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A New Breakthrough in Green and Efficient Peptide Synthesis: Fluoride-Sensitive Hydrophobic Labels Enable Continuous-Flow Peptide Synthesis

Peptide drugs are widely used in fields such as immunomodulation and disease treatment, and the development of green, efficient, and low-cost synthesis technologies is a key focus for the industry. Recently, a research team has innovatively proposed a new peptide synthesis strategy that combines fluoride-sensitive hydrophobic tags (PTESE) with continuous-flow technology. Using thymosin as a model compound, they achieved high-purity green synthesis, providing a novel pathway for the industrial production of peptides and advancing the transition of peptide synthesis toward sustainability.

I. Research Background

Traditional solid-phase peptide synthesis (SPPS) is highly automated but suffers from issues such as high resin costs, highly toxic solvents (e.g., DMF), excessive reagent consumption, and poor atom economy, making it inconsistent with the principles of green chemistry. Conventional liquid-phase synthesis and purification are cumbersome, inefficient, and difficult

to scale up. Continuous-flow technology offers advantages such as precise and controllable reactions, high efficiency, and ease of scale-up. Hydrophobic tagging-assisted liquid-phase synthesis can simplify purification processes. The combination of these two approaches holds promise for overcoming the bottlenecks of traditional processes and developing efficient, low-toxicity, and low-consumption green peptide synthesis technologies.

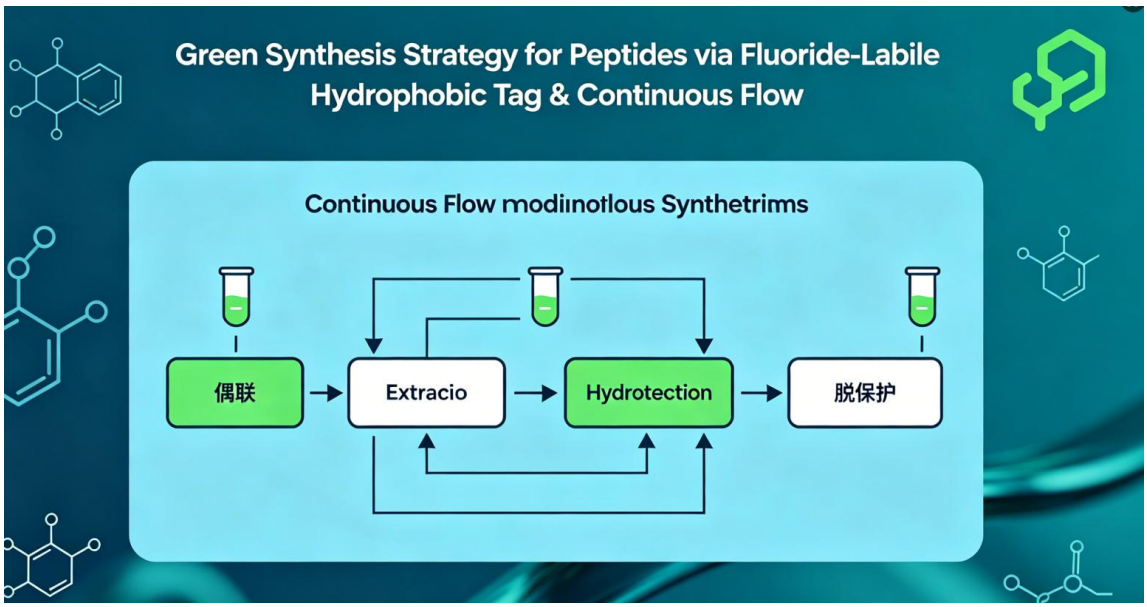
II. Research Objectives and Significance

This study aims to design novel fluoride-sensitive hydrophobic tags and establish a continuous-flow liquid-phase peptide synthesis (CF-LPPS) system to replace traditional processes that are highly polluting and resource-intensive. The findings significantly reduce solvent and reagent consumption, eliminate the use of toxic solvents and controlled reagents, and improve synthesis efficiency and product purity, thereby providing a green synthesis strategy for peptide drugs such as thymosin beta-4. Additionally, this approach offers a new strategy for the synthesis of fully protected peptides, supporting the peptide industry's transition toward sustainability, lowering production costs, and advancing the industrialization and sustainable development of peptide drugs.

III. Research Content

The research team designed and synthesized a fluoride-sensitive hydrophobic tag, 2-phenyl-2-triethylsilylethanol (PTESE), and established

a fully continuous synthetic system incorporating coupling, extraction, and deprotection units using flow chemistry technology. Ethyl acetate, a green solvent, was used to replace DMF. Cbz-protected amino acids served as the starting materials, and efficient deprotection was achieved via hydrogenation using a palladium-on-carbon packed column, thereby avoiding the use of controlled reagents such as piperidine; Optimized reaction parameters resulted in a coupling reaction time of just 9 seconds, deprotection in 28.3 seconds, and extraction in 12 seconds, yielding a crude thymosin pentapeptide with 98.8% purity and a 78% yield. Compared to traditional solid-phase synthesis, the new process significantly reduces the process mass intensity (PMI), decreases solvent consumption, and markedly improves atom economy. Furthermore, the PTESE label can be efficiently removed using fluoride reagents, making it suitable for the synthesis of fully protected peptides.



IV. Conclusions and Outlook

Research has shown that the combination of fluoride-sensitive hydrophobic tags and continuous-flow technology has successfully enabled the green and efficient synthesis of thymosin beta-4, offering advantages such as low pollution, low material consumption, high purity, and high efficiency, thereby effectively addressing the challenges of traditional peptide synthesis. This strategy is suitable for both standard peptides and fully protected peptides and holds potential for large-scale application. In the future, green peptide synthesis will continue to focus on optimizing hydrophobic tags, scaling up continuous-flow systems, and expanding process versatility. This will further reduce costs and enhance adaptability, driving the implementation of green synthesis technologies in more peptide drugs, supporting the high-quality and sustainable development of the peptide industry, and providing safer and more cost-effective peptide drugs for clinical use.