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Impact of continuous flow chemistry in the synthesis of natural products and active pharmaceutical ingredients

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ABSTRACT

We present a comprehensive review of the advent and impact of continuous flow chemistry with regard to the synthesis of natural products and drugs, important pharmaceutical products and definitely responsible for a revolution in modern healthcare. We detail the beginnings of modern drugs and the large scale batch mode of production, both chemical and microbiological. The introduction of modern continuous flow chemistry is then presented, both as a technological tool for enabling organic chemistry, and as a fundamental research endeavor. This part details the syntheses of bioactive natural products and commercial drugs.

Key words: Continuous flow, natural products, APIs, synthesis.

INTRODUCTION

The apothecary prepared his medications from natural sources, usually as a concoction of a complex mixture of compounds. Progress then brought in the production of isolated natural products, still as mixtures with occasional pure compounds. This approach is still the most common form of disease treatment throughout the world due to the much lower cost and greater availability of such medications, and obviously the direct use of the natural sources. Beginning in the 19th century, research labs and chemical companies had routinely begun to perform reactions and thus molecular modifications, with the intent of creating new compounds of increased social and commercial value. Discussions of important remedies viewed from the molecular aspect can be found in two very relevant textbooks, written by Corey et al. (2007), and Nicolaou and Montagnon (2008).

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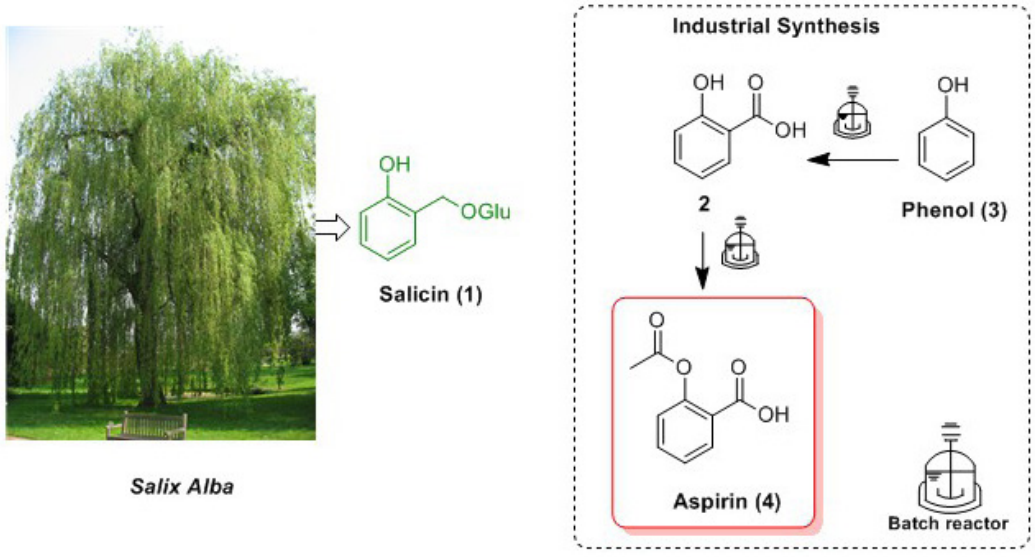
The case of aspirin (**4**) is a truly fascinating example, starting with the long-known activity of a crude weeping willow bark extract against several kinds of pain. These extracts contain salicin (**1**), and in the 19th century the conversion to salicylic acid was already well known, both compounds being recommended for treatment as a pain reliever. To reduce gastric acidity problems, the acetyl derivative of salicylic acid (**2**) was synthesized, becoming universally known as aspirin (**4**). Thus, the best known, most consumed and first synthetic drug was born, being accessible from phenol (**3**) and introducing the batch mode of performing organic reactions on a kilogram to ton-scale (Hafner et al. 2016) (Scheme 1). A very important aspect of the drug aspirin is its now well-known utility for the treatment of other health problems, and this approach is becoming very relevant.

The penicillin story starts with the serendipitous discovery by Fleming in 1928, and his decision not to clean or throw away the Petri dish, where the *Penicillium notatum* mold was destroying bacterial growths. However, this event passed almost unnoticed, the Second World War intervened and created an even bigger necessity for antibiotic medications. Thus, the isolation, structural identification of penicillin and the large-scale production, became multi-national endeavors. The culture of the *Penicillium notatum* microorganism leads to the large-scale production of natural penicillins, then fermentation transforms them into 6-aminopenicillanic acid (6-APA) (**6**), the starting material for the semi-synthesis of the many penicillin antibiotics available today (Scheme 2).

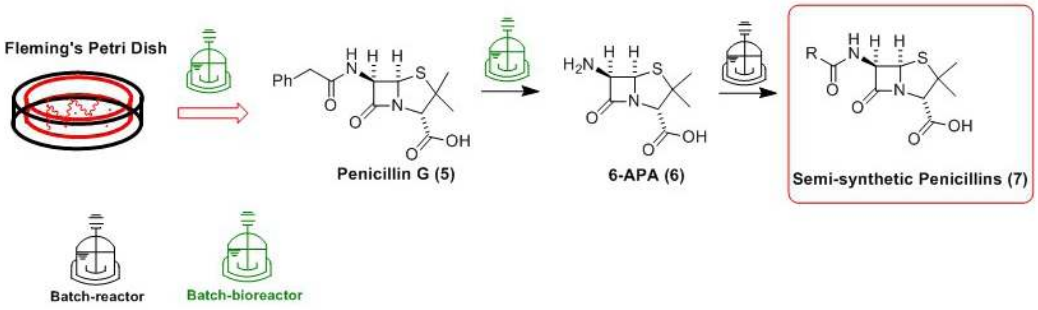
In the late 1940's and 1950's, steroid chemistry became very important due to Marker's discovery of a steroidal sapogenin (diosgenin (**8**)) found in the Mexican yam, its transformation into 16-DPA (**9**) and then progesterone (**10**) (Scheme 3) on a kilogram scale (Marker et al. 1947, perhaps the longest full paper to be published; DeCorte 2016). These two steroids thus became the starting materials for the large-scale production of corticosteroids and C-19 demethylated contraceptives (Hirschmann 1991) and the birth-control pill, and a social revolution provoked by a drug. The large-scale process development of both penicillin and cortisone (37 steps from cholic acid) were both performed at Merck, under the leadership of Tishler (Hirschmann 1991). The December issue of Steroids, 1992, volume 57, is dedicated to historical descriptions of the pharmaceutical industries endeavors in steroid chemistry. The steroid nucleus platform has also served as substrate for the discovery of many very important synthetic methodologies, a target for total synthesis, and the fundamental concepts of conformational analysis.

After the Second World War, the growing pharmaceutical industry began to look more seriously at totally synthetic molecules, as opposed to true natural products, their semi-synthetic derivatives, or molecules inspired or resembling natural products (analogues). The industrial building block era was then introduced, but with a strict preference for planar achiral hetero-aromatics: this is obviously a *strategic* copy of Nature, which has also always used a relatively small group of biosynthetic building blocks, but which are chiral enantiomerically pure, with many stereogenic centers, and not frequently hetero-aromatic. The present drug distribution based upon Nature or synthetic origins can be seen in the following Figure 1. We have simplified the groups of categories and rounded off the percentages, to be easier to analyze (based on Newman and Cragg 2016 and references cited therein).

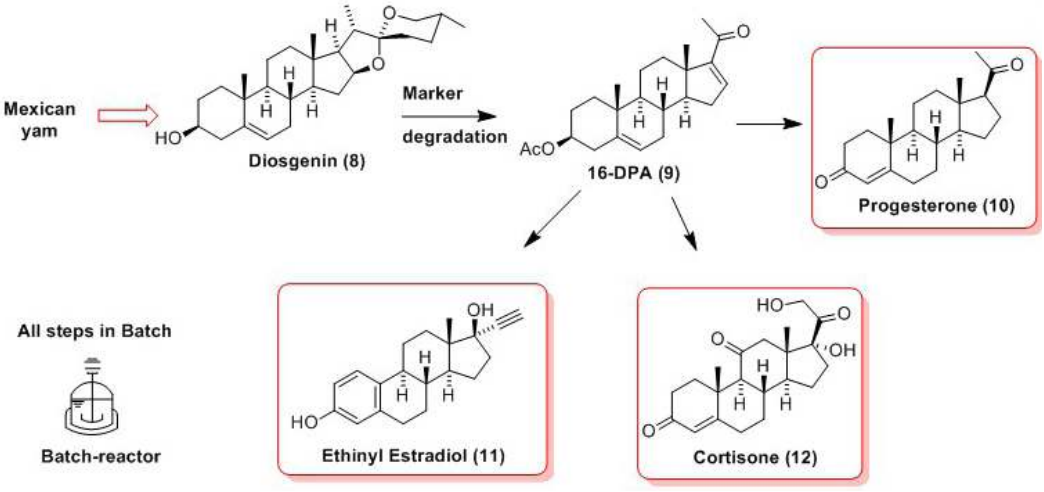
Useful examples of the totally synthetics are the erectile dysfunction drugs, introduced first with sildenafil (Viagra, Pfizer) in 1998, and then "honored" by the me-too imitations vardenafil (Levitra, Bayer), tadalafil (Cialis, Eli Lilly) and avanafil (Stendra, Vivus). The building block approach can be seen in the synthesis of sildenafil (Scheme 4) (Dale et al. 2000), and the four



Scheme 1 - The aspirin saga and the "first" synthetic drug.



Scheme 2 -The penicillin antibiotics.



Scheme 3 - From the Mexican yam to steroidal drugs and the birth-control pill.

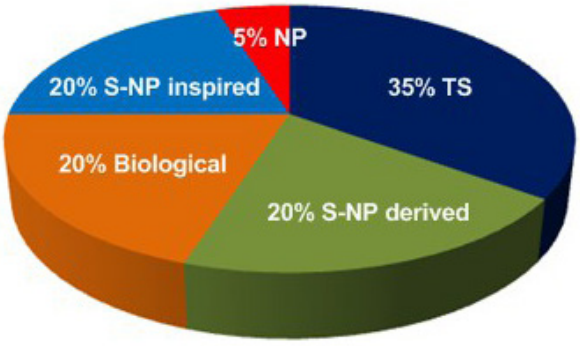


Figure 1 - Drug origins: TS, totally synthetic; S–NP inspired, synthetics inspired by NPs; S–NP derived, synthetics derived from NPs; Biologicals + vaccines; NP, isolated NPs.

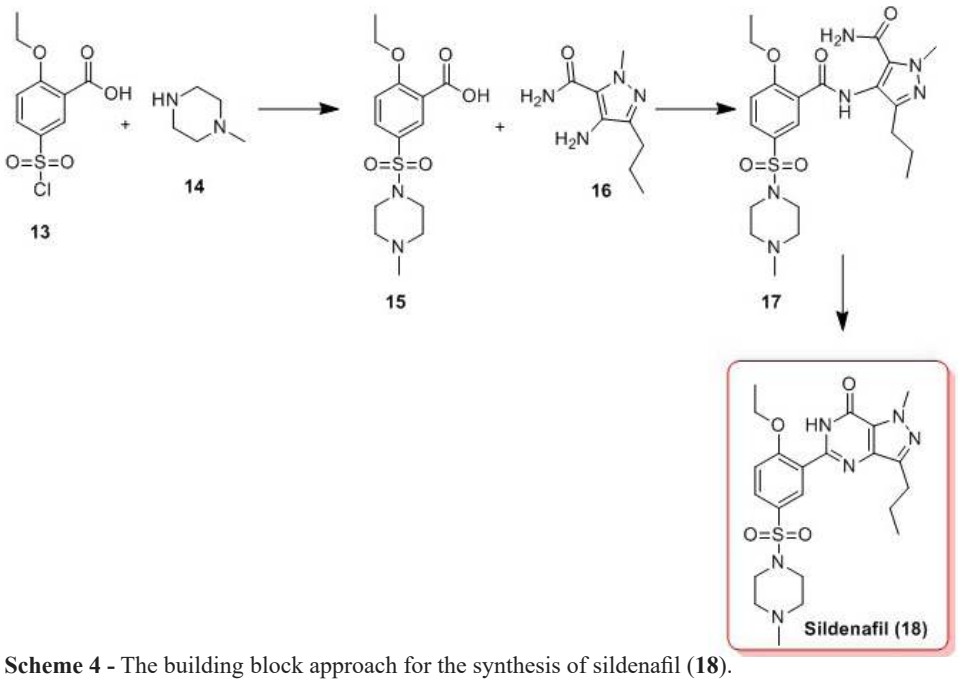
commercially available drugs can be structurally compared in Scheme 5.

Other drug highlights developed over the last 60 years include the statins, antivirals to treat HIV, anti-cancer medicines, immunosuppressants, and treatments for depression and anxiety, as exemplified in Figure 2. The so-called neglected or forgotten diseases, basically encountered in the southern hemisphere, have found more limited success only in the case of malaria (Figure 2). The Figures help to visualize the quite distinct molecular structures of natural product derived or totally synthetic drugs. Clearly, these structural differences lead to important synthetic variations and diverse chemical methodologies, and consequently practices of large-scale production. The conventional chemical transformations and the fermentation processes should be understood simply as being reactions conducted with different species of reagents, but requiring the very same capacities of organic chemists for their success.

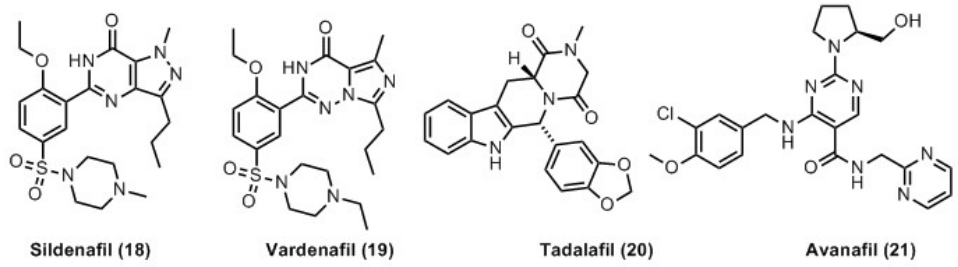
An important annual review of approved new drugs, as seen from the viewpoint of synthesis, has now reached year 2015 (Flick et al. 2017). We have reviewed the changing face of organic synthesis with special emphasis on the current century, dealing with natural products, synthetics and their use as drugs (Brocksom et al. 2015). The medicinal chemistry group (Holbrook and Garneau-Tsodikova 2017) designs and then synthesizes possible drugs (candidates, hits and leads) (Nadin et al. 2012) at the laboratory bench level (gram scale), then passes on to the process development group at the pilot plant level scale (up to kilogram scale), before eventually entering into commercial production on the ton-scale (Eastgate et al. 2017, Federsel 2009, 2013). All the drugs previously described are available worldwide on very large scales (up to hundreds of tons per year in some cases), usually produced in the batch mode.

After at least a century of accumulated experience in the fine chemical and pharmaceutical industries, the batch mode of production on a significant scale (at least multi-kilogram) is generally very effective. The batch reactor can be easily adapted to both chemical and microbiological reactions in the liquid phase, with addition, stirring, and extensive temperature and pressure variation facilities. The experimental conditions can be changed during use in the one-pot mode, being frequently multi-use for quite different reactions. The mechanics of the batch mode are difficult and laborious as far as the manipulation of reagents and solvents before, during and after the reaction, requiring highly qualified personnel. Next, the logistics become even more complicated with the necessity for transport to the separator, dryer, concentrator, precipitation and crystallization or other purification facilities.

These considerations have convinced process development and commercial production units of the necessity to investigate other equipment. The flow units in use industrially for many decades suggested modernization, with reduction in scale but with continuous operation to permit adequate production levels. This change brings many advantages in safety, economies of time, solvents, energy, equipment and space. The reaction parameters are more quickly optimized, on a much smaller scale with further economies, and principally safety. Without doubt, our chemical



Scheme 4 - The building block approach for the synthesis of sildenafil (**18**).



Scheme 5 - The totally synthetics sildenafil (**18**), vardenafil (**19**), tadalafil (**20**) and avanafil (**21**); a second social revolution?

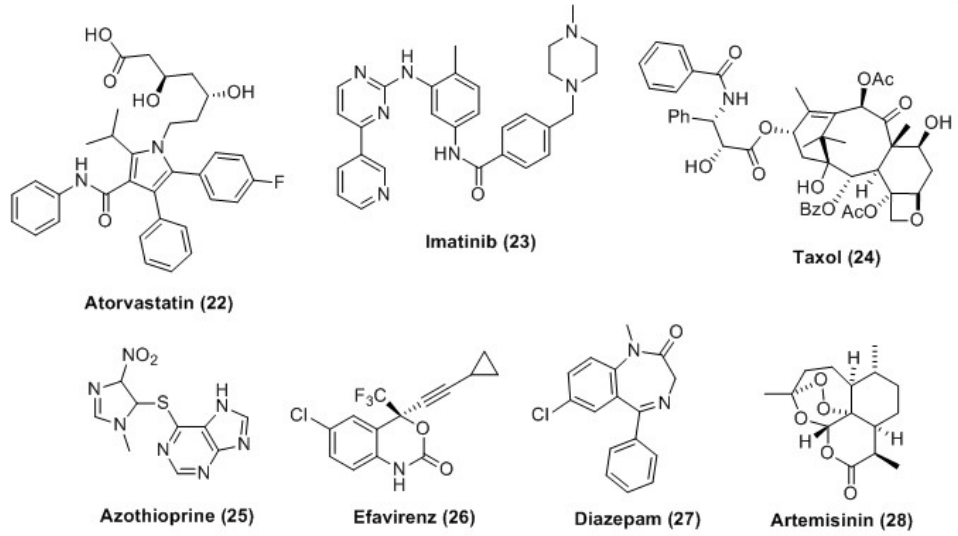


Figure 2 – Atorvastatin (**22**), imatinib (**23**), paclitaxel (**24**), azathioprine (**25**), efavirenz (**26**), diazepam (**27**) and artemisinin (**28**).

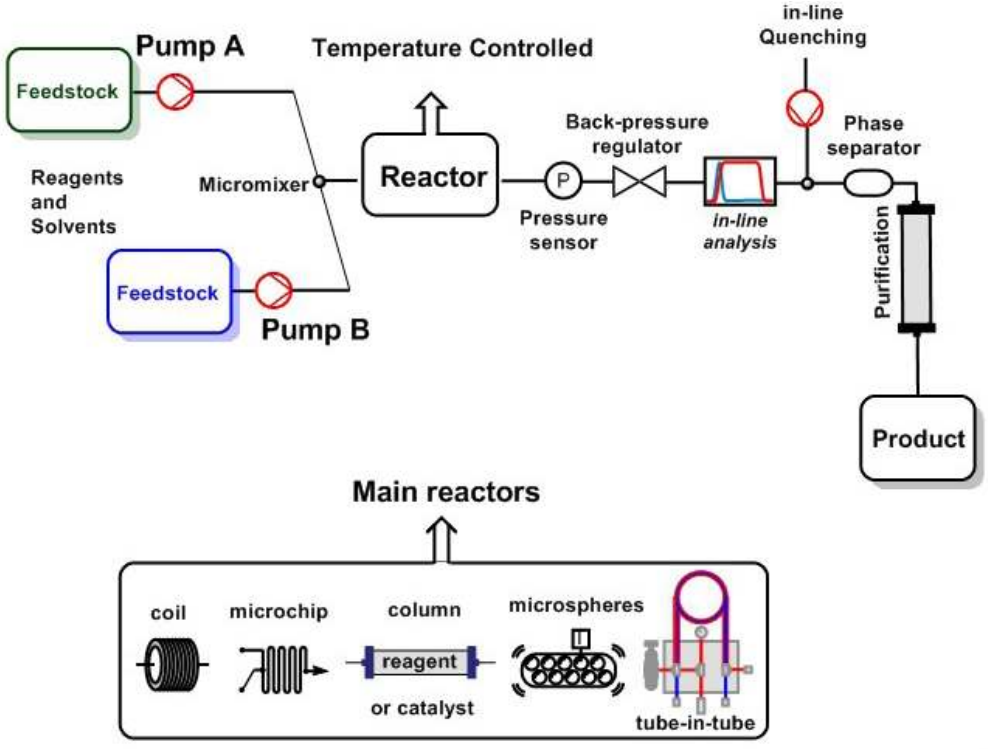
industries need less bad news on explosions, fires and environmental damage: certainly, flow chemistry (Hawkins 2015, Porta et al. 2016, Plutschack et al. 2017) is a very real solution as we will demonstrate in this review.

GENERAL REMARKS ABOUT CONTINUOUS FLOW CHEMISTRY

The use of continuous flow or simply flow chemistry, is not new in chemistry, but in the last 20 years it has spread to a much wider chemical community and found application for the production of many highly valuable intermediates and products (Plutschack et al. 2017, Gutmann et al. 2015).

