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Review

Understanding flow chemistry for the production of active pharmaceutical ingredients

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SUMMARY

Multi-step organic syntheses of various drugs, active pharmaceutical ingredients, and other pharmaceutically and agriculturally important compounds have already been reported using flow synthesis. Compared to batch, hazardous and reactive reagents can be handled safely in flow. This review discusses the pros and cons of flow chemistry in today's scenario and recent developments in flow devices. The review majorly emphasizes on the recent developments in the flow synthesis of pharmaceutically important products in last five years including flibanserin, imatinib, buclizine, cinnarizine, cyclizine, meclizine, ribociclib, celecoxib, SC-560 and mavacoxib, efavirenz, fluconazole, melitracen HCl, rasagiline, tamsulosin, valsartan, and hydroxychloroquine. Critical steps and new development in the flow synthesis of selected compounds are also discussed.

INTRODUCTION

Flow chemistry has been proved to have a great impact on engineering, science, and technology and created new opportunities in terms of commercialization of products prepared in batch processes. From Liebig's time to current state, round bottom flasks and other conventional vessels have been extensively and successfully employed for the syntheses of various important compounds (Wegner et al., 2011). However, for certain processes, continuous flow reactors were preferred due to their several advantages over classical batch reactors, which mainly prospered in an industrial environment (Dudukovic et al., 1999; Whitesides, 2006). Continuous flow reactors have been used industrially for more than 100 years for the synthesis of bulk chemicals and most suited for the larger production of chemicals (e.g., bulk chemicals). However, most of the organic compounds were synthesized at lab (small) scale, thus batch reactors were preferred. To meet the global demand for the large-scale production of organic compounds at reduced cost, synthetic organic chemists have shifted their attention to flow processes (Goršek and Glavič, 1997; Löwe and Ehrfeld, 1999).

Depletion of the resources, climate change, growing population, and the linear economy put the world at crossroads (Cole-Hamilton, 2020). The solution to this issue is a circular economy driven by renewable resources, by the development of sustainable technologies for the future. In recent past decades, many industrially important products (e.g., energy sector) were scaled up successfully in continuous flow. Microreaction technologies have adequately matured during the course of time, along with simultaneous efforts in process intensification (Jensen, 2017; Moulijn and Stankiewicz, 2000; Górak and Stankiewicz, 2011; Hessel, 2009). Compared to batch processes, reaction parameters such as reagent/reactant quantity, mixing, temperature, time, and the solvent amount can be controlled and assured in flow reactors (Wegner et al., 2011). Stoichiometry and reaction times are key factors to distinct batch and flow systems from each other. In batch processes, concentration of reactant/reagent or their volumetric ratios define the stoichiometry. However, stoichiometry is defined by the flow rates of the reagents/reactants of required concentration in flow processes (Wegner et al., 2011).

Flow processes show superiority over batch (Figure 1), but there are major issues in modern flow chemistry (Figure 1), which are very well discussed and elaborated by Wegner et al. in their review article (Wegner et al., 2011). Compared to batch, in continuous flow, few steps can be tactfully telescoped. However, integrating flow reactors with new components, features, and management of solids in a flow process still remain as challenges in the field (Figure 1). Flow chemistry provides solutions to the batch reactions which are not feasible due to insufficient heat and mass transfer. Batch reactors are the best options for the very slow reactions which are difficult to accelerate by heating effect (Hartman et al., 2011). Flow reactors can

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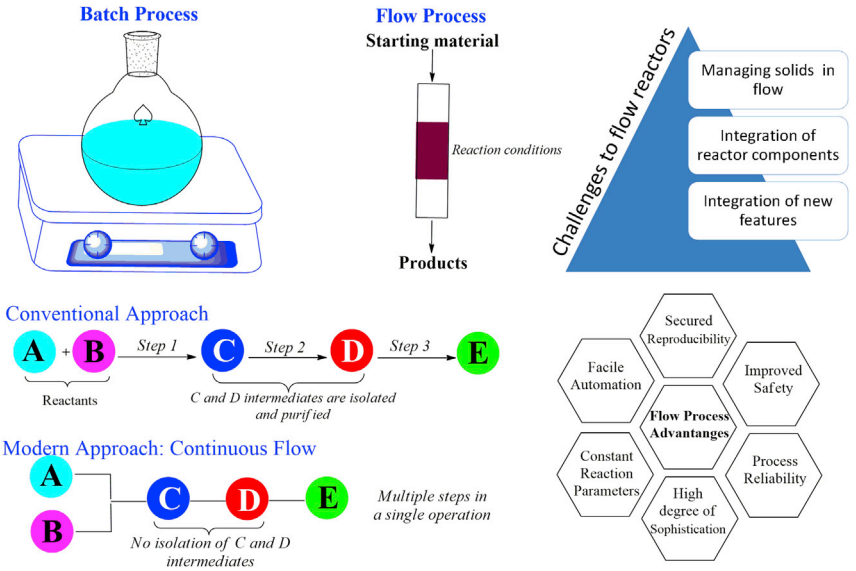


Figure 1. Comparison between batch and flow process; advantages and challenges in flow devices
Figures were adapted with the permission from Wegner et al. (2011) and Webb and Jamison (2010) (RSC).

help to generate the hazardous and unstable reagents *in situ* and further consume safely. Wherein, microstructured reactors allow consecutive reactions in a quick manner while dealing with the highly unstable intermediates (Hone and Kappe, 2021). Plutschack et al. very well reviewed the importance of flow chemistry as "Hitchhiker's Guide" in terms of control over the reaction parameters compared to the batch processes along with basic principles and critical aspects related to flow chemistry (Plutschack et al., 2017). There are various reviews published in area of flow chemistry. The present review discusses the basics and understanding of flow chemistry and their further applications to pharmaceutical industries along with significant enhancement in the field.

IMPORTANCE OF FLOW CHEMISTRY

Each and every chemistry developed at the laboratory scale is not always easy to scale up due to the significant gap between laboratory and industry. Flow chemistry is quite effective in bridging this mentioned gap. Mixing is the critical factor while comparing efficiency of batch and flow processes. The mixing is very well characterized and offers scaling up faster compared to batch processes. Role of flow chemistry in bridging this gap is very well reviewed and discussed by Hartman et al. (2011). In this review, the effect of mixing in the microflow on the product outcome in case of C-N bond formation, electrophilic aromatic substitution, oxidation, organometallic, and in the synthesis of natural products is very well discussed showing the importance of flow chemistry to bridge the mentioned gap.

Electrosynthesis of organic compounds was highly underestimated initially, however, in last few decades over 900 electrochemical reactions were reported. The limitations in terms of scaling up and commercialization could successfully be tackled by using electrochemical flow cells. Among flow chemistry applications, flow electrochemistry displayed its potential in organic electrosynthesis, one of the growing areas in need of additional exploration and investigations (Tanbouza et al., 2020). Miniaturization helped in integration and automation in case of complex systems. In case of electrochemical flow-devices, miniaturization includes the combination of various processes. Campo (2014), in his minireview discussed the systematic journey of miniaturization of flow devices (e.g., electroanalytical, microfluidic fuel cell, and microfluidic devices) used in electrochemical reaction.

Miniaturization in the field of flow chemistry can be helpful in bridging the gap between industry and academic research (Hessel, 2009; Geyer et al., 2009; Hartman and Jensen, 2009; Mak et al., 2009; Wiles and Watts, 2008; Fukuyama et al., 2008; Ahmed-Omer et al., 2007; Watts and Wiles, 2007; Mason et al., 2007; Kobayashi et al., 2006). It basically deals with the two types of reactor systems, i.e., micro- and mini-fluidic, with the former generally showing better heat transfer due to the less internal diameter

(10–500 μm) of channels or tubes along with the advantage of efficient mixing of reactants. However, shortcomings include high pressure-drop, restricted flow capacity, and sometimes blockage (clogging) due to the smaller diameter of channels. The latter is sometimes also referred to as mesofluidic reactors which are useful in synthesis of compounds from gram (g) to multikilogram (Kg) level and can also be successfully coupled with packed bed reactor. Meso- or mini-fluidic reactors are free from very high pressure-drops and channel clogging due to their larger internal diameter (>500 μm), however, poorer in terms of heat transfer. Micro- and mini-reactors differ in their dimensions and parameters, thus eventually useful for the different applications. Earlier times, microreactors were specifically used for selective processes dealing with operations including high pressure or high heat transfer, being expensive and with limited applications (Hessel et al., 2009).

In the current scenario, microreactors are fabricated with new materials including stainless tubes, perfluorinated polymers, etc. as compared to earlier stainless steel, glass, ceramics, and silicon glass. Advent of these cheaper tube reactors brought a revolution in the field of flow devices and flow chemistry. These devices are comparatively inexpensive as well as flexible in their applications (Ley et al., 2015a, 2015b). Recently, based on coiled flow inverter concept, tubular devices have been employed for the continuous cooling crystallization process at laboratory scale. This prototype works effectively with the flow rate of 10.0 g/min (Hohmann et al., 2018). A typically miniaturized extraction columns allow effective counter-current extraction wherein, stirred pulsed extraction column could handle throughputs of 5.0–40.0 mL/min with 15.0 mm internal diameter (Hohmann et al., 2016). Recent developments in flow devices and miniaturization is very well summarized in recent reviews by Epps et al. and Bittorf et al. (Epps et al., 2020; Bittorf et al., 2019).

Multi-step synthesis in flow reactors suffers from major drawbacks in integrating its components and added new features along with solid management (McQuade and Seeberger, 2013). Components of microreactors include pumps, flow meters, cooling/heating units, valves, separators, regulators, etc. Nowadays, varieties of commercial microreactors are available today which majorly deal with the issues related to pumps and valves while handling corrosive, oxidizing reagents and flow including solid particles. Often, researchers tend to make the developments and advances in their own prototypes. So far, several modifications have been brought into microreactors and their issues are well addressed in literature, some of them discussed herein.

