BETTER, FASTER SMALL-MOLECULE SYNTHESIS: LEVERAGING MODERN TOOLS TO EVALUATE AND OPTIMIZE PROCESS CHEMISTRY

In 2006, the average synthetic route process for an early-stage, small-molecule, active pharmaceutical ingredient (API) involved roughly 8 steps.[1] Today, that number has almost doubled, with process chemistry groups managing small-molecule routes involving 20 steps or more.[2] Increasingly sophisticated tools for probing biological functions and the causes of disease have allowed for the development of small-molecule drugs with new targets and mechanisms of action. These advances have led to a shift toward larger, more complex small-molecule APIs with intricate structures and longer synthetic processes.

Today's small-molecule APIs have moved beyond the limits of a "lock-and-key" approach, with new modes of action like molecular glues and covalent inhibitors entering the development spotlight. "In terms of drug targets, the 'low-hanging fruit' are starting to become exhausted," says Charles Johnson, senior director of commercial development, Lonza Advanced Synthesis. "As we're focusing on more complex drug targets, we see both the size and chiral complexity of small-molecule APIs starting to increase."

Drug development costs are also increasing, due in part to 90% of drug candidates failing in clinical stages.[3] Sponsors must streamline development to stay competitive in a crowded field. By partnering with a well-equipped contract development and manufacturing organization (CDMO) like Lonza, pharmaceutical researchers can access the tools and expertise they need to accelerate timelines and minimize risk.

"Most drug developers are trying to proceed as quickly as possible, and Lonza wants to provide a full spectrum of supportive services to meet that goal," says Jens Schmidt, associate director of manufacturing, science, and technology (MSAT), Lonza Advanced Synthesis. "Selecting the ideal synthetic approach

is a foundational step in facilitating faster development." Technologies such as artificial intelligence (AI)-enabled route scouting, high-throughput experimentation (HTE), and advanced model-based experimental design (MBED) are helping drug developers select reliable and scalable synthetic processes.

AI-ENABLED SYNTHETIC ROUTE SCOUTING

Experts within Lonza's Advanced Synthesis business platform have developed a method of synthetic route scouting that identifies synthetic pathways optimized for performance, chemical feasibility, efficiency, and manufacturability. "At Lonza, we've combined computer-aided synthesis planning (CASP) tools with real-world supply chain data to offer an AI-enabled route scouting service," explains Johnson. "This includes a proprietary database built from Lonza's 20-plus years of experience sourcing materials, going above and beyond commercially trading information." This database allows drug developers to assess synthetic pathways in the wider context of commercial conditions and scalability over time.

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In addition to ensuring process feasibility, CASP allows scientists to assess supply chain reliability and predict pricing fluctuations. Drug developers can avoid delays related to shortages of key chemicals or scalability issues as their candidate proceeds to commercialization. Additionally, these insights help determine the difficulty of developing a drug candidate, says Johnson. "Having a view towards the long-term viability of a process beyond what we're doing in these earliest stages increases confidence and can add value from an investor standpoint."

Using Lonza's tools, researchers can identify and rank potential routes based on technical criteria, such as the number of steps or challenging chemistries, and commercial factors, such as scalability and IP differentiation. "Once we've identified these routes and agreed which ones we want to prioritize, we need to narrow down those options as efficiently as possible," says Johnson. "That's where the HTE initiative comes in."

OPTIMIZING PROCESSES WITH HIGH-THROUGHPUT EXPERIMENTATION

HTE is a method that enables researchers to efficiently conduct many reactions in parallel, allowing them to accelerate pharmaceutical development. Biologists first demonstrated the concepts of HTE in the 1950s.[4] Since then, this method has matured and grown in popularity, with high-throughput screening of drug candidates against therapeutic targets now recognized as an essential part of drug discovery efforts. In recent decades, chemists and engineers have

leveraged HTE approaches to facilitate more efficient process chemistry testing and optimization.

But, successfully implementing chemical HTE requires specialized expertise and equipment, often including robotics and automated analytical instruments.[5] Conducting many process chemistry experiments in parallel with a range of reagents and reaction conditions reduces the overall time, effort, and materials required to identify the optimal synthesis pathway for an API.

