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Flow Chemistry: Recent Developments in the Synthesis of Pharmaceutical Products

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INTRODUCTION

Synthetic organic chemists have lately shown a lot of interest in continuous flow techniques, as an alternative to the standard batch approach of doing organic synthesis in closed vessels, test tubes, or round-bottomed flasks.1 The use of dedicated continuous plants in the petrochemical and bulk chemicals industries was the norm until very recently. However, these systems have recently gained popularity for the preparation of fine chemicals, including natural products2 and Active Pharma-ceutical Ingredients (APIs), particularly in academic institutions. There is clear interest in moving towards continuous flow manufacture of APIs, even if the pharmaceutical sector currently uses multipurpose batch or semibatch reactors.3 The synthesis of organic compounds is not the only use of flow technologies, however. The remarkable end-to-end continuous production of an API, aliskiren hemifumarate, was revealed in a groundbreaking study by researchers from the Novartis-MIT Centre for Continuous production in Cambridge.4 From a chemical intermediate, the procedure explains how to continuously carry out the reactions and extra operations (such as quench, work up, isolation, and purification) that are necessary. This allows for a completely automated continuous process that incorporates not only chemical transformations and separations but also crystallisations, drying, and formulation. The Novartis-MIT pilot plant has two synthetic steps—forming the API salt and crystallization—and delivers 100 g/hour of aliskiren, which is impressive.tablets with 112 mg of free aliskiren are the end result of this method. The work's continuous reactor, with a capacity of 0.7 L, could prepare 0.8 tonnes of API every year. The continuous reactor capacity needed to bring the method to a commercial scale of 188 tonnes of API/year is 136 L, which compares well with the actual batch reactor volume of roughly 1500 L. In addition, the reactions in the batch process take 48 hours at refluxing conditions, but the continuous process only takes 1 hour and doesn't use solvents. In total, the batch process takes 300 hours and uses 21 unit operations, while the flow process uses 48 hours and 13 unit operations. These figures lead to a smaller, more convenient environmental element and a smaller footprint for the automated flow process.4

There is a newfound interest in continuous flow processes, and the aforementioned example proves it. The fundamental properties of flow reactors are to blame for this trend. On a laboratory scale, a continuous flow process is usually carried out in a so-called "microreactor,"5 a small-diameter apparatus that contains a contained space and subjected the reaction to very regulated conditions. A flow system's unique selling point is its very efficient heat and mass transmission, which speeds up the reaction rate and, in comparison to a batch system, typically improves productivity.6 Temperature alone isn't enough

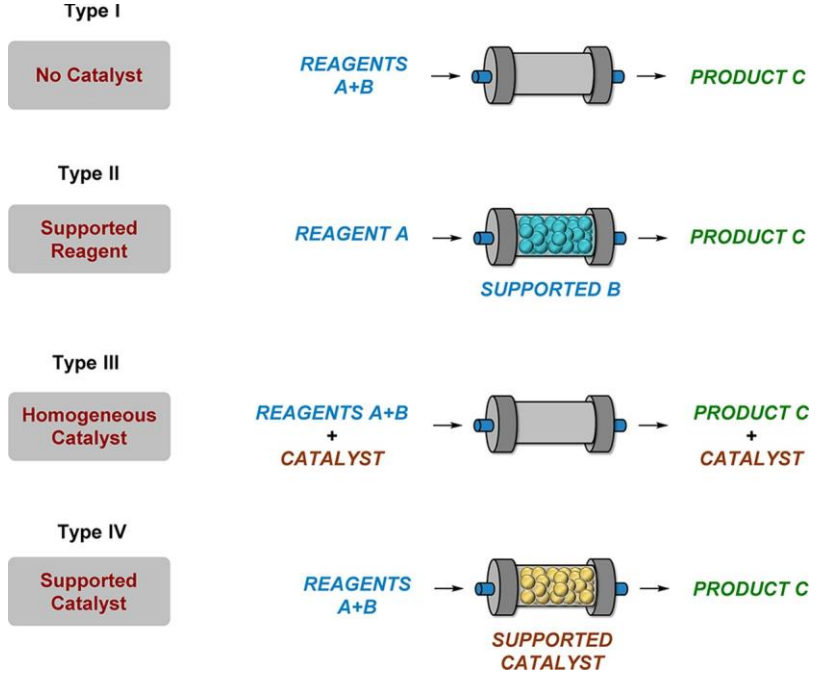


Figure 1. Types of continuous *fl*ow systems.

The tiny size makes it simple to apply and remove a heating source, allowing for highly accurate temperature control along the microreactor and preventing uncontrolled dangerous exothermic reactions. This not only promotes transfer but also allows for exact monitoring of the heat exchange. Compared to a batch process, a continuous flow system makes it easier to set up and monitor reaction parameters like temperature, pressure, and flow rate, leading to a more consistent and repeatable process.7 The minimal volume needed for flow processes allows for quick screening of reaction conditions; once optimised, the reaction may be ramped up. There are a lot of potential issues that could develop when scaling up a chemical reaction, such as runaway reactions, inefficient miXing, or the creation of byproducts. There are three ways to make a lot of chemicals in a microreactor, and the first and simplest is to run the process for longer, which is known as scaling-out. In theory, this is simpler than in batch reactions. Another option is to employ many reactors in simultaneously, which is called "numbering up," or to scale up to bigger continuous reactors and run the process there.8 Some safety concerns may also be eliminated by using the microreactor, which uses very tiny amounts of chemicals. For instance, the operator is kept safer by limiting their handling of potentially dangerous or toxic items. It is also feasible to conduct reactions involving transitory and reactive substances in a microreactor because of the short residence period.

