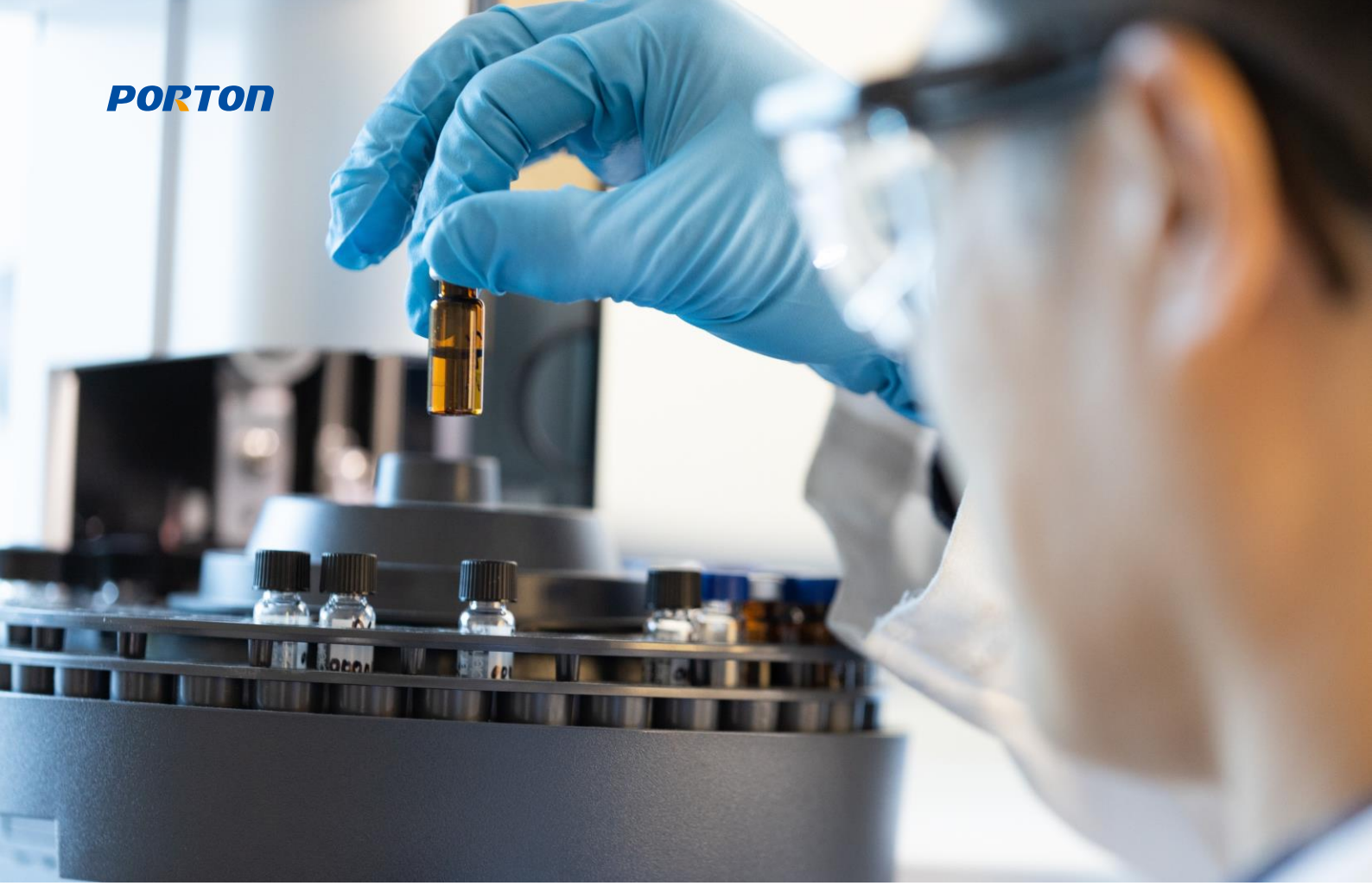
PORTON



Case Study

Facilitating PROTAC Drugs Development with Innovative Processes

Introduction

The PROTAC technology, through an innovative mechanism of "degradation rather than inhibition," provides a new pathway for targeting traditionally undruggable proteins and addressing resistance issues. Although it still faces challenges in drug design and delivery, its clinical potential in areas such as cancer and autoimmune diseases has driven pharmaceutical companies worldwide to accelerate their investment in this field. In the future, it is expected to become a pivotal breakthrough direction in small molecule drug development. By 2025, nearly 40 PROTAC drugs are anticipated to enter clinical trials, with indications covering cancers (such as breast and prostate cancer), autoimmune diseases, and neurodegenerative disorders. However, as a class of novel API molecules, PROTACs are characterized by large molecular weight and numerous functional groups. The presence of poorly soluble aromatic heterocycles and flexible linker structures that hinder crystallization further complicate these molecules, leading to challenges such as long synthetic routes, complex compatibility and selectivity among functional groups, as well as difficulties in purifying intermediates and final APIs through crystallization. These challenges pose new questions for the development of PROTAC drugs and CMC teams.

Project Background

