Beijing Dilun Biotechnology Co., Ltd.

Specializes in R&D and manufacturing of peptide synthesis equipment, providing comprehensive technical solutions and services.

Web: www.peptidescientific.com. Email: chengchao.wei@dilunbio.com

Recent Advances in the Study of Peptide Synthesis Condensers

Peptide drugs play a crucial role in the treatment of diseases such as cancer and diabetes, and have become a key focus of global new drug research and development. The core of peptide synthesis lies in the formation of stable amide bonds; as key reagents for amide bond formation, condensing agents directly influence the efficiency, purity, and safety of peptide synthesis. Recently, a research team from Hebei University of Science and Technology published a review that systematically summarizes recent advances in condensing agents for peptide synthesis, providing an important reference for the low-cost, large-scale development of peptide drugs.

I. Research Background

Due to their high specificity and minimal side effects, peptide drugs have become a hot topic in pharmaceutical research and development. The formation of amide bonds is a critical step in peptide synthesis, and the current mainstream synthetic methods include the acyl azide method, the acid anhydride method, and the condensation reagent method. The acyl azide method involves unstable intermediates and is prone to generating toxic byproducts; the acid anhydride method is cost-effective but requires harsh reaction conditions, which can easily destroy the chirality of amino acids; the condensation reagent method offers high atom economy and good product yields, making it the most commonly used and feasible peptide synthesis method today. Traditional condensing agents generally suffer from issues such as easy racemization, difficulty in separating byproducts, high toxicity of some reagents, and high costs, which hinder the R&D and mass production of peptide drugs. Therefore, the development of new, highly efficient condensing agents with low side-reaction rates is imperative.

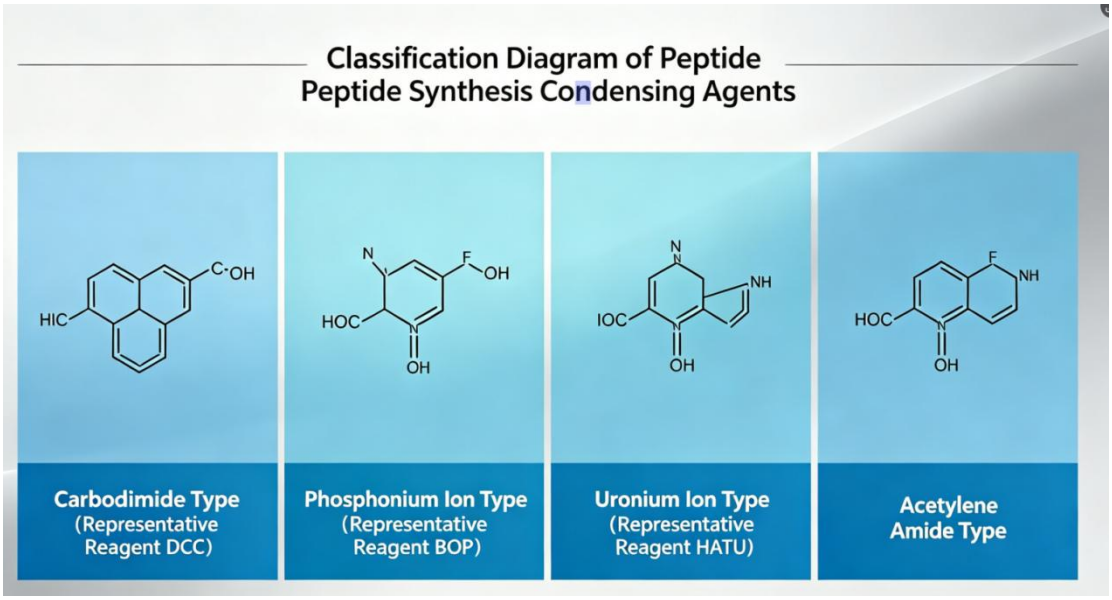
II. Research Objectives and Significance

This study aims to systematically review the development history, technical characteristics, and advantages and disadvantages of various condensing agents used in peptide synthesis, compare their applicable scenarios, and provide a scientific basis for researchers to select efficient, safe, and cost-effective condensing agents. The findings

of this study will help overcome the technical limitations of traditional condensing agents, drive the advancement of peptide synthesis technology, facilitate the transition of peptide drugs from the laboratory to industrial-scale production, reduce R&D costs, accelerate the market launch of new peptide drugs for treating cancer and diabetes, and provide more high-quality treatment options for clinical care.

III. Research Content

The research team comprehensively summarized the current state of research on the four major classes of mainstream condensing agents: carbodiimide-type, phosphonium-type, urea-type, and acetylamide-type, and conducted a detailed analysis of the performance characteristics, advantages, and limitations of each type. Carbodiimide-type condensing agents, represented by DCC, are low-cost and widely used, but their byproducts are difficult to separate and can easily lead to product racemization; Subsequently developed DIC and EDCI improved the solubility of byproducts, and when used in combination with inhibitors such as HOBT and HOAT, they can effectively reduce racemization. Among phosphonium-type condensing agents, early agents such as CloP and BroP were prone to causing severe racemization and have gradually been phased out; reagents such as BOP and PyBOP have improved performance and are suitable for cyclopeptide synthesis, but some generate carcinogenic byproducts, are expensive, and are difficult to apply on a large scale. Urea-based condensing agents represent the most mature and effective class currently available, with HATU as a prime example. They feature fast reaction rates, high yields, and low racemization rates, and do not require an anhydrous environment. However, they necessitate the addition of organic bases, some byproducts are difficult to remove, the reagents have poor solubility, and post-treatment is relatively cumbersome. Acetamidic condensing agents are a new class of highly efficient reagents that have emerged in recent years. Through structural optimization, they have resolved the issues of poor stability and susceptibility to racemization associated with traditional acetylamines. They feature mild reaction conditions, high condensation efficiency, and minimal disruption of amino acid chirality. They can be used for the synthesis of general peptides, sterically hindered peptides, and peptide fragment linkages, and hold great potential for development. However, their reaction efficiency still needs improvement, making them unsuitable for solid-phase synthesis at this stage and requiring further optimization.



IV. Conclusions and Outlook

Research indicates that while various types of condensing agents currently available each have their own advantages and disadvantages, no ideal reagent suitable for all scenarios has yet emerged: carbodiimide-based reagents are inexpensive but carry a high risk of racemization and are difficult to remove as byproducts; phosphonium-based reagents offer stable performance but are relatively expensive, and some pose potential toxicity risks; urea-based reagents have the best overall performance and are the most widely used, but their post-treatment processes are complex; acetylamide-based reagents, as a new class of reagents, possess significant advantages such as low racemization and mild reaction conditions, and have broad prospects for development; however, they currently cannot meet the requirements of solid-phase synthesis and require continued research and development. In the future, the field of peptide synthesis will continue to focus on the core objectives of high efficiency, low toxicity, and low cost, continuously optimizing the structures and processes of existing condensing agents to address key issues such as solubility and byproduct removal; simultaneously accelerating technological breakthroughs in novel condensing agents such as acetylamides, exploring development pathways for composite condensing agents and green, non-toxic reagents, and driving peptide synthesis technology toward high efficiency, environmental sustainability, and cost-effectiveness, thereby providing robust support for the industrial production and clinical application of peptide drugs.