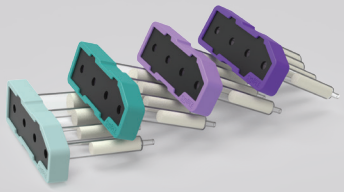
Case Study

Synple-accessible virtual space for the “on-demand” preparation of saturated N-heterocyclic libraries



SYNPLE

Bridging the gap - accelerating the DESIGN – MAKE process

- ML and rules-based approach for **reaction outcome predictions** (> 85%) when using Synple's technology
- Applicable to **commercial and proprietary building blocks**
- Vast new regions of **chemical space (> 7 trillion)** accessible via automated synthesis
- Direct and **rapid analogue synthesis** using pre-optimised methods (1 - 200 compounds in 2 - 4 weeks)

Synple automated synthesis technology

Synple's easy to use, cartridge-based automated synthesis technology provides "off-the-shelf" highly optimized reaction capabilities, enabling discovery chemists to vastly reduce the amount of time spent on both reaction setup and execution, as well as reaction optimization.[1] Available today in the original machine and cartridge format as well as the new parallel synthesis Synple Kit format,[2] Synple's technology offers the potential to relieve significant synthesis bottlenecks.

Synple-accessible virtual chemical space

Synthesis bottlenecks can impact all stages of discovery, including the very early hit discovery stages. In recent years, there has been an increasing shift towards the use of virtual screening as a cheaper, higher scale alternative to the more traditional high-throughput screening approach. However, this approach is not without its limitations. One such limitation concerns the tractability of the virtual chemical space being screened. While in theory, any two given building blocks with the correct functional groups could potentially react with each other to give the desired product, in reality many other factors affect whether or not the intended reaction will actually occur.

Although some virtual libraries providers have already acknowledged and started to address this limitation, in many other cases, the assumptions still persist that all theoretically accessible molecules can actually be made. This creates a problem for the chemists downstream, who are left with the task of determining if and how a virtual screening hit can be made (Fig. 1).

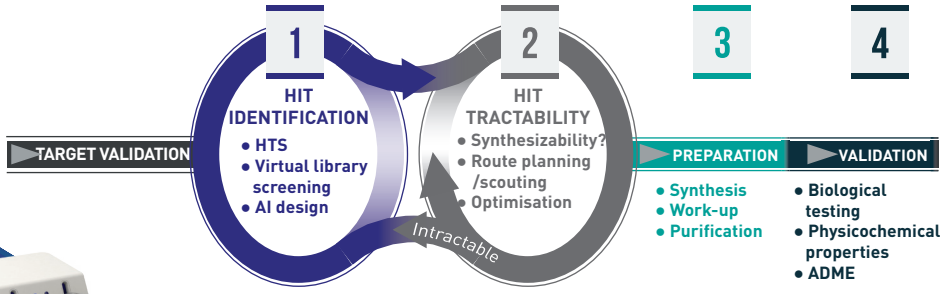
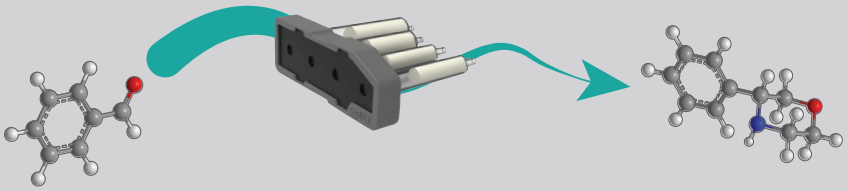


