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Challenge and opportunity: The two edges of continuous-flow photochemistry

Gabriela Oksdath-Mansilla,[1,*] Fabricio Román Bisogno,[1] Brenda Pijper,[2] and Jesus Alcázar[2,*]

In this Activity article, 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]) and 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) discuss the importance of implementing continuous-flow photochemistry as a tool in drug-discovery programs as they wonder about the next challenges in the field.

G.O.-M. and F.R.B. emphasize the benefits of combining photocatalysis and continuous-flow technology in both academia and industry

For the last two years, the world has faced the COVID-19 pandemic and realized the importance of taking quick and smart action. In this scenario, scientists played a key role by using every tool available not only to develop new vaccines but also to discover alternative therapeutic agents. Indeed, in the field of drug discovery, the dramatic COVID-19 pandemic accelerated the search for how to access complex molecule architectures in easier ways. In this sense, successfully reaching the sought-after process intensification requires implementation of new technologies linked to greener organic synthesis strategies.

Starting from target-hit identification to the final selection of the best drug candidate, continuous-flow chemistry is a pivotal piece to be introduced in drug-discovery programs. Continuous-flow technologies have demonstrated their potential for rapid access to novel scaffolds. Straightforward control of reaction parameters allows for improvement of the safety and scalability of processes. These conditions make continuous-flow processing widely applicable for the manufacture of active pharmaceutical ingredients. Additionally, the implementation of analytical techniques, high-throughput screening (HTS), computational modeling, artificial intelligence (AI), and machine learning (ML) fosters an interesting combination that promotes the development of continuous-flow automated platforms. This type of cutting-edge setup allows control of a vast portion of chemical space, optimizing time and resources and increasing efficiency in the chemical process. As proof of its relevance, the International Union of Pure and Applied Chemistry and US Food and Drug Aministration declared flow chemistry and continuous manufacturing as one of the top-ten emerging technologies and innovative tools to be considered in the pharmaceutical industry in 2019.

Together with this big development, planning and designing a more sustainable synthetic route is an additional challenge. In this sense, catalysis plays a key role in the synthesis of modern drugs, driving greener processes. In the past few years, chemists in organic synthesis laboratories have enthusiastically expanded the synthetic toolbox by developing protocols for visible-light photocatalysis, new catalysts for cross-coupling reactions, electrocatalysis, direct C–H bond activation, and late-stage functionalization to create libraries of potentially active compounds.

Among the above-mentioned tools, visible-light photocatalysis has great potential in the pharmaceutical industry because it uses extremely mild conditions (such as room temperature) and visible light as a clean and environmentally friendly reagent and has inherently broad functional-group tolerance and biocompatibility. In addition, electron-transfer and energy-transfer processes induced under visible light have allowed access to a wide range of chemical transformations that are highly desired in drug development, such as C–H functionalization,[1] the incorporation of fluorine atoms, or the generation of complex ring systems with the ability to introduce multiple $C(sp^3)$.[2,3] Moreover, photocatalysis can be successfully combined with other catalyses to achieve synthetic methodologies that are not possible with a single mode of catalytic activation. This versatility has allowed photocatalysis to work

[1]INFIQC-CONICET-UNC, Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, X5000HUA Córdoba, Argentina

[2]Discovery Chemistry, Janssen, Pharmaceutical Companies of Johnson and Johnson, Janssen-Cilag, S.A., Calle Río Jarama 75A, 45007 Toledo, Spain

*Correspondence: gabriela.oksdath@unc.edu.ar (G.O.-M.), jalcazar@its.jnj.com (J.A.)

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together with organocatalysis, transition-metal catalysis, and more recently biocatalysis[4] to explore and reach a broader chemical space.

With the implementation of continuous-flow technologies, photocatalysis has been completely favored in term of efficiency, productivity, and scalability. As such, photochemical transformations previously developed in batch are not the only ones that have improved. Because flow chemistry technology has the capacity to work easily within novel process windows, novel chemical transformations—otherwise unimaginable—can be successfully attained under continuous-flow conditions. As a consequence, photochemistry scientists are continuously developing new and more sustainable methods and even carrying out light-driven industrial processes for drug discovery.

