Compound library generation using flow chemistry

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The use of flow chemistry to generate compound libraries for screening against a biological target enables faster exploration of potential drug candidates, accelerating early drug discovery projects. Modern, modular flow chemistry platforms offer many benefits over traditional batch processes, increasing the scope of reactions that can be performed while improving both reproducibility and cost compared to the equivalent manual synthesis. This article discusses the advantages of using flow chemistry for library generation – from streamlined workflows that enhance efficiency to the automation of complex syntheses – and describes how the technology can be complemented by under-used techniques such as photochemistry and electrochemistry. It also explores how machine learning or AI-based automation could potentially be coupled with flow chemistry to change the drug discovery landscape of the future.

The benefits of flow chemistry have seen this enabling technology applied to a growing number of applications over recent years. One such application is early phase drug discovery, where it is being used to generate libraries of compounds for screening against a biological target of interest, allowing the faster exploration of potential drug candidates. The use of flow chemistry for compound library generation has many benefits over traditional batch protocols, offering improved reproducibility and cost compared to equivalent manual syntheses. Even when compared to automated batch processes, flow chemistry approaches increase the scope of reactions that can be performed, and enable several operations to be telescoped together, allowing more efficient processing for further cost reductions.

Challenges with traditional batch methods

Organic synthesis is currently dominated by batch processes, with iterative generation of compounds over multiple steps. Each step involves synthesis in a round-bottomed flask or batch reactor of some sort (96-well plates are often adopted for batch library synthesis), then subsequent isolation and purification before the next step is carried out (*Figure 1*). This process is a mainstay of compound library generation in drug discovery, partly due to the complexity of the syntheses being performed.

More recently, automation of batch reactions – using liquid handlers and automated purification platforms – has aided the development of parallel / combinatorial library generation by allowing miniaturisation of reactions. However, library synthesis through these techniques is limited as reaction scales are decreased. The scope of chemistry available often delivers low yielding and unreliable reactions, requiring extensive re-optimisation during subsequent resynthesis and scale-up. In addition, the time-consuming purification needed after each reaction step wastes resources and delays the delivery of the final compounds, resulting in significant time delays between design of the experiment and obtaining the results. This limits the number of compounds that can be advanced into clinical studies and, ultimately, has a huge impact on the timelines and success rates of the drug discovery process.

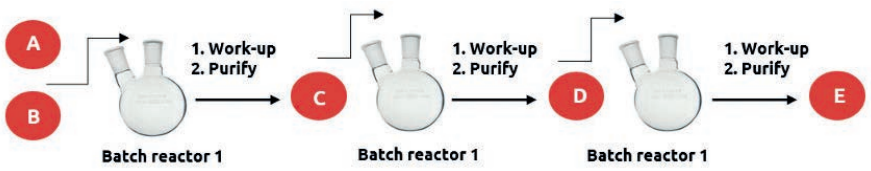

Figure 1: Synthetic workflow using traditional batch techniques.

Flow chemistry methods for library generation

Flow chemistry platforms are increasingly being used to help address these challenges with library generation. This approach increases the available chemical space and range of chemistries suitable for automation, as well as improving the efficiency, safety, and environmental impact of workflows. The core benefit of flow chemistry is that it enables researchers to perform chemistries in series, integrating downstream processes to reduce work-up and isolation steps in a single experiment (*Figure 2*). It can reduce both the time and costs associated with library generation, offering fast process optimisation and the straightforward preparation of diverse compound series to increase the scope of early stages of drug discovery programs, providing valuable additional information that could increases the chances of success. It also offers a direct route to scaling-up synthesis of hit or lead compounds without the need for re-optimisation. Users can simply synthesise exploratory compounds on a small scale for screening, then resynthesise larger amounts using the same methodology later.

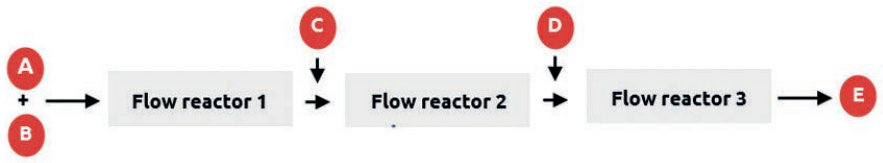

Figure 2: A multistep synthesis approach using flow chemistry techniques.

Automating flow chemistry

The ability to automate any chemical process not only frees up chemists to perform other tasks, but also provides more precise control of reagent additions, mixing rates, temperatures and pressures – as well as robust data logging and recording – helping to improve overall process reproducibility and, therefore, performance. This strategy lends itself well to flow chemistry approaches, allowing the full automation of experiments with increasing complexity. Using modular flow chemistry systems, chemists can control various devices in concert to perform multiple operations as part of a continuous process. These modular platforms can also combine heated or cooled flow reactors with access to previously restricted or underused activation methods, such as photochemistry and electrochemistry. Furthermore, state-of-the-art flow chemistry platforms can couple synthesis with in-line purification and analysis – to work-up and identify what's been made – to create platforms capable of further shortening the medicinal chemistry discovery process [1,2]. This modular approach makes it possible to combine multiple techniques to synthesise molecules over several reaction steps as part of a truly continuous process (*Figure 3*), then simply reconfigure the system as required [3].

