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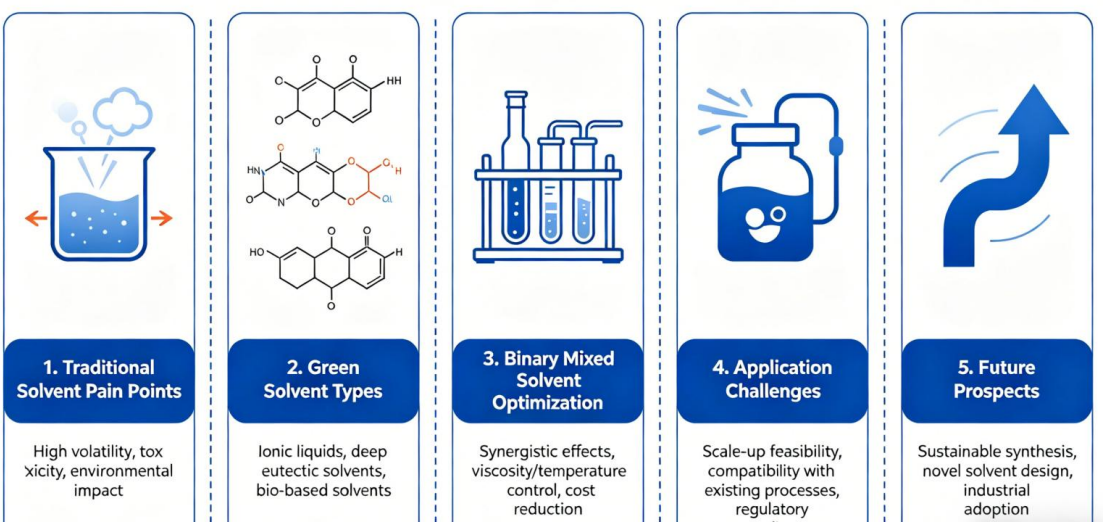
Progress in the Development of Green Solvents in Solid-Phase Peptide Synthesis

Solid-phase peptide synthesis (SPPS) is the mainstream technology currently used in laboratories and the pharmaceutical industry for preparing peptide drugs. Its core steps are the coupling of amino acid residues and the removal of protecting groups, which require large amounts of solvents to ensure reaction and purification efficiency. Traditional processes have long relied on polar aprotic solvents such as DMF, DCM, and NMP. While these solvents exhibit excellent solubilizing and swelling capabilities, they are toxic, irritating, and pose reproductive hazards. They have been included on the European Union REACH high-concern substances (SVHC) list, and their use and discharge are strictly regulated. Driven by both environmental and production safety requirements, developing green alternative solvents has become an important research direction in the field of peptide synthesis.

This paper systematically reviews the research status of green solvents in solid-phase peptide synthesis, focusing on the two key steps of coupling and deprotection, summarizing the application progress, existing problems, and optimization strategies of single green solvents and binary mixed solvents. In traditional SPPS processes, coupling reactions commonly use reagents such as DIC, HBTU, and HATU, which are efficient but some of which pose sensitization, flammability, and explosion risks. Fmoc deprotection primarily uses piperidine, which, as a controlled precursor chemical, can generate harmful nitrosamines and is subject to strict regulation. Therefore, green alternatives are not limited to solvents but also include an overall upgrade of reagents and processes.



Reported green alternative solvents currently include water, acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran, cyclopentyl methyl ether, γ-valerolactone, N-formylmorpholine, propylene carbonate, and N-butylpyrrolidone. These solvents are less toxic and more biodegradable, and in the synthesis of certain peptide sequences, can achieve coupling efficiency and purity close to those of traditional solvents. However, single green solvents generally have limited solubility, insufficient resin swelling, and slower reaction rates, making it difficult to completely replace DMF. To address this, researchers have turned to binary green solvent systems such as NBP/ethyl acetate, DMSO/ethyl acetate, DMPU/ethyl acetate, dehydro-D-glucitol/dimethyl carbonate, which, through complementary polarity and viscosity, enhance overall performance.

Reference:Zhang, J. J., Ma, J. P., Ma, Y. P., Wang, Y. E., & Liu, D. X. Progress in the development of green solvents for solid-phase peptide synthesis[J]. Journal of Chinese Mass Spectrometry Society, 2025, 46(5): 144-146.