A synthetic organic chemist works with round bottomed flasks (RBFs) where the scale-up of the optimized process is always a challenge due to the need for many additional adjustments of the reaction parameters. To overcome these and other experimental difficulties, continuous flow reactors can be used as apparatuses for optimization and process development in organic synthesis. Continuous flow reactors are devices in which synthetic transformations take place in a continuously flowing stream within structures with general lateral internal dimensions from 1/16 to 1/8 inches. Several different types of flow reactors are commercially available, and customization to a desired process is generally needed depending on the reaction characteristics (Scheme 6) (Plutschack et al. 2017).

A general continuous flow chemistry set-up is presented in Scheme 6 where the reagents are separately pumped through a micromixer into the reaction zone (reactor). The reaction zone is temperature controlled and can be customized in order to meet the reaction needs in terms of length and reactor type, such as: coils (polytetrafluoroethylene (PTFE), perfluoroalkoxy (PFA), stainless steel, among others), microchips, fixed-bed reactors, agitating microsphere reactors and tube-in-tube reactors. Among the reactors cited



Scheme 6 - General scheme for a continuous flow set-up.

above, tube-in-tube is a very interesting alternative for gas-liquid reactions involving CO_2, H_2, O_3, NH_3 among others (Pastre et al. 2013c). This special type of reactor called "tube-in-tube" (TIT) generally comprises a 1.0 mm o.d. / 0.8 mm i.d. Teflon AF-2400 permeable tubing inside a PTFE or stainless-steel tube (3.18 mm o.d. / 1.59 mm i. d.). With the TIT reactor, a gas can be pressurized in the inner (or outer) tube and diffuse to the other tube where the reaction mixture is passing through. After the reaction zone, a back pressure regulator is normally installed giving the opportunity to tune the reaction pressure to the desired value. This allows researchers to explore reaction conditions not possible in the batch set-up, such as heating organic solvents at much higher temperatures then their boiling point. As shown in Scheme 6, in-line reaction analysis is also possible by the use of FT-IR, HPLC, NMR, MS and/or UV-Vis, as well as quenching and purifications, allowing a researcher to begin with the crude starting material and arrive at the purified product in a telescoped protocol (Plutschack et al. 2017, Movsisyan et al. 2016, Reizman and Jensen 2016)

The advantage of using flow reactor technology, in most cases, is directly related to the size of the reactor, which can achieve a series of properties unreachable in batch reactor conditions. Therefore, the major advantages for using continuous flow conditions (Noël et al. 2015, Hartman et al. 2011, Elliott et al. 2016) are:

- Rapid and efficient mixing of reactants;
- Efficient heat transfer;
- Low operating volumes;
- High temperature and pressure conditions;
- High concentrations or no solvent;
- Inherently safer than batch (Alves et al. 2015);
- Inherently greener;
- Easily scaled-up (e.g. by numbering up – parallel processing or process intensification);

Regulation of many parameters such as heat and mass transfer, mixing and residence times is much improved in comparison with related batch processes. Mixing describes the way in which two or more phases come together and become intertwined. Batch and flow reactors exhibit different mixing mechanisms, where tube reactors inherently have much smaller diffusion times and achieve mixing much faster (higher surface to volume ratio, Figure 3) than in batch. This, in combination with reaction kinetics will determine if flow conditions are beneficial, based, most of the time, on the reaction Reynolds numbers (R*e*) (Plutschack et al. 2017).

Furthermore, some batch processes pose operational hazards, particularly with the use of highly reactive reagents. These hazards can be diminished under continuous flow conditions due to increased temperature control and short residence times. Most importantly, since the size of the reactors is very small, the amount of hazardous reagent or intermediates in an operation is minimal, increasing further the safety of the process (Hessel et al. 2013). Although the instant scale is relatively small, the continuous operation over many hours

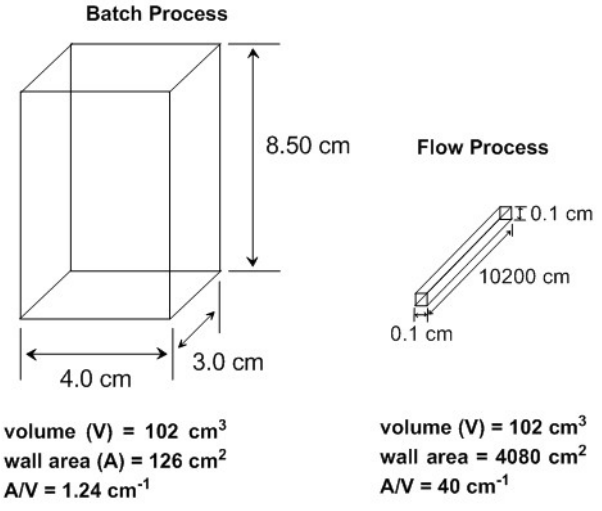


Figure 3 - Surface to volume ratio, Flow *vs* Batch reactors.

produces much improved quantities (STY = space time yield = grams-tons per hour or day).

Scale-up under continuous flow conditions can be performed by two different approaches, in a different design when compared to the batch process:

1) by scaling-up with increased reactor size, without losing microfluidic characteristics, using longer coils and higher flow rates;
2) by numbering-up or scaling-out, a common strategy in continuous-manufacturing where several smaller reactors work in parallel towards a common product (Su et al. 2016 and Kuijpers et al. 2017);

Thus, we can summarize continuous flow chemistry as a real revolution of the present and future in the way to perform chemical synthesis in machine-assisted processes. Telescoped flow chemistry also has a further advantage which permits the combination of "incompatible" reactions. Large scale continuous flow protocols are not new in chemical engineering. However, the last 20 years has established this approach as a consistent enabling technology for chemical transformations.

NOVEL PROCESS WINDOWS (NPWS)

Enabling technologies allow the execution of many "impracticable" reactions, mainly on the industrial scale by processes intensification (PI). In this context, PI has become a concept of great relevance, since it aims to develop more sustainable and environmentally friendly processes. This concept was introduced by Ramshaw (1999), and then Stankiewicz and Mouljin defined this as the use of new equipment or techniques which promote a significant improvement of production processes on a large-scale. This leads not only to smaller plants but also to significant reduction of energy consumption and waste, resulting in cheaper and greener processes (Stankiewicz and Mouljin 2000).

Therefore, the Novel Process Windows (NPWs) concept emerges as the use of new equipment, micro/macro reactors and reaction conditions to perform chemical transformations in a vigorous, but completely safe and scalable manner (Hessel et al. 2008, 2013, Stouten et al. 2013, Illg et al. 2010) (Figure 4).

The NPWs concept is quite recent, first introduced in 2005 by Hessel, but only in 2009 named as NPWs (Hessel et al. 2005, Hessel 2009). Different from the PI and micro-process technologies, which are capable of increasing mass and heat transfer in reactions with defined kinetics, NPWs aim to accelerate the rates and drastically reduce the reaction time by applying pressurized and superheated conditions. Therefore, the kinetics of the reaction can be completely exploited changing the reactivity of the substrates and maintaining their selectivity at an acceptable level with increase in productivity (Hessel et al. 2011, 2015). In general, NPWs encompass reaction conditions that are far from conventional laboratory practices such as the use of high pressures (p), high temperatures (T), high concentrations (c) or even solvent-free, and reactions that occur on an explosive regime, which make possible the attainment of new chemical transformations (Razzaq and Kappe 2010).

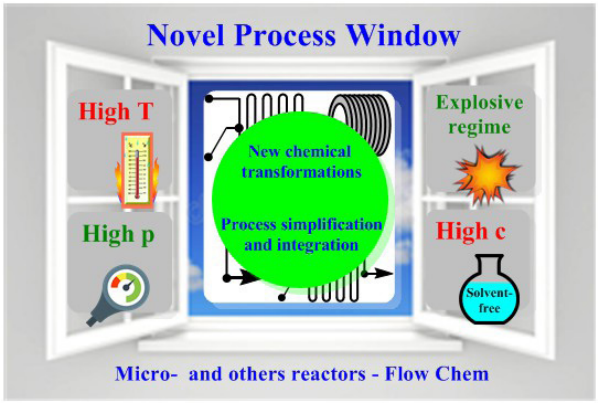


Figure 4 - An overview on Novel Process Windows (NPWs).

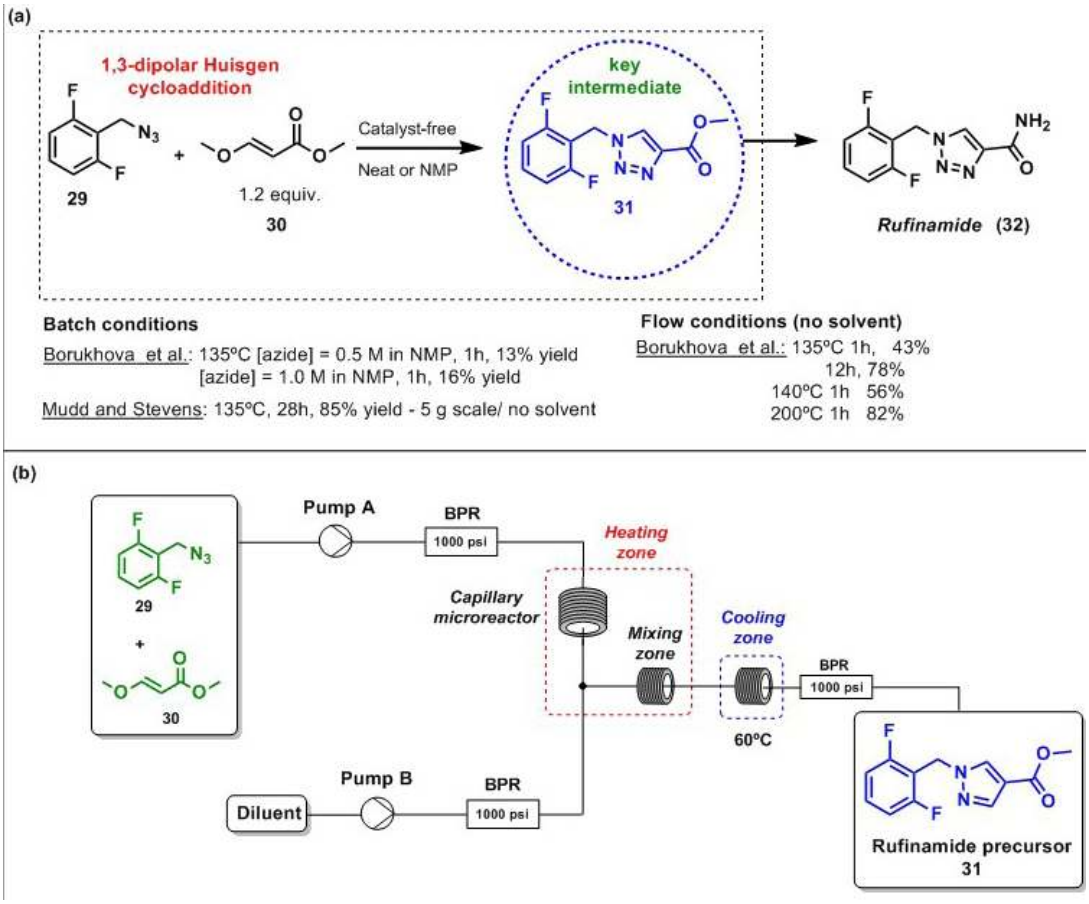
DRUGS OBTAINED UNDER SUPERHEATED PROCESSING (HIGH T) AND SOLVENT-FREE CONDITIONS (HIGH C)

Rufinamide (**32**) (Scheme 7) is an antiepileptic drug containing a 1,2,3-triazole moiety and is among the best-selling five-membered heterocyclic pharmaceuticals developed by Novartis (2004) and manufactured by Eisai (Inovelon® and Banzel®) (Baumann et al. 2011a, b).

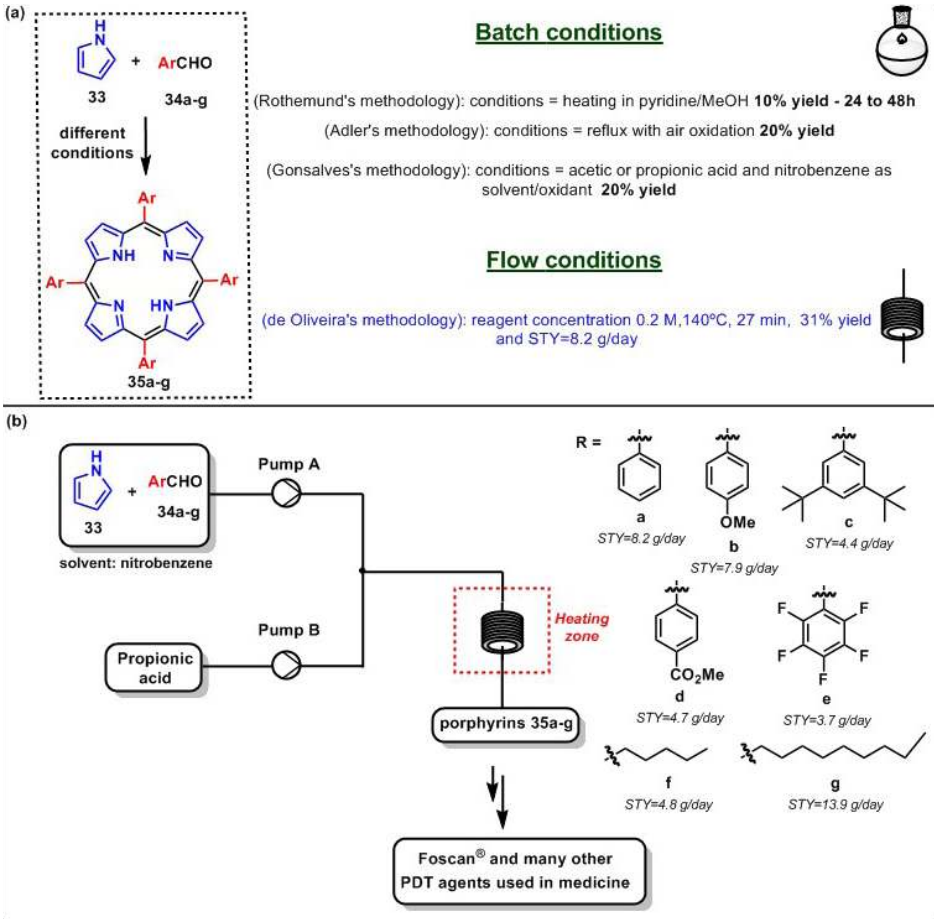
The key intermediate **31** can be obtained by a 1,3-dipolar cycloaddition reaction (Scheme 7a) (Mudd and Stevens 2010). Hessel and coworkers (Borukhova et al. 2013) have shown that in batch experiments, a rapid decrease in reaction rate under diluted homogeneous reaction conditions was observed. Therefore, the solvent-free protocol under continuous flow conditions was preferred to attain a higher reaction rate (Scheme 7b). At 200 °C the intermediate **31** was obtained in 82% yield.

Recently, NPWs have been exploited in porphyrin synthesis (Scheme 8). These dyes are natural or synthetic compounds which present relevant physical and chemical properties and numerous applications as photocatalysts, dye-sensitized solar cells, sensors, molecular electronics, non-linear optics and in medicine, especially with regard to photodynamic therapy (PDT) for some cancers treatments (de Oliveira et al. 2015, Barona-Castaño et al. 2016).

De Oliveira and coworkers investigated the one-pot synthesis of *meso*-tetraarylporphyrins and *meso*-tetraalkylporphyrins under continuous



Scheme 7 – Rufinamide (**32**) synthesis: (a) Solvent- and catalyst-free Huisgen cycloaddition between **29** and **30**. (b) Schematic representation of the microcapillary assembly.



Scheme 8 - a) Comparison of the most common tetraphenylporphyrin (**35a**) syntheses in batch and flow conditions. **b**) Set-up for the one-pot **35a** synthesis under continuous flow conditions.

flow conditions, and demonstrated improvements and a multi-gram-scale protocol. A safe scale-up, cost-competitive and reproducible protocol was achieved (Momo et al. 2015).

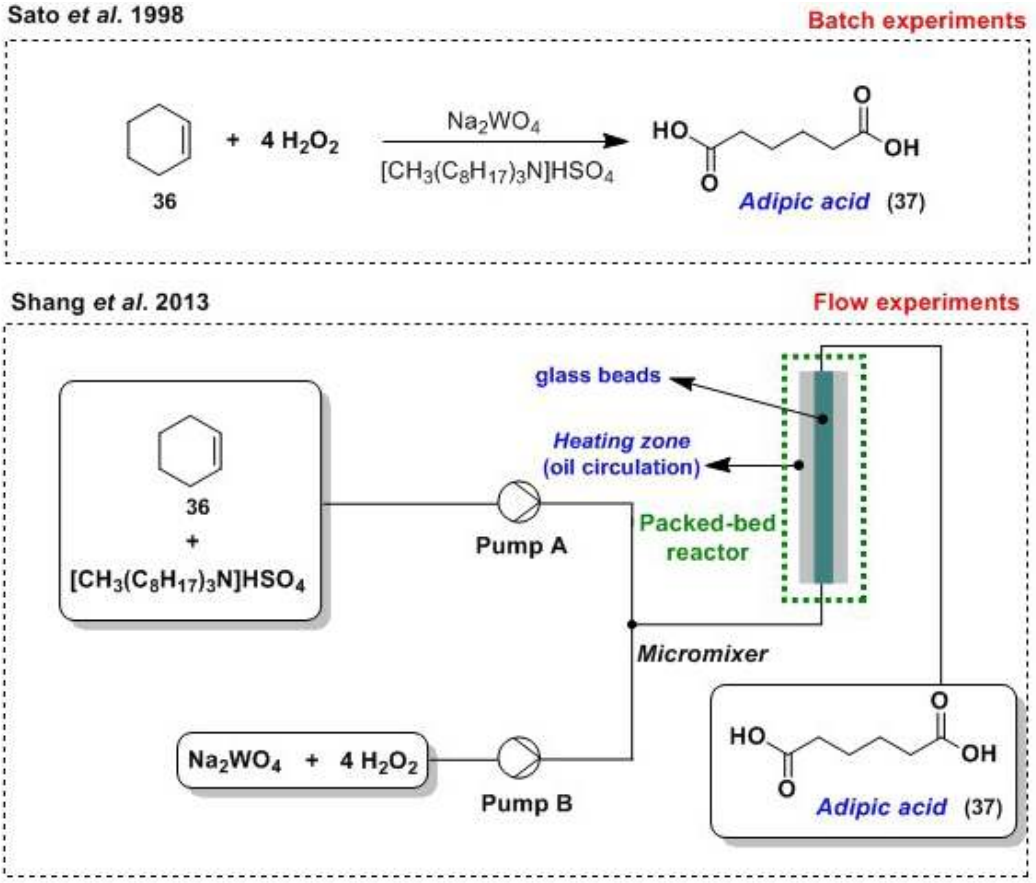
NEW CHEMICAL TRANSFORMATIONS

A relevant example of NPWs for new chemical transformations is the adipic acid synthesis from cyclohexene by Hessel and coworkers (Shang et al. 2013). From an industrial perspective, this is the most important dicarboxylic acid in use as about 2.5 billion kilograms of this compound are produced annually, mainly for nylon-6,6 production (Musser 2005, Castellan et al. 1991).

Different from other methods described in the literature (Davis 1985), which present N_2O as byproduct, Hessel and coworkers studied the direct cyclohexene (**36**) oxidation by hydrogen peroxide. Adipic acid (**37**) is produced by means of a packed-bed microreactor in continuous flow (100 °C), using $Na_2WO_4 \cdot 2H_2O$ as catalyst and $[CH_3(n\text{-}C_8H_{17})_3N]HSO_4$ as a phase transfer without solvent addition. This process is based on a Noyori group seminal publication (Sato et al. 1998) (Scheme 9).

HIGH TEMPERATURE/PRESSURE PROCESSING - (HIGH -T/P)

Several methodologies that lead to the oxidation of 2-benzylpyridines to the corresponding benzoyl derivatives have been reported (Crook and McKelvain 1930, Akhlaghinia et al. 2012, Zhang et al. 2009, Nakanishi and Bolm 2007). Houwer et



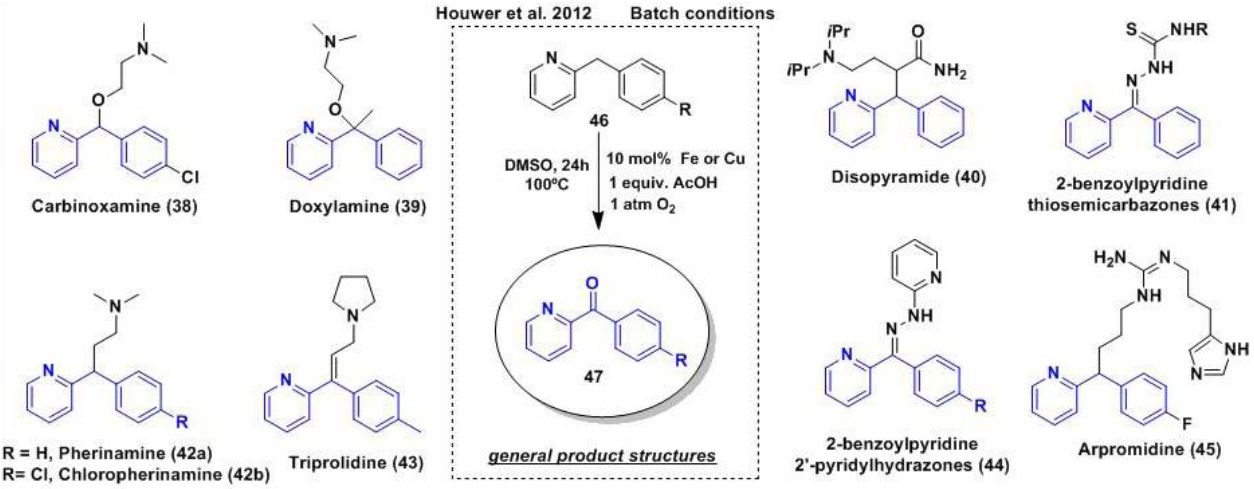
Scheme 9 - Adipic acid (**37**) synthesis – Set-up of the packed-bed reactor.

al. (2012) discovered that this oxidation can also be carried out using molecular oxygen in the presence of catalytic amounts of iron or copper salts in combination with acetic acid as additive. The ketones obtained as result of this transformation, can be used as building blocks for API synthesis, including the antihistamines, antiarrhythmic agents and others (Houwer et al. 2012) (Scheme 10).

