CliCr®: site-specific peptide functionalisation during SPPS

The challenge

The growing demand for targeted therapeutics, advanced biomaterials, and selective diagnostic tools drives the need for (site-specific) peptide functionalisation. While Solid Phase Peptide Synthesis (SPPS) allows for extensive peptide modification, the incorporation of Strain-Promoted Azide-Alkyne Cycloaddition (SPAAC) reagents (such as BCN or DBCO) was so far not feasible[1,2]. This limitation is due to the instability of these reagents under the harsh cleavage conditions typically applied at the end of SPPS.

The solution

TMTHSI, marketed as CliCr®, is stable under the strong acidic conditions required for peptide cleavage and deprotection. After its introduction in 2020[3], TMTHSI derivatives have been successfully applied in peptide derivatization[4,5] among others by direct incorporation as a strained alkyne during SPPS[4]. The intact peptide generation demonstrates CliCr® compatibility with SPPS and enables precise placement at the N-terminus or at defined positions closer to the C-terminus using orthogonal protecting group strategies.

How it works

TMTHSI functionalised with succinic acid *(Iris Biotech catalogue: RL-4200)* is directly conjugated to either the native N-terminus or an orthogonally-deprotected lysine positioned anywhere in the sequence (Figure 1). This coupling can be achieved using standard SPPS conditions (3 eq. of the TMTHSI-derivative, 3 eq. HCTU and 9 eq. DIPEA for 2 hours).

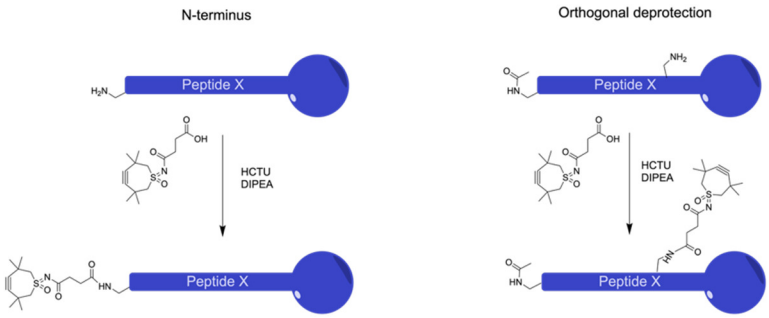

Figure 1: TMTHSI functionalization of peptides on resin

After coupling, the peptide is cleaved from the resin and deprotected under standard acidic conditions (30 min incubation of the resin with 96.5:2.5:1 TFA:MQ:TIS). LC-MS confirms successful functionalization with TMTHSI (Figure 2).

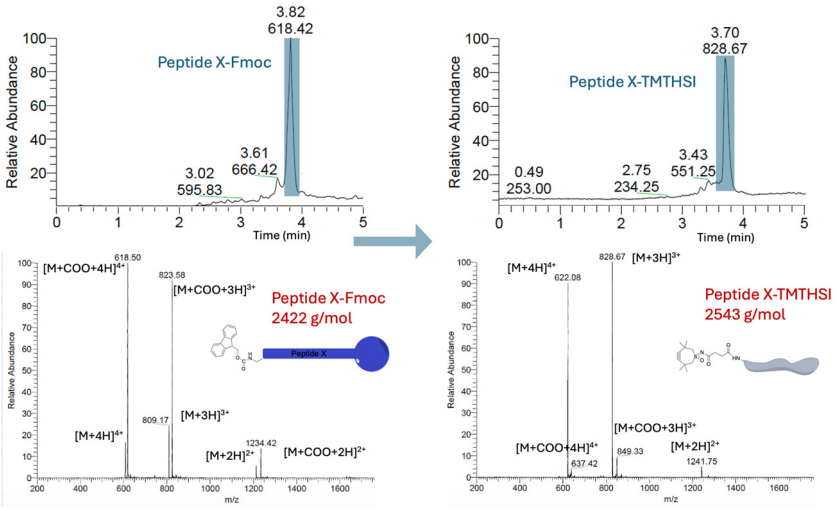

Figure 2: LC-MS confirmation of intact peptide-TMTHSI derivative after resin cleavage and deprotection

Why this matters

For peptide discovery and development teams, TMTHSI provides a practical route to clickable peptides. It allows for on-resin synthesis and combines positional control with stability under standard cleavage conditions. This enables fast and reliable access to well-defined peptide conjugates.

Conclusion

TMTHSI derivatives enable precise peptide functionalization during SPPS, thereby offering a robust and controllable path to high-quality clickable peptides across a multitude of applications.

References

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