Some examples of flow chemistry include microwave irradiation, photochemistry, inductive heating, electrochemistry, novel solvent systems, microreactor technology, 3D printing, and assisted reagents or catalysts. A completely automated process with enhanced throughput might be developed with this combination.
It is not unexpected that continuous processing is becoming a method that may greatly influence the synthesis of APIs (or API intermediates) due to all these benefits. A recent study by Professor Kappe and colleagues thoroughly investigated the use of

continuous flow conditions for the safe production of organic intermediates and APIs.10 Some previously forbidden synthetic steps may now be carried out under flow circumstances with little danger, as pointed out by the authors. These steps include the employment of potentially toxic or explosive intermediates, reactions operated under high pressures, or above the boiling point of the solvent. This is why flow chemistry is a cutting-edge field that paves the door for more efficient ways to produce important chemicals.

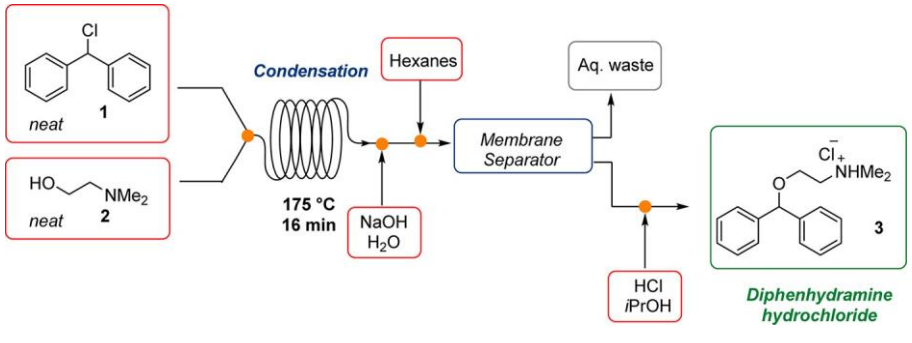
Figure 1 shows the four main categories into which the continuous flow systems described in the literature so far fall, according to Kobayashi and colleagues.11 Type I reactions include flowing all chemicals through the reactor and collecting the result at the end. The second sort of reactor involves connecting one of the reactants to a solid and then passing the substrate through it. If the process proceeds to

processing steps that would be too difficult to manage or store in

finalisation, the departing response

conventional batch processing. In addition, the amount of solvents and reagents needed is much less, making it easy and cost-effective to screen reaction conditions. This opens the door to automated library synthesis and faster processing times. This would make it easier to find a prospective medicine and produce it in bigger quantities for use in biological testing.
To further boost efficiency, continuous flow synthetic techniques are also readily combinable with other supporting technologies.9 Common enabling technologies coupled with just the thing you want. Catalysts are not necessary for reactions of types I and II. A homogeneous catalyst is used in type III reactions; the catalyst flows through the reactor with the reactants, therefore a separation step is needed at the end to retrieve the product without the catalyst (and any byproducts). In type IV, the catalyst is housed within the reactor and the reagents pass through it. A solid support is needed for catalyst immobilisation, but in theory, the product and catalyst don't need to be separated. Additionally, the catalyst could be easily

Scheme 1. Continuous Flow Synthesis of Diphenhydramine Hydrochloride



recycled. Since catalytic techniques are currently crucial for the development of sustainable and efficient processes, the latter kind is often thought of as the most convenient way to carry out a reaction under continuous-flow circumstances.12 All four reactor typologies are used or combined in the cases discussed in this study. Finally, this study will go over type III and type IV flow systems, concentrating on how stereoselective chiral organocatalysts are used.
One potential issue with using microreactors to synthesise APIs is the possibility of the reactor being clogged, namely the channels becoming blocked owing to solid precipitation. For synthetic organic chemists, dealing with the precipitation of inorganic salts or insoluble materials during reactions is a regular occurrence. For example, when the reaction product separates from the reaction mixture and can be easily purified, this may be a suitable scenario.

views, as well as potential and anticipated advancements in the field.
Here is a list of typical reactor materials and the acronyms used for them, as we will be describing many kinds of continuous flow reactors: The acronyms FEP, PEEK, PFA, and PTFE stand for fluorinated ethylene propylene, polyether ether ketone, perfluoroalkyl alkanes, and polytetrafluoroethylene, respectively.

To clarify for the schemes, the following is a list of colours used to denote different components: red for starting materials, green for products, yellow for isolated intermediate products, dashed yellow for nonisolated intermediates, and light blue for catalysts.

1. MULTISTEP SYNTHESIS OF ACTIVE PHARMACEUTICAL INGREDIENTS IN FLOW
2. Here are a few instances of the continuous flow creation of APIs that have been shown in

process. In the context of a flow system, however, the issue this poses becomes immediately apparent. This is why, despite the fact that more technological advancements are required, more advanced methods for dealing with solids in continuous flow processes have been created in recent times.

Given the abundance of recent reviews covering the synthesis and manufacturing of APIs and related advanced intermediates, we will narrow our focus to recent developments in the continuous flow multistep synthesis of organic molecules that have found API applications. This will include contributions described in the literature from 2013 to 2015, as well as unreported examples from this time period. In an effort to help bridge the gap between pharmaceutical research and production, we will provide a broad review of the many techniques, technologies, and synthetic methodologies that have been employed so far.

Section 2 will focus on the most notable cases from 2013 and 2014 that emerged in the literature, while Section 3 will explore in depth only the most recent works that have not been covered in any other study.

