Budapest University of Technology and Economics
Department of Organic Chemistry and Technology
George Olah Doctoral School

Flow Chemistry Techniques in the Development of the Synthesis of Active Pharmaceutical Ingredients and Their Intermediates

Ph.D. Thesis Abstract

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GEDEON RICHTER LTD.

1. Introduction

Over the last few decades, the field of continuous-flow processing has received extraordinary amount of attention, especially in the pharmaceutical industry. Flow chemistry has been broadly implemented from the early discovery phase through the development of the synthesis of the new chemical entities (NCEs) to the pilot scale production of active pharmaceutical ingredients (APIs). The introduction of continuous processing into the manufacturing of APIs is actively encouraged from regulatory agencies and some of the first examples of Food and Drug Administration (FDA) approved, industrial production campaigns have been recently made public. Furthermore, moving to continuous processes in API production is expected to be economically beneficial. However, these efforts are highly knowledge intensive and translating them into practice is admittedly more difficult than in the case of batch processes.

To address this issue, my main task during my *Ph.D.* studies was to implement flow chemistry at Gedeon Richter Plc., and to gain as much experience and know-how about this technique as possible.

My research is divided into two main parts. One of my assignments was to investigate the synthesis of melanin-concentrating hormone receptor 1 (MCHr1) antagonists with 1*H*,2*H*,3*H*,4*H*,5*H*-[1,4]diazepino
[1,7-*a*]indole (**1**) scaffold for the treatment of obesity through regulation of appetite (**Fig 1.1.**). Although the discovery chemistry route enabled to provide sufficient amount of material for *in vitro* and *in vivo* studies, during the preclinical development phase, revision and optimisation of the original synthetic route was inevitable to deliver the required quantity of a selected derivative of **1** for further studies (clinical trials).

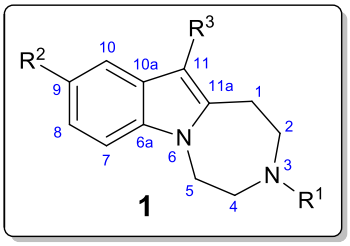


Figure 1.1. The general formula of the NCEs: 3,9,11-trisubstituated-1*H*,2*H*,3*H*,4*H*,5*H*-[1,4]diazepino[1,7-*a*]indole (**1**).

My other main appointment was to develop a new continuous-flow final product purification method using centrifugal partition chromatography (CPC). This purification

technique has many advantages over high performance liquid chromatography (HPLC), such as higher resolution and no need for column replacement or silica recycling, and it does not suffer from irreversible adsorption. Our aim was to accomplish the coupling of a multistep flow reaction system to CPC in multiple dual-mode (MDM) in order to continuously produce the main product's solution in high purity (**Fig 1.2.**).

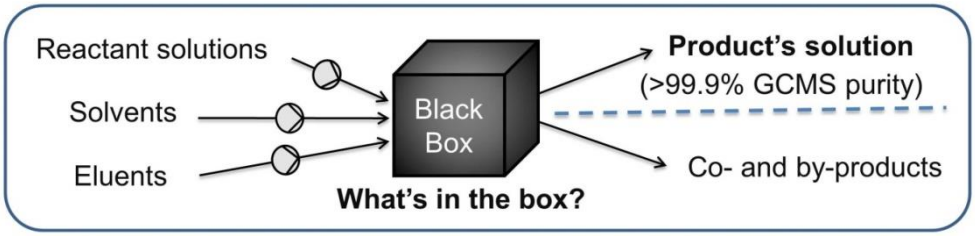


Figure 1.2. Scheme of our main research objective.

2. Literature overview

2.1. Flow chemistry in pharma industry

As it was mentioned in the Introduction section, over the last few decades the field of continuous-flow processing has received an extraordinary amount of attention. This is well-demonstrated in the review by P. Seeberger *et al.*[1] published in Chemical Reviews, in which almost 800 publications related to flow chemistry are interpreted.