Syringe pumps often used for lab-scale experiments are cost-effective, however, have a major hurdle of limited charging volume. Compared to syringe pumps, HPLC pumps are effective in terms of flow rate, but suffer from damage of seals due to particles and/or gas bubbles during operation. Metering pumps show advantage over mentioned pumps with range of 1.0–10.0 mL min^{-1}. Backpressure regulators (BPRs) are required to increase the reaction rates, particularly for the operations at higher temperatures and pressures. During such operations, spring-loaded BPRs generally get corroded; it can be tackled by the use of modern diaphragm-based BPRs with corrosion resistant materials. Issues of mass and heat transfer in flow systems are very well addressed by keeping static mixture units into channels and reaction layer between the cooling plates (Jensen, 2017). One of the limitations of microreactors (mentioned above) is the handling of solids/particles formed during the operation. Particles of the formed solids, further agglomerate and eventually clog the reactor. The appropriate use of ultrasounds helps to break larger particles, avoiding clogging to the much extent along with its other applications in chemical reactions (Hartman et al., 2010a). Various commercial reactors, systems, and features have been developed so far, showing their applications in multi-step synthesis and scale up, some of them along with equipment and units of flow devices are represented below (Figure 2).

Moreover, microreactors are also found quite useful in optimizing reaction parameters, kinetics, and understanding to the reaction mechanisms (Elvira et al., 2013; Jensen et al., 2014).

For academic interest, microfluidic devices are generally used and same is true with mesofluidic devices when hyphenated with fixed-bed materials. Reactions which specifically needs longer reaction time (>20 min) need heating to reach the reaction temperature. The reaction temperature can be achieved quickly by flash heating where flow devices can be coupled with microwave (MW) irradiation. Flow devices have also been found effective in carrying out reactions under supercritical conditions. Another important feature includes syntheses of organic compounds using hazardous and reactive, reagents and intermediates, respectively. For instance, fluorination reactions can be safely handled by using flow devices as

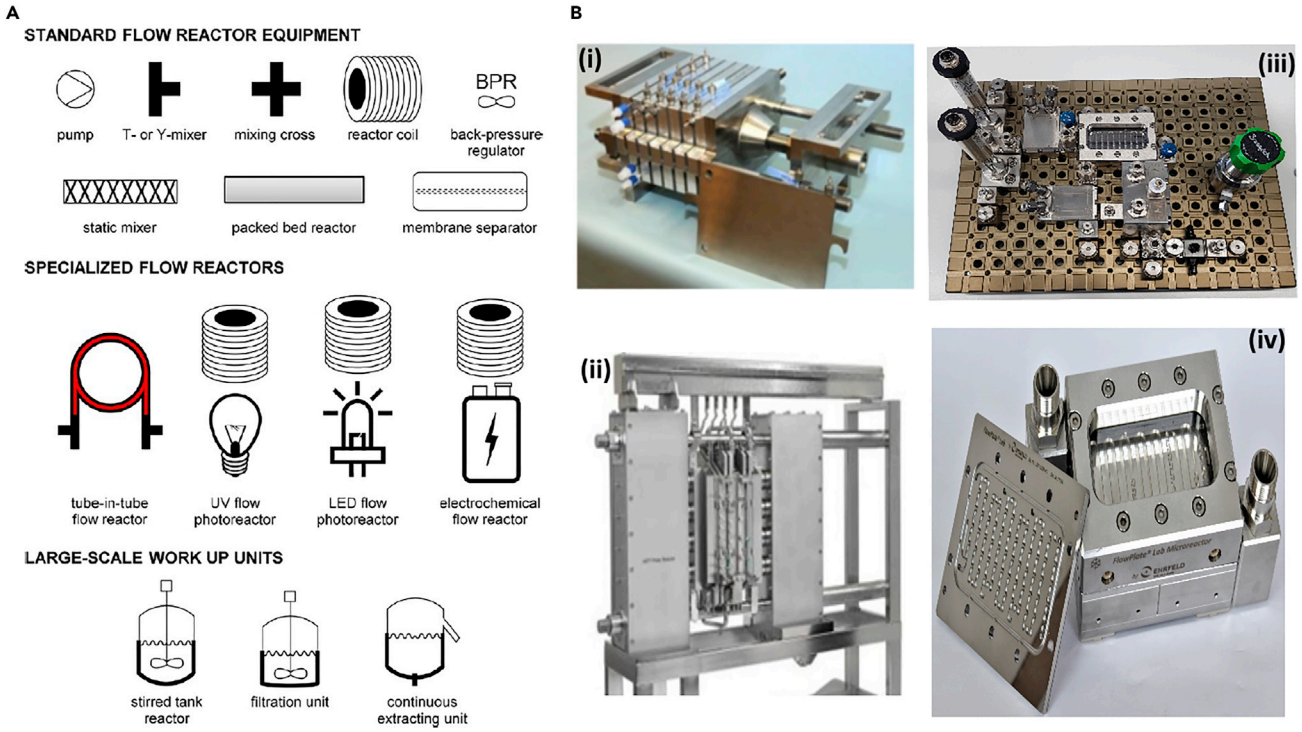


Figure 2. Legends of flow reactor devices and recent developments

(A) Legend of flow reactor devices

(Reprinted with permission from ref. Bogdan and Dombrowski, 2019).

(B) Recent development in flow reactors by Ehrfeld Mikrotechnik: (i) Lonza FlowPlate A5 for large scale production (1–20 L/h) (ii) ART PR49 reactor for production scale (20–1000 L/h) (iii) Modular Micro Reaction System (MMRS) for lab-scale and (iv) FlowPlate Lab reactor (Adapted with the permission from EHRFELD Mikrotechnik)

compared to conventional batch reactors. The applications of flow devices, when coupled with MW, light, ultrasound, and supercritical conditions are exemplified and few of them are discussed below.

In case of esterification reactions, Glasnov and Kappe observed no product (ethylbenzoate) formation from benzoic acid (**1**), when reaction was carried out in ethanol below 200°C (Razzaq et al., 2009). However, under supercritical conditions, 87% yield of ethylbenzoate (**2**) was achieved in merely 12 min. Supercritical water could facilitate hydrolysis and cyclization of 6-aminocapronitrile (**3**) to form ε-caprolactum (**4**) precursor to Nylon-6 in one step. MW-assisted flow synthesis of 1,3-thiazine (**5**) to corresponding hydropyrimidine(**6**) was reported by Glasnov et al., in 2006 (Glasnov et al., 2006). Recently, continuous MW-assisted flow synthesis of 1,4-dihydropyridines (**7**) was achieved using microflow system over γ-Fe_2O_3 NPs prepared using valve-assisted micromixer (He et al., 2018). Microwave flow systems other than organic synthesis also showed applications in synthesis and fabrication of polyesters and nanoparticles (Ching Lau et al., 2019; Bayazit et al., 2016).

Other than MW, ultrasound systems are also well coupled with flow reactors, particularly for the synthesis of barium sulfate. In this work, Delacour et al. studied the effect of acoustic pressure distribution and ultrasound frequency on particle size distribution. With very low ultrasound power (0.48 W/mL), remarkable amount of $BaSO_4$ (14 g/h) was achieved. It certainly opens the door for the scalable ultrasound-assisted flow syntheses (Delacour et al., 2020). Performic acid (PFA) is an unstable, but industrially useful compound. It forms in very low yield in batch reactors; however, it could be successfully synthesized using ultrasound-assisted flow synthesis using micro-structured reactor (Jolhe et al., 2017).

Looped flow processes emerged as effective way in syntheses of complex macromolecules. Beaten et al., successfully carried out a ring closure reaction assisted by light in looped flow reactor (Figure 3). It involves the reaction between an aldehyde end group of a precursor polymer and a dithioester to form a cyclic macromolecule (**8**) (Baeten et al., 2017).

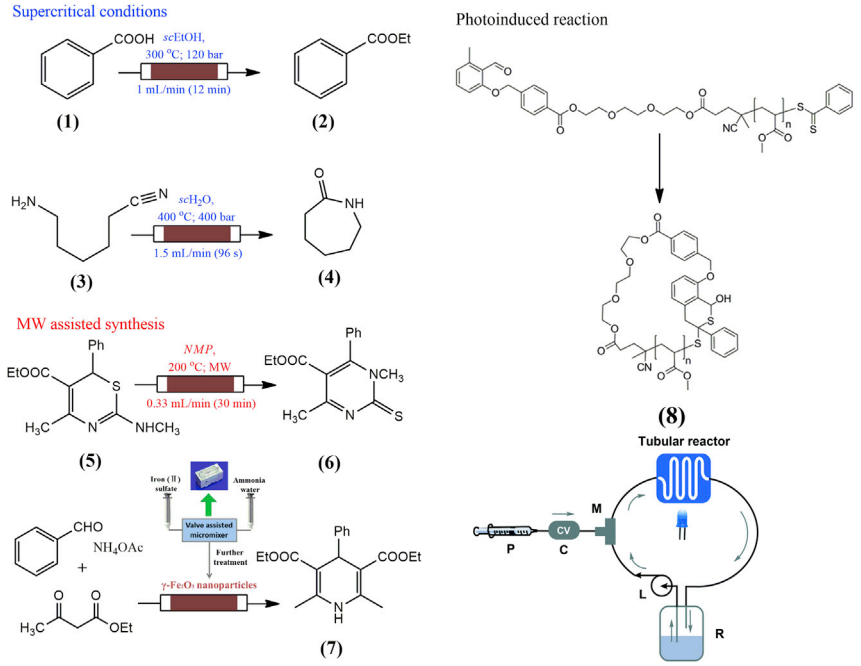


Figure 3. Continuous flow synthesis under MW, light and supercritical conditions

Figure were adapted/reproduced with the permission from Wegner et al. (2011) (RSC); He et al. (2018) (Elsevier) and Baeten et al. (2017) (RSC).

Photochemical reactions in flow are highly beneficial due to the major advantages of short optical-path and exposure, along with the wavelength (λ) filtering (Cambié et al., 2016). In another efforts, Elliott et al. developed scale up of photochemical reactors by systematic arrangement of light (UV) source and quartz tubes (Elliott et al., 2016). Overall, the studies showed the potential of the flow chemistry in sustainable synthesis of polymers, speciality chemicals (Leibfarth et al., 2015), active pharmaceutical ingredients (Gutmann et al., 2015; Baumann and Baxendale, 2015), nanomaterials (Marre and Jensen, 2010; Sebastián and Jensen, 2016), peptide (Simon et al., 2014), and in catalysis (Garcia-Olmo et al., 2017; Marquez-Medina et al., 2018; Ouyang et al., 2018). In few cases, intermediates formed during the synthesis of pharmaceutically important products are hazardous. Flow chemistry is a solution to avoid direct handling of such hazardous intermediates by using alternative methods, typically emulating batch processes (Newman and Jensen, 2013). These also include the use of "chip" purification devices (Hartman et al., 2009; Kralj et al., 2007; O'|'Brien et al., 2012). Selected important reviews in the area of flow chemistry describing renaissance, hurdles, development, and key aspects are tabulated below Table 1.

