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Continuous-flow photochemistry as an automated platform integrated with closed-loop AI/ML approaches

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In this Activity article, Brenda Pijper (Horizon 2020 PhotoReAct early-stage researcher in the Chemical Technologies group at Janssen, the Pharmaceutical Companies of Johnson & Johnson) and Jesus Alcázar (head of the Chemical Technologies group at Janssen) and Gabriela Oksdath-Mansilla and Fabricio R. Bisogno (both professors at the Universidad Nacional de Córdoba and researchers at the National Scientific and Technical Research Council of Argentina [CONICET]) discuss the current state of continuous-flow photochemistry in drug discovery and its future as an automated platform integrated with closed-loop artificial intelligence and machine learning (AI/ML) approaches.

B.P. and J.A. emphasize the impact of automated flow photochemistry and the potential for an automated platform integrated with closed-loop AI/ML approaches

Increasing the speed of drug discovery to provide rapid access to novel drugs is a clear need in the pharmaceutical industry. The discovery rate of novel chemicals depends on how molecules are synthesized: the quicker the exploration of the structure-activity and structure-property relationships, the faster the discovery of clinical candidates. Recently, automation has brought a new window of opportunity to perform a large number of reactions in parallel format in an unattended manner, and its combination with integrated process analytical technology minimizes human error and provides more reliable results.[1] Nevertheless, current high-throughput experimentation (HTE) and library synthesis are often restricted to a reduced number of transformations. For instance, novel tools such as photochemistry have limitations in HTE platforms because of the limited control of parameters such as temperature and are not yet robust enough to be used by medicinal chemists for library synthesis.

Flow photochemistry has appeared as a novel tool for accessing novel chemical transformations that would be available for library synthesis when combined with automation. Flow photochemical reactors offer a large surface-to-volume ratio, resulting in a homogeneous photon flux that allows a uniform irradiation of the reaction mixture and thus limits side-product formation.[2] Moreover, they also improve mass and heat transfer, allowing full control of reaction parameters, which means enhanced reproducibility and predictable scaling behavior. The main drawback of this approach is downscaling for HTE approaches given that dispersion will prevent the steady state of the reaction from being reached. This can be overcome with the use of segmented flow either by a physical separation with an immiscible carrier solvent or by the injection of small amounts of concentrated reagents and dispersion into the carrier solvent while keeping an appropriate time for a separated collection of different slugs. The last automated system was coupled with in-line liquid chromatography-mass spectrometry analysis to obtain data from 1,500 reactions in 24 h, showing the potential of flow chemistry in data generation.[3]

The ease of connecting analytical techniques in line and the possibility of controlling the flow system's components remotely make flow photochemistry an ideal candidate for closed-loop automation. Most of the systems that are designed for automation include self-optimization algorithms where the computer can handle the data obtained in separated experiments to decide the next set of reactions to be performed. These systems have been used to quickly find new reaction conditions and the scope of the chemistry. Considering the amount of reliable data that can be obtained in sequential flow, the integration of self-optimization with artificial intelligence and machine learning (AI/ML) approaches can be used for exploring new photochemical transformations to access novel chemical space for drug discovery. These novel transformations can be then optimized with design of experiments (DoE) and used in automated library synthesis for the fast production of analogs to accelerate the finding of drug-like molecules (Figure 1).[4]

In the future, multi-step flow chemistry will allow the combination of different

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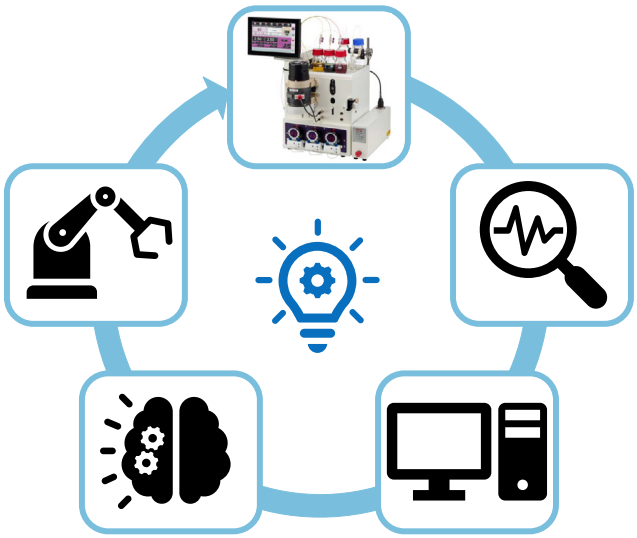

