On-Resin Parallel Synthesis and Evaluation of Stapled Oligopeptides: Advancing Macrocyclic Peptide Libraries

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Recent advancements in solid-phase peptide synthesis have enabled the efficient creation of diverse macrocyclic peptide libraries. A key technique in this evolution is 'stapling,' which stabilizes peptide structures through the formation of covalent bonds between amino acids, enhancing resistance to enzymatic degradation and optimizing pharmacokinetic profiles.[1]

This work[2] introduces an expedited protocol for on-resin stapling, which allows for simultaneous macrocyclization and stapling directly on the resin. This streamlined process minimizes the need for high dilute conditions and facilitates the generation of large, structurally diverse libraries. These libraries play a crucial role in identifying high-affinity peptide binders for specific biological targets, thereby accelerating drug discovery.

Through high-throughput experimentation, we have achieved multiparametric optimization of stapling conditions, solvents, and pseudo-dilute environments, significantly reducing the time required for peptide library generation. Furthermore, the protocol incorporates principles of green chemistry and sustainability, utilizing environmentally friendly reagents and minimizing waste. This sustainable methodology enhances both the efficiency of synthesis and the chemical diversity of macrocyclic peptides, while also improving their ecological impact.

By addressing environmental considerations, the new approach not only opens up new possibilities in therapeutic development but also aligns with the growing emphasis on sustainability within the scientific community. This advancement offers the potential for broader application and impact, fostering innovation in tackling complex medical challenges with environmentally conscious practices.

[1] B. Deng et al *J. Med. Chem.* **2025**, *68*, 8516–8529
[2] S. V. Chankeshwara, F. Göbel, P. Zlatoidsky, T. Nguyen, A. Nikitidis, Göran Dahl, W. Czechtizky, **2025**, *Manuscript in preparation*