Section 4 provides an overview of a new and mostly uncharted area of study: stereoselective organocatalysis under flow conditions. We aim to show the many possibilities of this method and

provide a foundation for future work in this area so that we can create better tools for the stereoselective synthesis of chiral drugs.

Section 5 concludes with some suggested broad strokes on the subject and some thoughts on the

We will go over the literature from 2013 and 2014.13 The key synthetic pathway to the final target molecule and the major advances in each case will be emphasised.

Over 100 tonnes of diphenhydramine hydrochloride are required annually to provide the global demand for several popular drugs, including Benadryl, Zzzquil, Tylenol PM, and Unisom.

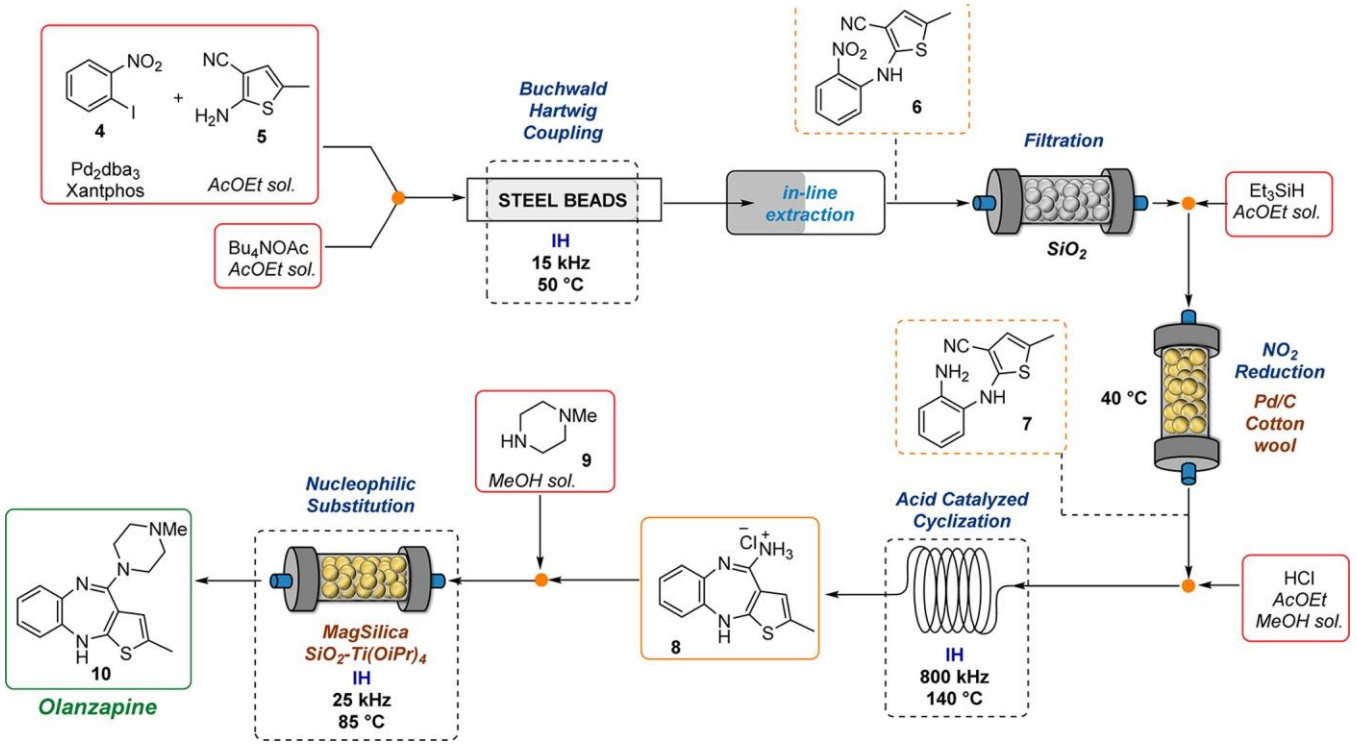
Jamison and colleagues came up with a continuous flow method for synthesising 3 in 2013, cutting down on production time, waste, and purification stages compared to current batch synthetic approaches (Scheme 1).14 A 720 μL PFA tube reactor (i.d. = 0.5 mm) was used in the optimised process to mix chlorodiphenylmethane 1 and dimethylethanolamine 2, with a residence period of 16 minutes and at a temperature of 175 °C. A rapid rate of reaction was achieved by conducting the reaction above the boiling point of water and in the absence of solvent. Unlike under batch circumstances, Product 3 could be readily conveyed in the flow system when it was acquired as molten salt, meaning it was above the salt's melting point.

