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Review

Micro reactor and flow chemistry for industrial applications in drug discovery and development

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Abstract

In this review, case studies focused on syntheses of active pharmaceutical ingredients, intermediates and lead compounds are reported employing micro reactors and continuous flow technology in areas such as medicinal chemistry, chemical development and manufacturing. The advantages of flow technology are currently very clear as opposed to conventional batch methods. Most strikingly and relevant for pharmaceutical's time-to-market needs, flow processing has the important advantage of the ease with which reaction conditions can be scaled. As this technology is new and has major full-process scale implications, we also wanted to point out that this cannot be applied and released to all chemistries yet, thereby also critically mirroring disadvantages and advantages of the step-change technology. However, the positive impact has been dominating and thus pharmaceutical and fine-chemical industries have increased their awareness and interest in flow chemistry applications. Beyond pharmaceutical syntheses, this review aims to conclude with the special needs of pharmacy on flow and micro reactor chemistry, which is not the same as for the fine-chemical industry. Here, the needs of Brazil are considered, as the mirroring of micro reactor and flow chemistry was done from a European – academic and business – perspective. The hope is to stimulate and promote flow developments in emerging developing nations.

Keywords: active pharmaceutical ingredients; continuous flow; flow systems; micro reactors.

1. Introduction

1.1. Micro reaction technology: chemistry in flow

Chemists are searching for ways to simplify, improve and automate synthetic protocols, for example, by the use of polymer-assisted solution-phase synthesis, microwave-assisted organic synthesis [1, 2], micro reactors, flow chemistry [3, 4] and green chemistry [5].

In 2000, Hessel summarized the advances of micro reactors for chemistry, describing elemental operations such as mixing and heat exchange with microchannels and their first applications in gas-phase, liquid- and gas-liquid fine-chemical synthesis [6]. One year previously, a forecast that specialized on biochemical and pharmaceutical applications of micro reactors was added to fine- and process-chemical perspectives [7].

Continuous flow reactors for drug discovery have been reported as a tool used in pharmaceutical companies to increase the numbers of compounds synthesized and evaluate biological activity faster [3, 8, 9], as well as use in industrial production [10, 11]. Many more reviews followed, and increasingly specialized either on chemistry [12], chemical engineering [13] or devices [14].

Approaching from a chemical rather than a chemical engineering perspective and with different motivation, for example, on process automation, the continuous flow operation has been coined flow chemistry, being made with microstructured devices or simple (filled) capillary/tube reactors [9, 11, 15–17]. In addition to the above, this has given a second, major push to perform chemical syntheses not batchwise in flasks, but using continuous flow through milli- and microstructured reactors [18].

An important advantage of micro reactor/continuous flow technology compared with conventional batch methods is the ease with which reaction conditions can be scaled – without the need for reoptimization – through the operation of multiple systems in parallel or other techniques (numbering-up, smart scaling out, "intensifying-up"), thereby readily achieving production-scale capabilities [19].

Generally, a continuous process has major advantages compared with the corresponding batch process not only on the reaction scale but also its affect on the whole process chain in a holistic manner. These advantages are related to quality on the reaction scale, safety/processability on a process scale, sustainability/economics on a society/business scale (see [20–23] for more details).

The three scales are affiliated with three types of intensifications – transport, chemical and process-design intensification [13, 24].

1.2. Intensification for boosting chemistry and step-changing process design

Process intensification emerged in industry and was initially aimed to reduce the physical footprint of plants, and hence to reduce capital investment and improve safety [25–27].

It often goes hand-in-hand with unconventional reaction conditions in this field. This concept is now widely accepted in the broader meaning of the reduction in the overall impact of chemical processes over their entire lifecycle [28].

Thus, based on this, in 2009, Hessel used the term Novel Process Windows (NPW) for massive intensification of the kinetics (reactivity) and developed a classification and methodological approach [29, 30]. It signifies making use of the classical process parameters (temperature, pressure, concentration and reaction environment), however, set to unusual and most often harsh conditions. Reaction rates can be accelerated by orders of magnitude and reaction times shrink from hours to minutes and seconds. The accompanied large increase in productivity is a further cornerstone in making micro-process technology a competitive concept as opposed to the economics of scale, practiced for decades in production chemistry aiming at increasing the vessel size more and more. Even new chemical transformations could be achieved.

In a submitted paper, Hessel continued on the latter and coined process-design intensification for process simplification and process integration which finally resulted from the reaction achievement of micro reactors [13].

1.3. Micro reaction technology for use in pharmacy and its processing

There is, meanwhile, a consensus that micro reactors and continuous flow are powerful tools for various applications for the discovery and development process in research laboratories within the pharmaceutical, agro, fine-chemical, petrochemical and fragrance industries [3, 31]. This is, for example, demonstrated by giving continuous processing Top-1 priority in the 10 Green Engineering prime measures stated by the multi-industrial American Chemical Society's Green Chemistry Institute Pharmaceutical Roundtable [32].

The economic pressures on the pharmaceutical industry to provide higher quality therapeutics in a shorter amount of time at a reduced cost has driven the adoption of several new technologies and components that enables the rapid synthesis and screening of Novel Chemical Entities [3, 7, 8].

Academic laboratories have been employing this technology as routine work [33, 34], in industry there is clearly considerable interest in the introduction of continuous processing [34], for example, chemical companies such as Bayer [10], AstraZeneca [4], Bristol-Myers Squibb [35], Lonza [11] and others [36].

Lamb and his team made face-to-face interviews with pharmaceutical companies. From such information they deduced the motivation for using flow processing in their daily laboratory work [34]. Although relevance and enthusiasm can be different in each company, they were able to extract some commonly believed benefits and challenges to be overcome, for example, reduced risks associated with process scale-up; decreased time to scale-up in plant manufacture; saving money regarding sites and operating costs; reduced environmental risks; reduced reactor documentation as best hazards control is achieved and market demand can be done faster [34].

Although companies started to recognize the importance of this new technology, there were still hurdles to be overcome regarding a real deep penetration into pharmaceutical industry, such as:

- when a regulatory approval for the production of a drug has been obtained, it is difficult to explain changes into a flow process. Because any change can be modified reactions, byproducts and the purity of the active pharmaceutical ingredients (APIs) can be affected;
- batch processes have been used in decades in a pharmaceutical site, and thus batch reactors are more available. A new API manufacturing can be prepared relatively easily using batches;
- batch processes minding are used in whole development of drug discovery and sometimes innovative technologies require adjustments in a classical manner to carry out chemistry/reactions.

Accordingly, continuous processing can be introduced into the pharmaceutical area and the methodology and equipment can be used in the whole process development line from laboratory bench top, to pilot scale, to plant scale and even in drug discovery. The amounts of byproducts could be determined relatively easily and the processing could be adjusted before the drug is to be tested in a clinical trial. The use of flow processing technology can be extended towards a recognized drug that may now be produced as a generic drug. Despite resistance in implementation, progress clearly moves towards use in pharmaceutical and fine chemistry. This review intends to illustrate how this new technology, micro reactors and reactors in continuous flow, could revolutionize pharmaceutical areas such as medicinal chemistry, chemical development and chemical manufacturing through the implementation of this innovative technology.

2. Applications using micro reactors and reactors in flow processes in pharmaceutical industry

In recent years, micro reactors and reactors in flow continuous processing have been used in the pharmaceutical industry, for example, medicinal chemistry to obtain lead compounds in drug discovery in an easy and fast manner and in fine-chemical production of active intermediates or APIs [37, 38].

In drug discovery, a flow-assisted chemical process has been used, for example, to produce derivatives from an active compound. The imidazo[1,2-*b*]pyridazine moiety has recently been reported by Sanofi-Aventis as an inhibitor of casein kinase I. A small collection of imidazo[1,2-*b*]pyridazines analogs were described using a four step sequence of reaction. The final 19 imidazopyridazine analogs were obtained in excellent purities (>95%) and at moderate to good yields (25–90%) [39]. Tachysterol, vitamin D3, an industrial product was recently obtained by using a photo-micro reactor in a highly efficient, two-stage, flow synthesis from provitamin D3 [40].

APIs are not only considered compounds which are on the market but also as active compounds in clinical phases to

obtain approval. In this stage, chemical processing and manufacturing issues become very important, and flow processing, despite its still recent introduction, has proven its robustness and versatility towards industrial chemical manufacturing.

In 2009, a manufacturing contract was made between DSM and NicOX. NicOX developed Naproxcinod which is the first compound in the Cyclooxygenase-Inhibiting Nitric Oxide-Donating (CINOD) class of anti-inflammatory agents and is being investigated in Phase III studies to treat patients with osteoarthritis [41]. Naproxcinod is a naproxen derivative which contains a nitrate group as a substituent. Compounds containing a nitrate group are difficult to make, as nitration reactions must be handled carefully due to producing products that can violently decompose. Beyond this safety issue, selectivity in nitration reactions and work-up are to be considered to permit extraction and neutralization of nitrated product. Highly diluted, biphasic conditions and specialized safety equipment are necessary to realize this type of processing in a classical batch manufacturing process. Thus, DSM designed a micro reactor system to produce a few hundred tons of Naproxcinod per year which combined three main steps: the nitration reaction, neutralization and work-up [41].

In the following section, some recent examples focus on pharmaceutical and fine-chemical micro reactor/flow synthesis and applications will be given in more detail. Whenever available and appropriate, the flow process is compared with the batch process.

2.1. Aminonaphthalenes derivate (1)

The aminonaphthalene derivate **1** is an important key intermediate in the synthesis of the duocarmycin based prodrug **2** for selective treatment of cancer (Figure 1). Owing to the requirement of large amounts of the prodrug **2** for clinical trials, a multi-step synthesis using a micro reactor (CYTOS® 13 College) was needed to allow preparation of **2** at a kg-scale level [42].

Modification of the classical reaction conditions allowed avoiding the use and formation of solid material, and only in this way the use of a micro reactor was made possible. A nine-step synthesis of the aminonaphthalene (**1**) was compared in batch mode and flow mode (Scheme 1).

For the synthesis of the *tert*-butyl ester **4**, bromoacetyl bromide **3** was used as starting material and *tert*-butanol (*t*-BuOH) as a solvent which was needed to avoid formation of precipitates. This procedure has given 80% yield in batch mode within 20 h at r.t., whereas for micro reactor processing only 50% yield of **5** was obtained at 25ºC in 34 min residence time at 25°C. Compound **5** is solid and was dissolved in dichloromethane for the acid-catalyzed cleavage of *tert*-butyl ester function. Such solution was pumped into a micro reactor to react with trifluoroacetic acid (TFA) to furnish **6** in good yield 82% in 5 min, which is faster when compared with batch mode (16 h). A Friedel-Crafts reaction was employed using Ac_2O and triethylamine (NEt_3) obtaining product **7** in 100% yield in a micro reactor. Solvolysis was also possible at lower flow rate with 20 mol% of NaOEt. The reaction temperature must not be increased over 70°C, as ethanol would then form gas bubbles, which is not desirable using a micro reactor. The protection of the benzyl ether of the naphthol **8** could be achieved conventionally using benzyl bromide in good yields (72%) in a very short time (31 min) when compared when batch mode (2 h). For the hydrolysis of the ethyl ester **8**, aqueous NaOH was used and the obtained carboxylic acid was used one-pot for the reaction with the Shioiri-Yamada reagent DPPA (diphenhylphosphoryl azide) in the presence of *t*-BuOH to give the desired final product **1** in 52% yield in a micro reactor.

