Synthesis and Characterization of a Novel PROTAC Containing a Beta Hairpin Sequence Motif

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This study developed and characterized a novel proteolysis targeting chimera (PROTAC) incorporating a beta hairpin sequence motif. PROTACs facilitate the proteasomal degradation of ‘undruggable’ targets to overcome limitations with active site homology. All peptide-based PROTACs are plagued by low cell permeability and high protease susceptibility associated with unstructured peptide sequences. These limitations motivated the development of a library of new PROTACs utilizing a beta hairpin sequence motif that is protease resistant, cell permeable, and capable of rapid intracellular ubiquitination. The capabilities of the beta hairpin-based PROTAC are demonstrated by conjugating the beta hairpin sequences OWRWR (Ac-OWVRVpGOWIR-NH2) and RWRWR (Ac-RQVRVpGOWIRQ-NH2) to a previously identified Tau binding region (YQQYQDARADEQG). Concentration and time-dependent Western blots were performed using mouse neuroblastoma cells (N2A) to assess Tau degradation. Initial results identified that the RWRWR PROTAC effectively degraded Tau in a concentration-dependent manner. Moreover, it was found that the position of the beta hairpin strongly affected PROTAC degradation potential. Recent efforts have yielded some inconclusive results in terms of assay reproducibility; however, these have been attributed to challenges in performing the Western blots. As such, further testing must be conducted to better characterize the capabilities of the beta hairpin motif as a cell penetrating peptide and degron in PROTACs.