# Investigation of microwave and flow chemical synthetic methods

## Thesis book


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# 1. Introduction and literature background

The tools used for the synthesis of the chemical products enabling the modern standard of living (such as drugs, pesticides, functional materials) have remained virtually unchanged throughout the 20th century, despite the rapid development of chemical knowledge and scientific understanding. The physicochemical and operational parameters obtainable in the laboratory or plant-scale reactors, predominantly operated with external heating, in a batchwise manner, limit the deeper exploitation of the chemical space.

By the turn of the new millennium, technological progress has reached a level, which allowed the introduction of **microwave reactors**, providing a radically different mode of heating in preparative chemistry; as well as the spread of continuous flow methods to organic chemistry leading to the emerging field of **flow chemistry**.

## 1.1. Basics and experimental methods of microwave chemistry

The idea of microwave (MW) "activation" of organic reactions is almost as old as the use of MW heating in preparative chemistry.[1] The concept of MW effects was introduced to describe the differences (altered reaction rate, yield or product composition) observed in the MW reactor compared to the conventionally heated control experiments (at the same nominal temperature). According to the current literature consensus, the existence of the previously postulated non-thermal MW effects can be precluded, only thermal effects of MW heating are relevant. These can be interpreted by temperature differences in macroscopic scale domains (bulk phase, or smaller regions of the sample), or alteration of the kinetic energy defined on the microscopic scale (environment of individual molecules).

Accurate temperature measurement and control in the MW reactor is essential for the study of these phenomena. For this purpose, the infrared (IR) pyrometer measuring the temperature of the outer surface of the reaction vessel and the internal fiber optic (FO) sensor should be used simultaneously.[2] Comparison of MW and conventional heating experiments should be carried out by providing similar temperature profiles, in reaction vessels of the same geometry.[3]

A number of phenomena have been described in the MW chemistry literature, in which the altered reaction rate is not explained by measurable (macroscopic) temperature differences. In these cases, microscopic-size domains (depicted as "hot spots") with higher temperature (or kinetic energy) are presumed within the homogeneous sample, formed as consequence of the MW irradiation. Such local overheatings cannot be detected by practical temperature measurement methods. To study their origins, Dudley and his co-workers used "MW-

[1] (a) C. O. Kappe, A. Stadler, D. Dallinger; *Microwaves in Organic and Medicinal Chemistry* (Wiley-VCH, 2012); (b) A. de la Hoz, A. Díaz-Ortiz, A. Moreno; *Chem. Soc. Rev.* **34** (2), 164–178 (2005).
[2] C. O. Kappe; *Chem. Soc. Rev.* **42** (12), 4977–4990 (2013).
[3] S. Hostyn, B. U. W. Maes, G. Van Baelen, A. Gulevskaya, C. Meyers, *et al.*; *Tetrahedron* **62** (19), 4676–4684 (2006).

actuated" reaction systems, specifically designed for this purpose. The first of these was a Friedel–Crafts type benzylation (Fig. 1), in which an ionic reagent (**8**) reacting with the *p*-xylene-$d_{10}$ (**9a**) used as solvent provides a single product (**10a**).[4,5] Performing the reaction at constant MW power, significantly higher conversion was reported than in the conventional control experiments. However, during the independent re-investigation of the reaction, Kappe and his co-workers were unable to detect the MW rate enhancement. The following debate led to no agreement on the existence of the MW effect proposed by Dudley, so the related theoretical questions remained unresolved.[6]

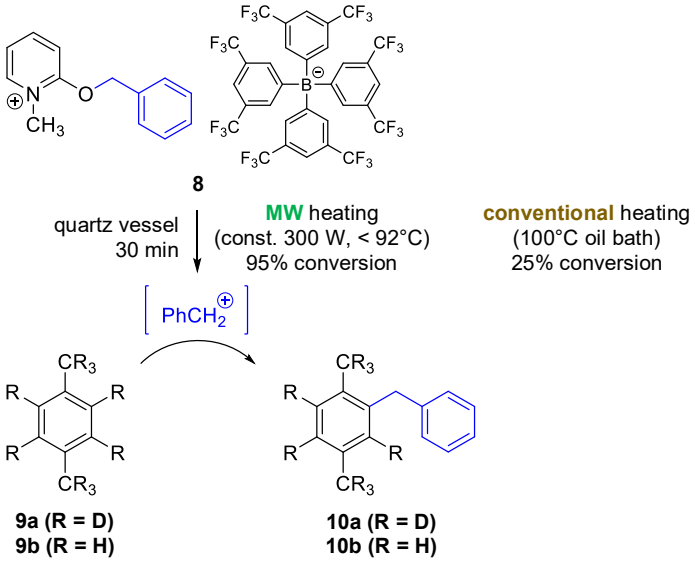


Fig. 1. "MW-actuated" benzylation of *p*-xylene-$d_{10}$ (and its non-deuterated isotopologue.

(Literature conversion values refer to the **9a** → **10a** transformation.)