In recent years, Lonza has focused on expanding its HTE services. A new, dedicated robotics system is a centerpiece of these offerings, introducing powerful HTE capabilities to partners seeking efficient and comprehensive synthetic process development. Lonza's HTE robotics enable round-the-clock experimentation to work efficiently through a full spectrum of potential reaction conditions.

FEATURES OF THE HTE ROBOTICS SYSTEM

Lonza's HTE robotics system provides powerful and versatile experimentation capabilities with a broad range of reaction conditions, analytical functions, and automated features:

- Temperature ranges from –55 °C to 180 °C
- Pressure up to 100 bar
- Automated liquid and solid handling on a submilligram-to-gram scale
- Kinetic module with eight parallel reactors that allow for sampling at elevated temperature and pressure
- Magnetic stirring, overhead stirring, and shaking
- Automated capping/decapping
- Handling of viscous liquids with positive-displacement tips

The system also provides broad, phase-appropriate experimentation capabilities, making it a versatile tool for users across the process development landscape. Researchers can conduct multiple small-scale 96-well plate reactions in parallel or eight reactions at up to 20 mL. Conducting HTE at these intermediate volumes enables a deeper understanding of reaction kinetics and mitigates scale-up risks at the earliest stages of the development process.

The HTE robotics system is housed in a two-chamber glove box and purge box system, which further expands experimental capabilities. "Being able to purge the chamber not only enables us to access low-moisture, low-oxygen chemistries but also gives us the ability to work with highly potent compounds," says Schmidt. "Since much of oncology drug development involves this level of containment, bringing everything together into this one system is a differentiator for us."

CASE STUDY: APPLYING MODERN TOOLS TO ACCELERATE PROCESS CHEMISTRY

Background

A client came to Lonza with a preclinical-phase candidate API and sought route optimization services. The original synthesis route for the API included a coupling of an amine and acid to yield an amide.

Challenge

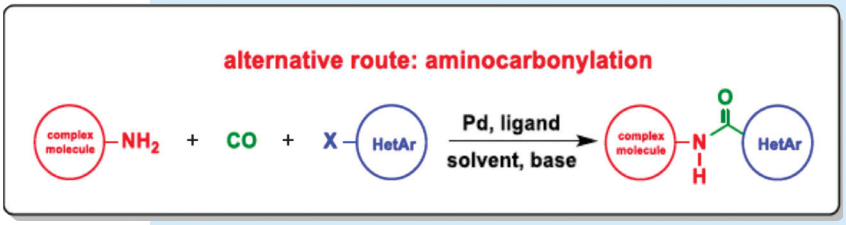
This reaction used the sodium salt form of the acid, which posed several drawbacks. Because this salt form was very hygroscopic (moisture-absorbing), it was difficult to handle. It was also poorly soluble and would decarboxylate quickly, making synthesis of gram quantities challenging.

Lonza researchers investigated two possible solutions:

1) An alternative counterion to form a stable nonhygroscopic salt
2) An alternative route to synthesize amide with high atom economy that avoids intermediates with difficult handling properties

Solution

Using HTE tools, Lonza identified and assessed 90 alternative solvent/base combinations and quickly identified 10 candidates during the salt screening. Lonza researchers also explored alternative synthetic routes to circumvent the limitations of amide coupling. Among these was aminocarbonylation, a common and efficient approach typically challenging to investigate at a small scale due to the use of carbon monoxide. Lonza's small reactor can operate at pressures of up to 100 bar, which allowed them to complete this reaction.