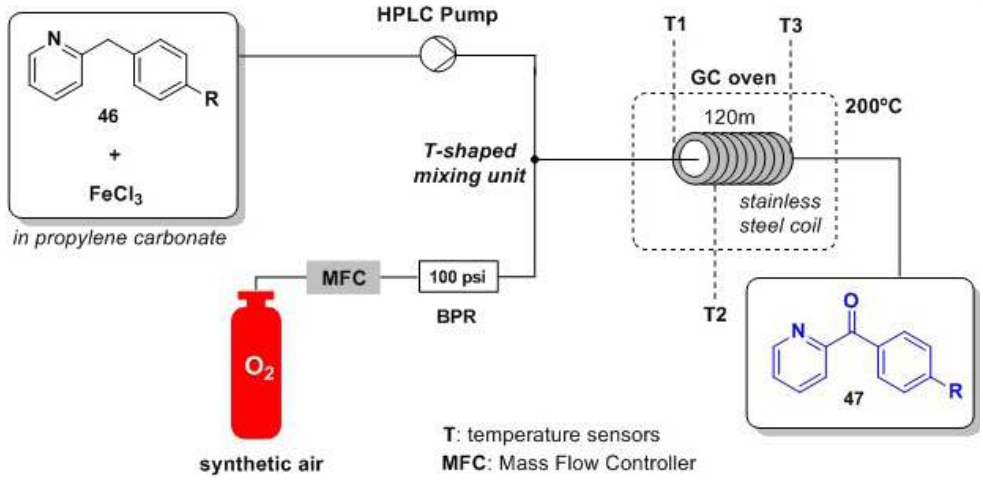
Kappe and coworkers have described a gas–liquid continuous flow protocol for this 2-benzylpyridine oxidation (Scheme 11), using propylene carbonate as a solvent instead of DMSO, providing several advantages of the NPWs concept such as high-T/p (Pieber and Kappe 2013). The authors detected limitations for the temperature when working with aprotic polar solvents such as NMP or DMSO in a continuous flow regime, which makes propylene carbonate a very attractive alternative (b.p. 242 °C).

Jamison and coworkers reported the use of high-T/p continuous conditions for β-amino alcohol formation by using an epoxide aminolysis in the synthesis of metoprolol and indacaterol. Drugs such as Oxycontin®, Coreg® and Toprol-XL® present this functional group pattern, and other drugs such as Zyvox® and Skelaxin® feature oxazolidones which can have amino alcohols as precursors (Scheme 12) (Bedore et al. 2010, Bergmeier 2000, Desai et al. 2007).

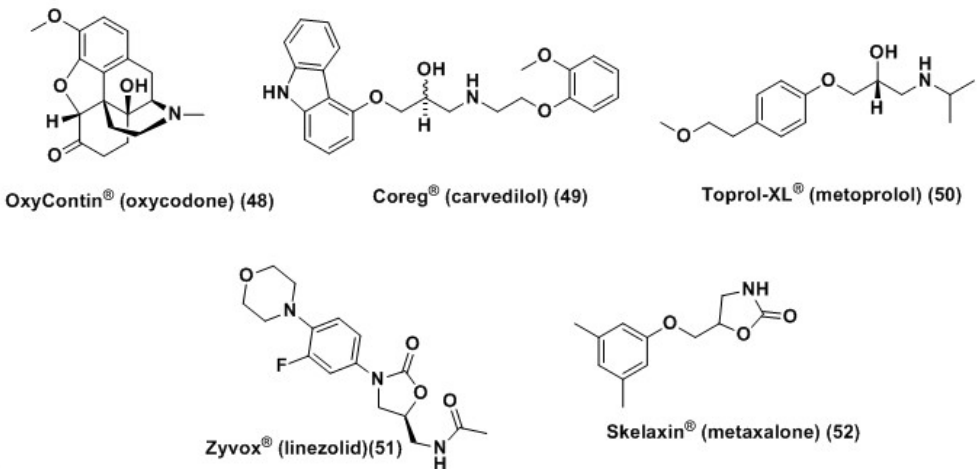
The synthesis of metoprolol (**55**) in a microwave (MW) batch or under continuous flow conditions is summarized in Scheme 13. The microreactor



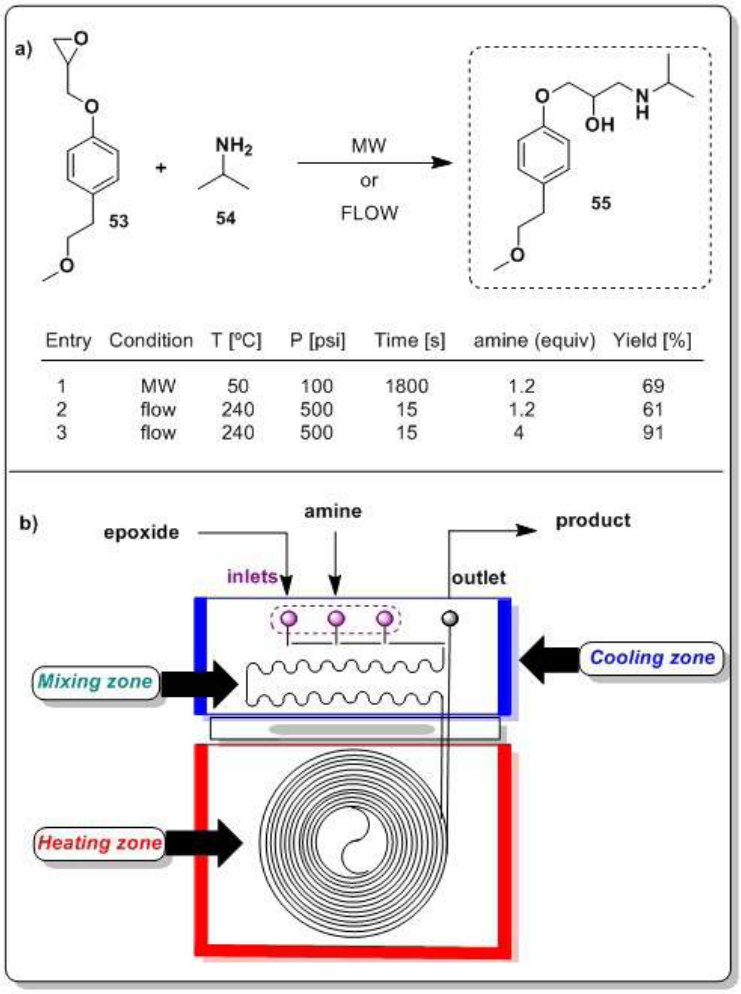
Scheme 10 - Metal catalyzed molecular oxygen oxidation of 2-benzylpyridines, and some important intermediates for API synthesis.



Scheme 11 - Set-up of the gas–liquid continuous flow reactor used by Pieber and Kappe.

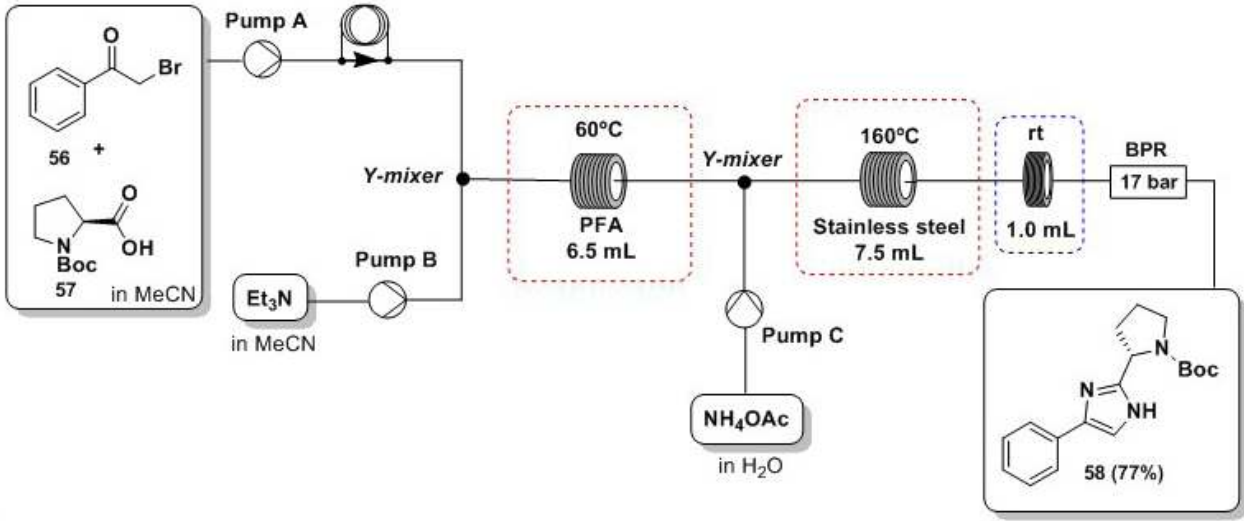


Scheme 12 - Pharmaceutically relevant compounds having β-amino alcohol moieties.



Entry	Condition	T [°C]	P [psi]	Time [s]	amine (equiv)	Yield [%]
1	MW	50	100	1800	1.2	69
2	flow	240	500	15	1.2	61
3	flow	240	500	15	4	91

Scheme 13 - **a**) Metoprolol (**55**) synthesis – comparison between microwave (MW) and flow conditions. **b**) Flow chemistry set-up.



Scheme 14 – Set-up for the 1*H*-4-substituted imidazoles synthesis in continuous flow conditions and high*T*/*p*.

working at high-T (240 °C) and high-p (500 psi) resulted in high yields with residence times of about 15 seconds.

Eli Lilly described a continuous flow process for the high-T synthesis of 1*H*-4-aryl imidazoles in 2012 (May et al. 2012). After this, Kappe and coworkers achieved a machine assisted process intensification synthesis under high-T/p of 1*H*-4-substituted imidazoles, using α-bromoacetophenones and α-aminoacids as starting materials (Scheme 14). Such imidazole derivatives are key building blocks in the synthesis of NS5A (a viral phosphoprotein) inhibitors, highlighting daclatasvir (**62**) as an important drug for hepatitis C (HCV) treatment (Carneiro et al. 2015). The two-step continuous flow protocol described by Kappe et al. afforded the imidazoles with residence times of about 4-10 min (Scheme 14), and daclatasvir (**62**) (Scheme 15) again demonstrating a very relevant application of the methodology.

Fülöpa and coworkers reported an oxidative homo-coupling of aniline derivatives to azobenzenes in continuous flow high-T conditions (Scheme 16). Approaches to azobenzenes typically require vigorous or special reaction conditions (e.g. the use of strong oxidizing agents, strong inorganic bases or acids), which often lead to extensive byproduct formation and low yields (Georgiádes et al. 2015). Therefore, a simple flow reactor was assembled having as the key element a heated cylindrical column charged with copper powder for the oxidative coupling (Scheme 16).

Kappe and coworkers reported a scaled-up synthesis of 4-aryl-2-butenones under continuous flow conditions, which produces Nabumetone (**67**), a nonsteroidal anti-inflammatory drug (NSAID) known as Relafen® or Noracet® (Scheme 17) (Viviano et al. 2011).

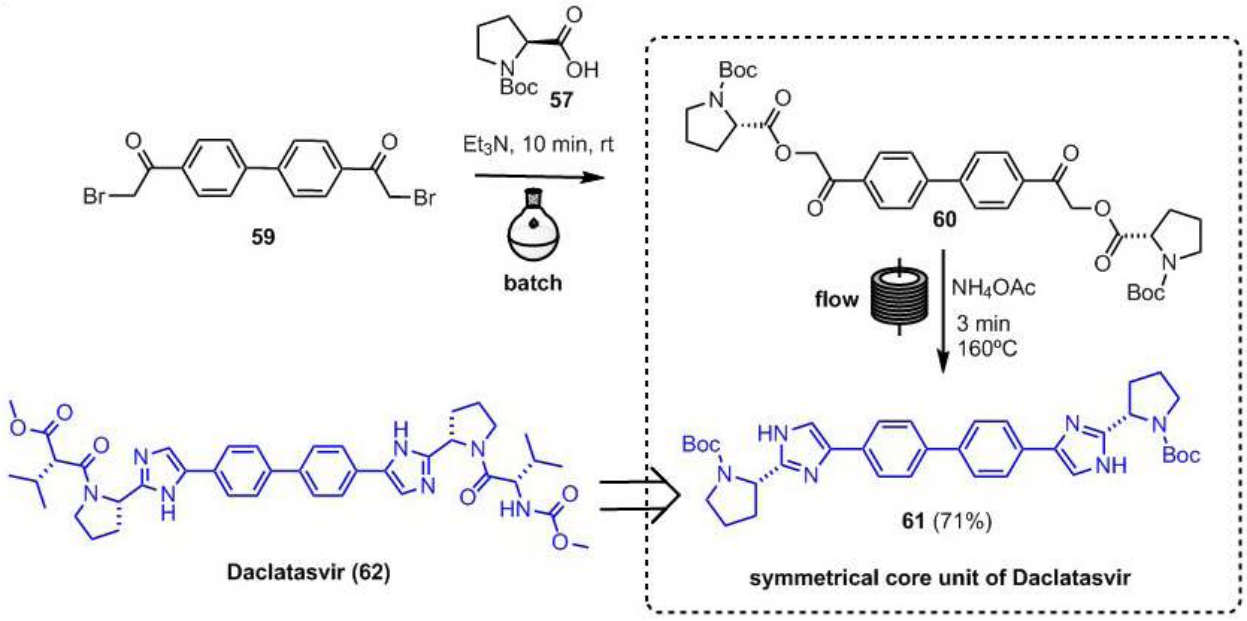
In the flow experiments, a "two-feed" concept was adopted and the organic stream containing the aromatic aldehyde in acetone was pumped separately and mixed with the aqueous NaOH stream. Assuming a one-hour processing time for the cross-condensation of *p*-anisaldehyde (**65a**) at 120 ºC and 1 min residence time a throughput of ~40 g of **67** per hour can be calculated. When it comes to the large-scale aldol condensation, a mesofluidic flow set-up was designed with one/two feed modules, which enables a multipurpose functionality to continuous flow plants. The optimized overall reagent flow processing was 2.4 kg/h which corresponds to 0.35 kg/h of product. When a 4.65L reaction mixture was processed at 120 ºC, 1.75 kg/h of product was obtained (Scheme 18).

The selective reduction of the products **66** double bond to obtain compounds such as **67** in 90% yield was also performed under continuous flow conditions, employing a fixed-bed catalyst at temperatures up to 100 °C and 100 bar of hydrogen pressure.

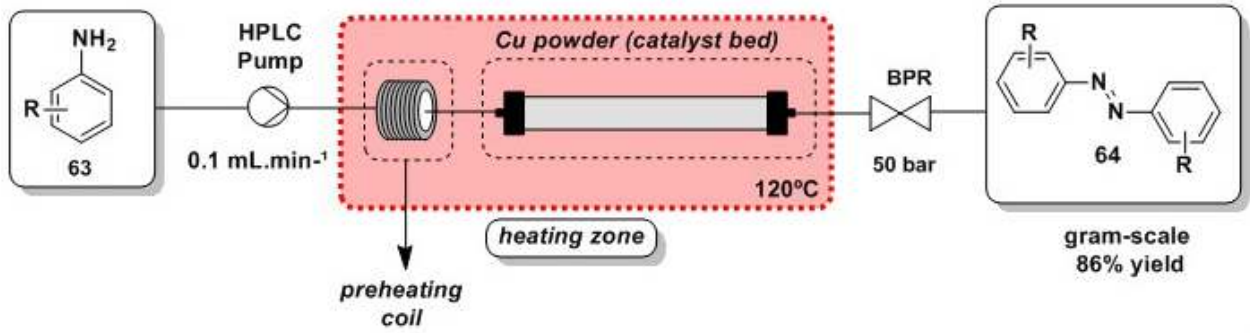
In general, NPWs have allowed many improvements in continuous flow protocols, and opened up several possibilities to discover and perform new reactions. There are many conditions to be explored under more extreme conditions, particularly when it comes to "forbidden" and "forgotten" chemical reactions.

PHOTOCHEMICAL REACTIONS AND CONTINUOUS PHOTO-FLOW PROCESSES

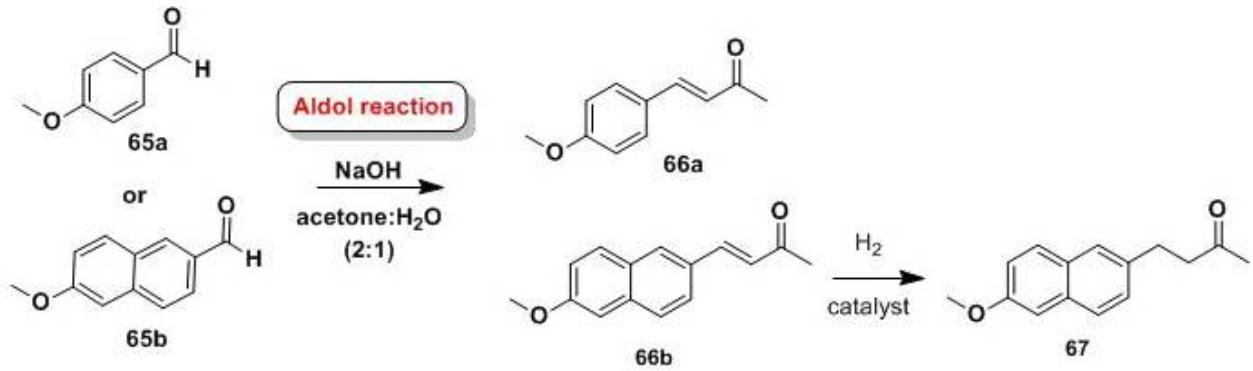
Photochemical transformations have regained a new perspective in organic synthesis since they started to be performed in continuous flow conditions. Many old and inefficient photochemical processes have been revisited since a number of technical limitations have been solved by machine-assisted protocols. Recently, the efficiency of these reactions has been significantly improved under continuous flow conditions compared to batch due to homogeneous light irradiation allowed by the use of polymer tube reactors (PFA, FEP). In batch conditions, a number of limitations prevent



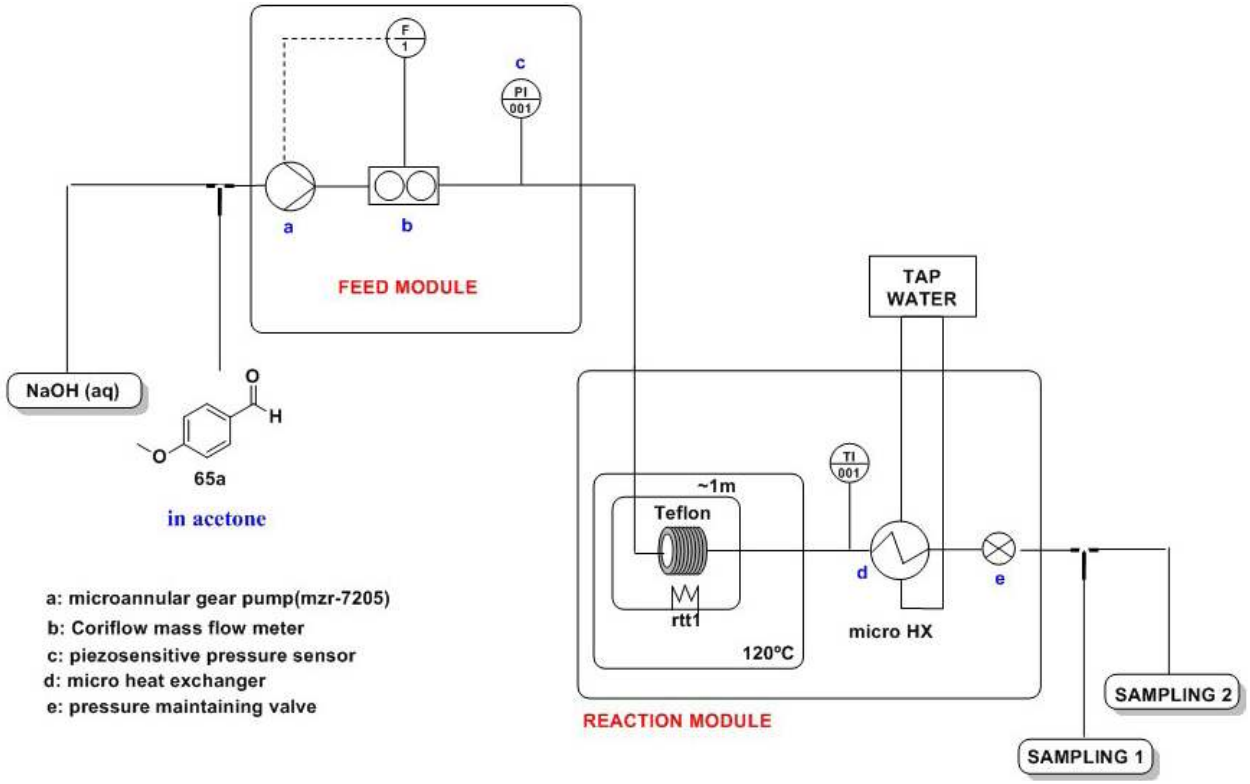
Scheme 15 - Bisimidazole **61** synthesis - symmetrical core unit of daclatasvir (**62**).



