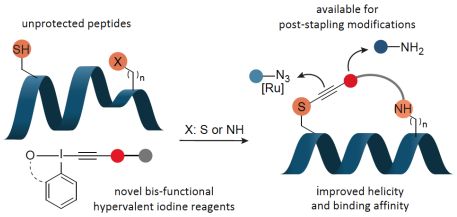
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Cys-Cys and Cys-Lys Stapling of Unprotected Peptides Enabled by Hypervalent Iodine Reagents

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Protein-protein interactions (PPIs) are responsible for regulating many processes in our bodies. These interactions are often mediated by helical segments.[1] Therefore, short helical peptides have a potential to act as inhibitors of PPIs, making them a desirable synthetic target. Nevertheless, isolated helical sequences lack the helicity, binding affinity and cell-permeability. Peptide stapling - covalent linkage of two amino acid side chains, can be used to improve the properties of helices. Therefore, an easy access to a wide range of structurally varied stapled peptides is crucial for the development of efficient inhibitors of PPIs. Alkynylation of cysteines has been previously developed in our group using various hypervalent iodine reagents.[2] Recently, this reactivity has been extended to two-component cysteine-cysteine and cysteine-lysine peptide stapling.[3] Herein, we will show the application of the novel bis-functional hypervalent iodine reagents that yield structurally diverse thioalkyne linkers. This metal free method utilizes unprotected peptides and enables post-stapling modifications via amidation of an activated ester, or via cycloaddition onto the formed thioalkyne group. Stapling of a peptide, derived from p53 protein, showed significant increase in helicity and binding affinity to MDM2 protein - a known cancer target.



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