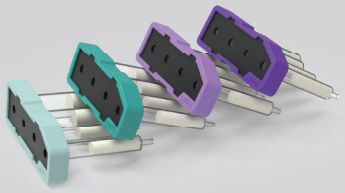
Case Study

Rapid, predictable, and efficient virtual hit identification and synthesis with automated, cartridge-based synthesis technology and Synple accessible chemical space

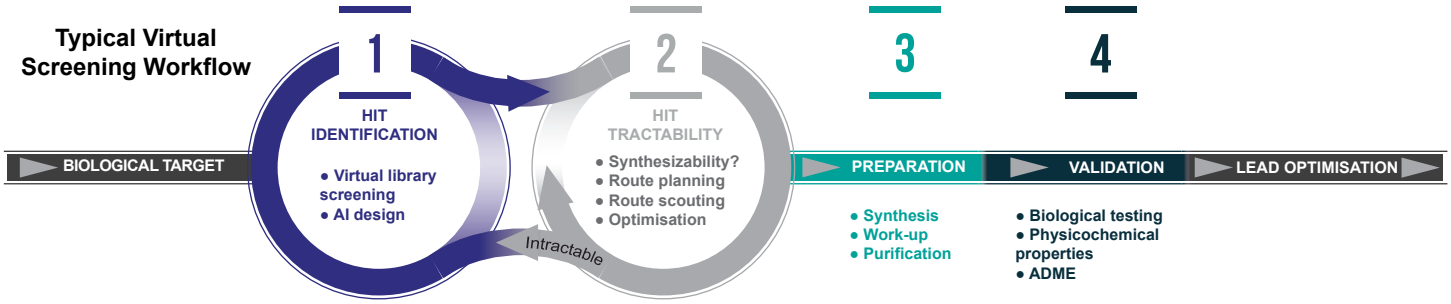


Accelerating drug discovery with virtual screening

The generation and screening of virtual chemical libraries is highly attractive since it offers the potential to rapidly probe unexplored areas of chemical space for new biologically active molecules, without a large investment in synthetic and screening resources, which would otherwise be required to prepare and test physical samples. As such, many academic and industrial research groups have focussed their efforts on the enumeration of virtual libraries and the development of virtual screening tecniques capable of handling such large data sets.[1]

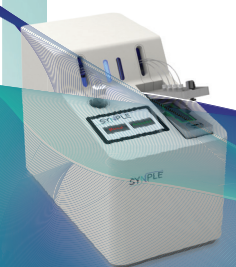
What limitations still exist with the virtual approach?

Despite the obvious advantages of virtually “making” and “testing” new molecules, this approach has not yet managed to replace the classical chemical synthesis and assay route. Fundamentally, predicting exactly how a given molecule will interact with its target is no easy task, due to the complexity of the interactions that govern whether or not a molecule reaches its target and forms a specific strong interaction. As a result, virtual screening is not yet as predictive as we would like it to be so many molecules still need to be physically prepared in order to test and validate the virtual screening method. Unfortunately, many virtual libraries give insufficient consideration to synthesizability, meaning that chemists often face the difficult and time-consuming task of trying to make analogues that are unattractive from a synthetic standpoint, which ultimately reduces the number of hits that can be validated.

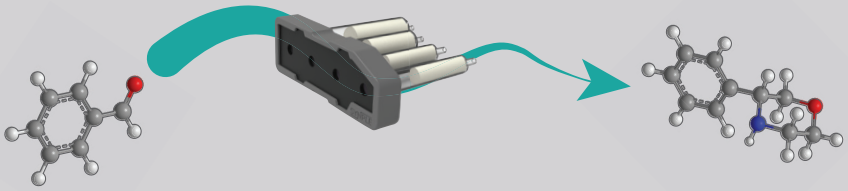


Synthesizability as a priority

Synple’s virtual library was designed with synthesizability in mind. Assembled using multistep synthetic sequences, based on various combinations of chemical reactions offered by Synple, and a diverse range of commercial building blocks that have been carefully filtered to ensure high degree of confidence in a successful reaction outcome, all Synple virtual library members can be directly, rapidly and predictably synthesized using Synple’s automated cartridge-based synthesis platform, thus avoiding the need for a hit tractability assessment stage.