General advantages of continuous-flow processing are widely known and well-emphasised; nonetheless, it is important to point out that flow conditions are not the cure-all for chemistry, the flow approach is advantageous for just certain transformations. For this reason, a flow *versus* batch analysis must be conducted in order to strike a balance between convenience and achieving the overall goal. Since a flow *versus* batch decision is never black and white, to pigeonhole similar reactions as batch or flow would be foolhardy. However, several generalizations are possible in order to expedite a cost-benefit analysis, once all factors are taken into consideration and flow chemistry is chosen to be implemented in order to solve the certain situation; a skilled expert could take advantages of this technique.

2.2. Purification in multistep flow synthesis of APIs

Continuous-flow synthesis is usually followed by discontinuous purification, because of the fact that the number of available continuous solutions is limited.[2,3] The existing methods[4,5] can be classified as in-line work-up or final product purification techniques, according to the position in a multistep sequence, where they are preferably used (**Fig 2.1.**).

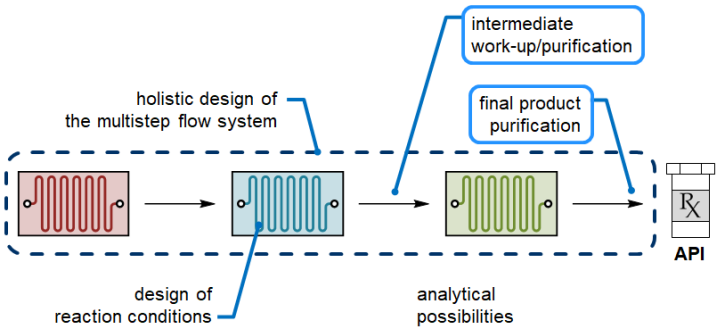


Figure 2.1. Hidden traps in the realization of multistep flow synthesis of APIs and the two types of purification based on their position.[2]

To sum up, the chemical knowledge and technology for the realisation of multistep flow syntheses and subsequent purification exist, but connecting individual chemical steps holds hidden traps. The utility of the available continuous purification methods (**Table 2.1.**) can be maximized by a proper design of the synthetic process; however, we hope that our proposal for a novel purification method of using centrifugal partition chromatography will be given wide applicability for the synthesis of complex molecules and APIs even on large scale, due to its advantages that are presented in the introduction.

Table 2.1. Summary of purification methods in flow.

	In-line workup	**Final-product purification**
'Co-' product type	**1.** Side-product filtration **2.** Liquid-liquid phase separation **3.** Gas-Liquid phase separation **4.** Use of solid phase supported scavengers	**1.** Catch and release chromatography (with semi-batch processing) **2.** Salt formation – neutralization sequence using multiple extraction steps
'By-' product type	–	**1.** Simulated Moving Bed (SMB) Chromatography **2.** Crystallization or recrystallization (with semi-batch processing) **3. Centrifugal Partition Chromatography (CPC – this work)**

3. Results

3.1. Development of the synthesis of MCHR1 antagonist's scaffold[6]

Based on the literature overview the following synthetic route (**Fig 3.1.**) was chosen for the synthesis of *tert*-butyl 9-bromo-1*H*,2*H*,3*H*,4*H*,5*H*-[1,4]diazepino[1,7-*a*]indole-3-carboxylate (**2**).

