WuXi TIDES

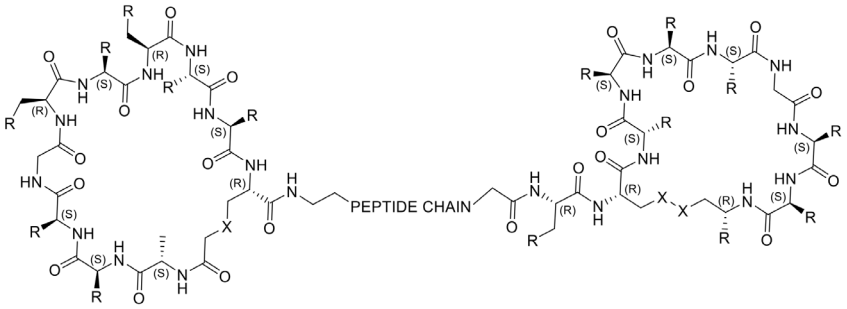
Case Study

From Discovery to Phase I, Rapid Delivery of a Complex Peptide Conjugate in 10 Months

In the highly competitive peptide market, speed is critical for the success of novel peptide therapeutic development. This case study shows how WuXi TIDES scientists accelerate the development of a complex peptide conjugate in terms of both speed and quality. In just 10 months, we were able to optimize the process of an 87-step synthesis and provide GLP and GMP API supplies.

Background

A client was developing a complex peptide conjugate, consisting of two short cyclic segments and a long linear segment. The original process had a low yield and purity, making it difficult to scale up for manufacturing. Faced with these challenges, the client turned to WuXi TIDES, aiming to advance the project toward IND submission.



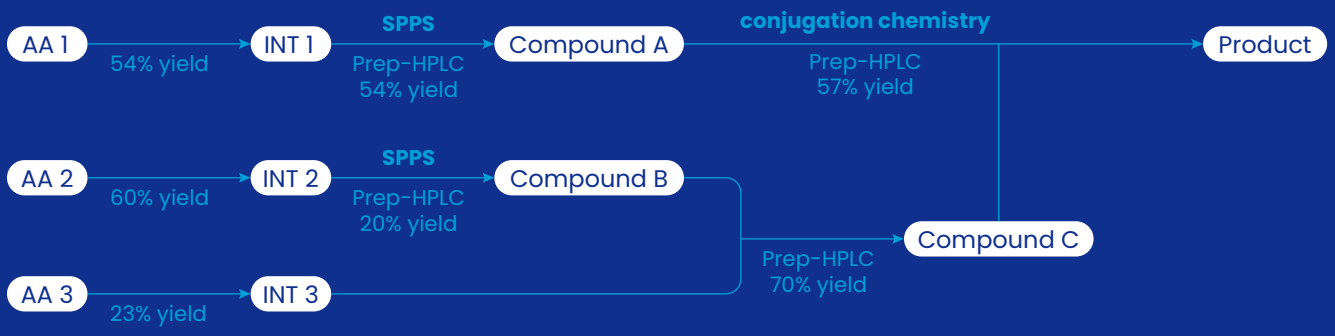
Target product

Challenges

Factor	Challenge
Limited supply of three starting materials	Long lead time and high risk of supply chain disruption if purchased from an external supplier
Complex structure with 87 synthesis steps	• Low overall yield (< 0.1%) • Scale-up challenge

Solution

Instead of purchasing from external suppliers, WuXi TIDES has dedicated teams to synthesize unnatural amino acids (UAAs) in-house, which solves the supply challenges of the key starting materials for peptide drug development. In this project, faced with the challenge of limited supply for three UAAs as start materials, our team rapidly developed viable synthetic processes and produced over 3 kg of the UAAs to support the peptide GLP and GMP production. This internal supply source, by avoiding dependence on external suppliers, led to better timeline management and reduced overall turnover time.



Synthesis scheme

At the same time, the peptide team was focusing on improving the process chemistry efficiency. When synthesizing peptides longer than 50 AA with conventional solid-phase synthesis, the coupling efficiency and the overall yield drop sharply. To solve this problem, our experts designed an alternative route of fragment synthesis combined with chemical ligation – The target peptide was synthesized in multiple fragments under 50 AA, which were more amenable for solid phase synthesis. These fragments were then linked via chemical ligation to form the target peptide. By applying this new method, the overall yield increased from less than 0.1% to 3%. Another benefit of applying fragment synthesis was that the synthesis tasks could be simultaneously carried out by multiple teams, which greatly shortened the project timeline.

Every detail for a long synthesis route ultimately impacts the result. With that in mind, our scientists performed multiple rounds of screening and optimization of synthesis and purification conditions to further improve the yield and purity. During the scale-up, the optimization of the preparative-HPLC purification strategy had the most significant impact. The original results had broad peaks and tailing, reducing the purity and yield. Our scientists identified that the problem was due to the unstable stationary phase under particular conditions, which lowered the purification efficiency. To address this issue, we screened various packing materials and selected special alternative materials. Our team worked closely with the vendor to design a customized blend of packing materials especially for this project. The new column packed with this customized stationary phase reduced impurities by 80% and increased the final overall yield by 20%.

With the close collaboration among the UAA team, the solid phase peptide synthesis teams, and the analytical team, it took us just four months to develop and optimize the process and deliver two 100-gram GLP batches after

initial route scouting. Three months later, we produced a GMP batch of one kilogram API with 3% yield and 97.4% purity.

From the late discovery, to process development, and to GMP manufacturing, took WuXi TIDES only 10 months to complete the synthesis, scale-up, and manufacturing of this challenging complex peptide conjugate with an 87-step synthetic route. The timeline was four months ahead of the client's original schedule. To date, the project is under phase I clinical trial.