Addition of Hydrogen Bonding Groups to Peptoid Catalysts to Increase Enantioselectivity

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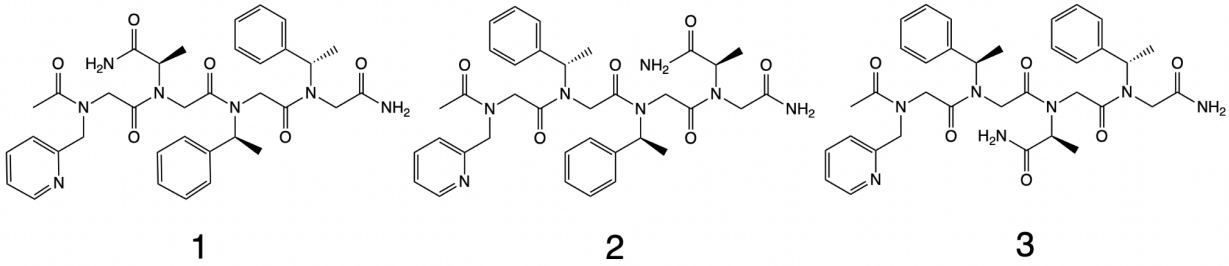
As the need for new medicines and pharmaceuticals continues to rise, the addition of a fluorine atom to a pharmaceutical compound has become an increasingly popular way to address some of the largest challenges facing the drug development industry today, including metabolic stability, bioavailability, and lipophilicity.[1] About a quarter of pharmaceutical compounds on the market or in clinical trials contain at least one fluorine atom.[2] Trifluoromethyl groups, three fluorines attached to a singular carbon, are especially common additives, as they can increase the steric bulk of the compound relative to hydrogen groups and provide more conformational control.[3] In order to ensure drug safety and effectiveness, the trifluoromethyl group must be added on enantioselectively, which means the group must be in the correct three dimensional manner relative to the other atoms on the molecule. Enantioselectivity can be quantified by measuring the resulting compound's enantiomeric excess, which is the degree that a sample contains one three-dimensional molecule over the other. Because the complication of fluorine addition can impede the study and development of new compounds, further research into effective enantioselective trifluoromethylation can help address existing gaps in the pharmaceutical industry.

A common source for enantioselective trifluoromethylation is the Ruppert-Prakash reagent, which requires a catalyst to complete the reaction.[4] Peptoids, biological mimics of peptides, are a promising catalyst for the reaction, as they maintain their secondary structure in the presence of polar solvents and are easily modifiable. Previous work in the Gorske lab has shown peptoids to be effective enantioselective catalysts. A peptoid's ability to perform enantioselective catalysis can be affected by steric and electronic interactions as a result of altering the peptoid side chains. In her 2020 Honors project, Rebecca Londoner proposed that adding side chains with the ability to hydrogen bond could activate the ketone substrate to promote enantioselective trifluoromethylation.[5]

I spent this summer building off this research by synthesizing three peptoids, each with a singular L-alaninamide sidechain and two S-1-phenylethylamine side chains (Figure 1). The L-alaninamide sidechain has hydrogen bonding capabilities, and the S-1-phenylethylamine side chains help to promote the cis-conformation of the molecule, which makes the compound form the optimal shape for catalysis.[6]



1 2 3

Figure 1. The three peptoids that were synthesized. The L-alaninamide side chain is in a different position relative to the proposed catalytic site (the 2-picolylamine group on the left of the peptoid) to test if steric or electronic reactions have an impact on the reaction.

All three peptoids were synthesized using solid-phase synthesis. Peptoid 1 was synthesized, analyzed via low resolution liquid chromatography/mass spectrometry (LC-MS) and purified via preparatory high-performance liquid chromatography (HPLC). Purification resulted in a 31% product yield, and the product identity was then re-confirmed via proton nuclear magnetic resonance. Peptoids 2 and 3 were synthesized, analyzed via LC-MS, and are in the process of being purified using preparative HPLC. Peptoid 1 was also synthesized again in an attempt to produce enough product yield to test perform the trifluoromethylation reaction and is undergoing purification.

In future work, I hope to continue to purify the peptoids in sufficient yield. Once isolated, the peptoids will undergo an aqueous workup for the trifluoromethylation reaction, and the products will be analyzed using normal-phase HPLC to determine enantiomeric excess.

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