2.2. Steroid intermediate (11)

The key steroid intermediate **11** is used to furnish **12** (an endothelin receptor antagonist). A Barton reaction (nitrite photolysis) was carried out by using a glass-covered stainless steel micro reactor (Dainippon Screen Mfg. Co. Ltd., Japan), coupled to an energy saving compact light source [43] (Scheme 2). Photo-micro reactors have been claimed to be more useful to conduct photochemistry reactions compared with conventional batch reactors. Some advantages have been described as being related to (i) the thinness of the reaction mixture (micro space) improves efficiency of the photoenergy; (ii) undesirable side reactions are avoided due to low residence time; (iii) microdevices could be used in large scale, i.e., relying on the numbering-up principle; and (iv) an energy-saving compact light irradiation system can be accommodated by the reaction system.

The optimization of this reaction was made using a micro reactor having a serpentine single microchannel. Two types

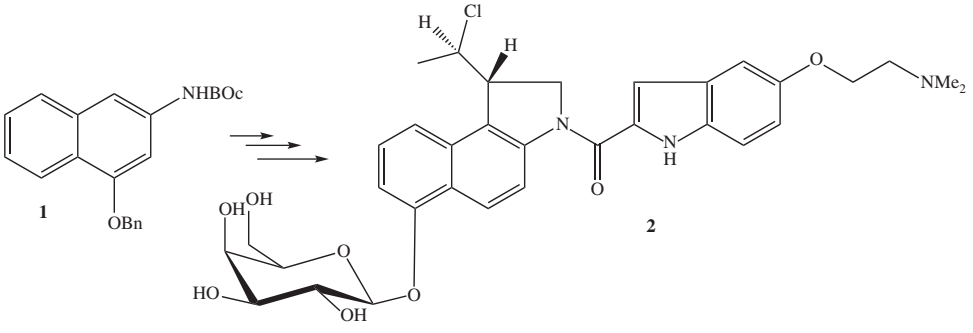
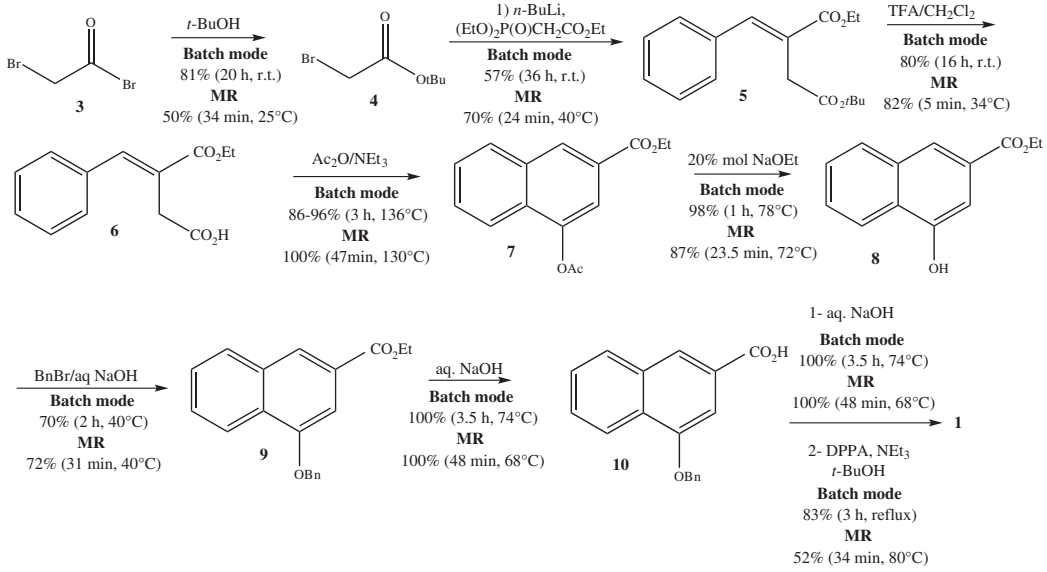


Figure 1 Compound **1** as a building block of prodrug **2** for selective treatment of cancer.



Scheme 1 Synthesis comparison batch mode and micro reactor of **1** (MR time means residence time).

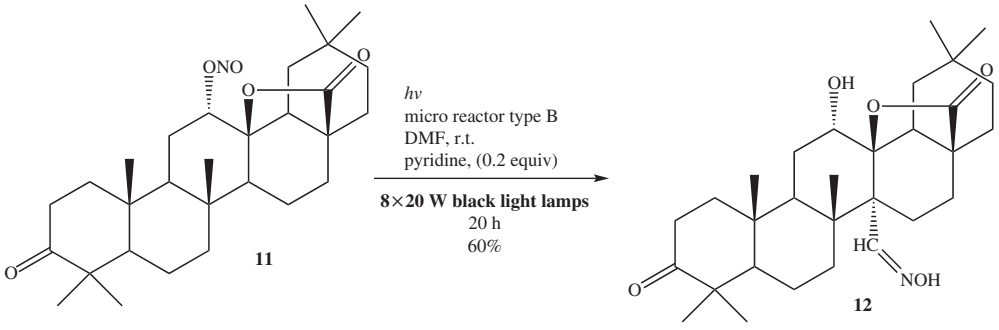
of light sources were used: a 300 W Hg lamp and 15 W black light. The initial results were not so promising concerning obtained yields (21–71%). Then, a micro reactor type with 16 channels and a larger hold-up volume was used in conjunction with a low-power black light source. The result was a production on a gram scale for product **12** in 60% yield.

2.3. Artemisinin (13)

Artemisinin (**13**), a sesquiterpene endoperoxide, currently provides the most effective treatment against multi-drug resistant *Plasmodium* species, and in combination treatments to treat malaria. Artemisinin **13** is a natural product extracted from the plant *Artemisia annua* (sweet wormwood) and is currently cultivated in many countries for this purpose, which restricts the application of the drug and elevates costs for patients [44].

Regarding the complex chemical structure of artemisinin **13**, a total synthesis of artemisinin **13** is too laborious to be considered a viable alternative for supplying the highly cost-sensitive market, as malaria is considered a neglected disease. Instead, a flow synthesis of the anti-malaria drug artemisinin **13** was developed converting **14** into artemisinin **13** by a three-step reaction sequence of photochemically induced oxidation with singlet oxygen, acid-mediated cleavage of the oxygen-oxygen bond (Hock cleavage), and oxidation with triplet oxygen. The reaction sequence was performed as a single flow chemical process that did not require purification and work-up of intermediates after an individual study for each step.

The photooxidation of **14** to tertiary allylic hydroperoxide **14** was explored in a homemade flow system. The 20-ml volume device consisted of fluorinated ethylene propylene tubing wrapped around a Schenk photochemical reactor containing a 450 W medium-pressure lamp. Best results were obtained when a 42-ml reactor was used with the solution of **15** in dichloromethane added at optimized continuous rates of oxygen and TFA/dichloromethane. The first portion of the reactor (32 ml) was maintained at r.t., whereas the last portion (10 ml) was heated to 60°C to push the reaction to completion. Under these conditions the desired product **13** was produced. Subsequent purification by chromatography yielded



Scheme 2 Barton nitrite photolysis of a steroidal compound **11** leading to an oxime **12**.

46% of artemisinin **13** from dihydroartemisinic acid **14** in this sequential flow reaction (Scheme 3).

2.4. Quinolone derivative (18)

The quinolone derivative **18**, a potent 5HT1B antagonist developed by Astra-Zeneca, was synthesized in a seven-step synthesis with an overall yield of 7% by Horchler and coworkers in 2007. Flow chemistry was proposed to improve this yield and the efficiency of the synthesis. The development was made via six-step flow sequence to **18** employing the commercially available Vapourtec R2+/R4 reactor in combination with the ThalesNano HCube flow hydrogenator and using polymer-supported reagents and scavengers to aid reaction telescoping and purification (see Scheme 4) [45].

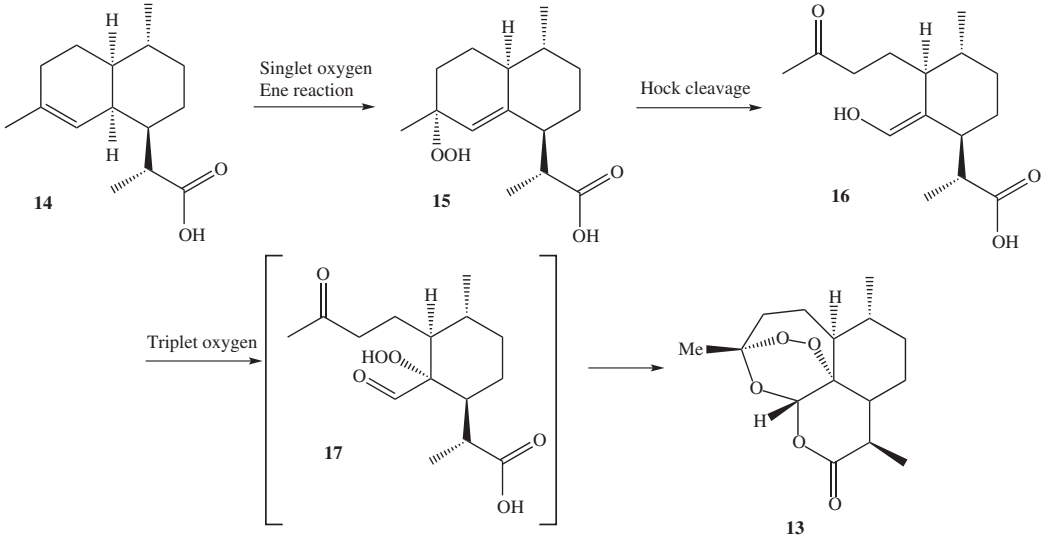
The flow sequence started with a separate introduction of each of the solutions of **19** and **20** in ethanol to the main flow and then this combined stream was directed through a heated convection flow coil attached via a glass jacket, at 135°C and a residence time of 10 min. To scavenge the hydrofluoric acid generated during the S_NAr reaction the existing flow stream was then directed into a glass column filled with quadrapurebenzylamine (QP-BZA). The resultant flow of the nitro compound was immediately subjected to flow hydrogenation utilizing a ThalesNano H-Cube® hydrogenation reactor, which contained a cartridge with 10% palladium on charcoal as catalyst. Any leached palladium was removed using a quadrapure thiourea (QP-TU) from outflow and the desired product **21** (99%) was collected after 25 min.