## 1.2. Implementation of flow chemistry in the synthesis of active pharmaceutical ingredients

As a result of the rapid development in flow chemistry, the multi-step continuous-flow synthesis of active pharmaceutical ingredients (APIs) has become possible in the last decade.[7] In systems constructed by connecting two or more continuous reaction steps, the mixture exiting each reactor is transferred to a subsequent unit, where it undergoes further chemical reactions. The reactors can be connected directly, or by using *in-line* separations. *In situ* analysis of the mixture emerging from the system allows continuous quality control of the product, as-well-as rapid optimization of the reaction conditions. Among others, *in-line* Raman, NMR, and Fourier-transform infrared (FTIR) spectroscopy based on the attenuated total reflection (ATR) technique were used for this purpose.

[4] Chemical formulae in the thesis book are numbered in accordance with the dissertation.
[5] M. R. Rosana, Y. Tao, A. E. Stiegman, G. B. Dudley; *Chem. Sci.* **3** (4), 1240–1244 (2012).
[6] (a) C. O. Kappe, B. Pieber, D. Dallinger; *Angew. Chem. Int. Ed. Engl.* **52** (4), 1088–1094 (2013); (b) G. B. Dudley, A. E. Stiegman, M. R. Rosana; *Angew. Chem. Int. Ed. Engl.* **52** (31), 7918–7923 (2013); (c) C. O. Kappe; *Angew. Chem. Int. Ed. Engl.* **52** (31), 7924–7928 (2013).
[7] (a) B. Gutmann, D. Cantillo, C. O. Kappe; *Angew. Chem. Int. Ed. Engl.* **54** (23), 6688–6728 (2015); (b) R. Gérardy, N. Emmanuel, T. Toupy, V.-E. Kassin, N. N. Tshibalonza, *et al.*; *Eur. J. Org. Chem.* **2018** (20–21), 2301–2351 (2018); (c) A. R. Bogdan, A. W. Dombrowski; *J. Med. Chem.* **62** (14), 6422–6468 (2019).

The multi-step synthesis of drug molecules has been at the forefront of flow chemistry research, and the increasingly complex syntheses of widely used drugs have been published, utilizing laboratory-scale devices. Recent examples include the uninterrupted synthesis of *ciprofloxacin* consisting of 4 chemical transformations (and a reaction for byproduct scavenging), and the 7-step (with a linear sequence of 5 reactions) continuous-flow system for the preparation of *linezolid*.[8,9] Despite the success of this field, the replacement of general-purpose batch reactors with a network of interconnected flow equipment is still not trivial. It requires the comprehensive application of flow chemistry's toolkit,[10] and designing the synthetic route specifically for implementation in the integrated continuous-flow reactor system.

## 2. Experimental methods

MW experiments were performed in a CEM Discover® type monomode reactor, following thermal conditioning of the MW cavity. The temperature of the stirred reaction mixtures was monitored simultaneously using a calibrated external infrared pyrometer (IR) and an internal fiber optic (FO) temperature sensor. Experiments using preheated oil bath were performed in identical reaction vessels, using internal FO temperature measurement. During the comparative studies, matching internal temperature profile was ensured between the MW and conventionally heated reactions. The material of the reaction vessels was Pyrex® or quartz. Optionally, the inner wall of the vessel was coated with a Teflon® PFA (perfluoroalkoxy alkane) fluoropolymer liner. Conversion was determined directly from the reaction mixtures using GC-FID or $^{1}$H NMR methods.

The starting materials used for the continuous-flow syntheses were prepared by known batch methods. Commercially available modules, connecting tubing (PTFE, PEEK) and standard connectors were used for the construction of multi-step continuous-flow systems. Optimization of the reactions were carried out using *in-line* FTIR spectroscopy or *off-line* analytical methods. In the systems of simultaneously operated flow reactors, yield was determined from samples taken during steady-state operation, after *off-line* isolation and purification of the product. The structures of the prepared products and intermediates were confirmed by $^{1}$H and $^{13}$C NMR spectroscopy and HRMS measurements.

[8] Active pharmaceutical ingredients are referred to using their International Nonproprietary Name (INN), in italics.
[9] (a) H. Lin, C. Dai, T. F. Jamison, K. F. Jensen; *Angew. Chem. Int. Ed. Engl.* **56** (30), 8870–8873 (2017); (b) M. G. Russell, T. F. Jamison; *Angew. Chem. Int. Ed. Engl.* **58** (23), 7678–7681 (2019).
[10] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger; *Chem. Rev.* **117** (18), 11796–11893 (2017).

# 3. New scientific results

## 3.1. Comparative studies in microwave chemistry

After examining the factors influencing the heating-up phase in the MW reactor, the thermal conditioning of the MW cavity was deemed necessary, in order to ensure reproducibility. With this in mind, an improved method was developed for accurate comparative experiments between conventional and MW heating, in which the simultaneous measurement of external and internal temperatures provides detailed information about the sample's thermal conditions.

The method was validated using two reactions of the 2-substituted pyridine derivatives (Fig. 2), in which a specific role of MW heating can be assumed based on literature reports.[11] Similar behavior was observed in both of the reaction between 2-chloropyridine and piperidine, and the "Dudley-like" rearrangement reaction of 2-(benzyloxy)pyridine (**25**). Using FO sensor-based temperature control, identical conversions were measured in the conventional and MW heated experiments, even at higher MW power (achievable using external cooling during MW heating). In fact, the presence and intensity of the MW field had no effect on the outcome of the reactions. In contrast, significant differences were observed in MW experiments with IR temperature-based control, which could be traced to large, hidden temperature differences by using the internal (FO) temperature measurement. These findings confirm that IR temperature measurement alone is not suitable for studying MW effects in complex, reacting systems.