To respond to the rapidly changing market demands, the client needs to swiftly advance a PROTAC innovative drug product through IND registration while facing challenges such as immature processes, difficulties in scale-up, and insufficient impurity control. As a CDMO company serving global innovative drugs, Porton has extensive experience in research and manufacturing services, particularly in the field of PROTAC drug development. We've participated in the development of over ten PROTAC projects for various global clients, providing comprehensive, reliable, rapid, compliant, and one-stop services. From R&D to delivery, we meet clients' supply chain needs and support the commercial success of their projects.

- Clinical Stage: IND/Phase I to Phase II
- Synthesis Steps: 5 GMP chemical steps
- Production Scale: 50 kg

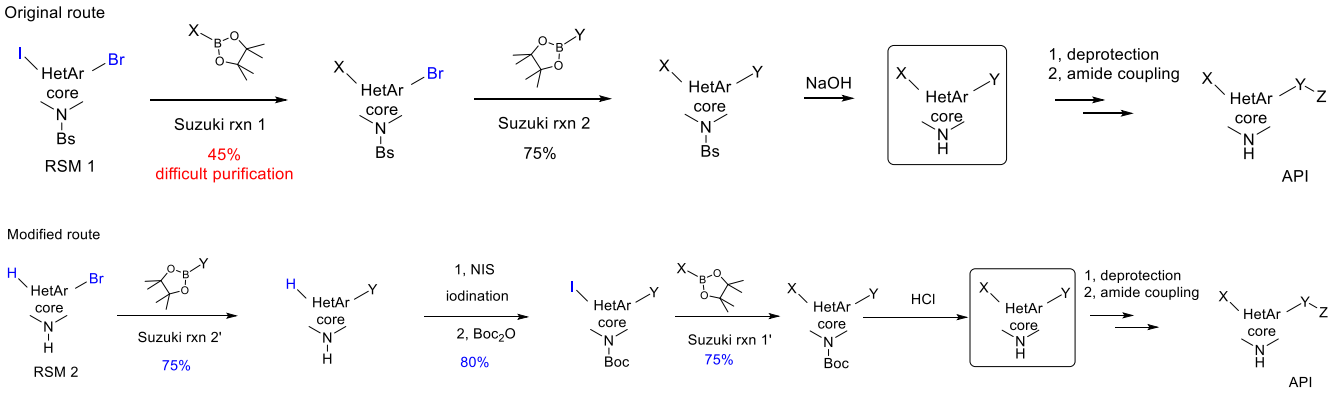
Multidimensional Process Innovation to Overcome CMC Challenges

In this PROTAC project, based on a rapid understanding of the client's original route and process, Porton addressed the difficulties and challenges faced in CMC by proposing a comprehensive and innovative optimization plan. This plan covered three main areas: exploration and development of new routes, crystallization process development, and a stepwise strategy for the removal of palladium residues.

Exploration and Development of a New Route

The existing synthetic route provided by the client was established during the medicinal chemistry research phase. It is based on combinatorial chemistry design and has given less consideration to factors such as scale-up, impurity control, and cost-effectiveness. As a result, the first step, a Suzuki coupling reaction, has poor selectivity, produces a significant amount of by-products, and makes it difficult to purify the intermediate through crystallization.