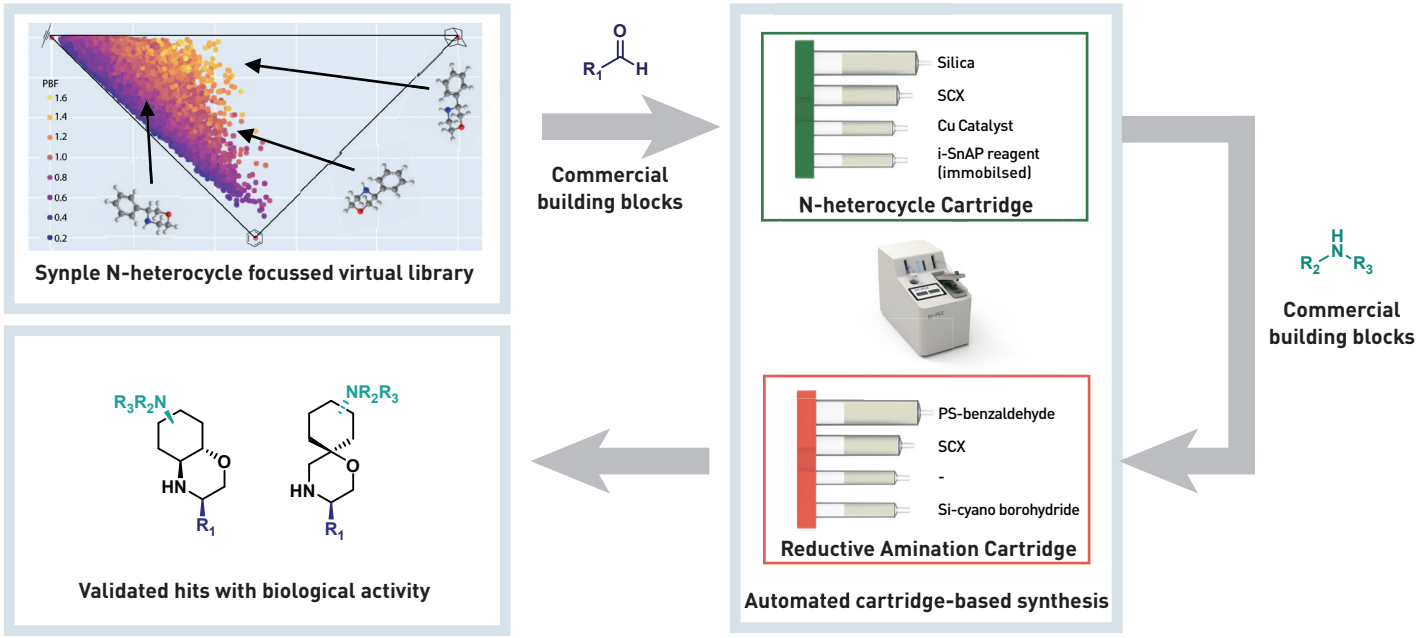


[1] van Hilten, N.; Chevillard, F.; Kolb, P.; Virtual compound libraries in computer-assisted drug discovery, J. Chem. Inform. Model., **2019**, *59*, 644-651.