MULTI-STEP SYNTHESIS AND PHARMACEUTICAL PRODUCTS

The world was affected badly due to Covid-19 outbreak (SARS-CoV-2). Many poor and developing countries faced severe consequences due to the unavailability of appropriate infrastructure and medicines. Thus, the healthcare access is always of prime importance for life saving to meet the global demands. Continuous flow process played a game changing role in revolutionizing the industrial sector in reducing the cost of drugs. The role of flow chemistry in drug development is clearly evidenced with the number of patents in last few years (Hughes, 2018).

Most of the drugs and active pharmaceutical ingredients (APIs) have a large molecular structure. Preparation of such compounds practically needs more steps, so called multi-step synthesis. In batch processes, multi-step synthesis has the major disadvantage of low yield of the desired/final product. It happened due to the loss of the intermediate products during practical handling as well as in downstream processing. Significant efforts have been reported to solve issues posed by downstream processes during multi-step synthesis (Ley et al., 1995, 1998; Hinzen and Ley, 1997, 1998; Bolli and Ley, 1998; Habermann et al., 1998). Organic synthesis of such compounds by multi-step synthesis conventionally is not a sustainable

Table 1. Library of important reviews/perspectives in area of flow chemistry and related areas

Entry	Concepts discussed	Reference
1	Development in large scale flow-electrosynthesis	Tanbouza et al. (2020)
2	Materials, methods, and multi-step synthesis	McQuade and Seeberger (2013)
3	Green chemistry: sustainable aspects, continuous manufacturing	Ley (2012); Alfano et al. (2021); Rogers and Jensen (2019)
4	Superiority of flow chemistry over batch processes in terms of technology and applications to multi-step synthesis	Wegner et al., 2011
5	Strategies for continuous flow multi-step synthesis	Webb and Jamison (2010)
6	Role of chemical engineers and chemists in sustainable development	Cole-Hamilton (2020)
7	Opportunities for chemical engineers and chemists	Hartman, 2020
8	Natural products syntheses	Pastre et al. (2013)
9	Development in microreactors	Jensen (2017)
10	Drug discovery and development	Baraldi and Hessel (2012)
11	Additive manufacturing	Capel et al. (2013)
12	Modern flow-chemistry: Issues	Wegner et al. (2011)
13	Applications to APIs and pharmaceutical products and industry	Baumann and Baxendale (2015); Bogdan and Dombrowski, 2019; Porta et al. (2016); Baumann et al. (2020)
14	Limitations and challenges of flow chemistry	Akwi and Watts (2018)
15	Continuous processes: Advantages	Gutmann et al., 2015
16	Green Syntheses using flow chemistry	Lummiss et al. (2017)
17	Pharma perspective	Malet-Sanz and Susanne, 2012
18	Multi-step synthesis	Britton and Raston (2017); Jiao et al. (2021)
19	Synthesis of nanomaterials	Makgwane and Ray (2014)
20	Patent literature on drug development	Hughes (2018)
21	Photochemical and photocatalytic applications	Su et al. (2014), Dong et al. (2021); Cambié et al. (2016); Sambiagio and Noël (2020)
22	Asymmetric synthesis	Ötvös and Kappe (2021)
23	Cycloaddition reactions	García-Lacuna et al. (2020)
24	Integration of flow chemistry with 3D-printing technologies	Sans (2020)
25	Circular synthesis to material manufacturing	Sivo et al. (2021)
26	Standardization of flow chemistry for organic reactions	Hone and Kappe (2021)
27	Bridging Lab and Industry with Flow Electrochemistry	Tanbouza et al. (2020)
28	Chiral drugs	Guan et al. (2021)
29	Medicines: Scale up	Guidi et al. (2021)

practice, because it is highly dependent upon labor and resources (Trost, 1991; Hudlicky, 1996; Anastas and Kirchhoff, 2002).

In conventional multi-step synthesis, products are recovered after each step, purified and used further for the next step. The time for the multi-step synthesis can be truncated using telescoping steps which include consecutive addition of catalyst/reagent to the reactor to initiate next reaction step and quenching of

reactive species *in situ* (Anderson, 2000). The mentioned approach is very well suitable for the flow chemistry to address the hurdles in multi-step synthesis. Earlier studies showed the successful continuous flow multi-step synthesis using reactive organolithium (Yoshida et al., 2008) and halogen-lithium exchange (Usutani et al., 2007) reaction during one of the steps in controlled conditions. The mentioned work was reported using flow devices made up of stainless steel where syringe-pump devices were used to control the flow of reagents. These protocols reported high success in multi-step synthesis due to two important features, i.e., controlled residence time (t_R) and temperature, which helped in letting the unstable/highly reactive intermediates to the next reaction step before their decomposition. Most of the organic reactions require quick mixing times due to very short t_R which is very well assessed by using micro-structured mixers (Schwolow et al., 2012).

The strategies take a further leap in the development of various industrially important compounds using continuous flow multi-step synthesis of ibuprofen (Bogdan et al., 2009), mur ligase inhibitor (Herath et al., 2010), enol ethers (Hartman et al., 2010b), oxomaritidine (Baxendale et al., 2007), triazole (Baxendale et al., 2009), α, β-unsaturated compounds (Wiles et al., 2007), BMS-275291 (metalloproteinase-inhibitor) (France et al., 2005), and chemokine-receptor ligands (Petersen et al., 2009) among others. Syntheses of these compounds using flow devices comprise efforts and strategies based upon the hurdles and problems varied case to case and thoroughly discussed by Webb and Jamison in their review (Webb and Jamison, 2010). In the last several years, the role of flow devices in continuous multi-step synthesis of APIs has been clearly demonstrated. Few important APIs synthesized in last decade using flow devices include pregabalin (Ghislieri et al., 2015), imatinib (Hopkin et al., 2010, 2013), artemisinin (Lévesque and Seeberger, 2012), and efavirenz (Correia et al., 2015). Syntheses of many APIs and pharmaceuticals require metal-based catalysts, mostly organometallics, in one of the synthetic steps. Reactions, such as oxidation and hydrogenation, based on the metal-based catalytic systems have been developed by using packed bed reactors (Zaborenko et al., 2015; Shang et al., 2013); however, toxicity is the major issue in case of the organometallic catalysis. The leached metal contaminates the product(s) and thus decreases the product quality. The leaching in case of supported catalysis can be arrested by improving metal support interaction with deliberately developed surface defects (Burange et al., 2016) and among others (Burange et al., 2021). Coupling reactions over non-precious metals complexes are also reported in order to reduce the cost of the final catalyst (Sahani et al., 2018a, 2018b, 2019). However, such homogeneous catalysts are difficult to recycle; therefore, there are few attempts on immobilization of them onto solid support (Collis and Horváth, 2011). In flow chemistry, these problems are considered and tackled to some extent by using OSN membranes (Organic Solvent Nanofiltration) which help to recycle homogeneous catalysts (Peeva et al., 2016; O'Neal et al., 2015).

Most of crystallization processes in pharma industries are performed using batch processes. The problem with batch crystallization is batch to batch inefficiency due to inconsistency and invariability. Continuous crystallization is one of the emerging areas in pharmaceutical industries (Zhang et al., 2017) and it is believed that it can save 9%–40% of manufacturing production-costs (Schaber et al., 2011).

FLOW SYNTHESES OF PHARMACEUTICAL PRODUCTS: RECENT TRENDS

A large number of publications, exhaustive reviews, and patents are indicative of the role of flow chemistry in sustainable syntheses to meet the future demands. This section is purely dedicated to selected recent advancement in a pharma sector, particularly in last five years. Before taking this discussion ahead, one must understand the classification of continuous-flow systems (Figure 4) proposed by Kobayashi research group (Tsubogo et al., 2015). In all cases, the product is collected at the end whereas an additional step of catalyst separation is required while dealing with homogeneous catalysts.

Flow chemistry helps to solve the issues associated with the multi-step syntheses of complex compounds. In this review, flow syntheses of various pharmaceutically important compounds are classified and discussed further based on their core structure such as piperazine, pyrazole, cyclic carbamate, triazole, tetrazole, and quinoline, among others (Figure 5).

Piperazine compounds

Let us start the discussion with the examples of aryl piperazine-containing relevant compounds (Figure 6). These are key features and structural part of various CNS active agents including buspirone, trazodone, cariprazine, and flibanserin among others, used for the treatment on anxiety disorder, depression, schizophrenia, and female hypoactive sexual desire disorder (HSDD), respectively (Bana et al., 2019).