Scheme 16 - Set-up for the copper-catalyzed continuous flow couplings of aniline derivatives.



Scheme 17 - Synthesis of 4-aryl-2-butanones – Nabumetone (**67**).



Scheme 18 - Flow-plant system for aldol condensations.

efficient photochemical reactions or photocatalyzed processes when using UV irradiation and common borosilicate glassware, due to UV light absorption. In addition, high dilutions are frequently necessary to avoid the excess of by-products occasioned by the intrinsic non-homogeneous batch-irradiation with the light penetration diminishing in *ca* 90% after 5-10 mm of light pathway (Su et al. 2014, Cambié et al. 2016, Nöel et al. 2017). Under continuous flow conditions these problems can easily be solved by using falling film plates or long length fluoropolymer tube reactors (regularly 1/16 or 1/8 inch I.D. x 10-100 m) with multidirectional light irradiation inside the reactors (Figure 5).

Both numbering up (Su et al. 2016, Kuijpers et al. 2017) and process intensification of the photoreactors has allowed the scale up of many key molecules for the pharmaceutical industry (Cambié et al. 2016). Another important advantage of continuous conditions in photochemical reactions is related to safety. Since small amounts of reagents and solutions are continuously irradiated, very unstable or explosive intermediates can be produced with no incidents, such as endoperoxides and organic peroxides (Lévesque and Seeberger 2012, de Oliveira et al. 2016).

It is important to highlight the relevance of temperature-control in photochemical processes, mainly in photocatalyzed reactions which depend on the efficiency of the photocatalysts. In this case, it is well known that the triplet lifetime of photosensitizers can be strongly diminished at temperatures above 0 °C, impairing the efficient collision between the substrates and excited photosensitizers in both energy and single electron transfer processes. This factor is important in batch photochemical reactors, making them quite expensive. Now, continuous flow tube reactors are easily temperature-controlled thus keeping high levels of light irradiation with the use of LED light

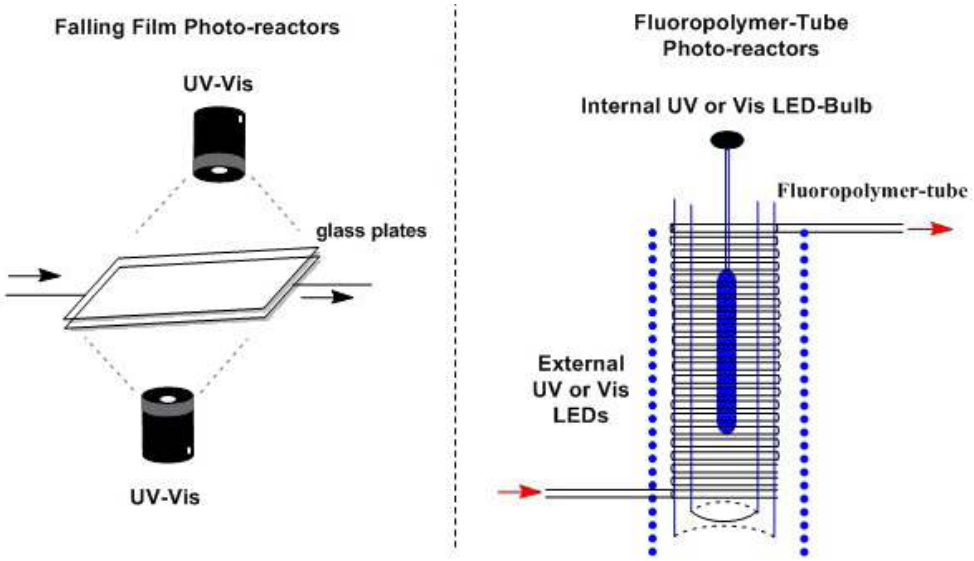


Figure 5 – The two main flow-photoreactor types.

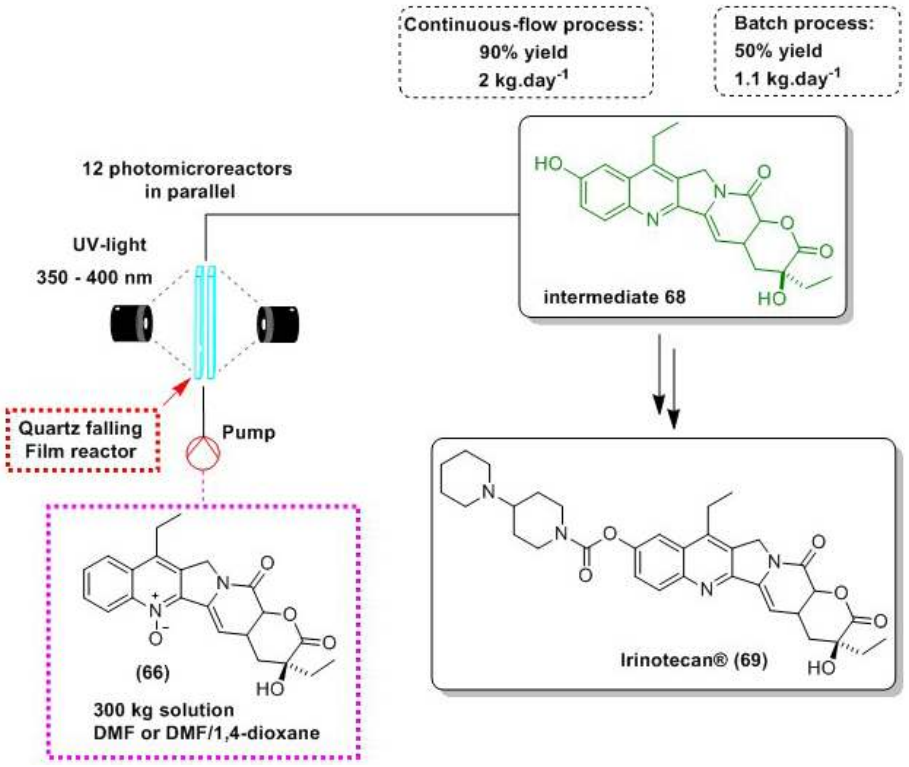
sources, which cover the ultra-violet to visible light regions with high energy efficiency and low heat dissipation. Considering all these advantages provided for continuous flow conditions, modern photochemical protocols have been improved for safety, reproducibility, minor dilutions, better selectivity, scalability and shorter reaction times, opening up new opportunities for research in both industry and academia (Matthew et al. 2010, Noel et al. 2017).

PHOTO-FLOW PROCESSES IN API SYNTHESIS

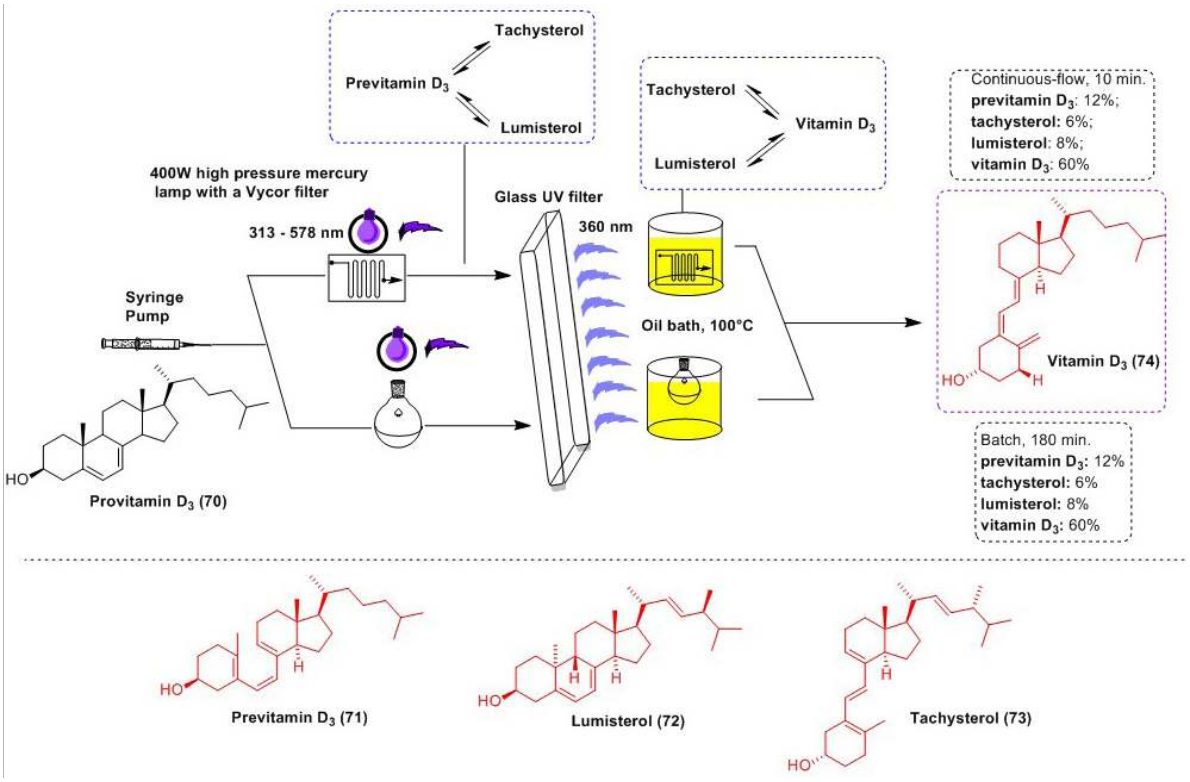
A significant industrial photochemical process was developed by Heraeus Noblelight (Germany) in which a very efficient falling film photoreactor was built and dedicated to the synthesis of the main reaction intermediate **68** of the anticancer drug camptothecin, commercialized as the medicine Irinotecan® (**69**) (Scheme 19). The annual demand of **69** is 1 ton and the capacity of this continuous flow plant is 720 kg.year^{-1}, thus supplying almost all the demand for rearranged intermediate **68** (Oelgemöller and Shvyndkiv 2011). In addition, the previously developed batch protocol involved a concentration 6 times lower than in the continuous protocol and gave only 50% yield. Under continuous flow the intermediate **68** was obtained in 90% yield, showing a relevant example of industrial improvements promoted by continuous photo-flow conditions. The Oelgemöller and Shvyndkiv (2011) review the original reference do not attempt to explain the transformation of **66** to **68** (Scheme 19).

Vitamin D_3 (**74**) is an important example of a valuable API for the pharma industry. This compound is responsible for several metabolic and immunity regulations and can be obtained from provitamin D_3 (**70**) (Scheme 20). In 2010, Takahashi and co-workers reported the synthesis of vitamin D_3 (**74**) combining batch and two-stage continuous flow conditions by optimizations of thermal and photoisomerization precursors. The method developed afforded **74** in HPLC-UV: 60%, isolated: 32% yield, and no intermediate purifications nor high-dilution conditions were necessary (Fuse et al. 2010).

One of the most significant syntheses reported under continuous photo-flow conditions is the synthesis of artemisinin (**28**) and derivatives, all of them well-known and potent antimalarial endoperoxides (Scheme 21) (Lévesque and Seeberger 2012). In 2014, the Sanofi laboratory



Scheme 19 - Continuous flow synthesis of Irinotecan® (**69**) by Heraeus Noblelight (Germany).



Scheme 20 - Batch and continuous flow syntheses of vitamin D_3 (**74**).

established a continuous photo-flow plant for an annual production of almost 60 ton.year^{-1} (Nöel et al. 2017). Artemisinic acid (**75a**) is isolated from natural sources and chemically reduced to dihydro-artemisinic acid (**75b**), the starting material for the photochemical process. Allylic peroxidation to **76** is followed by a photochemical cycloaddition and rearrangement with O_2 to artemisinin (**28**). The first part of this sequence is now executed by fermentation, while artemisinin (**28**) is further transformed chemically into the derivatives **77** to **79**.

In 2013, Lek Pharmaceuticals described significant improvements in the synthesis of a brominated intermediate **82** for rosuvastatin (**83**) production (Scheme 22), a super-statin used for cholesterol control (Šterk et al. 2013).

Fluorinations are considered to be very relevant functionalizations under continuous flow conditions, due to several safety issues involving these transformations. In addition, many API intermediates present fluorine atoms in their structures, thus justifying the recent studies in this field. For example, Britton and co-workers have recently described (Halperin et al. 2015) a fluorination protocol for natural leucine (Scheme 23), which is an intermediate for Odanacatib® (**86**), a drug under clinical trial against osteoporosis. This protocol was developed on a gram-scale by Britton's group and recently scaled up by Merck (Nöel et al. 2017).

Endoperoxidations with posterior rearrangements are relevant reactions that can be performed under continuous photo-flow conditions. Several protocols have been described using different photocatalysts for the generation of singlet oxygen (Yavorskyy et al. 2012a). Recently, de Oliveira and coworkers (de Oliveira et al. 2016) described a very efficient protocol for hydroxynaphthol oxidation using a home-made photoreactor (Scheme 24). The scope of naphthol oxidation was presented, producing a number of naphthoquinones including vitamin K_3 (**88**), an important big pharma API. TPP was used as the photocatalyst, which is produced in our laboratory by continuous flow (Momo et al. 2015).

As an example of a dehydrogenation reaction catalyzed by iridium complexes, Knowles and co-workers at Merck (Yayla et al. 2016) have described the Elbasvir (**91**) synthesis starting from an advanced indoline intermediate **89** (Scheme 25). In this protocol, the researchers reported a gram-scale transformation to the indole **90,** with several advantages when compared to the batch mode, and with no significant by-product formation.

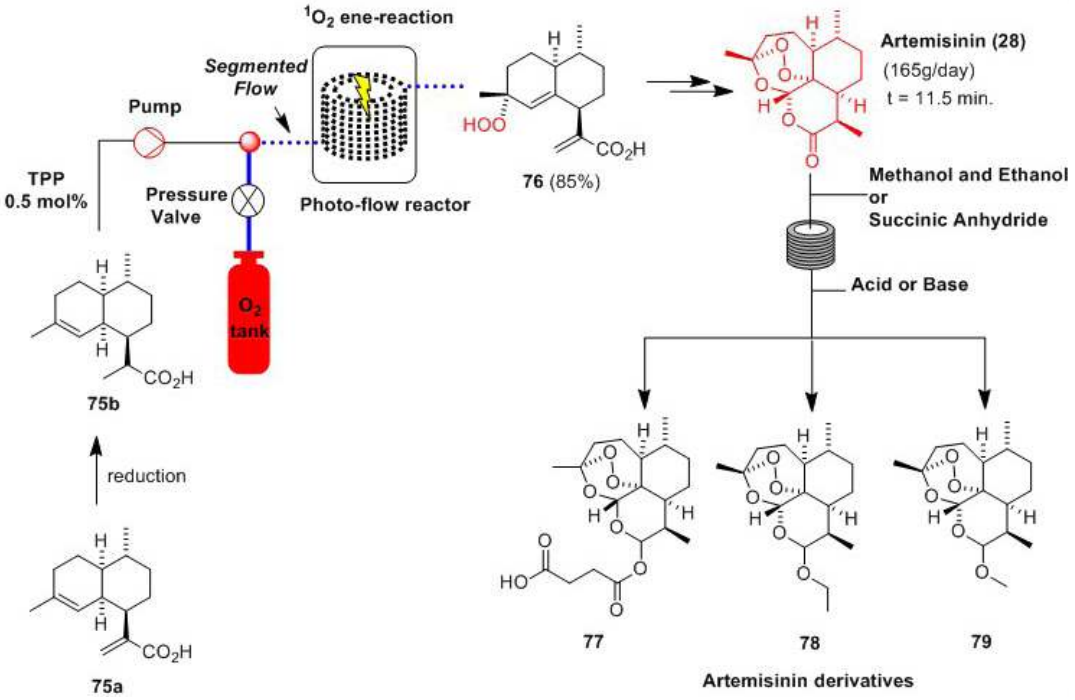
A photo-Favorskii rearrangement protocol was recently reported (Baumann and Baxendale 2016a) for the synthesis of Ibuprofen (Scheme 26). Improvements were obtained when compared to the previous methodologies described by McQuade (Bogdan et al. 2009) or Jamison (Snead and Jamison 2015).

Approaches to the synthesis of very important peptides such as oxytocin or modified arylated peptides (Bottecchia et al. 2016, 2017, Talla et al. 2015) are also described in the literature, opening up many possibilities for flow-photo-assisted biomedical chemistry.

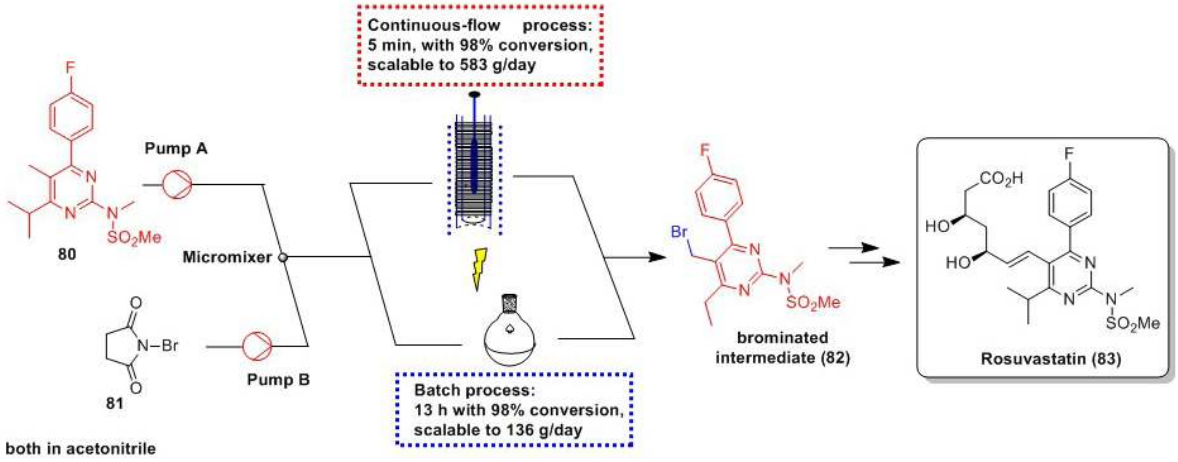
As shown in this section, photochemical transformations have routinely been incorporated by the pharmaceutical industry for API production, and the development of continuous photo-flow technologies has been responsible for this successful progress. Continuous flow chemistry is now very present in the pharmaceutical industry, and certainly photochemical processes already occupy an important place in this scenario.