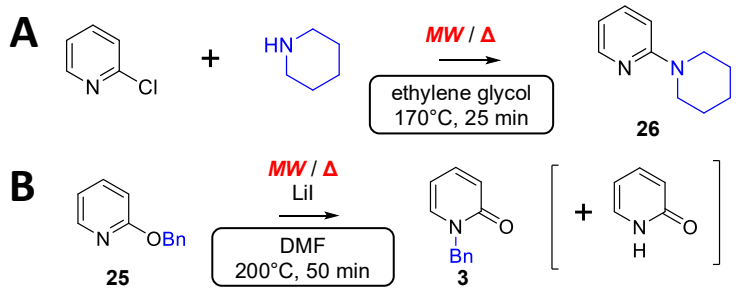


Fig. 2. The reaction between 2-chloropyridine and piperidine (A), and the rearrangement reaction of 2-(benzyloxy)pyridine (B), with the conditions used during the comparative experiments.

Before the investigation of Dudley's "MW-actuated" reaction (Fig. 1), the formation of by-products was explained by a more detailed interpretation of the reaction mechanism. It was also necessary to review the experimental methods (composition of the reaction mixture, execution of the reaction, sampling and analysis) with reproducibility and the issues encountered during the debate in mind. The comparative experiments were performed in vessels equipped with a cover assembly, using internal temperature measurement. Non-deuterated *p*-xylene (**9b**) was used as solvent, to allow the large number of parallel experiments.

[11] (a) R. S. Yaunner, J. C. Barros, J. F. M. Silva; *Appl. Organomet. Chem.* **26** (6), 273–276 (2012); (b) E. L. Lanni, M. A. Bosscher, B. D. Ooms, C. A. Shandro, B. A. Ellsworth, *et al.*; *J. Org. Chem.* **73** (16), 6425–6428 (2008).

In the experimental set-up based on these strict criteria, the behavior of the constant MW power experiments described in the literature could not be reproduced, so my own studies were performed with internal temperature control. Using the settings (100°C, 30 min) selected on the basis of preliminary experiments, the internal temperature profiles of the oil-bath and MW heated experiments were harmonized. In contrast to my expectations, MW heating provided significantly higher conversion than the conventional heating experiments with the same parameters (Fig. 3 (A)).

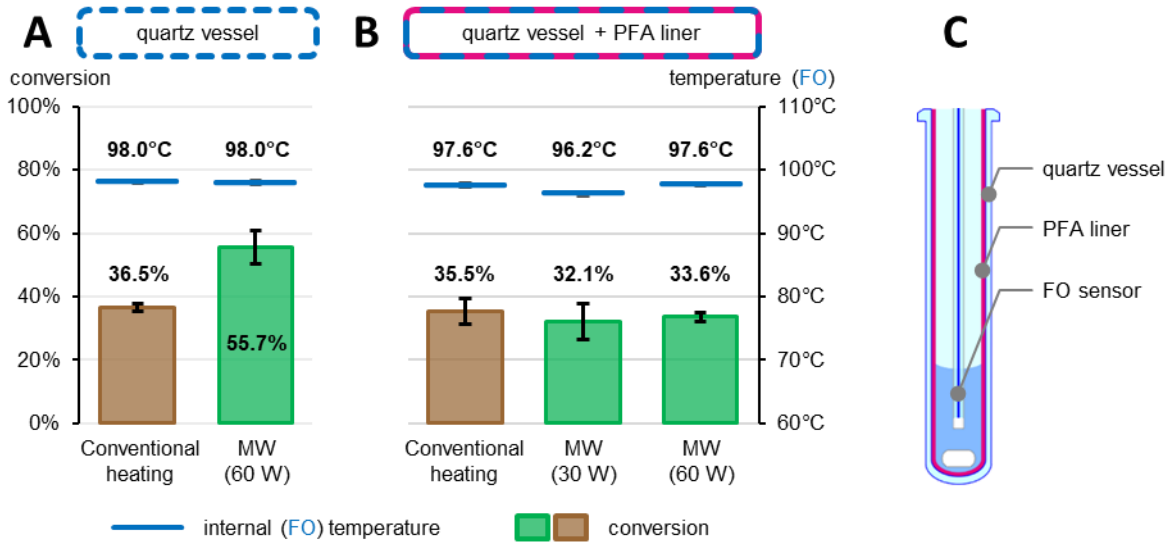


Fig. 3. Conversion and internal (FO) temperature measured in the conventional and MW-heating experiments of the benzylation of *p*-xylene using harmonized temperature profiles, in quartz vessels (A), or in quartz vessels equipped with Teflon® PFA liner (B). Schematic of the Teflon® PFA liner inside the reaction vessel (C).

In-depth examination of the simultaneously measured FO and IR datasets recorded during the MW heating runs revealed that in the early stages of the reaction, the temperature near the vessel wall is higher than in the bulk phase. After excluding the possible temperature measurement errors, a working hypothesis was established, in which the enrichment of the ionic reagent (**8**) in the boundary layer close to the wall was assumed. Due to the high concentration of the ionic component, more intensive heating is expected, leading to higher local temperature in this macroscopic region. This causes higher reactivity, which explains the increased conversion of the MW experiments.

