -lactones and  $\beta$ -lactams capable of directly acylating ACPs. We are now extending this idea to develop probes for ACP to study the downstream KS substrate tolerance. To systematically examine KS selectivity, we are developing a series of caprolactam-based, clickable probes bearing common polyketide functionalities. These probes can be readily modified beyond what is available in Nature, thereby providing additional insights into the scope and limitations of vital ACP-KS interactions.

### ACP- acylation with caprolactam-derived probes

