

“Chilling a biochemical hot potato: stable acyl-thioester analogs to study fatty acid and polyketide biosynthesis”

The biosynthesis of both fatty acids and polyketides involves a common reaction, the iterative carbon-carbon bond formation between acyl-thioesters and malonyl-thioesters. While fatty acids and polyketides are essential to society for a plethora of reasons, how the underlying carbon-carbon bond forming reactions occur remains an open question. Malonyl-thioesters are akin to biochemical hot-potatoes, because they are prone to hydrolysis and decarboxylation. While these two high-energy reactions are exploited by nature for biosynthetic purpose, they plague the structural biologist. We developed molecules that look like malonyl-thioesters but are much more stable, thus we have chilled the hot-potato. These stable malonyl-thioester analogs have provided us with insight into the catalysis of three enzymes. Our preliminary studies with these malonyl-thioester analogs demonstrate that we will be able to generate insight into fatty acid and polyketide biosynthesis, paving the way for new routes to drugs, agrochemicals and biofuels.