Stapled-Peptide PROTACs by Hypervalent Iodine Staples

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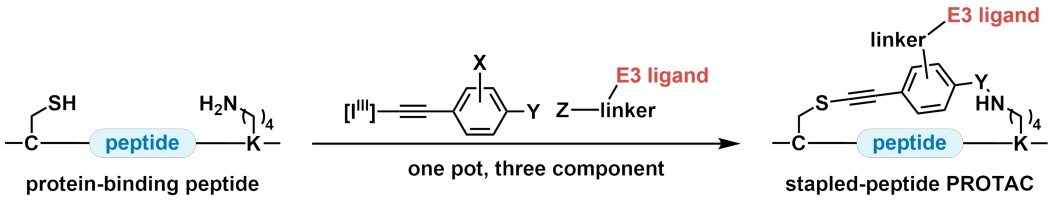
Protein–protein interactions (PPIs) are deemed undruggable due to the lack of well-defined binding pockets on corresponding proteins. Peptides can target undruggable proteins by mimicking PPIs. The development of peptide-based inhibitors of PPIs is one of the major topics in current medicinal chemistry. PROTAC (proteolysis targeting chimera) technology is an emerging modality to degrade pathological proteins.[1] Most of the PROTACs are synthesized by linking two small-molecule ligands: a POI (protein of interest) ligand and an E3 ligand. However, the development of small-molecule ligands for undruggable proteins is in itself challenging. Thus, the availability of POI ligands is hampering the development of PROTACs for undruggable proteins.

We developed trifunctional hypervalent iodine staples based on our previous report.[2] This reagent is first assembled with E3 ligand-linker conjugate and then readily transforms protein-binding peptides into stapled-peptide PROTACs in a one-pot three-component manner. Our platform would rapidly provide diverse analogues and pave the way for drugging currently untouched proteins, even if small-molecule ligands are unavailable. We are working on the degradation of transcriptional coactivators, applying this methodology.



[1] Kusal T. G. Samarasinghe, Craig M. Crews, *Cell Chem. Biol.* **2021**, *28*, 934-951.
[2] Javier Ceballos, Elija Grinhagena, Gontran Sangouard, Christian Heinis, Jerome Waser, *Angew. Chem., Int. Ed.* **2021**, *60*, 9022-9031.