

Full IND program: Exceeding requirements for submission

Thorough process designed to ensure quality and efficiency for successful submission.

Streamlined strategy: Reducing processing time while increasing yield and purity

Successful IND submissions require an intense coordinated effort to meet strict requirements while balancing speed to file. The processes involved in API development must continuously adapt to changes in regulations along with the unique traits of each API to achieve successful manufacturing strategies and IND approval. Even during beginning stages of API synthesis, the most successful design incorporates adjustments based on thorough analysis of each reaction step.

The starting point is often derived through medicinal chemistry and it may not be readily scalable, safe or meet regulatory standards for purity. Designing the best synthesis route for later success with IND submission must account for all impurities while aiming to reduce steps that are impractical for scale-up in terms of timing and cost.

Here, we follow this compound through a full cycle of IND development at Cambrex, from modifications to the synthetic route to formulation development and API manufacturing. Ultimately, more than 10 batches of drug substance (DS) and drug product (DP) including clinical trial material were released with 9 ICH stability studies set, all under one roof.

Across the organization, our teams meet challenges like those presented here with expert analysis and rapid problem solving to ensure your submission has the highest yield with a phase appropriate purity. Through our expert design process, we ensure quality that meets or exceeds requirements for IND submission.

Route to success: From medicinal chemistry to process chemistry

Developing a synthesis route that favors higher throughput and purity is a common task for CDMOs. Medicinal chemistry routes typically produce low yields and are not scalable for manufacturing.

In this case, the medicinal chemistry route yielded between 5-10% over 8 steps with a final step volume of >250mL/g. In addition, 5 of the steps included chromatography, which is not suitable for scale up. Many factors were considered when redesigning the synthetic route for this compound to achieve a reduction in synthesis steps from 8 to 5 steps with no chromatographic purifications.



Kyla Grham
Supervisor, Drug
Substance Manufacturing

Systematic and strategic.

While strict standards are the backbone of our process, maintaining flexibility to adjust steps for optimal yield and purity are critical to success of early development.

About Cambrex

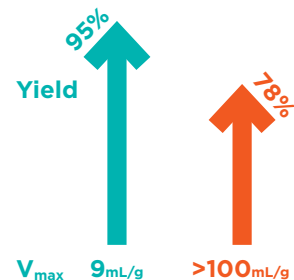
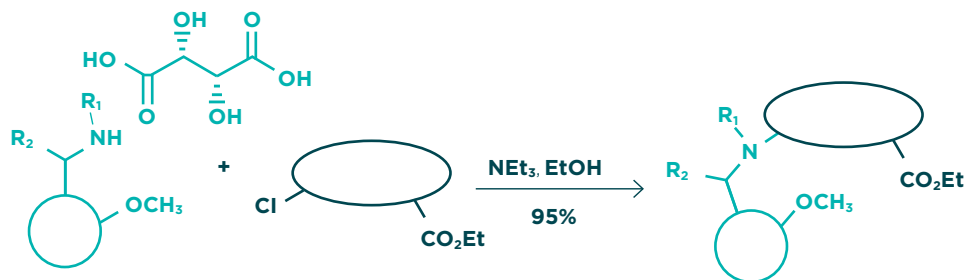
Cambrex is a leading global contract development and manufacturing organization (CDMO) that provides drug substance, drug product, and analytical services across the entire drug lifecycle.

With over 40 years of experience and a growing team of over 2,200 experts servicing global clients from North America and Europe, Cambrex is a trusted partner in branded and generic markets for API and finished dosage form development and manufacturing.

Redesign your route.

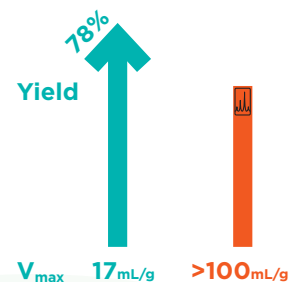
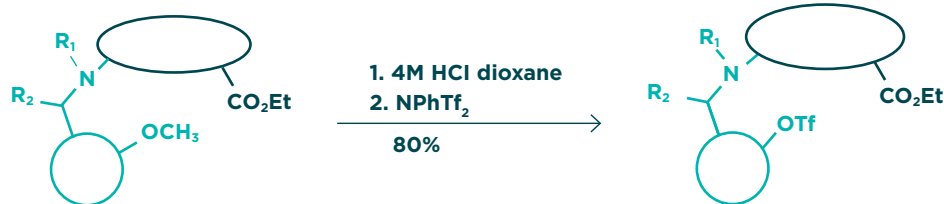
We tailor our process to be as unique as your molecule.

