Investigating how the Placement of Hydrogen Bonding Groups on Peptoid Catalysts affects Enantioselective Trifluoromethylation Reactions

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Many new medicines fail during development, often because they do not work well in the body, are broken down too quickly, or cause harmful side effects. One way scientists may improve medicines is by adding the element fluorine to their chemical structure. Fluorine is very small, very electronegative, and forms strong carbon-fluorine bonds, which can make medicines more stable and effective.

Several important drugs, like Paxlovid and Efavirenz, already use fluorine in their design. In some cases, the 3D arrangement of atoms, known as chirality, is also critical, since one form of a molecule may be helpful while the other can be inactive or even harmful, as seen with Thalidomide and Efavirenz.

One method to add fluorine is called trifluoromethylation, which can also create chiral centers in molecules. The Ruppert–Prakash reagent is often used for this, but it needs a catalyst to work well. Some natural catalysts, like cinchona alkaloid derivatives, can do this job, but they are difficult to change and work with a limited range of molecules. Our lab aims to develop synthetic catalysts, called peptoids, that are easier to modify and can work for a wider variety of reactions.

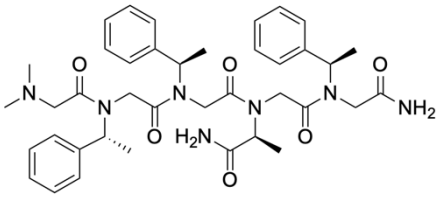
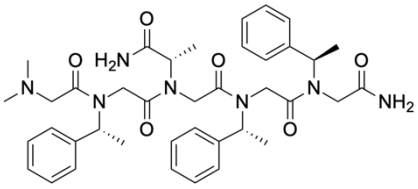
Peptoids are similar to peptides (the building blocks of proteins) but are more stable and better suited for working in the polar chemical environments used in our lab. By altering the side chains, they can take on a helical shape that can create asymmetrical binding pockets, which could act as catalytic sites and allow the production of the desired chiral product.

Earlier work in the Gorske lab showed that placing a hydrogen-bonding group called L-alaninamide near the catalytic site could improve results. In my project, I tested what happens when the L-alaninamide group is placed in different positions along the peptoid chain. I designed a small “library” of five-unit-long peptoids (Figure 1), each with a dimethylamine catalytic site and r-phenylethylamine stabilizing side chains, but with the L-alaninamide group in different spots.

Over the span of the summer, I made these peptoids, checked their structure using analytical mass spectrometry, and purified them using reverse phase high performance liquid chromatography (HPLC). I only produced enough of two of my peptoids to move on to the final reactions. Finally, I tested these two peptoids in trifluoromethylation (TFM) reactions with a model substrate (4-chlorobenzaldehyde) and used normal phase HPLC to determine if the reactions were successful and if there was any enantiomeric excess.

While both of my peptoids demonstrated successful trifluoromethylations, using peak integration I was able to conclude that they did not appear to lead to any significant enantiomeric excess.

Figure 1. Final Peptoid Library.

Peptoid Name	Peptoid Structire	TFM results
IRF1-034		Reacted for 96h. showed successful TFM but no significant enantiomeric excess.
IRF1-035		Reacted for 96h. showed successful TFM but no significant enantiomeric excess.

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