Innovative chemical transformation and process design have been accomplished in this field. Recently, a high-throughput experimentation (HTE) platform combining photoredox catalysis, droplet microfluidics, and mass spectrometry analysis was developed. For instance, the late-stage radical trifluoromethylation of complex pharmaceutical intermediates was evaluated on a picomole scale, showing the impact of a HTS platform and photocatalysis implementation in drug discovery.[5] Indeed, the implementation of photocatalysis in continuous-flow devices (Figure 1) has shown such an advancement that today it is easy to think about the use of heterogeneous photocatalysts and their in-line recovery and recycling, two important features to consider for large-scale production.[6]

It is clear that photocatalysis and flow technology, being a versatile and highly valuable synthetic tandem, fit perfectly together to match industry needs. At this point, synthetic chemists are thinking in advance of the challenges to come and aiming to tackle the main issues of medicinal chemistry. With this goal, fluid communication between academia and industry is key to establishing new and more dynamic relationships. It should go beyond simple contract research contributions. Both partners should exchange critical knowledge and share interests in order to successfully achieve the desired objectives.

To reach this goal, funding and human resources training are crucial. The CHEM21 project from the Innovative Medicines Initiative (a European partnership for health) and American Chemical Society (ACS) Green Chemistry Institute (GCI) Pharmaceutical Roundtable (an organization established by the ACS GCI and global pharmaceutical companies) are two examples of consortia that were assembled for that aim. Focused on the implementation of green chemistry and green engineering in drug manufacturing, both intend to link academic research projects with the pharmaceutical industry. However, when it comes to funding for this type of project involving research groups in academia and industry implementing flow technologies, the role of governments is very important.

In this sense, establishing a sort of network specialized in catalysis research in collaboration with industrial partners could lead to faster progress in the field of drug discovery. Particularly, one of the challenges in the field of multi-catalytic systems is the ability to combine non-compatible transformations in a single and orchestrated performance. Thus, it is important to redesign the system and develop strategies focusing on green process intensification. In this regard, we wonder whether the development of new technologies would allow photocatalysis, along with other kinds of catalysis, to enable the discovery of novel chemical transformations that could have an impact on drug discovery.

B.P. and J.A. respond to the new challenges and benefits of collaboration between industry and academia

At Janssen Pharmaceutica, flow chemistry has been developed as a key tool for library synthesis to rapidly gain access to new chemical space with inreased Fsp^3 in drug-discovery projects. This implementation has been successful because the major collaborations between industry and academia have enabled methodologies beyond the usual reactions used in a medicinal chemistry setting. Since 1984, the landscape for library synthesis has not changed drastically. Only Suzuki-Miyaura, Sonogoshira, and Buchwald-Hartwig have been added to the reaction types used in the medicinal chemistry environment. It is of high importance to increase the diversity of possible transformations to explore more quickly the disposition of donor, acceptor, and hydrophilic and lipophilic groups to determine the interaction with the target and thus improve the potency toward the target.

The Negishi reaction has been identified as an interesting methodology for scanning $C(sp^3)$ motifs in drug-like molecules, and flow chemistry has been recognized as the enabling technology for this transformation. Open collaborations with different academic partners have been instrumental in implementing this chemistry in a medicinal chemistry setting. First, the collaboration with Universidad de Castilla La-Mancha and Katholieke Universiteit Leuven allowed the use of a silica-supported palladium catalyst for Negishi cross-coupling in a very efficient and sustainable way given that compounds were obtained in an almost pure state with metal contents at parts-per-billion levels. In parallel, a collaboration with Florida State University enabled the in-line formation of organozinc with the use of a column filled with Zn metal.[7] Both protocols were merged in a subsequent article demonstrating the value of the approach: $C(sp^3)$–$C(sp^2)$ coupling could be achieved with stable

