Investigation of the Influence of Hydrogen-bond Donors Surrounding the Thionated Residue on Peptoid Secondary Structure

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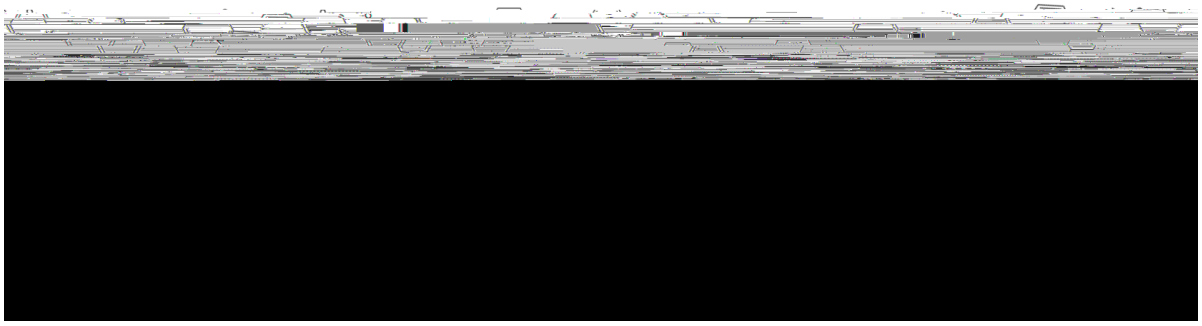
Both Alzheimer's and cancer are age-related diseases that have become increasingly more prevalent.[1, 2] One aspect that we could focus on is how aberrant signaling is implicated in both Alzheimer's and cancer. Thus a way to address both of these aforementioned diseases is through controlling the signaling proteins. By interrupting the signaling process, the diverse and complex underlying issues of these diseases don't need to be treated. We can turn to biomimicry in order to interrupt these signaling proteins and therefore develop new treatments.

A common ligand binding motif utilized by the signaling proteins in both cancer and Alzheimer's is the WW domain, which contains two conserved tryptophan residues. motif, it can bind to any of the WW-domain containing signaling proteins.[5] Therefore, a goal of the Gorske lab is to use rational design of biological probes to form PPII helix that can specifically bind to one of those WW domain containing signaling proteins.

These biological probes can be made using non-natural molecules called peptoids or N-substituted glycine oligomers. A peptoid's ability to fold to form the PPII helix depends on the steric and electronic interactions between the side chains.[6] More specifically, i side chains that contain hydrogen bond donors surrounding the adding

thionated residue can further encourage -conformation.[8] I first explored whether natural hydrogen bonding can influence the conformation of the peptoid by manipulating the position of the thionated residue. I incorporated the alanine side chain (which becomes thionated after synthesis) as the first or last residue in the tetramer, followed by three S-1-phenylethylamine side chains (peptoids 1 and 2 in Figure 1). I also built peptoids that incorporated the L-alanine residue. ion liquid chromatography/mass spectrometry (LC-CMS), followed by being purified by preparatory



high performance liquid chromatography (HPLC). Purification resulted in 20.3% yield of peptoid 1, and 5.8% yield of peptoid 2. There was only sufficient quantity of peptoid 1 to proceed with thionation with the Davy reagent. A new batch of peptoid 2 was synthesized and is in the process of being purified. Peptoids 3 and 4 were similarly synthesized, analyzed and purified. However, when confirming the identity of these peptoids through proton nuclear magnetic resonance, both peptoids were observed to have cyclized instead. A new batch of both peptoids 3 and 4 were synthesized again and is currently being analyzed.

In future work, I hope to purify the new batches of peptoids to have sufficient yield to proceed with thionation. I also hope to conduct structural analysis of these thionated peptoids with two dimensional nuclear magnetic resonance to see if the conformation is favored.

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References

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