To prevent the assumed "sticking" of the reagent, the inner wall of the vessel was coated with a liner made of Teflon® PFA, having an inert, non-polar surface. Then, the harmonized internal temperature profiles were readjusted. Conversion of the conventional heating experiments was unaffected compared to the previous ones. In contrast, MW heating performed with two different power settings gave reduced conversions, comparable to conventional heating (Fig. 3 (B)). In these MW experiments, the FO and IR temperatures did not show the previously observed abnormal behavior. These observations indirectly prove the working hypothesis. Thus, the difference in reaction rate caused by MW heating

can be characterized as a macroscopic thermal effect. Based on these results, the presence of a molecular-sized selective MW heating effect hypothesized by Dudley can be disproved.

## 3.2. Continuous-flow synthesis of urea derivatives

The preparation of urea derivatives in a flow microreactor system was based on a two-step batch process involving an isocyanate intermediate.[12] The arrangement of the flow system (Fig. 4) followed the order of the chemical transformations. In the first microreactor (**R1**) the carbamate (**61**) starting material is converted to an isocyanate intermediate (**62**) by using trifluoromethanesulfonic anhydride ($Tf_2O$) reagent in the presence of 2-chloropyridine (2-ClPy) base. From this intermediate, the desired urea derivative (**64**) is formed by the addition of a secondary amine (**63**) in the second microreactor (**R2**). The product stream is directed into a flow cell (**FC**) for *in-line* analysis.

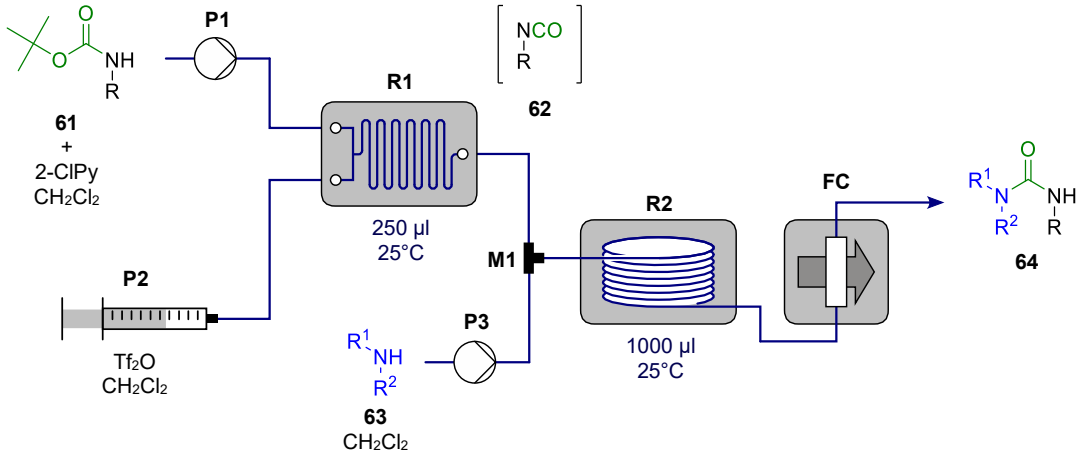


Fig. 4. Flow system for the synthesis of urea derivatives consisting of two sequential microreactors. **P1** – **P3**: pumps; explanation of further labels can be found in the text.

In the small-footprint flow system (Fig. 5 (A)) a glass *chip* microreactor (**R1**), resistant to the corrosive trifluoromethanesulfonic anhydride, provided excellent mixing in the first step. In the next reaction, a polytetrafluoroethylene (PTFE) *coil* reactor (**R2**) was used after a T-piece (**M1**). The reaction mixture's composition was monitored using transmission FTIR spectroscopy (this technique has been previously neglected in continuous-flow synthesis), as the starting material (**61**), intermediate (**62**), and product (**64**) give distinguishable, characteristic vibrational bands in the mid-infrared region.

The continuous-flow reaction steps were separately optimized using *in-line* FTIR analysis. Short residence times could be achieved at room temperature, and the high excess of reagents used in the literature could be significantly reduced. Investigation of the mechanistic role of 2-chloropyridine revealed that bases with weak nucleophilic character are required for the reaction to proceed.

[12] C. Spyropoulos, C. G. Kokotos; *J. Org. Chem.* **79** (10), 4477–4483 (2014).