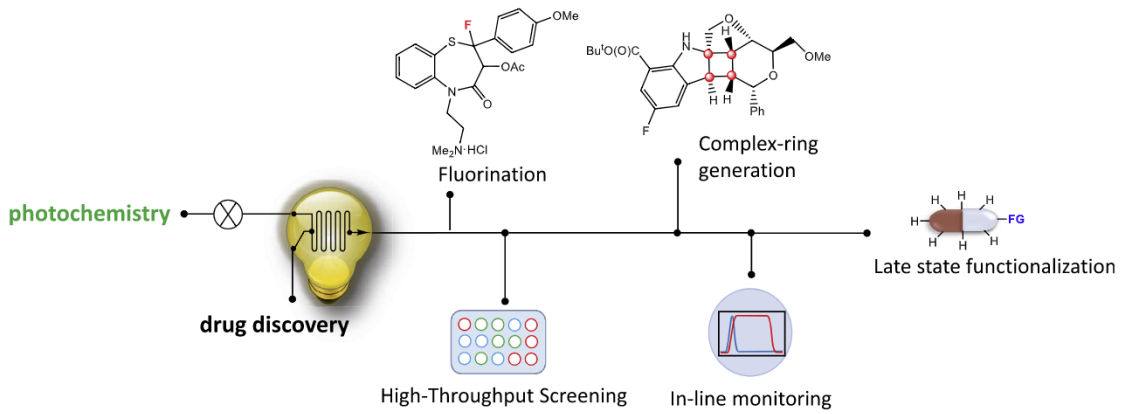

Figure 1. Schematic representation of continuous-flow photochemistry applied in the pharmaceutical industry

halogenated derivatives in a single step where the unstable organozinc reagent was formed and used *in situ*. All of these collaborations were critical to building up the methodology and finally implementing it in the drug-discovery process.[7]

Since the interest in photocatalysis increased, flow chemistry has been shown to be a key tool in the development of new photocatalytic transformations. Reproducibility of batch photochemical reactions tends to be difficult because of the attenuation of light as a function of distance, as described by the Bouguer-Lambert-Beer equation. Overirradiation can result in side products and complicate further isolation of the desired product. These limitations are dismissed in flow because all reactions are irradiated the same way as a result of the increased surface-to-volume ratio. To develop new transformations in flow, extensive collaborations have formed within the Photo4Future consortium, funded by the European Commission (MSC-ITN, project ID: 641861). An important finding came out of this collaboration: cross-coupling reactions can be accelerated by light by bimetallic interactions in the absence of any external photocatalyst. It was first discovered for the Negishi reaction catalyzed by nickel, where the formation of the nickel-organozinc complex absorbed light in the blue spectra and accelerated the reductive elimination step. Later, it was found that visible light also induced palladium-catalyzed Negishi cross-coupling by activating a Pd^0-Zn complex.[8] Another example of visible-light-promoted cross-coupling is the iron-catalyzed Kumada cross-coupling in flow, which was developed in collaboration with the Eindhoven University of Technology and the University of St. Andrews.[9] These findings expanded the scope of cross-coupling reactions and the possibilities for medicinal chemists to access novel chemical space.

More recently, our group has also been participating in the PhotoReAct consortium, funded by the European Commission (MSC-ITN, project ID: 956324), where the aim is to develop automated flow photochemistry as a key tool for library synthesis to increase fraction sp^3 and thus expand automated capabilities in a sequential fashion. As previously highlighted by Prof. Dr. G. Oksdath-Masilla, HTE is crucial for discovering new transformations on a smaller scale to identify novel transformations or optimized conditions. Pfizer was the first to report on an automated flow system that can screen 1,500 reactions in a day.[10] However, one of flow chemistry's main challenges is downscaling given that reaching a proper steady state is difficult. In this line, droplet microfluidics could play a crucial role in containing a slug and decreasing dispersion, as demonstrated by Stephenson and co-workers.[5] One of the first outcomes of this collaboration will be the development of the previously found PhotoNegishi reaction in library format to allow the reparation of diverse C(sp^3) libraries in flow and its combination with batch protocols for automated extraction and purification.

Still, there are many challenges ahead to be tackled, and collaboration between industry and academia will be mutually beneficial for overcoming them.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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