Step 1: SnAR reaction



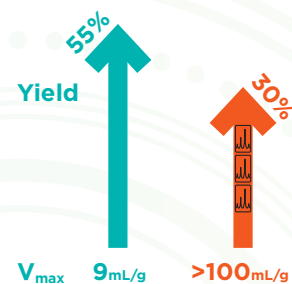
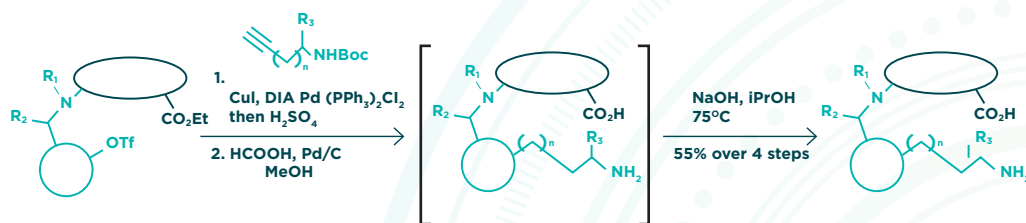
By replacing the chromatographic purification and aqueous workup with an EtOH/water precipitation, yield increased to 95% with a step volume of 9 mL/g.

Step 2: Demethylation/triflate formation



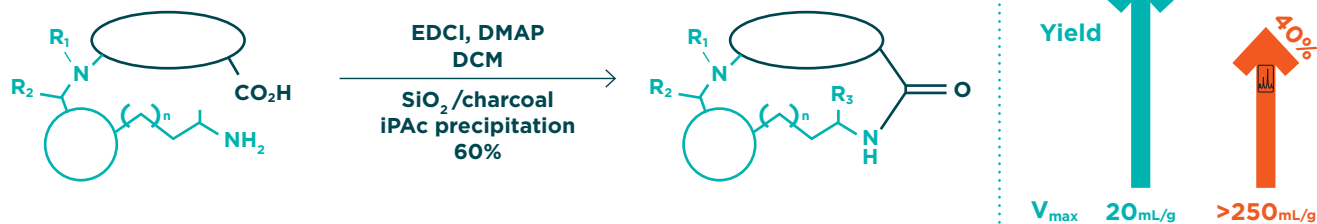
Chromatographic purification was replaced by MeOH/water precipitation. The revised synthesis telescoped the phenol intermediate into Compound 5 with a V_{max} of 17 mL/g, as compared to >100 mL/g.

Step 3: Sonogashira/reduction/hydrolysis



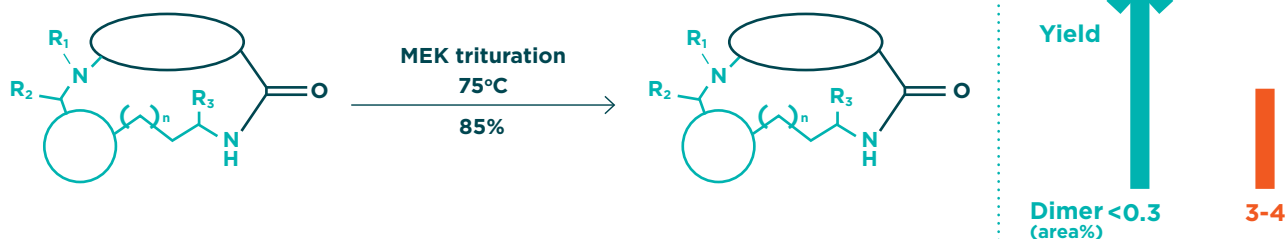
The number of separate isolation steps was reduced from 4 to 1. By changing the sequence of reactions, 3 chromatographic purification steps were removed from the process. Methodology was also simplified by using transfer hydrogenation for alkyne reduction, which requires no specialized equipment, instead of pressurized H_2 .

Step 4: Macrolactamization



HOBt was replaced with DMAP, which is less hazardous and easier to remove during purification. DCM was identified as an alternative solvent to resolve the API's solubility in other class 3 solvents. By dosing amino acid 8 into the solution over 5-6 hours, the reaction volume was decreased from over 250 mL/g to 20 mL/g and yield increased to 60% with >98% purity with the removal of chromatography.

Step 5: API isolation



Screening over 100 solvents and solvent combinations, MEK trituration was developed to purge a dimer by-product and isolate the desired polymorph. This yielded 84% on a 3.0 kg scale, with greater than 99 area% chiral purity and 99.7% potency. All solvents and metals were below ICH limits.

Planning ahead: Support from analytical and manufacturing teams

The gains in efficiency and purity that were achieved during development would be wasted if they did not align properly with future steps in the IND submission. Our analytical and manufacturing teams are full partners in the process to ensure the best design is carried forward from the start.