Fig. 1 Hit identification tractability bottlenecks



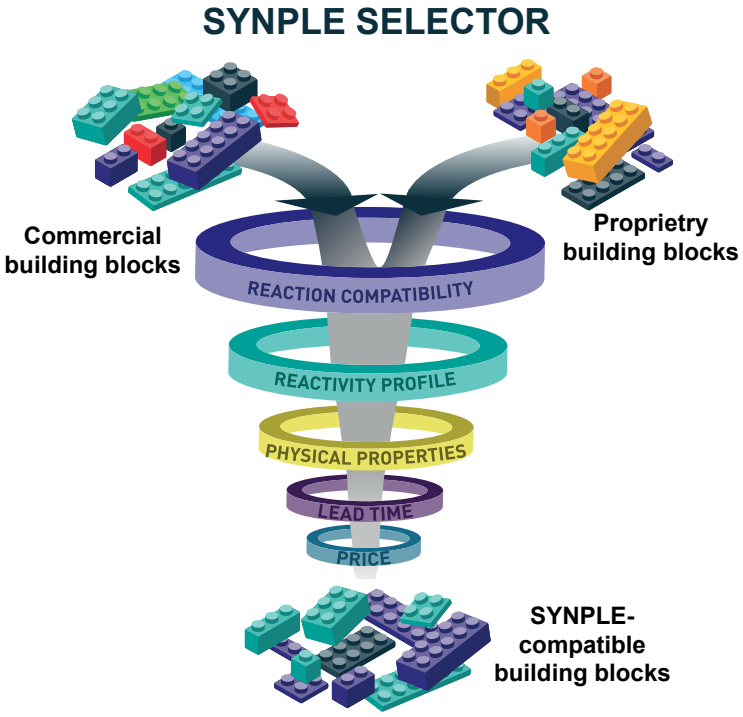


Fig. 2 Synple compatibility filters

In an effort to minimize or remove entirely this tractability assessment cycle, Synple has developed a series of models and filters to assess whether or not any given building block will give the desired reaction outcome when using the Synple technology and methods (Fig. 2). Using the compatible building blocks from diverse commercial sources, a virtual chemical space was created (predicted >85% synthesizable), encompassing several trillion molecules, which are all accessible using Synple's automated synthesis technology and pre-optimised reaction protocols. To reduce the computational burden, a representative diversity-picked library and a low-cost library are freely available to download and screen.[3]

Focused, tractable virtual library

In addition to the Synple Diversity and Low-cost Libraries, there is also the option to create further libraries, such as bespoke libraries using proprietary building blocks, or ones that are more focused on specific areas of the Synple-accessible chemical space. At the request of a large Pharma client, we created a focused, Synple-accessible virtual library based on the assembly of new N-heterocycle scaffolds using commercial aldehyde building blocks, Synple's N-heterocycle cartridges and the pre-optimized automated SnAP chemistry. As a second step, all the SnAP products would undergo N-acryloylation – a reaction class not currently enabled using the Synple platform (Fig. 3).

Fig. 3 Two-step virtual library enumeration based on one Synple step and one non-Synple step

A virtual library of 20'000 tractable SnAP products derived from 4 different SnAP reagents was prepared, and to ensure that the cost ceiling for this project would not be exceeded, the library was also encoded with building block price data. As specified by the client, only N-heterocycles with a single N atom were included, the aldehydes contained no chiral centers (to avoid diastereoisomer formation), and the MW of the final products were all in the range of 250 – 420.

Rapid synthesis of selected compounds

From this virtual library, 33 oxazepanes and benzoxazepanes were selected that were predicted to be synthesizable based on the SnAP chemistry alone since no predictive models currently exist for non-Synple-enabled acryloylation reactions. An additional six examples were also selected which actually failed one of the reaction compatibility filters. All 39 compounds required a unique first step, combining different aldehydes with the appropriate Synple N-heterocycle cartridges.

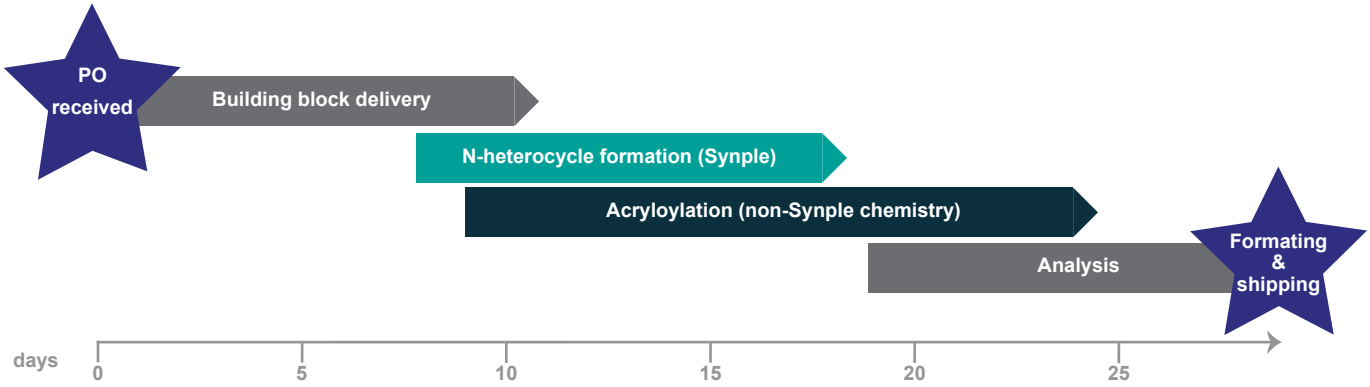
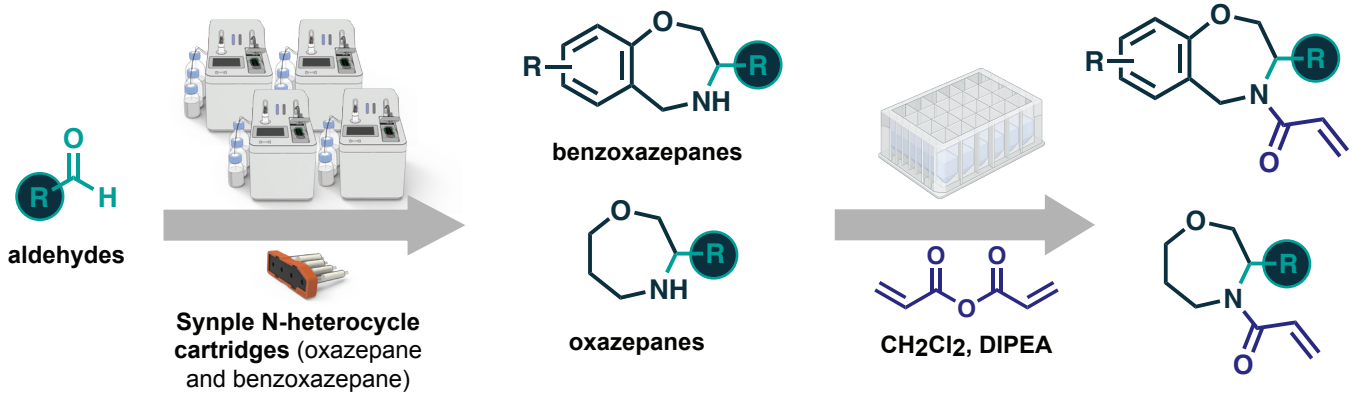