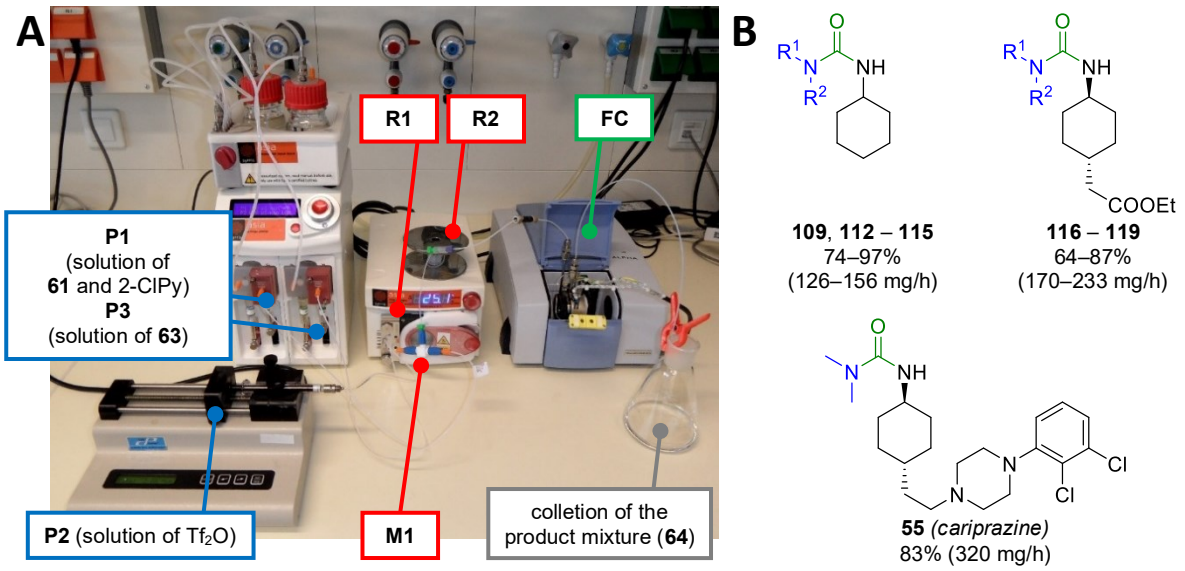


Fig. 5. Photograph of the system for the synthesis of urea derivatives with labeled fluidic components (A); and the prepared compounds ($R^1$, $R^2$ = -$(CH_2)_5$-, -$(CH_2)_4$-, -$(CH_2)_2O(CH_2)_2$-, $CH_3$, $CH(CH_3)_2$), showing isolated yields (and productivities) (B).

Starting from the corresponding *tert*-butyl carbamates, nine urea derivatives (**109**, **112 – 119**) and the API used in the treatment of schizophrenia and type I bipolar disorder, *cariprazine* (**55**) were prepared in the flow system (Fig. 5 (B)). Due to the rapid, controlled transformation of the instable isocyanate intermediate, high yields were achieved in all cases. The productivity of the laboratory-scale system is sufficient for providing the API required for the production of more than 1300 capsules of 6 mg dose of *cariprazine*, during 24 hours of operation.

### 3.3. Continuous-flow synthesis of flibanserin

The uninterrupted four-step continuous-flow preparation of the serotonin receptor modulator drug, *flibanserin* (**56**) was accomplished using a synthetic route specifically designed for efficient operation in flow reactors (Fig. 6). The unprecedented route utilizes the *tert*-butoxycarbonyl (Boc) protected *o*-phenylenediamine (**122**) as starting material. The two-carbon linker is formed by reductive alkylation with a protected aldehyde (**123**). Upon the base-mediated intramolecular cyclization of the intermediate (**127**), the carbonyl unit of the carbamate protecting group is incorporated into the resulting benzimidazolone heterocycle (**131**). This intermediate contains neither acid-sensitive, nor basic functions, so this point of the sequence offers an ideal opportunity for the acidic deprotection of the acetal moiety. In the final step, the resulting aldehyde (**132**) is utilized in a reductive amination with piperazine (**91**), to give the target molecule (**56**).

