BIOMOLECULES FUNCTIONALIZATION

Photo-gluing on peptides

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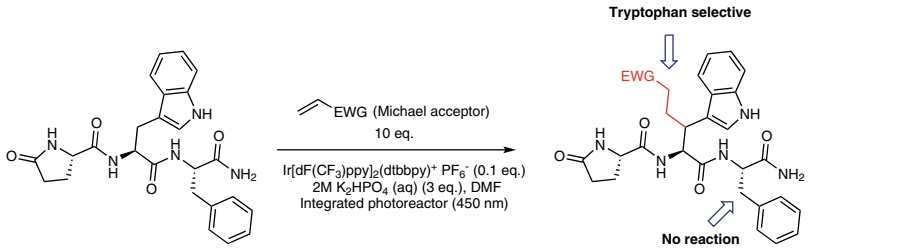
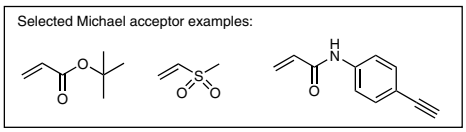


Examples:

Six linear/cyclic tryptophan-containing peptides;

Peptide hormones (glucagon, GLP-1).



EWG = electron-withdrawing group

Chemoselective strategies for the site-selective functionalization of peptides have a strong impact on the development of peptide–drug conjugates and peptide-based drug discovery in general. However, although some amino acids can be modified within a peptide chain using a variety of efficient methods, the selective modification of other specific residues remains elusive. Tryptophan, for instance, features limited derivatization possibilities despite its biological importance, and the very few existing methods are restricted to the reactivity of the indole ring.

Now, Zhi-Cai Shi and co-workers reported a photocatalytic strategy for the selective functionalization of tryptophan's β-position. Using the single electron transfer ability of a commercially available iridium photocatalyst under visible light irradiation, the team was able to induce the formation of a tryptophan-derived radical that can be thus trapped with different Michael acceptors (pictured). Remarkably, functionalization occurs selectively, without affecting the β-position of other residues such as phenylalanine, as shown by NMR and high-resolution mass spectrometry (HRMS) analyses of the isolated products. The method shows good compatibility with a variety of acceptors that can be further derivatized, anticipating the use of tryptophan containing peptides in chemical biology via conjugation strategies.

Both linear and cyclic peptides can be targeted and afford the corresponding functionalized products in good preparative yields and high chemoselectivity showing broad functional group tolerance. In this regard, histidine-containing peptides represented the only exception, resulting in the formation of by-products via addition of the Michael acceptor to the imidazole *N*-1 position. On the other hand, testing the protocol on larger peptide hormones suggested that the specific conformation and functional group pattern of a given amino acid sequence could eventually dictate the chemoselectivity of the reaction. In fact, both glucagon and GLP-1 — a gut peptide hormone — afforded selectively tryptophan β-position conjugated products under the optimized photocatalytic conditions and no conjugation on histidine residues was observed, whereas minor side reactivity was observed either at the C-terminus or at a lysine residue, in glucagon and GLP-1 respectively. The current report is expected to boost research on peptide leads by providing a unique tryptophan-specific functionalization strategy.

Davide Esposito

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