ETH researchers overcome synthetic bottleneck to validate virtual screening hits

Researchers at ETH in Zürich, along with the BASF Open Innovation Platform, successfully utilized Synple's N-heterocycle-focused virtual library to identify molecules with the potential to be crop protection agents. After screening this virtual library, consisting of half million molecules, BASF Open Innovation Platform selected 20k molecules of interest. Clustering of the selected molecules, based on 3D shape, enabled the chemists at ETH to choose approximately 40 representative examples from each cluster for synthesis. In just 15 minutes of hands-on time, each molecule was successfully prepared using a two-step Synple synthetic sequence consisting of an initial SnAP reaction (Synple N-heterocycle Cartridges plus commercial aldehydes), followed by a reductive amination reaction on the newly formed carbonyl intermediate (Synple Reductive Amination Cartridges plus commercial amines).



Improved efficiency and safety with Synple

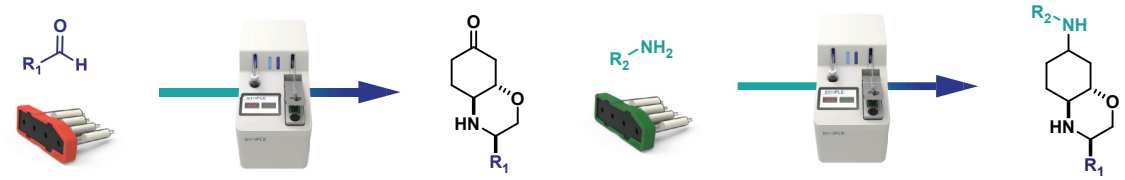
ETH researchers tracked the time needed to generate these virtual library hits for validation, and estimated that 23-39 h were required to complete the full automated instrument reaction workflow (3 synthetic steps) and generate one compound (or set of separated diasteroisomers). However, the majority of the time was the reaction time, with only 0.3 - 0.8 hours (depending on the scaffold) of the chemist's hands-on time required. This included a short final HPLC purification, which proved to be very simple due to the high purity material obtained following the multiple purification stages included in the Synple cartridges. In comparison, when carried out manually the same compound needed 35-51 h preparation time, with 5 h of the chemist's hands on time required. Therefore, the Synple system offers at least 7-10-fold improvement in a chemist's working efficiency (potentially even greater since this reaction workflow generates 2-4 diastereomers).

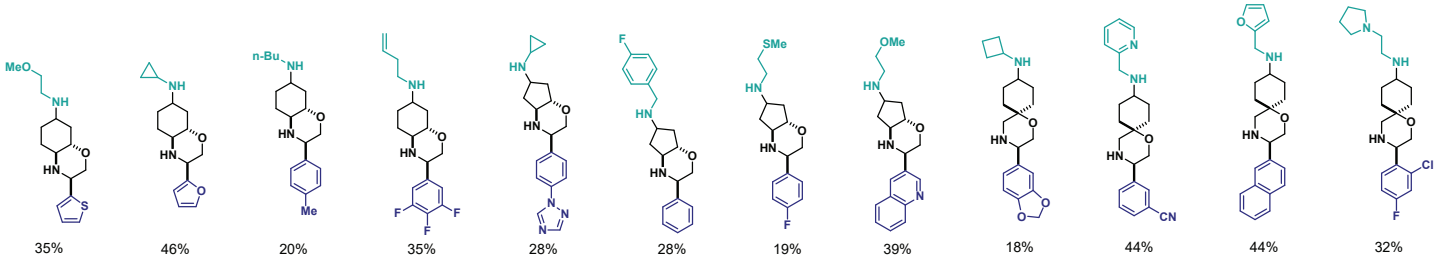
Such efficiency gains are more than just significant cost savings. With Synple, chemists are freed from the routine, mundane tasks that feature heavily in synthesis, enabling them to shift their efforts to more innovative, value-adding work, from which discovery can truly accelerate.