Then a second flow sequence had to be unified, and the first challenge involved switching ethanol from toluene. After a solvent switch, the aniline **21** and dimethyl acetylenedicarboxylate (DMAD) in toluene were loaded separately. Then the two compounds were combined in a standard T-piece mixer. The reaction stream was thereafter passed during a convection flow coil (CFC) at a temperature of 130°C. To sequester any residual, the dicarboxylate outflow was treated with a column of QP-BZA. The stream of the enamine was then directed through a column filled with anhydrous potassium carbonate. To eliminate any traces of water carried forward, the hydrogenation reaction was heated to 250°C. To avoid toluene boiling, an in-line backpressure regulator was fitted to the system. After 13 min residence time the desired ester from **22** was obtained and the output stream was rapidly cooled to ambient temperature to avoid product decomposition. A mixture of tetrahydrofuran (THF)-H_2O was given to show how a third ingredient enters in the course of a glass resin filled column containing Ambersep 900 hydroxide this last step was important to support efficient ester hydrolysis of ester from **22** inside the column. The resulting carboxylic acid **22** was immediately deprotonated and retained within the basic resin column.

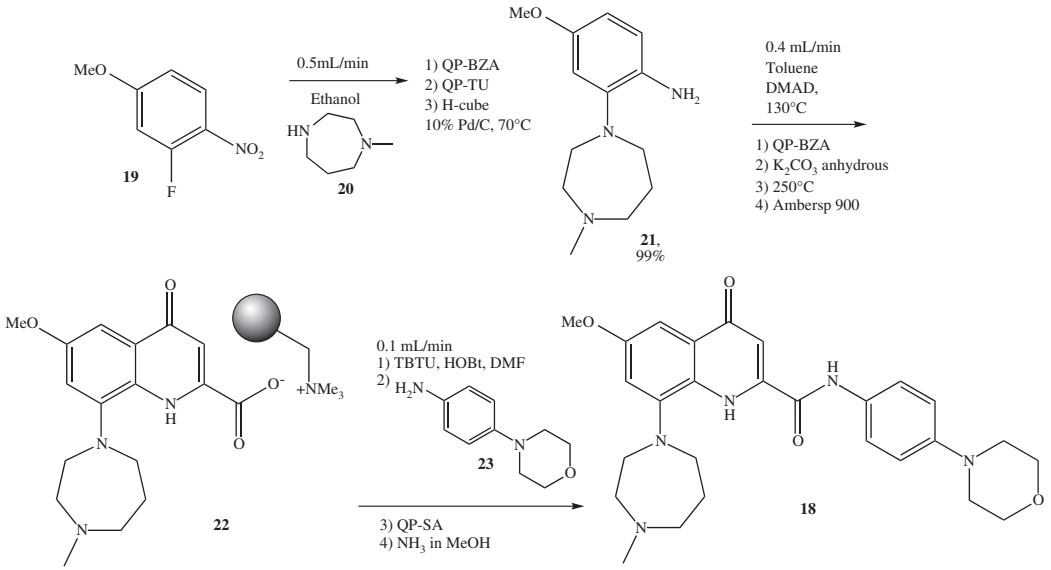
An amide coupling reaction was completed to finalize the synthesis. Initially, a solution of *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate and 1-hydroxybenzotriazole (HOBt) in dimethylformamide (DMF) was pumped in the course of the column containing the Ambersep 900. The output stream from this step with the newly generated activated ester was coupled directly to a second stream of 4-morpholinoaniline in DMF, which was pumped from the sample loop. The ensuing flow stream next entered a CFC, which was maintained at r.t. at a residence time of 50 min. The desired product was trapped onto a column of quadrapure-sulfonic acid and the product was delivered by passing a solution of NH_3 in MeOH through the column; the solution was simply concentrated *in vacuo*, after the recrystallization of the product **18** was obtained in 18% overall yield in better than 98% purity.

2.5. Imatinib (19)

The Imatinib mesylate (**19**) is an API from Gleevec, which is a tyrosine kinase inhibitor, developed by Novartis AG and used for the treatment of chronic myeloid leukemia and



Scheme 3 Reaction sequence for the synthesis of artemisinin **13** from **14**.



Scheme 4 A general scheme showing the obtained intermediate for the synthesis of quinolone derivative **18**.

gastrointestinal stromal tumors [33]. This compound imposes significant solubility restrictions and intermediate handling difficulties, currently perceived not to be ideal for flow chemistry platforms. The original process route to Gleevec was composed of several steps that afforded insoluble intermediates to assist in individual compound purification. Accordingly, other alternative routes have been developed claiming improvements over the previous route as, in batch mode, compound **19** was obtained in 72% yield xylenes as a solvent.

The flow strategy for Imatinib mesylate synthesis comprised similar reactions to those followed in batch-mode syntheses, although employed in a different order. This flow-based synthesis used a procedure requiring limited manual handling of reagents or intermediates (Scheme 5).

The first step involved the formation of the amide core via the reaction between the acid chloride **20** and the aniline **21**. A solution of the acid chloride **20** was preloaded onto polystyrene-supported by 4-dimethylaminopyridine (DMAP) to trap acid chloride. After washing the column with further dichloromethane, a solution of aniline **21** was pumped through the column, thereby reacting and releasing amide **22**. Compound **22** could be directly isolated following solvent evaporation in 78% yield and excellent purity (>95%).

The formation of the product **23** involved the S_N2 displacement of the chloride in **22** with *N*-methylpiperazine. A solution of dichloromethane/DMF was pumped through a column of $CaCO_3$ held at 80°C. To scavenge any unreacted *N*-methylpiperazine the output stream was then passed through a cartridge containing polystyrene-supported isocyanate resulting in a 70% conversion to **23**. A combination of the first two steps into one flow sequence was made which overcame some difficulties such as manual handling of intermediates in the synthesis of **23**, using a minimum excess of *N*-methylpiperazine, and solvent switch requirements. The last third step, a Buchwald-Hartwig reaction, afforded compound **19** in 32% overall yield.

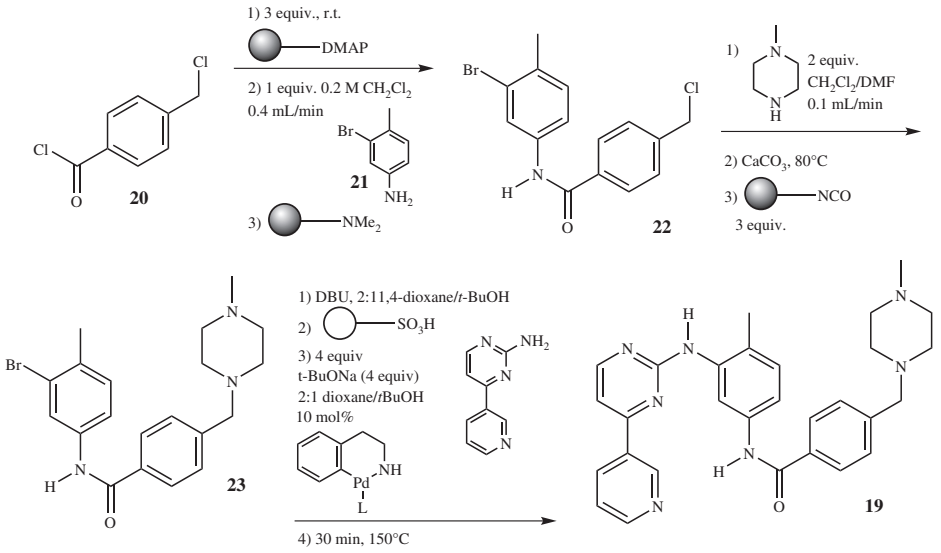
Such continuous processing represents a significant improvement over existing protocols that require manual intervention. The synthetic route, as outlined, also has the potential to be used for analog synthesis and clearly demonstrates the role of flow chemistry techniques in the assembly of challenging and poorly soluble molecules.

2.6. 2,2-Dimethylchromenes (24)

Benzopyran-based potassium channel activators (Figure 2) have generated intense interest in the synthesis of 2,2-dimethylchromenes, particularly those bearing an electron-withdrawing group in the special agent BMS-180448, which is used in the synthesis of a potassium channel activator drug candidate [46].

The starting material to obtain the benzopyran compound involves the reaction to analogs of 2,2-dimethylchromenes **24**, and is hazardous and very risky. On a small-scale batch, the reaction proceeded well, but in further laboratory scale-up an uncontrolled temperature rise occurred, when the substrate and solvent were mixed at r.t. and then heated, due to the rapid and highly exothermic reaction. Safety risk regards large heat release and product degradation if reaction will be done in a batch-wise manner. Calorimetric experiments revealed information to guide further experimentation in the development of a strategy to enable safe and consistent operations on pilot and (potential) commercial scale.

The use of a continuous plug-flow reactor (PFR) was thus demanded, as it minimizes the amount of material exposed to reaction conditions at any given time, further limiting liability in the event of a processing upset. Such a PFR improved the efficiency of heat transfer by maintaining a high surface-to-volume ratio as the operation increases in scale.



Scheme 5 Multiple step flow synthesis for Imatinib (**19**).

The compounds **26** and **24** were obtained by pumping through the coil using a syringe pump at rates equivalent to liquid residence times from 3.5 to 17.7 min. In all of these trials, the compound **26** underwent almost quantitative conversion to **24** of good quality (HPLC purity >96% and 98% yield) (see Scheme 6). The generality and usefulness of this method were further demonstrated by applying this technique for the conversion of other aryl 1,1-dimethylpropargyl ethers **25** to the corresponding 2,2-dimethylchromenes **26** in good yield (86%).

To provide quantities of material for subsequent process development, **24** was converted to **26** in a stainless steel PFR, which was a tubing coil immersed in a constant-temperature bath maintained at a temperature of 195–200°C. A flow of 20 ml/min furnished the reaction mixture a residence time of 4 min. Conversion reached completion in each of the five batches. The yields varied which was explained by losses of residual material in the reactor and physical handling losses. Thus, dimethylchromene **24** at "micro-" and "kilo-scales" was prepared using an enabled PFR large-scale jacketed reactor capable of producing 12.02 kg/h at 92% yield.

2.7. Nabumetone (27)

Nabumetone [4-(6-methoxy-2-naphthalenyl)-2-butanone] (**27**) is a nonsteroidal anti-inflammatory drug (NSAID) launched in 1985 under a variety of brand names (Relafen, Noracet). As model systems, Viviano and collaborators in 2011 have evaluated different continuous flow strategies for the generation of the anti-inflammatory drug nabumetone and related 4-aryl-2-butanones using a combination of two process-intensified flow reaction steps [19].