NATURAL PRODUCTS SYNTHESIS UNDER CONTINUOUS FLOW CONDITIONS

Since Wohler's urea synthesis (1828) from ammonium cyanate, and acetic acid was prepared by Kolbe in 1845, synthetic chemists have demonstrated exceptional creativity for the



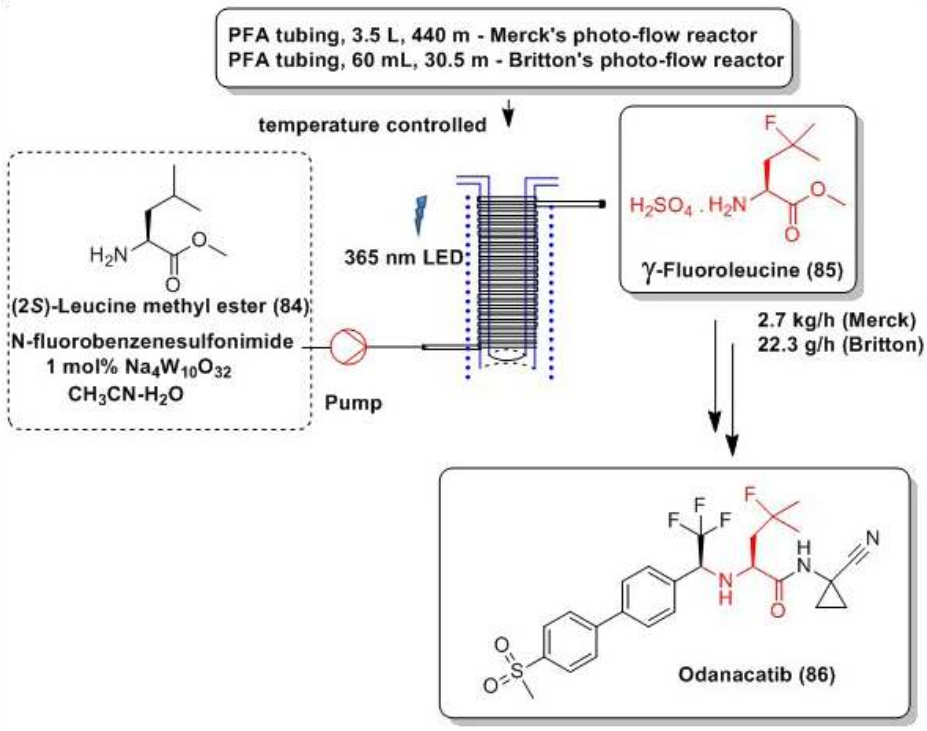
Scheme 21 - Synthesis of artemisinin (**28**) under continuous photo-flow conditions, and transformation into derivatives **77-79**.



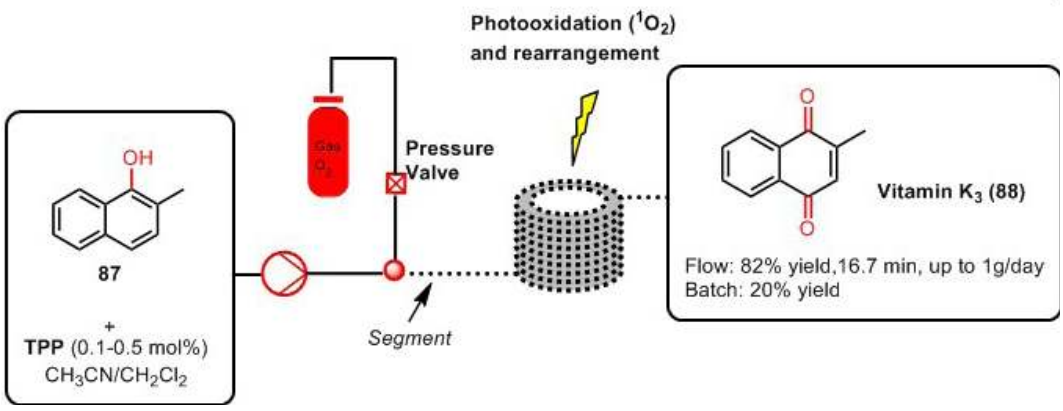
Scheme 22 – The brominated rosuvastatin intermediate (**82**) synthesis.

construction of natural and non-natural organic molecules (Nicolaou and Rigol 2017, Morrison and Hergenrother 2014). This becomes clear if we consider the outstanding total syntheses of complex natural products (NPs) performed in the last seven decades (Corey and Li 2013).

In NP synthesis, a complex target molecule is prepared and analytically characterized according to the naturally occurring compound, termed a natural product. Although there are a large number of new methodologies for the synthesis of NPs, the synthetic strategies and tactics have not followed the same development, and it is still a time-consuming and labor-intensive practice involving manual procedures performed by a highly-trained and skilled workforce (Ley et al. 2015). In this



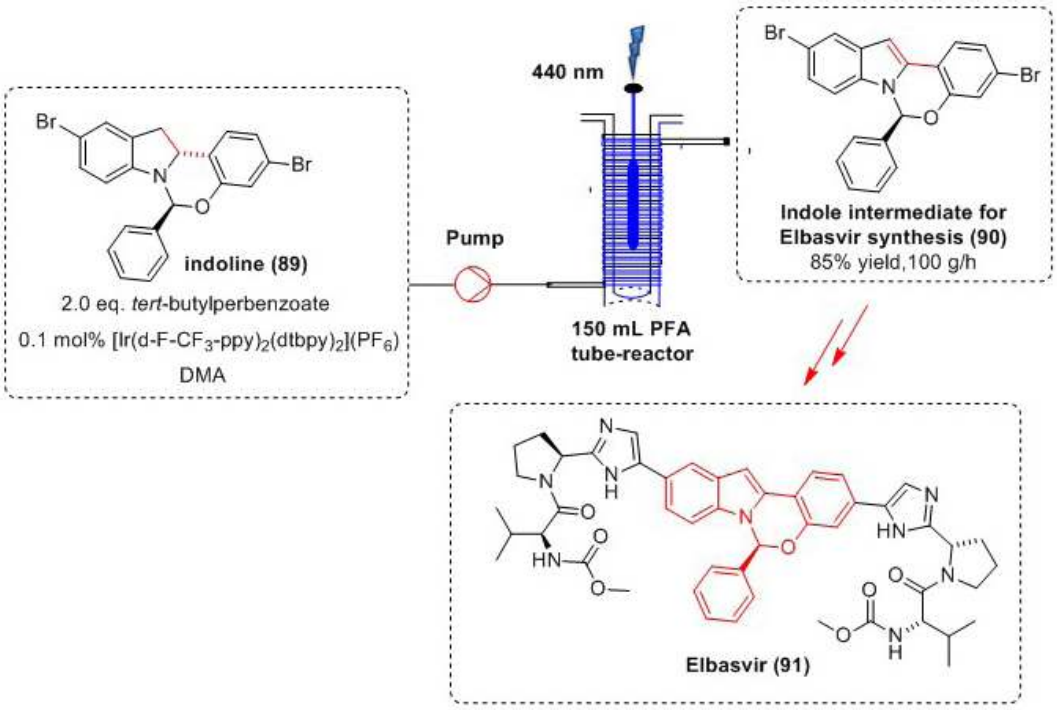
Scheme 23 - Leucine fluorination under continuous flow conditions; Odanacatib® synthesis.



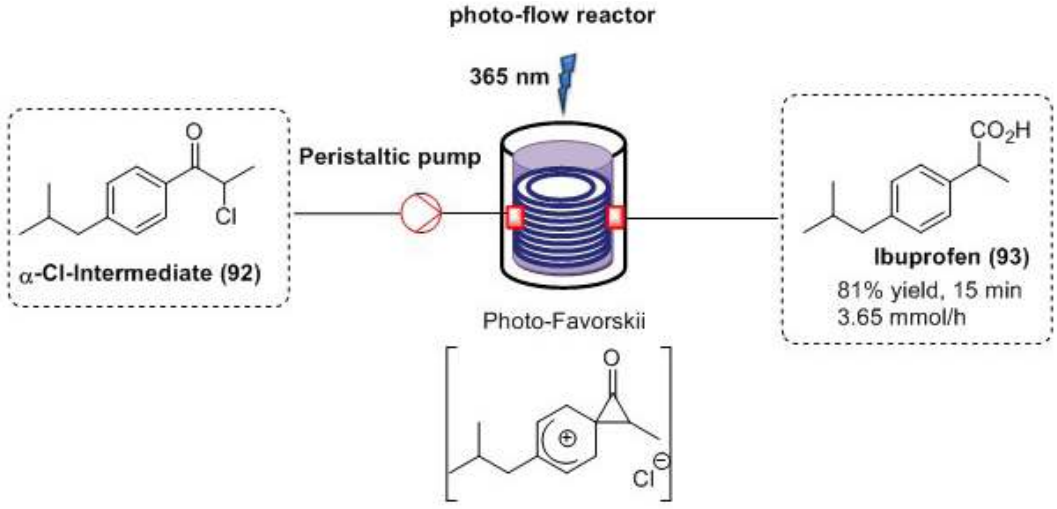
Scheme 24 - Naphthol photooxidations followed by rearrangement; vitamin K_3.

context, enabling technologies, such as continuous flow chemistry employing microreactors, have been broadly explored in order to circumvent the limitations of the traditional batch procedures for the synthesis of NPs (Pastre et al. 2013a).

In a multi-step synthesis performed in flow, the chemicals are directly pumped through the system containing mixers, coil reactors, microchips, columns, in-line liquid-liquid separators, analytical techniques for in-line and real-time monitoring, and back pressure regulators. A target molecule can thus be prepared in a well-designed continuous flow configuration, avoiding many manual operations, which are typically performed individually in batch (Scheme 27) (Fitzpatrick et al. 2016, Ley et al. 2015).



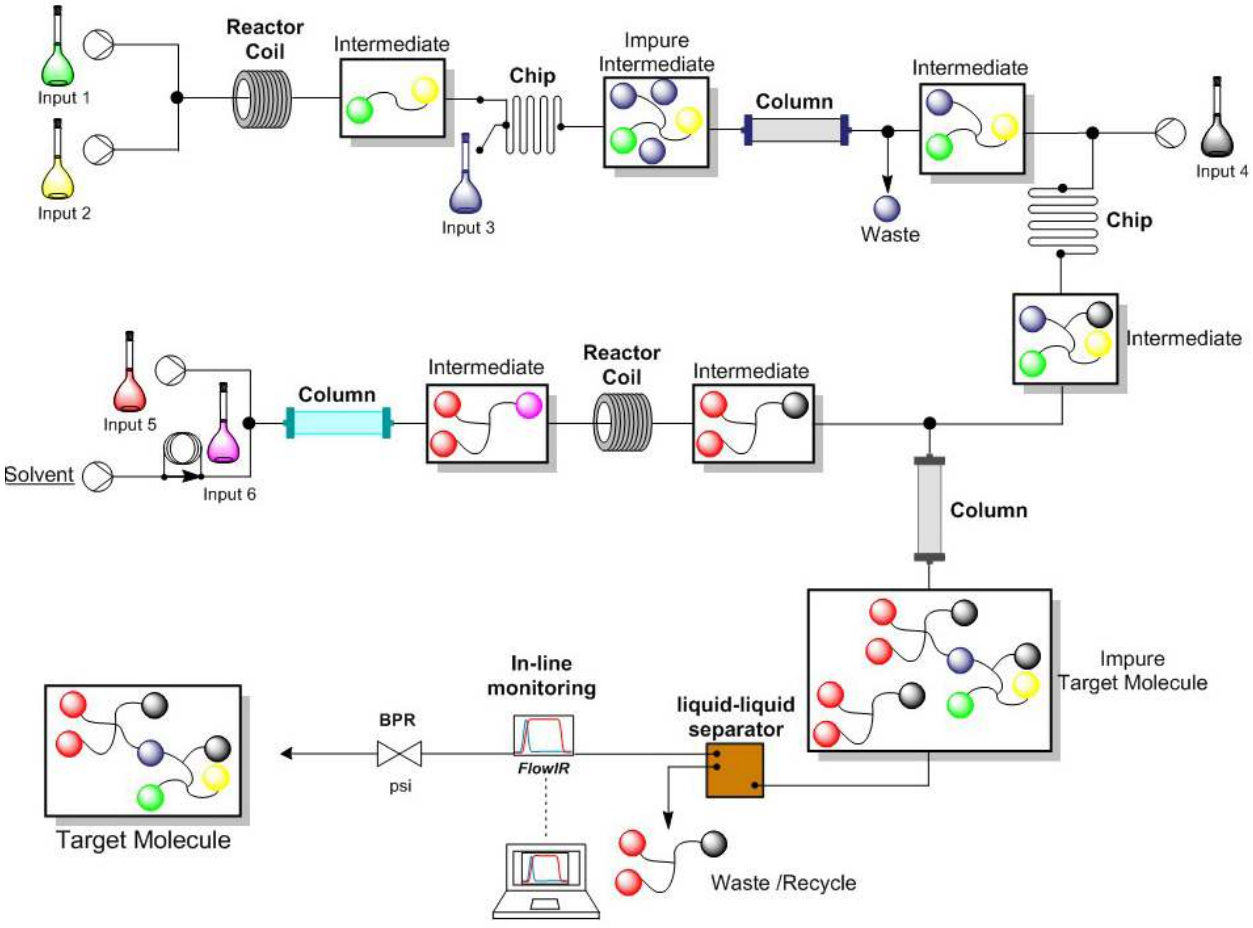
Scheme 25 - Elbasvir (**91**) synthesis.



Scheme 26 – Ibuprofen (**93**) synthesis by the photo-Favorskii rearrangement.

Over the last decade, the development of flow chemistry (or microreactor technologies) by several research groups has contributed to the improvement of the tools of organic synthesis towards a more sustainable practice (Fanelli et al. 2017). Multi-step telescoped synthesis, machine-assisted synthesis, in-line purifications and in-line reaction monitoring are some of the key features which have been extensively explored in the continuous flow regime (Elvira et al. 2013). In this section we will highlight these advances and the successful applications of flow chemistry for the synthesis of NPs.

In 2005, the first synthesis of a NP was demonstrated by the Ley research group using an automated flow system capable of preparing

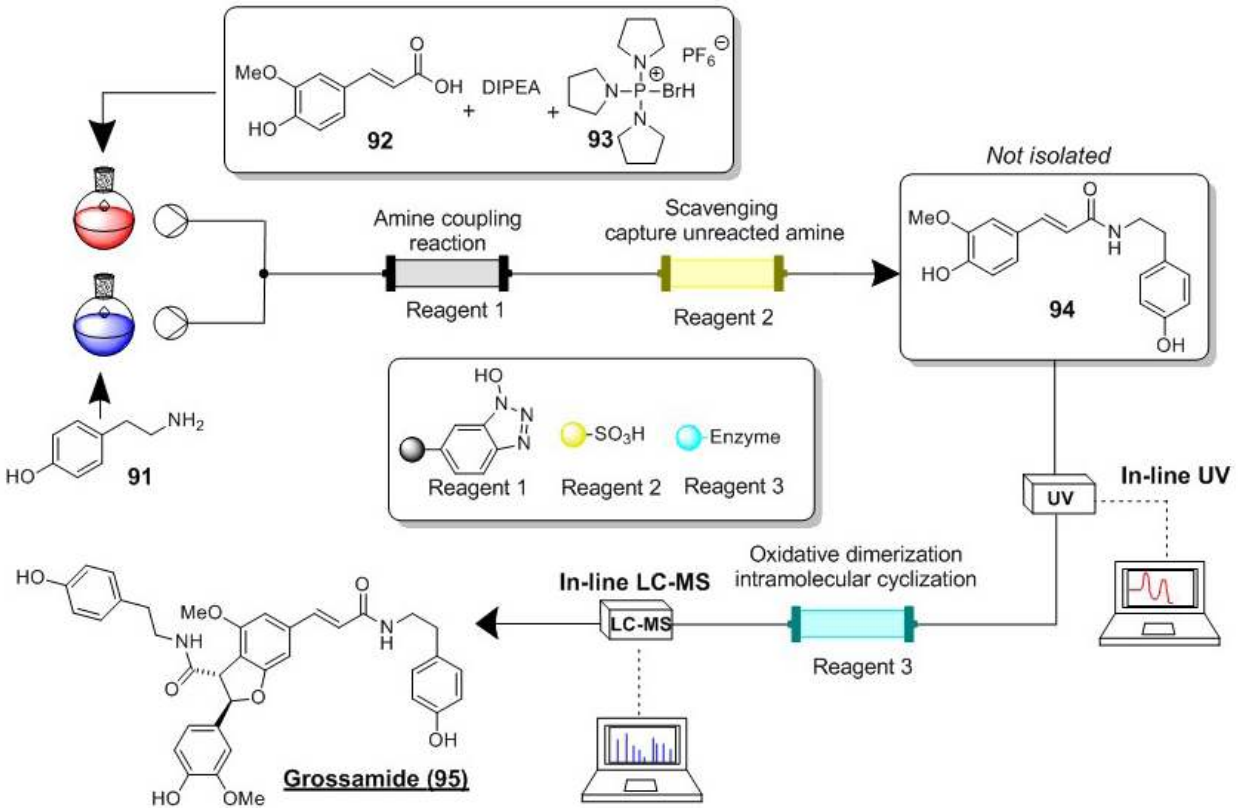


Scheme 27 - General strategy for the multi-step continuous flow synthesis of NPs.

the neolignan NP grossamide (**95**) in a gram scale (Baxendale et al. 2006a). For this purpose, several columns of immobilized reagents and scavenging reagents were used to mediate each individual reaction and also to avoid the need for exhaustive manual purification of the intermediates in the synthetic sequence (Scheme 28). For both coupling and intramolecular cyclization steps, in-line monitoring by LC-MS or UV-Vis techniques were used to optimize the reactions parameters and speed-up the whole process. Notice that these strategies of in-line purification and monitoring are part of the advantages which can be explored in flow, to give highly pure synthetic intermediates and to completely follow the reaction progress. Under optimized conditions, grossamide (**95**) was prepared after a three-step protocol including an enzymatic reaction.

Although it may be considered an easy task, the *three-step* synthesis of grossamide brought innovative concepts for multi-step assembly in flow. This opened up novel opportunities for multi-step syntheses of compounds using immobilized reagents in a fixed-bed reactor, and also in-line monitoring employing bench top analytical tools (Baxendale et al. 2006a).

In 2006, the second NP synthesized in flow was the alkaloid oxomaritidine (**104**) isolated from *Amaryllideacae oxomaritidine*, (Scheme 29) (Baxendale et al. 2006b). This is considered a milestone in method development given the fact that seven separate synthetic steps are combined



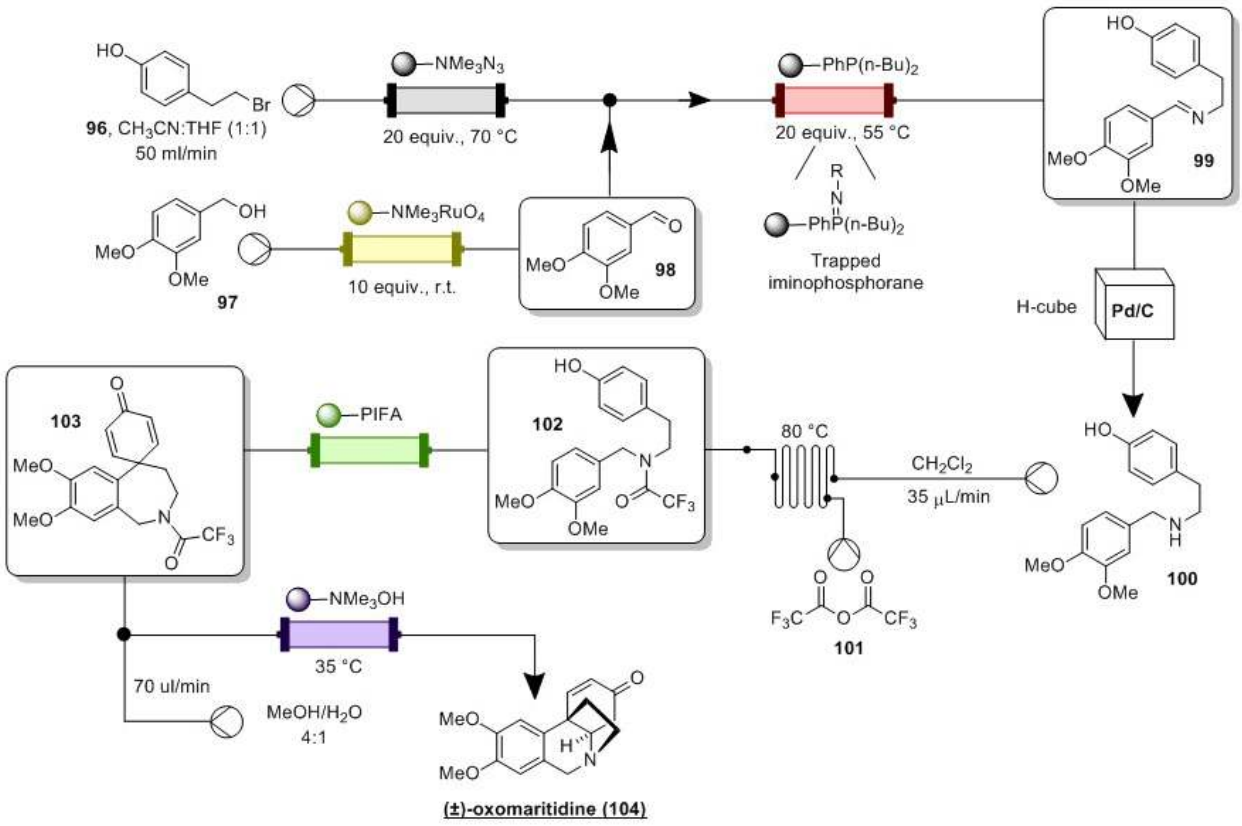
Scheme 28 - Simplified set-up for the synthesis of neolignan natural product grossamide (**95**) in flow.

in an elegant sequence in flow. For the sake of comparison, the synthesis in batch (Ley et al. 1999) using conventional RBFs requires at least four days of laboratory manipulation to prepare **104**, while in a few hours the same seven steps were performed in flow. In this flow process, immobilized reagents, catalysts, scavengers or catch and release agents were efficiently used.