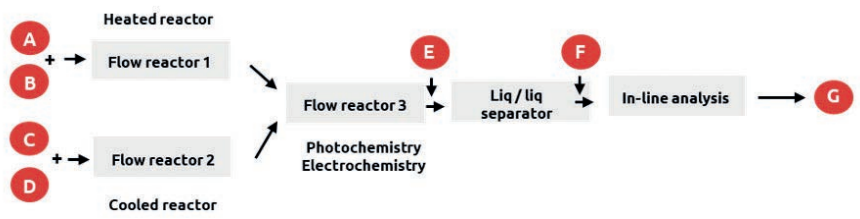

Figure 3: Multistep synthesis approach using flow chemistry techniques.

Flow automation for reaction optimisation

Automated experimentation can be used to rapidly optimise reaction conditions and evaluate novel methodologies, running a series of experiments to explore a full range of reaction parameters (*Figure 4*) [1]. Researchers can quickly screen continuous parameters such as residence time, reaction stoichiometry, reaction temperature and pressure. Automated reagent injectors can also be employed to explore discontinuous reaction parameters, such as reagent, catalyst or enzyme screening. With the correct control software, it is also possible to import files from Design of Experiment (DoE) software, making the process even more efficient. Once the optimum reaction conditions for a process have been identified, these can be used to synthesise a library of compounds, or to process larger quantities of material for downstream development.

Figure 4: Flow chemistry process for reaction optimisation.

Flow automation for library generation

Automating the generation of libraries of compounds to explore reactivity and chemical space using flow chemistry allows the efficient synthesis of complex molecules with multiple points of diversification. Structural diversity can be achieved in many ways when building molecules in this fashion, including using different starting materials; varying core structural motifs in multicomponent reactions; combining the synthesis of uncommon, low diversity starting material sub-sets; and creating diversity from convergent synthesis. Realising the full potential of this approach requires a modular and flexible system that can be configured to any flow chemistry application and fluid pathway desired by the chemist.

Automated reagent injection is also vital to allow the rapid exploration of chemistries by introducing a range of chemical 'building blocks' at each point in the synthetic route. These injector modules should enable parallel loading of samples using separate, dedicated liquid handing loops – to reduce the time associated with serial loading of samples – and have the ability to pre-pressurise the sample loops prior to injection, to avoid pressure drops and allow the use of smaller aliquots with greater segment tracking. With this in place, chemists can run a series of automated experiments to create diversity in structure. This is typically achieved using the same reaction conditions but can be tailored to the relative reactivities of the starting materials, adding even more control to the synthesis.

Closed loop optimisation and machine learning

The move towards more industry standards for device connectivity – offering the ability to communicate and control a diverse set of laboratory equipment through a central control system – is enabling flow chemistry platforms to be integrated with machine learning applications. These approaches can be combined with flow synthesis and real-time screening to provide a highly effective approach for optimising reaction methodologies and conditions. So far, these platforms are still mainly found in the academic arena, with several groups – such as Professor Richard Bourne (Univ. of Leeds, IPRD), Professor Steve Ley (Univ. of Cambridge), and Professor Alexie Lapkin (Univ. of Cambridge, iDMT) – actively exploring methods to integrate digital technologies with synthetic processes for the automation, optimisation and development of pharmaceuticals. However, this solution is also being actively pursued by the chemical and pharma industries to enhance their capabilities.

Flow synthesis can be coupled with a variety of in-line analytical techniques to give real-time feedback that can be used to interpret the outcome of a reaction. Machine learning or artificial intelligence algorithms can monitor these reaction conditions, then make decisions on the next set of parameters to select to optimise the workflow as part of a 'closed loop' system (*Figure 5*). Open-source industry standards – such as Open Platform Communications – Universal Architecture (OPC UA) – are vital to this approach, allowing users to connect a range of laboratory equipment from a variety of manufacturers to run fully automated, closed loop processes with seamless communication and control.

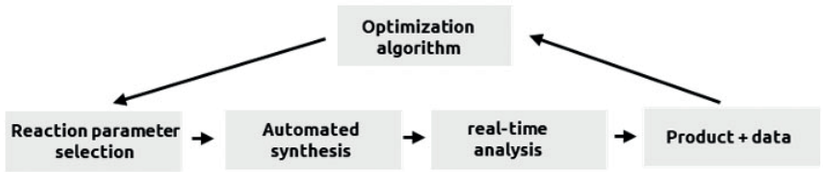

Figure 5: Closed loop reaction optimisation process for flow chemistry.

Conclusion

The use of flow chemistry to generate compound libraries has helped to accelerate early phase drug discovery. Flow chemistry undoubtedly increases the range and scope of chemistries available through automated processes, allowing greater exploration of the available chemical space. Modern, modular flow chemistry platforms allow the development of complex automated experimentation approaches and provide new access to under-used techniques – such as photochemistry and electrochemistry – further expanding the tool kit available to chemists. On top of this, the development of machine learning- or AI-based algorithms that can be used to create closed loop experimentation systems represents a key technology for the future of both flow chemistry and drug discovery.

References

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