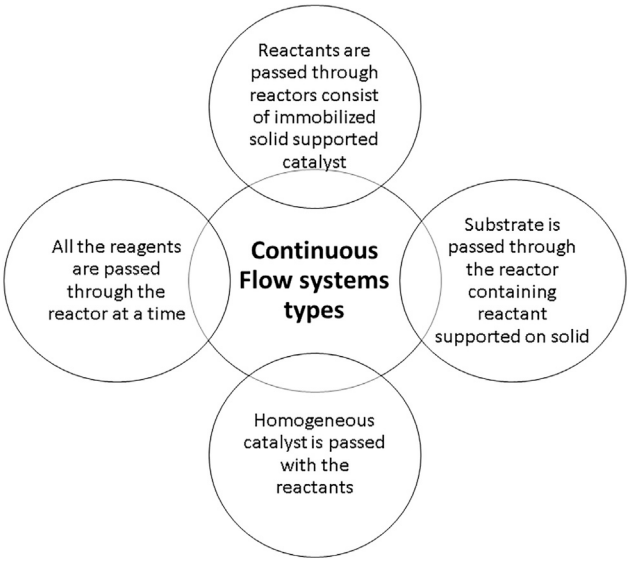


Figure 4. Classification of continuous-flow systems

Initially, flibanserin was developed to treat depression which later approved to treat HSDD with tradename Addyi™ (Mullard, 2015). Its synthesis involves the synthesis of the benzimidazolone scaffold via protection, selective alkylation, etc. These steps increase the reaction time with another drawback of using bases in stoichiometric volume. Thus, the effective synthesis of flibanserin is a challenging task

In recent studies, Bana et al. developed a continuous flow synthesis of flibanserin without intervention of any manual operation with successful implementation of steady state operations. The flow synthesis was completed in four steps, shown below in Scheme 1. Initially, starting materials, i.e., *tert*-butyl (2-aminophenyl)carbamate (**9**) and 2,2-dimethoxyacetaldehyde (**10**), were first dissolved in isopropyl acetate (*iPrOAc*), transferred using pumps **P1** and **P2**, respectively, to **M1** to form a mixture. The equimolar mixture was passed through reactor **R1** (H-Cube Pro) to carry out hydrogenation reaction over 10% Pd/C to form product (**11**). Reaction conditions with flow rate 0.5 mL/min at 100°C showed maximum conversion; however, further increase in the temperature led to the formation of byproducts. The excess of hydrogen was separated after **R1** using **BF1** (buffer flask). The monoalkylated product (**11**) is then subjected to the next step, i.e., ring closure reaction. For the same, product (**11**) was passed through heated **R2** (stainless-steel coil reactor) and the flow rate was managed using pump **P3**. The base DBU dissolved in *i*PrOAc, required for the cyclization was charged using pump **P4**. Maximum conversion of cyclized product (**12**) was recorded at 200°C. Product **12** is a dimethoxy compound which deprotected in **R3** further using hydrochloric acid using pump **P5** to an aldehyde (**13**) at 100°C **R3/H**, made up of inert material, i.e., polytetrafluoroethylene (PTFE), was heated to 100°C whereas before **R3/H**, **R3/M** column with inert packing was placed, kept at ambient temperature. **M2** placed before **R3/M** helped in static mixing; however, the pressure of this section was set by **BPR1**. Before the final step, **BF2** was placed to pressure-decoupling which helped in avoiding turbulences at H_2 input and the aqueous waste from **BF2** was collected to **CV1** using **P6**. In the final step, organic stream of **13** and **14** is passed to R4 for hydrogenation over 10% Pd/C at 100 bar pressures at 300°C to yield final product flibanserin (**15**). The crude solution of 15 is collected in **CV2** (for details refer to Scheme 1; Bana et al., 2019).

Synthesis of flibanserin (15) (Scheme 1) was effectively achieved under continuous flow in four steps at steady state operation (no manual operation). The developed process included the use of heterogeneous catalysts for reductive amination, benzimidazole synthesis at high temperature and biphasic deprotection steps carried out seamlessly (and swiftly) in flow.

Imatinib is also an important API for the synthesis of Gleevec (imatinib mesylate) which is a kinase inhibitor as found place in the list of essential medicines by WHO to treat gastrointestinal stromal tumor and chronic myelogenous leukemia (Buchdunger et al., 1996; Capdeville et al., 2002; Deininger et al., 2005). A noteworthy flow synthesis of imatinib and its analogs was recently reported by Fu and Jamison, using a new

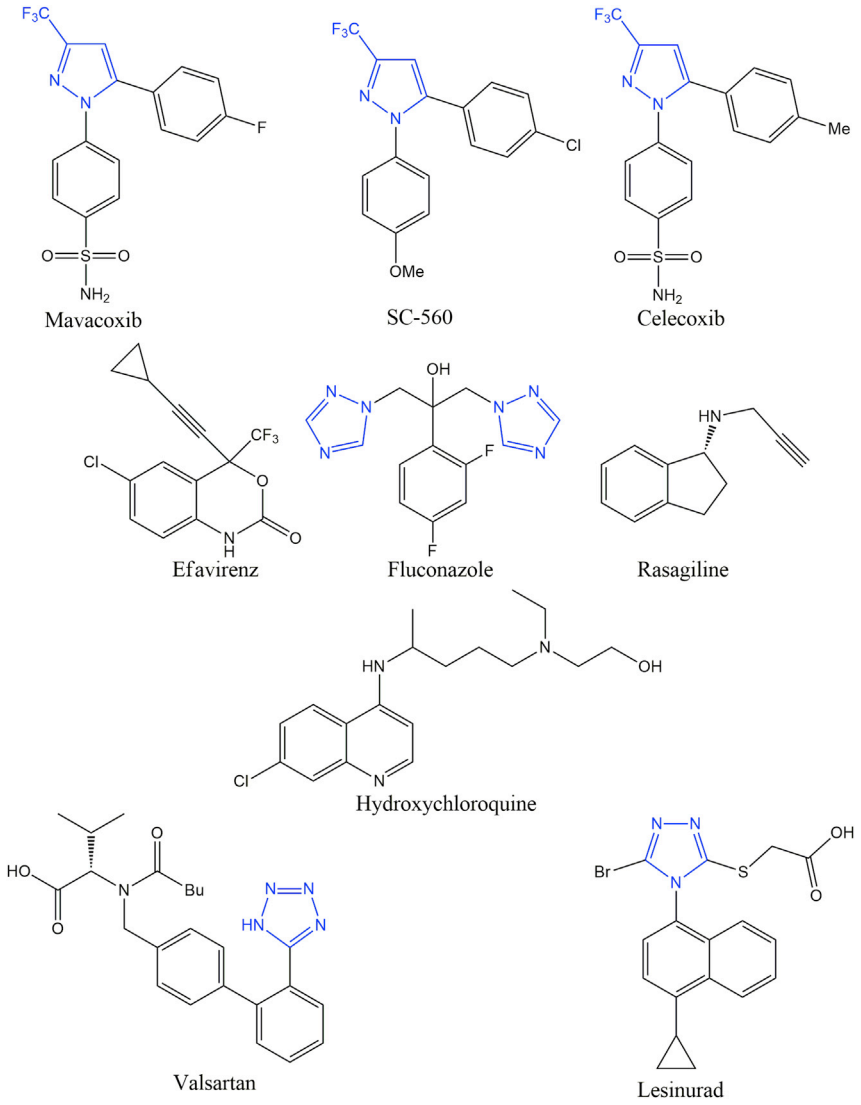


Figure 5. Pharmaceutically important compounds containing pyrazole, cyclic carbamate, triazole, tetrazole, and quinoline as a core structure

modular assembly. The protocol was also developed for chemoselective amidation of 4-bromo-2-chlorotoluene and other halogenated toluene using BrettPhos Pd G4 Buchwald's precatalyst, potassium phosphate at 120°C. Solvent systems such as water and 2-methyl THF provided segmented flow whereas water with dioxane formed near-homogeneous mixture, resulted from the vigorous mixing of dioxane and used alkali for the reaction. This selective amidation of 4-bromo-2-chlorotoluene using benzamide gave 69% yield with t_R of 15 min in a stainless-steel coil reactor, which improved significantly to 83% due to use of BPR with 200 psi allowing superheating of solvents without vaporization. The same is used in a continuous flow synthesis of imatinib and its analogs to improve the yield further (Scheme 2). A typical imatinib flow synthesis developed by Fu and Jamison is shown below as Scheme 2 (Fu and Jamison, 2019). Packed bed mixing was reported to be critical for the C-N coupling in flow synthesis in case of biphasic system (Naber and Buchwald, 2010; Yang et al., 2016). In this work, such critical aspect was addressed by the formation of microdroplets to enhance interfacial contact.

A noteworthy contribution from this reported work (Scheme 2) is the highest production of imatinib without using additional steps such as solvent exchange and in-line purification. In addition, the developed process did not require any packed bed apparatus.

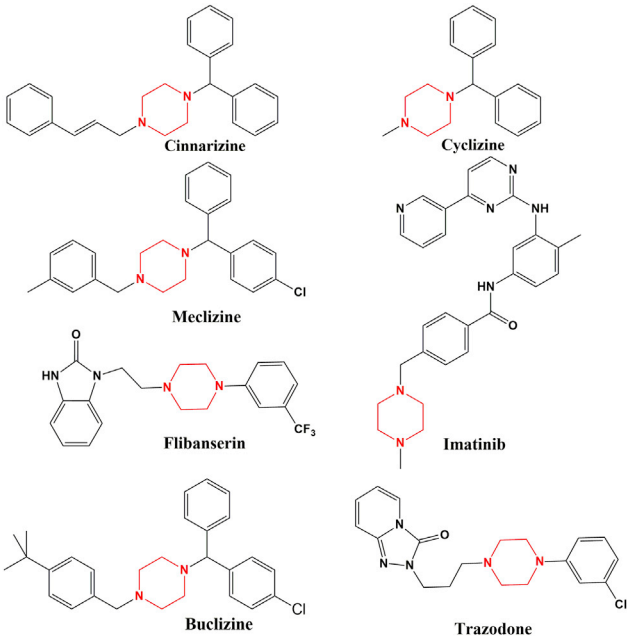
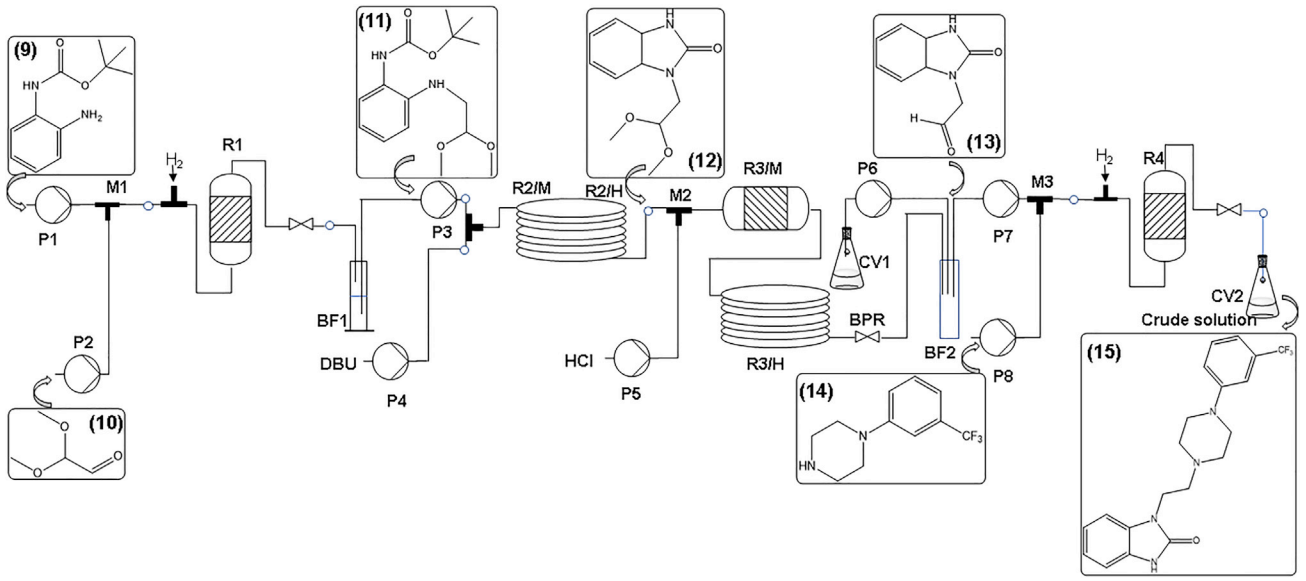