This seven-step sequence showcases the potential and what can be accomplished in flow for the synthesis of a complex target molecule. The sequence performed in flow reactors presents notable gains in terms of both the cost and efficiency of the process, since it reduces the use of extensive purification procedures. Moreover, the rapid optimization and precise control of reaction conditions allows a superior synthesis of oxomaritidine (**104**) with an impressive 40% overall yield.

In a review published in 2013, Ley and coworkers presented a wide variety of NPs already synthesized (Pastre et al. 2013a). Besides the syntheses of (±)-oxomaritidine (**104**) and grossamide (**95**) described above, other syntheses include the saturated isoprenoid pristine (**105**), asparagine-linked oligosaccharides (**106**), (–)-perhydrohistrionicotoxin (**107**), vitamin D_3 (**74**), aplysamine (**108**), pseudomonas quinolone signal (PQS) (**109**), (+)-dumetorine (**110**), *o*-methylsiphonazole (**111**), pauciflorol F (**112**), artemisinin (**28**), the ladder-shaped polyether yessotoxin (**113**), and (–)-hennoxazole A (**114**) (Figure 6). Most of these syntheses are integrated processes and combine batch and continuous flow processes, taking advantage of the benefits of each regime.

Since 2013 other important contributions in NP syntheses have been published, along with



Scheme 29 – Continuous flow synthesis of (±)-oxomaritidine (**104**).

the development of novel technologies in flow chemistry (Elvira et al. 2013, Fanelli et al. 2017, Ley et al. 2015).

In 2014, Ley's group reported the most ambitious synthesis of a complex NP, the spirocyclic polyketide spirodienal A (**147**), using a combination of batch and flow processes (Schemes 30-33) (Newton et al. 2014). Additional and innovative tools were demonstrated and used to accomplish the planned synthesis. The strategy adopted was based on the coupling of two key fragments, an aldehyde **135** and a bis-alkyne **144** (Scheme 33), both containing the same three stereocenters in the 1,3-dioxane ring. In order to prepare the aldehyde **135**, the homoallylic alcohol **122** was first synthesized in five steps under continuous flow conditions (Scheme 30), using the in-house tube-in-tube reactor (Matthew et al. 2010) for the catalytic hydrogenation reaction.

The aldehyde fragment **135** was synthesized in 11.6% overall yield for thirteen steps, nine of them performed in the flow regime (Scheme 31).

The synthesis of the bis-alkyne **144** (Scheme 32) required the use of several solid-supported reagents and different types of reactors such as coil, microchip and fixed-bed reactors. In addition, some reactions already used to prepare aldehyde **135** were again addressed here, demonstrating the versatility and reproducibility of flow reactions as reaction platforms.

Bis-alkyne **144** was prepared in 8 steps (7 in flow and 1 in batch) in 22% overall yield and, interestingly, a continuous flow liquid-liquid separator was employed to deliver this compound in high purity. Liquid-liquid separators based on membrane technologies are now commercially available and offer a viable alternative to polymer-supported reagents for in-line work-up procedures.

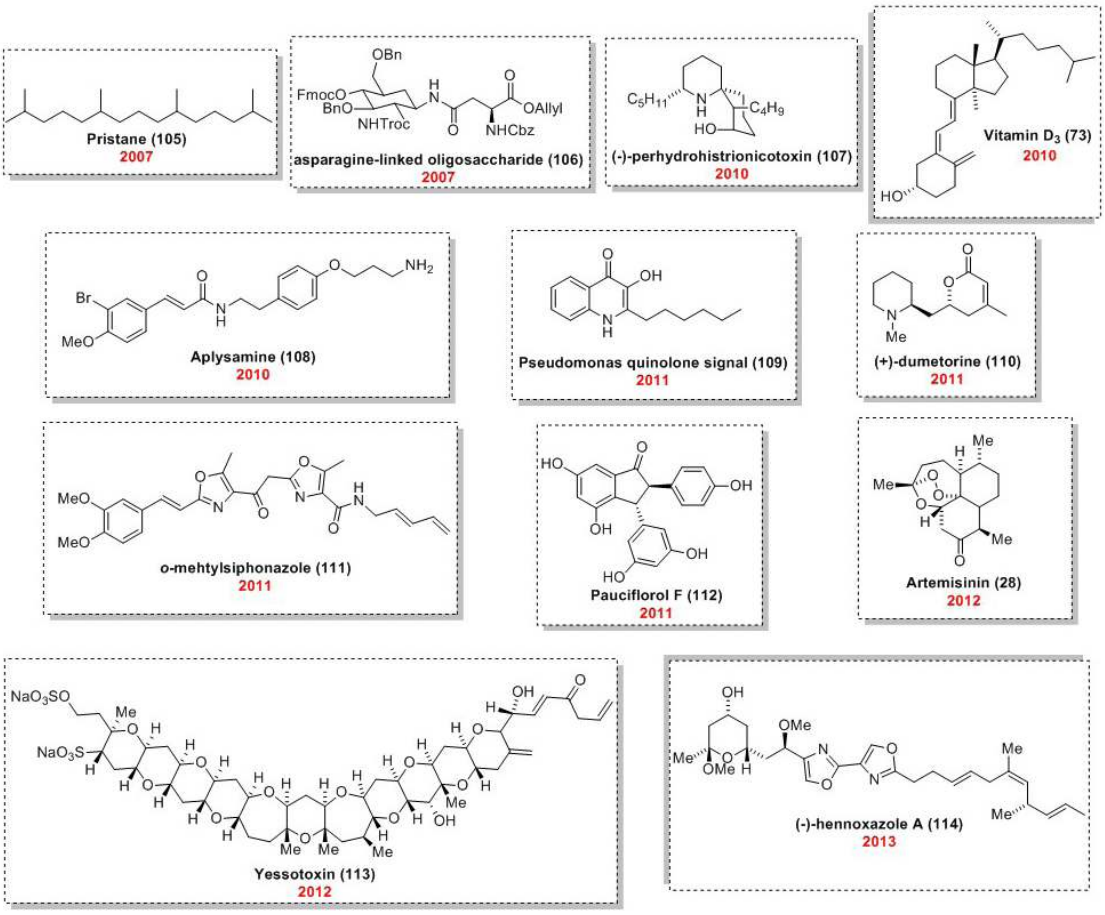
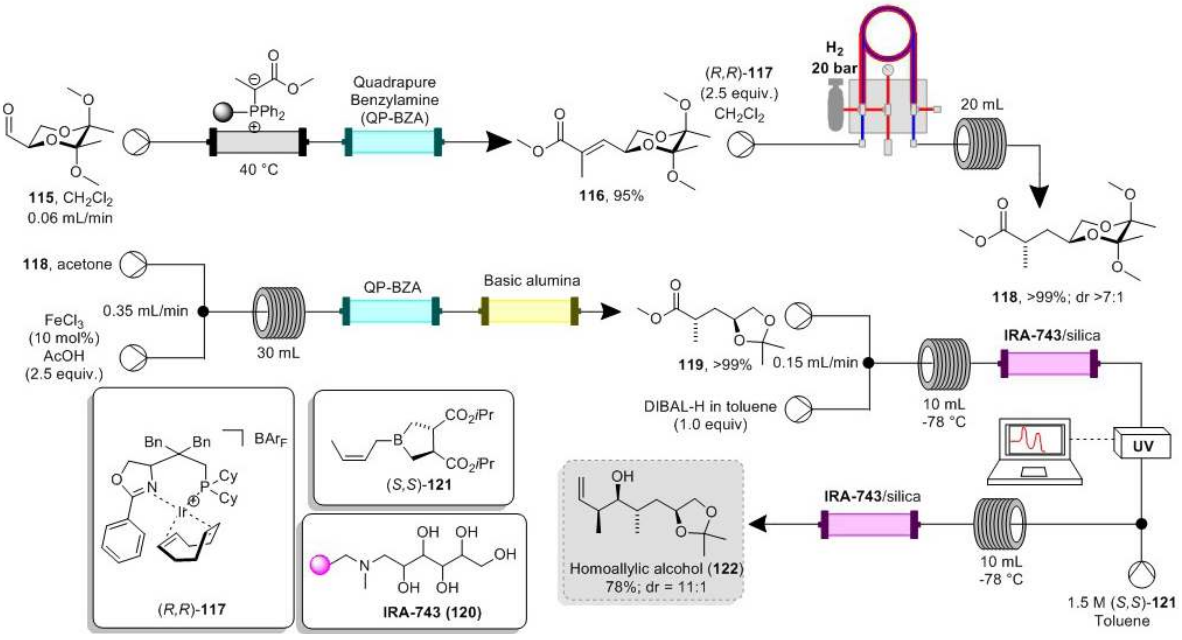
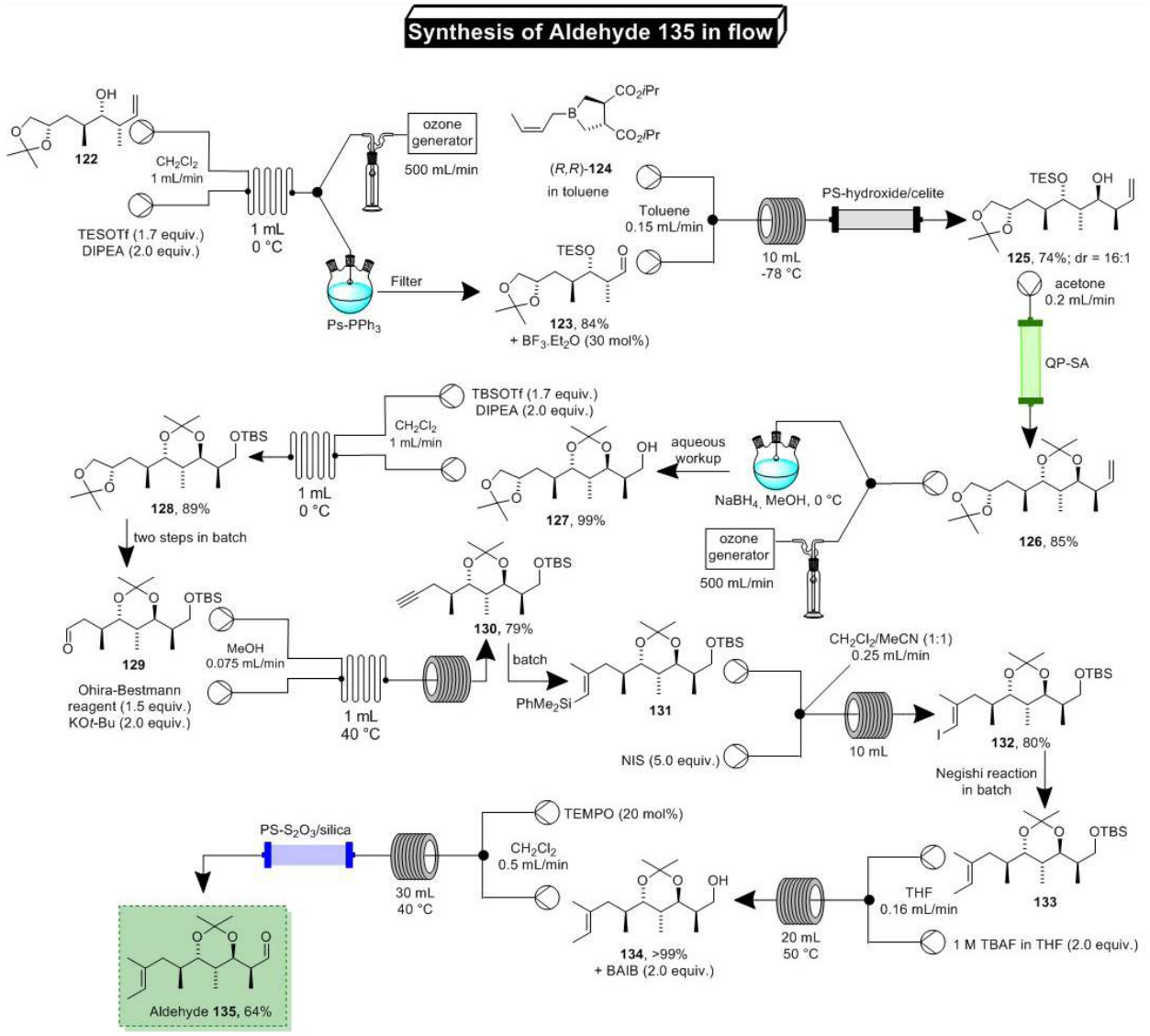


Figure 6 - NPs prepared using combined batch and continuous flow processes up to 2013.



Scheme 30 - Continuous flow synthesis of the homoallylic alcohol **122**.



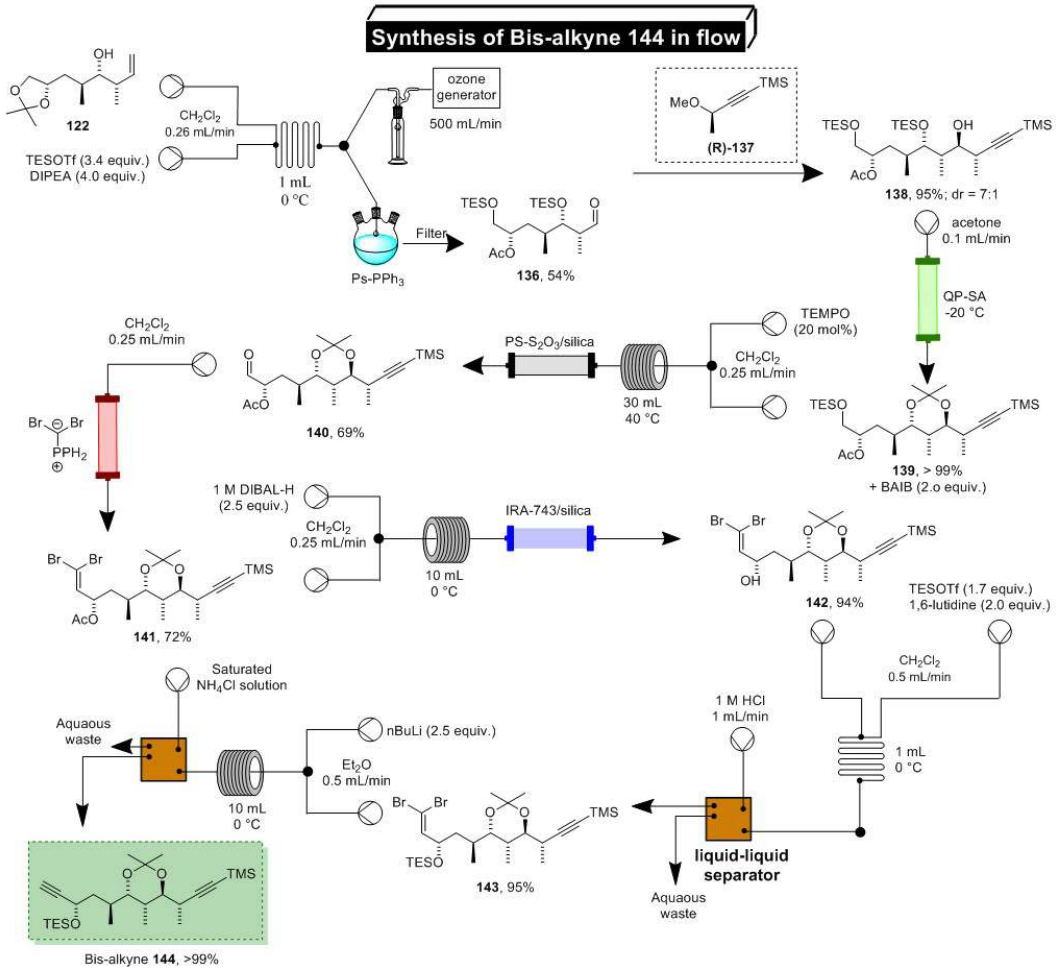
Scheme 31 - Integrated batch and flow synthesis of the key aldehyde **135**.

With aldehyde **135** and the bis-alkyne **144** in hands, 10 more steps were carried out in batch to complete the total synthesis of the spirocyclic polyketide spirodienal A (**147**) (Scheme 33).

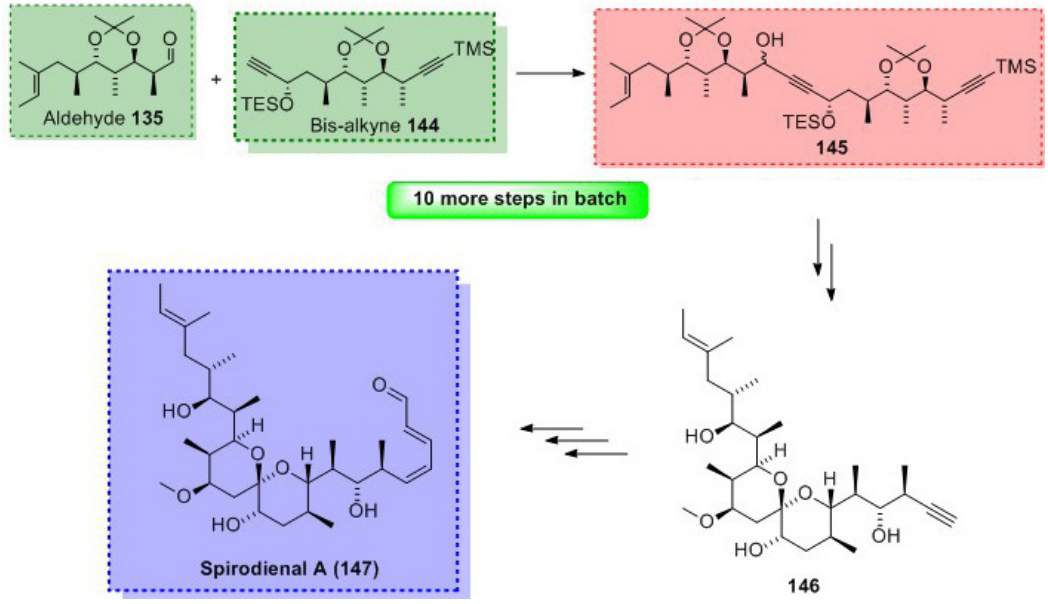
Valuable transformations such as automated reagent additions, ozonolysis, silylations/desilylations, olefinations, crotylations, and oxidations were efficiently carried out in flow (Fitzpatrick et al. 2016, Ley et al. 2015, Elvira et al. 2013), showing the potential for either method development or total synthesis.

Moving to more recent studies performed in flow, Figure 7 exhibits the latest NPs prepared in either the end-to-end approach or using a combination of batch and flow regimes.

In 2013, Ley's group demonstrated an integrated batch and continuous flow process for the synthesis of goniothalamin (**151**) (Pastre et al. 2013b). The addition of a Grignard reagent was performed in flow, proving that the handling of such sensitive materials (Browne et al. 2013) can be easily performed in a safe manner. The



Scheme 32 - Continuous flow synthesis of the bis-alkyne **144**.



Scheme 33 - Final steps of the spirodienal A (**147**) synthesis.

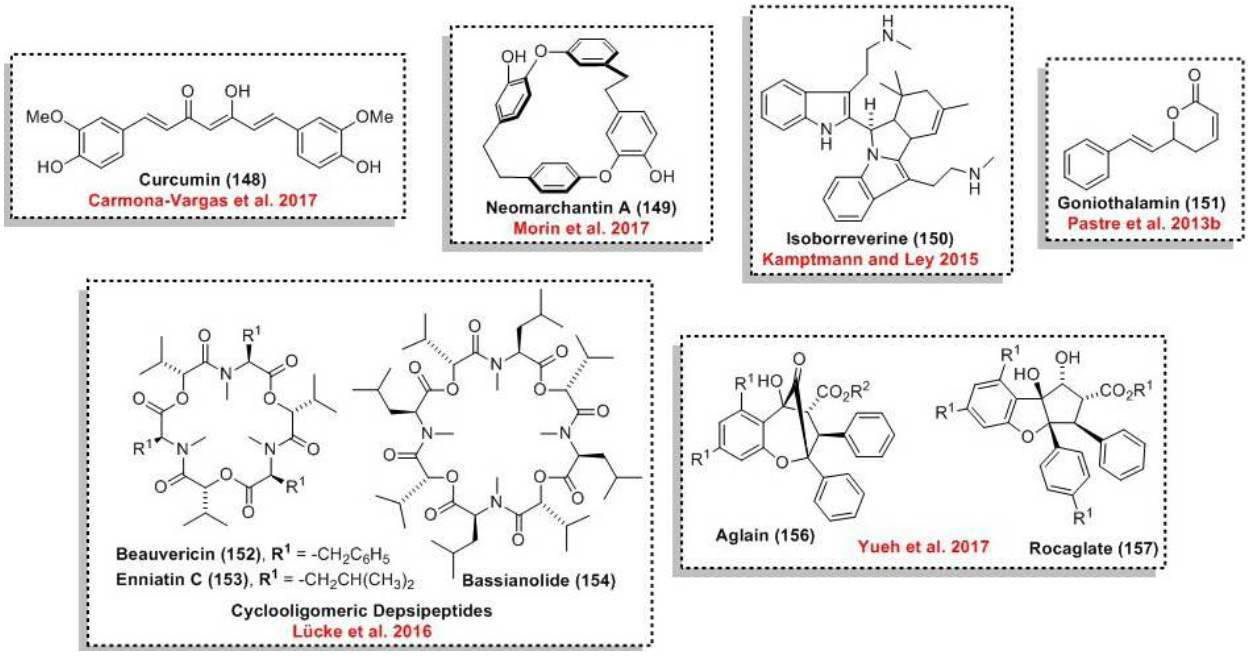


Figure 7 - NPs prepared using batch and flow integrated approaches, since 2014.

strategy used by the authors to introduce the a,b-unsaturated six-membered ring lactone was based on a metathesis reaction using the second-generation Grubbs catalyst (GII) in flow regime. In 2015, the same group reported the synthesis of isoborreverine (**150**) in flow regime (Kamptmann and Ley 2015). This NP was synthesized in a single step using a column packed with polymer-supported boron trifluoride which catalyzes the ring opening reaction of borrerine. A diene intermediate is generated in this process and rapidly undergoes a Diels-Alder reaction to afford isoborreverine (**150**). In this study, the ability to rapidly change temperature and flow rates was essential for a fast optimization of reaction conditions for the desired biomimetic synthesis.