The output of the reactor was then mixed with warmed

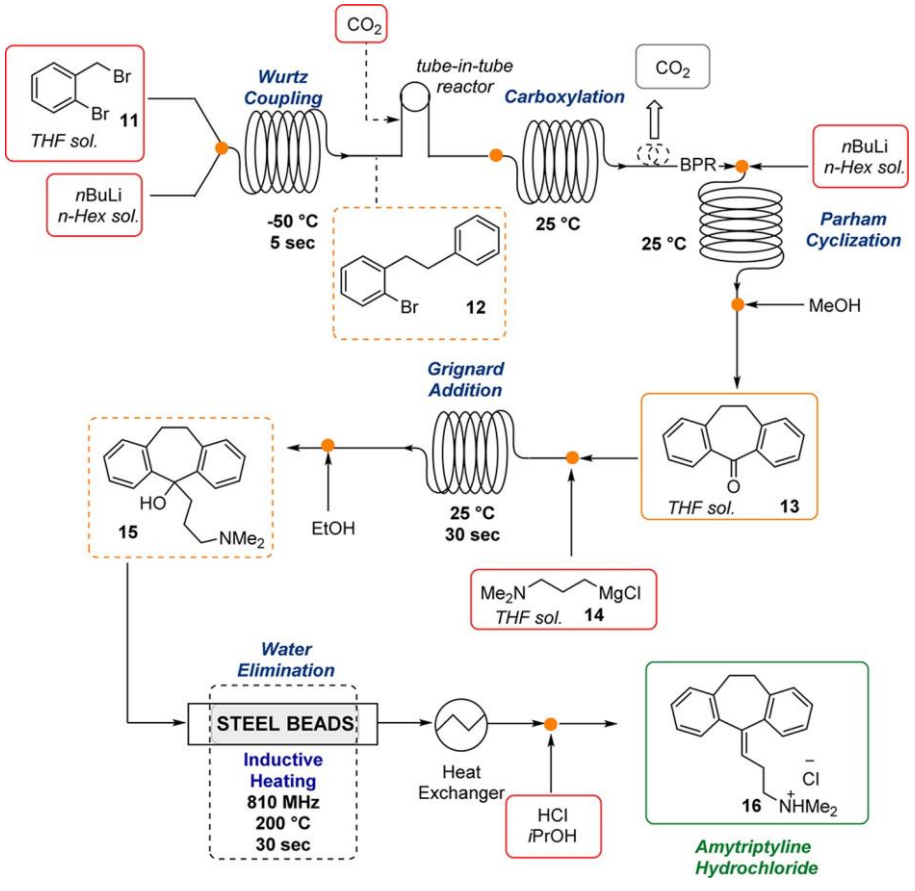
Ammonium salts may be neutralised using 3 M NaOH. The neutralised tertiary amine was removed into an inline membrane separator using hexanes after quenching. Diphenhydramine hydrochloride 3 was precipitated with an overall yield of 90% and an output of 2.4 g/h after the organic layer was treated with HCl (5 M solution in iPrOH).

Less side effects, such as extrapyramidal effects, bodily stiffness, and involuntary tremors, are a characteristic of atypical antipsychotic medications compared to traditional antipsychotics. Among the unusual ones, olanzapine 10,15, which is sold under the brand name of

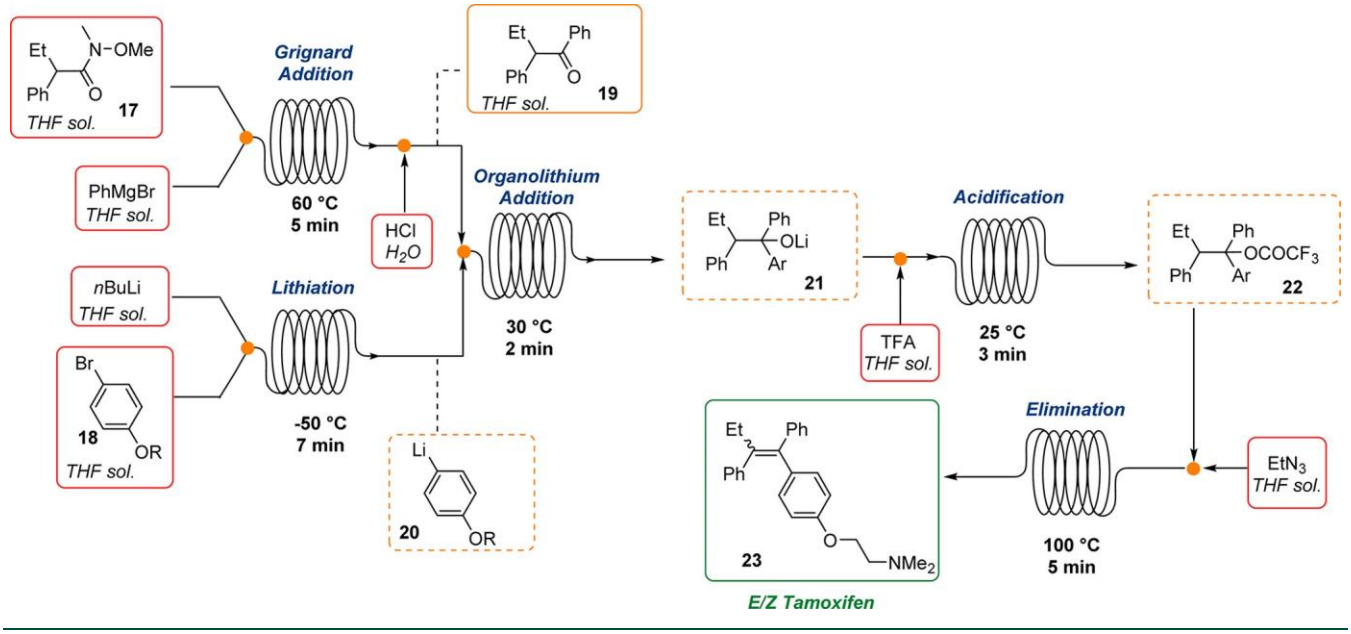
Scheme 2. Continuous Flow Synthesis of Olanzapine



Scheme 3. Continuous Flow Synthesis of Amytriptyline Hydrochloride



Scheme 4. Continuous Flow Synthesis of Tamoxifen



Zyprexa is a medication that may help with bipolar illness and schizophrenia. The multistep continuous flow synthesis of olanzapine 10 was created by Kirschning and colleagues in 2013