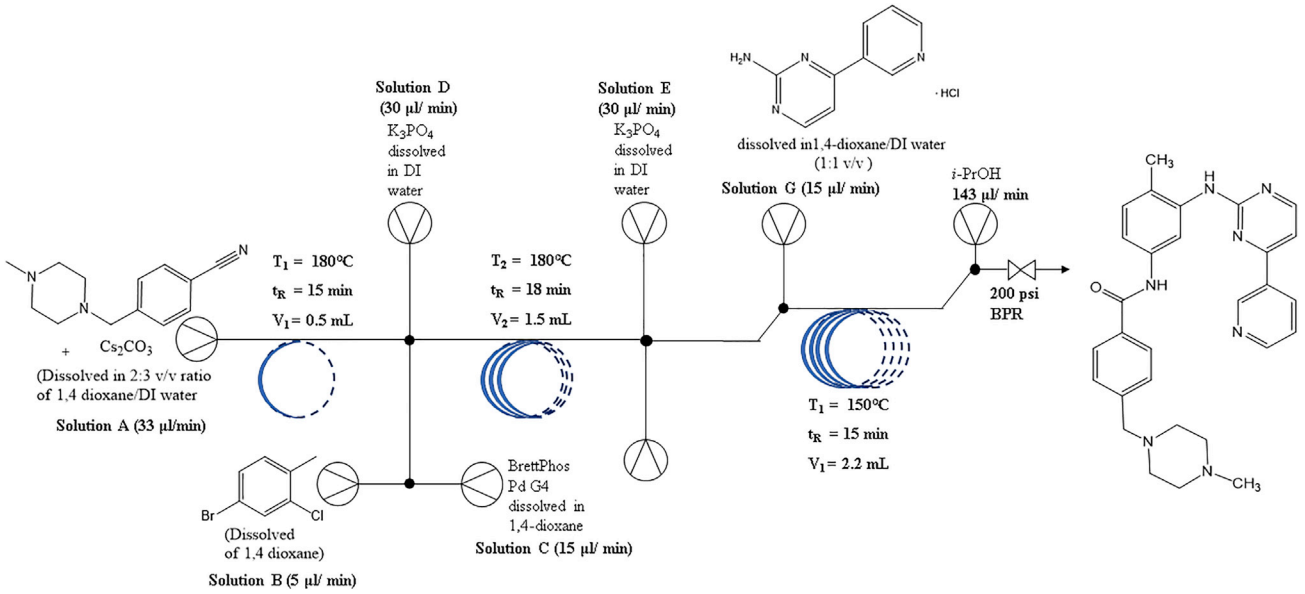
Figure 6. Selected piperazine-containing pharmaceutically relevant compounds

Buclizine, cinnarizine, cyclizine, and meclizine belong to antihistamines family with common structural unit of 1-diphenylmethylpiperazine (Figure 5). The syntheses of such compounds involve the nucleophilic substitution reaction over aryl chlorides. Syntheses of chloride derivatives from alcohols are a challenging step because it involves the use of toxic chlorinating agents. Borukhova et al. reported progress under flow chemistry in chlorodehydroxylation processes under milder condition in a capillary reactor with wider substrate scope (Borukhova et al., 2016b). Alkyl chlorides were prepared from bulk alcohols and hydrochloric



Scheme 1. Flow schematic of the four-step system for the preparation of flibanserin

Flow rates: P1: 0.500 mL min^{-1}; P2: 5.0 μL min^{-1}; P3: 0.500 mL min^{-1}; P4: 37.5 μL min^{-1}; P5: 50.0 μL min^{-1}; P6: 0.050 mL min^{-1}; P7: 0.538 mL min^{-1}; P8: 30.0 μL min^{-1}. Operating conditions (and residence times): R1: 10% Pd/C (30 mm CatCart), 100 °C, 10 bar, 50% gas-liquid ratio (tR ca. 8 s); R2: 200 °C (tR = 7.4 min); R3/M: ambient temperature (tR ca. 41 s); R3/H: 100 °C (tR = 6.8 min); BPR1: 17 bar; R4: 10% Pd/C (30 mm CatCart), 100 °C, 10 bar (tR ca. 12 s). Adapted with the permission from Bana et al. (2019)(RSC).



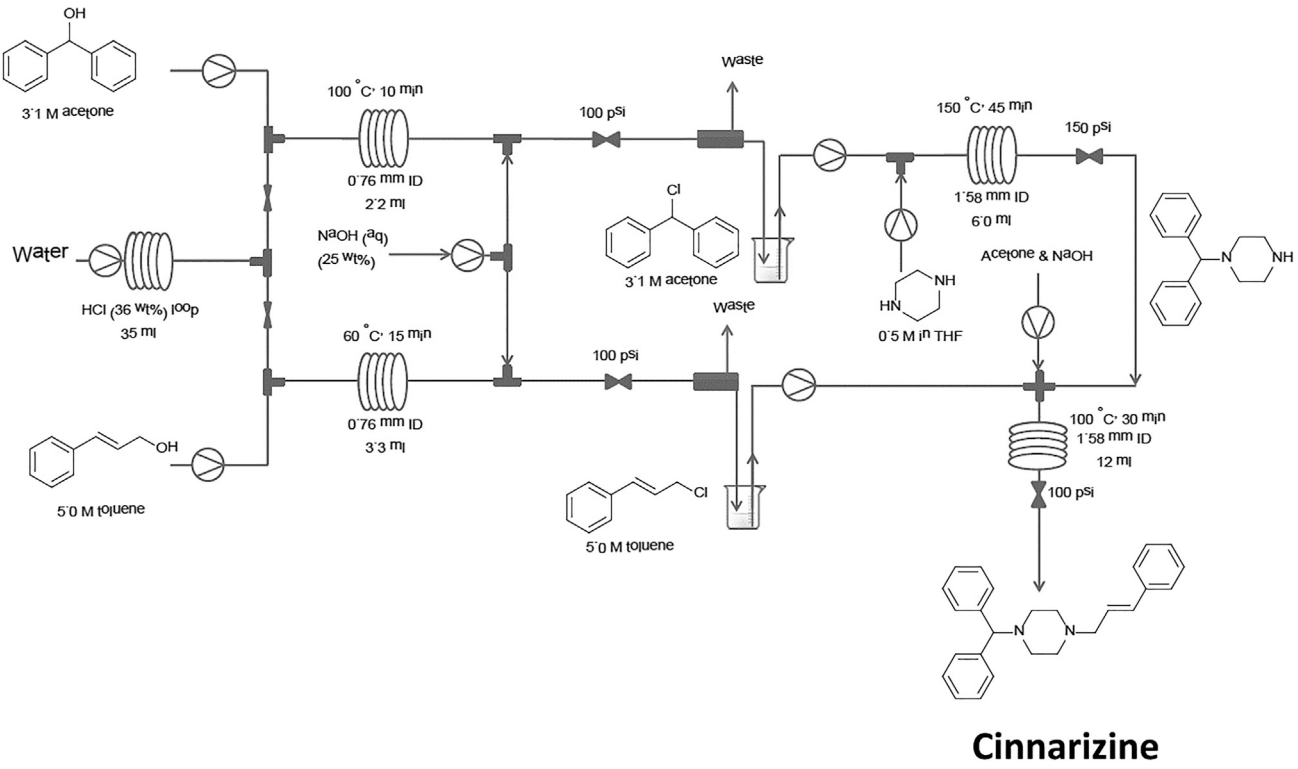
Scheme 2. Scale-up flow synthesis of imatinib
Adapted with the permission from Fu and Jamison (2019) (ACS).

acid using similar reaction conditions earlier reported by Kappe et al. (Reichart et al., 2013). In extended studies by Borukhova et al., the product alkyl chlorides were separated using liquid-liquid (L-L) separator and further subjected to micro-capillary flow reactor along with appropriate piperazine bases (160°C for 30 min). The efficiency of L-L separator was assessed visually using thymol blue added to NaOH solution.

This two-step process is found useful for the continuous synthesis of cyclizine using N-methylpiperazine and diphenylmethylchloride precursors. HPLC, acid-resistant pumps, inline BPRs, and FEP (fluorinated ethylene propylene) tubing were using during the operations. Borukhova et al. developed flow synthesis of cinnarizine and buclizine, meclizine derivative. The detailed experimental setup of cinnarizine flow synthesis is given below as Scheme 3 (Borukhova et al., 2016b).

Borukhova et al. used hydrochloric acid in the chlorodehydroxylation step. Malfunctioning of HPLC pumps were observed after a short time (the pump could not deliver the acid to the reactor). Such malfunctioning was due to the accumulation of HCl gas within the pump-head, solved by replacing pumps with loops. HCl loops were used for the mentioned purpose, through which 36 wt % HCl was passed to the reactor in the chlorodehydroxylation reaction. Introduction of NaOH (25 wt %) before BPR helped to avoid corrosion (Scheme 3). In case of benzyl alcohol, significant yields of benzyl chloride were achieved under superheated conditions (120°C), at a residence time of 15 min (100 psi) using hydrochloric acid. The major drawback of this process is the use of corrosive hydrochloric acid, with the optimized protocol in any case demonstrating a simple route to chlorides using loops.

