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Overview of Coupling Reagents Used in Modern Peptide Synthesis

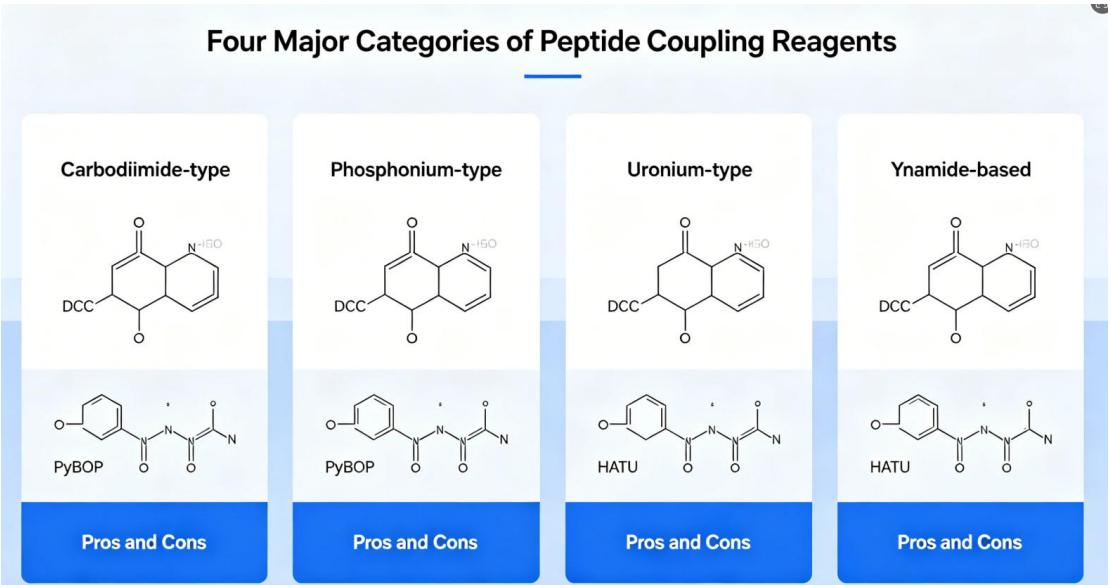
1.Research Background

Amide bond formation is the core step of peptide production, and coupling reagents directly determine synthesis yield, chiral purity and impurity level. Traditional coupling agents often trigger amino acid racemization and generate hard-to-remove byproducts, restricting mass production of high-quality peptide APIs. Continuous development of new coupling systems is essential to cut production costs and improve product quality for peptide drug industrialization.

2.Research Purpose and Significance

This article sorts four mainstream types of peptide coupling reagents, introduces their structural features, reaction advantages and inherent drawbacks, compares applicable scenarios of each reagent system. The summary provides practical reference for researchers to select appropriate condensation agents and optimize peptide synthesis process.

3. Research Content



- Carbodiimide-type (DCC, DIC, EDCI): Low cost and widely used; prone to racemization, usually matched with HOBt/HOAt additives to reduce side reactions, DCC byproduct DCB is poorly soluble.
- Phosphonium-type (BOP, PyBOP, PyAOP): Fast coupling speed, good for cyclic peptide preparation; early BOP produces toxic byproducts, Py-series greatly reduces toxicity yet remains expensive for large-scale manufacture.
- Uronium-type (HATU, TBTU): Currently mainstream industrial reagent, fast reaction, excellent anti-racemization performance, tolerates non-dried solvent; easy to form guanidine impurities when excess reagent is added.
- Ynamide-based new coupling reagent: Emerging eco-friendly system, effectively suppresses chiral racemization, high yield even for sterically hindered amino acids; still immature for solid-phase large-

scale synthesis.

4.Conclusion & Outlook

Traditional four categories of coupling reagents each have obvious pros and cons, no single reagent can satisfy all synthesis demands at present; uronium reagents dominate current industrial production while ynamide reagents display great developmental potential. Future research will focus on developing low-cost, low-toxicity, anti-racemization novel coupling agents, optimizing existing reagent matching schemes, promoting new ynamide reagents to adapt to solid-phase synthesis and large-scale industrial peptide production.