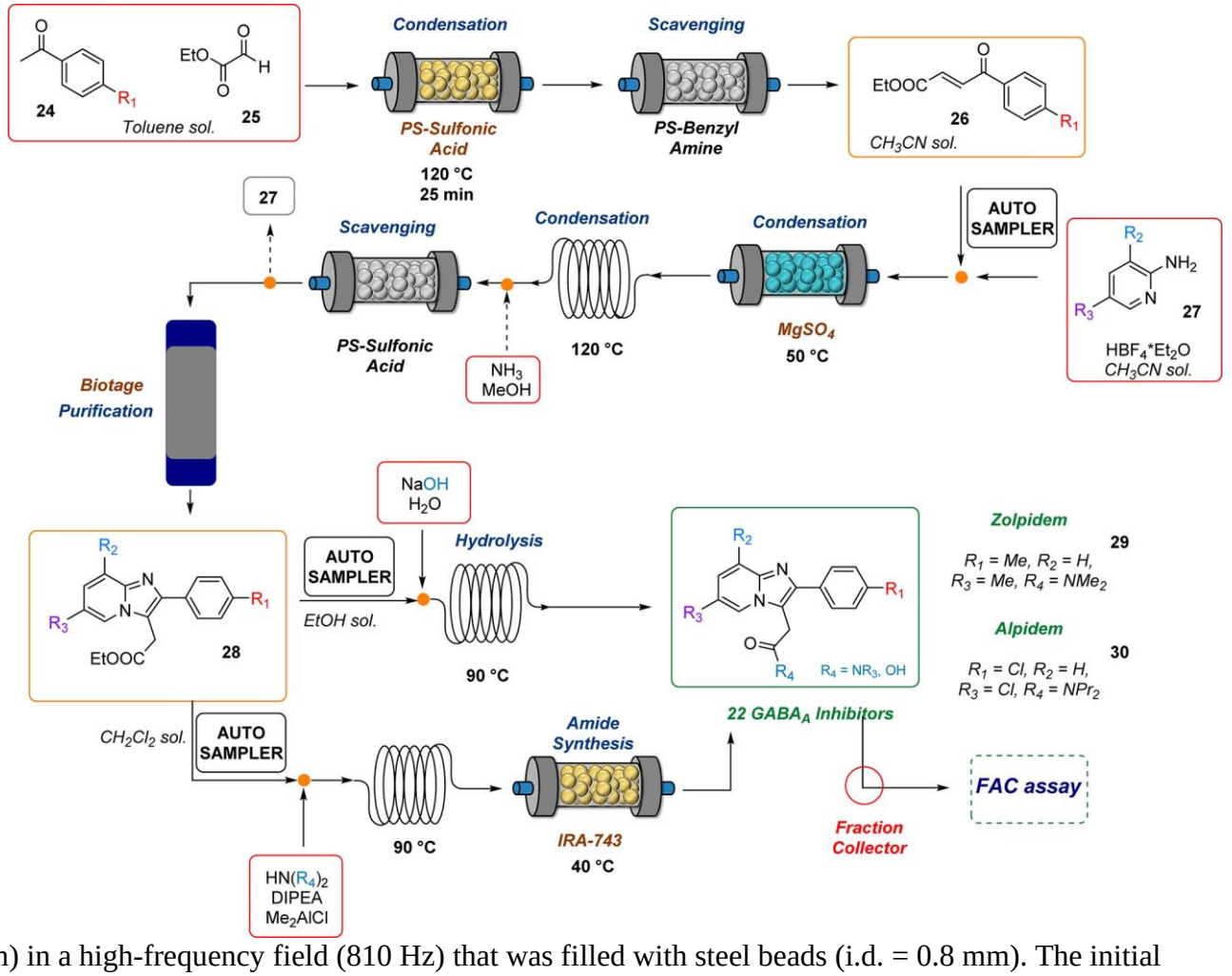
with the use of inductive heating (IH), a method that significantly decreased reaction times and increased process efficiency.16 Using magnetic nanoparticles and an electromagnetic field (operating at medium or high frequency according to the size of the nanoparticles) to rapidly raise their temperature is the basis of inductive heating, an unconventional method of heating.17 Using Pd2dba3 as a catalyst and Xantphos as a ligand, the first synthesis step included combining aryl iodide 4 and aminothiazole 5, as shown in Scheme 2. The Buchwald-Hartwig coupling process was carried out inside a PEEK reactor that was inductively heated to 50 °C (15 kHz) and included 0.8 mm steel beads. Since AcOEt was compatible with some of the

stages in the response that follow. The Pd catalyst was removed by passing the crude mixture through a silica cartridge after quenching with distilled water and in-line extraction in a glass column. Then, at 40 °C, nitroaromatic compound 6 was reduced with Et3SiH in a fixed bed reactor that also included Pd/C. The catalyst maintained its activity for over 250 hours after usage, and a nearly quantitative yield of aniline 7 was achieved. The output of the reactor was then mixed with hydrochloric acid (a 0.6 M methanol solution) and subjected to high frequency heating (800 kHz) at 140 °C. The total yield of product 8, which was obtained by acid catalysed cyclization, was 88%. The overall reactor capacity is just approximately 8 mL, and it is remarkable that the three-step process did not need any solvent swap.
In a 3 mL PEEK reactor using MAGSILICA as the inductive material and silica-supported Ti-(OiPr)4 as the Lewis acid, compound 8 was finally substituted with piperazine 9. Olanzapine 10 was produced in 83% yield by inductively heating the reactor at 85 °C with a medium frequency of 25 kHz.
Tricyclic antidepressants like amitriptyline inhibit channels for potassium, calcium, and salt. Migraines, tension headaches, anxiety attacks, and even some forms of schizophrenia are among the many medical conditions that it may alleviate.