The preparation of another kinase inhibitor, containing piperazine unit, i.e., ribociclib, was reported by Pellegatti et al., using two-step continuous flow procedure. Synthesis of ribociclib starts with the reaction of (**16**) with (**17**) from Figure 7A which is the Hartwig Buchwald condensation over Pd catalyst. To decrease Pd content from the product, further processing or treatments with activated carbon, resins, L-cysteine, etc. is required. To circumvent these additional steps, Pellegatti et al. developed transition metal-free synthesis of (**18**) from (**16**) and (**17**) using highly basic and non-nucleophilic, lithium hexamethyldisilazide (LiHMDS) solution (in THF). In this two-step flow synthesis of ribociclib, authors employed liquid-liquid extraction process along with semi-batch crystallization. In a typical two-step synthesis, a required molar concentration of (**16**) and (**17**) in THF and solution of LiHMDS in THF were flown as stream one and two, respectively. The streams were further passed to reactor one via T-piece to carry out amination reaction at 60°C to form (**18**). (**18**), later deprotected using aq. 3.0 M HCl in next reactor at the same temperature. **18** underwent deprotection as well as protonation. This crude product is purified using inline purification



Scheme 3. Flow synthesis of cinnarizine
Adapted with the permission from Borukhova et al. (2016a) (Wiley).

(**19**) system before the final step (Figure 7B), in which THF was removed and deprotected while the protected derivative of (**18**) was treated with succinic acid solution in isopropanol at 80°C to form ribociclib (Pellegatti et al., 2016).

Pd-based catalysts in coupling reactions are widely used and in most of cases mandatory to achieve high yields. In contrast, Pellegatti et al. achieved considerable yield of intermediate (18) in the absence of any Pd-based catalyst. The reported flow protocol is economically improved as compared to batch process when upstream and downstream operations were considered.

Pyrazole compounds

Other than piperazine, pyrazoles are also relevant building blocks of various APIs as well as agrochemicals. 3-Fluoroalkypyrazole is a structural unit of agrochemicals including fluxapyroxad and bixafen and pharmaceutical compounds such as celecoxib, SC-560, and mavacoxib. Britton and Jamison reported the multi-step synthesis of mentioned compounds using an assembly line after successful synthesis of AS-136A, Measles therapeutic agent (Britton and Jamison, 2017b)

The multi-step synthesis of the above mentioned non-steroidal anti-inflammatory drugs (celecoxib, SC-560, and mavacoxib) was carried out using modular assembly line where each reactor module was restricted to perform a selected transformation during multi-step synthesis. In module 1, fluorinated amines and *tert*-butyl nitrite were reacted together in presence of acetic acid to form diazoalkanes. The module 2 was dedicated to the formation of pyrazole cores via [3 + 2] cycloaddition reaction between alkynes and diazoalkanes, where nitrite and alkynes were diluted in chloroform. Module 3, 4, and 5 were used for C-N arylation, C-N methylation, and trimethylsilyl removal, respectively. Module 6 was dedicated to amidation reaction, to from mentioned agrochemicals along with their regioisomers (**21** and **22**) from (**20**) (Scheme 4). The overall yield for bixafen and fluxapyroxad was reported to be 38%. The flow process was successfully coupled with offline (batch), in which Ullmann coupling of synthesized trifloromethylpyrazole derivatives with substituted aromatic halides produced celecoxib, SC-560, and mavacoxib with 43%–70% yield in two to three steps. Temperature played a crucial role in the mentioned synthetic process. An increase in the temperature (above 60°C) of module 1 resulted into lower yields of

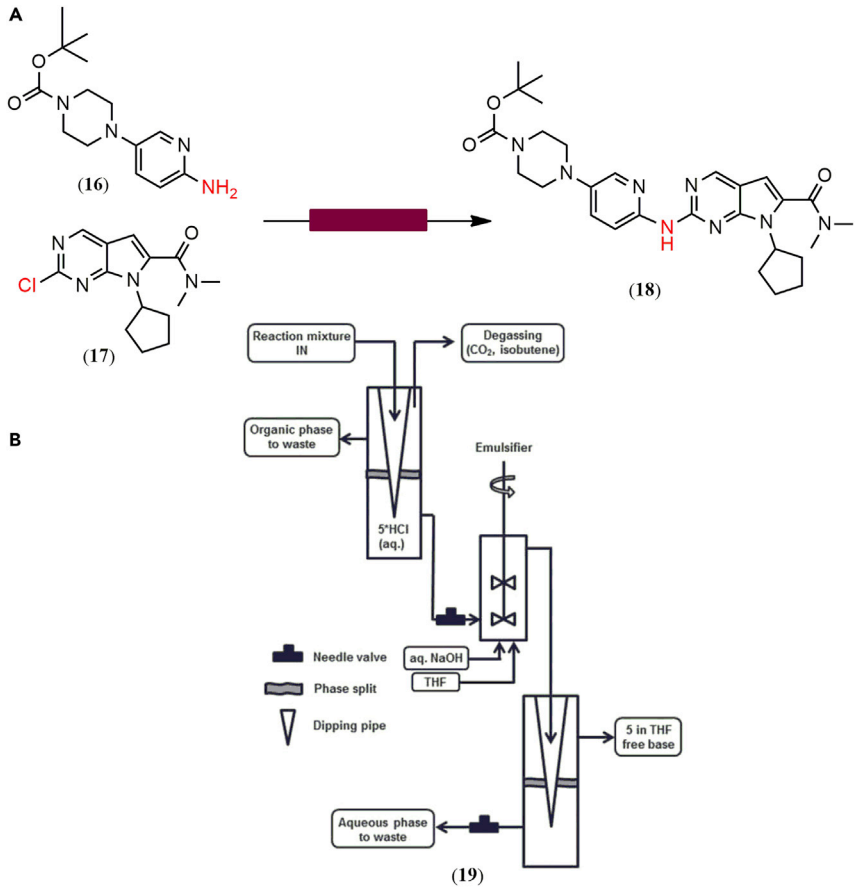


Figure 7. Synthesis of ribociclib intermediate and in-line purification

(A) Synthesis of intermediate (18) during the synthesis of ribociclib; (B) In-line purification system used for the purification of crude deprotected and protonated (18) intermediate

Adapted and reproduced with the permission from Pellegatti et al., 2016 (Springer)

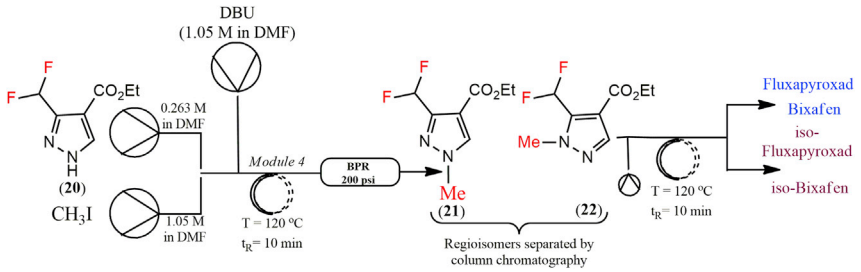
diazoalkane due to decomposition reactions. Similar observations were analogous for module 2, where, rapid gas evolution >90 °C resulted into lower yields of the desired product.

Cyclic carbamate compounds

Efavirenz is an important drug in the treatment of HIV having cyclic carbamate as a core part of its structure (Figure 5). Reported synthetic routes commercialized by Lonza (Dai et al., 2012) and Merck (Thompson et al., 1996) start from 1,4-dichlorobenzene and 4-chloroaniline, respectively. Lonza and Merck patented routes for the synthesis of efavirenz require four and five steps, respectively. Correia et al. reported shortest route so far using flow process. In step 1, 1,4-dichlorobenzene was subjected to *ortho*-lithiation followed by fluoroacylation to form intermediate (**23**) (Scheme 5). Synthesis of 23 was carried out using three reactor loops, where decomposition of the intermediate was evidenced in a loop 1. The clogging was observed due to the sudden temperature rise of reactor loops. It was addressed by controlling the temperature of the reactor loops. Trifluoroacetylmorpholine was used for fluoroacylation of ortholithiated 1,4-dichloro-benzene. The maximum yield (87%) of the same (**23**) was recorded at −45°C Scheme 5 displays second step, wherein, intermediate (23) was attacked by lithium cyclopropylacetylide to form intermediate (**24**). In the final step, the cyclization of **24** was carried out over copper catalyst using NaOCN to form efavirenz with 45% of overall yield (racemic mixture), where *in situ* of isocyanate is a key step (Correia et al., 2015).

Triazole compounds

Fluconazole (Figure 5) is the widely used anti-fungal which is also found useful in HIV-infected and cancer patients (Richardson, 1983). The drug was commercialized way back in 1988 with a given trade name



Scheme 4. Continuous flow synthesis of Fluxapyroxad and Bixafen along with their respective N^2 regioisomers
Adapted and reproduced with the permission from Britton and Jamison (2017a) (Wiley).

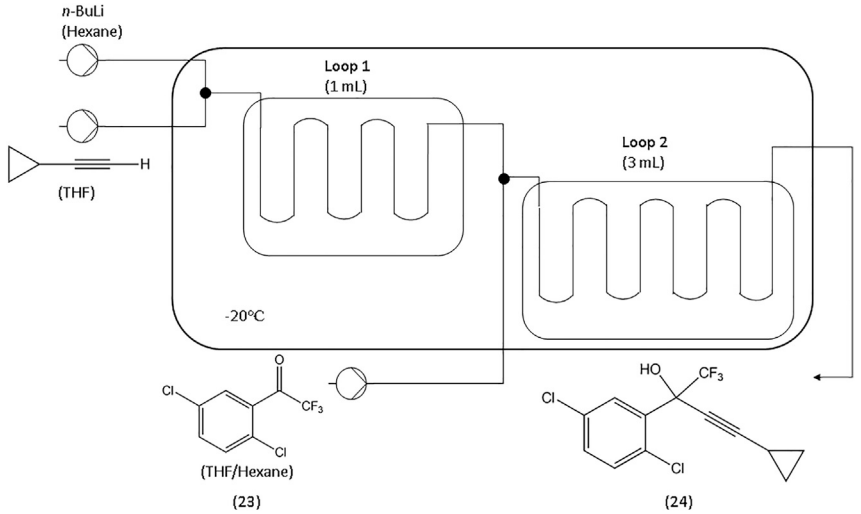
Diflucan with less overall yield (<35%). In many studies, the synthesis of fluconazole was restricted to batch (Chen and Fang, 2003; Heravi and Motamedi, 2005; Karimian et al., 2000; Shih et al., 1998; Zhang et al., 2011).