The synthetic routes to prepare **27** could be achieved via three different synthetic strategies employing different starting material (**29** and **30**) as preparation of intermediate **28** involved a Mizoroki-Heck reaction, Wittig olefination and Aldol condensation. All different reactions were first optimized on a small scale using controlled microwave batch technology and then translated to flow process.

Flow experimentation on the Mizoroki-Heck reaction was carried out in a high-temperature, high-pressure microtubular flow unit X-Cube Flash (Thales Nanotechnology Inc.). The reaction mixture was introduced to the reactor block

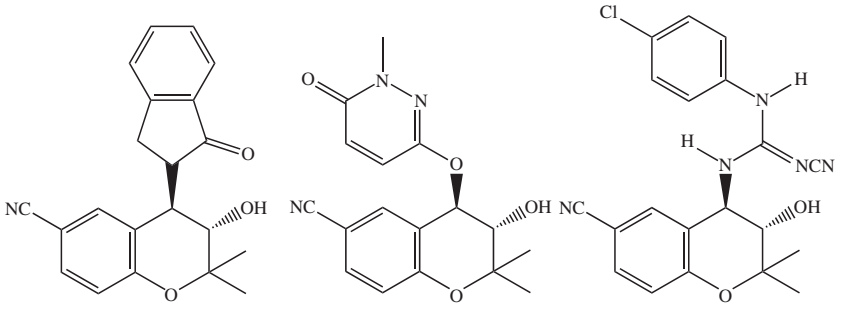
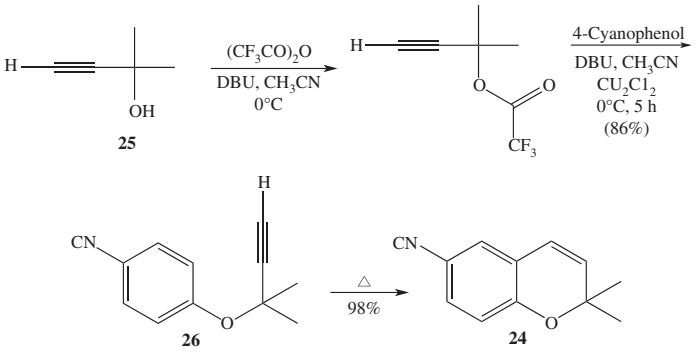


Figure 2 Benzopyran-based potassium channel activators.

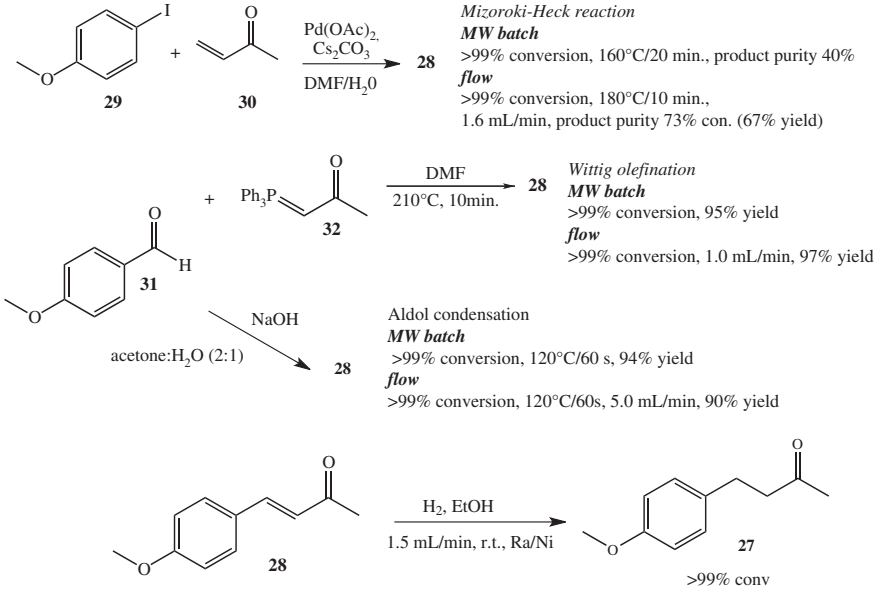


Scheme 6 Preparation of compound **24**.

containing steel coils and a heat exchanger via one or more standard HPLC pumps. The system pressure valve stabilizes the set pressure value between a pressure range of 50–180 bar. Employing the flow reactor system, the batch microwave conditions (MW batch) showed good results >99% conversion to **28**. Using flow conditions, a 16-ml stainless steel coil, at 180°C and a flow rate of 1.6 ml/min (10 min residence time), full conversion was observed providing 67% isolated yield of the desired 4-(4-methoxyphenyl)-3-buten-2-one (**28**) (Scheme 7).

As a second synthetic strategy, the Wittig olefination of aldehyde (**31**) in the presence of (acetylmethylene)triphenylphosphorane was investigated. The Wittig reaction is a strategic, widely applicable carbon-carbon double bond-forming process. The experimental setup for this particular transformation involved the use of a Uniqsis FlowSyn device. Applying the same reaction conditions as optimized for the microwave batch experiments (MW batch), full conversion was achieved using a 10-ml stainless steel coil heated at a temperature of 210°C at a 1-ml/min flow rate (10 min residence time). The desired **28** was obtained in very high isolated yield after flash chromatographic purification (95%) [19].

*Aldol condensation is one of the best-known and most widely used methods for generating carbon-carbon bonds. The reaction involved the condensation of aldehyde (**31**) with acetone. The experimental setup for the aldol condensation contained a Uniqsis FlowSyn device. Employing the flow reactor system initially the aldol reaction was carried out under optimized microwave conditions (MW batch) for the synthesis of **28** from *p*-anisaldehyde using a single-feed concept. The desired product **28** was isolated in 94% yield. For the synthesis of **28**, a 10-ml stainless steel coil at a 1.34 ml/min flow rate was utilized to ensure the required residence time of 450 s at 70°C to furnish **28** in 90% yield. A throughput of ~40 g of **28** per hour was given for a mesofluidic flow setup; for the aldol condensation of *p*-anisaldehyde (**31**) and acetone only 1 min residence time was needed.



Scheme 7 Different synthetic strategies to obtain 4-aryl-butanones **27**.

The Wittig olefination and the Mizoroki-Heck reaction were not suitable for a production route; instead, a large-scale flow aldol condensation was applicable. The scalability of the flow reaction conditions cited above was demonstrated using steel coils of 1000 µm i.d. (5–10 ml internal volume) and large productivities were approached, being more similar to those used in a pilot or production. The experiments in the FlowSyn reactor were revealed to be comparable results from the "one-feed" to "two-feed" strategy. Therefore, the mesofluidic flow setup followed the "one-feed" concept. Essential parameters for the reaction outcome are temperature control and residence time. Important for further scale-up is the control of the flow regime in the residence time zone. Following these requirements, the mesofluidic flow setup was considered out of one feed module and one reaction module. The overall flow rate in the experiments was 2.4 kg/h, which corresponds to a product **28** flow of 0.35 kg/h in 104 min. In this way, 4.65 l reaction mixture was processed at a temperature of 120°C.

2.8. 7-Ethyltryptophol (32)

7-Ethyltryptophol (**32**) is a key intermediate for the clinically effective analgesic and anti-inflammatory drug Etodolac (**33**). Etodolac (**33**) has been shown to possess an exceptional safety profile with respect to the gastrointestinal and renal tract, and it has also been proved to have the potential to retard the progression of skeletal changes in rheumatoid arthritis [47]. Despite the diverse and creative approaches to synthesize 7-ethyltryptophol (**32**) that have been developed so far, the classical Fischer indole synthetic methodology which involves hydrazone formation and subsequent [3+3] sigmatropic rearrangement remains the benchmark method (Scheme 8).

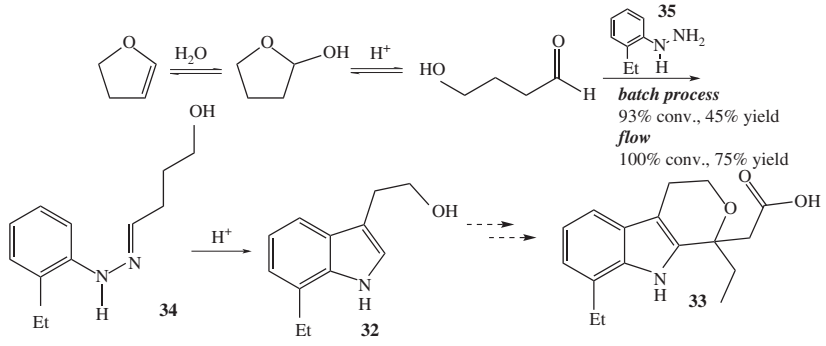
The development of one-pot approaches to the assembly of the indole skeleton which obviates the isolation of the unstable arylhydrazones (**34**) is attracting considerable attention due to both its economical and its ecological importance [47]. A scalable and efficient continuous process for the Fischer indole synthesis of **32** from **34** and 4-hydroxybutyraldehyde via a continuous flow reactor was established. This process was amenable both for the preparation of analogous compounds and for scaling-up by operating several reactors with high throughput in parallel. Owing to the rapid decomposition of **34**, it remains a challenging task to obtain a more satisfying yield. A new optimized process was then undertaken, and optimal conditions were achieved by streaming a solution of **35** in ethylene glycol/water (5:2) together with a flow of 4-hydroxybutyraldehyde in ethylene glycol/water (5:2) at 115°C for 2 s, followed by the introduction of 50% aqueous sulfuric acid into the loop reactor for approximately 4 min. The mixture was cooled when it flowed in the course of the cooling loop, and the reaction was terminated by neutralizing the residual acid with 30% aqueous NaOH. The yield of **32** was 73–75% corrected for purity. For comparative purposes, the reaction was run both as a one-pot batch process on a 1-kg scale.

2.9. Azetidin-2-ones (36a)

Azetidin-2-ones (β-lactams) are among the most investigated of all heterocyclic ring systems because of their well-documented impact on small-molecule drug discovery. The natural product Thienamycin and monocyclic β-lactam compounds exemplified by Aztreonam are carbapenem structures which possess *trans* stereochemistry at the two chiral centers of the azetidinone ring (Figure 3). When suitably functionalized, the β-lactam ring in enantiomerically pure (EP) form represents the core of a vast array of antibiotics, some of which are used to treat drug-resistant bacterial strains [48]. A new strategy was developed to obtain this strained four-membered ring system which regarded versatility, economy, safety and simplicity issues. In particular, the safety of the chemistry was carried out in compact fluorescent light (CFL) continuous flow reactors.