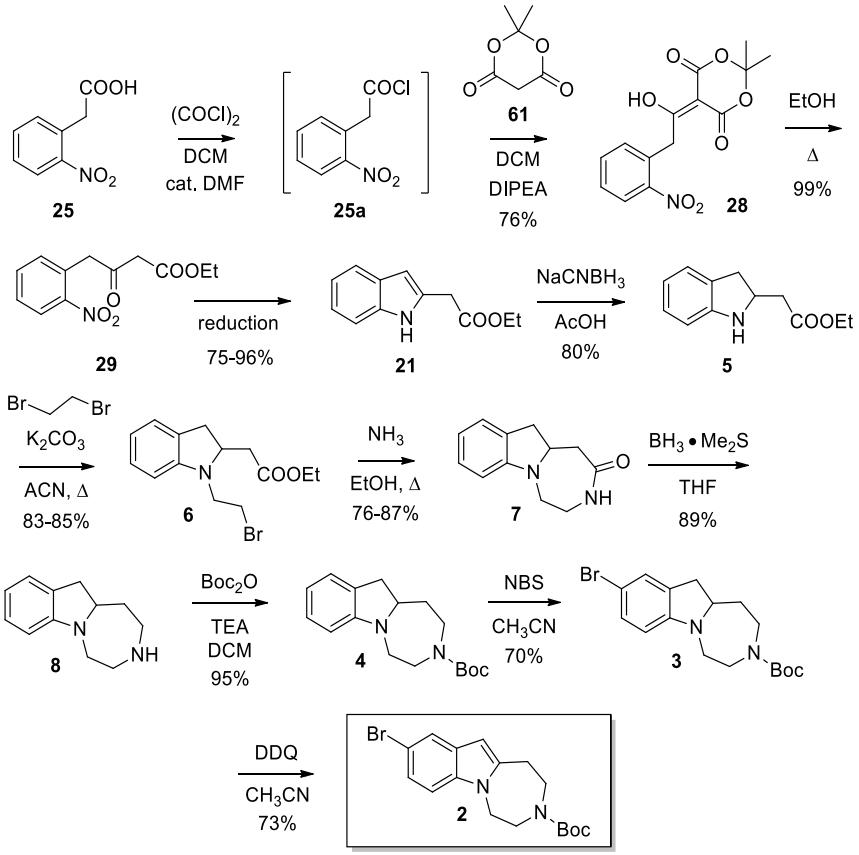


Figure 3.1. Original discovery chemistry synthesis of the target compound (**2**).

The reductive cyclization reaction (**29→21**) was investigated with the continuous heterogeneous catalytic hydrogenation reactors (H-Cube™ and H-Cube Pro™, from Thales Nano Inc.) (**Fig 3.3.**). We have also observed the formation of a small amount of the over-reduced indoline product (**5**) when charcoal supported palladium was used; therefore, it seemed logical to develop a consecutive catalytic hydrogenation method to produce compound **5** from **29** without the isolation of the indole (**21**).

We also investigated the *N*-alkylation reaction of **5** by 1,2-dibromoethane in order to decrease the reaction time, the dilution, and the high excess of the carcinogenic reagent.

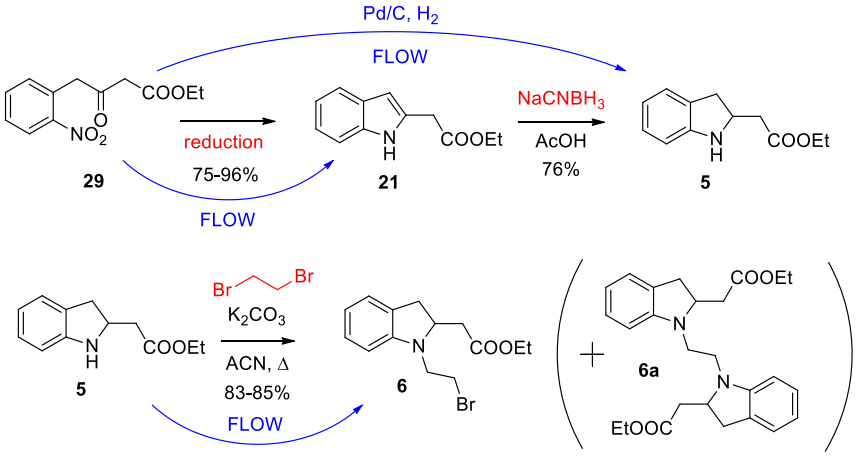


Figure 3.2. Application of flow chemistry in the synthesis of the intermediates of **2**.