Korwar et al. reported its synthesis using turbo Grignard reagent (GR) and 1,3-dichloroacetone (Korwar et al., 2017). Turbo GR is highly reactive; however, 1,3-dichloroacetone is highly susceptible to enolize, thus favoring various side reactions (Chen and Fang, 2003). In the first step, turbo GR was employed for insertion of magnesium and halogen to (**23**) in THF at reactor 1 and the product was quenched in methanol. GR generated from step 1 reacted with 1,3-dichloroacetone (**24**) in reactor 2 to form intermediate (**25**). For this continuous step, the volume time output (VTO) was recorded to be 8.962×10^{-7} m^3hKg^{-1} (VTO <1 is preferred). In the final step, the nucleophilic substitution of (**25**) was carried out using 1,2,4-triazole (nucleophile) in the presence of sodium carbonate to yield fluconazole (**26**) (Scheme 6).

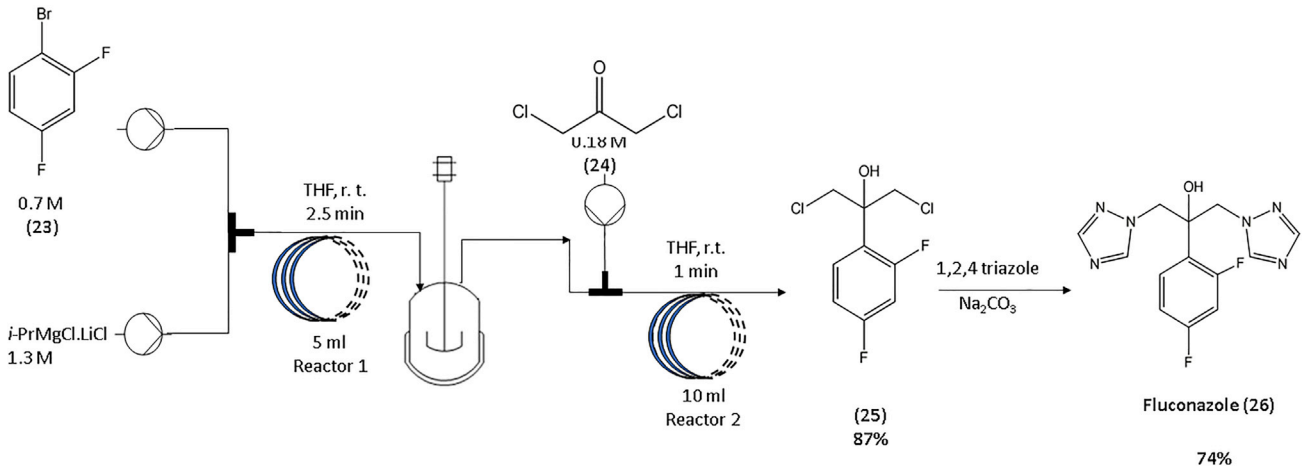
Korwar et al. reported a clean and safe synthesis of aryl-turbo GR and its further addition to 1,3-dichloroacetone in a continuous flow for the preparation of fluconazole (**26**). High throughput for flow synthesis of 1,2,4-triazole as well as 1,2,4-oxadiazole was recorded using an integrated synthesis along with purification platform. Specifically, a conjure flow reactor was used as a library synthesis platform and the system relied on segmented flow. This synthesis with integrated flow technology, popularly known as SWIFT, provided a high efficiency in the synthesis and purification of six compounds per hour (Bogdan and Wang, 2015).

Tricyclic compounds

Another GR-based process includes the synthesis of melitracen HCl. In this work, a GR-based batch process was designed to work under continuous reactor system (Pedersen et al., 2018). The use of a flow setup is



Scheme 5. Experimental set-up for the lithium-mediated alkynylation of (23)
Adapted with the permission from Correia et al. (2015) (Wiley).



Scheme 6. Continuous flow synthesis of fluconazole
Adapted with the permission from Korwar et al. (2017) (Wiley).

rather challenging when the solubility of compounds is low in the used solvents. Plug-flow reactors (PFRs) are recommended for a higher throughput when solubility in the solvent is higher. In this context, due to high product solubility and reactants, PFRs were employed for the study.

The first step involved the addition of Grignard reagent 3-(N,N-dimethylamino)propylmagnesium chloride (DMPC-MgCl) to 10,10-dimethylanthrone (10,10-DMA) to form magnesium alkoxide intermediate (T1,C1). In the next step, addition of HCl led to hydrolysis and dehydration (T2, C2) followed by addition of acetic acid. BPR was placed to avoid the boiling of a solvent THF, employed for phase separation. The aqueous waste was collected in a decanter and melitracen HCl could be collected in the final step (Pedersen et al., 2018).

Melitracen HCl was successfully crystallized in THF using 2.0 M hydrochloric acid in diethyl ether (isolated yield: 85%). Using a flow setup, 60.0 g/h of isolated melitracen HCl could be achieved along with the robustness of the setup toward stream fluctuations (Scheme 7).

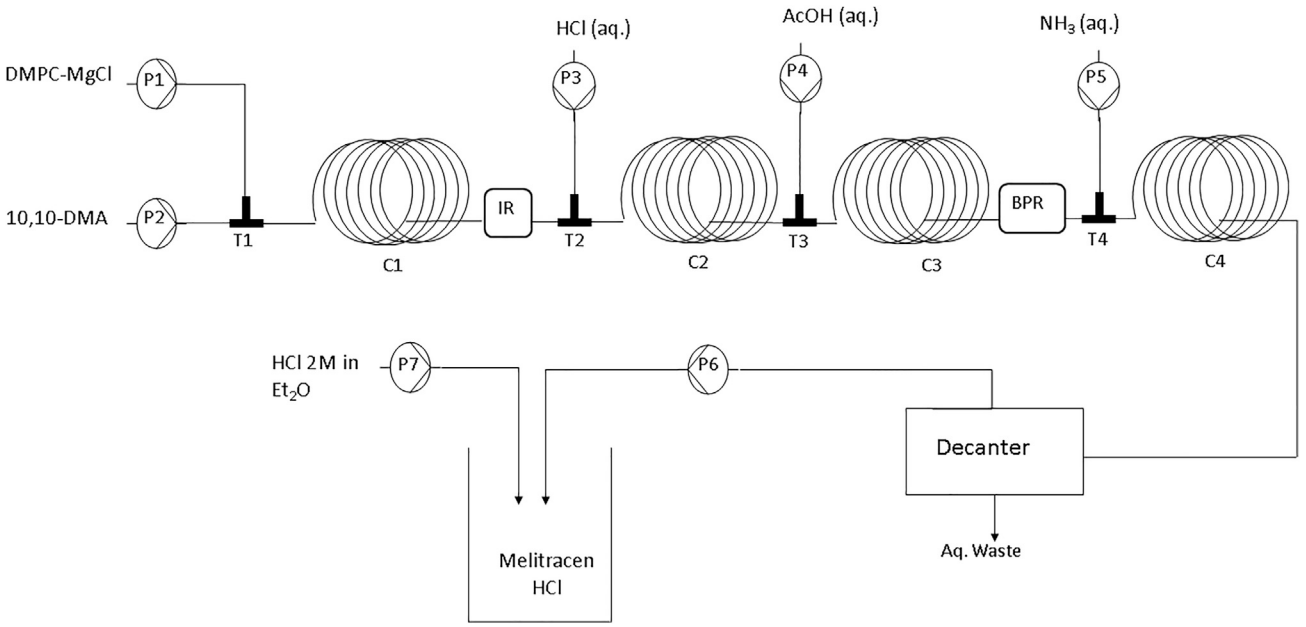
Chiral amines

Rasagiline derivatives constitute important pharmaceuticals for their known applications in the treatment of Parkinson disease. For the same, mesylate of rasagiline has been commercialized under trade name Azilect. In case of such asymmetric compounds, enantiopurity is of utmost importance. In this context, various studies aimed for high ees but eventually were proved to be rather inefficient to achieve a highly stereoselective synthesis of rasagiline (Selic, 2011; Thanedar et al., 2011; Malik et al., 2012; Ma et al., 2014; Colyer et al., 2006).

Brenna et al. reported a metal-free and stereoselective approach for the synthesis of rasagiline, tamsulosin, and other chiral amines under flow synthesis in a microflow reactor (Brenna et al., 2017). For the syntheses, chiral imines were stereoselectively reduced in presence of trichlorosilanes and the products, i.e., chiral amines, were obtained directly in the flow reactor after an aqueous work-up (amines), performed in a line or under continuous flow during hydrogenolysis (rasagiline). Experimentally, reactions were performed in a coil reactor immersed in a bath at required temperature. The reaction between chiral imines and $HSiCl_3$ (both dissolved in DCM) was carried out in a reactor at 17°C. The flow of both reactants was maintained using a syringe pump well equipped with Hamilton gastight syringes. Low conversion was observed at 17°C, significantly improved at 30°C with low diastereoisomeric ratio.

Tetrazole compounds

Deaths due to cardiovascular diseases are common. To avoid complications, a suitable hypertensive is prescribed to patients. Valsartan (Figure 5) is a popular hypertensive, with biphenyl structural motif. Valsartan was made commercially available by Novartis under trade name Diovan followed by many other combinations (Siddiqui et al., 2011; Li and Corey, 2013). It was patented in 1991 for the first time by Ciba-Geigy; however, their synthetic route involved the use of toxic tin reagent along with poor yields.



Scheme 7. Flow sheet of the flow reactor setup for the redesign of the Melitracen HCl synthesis; [Pump (P), Coil (C), T-mixer (T), Infrared In-line flow cell (IR), Back pressure regulator (BPR)]
Adapted with the permission from Pedersen et al. (2018) (ACS).