For example, the key intermediates **36a** with β-lactam structures were prepared in both CFL and medium-pressure mercury Vapor Lamp (MVL) continuous flow reactors. The Weinreb β-ketoamide **38** was prepared by a modified literature procedure (Scheme 7) using a photolysis of *R*-diazo-*N*-methoxy-*N*-methyl (Weinreb) β-ketoamides (**39**) derived from EP *R*-amino acids. The corresponding EP β-lactams were obtained via an intramolecular Wolff rearrangement.

Accordingly, serine imidazolide **40** was acylated with lithium enolate (LiHMDS) of *N*-methoxy-*N*-methylacetamide to give the desired β-ketoamide **39** in 86% yield on a 9-g scale. Treatment with a diazo transfer reagent gave the



Scheme 8 Synthesis of 7-ethyltryptophol **32**.

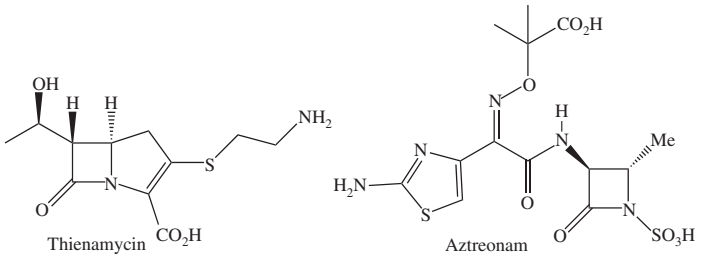


Figure 3 Representative β-lactam structures.

desired *R*-diazo-β-ketoamide **38** in 89% yield. Under standard photolysis conditions, the diazo compound **38** was irradiated with MVL continuous flow reactors, which afforded an easily separable mixture of β-lactams **36a** and **36b** at a rough ratio of 2.5:1, respectively, in 90% isolated yield. The identities of the two β-lactam isomers were confirmed by X-ray crystallography. The key intermediate β-lactam **36a**, employed in the synthesis of thienamycin and other carbapenems (**37**), was prepared using CFL continuous flow reactors also (Scheme 9).

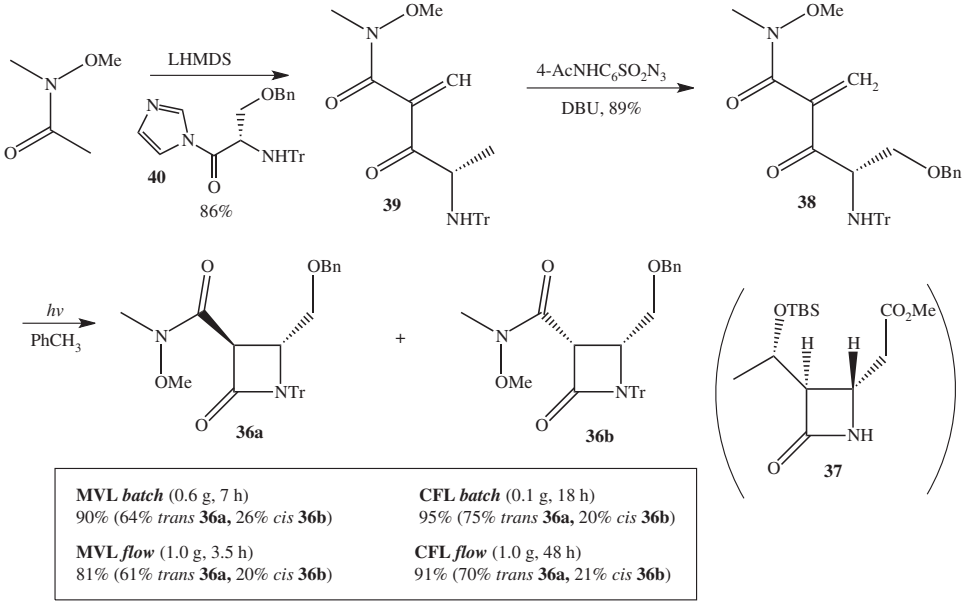
The simple continuous flow photochemical reactor was constructed from common laboratory equipment and consisted of the requisite tubing and a medium-pressure liquid chromatography pump in addition to standard flasks to improve upon processing capabilities. Thus, this different route to obtain β-lactam structures showed interesting results in both CFL and MVL continuous flow reactors [48].

2.10. 5-(Thiazol-2-yl)-3,4-dihydropyrimidin-2(1*H*)-one (41)

Thiazoles constitute a ubiquitous structural motif present in a broad range of biologically active small molecules and natural products. Dihydropyrimidin-2(1H)-ones (DHPM) derivatives also constitute a large family of medicinally significant compounds displaying a wide range of pharmacological properties. For example, Monastrol has received much attention in recent years because of its activity as a mitotic kinesin-5 inhibitor. 5-(Thiazol-2-yl)-3,4-dihydropyrimidin-2(1*H*)-one (**41**) has anti-HIV properties (Figure 4). Thus, combining thiazole and DHPM heterocycles moieties into one structure would constitute an interesting tool to furnish a novel drug-like scaffold [49].

The first example of a consecutive heterocycle formation/multicomponent reaction using an uninterrupted continuous flow micro reactor sequence was recently reported [50]. In this unique process, sequential thiazole formation, deketalization and Biginelli three-component reaction provided rapid and efficient access to a library of novel DHPM derivatives of **41** [49].

First of all, an optimization and development method was investigated for the synthesis of 1-(thiazol-2-yl)propan-2-one (**42**). Then, this reaction was joined with the Biginelli reaction in a single continuous sequence. Approximately 100 derivatives of **41** could be synthesized, purified and prepared



Scheme 9 Synthesis and reaction of α-diazo-b-ketoamide **38** comparing batch and flow process to obtain **36a**.

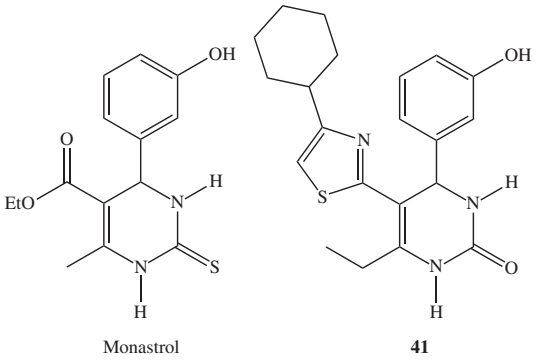
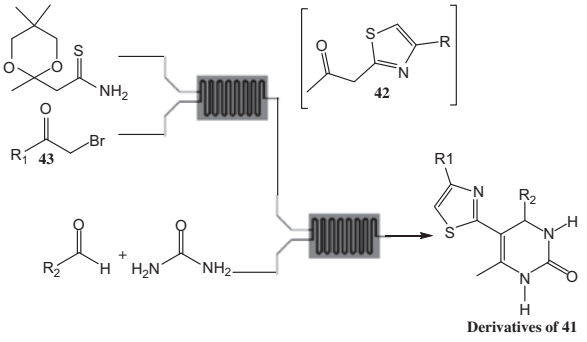


Figure 4 Examples of actives DHPM, Monastrol and **41**.

for biological testing within 1 week. The overall yields for the three-step two-chip sequence were high (39–46%) when using aromatic α-bromoketones **43**, averaging at approximately 70% yield for each chemical step. This methodology had two important advantages when compared with a standard batch synthesis of analog libraries. First, the optimization of each reaction step can be conducted very rapidly. Second, the fully automated multistep flow technology allowed for swift construction of compound libraries (Scheme 10).



Scheme 10 Final microfluidics setup for the synthesis of DHPMs **41**.

2.11. 6-Hydroxybuspirone (43)

Buspirone (**42**) is a potent and selective 5-HT1A receptor partial agonist that has been prescribed for the treatment of generalized anxiety disorders. More recently, 6-hydroxybuspirone (**43**) has been found to possess anxiolytic activity in rats using the fear-induced ultrasonic vocalization paradigm [51] (Figure 5). Although batch processing has successfully been used to prepare **43** from **42**, scale-up is still to be improved. The oxidation reaction times at pilot plant scale (16–24 h) are much longer than those experienced in the laboratory (~8 h). The batch reaction was carried out at a temperature of -70°C and thus a cryogenic-capable large-scale reactor was needed. Finally, sparging air into the batch is needed and sweeping the head space of the reactor with nitrogen. The larger scale makes uniform purging of the headspace more difficult and failure potentially has a greater impact [35]. Owing to these concerns, the development of a continuous, high-yield and scalable enolization, oxidation and quench process for the hydroxylation of the buspirone (**42**) to finally give **43** (6-hydroxy-8-[4-(4-pyrimidin-2-ylpiperazin-1-yl)-butyl]-8-aza-spiro[4.5]decane-7,9-dione) has been described [35].

The objective of Bristol-Myers Squibb laboratory studies was to build up a unit reactor with reasonable productivity which could then be scaled-up or numbered-up by operating multiple units in parallel to achieve productivity targets [35]. Conversion of a batch process to a fully continuous process was demonstrated for the production of 6-hydroxybuspirone (**43**). A much faster reaction was achieved due to higher operating temperatures and enhanced mass transfer in the continuous process. Very long and varying batch reaction times (from 8 to 24 h) were supplanted by continuous reaction times of <4 min. Low coolant operating was increased from temperatures of -80°C to -38°C with a significant improvement in cooling efficacy.

Compound **43** was prepared in a multiple reaction sequence. The sodium enolate of buspirone (with triethylphosphite present) was generated in batch at a temperature of -70°C. This preformed enolate solution was pumped in the course of a heat exchanger to rapidly bring the temperature to approximately

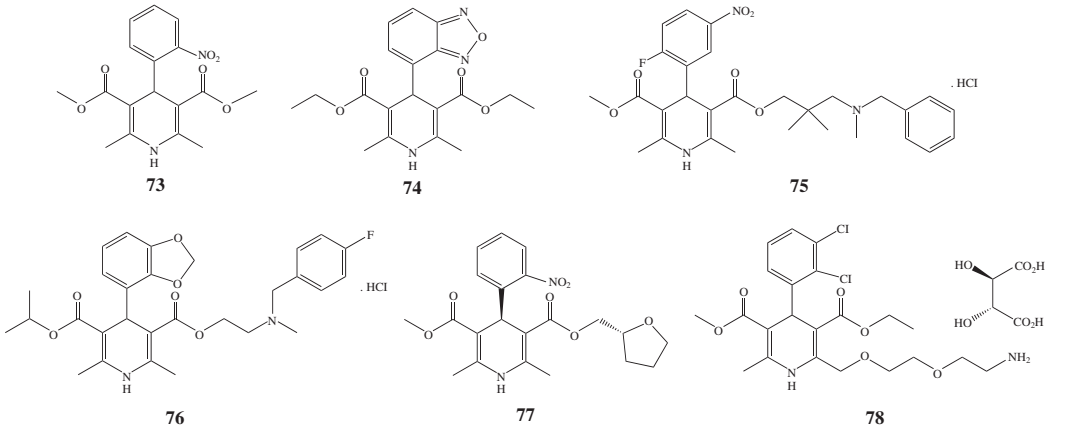


Figure 5 Representative 1,4-dihidropiridinas.