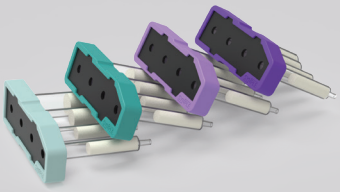
Fig 4. Library compound (1-50) preparation timelines

Upon receipt of the order, all building blocks were ordered and received within 10 working days (Fig. 4). For the synthesis itself, due to moisture sensitivity, the SnAP chemistry was all carried out using 4 Synple units rather than in an array format, meaning that step 1 of the library synthesis could be completed in 10 days (requiring < 1 hr hands-on time per day), with step 2 being effected in a small array format, as and when the new N-heterocycle intermediates were ready (Scheme 1).



Scheme 1. Preparation of benzoxazepane and oxazepane libraries

Of the 33 compounds predicted to successfully give N-heterocycle formation, 29 were successful (88% success) (Fig. 5). The four ones that failed involved either an aliphatic aldehyde, which are known to be low-yielding in the SnAP chemistry, or an aldehyde with a sterically bulky group close to the reactive center, which we believe hindered the copper-catalyzed cyclisation to form the new N-heterocycle.



In all other cases, due to the in-depth knowledge of automated SnAP chemistry, the Synple team was able to select upfront the most appropriate parameters for each individual SnAP reaction, without the need for the trial and error process that is often endured by chemists when trying to synthesize novel compounds. The team's expert knowledge also proved highly valuable in the case of the six compounds that failed one of the SnAP reaction compatibility filters. Even using a modified version of the platform's standard reaction protocol, all six SnAP reactions that were predicted to fail did so. However, the Synple team was able to make a more extensive modification to the method, which facilitated better intermediate imine formation and, as such, four of the six products predicted fail could actually be successfully obtained.

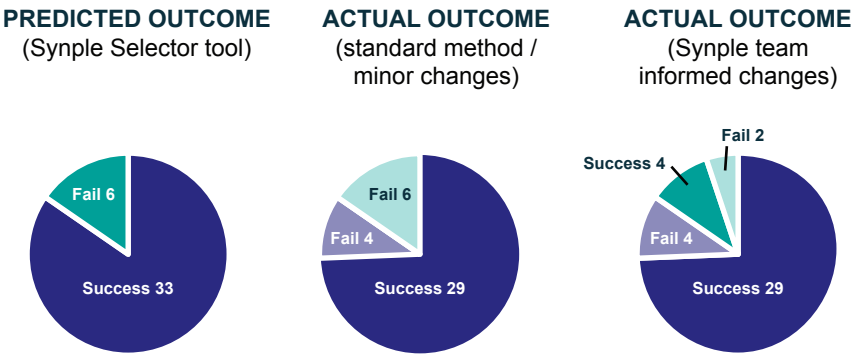


Fig. 5 Predicted vs actual reaction outcome

A significant trial and error process was required for the second synthetic step, despite the client providing a standard procedure, albeit a non-Synple-enabled one. Since the standard procedure was not effective for many substrates, these cases required optimization and refinement, with the chemistry needing to be repeated multiple times to achieve a similar level of synthesizability (85%) to that achieved for step 1. This process consumed much of the scheduled synthesis time. Despite the reaction itself requiring less than half of the time needed to complete the SnAP chemistry, 15 days of manual work were required to complete this synthesis stage (> 3 hours hands on time per day). Upon completion of the synthesis, an additional five days were required for completion of the analysis, which was highly complicated due to the presence of amide bond rotamers and the occurrence of acryloylation side-products that could not be identified using LCMS.