health problems. Synthesis of dibenzosuberone 13 from lithiated benzyl bromide 11 by Wurtz dimerization and one-pot Parham cyclization using CO2 as an electrophile is the most common synthetic method for its manufacture. After reacting ketone 13 with Grignard reagent 14, the next step was to remove water, which yielded API target 16.
Following this well-established synthetic technique, Kirschning and Kupracz (2013) devised a novel procedure for the continuous flow synthesis of Amitriptyline 16 (Scheme 3).18 Considering the utilisation of gas phase reagents (CO2) and highly reactive intermediates (aryl- and alkyllithium compounds), doing the multistep synthesis of 16 in continuo offers significant benefits over the typical batch technique. The first lithiation reaction involving nBuLi and benzyl bromide 11 was carried out at -50 °C in a 0.5 mL steel reactor coil with an inner diameter of 1.0 mm. The target aryl bromide 12 was successfully extracted in 79% yield after just 5 seconds of quenching with MeOH. The optimal reaction conditions for initial Wurtz coupling were determined, and then the telescoped synthesis of ketone 13 was investigated. Direct addition of CO2 to the raw stream of reactants was made possible by using S. V. Ley's19 tube-in-tube reactor technique. 0.5 mL of PFA reactor coil (i.d. = 0.8 mm) was used for the carboXylation phase, which was carried out at 25 °C. Following the removal of gas, a second stream of nBuLi was introduced to the reaction mixture. The last phase of cyclization was carried out at 25 °C using a 0.5 mL PFA reactor coil with an inner diameter of 0.8 mm. Upon adding MeOH, dibenzosuberone 13 was extracted with a 76% yield and a total residence time of around 30 seconds. It is easy to understand the flow methodology's superior performance when one considers that the 13-unit batch synthesis alone needed a 2-hour reaction time at -100 °C, with a yield of 56%.
A 0.5 mL PFA reactor coil (i.d. = 1.0 mm) was used to react with Grignard reagent 14 at 25 °C with a residence period of roughly 30 s after the pure ketone 13 had been extracted from the multistep flow synthesis. Using inductive heating technology, a 0.3 mL cartridge steel reactor (i.d. = 4.0) was used to

eliminate water from the carbinol 15 that was produced after protonating the crude reaction mixture with EtOH.

Scheme 5. Continuous Flow Synthesis of $GABA_A$ Inhibitors



mm) in a high-frequency field (810 Hz) that was filled with steel beads (i.d. = 0.8 mm). The initial substance was entirely transformed into amitriptyline after 30 seconds of residence time at 200 °C. In order to get the raw mixture down to room temperature, a heat exchanger had to be present. The 17-methyl amitriptyline hydrochloride salt was finally obtained in 71% yield by recrystallization from an EtOH/Et2O mixture and the addition of HCl (1 M solution in isopropanol).

Utilising organometallic reagents through flow chemistry technology has numerous advantages over conventional batch procedures. These include the ability to precisely control the temperature of reactions that could be exothermic, the safe handling of extremely reactive organometallic intermediates, and the rapid and stoichiometric reaction of Weinreb amide 17 in a 10 mL PFA reactor coil at 60 °C. Isolation of ketone 19 in 97% yield was achieved after 5 minutes of residence time and quenching with HCl aq. At -50 °C, using a 10 mL PFA reactor coil, aryl bromide 18 was simultaneously lithiated with nBuLi. Following a 7-minute reaction, the aryl lithium compound 20 was combined with a ketone 19 THF solution and fed into

a 0.4 mL PFA reactor coil at -50 °C with a 10-second residence period. The mixture was then heated for a second.

Cook the PFA reactor coil (5 mL) for 2 minutes at 30 °C. The 10 mL PFA reactor coil was heated to 25 °C for 3 minutes after adding TFA to the crude lithium alkoXide 21. After that, trifluoroacetate 22 was eliminated with triethylamine into two PFA reactor coils (10 mL) at 100 °C for a total of 5 minutes. The

