Engineering Orthogonal Substrate Specificity in Methyltransferases via Mutagenesis

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Natural Products have long been used as drugs and drug templates for many different therapies, ranging from antibiotics to chemotherapy. Microorganisms use a large suite of enzymes in order to create novel compounds that feature interesting chemical characteristics that are often difficult to reproduce using traditional synthetic chemistry. This project attempts to bend one such enzyme to our will to create new natural product-based compounds that will allow for more flexibility in drug design. This project is focused on engineering new products from methionine adenosyltransferases (MATs), which catalyze the formation of S-adenosylmethionine, a crucial methyl donor, from methionine and ATP. Our goal is to engineer different R-groups instead of the canonical methyl, which would facilitate engineering of natural product derived compounds with enhanced activity. To this end, we have solved the crystal structure of a thermostable MAT and mutagenized it with the goal of opening up the binding pocket to accept new and interesting substrates.

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