In 2016, Ley and coworkers presented the synthesis of cyclooligomeric depsipeptides, such as **152**-**154**, using a macrocyclization reaction to form the challenging *N*-methylated amides (Lücke et al. 2016). Superior yields were obtained using a telescoped process in flow when compared to batch procedures: beauvericin (**152**), 26% yield in batch and 36% yield in flow; enniatin C (**153**), 15% yield in batch and 44% yield in flow; bassianolide (**154**), 24% yield in batch and 43% yield in flow. Although the synthesis of oligopeptides can be performed using automated synthesizers, these results using microreactors bring opportunities for their synthesis, notably when scale-up is required.

Collins and coworkers performed the synthesis of neomarchantin A (**149**) using batch and flow combined procedures (Morin et al. 2017). Two key bond formations involving C−O (S_NAr reaction) and C−C (olefin metathesis reaction) bonds were intensified using continuous flow techniques.

Beeler and coworkers exploited the benefits of flow chemistry for the synthesis of aglain (**156**) and rocaglate natural product analogues **157** (Yueh et al. 2017). In this case, an ESIPT-mediated [3+2]-photocycloaddition reaction was performed with good productivity (1.0 - 1.9 $g.h^{-1}$) using a photochemical flow reactor.

Recently, the natural product curcumin (**148**) and two other curcuminoids were prepared by de Oliveira and coworkers in an end-to-end strategy

in flow regime (Carmona-Vargas et al. 2017). An interesting comparison between batch, flow and the combined strategies was demonstrated: curcumin (**148**) was obtained in 69% yield in batch (STY = 12.0 g per day), whereas a clear advantage was reported in the flow regime (60% yield; STY = 24.1 g per day).

Natural products and structures inspired by their molecular scaffolds have played a significant role in the drug discovery field, representing more than half of all small-molecule drugs approved between 1981 and 2014 (Appendino et al. 2014, Morrison and Hergenrother 2014). In view of their unique structural diversity, NPs are still considered privileged scaffolds for drug discovery. However, even considering all the advances experienced in the last decades such as new methodologies based on catalytic methods, protecting group-free syntheses, C-H activation approaches and late stage functionalization, there are many challenges to be addressed in order to achieve more efficient and concise syntheses.

Based on the NP syntheses presented herein, it is clear that enabling technologies, especially continuous flow chemistry, can play a major role in the synthesis of complex NPs, leading to a fundamental change in the way we perform total syntheses. Flow chemistry facilitates the scale-up of advanced intermediates, which is often limited in batch and by the use of in-line tools. The number of individual purifications can be dramatically reduced, allowing for the integration of several steps and decreasing the time spent to deliver a complex NP. It is time to make better use of our financial and human resources, and therefore the opportunities brought by machine-assisted NP synthesis should be emphasized.

API SYNTHESIS & CONTINUOUS MANUFACTURING

Active pharmaceutical ingredients (APIs) are, in general, synthesized in batch manufacturing plants and then shipped to other sites to be converted into a form that can be given to patients, such as tablets, drug solutions, or suspensions (finished medicines). This system offers little flexibility to respond to surges in demand and is susceptible to severe disruption if one of the plants has to shut down. Worldwide, companies such as Novartis, Lilly, Lonza and others are investigating continuous manufacturing of new drug substances in order to reduce their manufacturing costs, and to provide a more robust way of producing the desired molecules. This demand has an incredible effect on the development of new technologies such as flow reactors, phase separators, pumps, among others. Some companies have established new businesses by designing their own reactor systems, like the Lonza FlowPlate® micro and milli-reactors (Vaccaro et al. 2014, Wiles and Watts 2014, Gutmann et al. 2015, Kobayashi 2016, Britton and Raston 2017, Fanelli et al. 2017, Plutschack et al. 2017).

In academia, an initiative directed by Gupton at Virginia Commonwealth University - USA, in collaboration with the Bill & Melinda Gates Foundation, called Medicines for All, seeks cheaper and more efficient ways to manufacture drugs, particularly those needed to treat HIV and AIDS in developing countries. The main idea behind their strategy was to start with very simple commodity chemicals, in order to make it feasible for developing economies. So far these strategies are not completely applied in industry (Longstreet et al. 2013).

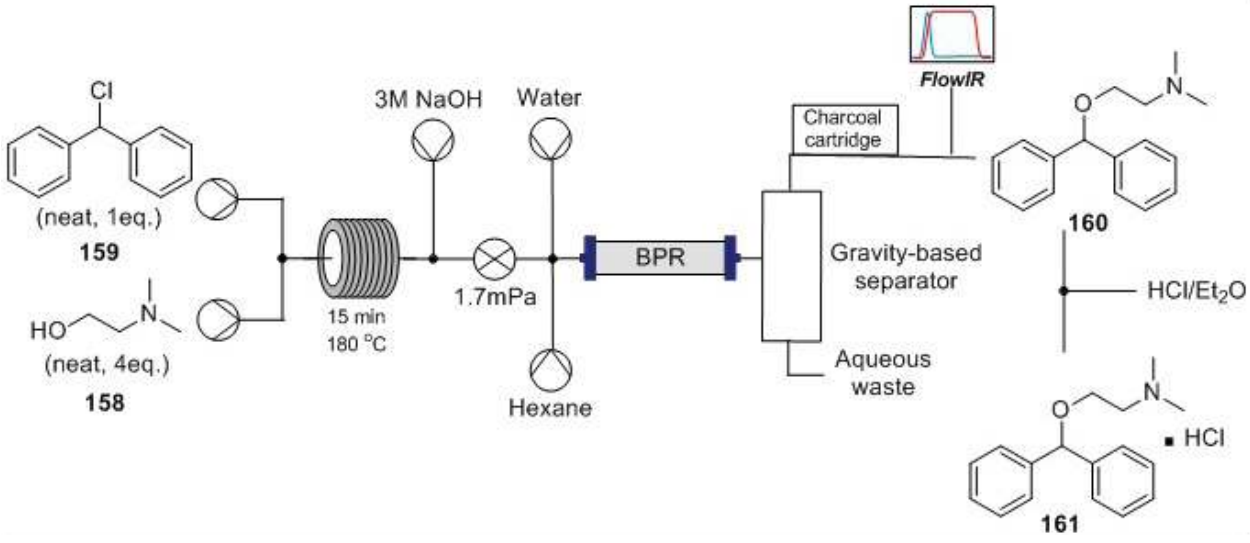
Another initiative funded by the Defense Advanced Research Projects Agency (DARPA) and MIT researchers came up with a small transportable device suitable for small-scale syntheses of drug molecules (Adamo et al. 2016). Their new system can produce 1,000 doses of four drugs formulated as solutions or suspensions in 24 hours; *i.e* benadryl, lidocaine, valium, and prozac. A refrigerator-sized continuous-flow apparatus [1.0 m (width)

x 0.7 m (length) x 1.8 m (height), ~100 kg] is capable of complex multistep synthesis, multiple in-line purifications, post synthesis work-up and handling, semi-batch crystallization, real-time process monitoring, and ultimately formulation of high-purity drug products. The continuous flow strategy towards the synthesis of diphenyldramine hydrochloride is shown in Scheme 34.

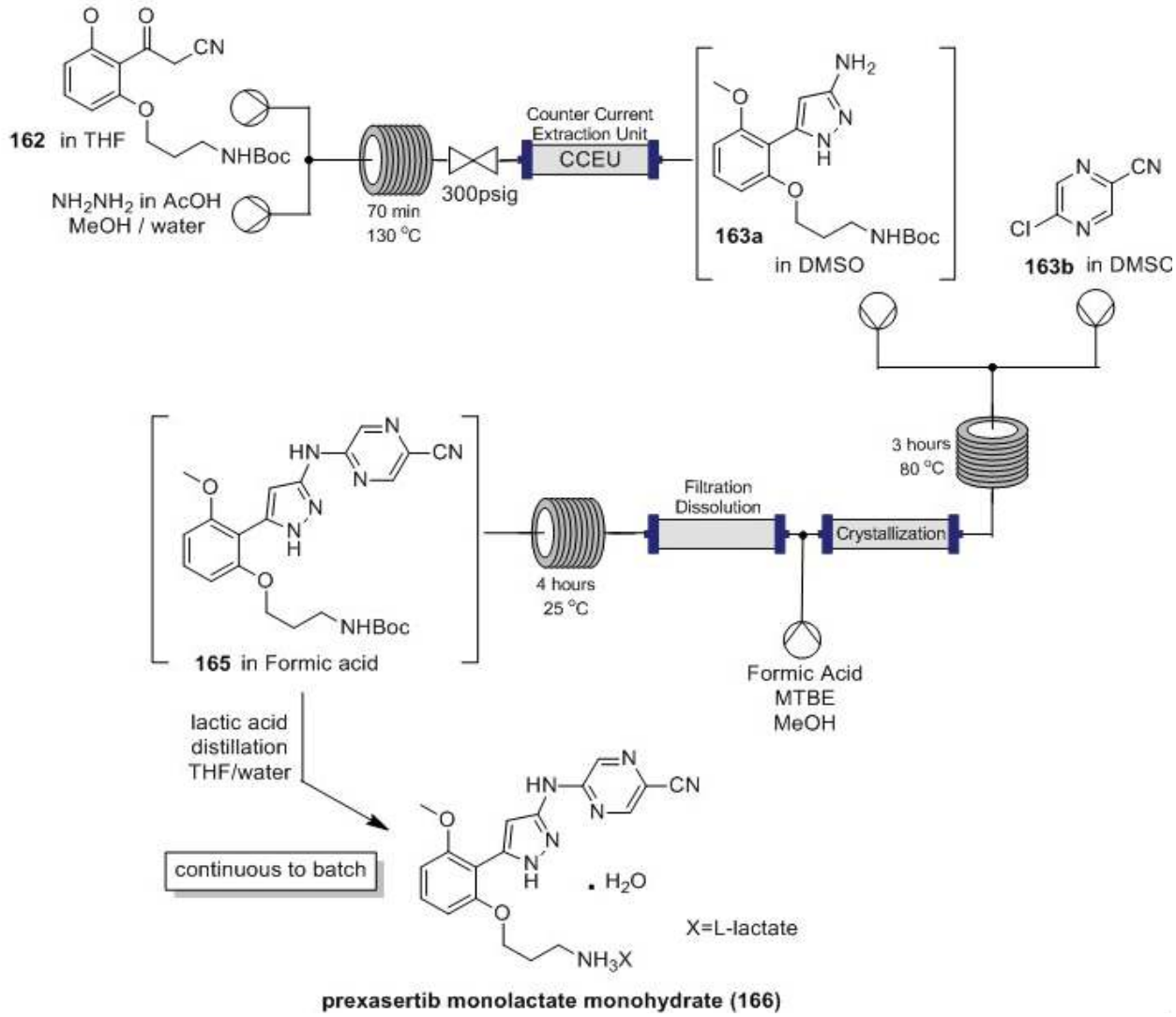
Recently, Lilly (Cole et al. 2017) has enabled a kilogram synthesis of prexasertib monolactate monohydrate (**166**) under continuous flow conditions and GMP (good manufacturing practice) qualifications. This medicine has been assessed in phase 1 and 2 clinical trials in combination with cytotoxic chemotherapy, targeted agents, and as a monotherapy, and is the first CHK1 inhibitor to demonstrate objective clinical responses as a monotherapy. During discovery and initial clinical trials a nine-step route was used, but deemed unsuitable for long-term manufacturing due to several hazardous reagents and moderate yields. Lilly has now opened up a new route to prexasertib by exploring the continuous flow environment (Scheme 35).

The first step has serious restrictions when conducted under batch conditions due to the use of hydrazine in a large excess and the high temperatures needed for reaction completion. Using continuous flow technology and a plug-flow reactor, it was possible to reduce the amount of hydrazine and operate safely at 130°C. It is important to note that only 0.49% of the overall production is inside the reactor at any time, reducing material at risk and increasing process safety. The first step was conducted with 89.6% yield at 3.08 kg/day, arriving at the final product with only 2 ppm of hydrazine and less than 1% of impurities. The next step was accomplished with 88.7% yield on a 2.56 kg/day basis. Unlike the first step, this intermediate needed further purification, since it was necessary to remove residual starting material, regioisomers and other minor impurities. The desired product was obtained on a continuous deprotection and batch crystallization process, leading to a final yield of 85% and 1.99 kg/day for the final step.

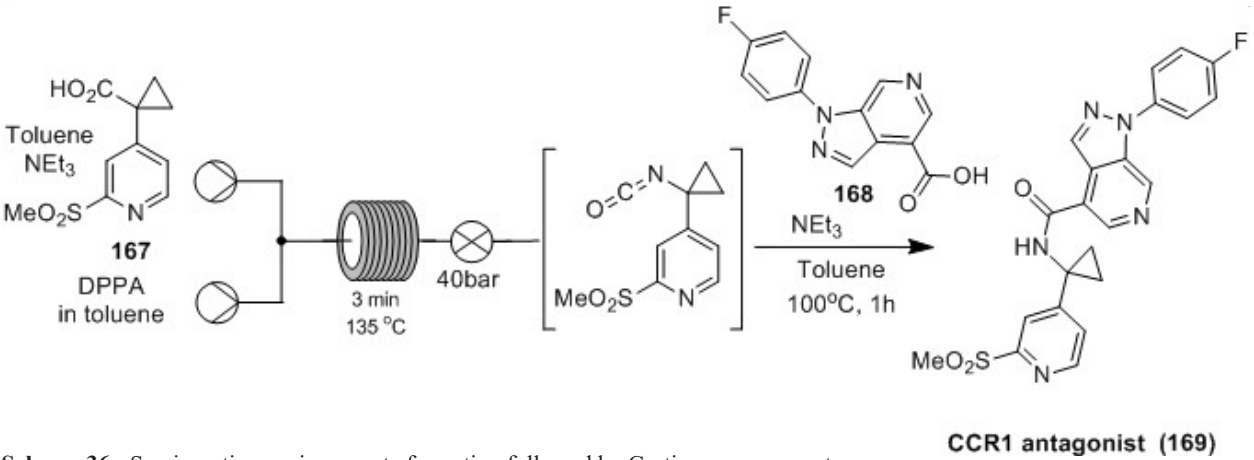
Safety is a decisive matter for Boehringer Ingelheim Pharmaceuticals (Marsini et al. 2017) when deciding to implement a continuous flow process for the synthesis of a CCR1 antagonist



Scheme 34 – An example of end-to-end continuous flow synthesis with integrated analysis and separation for diphenyldramine hydrochloride (**161**).



Scheme 35 – Continuous flow three-step synthesis of prexasertib monolactate monohydrate (**166**) under GMP conditions.



Scheme 36 - Semi-continuous isocyanate formation followed by Curtis rearrangement.

(**169**), which has an acyl azide and/or isocyanate as intermediates (Scheme 36).

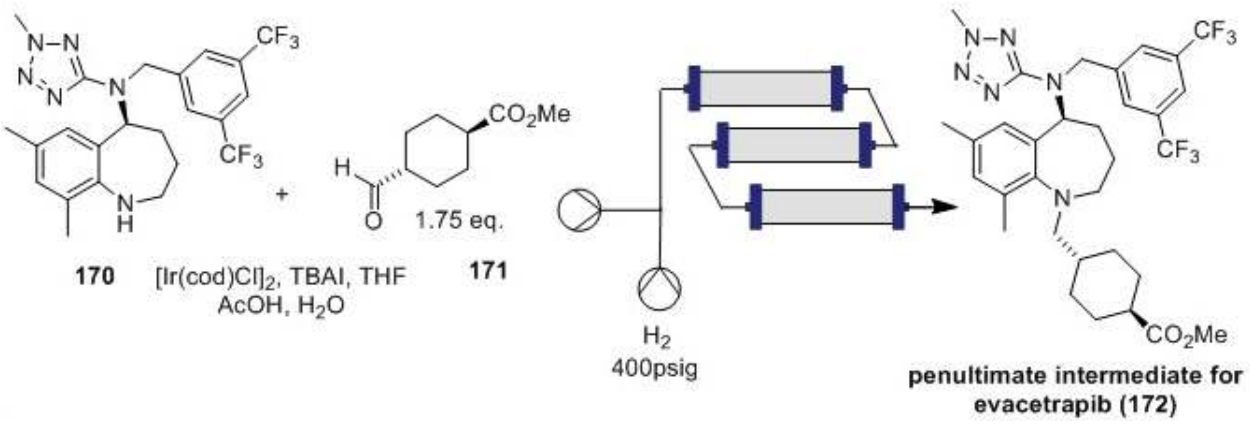
The batch process started with the formation of an acyl azide, in order to lead to the carbamate product by Curtis rearrangement. Decoupling azide formation from isocyanate trapping was successful, due to the key potential drawback of undesired acyl azide accumulation in the CSTR (continuous stirred-tank reactor) upon further scale-up. When implementing the continuous flow protocol the isocyanate intermediate formation was optimized for a residence time of 3 min in 76% overall yield, and 56% more efficient than the original Curtis batch process, allowing a further scale-up to 40 kg of the final product.

D&M Continuous Solutions, Eli Lilly and Lilly Research Laboratories (May et al. 2016) have developed an efficient continuous iridium-catalyzed homogeneous high pressure reductive amination reaction to produce the penultimate intermediate (**172**) in evacetrapib synthesis. The continuous process operated under GMP conditions for 24 days and produced over $2x10^6$ tons of **172** in 95% yield after batch workup, crystallization, and isolation (Scheme 37).

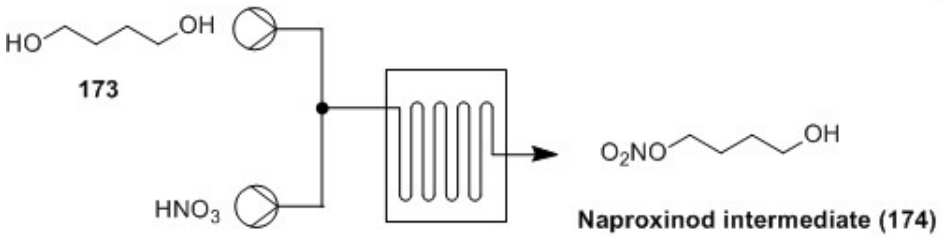
A final reaction condition was optimized where H_2 pressure and substrate/catalyst ratio maximizes product formation leading to minor undesired impurities such as the *cis* regioisomer. The presence of TBAI was crucial as it appears to hold the Ir(I) in a more stable anionic form which is less prone to degradation under the reaction conditions. For those who are afraid of working with hydrogenation reactions at large-scales, the authors say "*the reactor operates at >98% liquid filled with the hydrogen distributed throughout the 45 pipes and downflow tubes resulting in a steady venting of nitrogen-diluted hydrogen over time (20 g/h at scale)… It is for these reasons that the continuous process is viewed as a low risk process in spite of its operation at high pressure*". They could show the linear scale-up capability of the continuous flow process going from 48L reactors up to 360L reactors for production scale, giving the desired product in 95% isolated yield.

One of the first examples of a continuous flow process applied to APIs was presented by DSM (Braune et al. 2009) on the nitration reaction towards the production of naproxinod, an anti-inflammatory drug (Scheme 38).