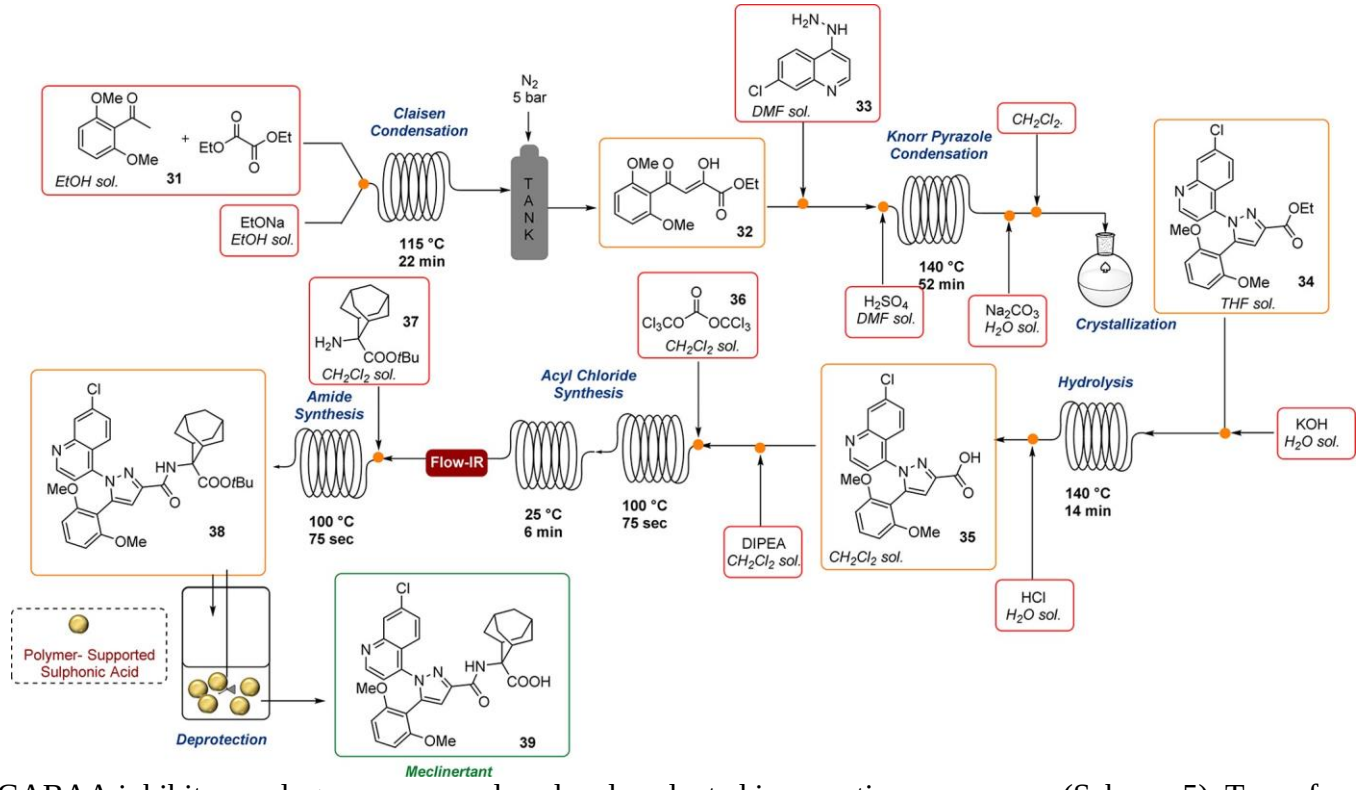
mixing substrates and reagents, quantified.20 This being the case,

Tamoxifen 23 was produced as an E/Z mixture using telescoped synthesis.

Organolithium and Grignard reagents are examples of very reactive and air-sensitive chemicals; hence, Steven Ley's lab investigated a novel flow platform based on fluoropolymer peristaltic pumps. The multistep synthesis of the antagonist prodrug tamoXifen 23, which is used to treat breast cancer at all stages, was shown in 2013 using this method.21 Schema 4 shows how this method reduced hazards associated with handling organometallic reagents by combining four separate chemical processes into one stream with little human participation.
The tetrasubstituted target alkene 23, which is produced using a flow synthesis, was first prepared by Grignard addition of PhMgBr to

from aryl bromide 18 in a yield of 84% (25:75). With the flow process running continuously for 80 minutes, 12.4 g of pure API was obtained; this quantity is enough to treat one patient for more than 900 days, which is comparable to taking one dosage every 5 seconds.
When the chemical and biological sciences are not properly integrated, it may lead to inefficient drug development processes and a loss of valuable data. The 2013 study by Ley's group looked at the possibility of creating a technology that could combine chemical synthesis with biological assays22 for potential new drugs. They used frontal affinity chromatography (FAC) as an inline screening tool and a flow chemistry platform for chemical synthesis.23 In a modest collection of 22

Scheme 6. Continuous Flow Synthesis of Meclinertant



GABAA inhibitor analogues were produced and evaluated in a continuous manner (Scheme 5). Two of them are agonists of GABAA receptors that are utilised as active medicinal ingredients: alpidem for anxiety and sleeplessness and zolpidem for certain brain problems. The imidazopyridines to which these compounds belong are active against cancer, viruses, and microbes.

The synthesis of imidazopyridines in continuous flow started with the acid-catalyzed condensation of ethyl glyoXalate 25 with ketone 24. A reactor containing 2 grammes of polymer-supported sulfonic acid was used for the reaction, which was carried out at 120 °C with a residence duration of 25 minutes. A cartridge containing 3 g of polymer-supported benzyl amine was used to scavenge the excess of 25 after the crude mixture was run through it. With an excellent yield ranging from 76% to 85%, three products were recovered without the requirement for workup or additional purifications. At 50 °C, three α,β-unsaturated ketones 26 and three aminopyridines 27 were pumped into a reactor containing MgSO4 as a dehydrating agent. The collection process was carried out using an auto sampler. The matching imines were quickly produced under superheating conditions and then 5-exo cyclized into a 14 mL reactor coil at 120 °C. It was possible to recover the excess aminopyridine 27 by injecting NH3 into MeOH to release the bound material after the crude reaction mixture had gone through a column filled with polymer-supported sulfonic acid. Eight imidazopyridines were obtained after in-line chromatographic purification using the Biotage system. In the final stage of the synthetic process, molecular diversity was introduced into the imidazopyridine scaffold through the use of an auto sampler to regulate two separate reactions. The first reaction involved the saponification of 28 ester moieties with NaOH aq. in a 14 mL reactor coil at 90 °C. The second reaction involved converting 28 esters into corresponding amides.

Through the use of Me2AlCl and two distinct secondary amines (HN(R4)2). To eliminate Al compounds, the reaction mixture was heated at 90 °C in a 14 mL reactor coil and then passed through a cartridge containing IRA-743 polyol resin. It just took four days to get a library of twenty-two imidazopyridine derivatives using this flow method. The synthetic platform ended with the introduction of a fraction collector. After the appropriate dilution, 10 µL aliquots were automatically obtained for each reaction output and submitted to FAC analysis.