-31°C after which it flowed into the oxidizing column while a countercurrent flow of oxygen was introduced from the bottom of the oxidizing column. The reactor was cooled by circulating coolant (-37°C) through the external jacket. Some operating parameters had to be examined such as the flow rates for the enolate solution and for oxygen, the oxygen pressure, the heat transfer rates and the operating temperature inside the oxidation column (Scheme 11).

The continuous process was inherently safer with much smaller reaction volume (~3 orders of magnitude) of a flammable solvent in the presence of oxygen. In addition, only a small fraction of the starting material or product was at risk (in the case of equipment failure or human error) at any time. Three continuous reactors were operated in succession for the production of a stable quenched product solution. Over 100 kg of APIs was produced during the pilot-plant campaign (three batches) using this setup. Moreover, the quality of the product produced by the continuous process was comparable to that of the batch process.

2.12. Ciprofloxacin (44)

Ciprofloxacin (**44**) is a potent gyrase inhibitor, marketed as CIPROL, and is one of the most frequently prescribed antibiotics for the effective treatment of bacterial infections; it belongs to the class of fluoroquinolone. The known Bayer approach for the synthesis of the drug is based on a one-pot batch procedure without isolation of intermediate compounds [52].

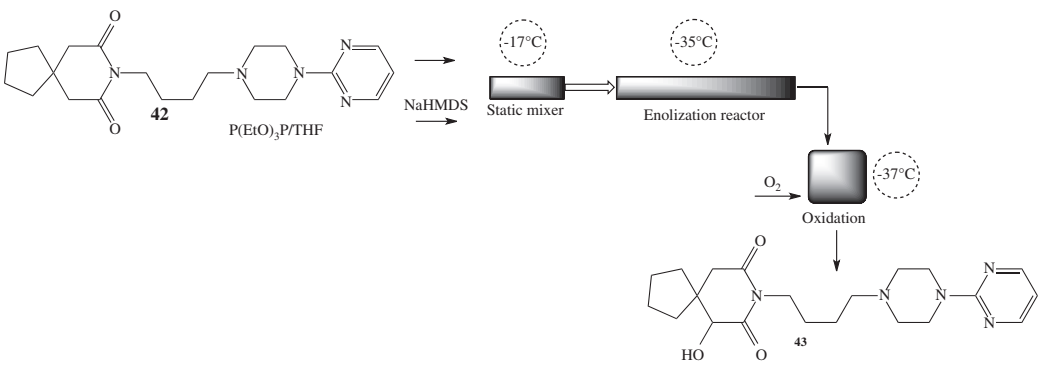
The importance of ciprofloxacin stimulated the synthesis of some analogs using micro reactors [53]. The strategy chosen was based on the Bayer approach for several reasons: first, the whole one-pot process can be easily dissected into its single reaction steps. Second, each single step is generally applicable to synthesis in micro reactors, and thirdly only two diversification steps, Michael addition and a nucleophilic aromatic substitution reaction, are needed to generate **44** (Scheme 12).

The first step involved a commercially available acid chloride and acrylate to yield compound **45** in 99% yield in throughput 1.3 g/h which easily reacted with cyclopropylamine via an addition-elimination mechanism and concomitant deliberation of dimethylamine to give compound **46** in 84% yield in throughput 0.4 g/h. By treatment with 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU), the desired nucleophilic aromatic substitution reaction took place and **46** could be successfully converted to the first key compound **47** in 75% yield. In a second nucleophilic aromatic substitution reaction with piperazine, compound **48** was obtained in >99% yield which gave after saponification the target compound ciprofloxacin **44** (92%).

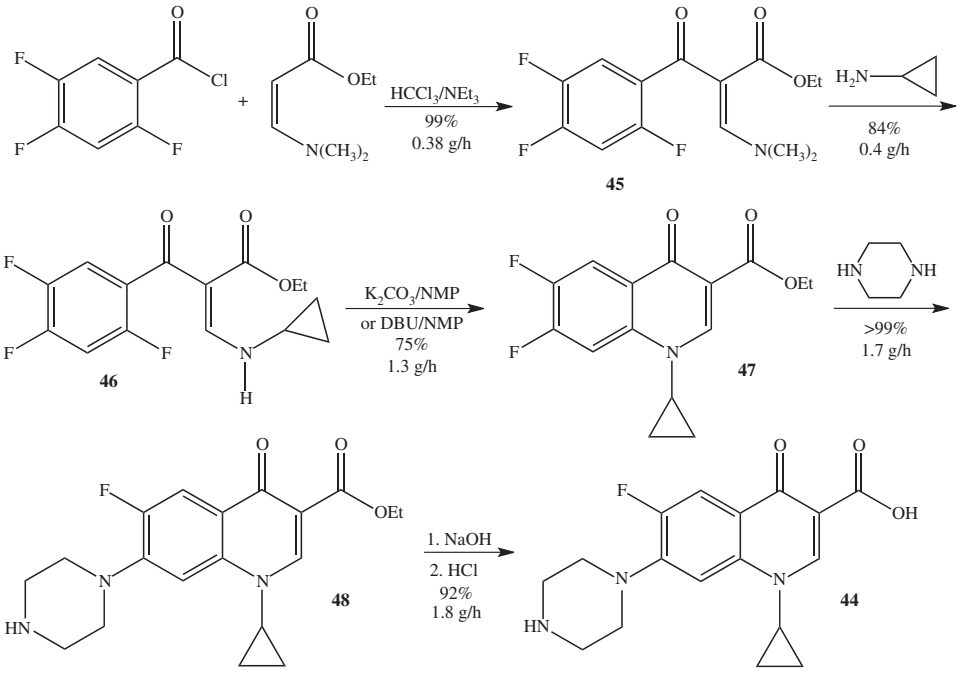
For structural diversification of the fluoroquinolone moiety, only amines are needed which are available in a huge variety. Thus, 28 ciprofloxacin analogs could be synthesized at good overall yield and purity. The isolated yields ranged from 71% to 85% in the first diversification step and from 59% to 99% in the second step [52].

2.13. Intermediate (50) for a new quinolone

An addition reaction of *tert*-butoxycarbonyl (*t*-Boc) to an amine group within compound **49** produces compound **50**, which is an intermediate for a new quinolone antibiotic drug. Using a Kenics-type in-line static mixer, the finding of optimum operating conditions resulted in higher yields of compound **50** [50]. The Kenics static mixer reactor was also employed to overcome the heat-transfer limitation of the batch reactor. The effect of residence time variation on product yield was investigated both by changing the flow rate and reaction volume. The highest yield was achieved when the residence time was longer than 10 min or shorter than 10 s. A CFD (computational fluid dynamics) study on the Kenics mixer shows that effective chaotic mixing is achieved both for creeping flow condition (i.e., longer residence time) and turbulent flow conditions (i.e., shorter residence time). The study also shows an improper mixing in laminar flow for ranges near creeping flow conditions. The experimental results indicated that a high yield comparable to a maximum was achieved in the creeping flow region when the residence time was higher than 10 min. The yield of the reaction gradually decreases as the residence time decreases. According to a study on residence time distribution (RTD) for the Kenics static mixer, it is the number of elements of this mixer that has the most significant effect on the mixing efficiency on RTD curves. In this experiment, a total of 135 Kenics static mixer elements were used, which is sufficient to assume a radially flat profile in axial velocity, as given for plug flow.



Scheme 11 Preparation of **43**.



Scheme 12 Linear Microreaction Technology approach to ciprofloxacin (**44**).

A flow process mixed first in a union T-tube fitting a stream of compound **49** in isopropyl alcohol (IPA) and di-*tert*-butyl dicarbonate (*t*-Boc_2O) with another stream with KOH. Such mixed stream was directed to a static mixer, and then flowed through the reactor tube. The product mixture was discharged from the final reactor tube into acid quench. With this continuous reactor, a high yield of 97% was reached at a flow rate of 100 ml/min without byproducts, when the feed temperature and the mixer wall temperature were set at 20°C and 0°C, respectively (Scheme 13).

2.14. Metoprolol (51) and Indacaterol precursor (52)

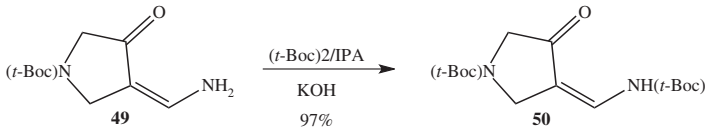
Metoprolol (**51**) is used in the treatment of hypertension which is a selective β-1-adrenoreceptor blocking agent. Indacaterol (**53**) is a novel β-adrenoreceptor agonist developed by Novartis, which is currently used in the treatment of chronic obstruction pulmonary disease [53]. The same approach was used in the synthesis of Metoprolol (**51**) and the Indacaterol precursor (**52**) employing a continuous flow micro reactor for β-amino alcohol formation by epoxide aminolysis.

The synthesis of Metoprolol (**51**) involved the aminolysis of the convenient epoxide (**54**) with isopropyl amine. Evaporation of isopropyl amine could be controlled using micro reactors. In this new method developed under continuous flow operation capability of delivery was 7.0 g/h (61 kg/year), it was possible to decrease the content of the bis-alkylation compound (**55**) until 91% yield and the reaction time to as short as 15 s at 98% conversion (Scheme 14).

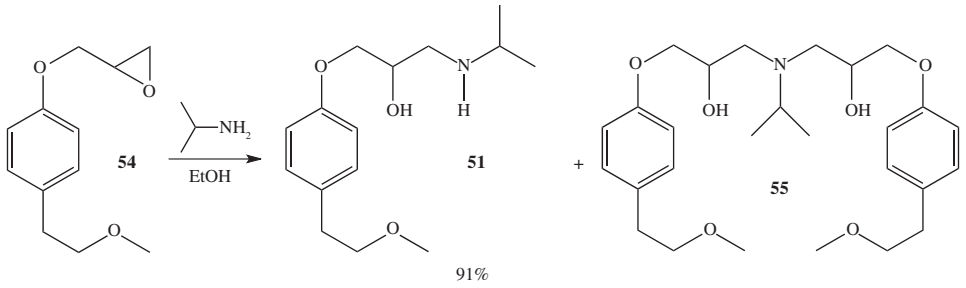
For the preparation of Indacaterol precursor (**52**) (Scheme 15), challenges had to be overcome, such as effect of the solvent on the aminolysis, the low solubility of the starting epoxide (**56**), the formation of solids in the micro reactor caused by a crystalline quinolinone structure, the screening of solvent to solve solubility of crystals, and the instability in organic solvents of **52**. Nevertheless, the Indacaterol precursor (**52**) could be furnished from a single 120 µl micro reactor with a good conversion of 97% and yield of 70% (Scheme 15).

