Peptide Hypervalent Iodine Conjugates:

Enabling Peptide Functionalization and Macrocyclization

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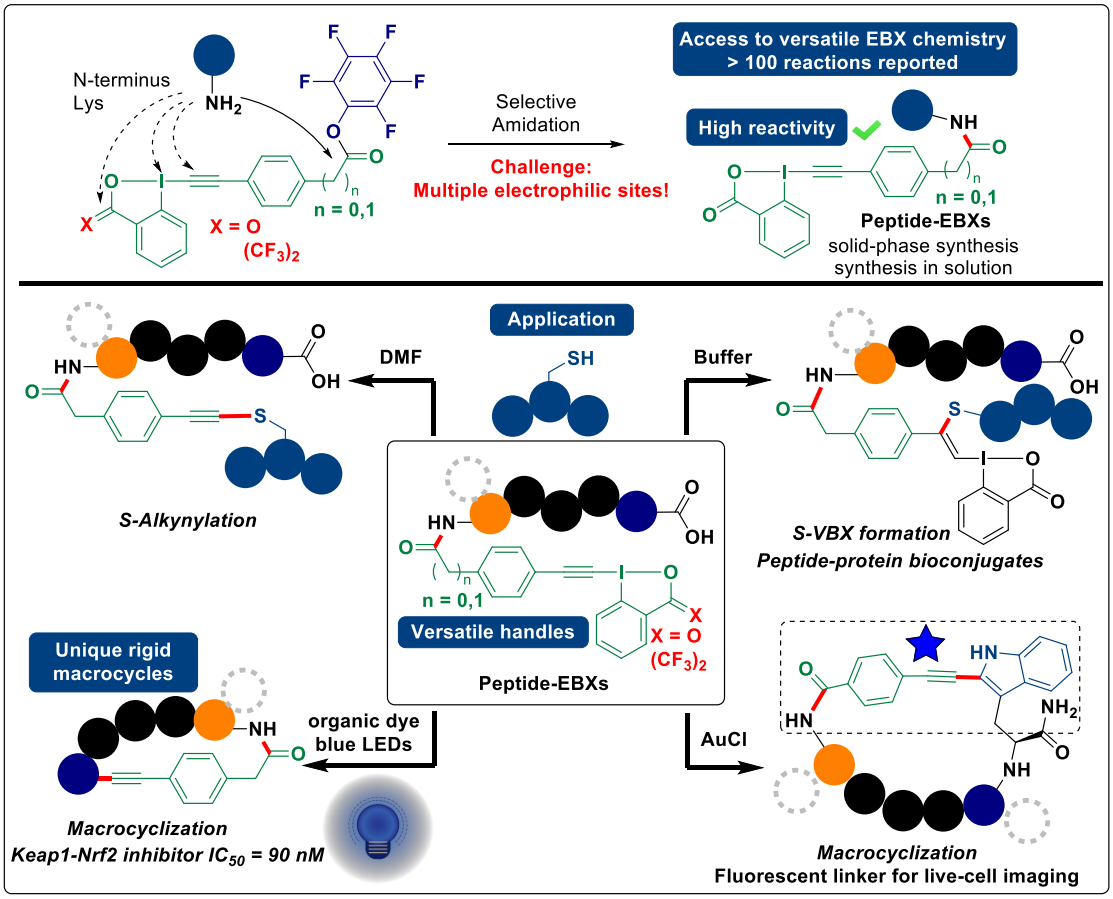

Hypervalent iodine reagents (HIRs) have been recognized as valuable and versatile reagents for peptide/protein functionalization owing to their low toxicity, high reactivity and good functional group selectivity.[1] Among these HIRs, ethynylbenziodoxolones (EBXs) are of particular interest due to their ability to transfer alkynes to specific residues. We developed a bifunctional EBXs reagent, enabling the incorporation of highly reactive EBXs core onto peptide sequences (peptide-EBXs).[2] To underscore the utility of peptide-EBXs, we achieved peptide/peptide and peptide/protein crosslinking through S-alkynyl/alkenylation by adjusting the reaction solvent. Additionally, two efficient macrocyclization methods were also achieved based on peptide-EBXs. One involved intramolecular C-terminal decarboxylative alkynylation under photoredox condition, leading to the formation of unique rigid macrocycles as KEAP1 binder. The other underwent intramolecular Trp C2 C-H alkynylation enabled by gold catalysis, resulting in a fluorescent cyclic linker for live-cell imaging.[3] We believe the development of peptide-EBXs will greatly expand the toolbox of peptide/protein modifications.

[1] Allouche, E. M. D.; Grinhagena, E.; Waser, J., *Angew. Chem., Int. Ed.* **2022,** *61* (7), e202112287.

[2] **Liu, X.-Y.**; Ji, X.; Heinis, C.; Waser, J., *Angew. Chem. Int. Ed.* **2023**, 62, e202306036.

[3] **Liu, X.-Y.**; Cai, W.; Ronceray, N. Radenovic, A.; Fierz, B.; Waser, J., *J. Am. Chem. Soc.* **2023**, 145, 49, 26525–26531.