Researchers assessed 96 combinations of bases, ligands, and solvents. Four of these combinations were very promising, as shown in the table below.

		no ligand	ligand 1	ligand 2	ligand 3	ligand 4	ligand 5	no ligand	ligand 1	ligand 2	ligand 3	ligand 4	ligand 5	
		1	2	3	4	5	6	7	8	9	10	11	12	
solvent 1	A	0.0	11.6	0.0	0.3	12.9	94.6	0.0	5.7	0.0	0.0	0.0	75.4	solvent 9
solvent 2	B	0.0	8.3	0.0	0.0	10.5	95.6	0.0	15.9	0.0	0.0	14.0	84.9	solvent 10
solvent 3	C	0.0	7.6	0.0	0.0	0.0	97.6	0.0	0.0	0.0	0.0	29.7	76.5	solvent 11
solvent 4	D	0.0	6.0	0.0	0.0	6.7	96.7	0.0	2.0	0.0	0.0	3.9	0.9	solvent 12
solvent 5	E	0.0	0.0	0.0	0.0	16.0	97.7	0.0	0.0	0.0	0.0	12.3	74.8	solvent 13
solvent 6	F	0.0	0.0	0.0	0.0	1.1	14.3	0.0	0.0	0.0	0.0	12.9	93.6	solvent 14
solvent 7	G	0.0	4.6	0.0	8.5	0.0	97.4	0.0	2.1	0.0	0.0	0.0	97.1	solvent 15
solvent 8	H	0.0	0.3	0.0	0.0	14.5	100.0	0.0	3.4	0.0	0.0	19.6	92.6	solvent 16

Conversion [%]

Outcome

Using these methods, the researchers identified two alternative synthetic routes in 2 weeks, which directly impacted timelines and enabled a "right first time" approach.

FROM DESIGN OF EXPERIMENTS TO THE DESIGN2OPTIMIZE™ PLATFORM

Lonza is also implementing a proprietary approach to experimental design strategies in synthetic process development. Ronald Fisher, a biologist and statistician, pioneered statistical design of experiments (DoE) in the early 20th century.[6] Incorporating statistical thinking during the planning stages of research rather than after the completion of experiments enabled researchers to work more efficiently. DoE leverages statistical modeling to study the relationship between multiple input variables, guiding experiments based on optimal conditions.

Working with the Fraunhofer Institute for Industrial Mathematics, Lonza researchers have developed the Design2Optimize™ platform, an in-house model-based platform. Model-based experimental design allows researchers to identify the experiments that maximize information gain.

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Even for reactions where the mechanism is not definitively known, credible options often can be proposed from first principles. Knowledge of the process is available from all prior experiments, including route scouting experiments. Based on the proposed reaction mechanism(s), researchers draft and test models to find which best fits the experimental data. Experimental data can be combined with the researcher's knowledge and refined into an accurate model. This model is more predictive than the empirical models based on linear (or near-linear) correlations used in statistical DoE.

One benefit of this approach is that it is based on a sound physicochemical model that requires fewer experiments than traditional methods, says Nichola McCann, senior principle scientist of process technologies and innovation, Lonza Advanced Synthesis. "While statistical DoE packages at this stage might involve 30 experiments or more, the Design2Optimize™ platform relies on physicochemical models that significantly reduce the number of experiments required."

These physicochemical models offer the chemist a better understanding of possible synthetic methods than empirical models generated with statistical DoE. "With only a few rounds of experiments, you can gain a very solid understanding of your chemistry," says McCann. "It puts you into a much stronger position to proceed to the next phase."

The utility of the Design2Optimize™ platform expands beyond improving the efficiency of synthetic process development, says McCann. With enough information, the platform can generate a "digital twin" that enables researchers to test "what if" scenarios for their chemistry and optimize processes based on multiple criteria. Users can explore the impact of changes in process parameters like temperature or reaction time on yield and purity without

further experimentation. “It’s a highly interactive and visual tool that helps guide subsequent direction and discussion,” says Johnson. The model can also provide valuable insights for later development phases, such as demonstrating the scalability of processes tested in HTE.