Porton, through efficient analysis of reaction impurities, identified quickly that the mechanism of their formation was due to insufficient selectivity between I and Br. Creatively proposing a new route, we reasonably adjusted the N-protecting group strategy during the route exploration, successfully developing the following new synthetic route. By introducing Br and I at different stages sequentially, the first step achieved exclusive selectivity in the Suzuki coupling, increasing the yield significantly. The relatively clean reactions simplified the purification process greatly. The total yield of the two-step Suzuki coupling and iodination reactions in the new route increased from 34% to 45% compared to the original path, thereby reducing production costs significantly.



Efficient Crystallization Process Development

In the original technical package provided by the client, all intermediates and the final API were purified using column chromatography, which is unsuitable for scale-up production. Porton discovered that after two Suzuki coupling reactions, the intermediate core was linked with multiple heteroaryl rings and a bis-4,4'-piperidylmethylene linker structure. This resulted in very poor solubility in common solvent systems and the tendency to precipitate as an oily or gel-like substance, posing a significant challenge to the development of a crystallization purification process.

Porton's crystallization team, composed of world-class scientists located in Shanghai and New Jersey, conducted efficient high-throughput solubility testing and crystallization condition screening on various intermediates and the API.

They successfully developed crystallization processes for each intermediate and the API, resulting in solids with good shape and excellent impurity removal capability, suitable for GMP industrial production. Furthermore, during the development of the API crystallization process, the team discovered three different polymorphs of the API and performed comprehensive characterization of each, laying the groundwork for the client to pursue polymorph patents in the future.

Development of Metal Residue Removal Strategy

The two Suzuki couplings in the synthetic route resulted in significant palladium residue issues. By integrating newly developed crystallization processes for each intermediate, Porton team designed the Pd removal strategies involving the work-up of three reaction steps respectively: adsorption with activated carbon, aqueous washing with Pd complexing reagent and treatment with HS-silica gel scavenger. This reduced the palladium content in the final API product to below 2 ppm successfully, which was consistently reproduced in subsequent scale-up production.

Efficient Resource Integration for Rapid GMP Delivery

To ensure concentrated efforts on addressing technical challenges, Porton coordinated R&D and production resources, including its R&D centers in Chongqing and Shanghai, and engaged in deep collaboration with crystallization experts in the United States. Leveraging excellent tech-transfer and project management capabilities, and by coordinating efficiently the supply chain for the procurement of new starting materials, the team worked collaboratively to deliver the first stage of the project, achieving the scale-up from lab-scale to 50 kg GMP production within six months. This supported perfectly the client's IND submission and the smooth progression of Phase I clinical trials.

Conclusion

As the CMC service provider for this PROTAC drug, Porton offered comprehensive and customized solutions to address the core challenges in PROTAC drug development, such as complex synthesis routes, difficult crystallization purification, and stringent impurity control. Through rapid and efficient tech-transfer, the development and optimization of new routes, crystallization process innovation, quality control studies, and supply chain support, Porton team adjusted CMC strategies flexibly. This enabled the successful scale-up from laboratory-scale in grams to GMP production and delivery in tens of kilograms within six months, assisting the client in smoothly completing the IND registration. Porton's end-to-end technical service platform, exceptional project management skills, and efficient production operations were fully validated in this project. Currently, Porton continues to support the client in advancing the drug's Phase II clinical development, showcasing its leading service capabilities and long-term partnership value in the PROTAC drug field.

Porton's PROTAC Drug CDMO Service Platform

With 20 years of experience in traditional small molecule drug services, Porton is equipped to offer comprehensive services for PROTAC drugs, including synthesis building block development, API process development and production, formulation development and production, extensive quality studies, and CMC registration support. Leveraging a globally leading technology platform, Porton is dedicated to providing one-stop CDMO services to global pharmaceutical companies, covering intermediates, APIs, and formulations throughout all stages of drug development and commercialization, adhering to international standards.

Porton Pharma Solutions Ltd.
www.portonpharma.com
business@portonpharma.com