In this case, method validation included forced degradation to test the detection of impurities and checking for residual solvents. Checking the methods themselves is also an important control in the overall process. In this case, the team developed ICP/MS methods for the Elemental Impurity analysis that could stand up to the new regulatory guidelines.

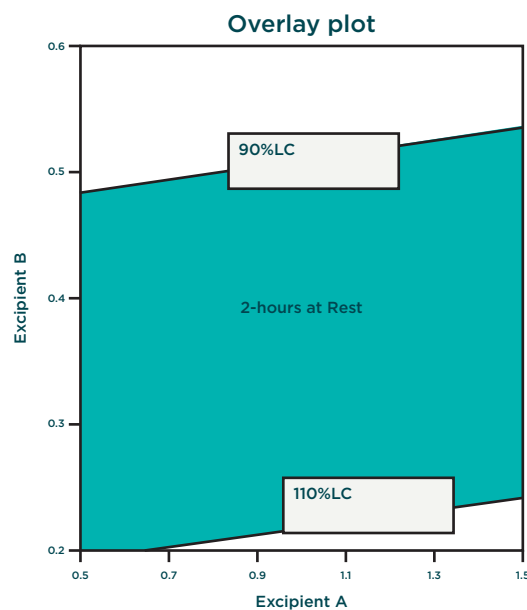
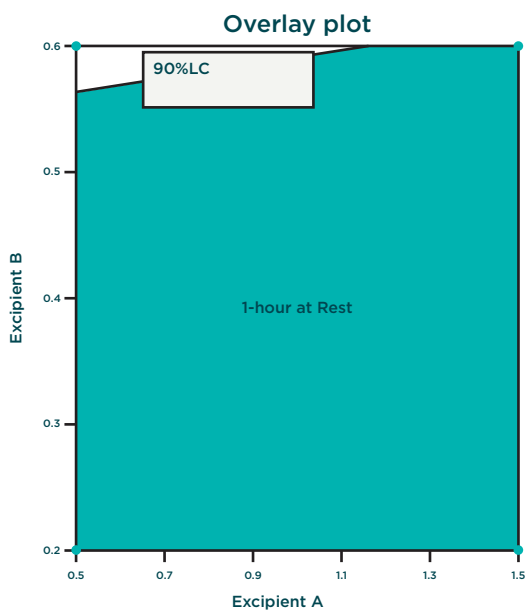
Partnering closely with cross-functional teams under one roof also eases a quick transition to next steps in preparing an IND submission. Here, the QC team verified the methods

were suitable for release testing of the drug substance, and later, for release testing of neat powder in capsulized (PIC) drug product. Qualified reference standards were prepared, and pilot stability studies tested multiple formulations, including DS, PIC, Ora-Plus®, and Ora-Sweet®.

Dual formulation development: Immediate pediatric dosing and commercial formulations

Cambrex mounted a rapid response to study dose uniformity, in-use stability, and time to achieve initial suspendability of the drug substance in a pediatric formulation to fulfill an immediate dosing need. The formulation was developed using a mixture of Ora-Plus® and Ora-Sweet®, which contain a mixture of known excipients that cannot be adjusted.

Step 4: Macrolactamization



Design of Experiments (DOE) revealed 4 excipients to be critical to suspendability. A 24 factorial design with 4 center point experiments exposed a large design space after suspension at rest for 1 hour (targeting a label claim of 90-110%). After 2 hours at rest, the design space narrows, as shown.

The studies determined that suspendability of the drug substance is maintained for 4 hours, with a 6-month stability window. An advantage of this formulation is its ability to be prepared in the clinical setting, however it is limited by predefined excipient levels. In addition, one of the preservatives (propylparaben) is discouraged in the EU.

In parallel with satisfying the requirement for an immediate formulation, Cambrex's formulation teams set out to engineer a commercial formulation with adapted excipients that would be suitable for filling. By designing experiments to reverse engineer Ora-Plus® and Ora-Sweet®, the team was able to determine which excipients were required to suspend the drug substance and replace propylparaben with an alternative and regulatory-accepted preservative. Their objective was to find a design space where the formulation maintained suspendability of the API after 1 and 2 hours of initial shaking.

Finish line: Drug product manufacturing

With API synthesis optimized for scale up, complete characterization of the stable form, and improved formulation, DP manufacturing of 4 batches at multiple strengths were completed within a month. Variable batch sizes were filled, ranging from 4k-30k powder in capsules utilizing multiple Xcelodoses. Manufacturing also included filling multiple weights of powder in Kylix syrup bottles for pediatric dosing in the clinic.

Cambrex's support continues through clinical shipments, including QP audits, and beyond. Ongoing support for future campaigns of both API and DP, as well as stability storage and testing are part of our full commitment to your success.

Our superior process secures your quality.

Need assurance of quality end product? Check the process from the beginning.