Expanding peptide diversity: synthesis and incorporation of non-natural ornithine derivatives (NNODs)

Rachel Le Gall*[1]

[1]Laboratoire d'Innovation Thérapeutique – université de Strasbourg, Institut de Chimie - CNRS Chimie, Centre National de la Recherche Scientifique – France

Résumé

Natural amino acids provide limited basicity, with lysine and arginine being the main naturally occurring cationic side chains. To expand the chemical space available for biomimetic peptide design, we developed a series of non-natural ornithine derivatives (NNODs) compatible with solid-phase peptide synthesis (SPPS). These building blocks were obtained through a scalable and efficient synthetic route, giving excellent yields without requiring purification, and were isolated as stable HCl salts.
We then investigated their incorporation into peptides, as standard SPPS conditions proved challenging due to the lower reactivity of NNODs and their sensitivity to base-promoted Fmoc deprotection, which can lead to side-product formation. To overcome these limitations, a systematic optimization of the coupling conditions in liquid-phase model studies was conducted. Our results showed that a preactivation step is unnecessary and may even reduce coupling efficiency. In contrast, the use of DIC/Oxyma, with repeated coupling cycles when needed, significantly improved NNOD incorporation.

The optimized conditions were defined as 1/2/1 stoichiometry for NNOD/DIC/Oxyma, with two to three coupling cycles and capping using acetic anhydride. This strategy enabled efficient assembly of tripeptides with very good yields and high purity.
Overall, this work provides a practical and robust method for the synthesis and incorporation of NNODs into peptides. By combining a scalable preparation of non-natural basic amino acids with optimized SPPS-compatible coupling conditions, this study opens new opportunities for expanding peptide diversity and designing biomimetic molecules with tailored properties.

Mots-Clés: Solide phase peptide synthesis, non, natural aminoacids

*Intervenant