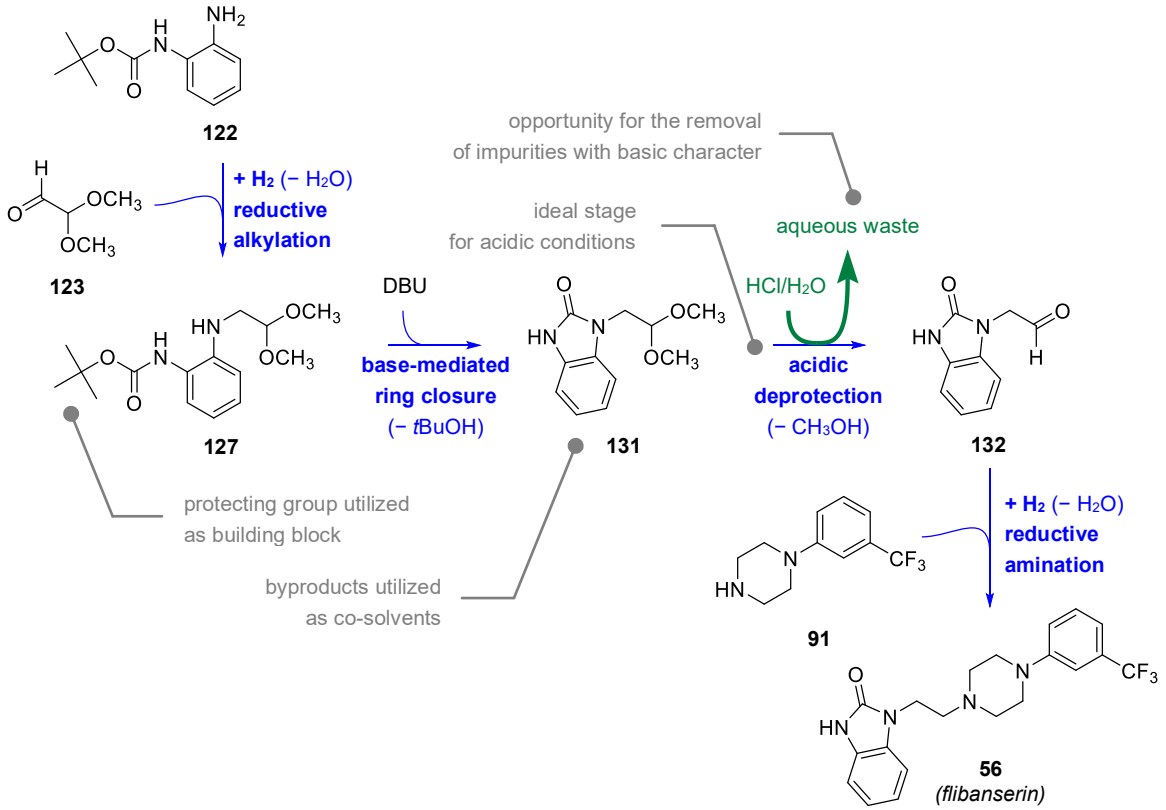


Fig. 6. Four-step synthetic route leading to *flibanserin*, designed for implementation in interconnected flow reactors.

Each of the synthetic steps was performed in isopropyl acetate (iPrOAc) solvent. The presence of *tert*-butanol (*t*BuOH) and methanol cosolvents (formed as by-products during the synthesis) were required to prevent precipitations. Flow reaction steps were optimized by taking the earlier and later steps into account.

In the flow system (Fig. 7), the reductive alkylation and reductive amination steps were performed in H-Cube Pro™ (**R3**) and H-Cube® (**R6**) continuous-flow hydrogenation reactors using 10% Pd/C catalyst in both cases. The high temperature required for the 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) base promoted cyclization was provided in a stainless steel *coil* reactor (**R4/H**). Deprotection was performed using aqueous hydrochloric acid. The biphasic stream was passed through a static mixer (**R5/M**) for proper contact of the phases, followed by a corrosion-resistant coil reactor (**R5/H**) to provide the required residence time.

The third step was connected directly to the second step. The connection of the other units of the system was facilitated by buffer flasks: **BF1** for the removal of excess hydrogen gas and **BF2** for the separation of the biphasic reaction mixture of the third step. The phase separation serves as *in-line* purification, which is suitable for the removal of DBU base and residues of previous intermediates. Thus, harmful side reactions in the next step are prevented and the purification of the final product is simplified.

