Electronic Interactions of Thionated Peptoid Side Chains for Polyproline Type II Helix Mimicry

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As cases of Alzheimer's disease and cancer continue to grow, current research is focused on understanding the biological processes underlying these diseases. By gaining a better understanding of how these diseases develop, we can work to find new treatments. Although Alzheimer's disease and cancer have distinct symptoms, the Hippo pathway is thought to underly both[1,2]. The Hippo pathway functions to phosphorylate the YAP and TAZ proteins and is involved in cell growth, transcription, and organ size[1]. When the YAP and TAZ proteins remain unphosphorylated, they can enter the cell nucleus where they bind to the TEAD transcription factor and cause uncontrolled cell growth[2]. The Hippo pathway is characterized by the uniquely high prevalence of the WW domain binding site[3] (Fig. 1). The WW domain contains two highly conserved tryptophan residues that form aromatic grooves, allowing for the polyproline type II (PPII) helix to bind[4,5]. The PPII helix is a helical structure with three proline residues per turn[6]. These proline residues favor the *trans* conformation[6].

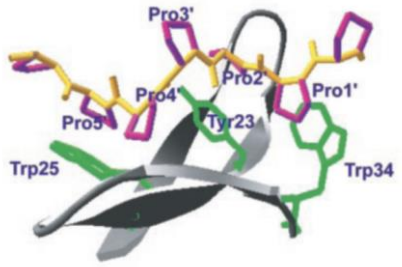

Figure 1: Representation of the group II/III WW domain binding to the polyproline type II helix. The WW domain backbone is shown in grey and the side chains are shown in green. The polyproline type II helix backbone is colored yellow and the sidechains are colored purple. Adapted from Kato et al., 2004.

Current work in the Gorske lab is aimed at designing a class of protein mimics called peptoids that will form the PPII and allow us to better under how diseases like Alzheimer's disease and cancer develop. One method for stabilizing the *trans* amide backbone conformation found in the PPII helix is by increasing the sidechain to backbone $n \rightarrow \pi^*$ interactions, in which lone pair (n) electrons are donated to the empty π^* orbital of a nearby carbonyl group[7]. To quantify the strength of these $n \rightarrow \pi^*$ interactions, we can find the *cis/trans* conformation ratio ($K_{cis/trans}$) of the amides at each peptoid residue. Thionation (a method of replacing amide oxygen atoms with sulfur) can be used to strengthen the sidechain to backbone $n \rightarrow \pi^*$ interactions and lower the $K_{cis/trans}$ in peptoids[9]. Previous work in the Gorske lab thionated an alanine sidechain using the Lawesson's reagent and found this to successfully stabilize the *trans* conformation of the peptoid at two out of three residues[10].

This project was aimed at synthesizing a four residue peptoid with phenylalanine sidechains to continue to study how thionation can be used to stabilize the *trans* amide backbone conformation in peptoids (Fig. 2). First, we synthesized the phenylalanine side chain by amidating the Boc-protected phenylalanine amino acid and then removing the Boc group. Next, we synthesized the phenylalanine peptoid tetramer using solid phase synthesis and confirmed that the synthesis was successful using LC-CMS. Future directions of this project include thionating the peptoid by using the Lawesson's reagent and conducting a conformational analysis to determine the $K_{cis/trans}$ at each residue. Stabilization of the *trans* conformation at each residue would suggest thionation of the phenylalanine peptoid tetramer as a successful strategy for PPII helix mimicry. Stabilization of the *cis* conformation at any residue in the peptoid tetramer would provide evidence for other electronic interactions at play that can weaken the $n \rightarrow \pi^*$ interactions of thionated phenylalanine sidechains.

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