The employment of machine-assisted flow methodologies24 allows for better efficiency and high throughput, however batch methods are still the most common approach for executing chemical reactions. Ley and colleagues published a study in 2013 (Scheme 6) that directly compared the flow multistep synthesis of the selective neurotensine probe SR48692 (Meclinertant) with traditional batch preparation.25 The authors of this case study set out to determine if flow technology might solve several synthetic problems—such as solid precipitation and the buildup of byproducts—and speed up a multistep synthesis (i.e., improve yields or decrease reaction times). Product 32 is produced in 60% yield after 3 hours of stirring in an initial Claisen condensation between ketone 31 and ethyl glyoXalate in the presence of NaOEt as a base and EtOH as a solvent in a batch operated at room temperature. A speedier approach was to superheat the reaction in flux, which involves heating the solvent over its boiling point. For example, a 52 mL PFA reactor coil was heated to 115 °C with a residence period of 22 minutes, yielding 32 of the respective products in 74% yield. An impromptu pressurised stainless-steel tank was constructed to address solid accumulation issues; this tank was meant to conduct the reaction constantly, without the risk of precipitation or obstruction, using 5 bar of nitrogen.

In a DMF reaction, the following was carried out with 32 and a commercially available hydrazine 33:

5. OUTLOOK AND PERSPECTIVES

It is hardly surprising that pharmaceutical companies have also begun to focus on flow chemistry for the preparation of active pharmaceutical ingredients (APIs) given the obvious benefits of continuous flow technologies in the industrial process. The potential to integrate flow-based chemical synthesis with new analytical tools for in-process monitoring and enabling technologies to expedite isolation and purification steps is driving this trend, which will only grow stronger in the years to come.

Microreactors provide many benefits, including as tiny dimensions, improved mass and heat transfer coefficients by 1-2 orders of magnitude, high volumetric productivity, and laminar flow conditions, as well as high surface to volume ratios. When considering potential uses in industrial synthesis, it is important to consider the following factors: low power consumption; greater safety owing to minimal quantity of materials utilised in the process; and cheap operating, maintenance, and manufacturing costs. Scalability in parallel is also an appealing characteristic.

Despite the availability of technology to produce micro-reactors from silicon, glass, steel, and other metals, their widespread application is surprising. The need for an active, stable catalyst and very rapid reactions is a problem because of the short residence durations involved. Recent research by a large pharmaceutical manufacturer found that while continuous processing would improve approximately half of their synthesis reactions, 63% of those reactions could not be done in a microreactor at the time because of solids. Finally, the most important thing is to create microreactors that can handle solids and are adaptable enough to be employed in continuous plants with several purposes. Some recent multistep synthesis flows are also included in this study, demonstrating the tremendous development achieved in this field. It is possible to imagine many more significant technical improvements in the future. When thinking about the economics of flow processes, it's important to keep in mind

that it often takes more time and sometimes not trivial expenditures to construct such processes compared to batch processes.
Furthermore, existing installations may be reluctant to be replaced because of the perceived high risk associated with micro reactors, which is exacerbated by their tiny size, susceptibility to fouling and clogging, leakage between channels, and the lack of information on their dependability and life on stream. Additional drawbacks of catalytic reactors include the possibility of catalyst deactivation, the need to repack or reactivate the reactor often, and the reactor's dependability over an extended period of time while operating.
One major advantage of in-flow processes, nevertheless, is the ability to realise very flexible modules that can carry out on-demand synthesis. The result will be a regional distribution and manufacturing network that can adapt more quickly to changes in demand thanks to "ad hoc" tailoring of industrial processes that alter production size and timing. For instance, (micro)reactors technology has made it possible to synthesise unique molecules with less risk of medicine shortages, and in-situ preparation of explosive and dangerous chemicals is now a real possibility.
Lastly, our capacity to carry out catalytic, enantioselective reactions in flow is an important and likely to be the focus of future research. All of the reaction sequence examples reported in the last few years pertain to the synthesis of achiral compounds or the racemic form of a chiral product; there is a lack of development in the stereoselective synthesis of chiral products. The utilisation of chiral catalytic reactors to produce pharmaceutically relevant enantiomerically pure compounds was only made possible in 2015 thanks to the Kobayashi report on Rolipram11. But

A successful use of catalytic reactors in an applied process requires optimisation and study of various subjects, including activation, efficiency, longevity, degradation, and probable reactivation of supported chiral catalysts. Future difficulties may include integrating the whole manufacturing process into a single, all-in-continuo process, in addition to the synthesis of complicated compounds. There are a number of potential benefits: moving directly from research to manufacturing will reduce overall process timelines and speed up time to market. In addition, by integrating and colocating production processes in one facility, one may get savings on COGS (cost of products sold), have more flexibility, have a smaller footprint, and reduce inventory. According to reference 4, the astounding outcome for the manufacturing of alkiskiren's final tables has

> opened new avenues in this area; however it should be noted that the whole in *fl*ow manifacturing of aliskiren tablets was accomplished by studying only the two *fi*nal steps of the synthesis, a condensation reaction starting from an advancedprecursor of the *fi*nal product where the absolute con*fi*gurationof all four stereocenters has been already established. The future challenge is to accomplish e*ffi*cient synthesis of enantiomerically pure products under continuous *fl*ow conditions and integrate the in *fl*ow synthesis in a single "allin *fl*ow" process featuring also in line analysis, puri*fi*cation, and crystallization steps, and leading to the production of the *fi*nal, ready for the market drug. The road is long and full of obstacles, but, considering the impressive progress made in the continuous *fl*ow technologies in the past few years, the *fi*nal goal might be accomplished in shorter times than expected.

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