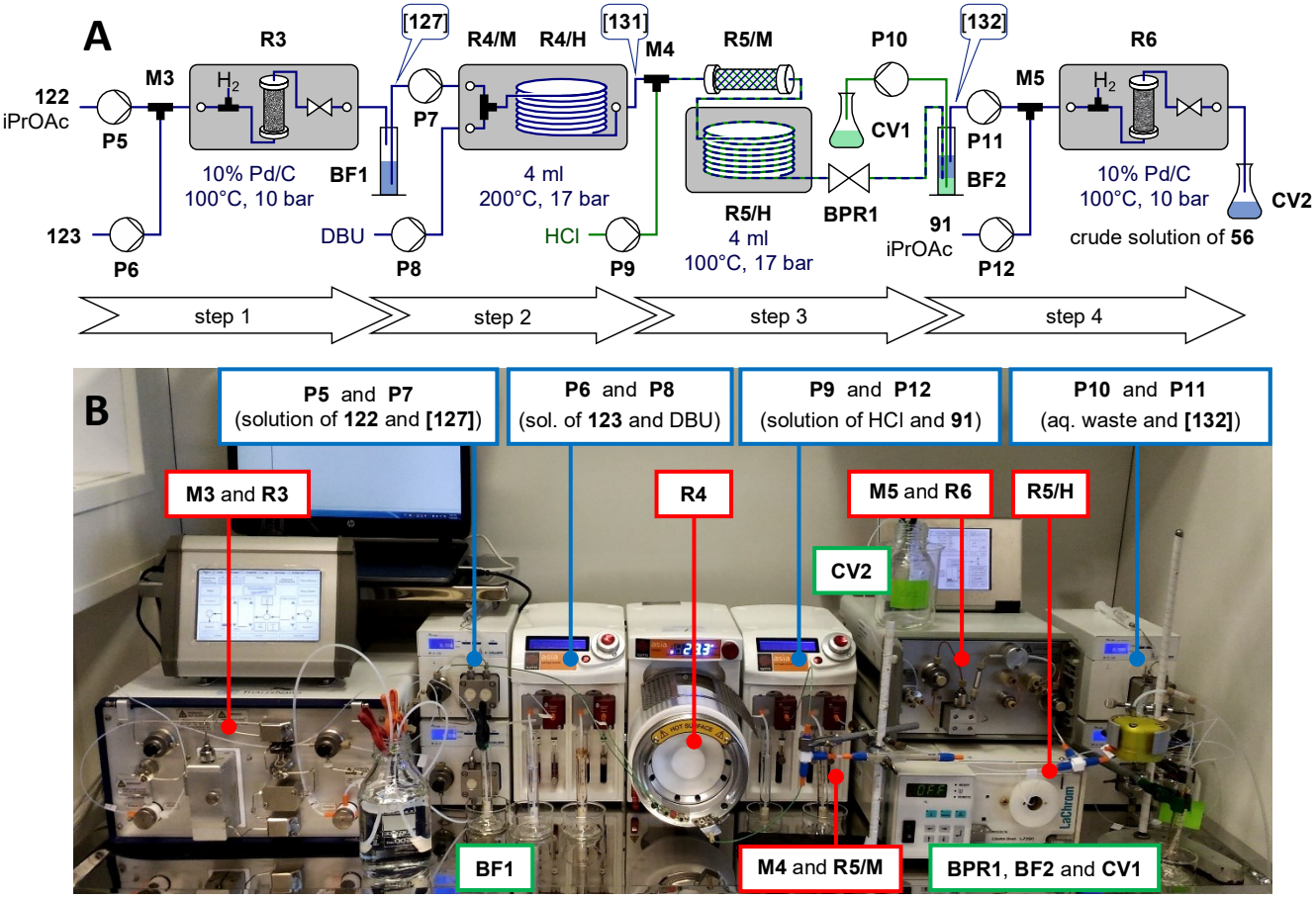


Fig. 7. Schematic of the four-step flow process to produce *flibanserin*, with labeled fluidic components (A); and the photograph of the system housed in a single fume hood (B). Blue lines represent the main organic stream, green lines are used for the aqueous stream in the biphasic step. **P5** – **P12**: pumps; **M3** – **M5**, **R5/M**: mixing elements; **BPR1**: back-pressure regulator; **CV1**: collection vessel for the acidic waste; **CV2**: collection vessel for the product mixture; explanation of further labels can be found in the text.

During steady-state operation of the entire system, a product stream with constant composition can be collected. The product was isolated as the hydrochloride salt (**56** · HCl) in 31% yield over the four-step reaction sequence, using *off-line* salt formation followed by selective crystallization. This is comparable to the total yields of the batch methods described in the literature, while the total residence time in the flow reactors is less than 20 minutes. The productivity of the synthesis is 184 mg/h, which would provide the API for approximately 44 tablets containing 100 mg of *flibanserin* during 24 hours of operation.

## 4. Theses

1. An improved method has been developed for the precise comparison of conventionally and MW heated experiments, and the reproducibility of MW reactions was improved by thermal conditioning of the MW cavity. This methodology was validated using two reactions of the 2-substituted pyridine derivatives. [1, 2]

2. The experimental study of the MW-assisted benzylation reaction of *p*-xylene has been designed with reproducibility in mind. The formation of by-products has been explained by a more detailed interpretation of the reaction mechanism. [2]

3. It has been determined that the rate enhancement observed in the MW-assisted benzylation reaction of *p*-xylene is a consequence of a hidden, macroscopic temperature inhomogeneity. An experimental detail was identified, which was suitable for verifying this working hypothesis by suppressing the effect. Based on my results, the presence of the hypothesized microscopic thermal MW effect can be disproved. [2]

4. A two-step continuous-flow reactor system has been designed and constructed for the preparation of urea derivatives. The reaction steps were optimized using *in-line* FTIR spectroscopy, and the role of the unusual base was clarified. The continuous-flow system was used for the synthesis of nine urea derivatives and the API *cariprazine*. [3]

5. A novel four-step synthesis has been developed for the preparation of the API *flibanserin*. The route was designed with implementation in interconnected continuous-flow reactors in mind. A uniform solvent strategy was used throughout the process and each reaction was optimized in standalone flow reactors with the other steps in mind. [4, 5]

6. An uninterrupted continuous-flow reactor system has been designed and constructed for the synthesis of the API *flibanserin*, in which an integrated *in-line* purification (liquid-liquid extraction), as well as two gas-liquid separations allowed connecting the four reactors, and the steady-state operation of the system without manual interaction. [4]

## 5. Potential applications

The thermal conditioning method and experimental set-ups presented in the dissertation facilitate the reproducible execution of the comparative studies with conventional heating experiments, a vital part of MW chemistry. Clarification of the issues related to the controversial, temperature-independent MW effects (such as Dudley's "MW-actuated" reaction) is expected to increase confidence among researchers in the MW technique and help its further spread in preparative laboratories.

The two-step flow system for the preparation of urea derivatives can be used for the rapid synthesis of further variously substituted ureas, derived from the widely available Boc-protected amines. The procedure is also suitable for the production of the API *cariprazine*.

The synthetic route and continuous-flow technology developed for the synthesis of the drug *flibanserin*, which form the basis of a patent application, allow the end-to-end production of the API in a closed system, without human intervention. Intermediates or final products can be prepared in the laboratory-scale continuous-flow systems in amounts needed in the early stages of medicinal chemistry research, or for supplying medicine to small communities living in remote, isolated areas. The spread of continuous technologies in the pharmaceutical industry is expected in the near future, which is supported by the already available scale-up possibilities.