2.15. Mur ligase inhibitor 57

Compound **57** is a Mur ligase inhibitor with potential antibacterial activity which belongs to the chemical class of imidazo[1,2-a]pyridine-2-carboxamides [40]. Initially, a study in flasks was made to prepare imidazo[1,2-a]pyridine-2-carboxylic acids and imidazo[1,2-a]pyridine-2-carboxamides.



Scheme 13 Preparation of compound **50**.



Scheme 14 Preparation of Metoprolol **51**.

Then a flow method was developed to furnish a library of imidazo[1,2-a]pyridine-2-carboxamides which have important application in drug discovery. This methodology can be used to prepare compound **57** without isolation of intermediates in 46% yield in a single step, whereas in-flask synthesis of compound **57** was reported to proceed in 16% overall yield over two steps [54].

A continuous flow method was started through mixing of streams of 2-aminopyridines and bromopyruvic acid which are then reacted at 100°C and 20 min to furnish the corresponding imidazol-carboxylic acid. The first outlet stream was combined with a stream comprising HOBt/EDC(1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) and a stream comprising DIPEA (*N*,*N*-diisopropylethylamine) and a chiral amine at 75°C and 10 min to obtain **57** in 46% yield (Scheme 16).

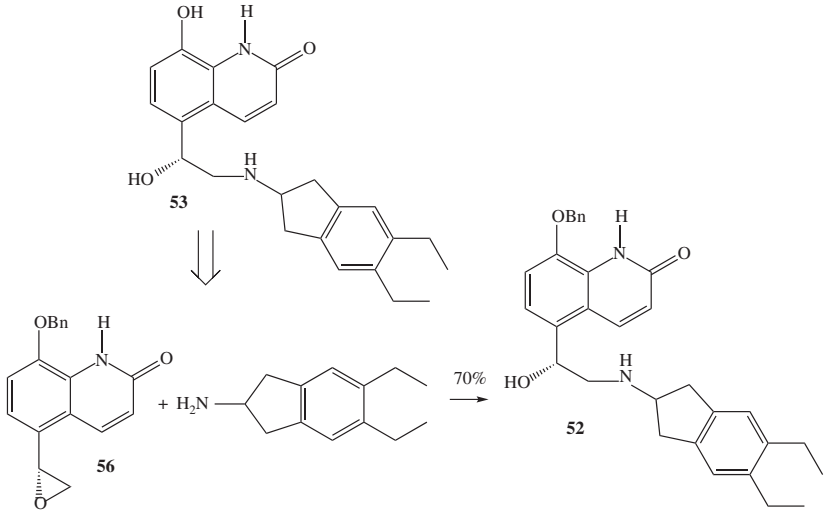
2.16. Ibuprofen (58)

The three-step flow synthesis of Ibuprofen (**58**), which is a NSAID, was developed using a simplified micro reactor without purification and isolation steps [55]. First of all, the three reactions were investigated individually regarding byproducts and excess reagents from each reaction. Then, the process was joined and the flow synthesis required no intermediate purification steps, byproducts and excess reagents from prior steps which must be compatible with downstream reactions. The flow synthesis was carried out in 500 cm tubing with five syringe pumps. The flow synthesis generated approximately 9 mg/min of crude Ibuprofen (**58**) (see Scheme 17).

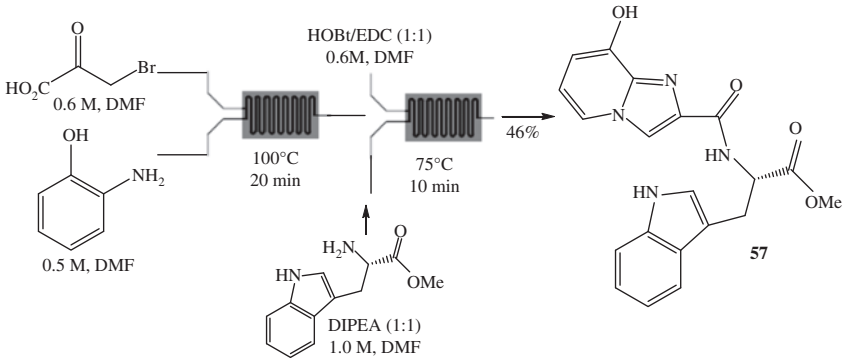
A Friedel-Crafts acylation was made in flow using a solution of isobutylbenzene (IBB) and propionic acid through mixing with a stream of trifluoromethanesulfonic acid (TfOH) at 87 µl/min flow rate, 5 min residence time and 150°C to furnish the acylation product. The outlet stream was mixed with $PhI(OAc)_2$/TMOF (trimethyl orthoformate) at 0°C to facilitate the 1,2-aryl migration. The final phase continuous flow was achieved by saponifying methyl ester with KOH. The outlet stream from the second step was combined with a stream of 5 M KOH and heated to 65°C for 3 min. The intensified heat transfer in the micro reactor allowed the acidic stream to be reacted with the base stream without danger from the exotherm. After an acidic work-up, Ibuprofen **58** was obtained in 51% yield.

2.17. Rimonabant (59)

Rimonabant (**59**) from Sanofi-Aventis was an anorectic and anti-obesity drug that has been withdrawn from the market.



Scheme 15 Preparation of Indacaterol precursor (**52**).



Scheme 16 Continuous flow preparation of Mur ligase inhibitor **57**.

It was the first selective cannabinoid CB1 receptor blocker approved for use anywhere in the world [56] (Scheme 18). The last step of the synthetic sequence, the union of an acid chloride and 1-aminopiperidine, may be replaced by direct amide formation. The entire sequence to **59** was carried out in a micro reactor starting with treatment of ketone **60** with LiHMDS [lithium bis(trimethylsilyl)amide] at r.t. (1 min retention time), followed by exposure to ethyl oxalate at temperature of 50°C in a second reactor (10 min retention time, 70% yield). After work-up and purification, **62** was treated with HCl salt of 4-chlorophenylhydrazine in AcOH at 125°C for 16 min to provide pyrazole **63** in 80% yield. The last step involved an amidation reaction using trimethylaluminum ($AlMe_3$) to obtain Rimonabant **59** in gram quantities in 49% overall yield.

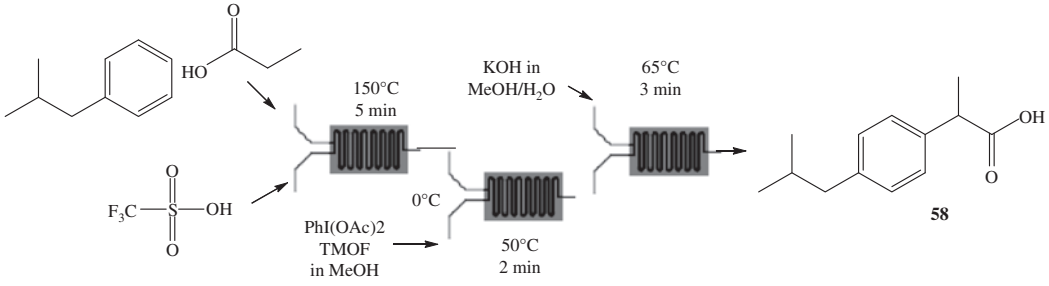
2.18. Efaproxiral (64)

Efaproxiral (**64**), developed by Allos Therapeutics, is an analog of the cholesterol drug bezafibrate developed for the treatment of depression, ischemia, stoke and other diseases. Both are prepared using a safe, functional group-tolerant and high-throughput version of the trimethylaluminum-mediated amide bond formation reaction in a micro reactor system [56]. Efaproxiral (**64**) can be synthesized from the ester **65** followed by alkylation of the phenol. Phenol alkylation relies on heterogeneous mixtures of inorganic bases in organic solvents, rendering this step less suitable for micro reactors. Therefore, the phenol was first alkylated using the *tert*-butyl ester of 2-bromo-2-methylpropionic acid. The methyl ester was converted to the amide (**67**) with complete selectivity over the *tert*-butyl ester employing 3,5-dimethylaniline and trimethylaluminum. The *tert*-butyl ester was removed in the final step using formic acid at 90°C in continuous flow with a throughput of 24 mmol/h of Efaproxiral **64** (see Scheme 19).

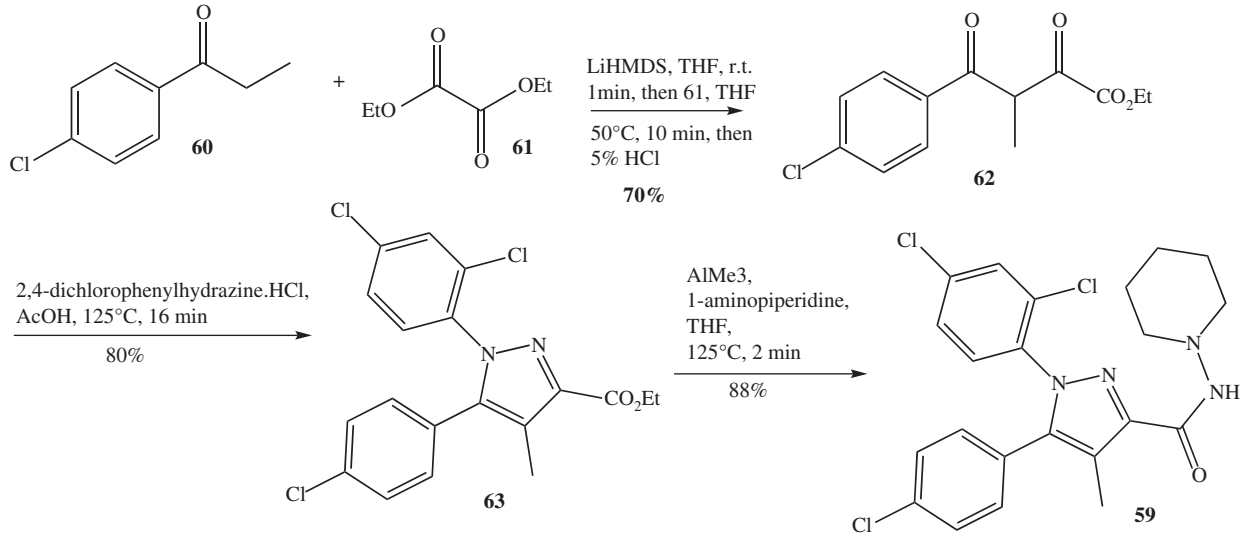
2.19. *N,N*-Diethyl-4-(3-fluorophenylpiperidin-4-ylidenemethyl)benzamide (68)

N,*N*-Diethyl-4-(3-fluorophenylpiperidin-4-ylidenemethyl) benzamide (**68**) is an exceptionally selective and potent δ-opioid receptor agonist developed by AstraZeneca which is being used in pain relief without the side effects associated with other members of the family (e.g., respiratory depression, dependence liability and dysphoria) [57]. A five-step synthesis was published with an overall yield of 6% of **68**. To increase this yield and the efficiency of the synthesis, a flow-based methodology was developed relying on a four-step synthesis to obtain **68**. For this process, a commercially available Vapourtec R2+/R4 reactor and Mettler-Toledo ReactIR was employed to guarantee in-line analytical analysis (Scheme 20).