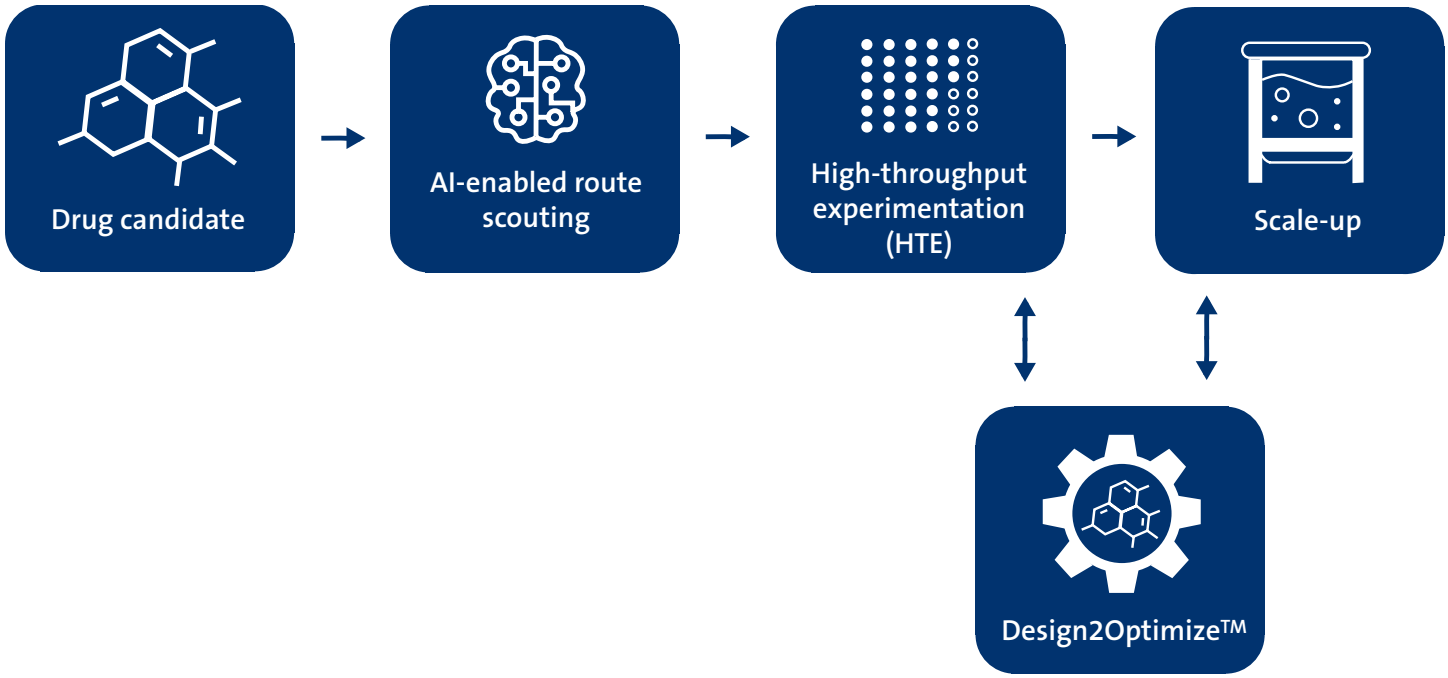
Schmidt notes that gaining this knowledge early on can make a massive difference in outcomes. “Once a process is validated on a large scale, it’s difficult to make changes or improvements. You lose out on the opportunity to optimize,” says Schmidt. “That’s why it’s important to get it right the first time, and the Design2Optimize™ platform makes that more likely.”

The insights from the Design2Optimize™ platform translates to significant savings in time and resources. “With classical DoE platform translates, we might be working on experimentation over 3 to 4 weeks, while the Design2Optimize™ platform can reduce that to a week or less,” says Johnson. “By identifying potential synthetic routes with AI-enabled route scouting, testing and optimizing those options with HTE, and further improving processes with the Design2Optimize™ platform, we can significantly reduce development time before moving to manufacturing.”

CONTINUED SUCCESS IN SMALL-MOLECULE INNOVATION

Lonza’s Advanced Synthesis family of solutions for testing and optimizing synthetic processes will assist drug developers in navigating the path from discovery to commercialization. As small-molecule APIs become more complex, AI-enabled route scouting, HTE, and the Design2Optimize™ platform improve manufacturability, commercial viability, and other key factors without sacrificing time or resource efficiency. These capabilities help the next generation of innovative therapies reach patients faster.

Lonza’s development workflow



"My hope is that, even given the rising complexity of APIs, we can halve the time it takes to move from early candidate selection to first-in-human materials," says Johnson. "It's an ambitious goal, but by applying these tools in combination, our clients can gain confidence that the routes they're going to develop are truly feasible for the future. That makes a big difference."

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