Reaxys

Smarter synthesis routes *cut time and costs*

Lonza's Small Molecules division proves Reaxys Predictive Retrosynthesis delivers shorter and more effective routes to enhance its new Route Scouting service.

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Background

Bringing small-molecule drug candidates to the market has become increasingly complex over the last two decades. A key factor in this complexity is the growing number of synthetic steps that has made the development of therapeutics slower and more expensive. Using a predictive tool to identify shorter and more effective routes is a state-of-the-art way to save time in R&D and manufacturing costs.

Introduction

Headquartered in Basel, Switzerland, Lonza is an international healthcare manufacturing organization that helps companies bring their products to market. Its Small Molecules division provides development and manufacturing services to pharmaceutical and biotechnology companies at every stage, from early development to commercialization.

Lonza recently launched its Route Scouting service to help its customers design synthesis routes for active pharmaceutical ingredients (APIs). This involves using its intellectual property and in-house expertise to evaluate a variety of factors, both scientific and commercial, and recommend the optimal synthetic routes. Always looking for ways to improve customer outcomes, Lonza tested Reaxys Predictive Retrosynthesis, Elsevier's artificial intelligence (AI) enabled predictive retrosynthesis tool, to determine if it could deliver even greater benefits to their clientele.

Using Reaxys Predictive Retrosynthesis, Lonza was able to identify more efficient synthesis routes and cheaper starting materials.

17%

Reaxys Predictive Retrosynthesis resulted in **17% fewer** synthesis steps on average.

Lonza's Challenges

In its Route Scouting service, Lonza examines a variety of factors, both scientific and commercial, and recommends the optimal synthetic routes. Lonza faced two key challenges in establishing its new service.

Challenge 1: Molecular complexity

The growing number of synthesis steps is a challenge for Lonza, its clients and the pharma industry in general. It makes the synthesis of APIs more complex, increases spending on raw materials, and expands the time it takes to test and manufacture new drug candidates. Drug companies strive to rule out failed candidates quickly, to fast track successful products to market, and to keep costs as low as possible — all of which are difficult with a complicated manufacturing process.

Designing synthesis routes for drug candidates is not as simple as coming up with a recipe that works. Process chemists must also make sure their designs are robust enough to meet standards for quality and reproducibility.[1] They must also consider whether the raw ingredients they select will be readily available, so the whole enterprise isn't derailed by supply-chain problems.

Molecular complexity is a serious issue. In 2006, GSK, AstraZeneca and Pfizer analyzed the synthesis process for 128 early-stage drug candidates and found that, on average, they required 8 steps.[2] By 2017, it was common for small-molecule synthesis to require more than 20 steps, according to Bristol Meyers Squibb and Boehringer Ingelheim.[3] And in 2019, the Japanese pharma company Eisai was working on a drug candidate for cancer that required 92 processing steps.[4]

Challenge 2: Raw material and synthesis costs

The cost of raw materials for new drugs is increasing. According to Mordor Intelligence, the market for active pharmaceutical ingredients was $204 billion in 2023 and is expected to increase at a compound annual growth rate of 7%, rising to almost $286 billion by 2028. The analysis indicates rising demand is driving rising costs. Factors influencing demand include the availability of lower-cost generic drugs, an uptake of biopharmaceuticals, an aging population and the growing prevalence of chronic diseases, including cardiovascular disease.[5]

Solution

To overcome the challenges in synthetic route design, Lonza selected Reaxys Predictive Retrosynthesis to run a series of experiments. The goal was to determine if the application of this computer-aided synthesis tool could result in time and cost savings for its customers compared with earlier-generation tools.

Why Lonza selected Reaxys Predictive Retrosynthesis for the test

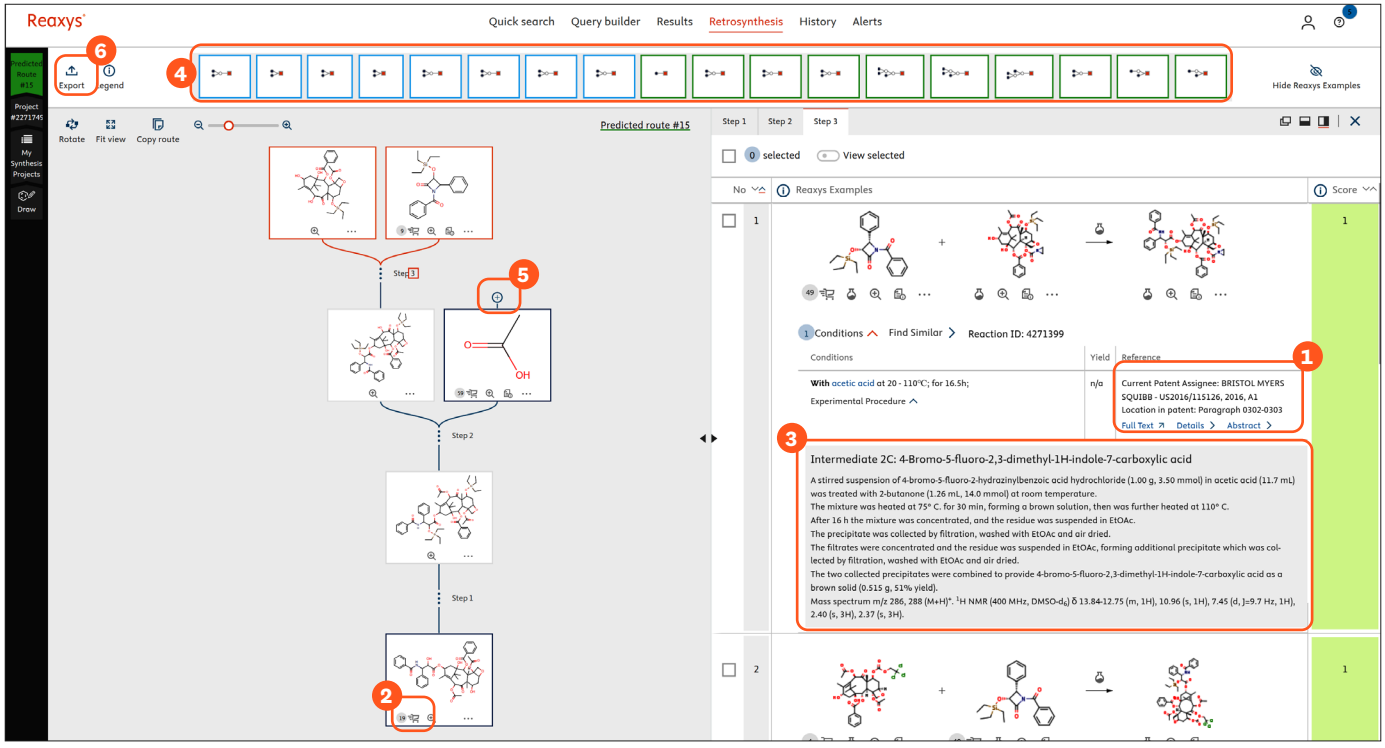
Lonza selected Reaxys Predictive Retrosynthesis for its computer-aided synthesis planning test because of the tool's:

- High-quality reaction data
- Comprehensive literature references informing the synthesis routes
- Robust library of building blocks (starting materials)
- User-friendly and intuitive interface
- Flexibility to add in-house data (see Results section for the significant impact of Lonza's adding its own building-block library)

Reaxys Predictive Retrosynthesis deconstructs a target molecule, breaking its bonds to arrive at commercially available building blocks. Within minutes it provides multiple options for published and predicted synthesis routes that chemists can quickly take to the lab. Chemists can then reverse the direction and apply the transformations forward to build the target molecule in the lab.

Reaxys Predictive Retrosynthesis combines high-quality reaction data with AI to deliver scientifically robust predictions. In addition, it contains numerous building-block libraries that can be supplemented by the user's own library of starting materials, stockroom compounds or proprietary molecules to tailor routes for custom needs and considerations.

Figure 1: Exploration of Reaxys Predictive Retrosynthesis intuitive interface



Scientifically robust predictions

1. Link to literature that informed the routes
2. End in purchasable starting materials
3. Access experimental procedures to execute plans

Intuitive experience

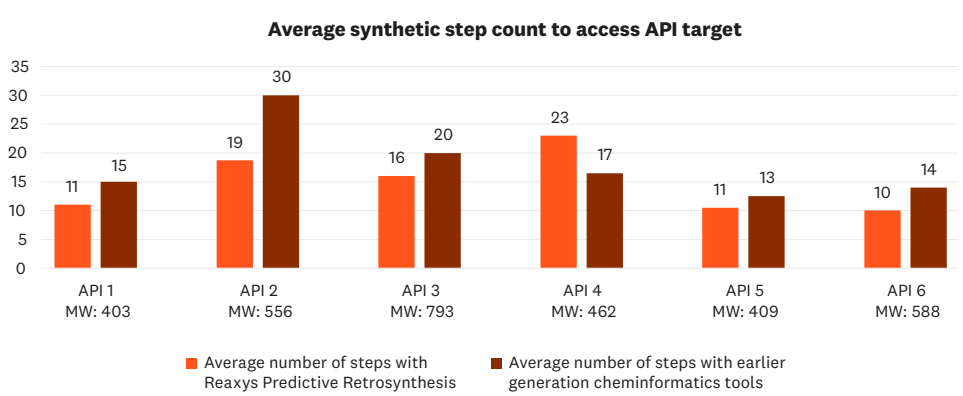
4. Published, predicted and custom routes in one view
5. Tailor results by editing synthesis routes
6. Export easily to collaborate on route design

What experiments did Lonza run?

Lonza ran a series of experiments on molecules with different molecular complexity, in terms of molecular weight and chiral centers, using six different preclinical and Phase 1 targets. In separate tests, they used Reaxys Predictive Retrosynthesis and earlier-generation cheminformatics tools, and then compared the synthesis routes that the tools predicted.

Results

Figure 2: Synthesis steps using Reaxys Predictive Retrosynthesis versus earlier-generation cheminformatics tools



De novo route design outcomes for six preclinical and Phase 1 API targets. MW = molecular weight.

Reaxys Predictive Retrosynthesis resulted in 17% fewer steps on average.

In the most dramatic difference, Reaxys Predictive Retrosynthesis suggested 11 fewer steps for a molecule containing nine chiral centers. In only one of the six cases did the alternate tool outperform Reaxys Predictive Retrosynthesis.

Lonza also checked whether supplementing the pricing information, by integrating its own proprietary building-block library to the very large set in Reaxys, would influence route selection. In most cases they observed that the integration had a significant impact on reduction in the price of the building blocks. (Data is proprietary and not shown.)

Impact for Lonza

Lonza's integrated approach combines sophisticated route evaluation and design using Reaxys Predictive Retrosyntheis, with a firm grounding in market intelligence. This allows identification of pathways that are not only synthetically elegant, but also aligned with supply chain fundamentals from the start. Rather than pursuing an optimized route only to encounter roadblocks during scale-up, Lonza can proactively map out a robust and commercially sound manufacturing process by integrating its building block library within Reaxys Predictive Retrosynthesis. This accelerates the journey from discovery to market by avoiding costly late-stage redesigns and delays.

Ultimately, this technology-forward and holistic perspective on route design and developability is a key advantage for rapidly delivering new therapies to patients in need.

References

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Learn more about Reaxys Predictive Retrosynthesis.