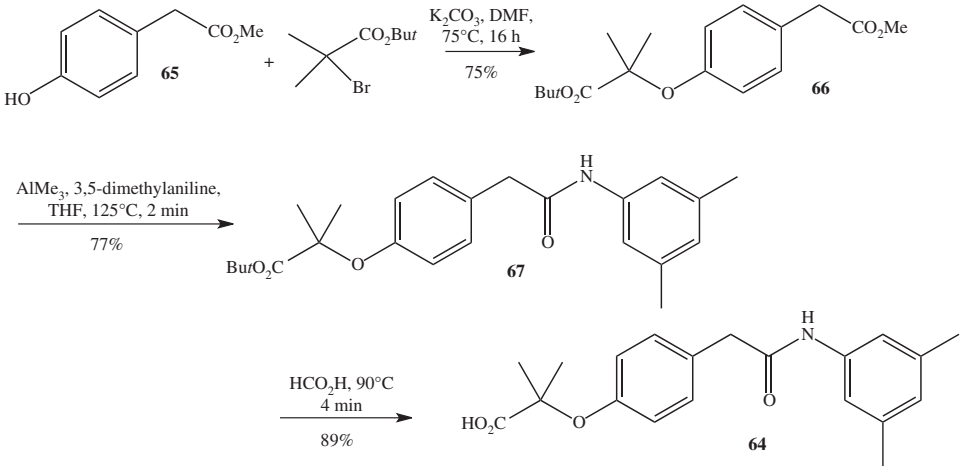
The initial step required the development of an amide bond-forming process through a switching to a solution of Grignard reagent Isopropylmagnesium chloride lithium chloride (iPrMgCl·LiCl) with diethylamine and ester **69** at temperature of 25°C in THF and were filled into two identical sample loops made from polyether ether ketone (PEEK). The two sample loops were simultaneously injected into the main



Scheme 17 A three-step continuous flow synthesis to prepare Ibuprofen **58**.



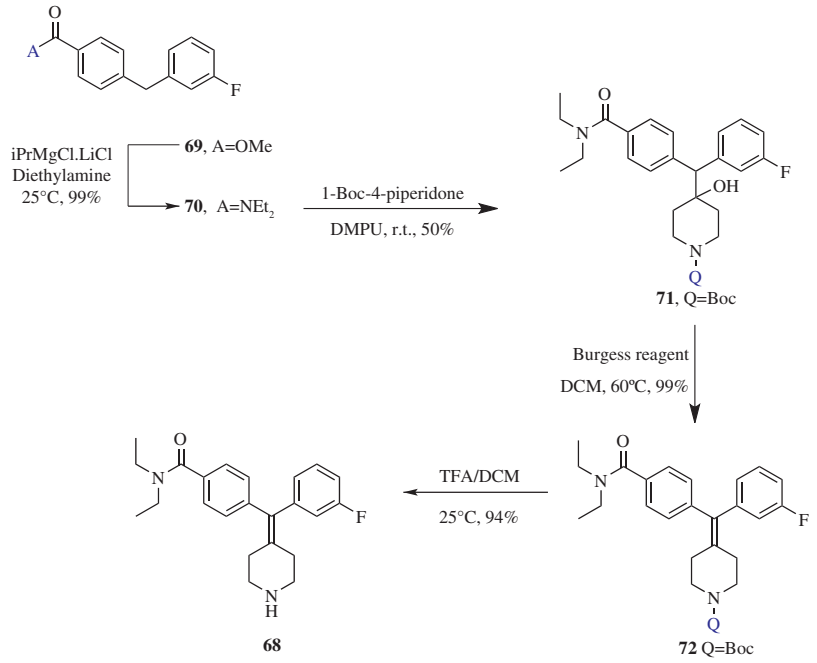
Scheme 18 Continuous flow synthesis of Rimonabant (**59**).



Scheme 19 Synthesis of Efaproxiral (**64**) combining batch and flow regime.

flow in the course of a T-piece connector at a flow rate of 0.125 ml/min per channel. The combined stream was then directed in the course of a CFC submerged in a mixture of acetonitrile and dry ice, which was maintained at 25°C giving a residence time of 40 min. The outflow from the CFC reactor was then directed into a glass column filled to work up the product stream and scavenge the residual amine starting material and base. A second glass column loaded with silica gel (600 mg) was then employed to trap the magnesium salts generated during the process which gave the desired product **70** in fundamentally quantitative yield. Owing to cross-coupling reaction, a solution of 1-Boc-4-piperidone in DMPU [1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone] was introduced later using a third pump at 0.25 ml/min. The resulting flow stream was then passed in the course of a CFC maintained at r.t., followed by in-line treatment comprising three successive columns: Quadrapure-sulfonic acid (QP-SA), polystyrene sufonyl hydrazide resin ($MPTsNHNH_2$) and silica gel to furnish the desired product **71** in 50% yield.

On the third step of the process, the dehydration of intermediate **71** in THF was accomplished using the Burgess reagent in dichloromethane to be loaded into two separate PEEK sample loops. A solvent flow rate of 0.25 ml/min was used to combine the two compounds in a standard T-piece mixer. The reaction stream was then passed in the course of a CFC, which was heated at 60°C, followed by a column filled with a mixture of QP-SA and QP-BZA to sequester the excess Burgess reagent and associated byproducts. The resultant solution was then concentrated *in vacuo* to furnish the desired product alkene **72** in near quantitative yield (99%). In-line IR in this step was used to decrease waste and to allow reuse of the Burgess reagent.



Scheme 20 General synthetic route following inflow continuous process to obtain **68**.

The last step reaction involved a Boc deprotection. Two solutions, one comprising TFA in dichloromethane and the second containing the Boc-protected amide **72** in THF were loaded into PEEK sample loops. These solutions were then introduced to a main stream via a T-piece connector. The reaction stream was progressed in the course of a CFC, which was held at a temperature of 25°C to give the product **68** in 94% yield after purification by passage through a column of QP-BZA. Elution of the acidic column using a solution of NH_3 in MeOH completed the synthesis in a continuous mode, and gave the product **68** in 35% overall yield and in high purity over the four steps [57].

3. Outlook

In this review, we present different types of tangible, real-case applications in pharmaceutical and fine-chemical companies for which micro reactors and flow processes were recently employed. The presentation has been grouped by the type of API actually synthesized – and to our best knowledge this grouped compilation is the first in the micro reactor literature. Therefore, this paper is especially helpful for newcomers to the pharmaceutical and fine-chemical industries and decision-makers to obtain ideas about the possibilities, challenges and impact of the new flow technology. The most important advantage refers to fast and readily achievable scale-up as it is possible to avoid problems with temperature control, mixing, formation of impurities, and safety; commonly encountered when upsizing batch technology.

The importance of this new technology is accordingly to provide in a faster and easier manner the lead compounds, the API for clinical trials, formulation development and drug safety evaluation. The pharmaceutical industry has increased its experience with such continuous processing and thus increasing interest in flow processing is shared in the highly regulated sites. This is not amenable only to a few niche processes; on the contrary, it can be applied towards a range of reaction types, so that more and more process examples in API synthesis can be approached in the near future.

Since around 10 years ago, fine-chemical research and valorization has discovered flow processing, it is now high time that institutions focused on pharmaceutical research, such as for the discovery of new chemical entities with biological activity, or pharmaceutical companies are more involved in micro reactors and flow chemistry as a tool to minimize costs, maximize results and decrease wastes. With flow processing having become more usual and micro reactor products become more commercial, there are increasing possibilities for institutions and even countries as a whole with no exposure to the technology yet.

In Brazil, being the home country of one of the two authors, the government has taken some important initiatives in the area of Complex Industrial Health; however, there is a need to increase the force with government investment unapplied research to develop innovation in the industry. Financial support agencies such as FINEP have been directed in this way. However, in Brazil the movement towards flow chemistry or micro reactors is still concentrated in universities and research institutions. Pioneers include R.O.M.A. de Souza and L. Soter de Mariz e Miranda, both are Professors at Federal University of Rio de Janeiro, whose studies have been published in principal journals in this area [58–60]. These Professors organized

the 1st Flow Chemistry Symposium at Federal University of Rio de Janeiro which was supported by the Europe-based Flow Chemistry Society. The symposium attracted the top researchers in the world and this led to substantial interaction between the invited speakers and the audience members to present this new technology and its benefits to the Brazilian Community.

Another movement is from the Vita Nova Institute which is looking towards the use of this technology in drug discovery and chemical process studies. The institute has just started research on flow chemistry and micro reactors through a partnership with V. Hessel from Eindhoven University of Technology. As a first step, a post-doc student aims at developing a flow synthesis from the heterocyclic compounds 1,4-dihydropyridines (DHPs) which are bioactive compounds, including for vasodilator, anti-hypertensive action and anti-diabetes, such as Nifedipine (**73**), which act as a calcium channel blocker, which is an important compound on the market [61]. In 2010 worldwide sales totaled 1.4 billion, whereas in 2011 the value was 1.3 billion. Consumption from APIs in 2011 was 131,046.6 kg. Currently, new DHPs are being developed and investigated in clinical Phase III, such as Darodipine (**74**), Palonidipine (**75**), Elgodipine (**76**) and Furaldipine (**77**) (Figure 5). The goal of the post-doc project will be study and develop a flow process to obtain **74** and **76** and to compare the respective batch and flow processes. The process to prepare **74** and **76** will employ a well-known Knoevenagel flow process in a micro reactor [62–65]. The Hantzsch reaction will be investigated for the first time in micro reactors to prepare DHP. The process is focused on short synthetic steps, intensification using high-T or high-P, use of co-solvent or super critical fluid, improve yield and reaction times.

Finally, although this review is focused on pharmaceutical applications, flow chemistry and micro reactors have been employed in other chemical areas such as (i) agrochemical to furnish compounds in an easier and faster manner as given for fine chemicals or cosmetics; (ii) cosmetics to furnish starting materials to prepare soaps, candles and rubber products; and (iii) biofuels to develop products with higher added value.

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