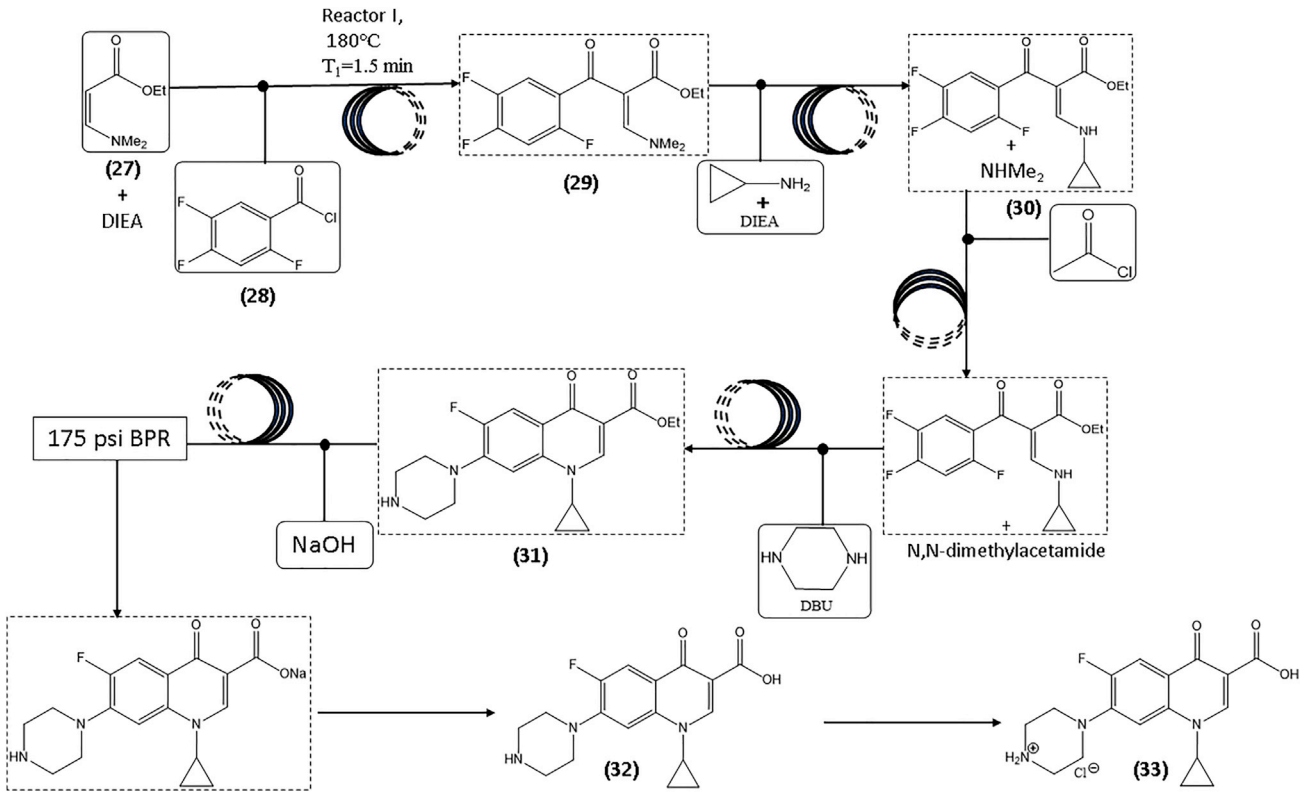
Recently, Hiebler et al. reported the continuous flow synthesis of a valsartan precursor (cyano-derivative), which can be further converted to valsartan (tetrazole) by reaction with organic azides (Hiebler et al., 2020). Suzuki-Miyaura (SM) cross coupling over heterogeneous $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$ catalysts in a packed bed reactor is a key step to the synthesis. A typical synthesis involves three steps, i.e., N-acylation, SM coupling, and ester hydrolysis, which were performed in differently designed reactors whereas for the first and third step, a coil reactor setup was utilized. A coil reactor setup was reported for the N-acylation step, using high-pressure syringe pumps (Flow rate: 0.10 mL min^{-1}). An SM coupling over $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$ was a key step, in which reactant solutions were passed through the catalyst bed in plug and play reactor mode with subsequent process stream combined with NaOH solution from syringe pump to assess ester hydrolysis. Hiebler et al. reported overall 96% yield of valsartan precursor using a developed (in-house) packed bed reactor (Hiebler et al., 2020).

Damião et al. recently reported the successful continuous flow synthesis of lesinurad (Figure 5), a urate anion exchange transporter 1. In their recently reported synthesis, three steps namely condensation, cyclization, and S-alkylation were successfully accomplished in one operation where no solvent exchange or purification of intermediate was required. In the next step, bromination of 1,2,4-triazole and hydrolysis of ester were performed to get lesinurad with overall yield of 68% (t_R = 2h) (Damião et al., 2020).

Fluoroquinolone and quinoline compounds

Ciprofloxacin has a fluoroquinolone structural core along with piperazine substituent. It is one of the listed medicines in WHO's essential medicines. Lin et al. reported total synthesis of ciprofloxacin with overall yield of 60% and residence time of 9 min (Lin et al., 2017). Acylation of vinylogous carbamate (**27**) was carried out using (**28**) in presence of N,N-diisopropylethylamine (DIEA) base followed by addition of cyclopropylamine to form (**30**) along with $NHMe_2$. $NHMe_2$ was further converted to N,N-dimethylacetamide which remained neutral for further cyclization reaction. (30), on reaction with piperazine in presence of DBU yielded (**31**) which upon hydrolysis followed by protonation yielded ciprofloxacin hydrochloride (**33**). A detailed flow synthesis is well represented below as Scheme 8. Key features of this flow synthesis are acylation of byproduct ($NHMe_2$) inline to avoid problems due to basicity and to keep crude solution of (31) warm before entering the reactor to avoid formation of solid (Lin et al., 2017).

During Covid-19 pandemic (initial days), most of the infected patients were treated using the combination of various drugs along with hydroxychloroquine (HCQ) (Figure 5). Yu et al. reported the continuous flow synthesis



Scheme 8. Flow scheme of continuous total synthesis of ciprofloxacin

1.0 equiv of (**27**), 1.2 equiv of (28), 1.15 equiv of DIEA, 1.25 equiv of 5, 1.15 equiv of DIEA, 1.2 equiv of acetyl chloride, 3.5 equiv of DBU, 3.5 equiv of piperazine, 6.0 equiv of NaOH. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene. Adapted with the permission from Lin et al. (2017) (Wiley).

of HCQ, antimalarial drug, with improvement in the overall yield as compared to currently existing process (Yu et al., 2018). In this newly reported method, protecting groups from the synthesis were successfully eliminated, and the combination of continuous-stirred tank with packed bed reactor, helped to generate high yields of HCQ. Reaction of 2-((4-aminopentyl)(ethyl)amino)ethan-1-ol and 4,7-dichloroquinoline were successfully transformed into HCQ in a continuous stirred tank reactor (CSTR). All optimization studies were firstly performed in batch and later implemented using CSTR. Reductive amination of (E)-5-(ethyl(2-hydroxyethyl)amino)-pentan-2-one oxime was performed in HEL CSTR using Raney Ni (heterogeneous catalyst) to yield 2-((4-aminopentyl)(ethyl)amino)ethan-1-ol. To retain the catalyst in CSTR, a metal filter frit (2 μm) was employed, kept on the dip-tube of an exit stream (Yu et al., 2018).

Other

Dolutegravir is another important API useful in the treatment of HIV-infected patients. Ziegler et al. reported its seven steps telescoping flow synthesis using separate three flow operations, with overall yield of 24% (Ziegler et al., 2018). When the third step was separately carried out, the overall yield could improve to 37%. Direct amidation of substituted pyridone ester in one step makes the protocol interesting (for details refer to Ziegler et al., 2018). ÖtvÖs et al. recently reported the enantioselective flow synthesis of (−)-paroxetine, antidepressant at multigram scale level where a solvent free protocol was employed using heterogeneous organocatalyst. Three steps in the synthesis (−)-paroxetine including reductive amination, lactamization, and amide/ester reduction were successfully accomplished. The developed methodology found sustainable and productive compared to earlier reported batch processes (Ötvös et al., 2019).

Recent developments in API syntheses also include the flow synthesis of gefapixant citrate (MK-7264) (Ren et al., 2020), ticagrelor (Hugentobler et al., 2017), darunavir (Leão et al., 2015), ciprofloxacin (Armstrong et al., 2021), rufinamide (Borukhova et al., 2016a), among others.

CONCLUSIONS

Flow synthesis of a wide range of APIs has been successfully reported in a wide range of conditions, making the processes safer and feasible (as well as often scalable to reasonable quantities). The proposed methodologies have a remarkable potential and scope for the greener synthesis of numerous organic compounds in the future including some of the discussed APIs in this contribution. The proposed chemistries involved multi-step syntheses of flibanserin, imatinib, buclizine, cinnarizine, cyclizine, meclizine, ribociclib, celecoxib, SC-560 and mavacoxib, efavirenz, fluconazole, melitracen HCl, rasagiline, tamsulosin, valsartan, hydroxychloroquine, among others, discussed thoroughly in this contribution, that illustrate the potential of flow chemistry as a tool in greener organic syntheses.

Steady state operations assisted in the efficient preparation of flibanserin, without any manual interventions and processes including reductive amination over Pd/C and benzimidazole synthesis carried out seamlessly. In case of imatinib, packed bed mixing was reported during a critical C-N coupling step while dealing with a biphasic system. The issue of mixing was nicely addressed by forming microdroplets with enhanced interfacial contact. Without using any packed bed apparatus and by circumventing in-line purification and solvent exchange steps, optimum production of imatinib was achieved. In case of buclizine, cinnarizine, cyclizine, and meclizine, alkyl chloride products were effectively separated using an L-L separator. In this work, authors also addressed pumps malfunctioning (due to handling of corrosive hydrochloric acid). In case of efavirenz and ribociclib, reactive organolithium compounds and GR in synthesis of melitracen HCl were safely handled in a flow system. In case of ciprofloxacin hydrochloride synthesis, to avoid the complications due to formed byproduct, was successfully addressed by converting it to non-reactive amide by inline acylation step. However, by tactfully keeping a crude solution of (**31**) warm before entering the reactor, the solid formation inside the reactor was successfully arrested.

In case of very slow reactions or the processes where high fouling is expected, batch processes are preferred. However, recent studies clearly reflect the scope to remove the limitations while moving from batch to flow. Understanding of thorough process and a miniaturization with appropriate modification can certainly help in scaling up. Flow chemistry is certainly, the future for a safer, more scalable and effective multi-step synthesis of pharmaceutically relevant products to meet global demands that we hope to witness for a larger number of compounds in the years to come.

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