Preparation (1 molecule)	Manual workflow	SYNPLE
Time to obtain molecule	35 - 51 h	23 - 39 h
Chemist "hands-on" time	4.25 - 5.4 h	0.3 - 0.8 h
Working efficiency	1	7-14 fold

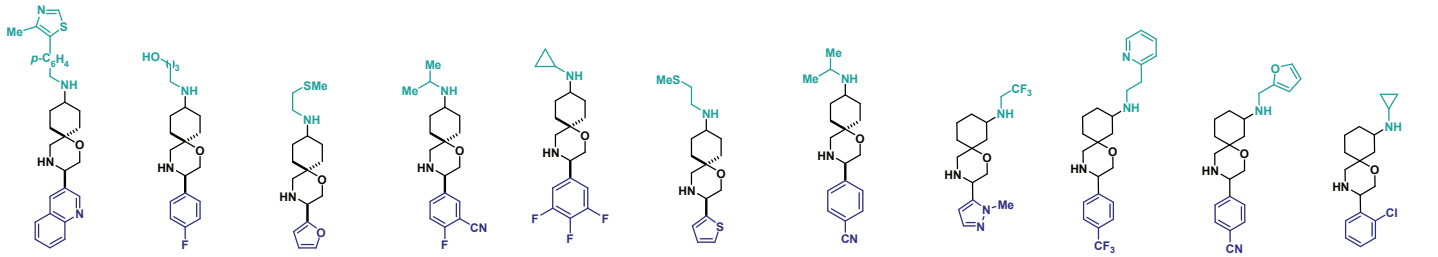
*Calculated for one set of diastereomers separated by HPLC

Automated synthesis of selected hits from virtual library





35% dr 14:11 A 28, B 16 mg | 46% dr 17:8 A 12, B 16 mg | 20% dr 18:7 A 18, B 12 mg | 35% dr 3:2 A 30, B 17 mg | 28% dr 1:1 A+B 20 mg | 28% dr 1:1 A+B 14 mg | 19% dr 3:2 A+B 46 mg | 39% dr 13:9 A+B 18 mg | 18% dr 7:3 A 14, B 6 mg | 44% dr 16:9 A 46, B 19 mg | 44% dr 3:2 A 25, B 15 mg | 32% dr 16:9 A 45, B 12 mg



54% dr 29:22 A 17, B 9 mg | 24% dr 31:19 A 13, B 18 mg | 33% dr 16:9 A 11, B 13 mg | 38% dr 27:23 A 26, B 22 mg | 40% dr 1:1 A 19, B 8 mg | 26% dr 1:1 A 17, B 8 mg | 43% dr 9:11 A 46, B 23 mg | 19% dr 2:3:2:3 A 10 mg | 35% dr 3:5:8:10 A 5 mg | 50% dr 5:11:7:20 D 3 mg | 35% dr 4:2:3:2 A 8, B 4, C 8, D 6 mg

Preparation of library members; crude yield prior to resolution as determined by 1H NMR using 1,3,5-trimethoxybenzene as an internal standard; dr determined by HPLC; isolated mass after resolution in mg

Overal project speed and output

During the project, a total of 23 compounds were synthesized for biological evaluation. Each of the compounds required three synthetic steps (two instrument runs), requiring on average 30 hours each, equalling a total preparation time of 690 h for all analogues. Since 4 instruments were in use for an average of 18 hours per day, this synthethic work was completed in only 9 working days. This time could also be shortened further by using additional Synple 2 units.

The chemist, however, spent only 14 hours (2 working days) on the project, leaving more time for other tasks. It was estimated that it would have taken a skilled chemist 13-16 full working days to generate these same 23 compounds using manual methods.

Project time	Manual workflow (1 chemist)	SYNPLE (1 chemist + 4 instruments)
Molecules preparation	13-16 days	9 days
Chemist total "hands-on" time	12-15 days	2 days

Additional information

The virtual libraries used in this project, as well as others based on various combinations of Synple reactions, are available for download. Please contact us in order to use these in your project. Detailed information about reaction procedures, conditions and scope for all Synple reactions can be downloaded as application notes from our homepage. For any questions please contact us:

info@synplechem.com www.synplechem.com

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