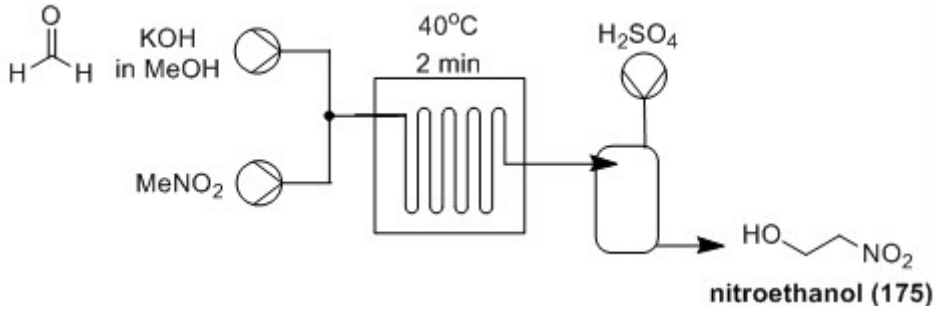
The task faced by DSM was to develop a safe and highly efficient nitration process, selectively nitrate only one hydroxyl group and handle the very hazardous nitrated product. After optimization found the exact nitric acid concentration needed (65%), it could be taken for scale-up. The operation unit has a total volume around 150 mL and process capability of 13 kg/h working at GMP conditions.



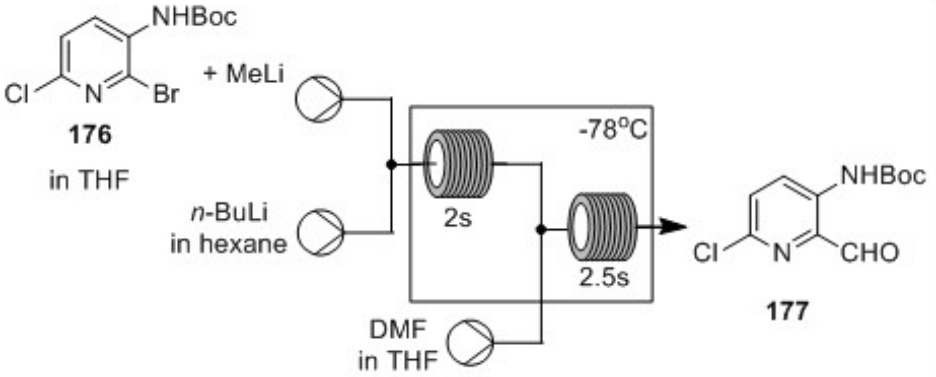
Scheme 37 - Homogeneous continuous flow reductive amination of an intermediate of evacetrapib synthesis.



Scheme 38 - DSM continuous-flow nitration process.



Scheme 39 - Nitroethanol continuous flow synthesis developed for aliskiren production.



Scheme 40 – The formylation process developed by Merck, in order to avoid batch scale-up problems.

During the pilot plant campaign 500 kg of qualified product could be produced under the developed conditions.

Lonza and Novartis (Roberge et al. 2014) have worked together in order to overcome a problem related to starting material nitroethanol in the aliskiren API synthesis. This reagent is required in kg amounts, since it is used in an organo-catalytic reaction between nitroethene and isovaleric aldehyde to form 2(*R*)-isopropyl-4-nitro-1-aldehyde, subsequently reduced by sodium borohydride to furnish the desired 2(*R*)-isopropyl-4-nitro-propan-1-ol. Since lower nitroalkanes are potentially explosive, a continuous flow process was developed for the production of nitroethanol (**175**) in high yields (95%) and very short residence times (Scheme 39).

An API developed by Merck (Grongsaard et al. 2012) as an allosteric Akt inhibitor used for cancer treatment, had one step optimized under continuous flow conditions in order to ensure the production of kilogram quantities for clinical trials. During reaction optimization under batch conditions and gram scale, the design process worked as expected,

but under a larger scale the formylation reaction did not behave as expected. The reaction solution turned into a thick gel, a phenomenon that had not been observed in gram scale experiments. The batch temperature had to be raised to − 45°C and the agitator manually manipulated until the mixture was sufficiently mobile to allow stirring to continue automatically. The final yield was not affected but raised concerns about a possible scale-up. With these results in hands, the authors decided to develop a continuous flow protocol in order to overcome the reaction media instability observed under batch conditions (Scheme 40).

The continuous flow process was performed mixing the amine and MeLi. This solution was fed into a stainless-steel tube reactor with an internal diameter of 6.35 mm, and kept at -78ºC using a dry-ice/ acetone bath. After the first deprotonation the amide stream was mixed with *n*-BuLi, to form the dianion in the first residence tube, and the dianion was then combined with the DMF/THF feed solution in order to produce the desired formylated product **177** in 65% yield and purity equal to that obtained under batch conditions. The very short residence times operated in this process which uses flow rates up to 175 mL min^{-1}, allow the production of 1kg of the aldehyde after just 1 hour.

Continuous API production is a reality for big pharma, which certainly intends to migrate from batch to flow protocols in a few years. Many safety and low-cost production problems are addressed with this change, but most importantly the logistics will be significantly improved with much smaller GMP areas required for flow plants.

APPLICATION OF CONTINUOUS FLOW CHEMISTRY TO MEDICINAL CHEMISTRY

Lead compound identification and optimization, synthesis of chemical libraries, and supply of materials in sufficient quantity for clinical assays, are time-consuming and a laborious task for medicinal chemists. Therefore, further advances are needed to reduce the time taken to synthesize libraries of compounds, identify potential hits/leads, optimize synthetic routes to afford the final compounds, and put drug candidates into production.

Continuous flow chemistry is finding increasing use as an enabling technology in academic and industrial environments, providing a number of advantages over batch processes, and leading to a variety of interesting and exciting opportunities. As we have mentioned before, continuous flow processing enables simple scale-up of reactions, enhanced mixing, temperature and pressure control, decrease of waste generation and energy consumption, and integration of several reaction steps (telescoped synthesis). Furthermore, the volumes of reagents/solvents are reduced, which facilitates the screening of reaction conditions, and consequently, the rapid generation of focused compounds libraries (Malet-Sanz and Susanne 2012, Yavorskyy et al. 2012b, Baraldi and Hessel 2012). These advantages become more appealing if one considers that solvents account for *ca.* 80% of the waste generated in the production of APIs.

Although the pharmaceutical industry still relies on the use of multipurpose batch reactors in its production lines, it is clear that continuous flow chemistry is already making the manufacturing of APIs faster and simpler. It should also have a profound impact on the discovery of new drug candidates, synthesis of chemical libraries, and scale-up of reactions for clinical trials (Fitzpatrick et al. 2016, Baraldi and Hessel 2012, Malet-Sanz and Susanne 2012, Rankovic and Morphy 2010, Poh et al. 2016).

In this context, an increasing number of studies have been reported, and selected families of heterocycles with pharmacological importance prepared in flow are shown in Figure 8. These efforts highlight the application of continuous flow chemistry as a reliable enabling technology for the

fast generation of compound libraries for biological screening in drug discovery programs.

For those interested in the molecules shown in Figure 8, the publication by Britton and Jamison for the synthesis of pyrazoles and pyrazolines is a good example of the use of flow chemistry in the synthesis of chemical libraries (Britton and Jamison 2017). A sequence of coil reactors was used to generate substituted diazoalkanes *in situ* which then undergo a [3+2] cycloaddition reaction with alkynes and alkenes to afford pyrazoles and pyrazolines, respectively. More than thirty compounds were prepared using the optimized conditions in a straightforward manner (Scheme 41) (He and Jamison 2014, Mykhailiuk 2015).

The ability to perform several steps in flow without the need for individual purifications was also explored (Britton and Jamison 2017). Three flow modules were added which allows further reactions with the recently formed azole core. Thus, C-N arylation/methylation, amidation and TMS removal reactions were sequentially performed and gave access to some therapeutics and a human lung cancer suppression candidate. For example, Scheme 42 shows an integrated sequence of five steps in a continuous flow regime to prepare the measles therapeutic AS-136A (**183**). Other highly substituted pyrazoles can be prepared using this unified continuous flow assembly for their evaluation in a MedChem program.

Another concept of flow chemistry that has stimulated research in the field of medicinal chemistry is the possibility to integrate steps that are typically performed alone: synthesis, purification, and evaluation of biological activities. (Guetzoyan et al. 2013, Baranczak et al. 2017). In this regard, many synthetic and biological laborious manual procedures can be avoided employing a machine-assisted approach for complete evaluation of a target molecule (Ley et al. 2015).

In this context, Ley's group reported in 2013 the use of flow chemistry to perform the synthesis and biological evaluation in an integrated flow platform (Scheme 43) (Guetzoyan et al. 2013). The continuous flow synthesis of a series of imidazo[1,2-*a*]pyridines, including two anxiolytic drugs (zolpidem and alpidem), was evaluated and directly coupled to a frontal affinity chromatography (FAC) screening assay in order to investigate their interaction with the Human Serum Albumin (HSA) protein (Kragh-Hansen 1990).

Advantages of flow processes in this set-up are evident, since it allows different aminopyridines and unsaturated ketones to be dispensed into the reactors to achieve a collection of compounds in a computer- and machine-assisted manner. Moreover, this transformation typically takes 24 hours in batch procedures (Guetzoyan et al. 2013).

By the use of immobilized reagents, this strategy proves that both the desired set of reactions and the workup and purification procedures can be accessed in a single process avoiding exhaustive manual operations. The authors did not present a fully integrated platform for the synthesis of compound libraries and their biological evaluation, but the instrumental components and assembly demonstrated in this study form the basis for future developments towards this goal.

Summarizing, flow chemistry has brought a new dimension for traditional medicinal chemistry with a huge difference when compared to combinatorial chemistry. Continuous protocols are more focused and deliver fast solutions for extensive screenings. The incorporation of in-line biological assays will speed up the process of drug discovery, placing continuous flow chemistry at the frontier of modern medicinal chemistry.

CONCLUSIONS

Chemical syntheses assisted by enabling technologies have been widely used in the last six decades by the petrochemical and chemical industries, and it is well accepted that continuous flow chemistry has been the key technology in

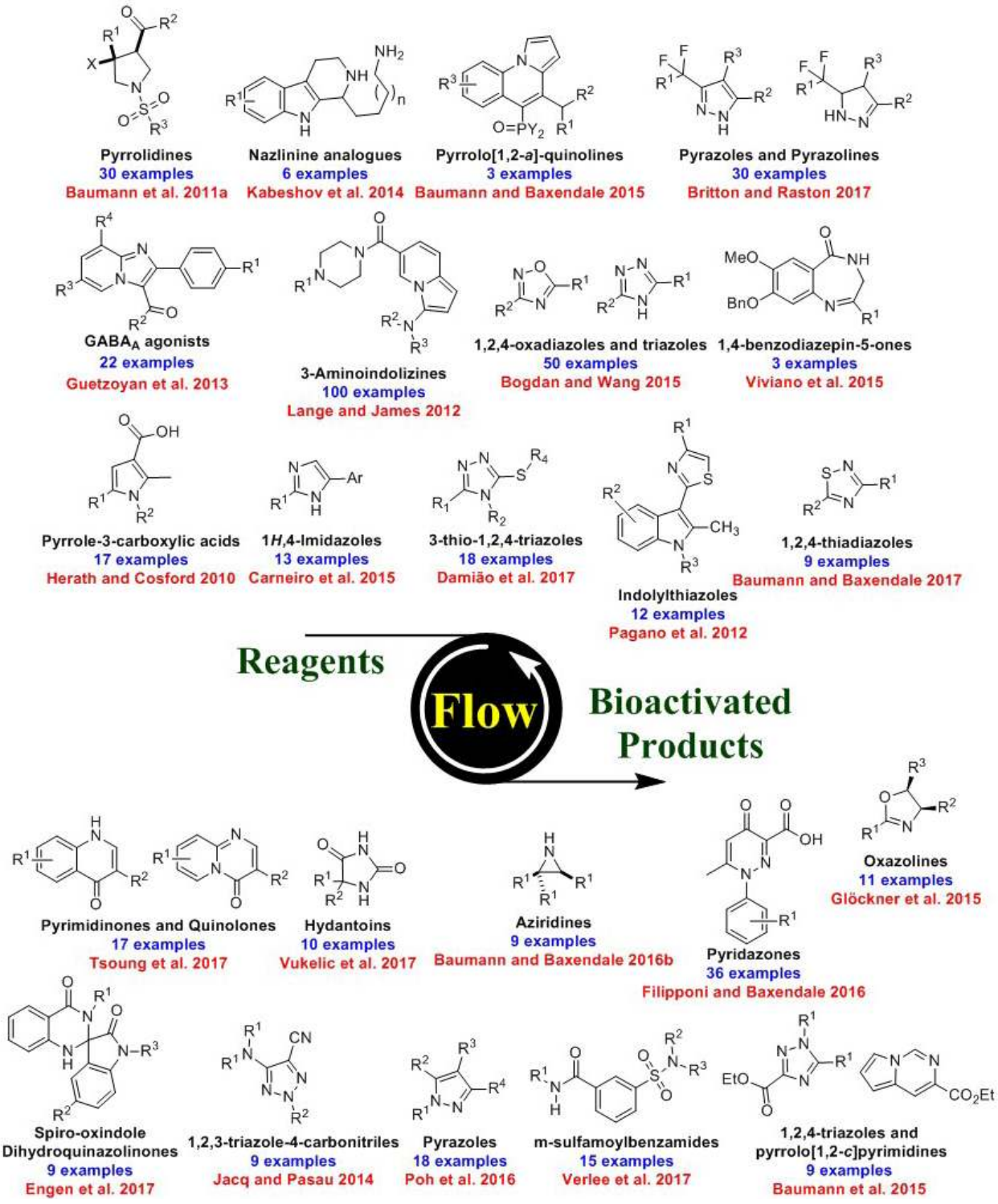
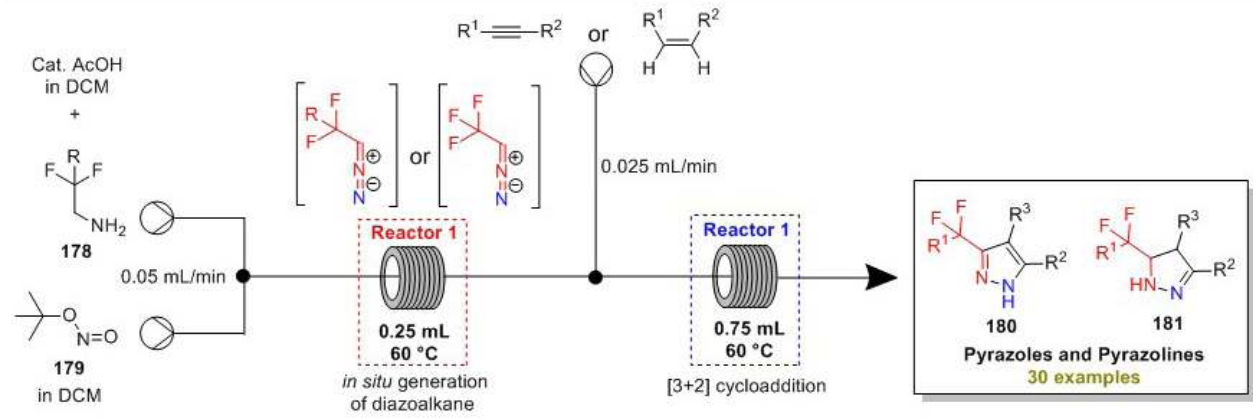
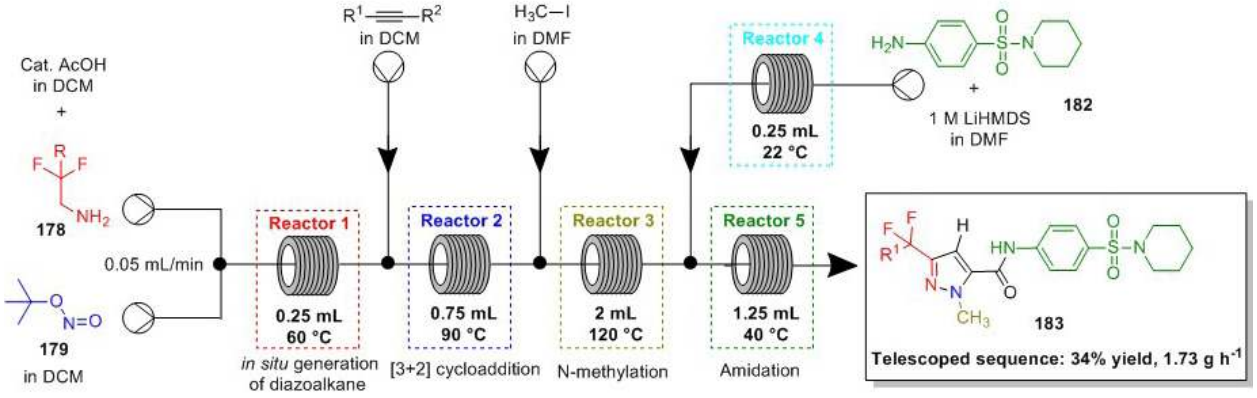


Figure 8 - Selected examples of bioactive heterocyclic molecules prepared in continuous flow regime.



Scheme 41 - Continuous flow synthesis of highly substituted pyrazoles and pyrazolines.



Scheme 42 - Synthesis of AS-136A using a unified continuous flow platform.

this scenario. However, only in the last 20 years has this technology attracted the attention of big pharma and academia as a real and useful tool to expand accessible chemical space and support scale-up, safety, profitability and sustainability of chemical and API synthesis. In this review we have shown the many facets and possibilities of enabling technologies in chemical synthesis, highlighting essential examples using flow chemistry but, most importantly, trying to show the broad scenario in which chemists and chemical engineers are inserted. To finish, we should always remember that Nature knows best; biosynthesis is much more a continuous flow process than batch.

Our principal perspective is that enabling technologies such as continuous flow chemistry are not a promise, but are very important tools already present, and certainly are the future of developments in chemical synthesis.

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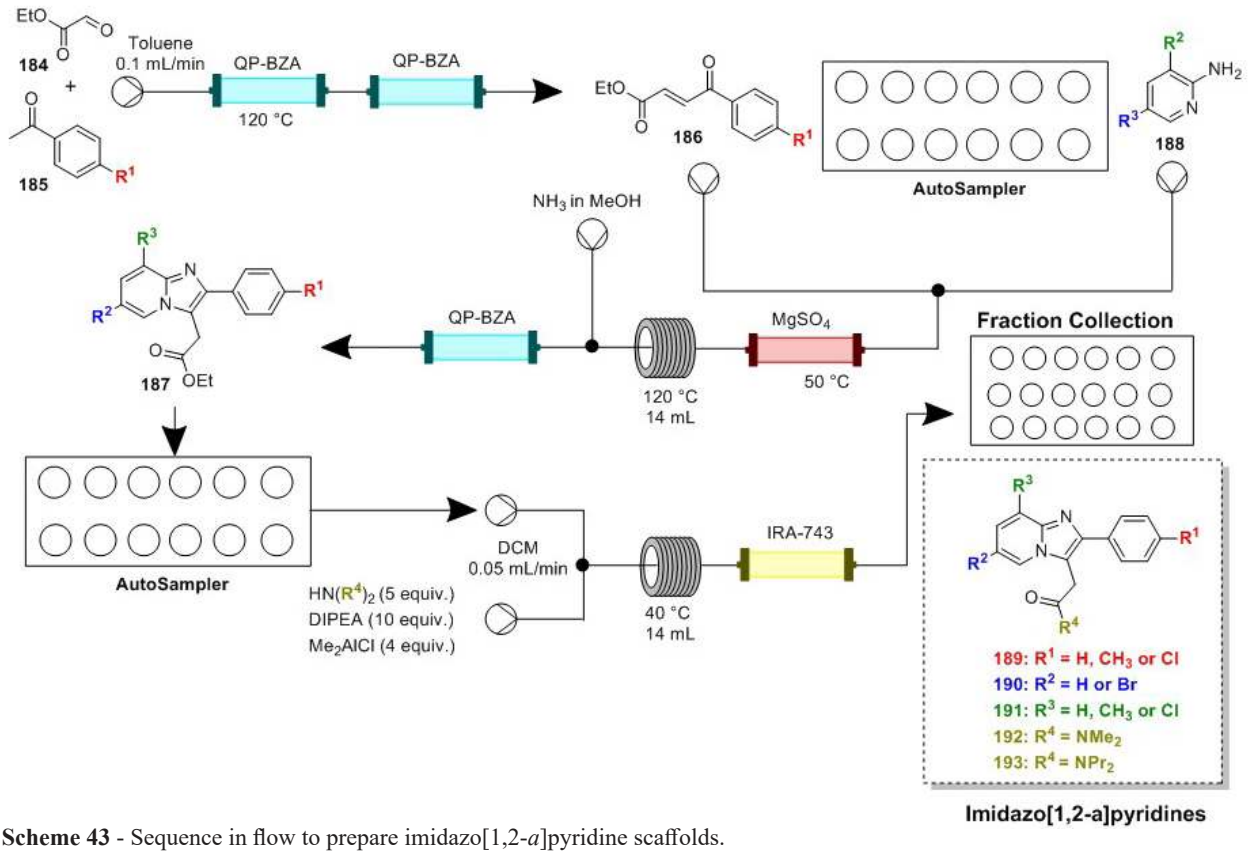

Scheme 43 - Sequence in flow to prepare imidazo[1,2-*a*]pyridine scaffolds.

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