# 6. Publications

## 6.1. Scientific publications related to the PhD Thesis

[1] **Bana, P.**; Greiner, I.: Comparison of Conventional and Microwave Heating for Evaluation of Microwave Effects; *Aust. J. Chem.* **69** (8), 865-871 (2016).
[IF: 1.328; contribution by the author: 100%; citations: 6; independent citations: 5][13]

[2] **Bana, P.**; Greiner, I.: Investigation of Selective Microwave Heating Phenomena in the Reactions of 2-Substituted Pyridines; *Aust. J. Chem.* **70** (7), 776-785 (2017).
[IF: 1.059; contribution by the author: 100%; citations: 2; independent citations: 2]

[3] **Bana, P.**; Lakó, Á.; Kiss, N. Zs.; Béni, Z.; Szigetvári, Á.; Kóti, J.; Túrós, Gy. I.; Éles, J.; Greiner, I.: Synthesis of urea derivatives in two sequential continuous-flow reactors; *Org. Process Res. Dev.* **21** (4), 611-622 (2017).
[IF: 3.584; contribution by the author: 80%; citations: 4; independent citations: 3]

[4] **Bana, P.**; Szigetvári, Á.; Kóti, J.; Éles, J.; Greiner, I.: Flow-oriented synthetic design in the continuous preparation of the aryl piperazine drug flibanserin; *React. Chem. Eng.* **4** (4), 652-657 (2019).
[IF: 3.441; contribution by the author: 90%; citations: 4; independent citations: 4]

## 6.2. Patent applications related to the PhD Thesis

[5] **Bana, P.**; Greiner, I.: Process for the multistep continuous-flow preparation of flibanserin; *PCT Int. Appl.* WO2020/026162 A1 (2020).

## 6.3. Review and mini-review articles related to the PhD Thesis

[6] **Bana, P.**; Greiner, I.: Interpretation of the Effects of Microwaves; in *Milestones in Microwave Chemistry* (ed.: Keglevich, Gy.), 77-110, Springer International Publishing (2016).
[contribution by the author: 100%]

[13] Impact factor (IF) is given for the year of publication (except noted). Citation data are based on Scopus® database (last accessed: Sep 22th, 2020).

[7] Lövei, K.; **Bana, P.**; Örkényi, R.; Túrós, Gy. I.; Éles, J.; Novák, Z.; Faigl, F.: Continuous flow synthesis of heterocyclic scaffolds: Design principles of multistep systems - A review; *Chimica Oggi/Chemistry Today* **34** (4), 18-21 (2016).
[IF: 0.597; contribution by the author: 39%; citations: 1; independent citations: 1]

[8] **Bana, P.**; Örkényi, R.; Lövei, K.; Lakó, Á.; Túrós, Gy. I.; Éles, J.; Faigl, F.; Greiner, I.: The route from problem to solution in multistep continuous flow synthesis of pharmaceutical compounds; *Bioorg. Med. Chem.* **25** (23), 6180-6189 (2017).
[IF: 2.881; contribution by the author: 51%; citations: 27; independent citations: 23]

[9] Fülöp, Zs.; Szemesi, P.; **Bana, P.**; Éles, J.; Greiner, I.: Evolution of flow-oriented design strategies in the continuous preparation of pharmaceuticals; *React. Chem. Eng.*, *React. Chem. Eng.*, **5** (9), 1527-1555 (2020).
[IF: 3.441 (2019); contribution by the author: 30%; citations: –]

## 6.4. Scientific publications not included in the PhD Thesis

[10] Ilkei, V.; **Bana, P.**; Tóth, F.; Palló, A.; Holczbauer, T.; Czugler, M.; Sánta, Zs.; Dékány, M.; Szigetvári, Á.; Hazai, L.; Szántay, Cs. Jr.; Szántay, Cs.; Kalaus, Gy.: A simple synthesis of bannucine and 5'-epibannucine from (−)-vindoline; *Tetrahedron* **71** (51), 9579-9586 (2015).
[IF: 2.645; contribution by the author: 5%; citations: 1; independent citations: –]

## 6.5. Oral presentations related to the PhD Thesis

[11] **Bana, P.**; Greiner, I.: A mikrohullámú szintézistechnika aktuális kihívásai; Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium ’13, Herceghalom, September 30th – October 1st, 2013.

[12] **Bana, P.**; Greiner, I.: Nem-termikus effektusok vizsgálata a 2-es helyzetben szubsztituált piridinszármazékok mikrohullámú reakcióiban; Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium ’14, Herceghalom, September 18 – 19th, 2014.

[13] **Bana, P.**; Greiner, I.: Érdekes tapasztalatok a 2-es helyzetben szubsztituált piridinszármazékok mikrohullámú reakcióiban; Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium ’15, Herceghalom, September 17 – 18th, 2015.

[14] **Bana, P.**; Lakó, Á.; Greiner, I.: Több lépéses áramlásos kémiai rendszerek vizsgálata; Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium ’16, Herceghalom, September 15 – 16th, 2016.

[15] **Bana, P.**; Éles, J.; Greiner, I.: A flibanserin többlépéses folyamatos áramú szintézise; Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium ’18, Szeged, September 6 – 7th, 2018.

[16] **Bana, P.**; Éles, J.; Greiner, I.: Gyógyszerhatóanyagok szintézise többlépéses folyamatos áramú rendszerekben; I. Fiatal Kémikusok Fóruma Szimpózium, Debrecen, April 3 – 5th, 2019.