Elucidation of Structure-Function Relationships for Peptoid Catalysts of Enantioselective Trifluoromethylation

Stephan DeCarlo, 2018

Pharmaceutical development is an important field in science that provides methods for manufacturing drugs. Chemistry can be employed in designing and constructing drugs to perform a specific function with minimal side effects. Many drugs are designed containing a "trifluoromethyl group", which is a functional group that consists of three fluorine atoms bonded to a single carbon atom. The trifluoromethyl group can increase the efficacy of a drug greatly by enhancing its stability as well as its bioavailability. Attaching the group onto drugs can be difficult, however, as there are two possible ways for it to substitute at a particular site and both products can possess different chemical properties. As a result, methods for attaching the trifluoromethyl group in a highly selective manner is extremely useful for determining each of the two product's effects in the process of drug discovery.

My project was centered on developing a "peptoid catalyst", which is an enzyme mimic that is capable of adding the trifluoromethyl group to the desired position at high specificity. Many of the methods for synthesizing these peptoids were only capable of producing them on the milligram scale. Over the summer our lab developed a new solution-phase method that was successful in producing peptoids on a gram scale, which was significantly larger than before, and in a fairly rapid fashion. Furthermore, the synthesis only requires one purification at the end of all synthetic steps. In fact, I was able to successfully synthesize and purify a peptoid requiring 11 steps of synthesis twice at 5.6% yield and 13.2% yield, respectively. In the second synthesis I was able to achieve nearly a full gram of pure material. Initially we were using high-performance liquid chromatography (HPLC) as a method of purification, but the method can take over 24 hours just to purify under 100 milligrams of material. Our lab was able to optimize a method on the Biotage, which similarly uses column chromatography to purify material, to purify hundreds of milligrams of crude material in less than 30 minutes. Developing this new method of purification cuts down a huge amount of time and waste during the purification stage and allows for a much more feasible method of purification since we're synthesizing on a gram-scale. Lastly, I was able to successfully synthesize and purify a peptoid useful for catalysis of trifluoromethylation using the methods of synthesis and purification that our lab developed over the summer. The peptoid requires one more reaction, an oxidation, before it is capable of catalyzing trifluoromethylation. Since I was able to purify 160 milligrams of the peptoid before my summer research ended, I will have a sufficient amount of pure material to test a new oxidation method and explore the peptoid's catalytic capability beginning in the fall.

Faculty Mentor: Professor Gorske

Funded by the James Stacy Coles Summer Research Fellowship in Chemistry