Figure 1. Close-loop approach to self-optimizing flow systems
Picture of a flow reactor. Reprinted with permission from Vapourtec Ltd.

fragments to form new compounds in a streamlined process. This way, matrix libraries can be produced for the exploration of two or more vectors in a single run. Prof. Seeberger has already shown a recent example of a modular multi-step synthetic approach that allowed access to a diverse set of compounds by combining different chemical reactions in the same automated protocol.[5] Beyond diversity, productivity measured as the number of products per time unit will be a key parameter for the future production of multi-step flow libraries. We think that the use of flow as an assembly line for molecules will be of great importance for faster explorations in medicinal chemistry programs. Herein, novel photochemical procedures discovered by self-optimizing AI/ML platforms would play an important role in further expanding chemical space in a high-throughput way.

F.R.B. and G.O.-M. respond to how continuous-flow chemistry with closed-loop AI/ML approaches can accelerate the exploration of new chemical spaces

Given that the speed of the discovery of novel chemical entities that are active toward a given molecular target has become a bottleneck in the pharmaceutical industry, the development of reliable and robust methodologies is one of the everlasting challenges in academia. Indeed, a growing number of very useful catalytic reactions are being adapted to continuous-flow regimes in order to be integrated in modular approaches. As highlighted by B.P. and J.A., such an approach is very appealing given that automation—and even more challenging, integrated AI/ML closed-loop automated systems—will enable impressively large chemical space to be screened in shorter times.

The combination of different classes of catalytic reactions in a single reaction vessel has attracted a great deal of attention in synthetic organic chemistry. Combining metallocatalysis, biocatalysis, photocatalysis, and organocatalysis can enhance the virtues of every single catalysis and therefore make them profitable. This is particularly interesting in the development of a cascade reaction, where the product of the first reaction does not accumulate because it is immediately consumed by the following reaction as soon as it is formed. This feature minimizes side reactions by improving selectivity, shortening downstream processes, and overall enhancing productivity. But, of course, combining different classes of catalytic reactions is not an easy task. Compatibility issues are the main obstacle. This is particularly challenging in continuous-flow reactors, where changes in solvent composition can lead to clogging. An extremely useful trick is the use of biphasic systems that allow compatibilization of aqueous media (as required by most enzymatic reactions) with immiscible non-aqueous media, the common reaction media for a vast number of metal-, organo-, and photocatalyzed processes. Moreover, biphasic continuous-flow setups provide the opportunity to use gases with low solubility in a gas-liquid slug flow design.

The application of DoE protocols can facilitate the quest for conditions under which different catalytic systems can be successfully combined, thus shortening time and saving costs. Besides, compatibilization of multi-catalytic systems can be substantially sped up by AI/ML approaches. Indeed, optimization platforms can be trained to reach optimal common parameters for (at least) a pair of combined catalytic processes (although suboptimal parameters for a single catalytic reaction).

Although stereoselectivity has been extensively controlled by chemists, chemoselectivity has not yet been fully conquered.[6] An example of limited chemoselectivity is the use of protecting groups in organic synthesis. In recent protecting-group-free synthetic strategies, the key is the exquisite chemoselectivity of the involved chemical steps, most of which are achieved through the precise adjustment of certain reaction parameters, such as light irradiation, temperature, and solvent. By avoiding protection-deprotection sequences, synthetic strategies get more sustainable as fewer chemicals are used, less waste is generated, and a lot of energy is saved. In this regard, multi-catalytic continuous-flow designs have tremendous potential to

achieve a high level of chemoselectivity by channeling the reaction outcome to a single reaction path over the several possible ones. Given that AI/ML protocols are becoming more and more available, it seems likely that closed-loop integrated systems will revolutionize organic synthesis in general and drug discovery in particular. This can be made available by suitable analytics, such as integrated mass spectrometry.

Another scenario will be displayed when quantum computation means become readily available, so every decision-making step in a closed-loop system shall take place in meaningless time.[7]

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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