SYNTHESIS AND CHEMICAL MODIFICATIONS OF PEPTIDE CONJUGATES: INVESTIGATING PEPTIDE-PROTEIN INTERACTIONS

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With molecular weights between those of small molecules and biomacromolecules, peptides represent a unique class of therapeutic compounds with distinct physicochemical and pharmaceutical properties. During the 1950s, advances in the chemical synthesis and sequence elucidation of peptides marked the beginning of a new era where peptide-based therapeutics started to see clinical use. Bioactive peptides have been systematically used in bioanalytical and diagnostic applications. Synthetic engineering of peptide sequences through the introduction of unnatural amino acids remains a novel approach for the development of multifunctional peptides with improved pharmacokinetic properties. Investigation of the molecular interactions between peptide conjugates and protein targets could provide essential information and facilitate the prediction of potential non-proteinogenic peptide therapeutics. This work presents the utilization of non-canonical residues to develop peptide conjugate libraries and improve the recognition of proteins of biomedical interest. Molecular interactions between chemically synthesized polypeptides and protein targets were elucidated. In addition, the derivatization of several cyclic amino acids prior to peptide synthesis were achieved using 8-Aminoquinoline directed C(sp3)–H functionalization chemistry. With this directing group in was possible to exert regio- and stereocontrol in the C–H functionalization reactions through a palladium cycle intermediate.