From virtual hits to physical samples – unique Synple advantages

For initiating this project, creating and using an N-heterocycle focused Synple-accessible virtual library proved highly enabling, allowing the client to rapidly select compounds of interest for synthesis. The value of Synple's predictive reaction outcome tools was also clearly evident, since almost 90% of the compounds predicted to work were successfully synthesised, with only very minimal need for reaction optimisation. The Synple team's expertise in the reaction classes enabled by the platform also played an important role in the project's success. Troubleshooting was greatly simplified in the case of Synple-reactions, in this case the SnAP chemistry, since much of it could be done ahead of time, before any wet chemistry had even been initiated.

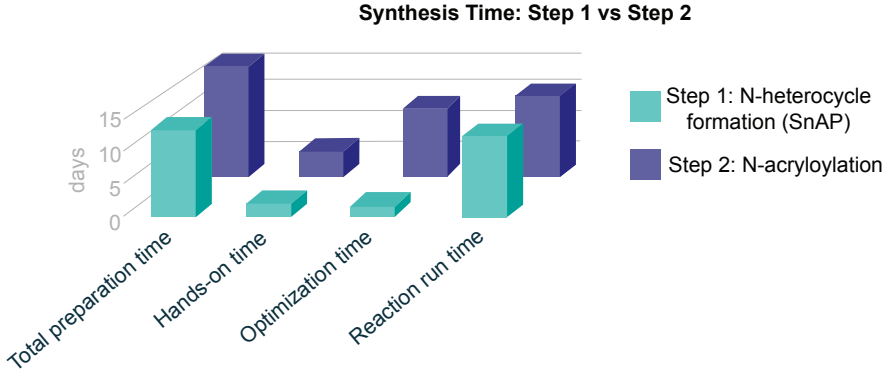
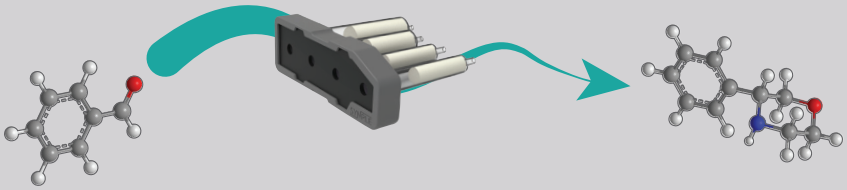


Fig. 6. Synple vs non-Synple reaction statistics



As one would expect, the lack of predictive tools and reduced in-depth reaction-specific knowledge negatively impacted step 2 of the synthesis, evidenced by the significantly longer timelines compared to step 1 (Fig. 6).In conclusion, identifying hits from Synple-accessible, highly synthesizable virtual chemical space can greatly accelerate the hit identification process. Hits selected from within this space can be rapidly prepared with very minimal need for reaction optimization, saving time and maximizing resources. Additional time-saving benefits are provided through the use of Synple automation, which significantly reduces the amount of manual, hands-on time required for synthetic work. In addition, outsourcing the synthetic work to the Synple team enables the client to benefit from our in-depth knowledge of the each and every reaction class we offer, making any necessary fine tuning or troubleshooting a quick and simple task.

References

1. Jiang, T.; Bordi, S.; McMillan, A. E.; Chen, K.-Y.; Saito, F.; Nichols, P. L.; Wanner, B. M.; Bode, J. W. An integrated console for capsule-based, automated organic synthesis. Chem.Sci., 2021, 12, 6977-6982.
2. https://www.synplechem.com/solutions/synple-reaction-kits
3. https://www.synplechem.com/solutions/synple-4-0

Client testimonial

"We were interested in N-alpha substituted (benz)oxazepane scaffolds as part of a medicinal chemistry program. We chose to work directly with Synple Chem, given their expertise in synthesising such scaffolds using their solid cartridge technology.

Synple Chem generated a vast virtual library catalogue comprising accessible products based on known functional group tolerances and reaction limitations. From this, our project team could pick-and-choose desired compounds. The selected compounds were delivered in a timely fashion and overall the collaboration was a success due to effective communication with the Synple Chem team."

Getting started with Synple

Interested in accelerating your hit discovery? Our Diversity and Low-cost virtual libraries are freely available to download from the Synple website. You can also request the application of bespoke parameters, such as specific physical property ranges or the inclusion of certain functional groups or fragments. Virtual screening hits can then be rapidly prepared by Synple!

Access Synple Virtual Libraries

Visit Synple Chem Homepage

For further information or to enquire about bespoke Synple virtual library solutions, please get in touch:

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