After the optimisation, the best reaction parameters in case of consecutive heterogeneous catalytic hydrogenation were also used in a batch reaction, in which **5** was obtained with 75% of isolated yield. By this, we have developed a novel synthesis of **5** indoline from **29** that has higher yield than any known two-step synthesis. Moreover, this procedure replaces all chemical reducing agents (e.g. heavy metal zinc, or cyanide containing $NaCNBH_3$) by environmental-friendly catalytic hydrogenation.

Nevertheless, significant results were achieved by flow chemistry techniques in the N-alkylation step, several other method were also tested, out of which the reductive *N*-alkylation gave the most economical beneficial outcome.

In this reaction, sodium [tri(2-bromoacetoxy)-hydrido-borate(III)] was generated *in situ* from bromoacetic acid and sodium [tetrahydrido-borate(III)] (**Fig 3.3**), which reduced itself to form 2-bromoacetaldehyde. This 2-bromoacetaldehyde created a iminium salt intermediate with the secondary amine function of the indoline **5**, which was reduced by the reagent excess to the desired *N*-alkylated product **6** in 67% isolated yield.

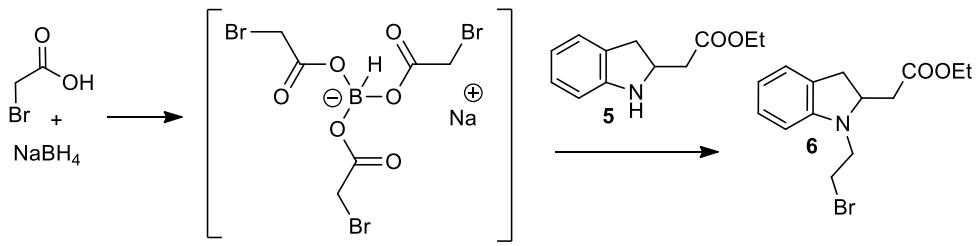
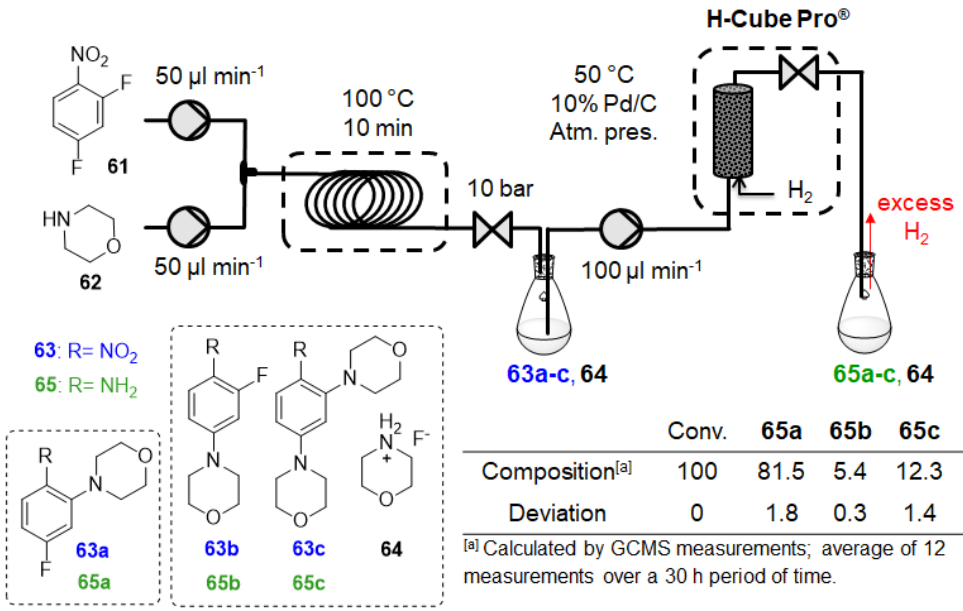


Figure 3.3. Reductive *N*-alkylation by sodium [tri(2-bromoacetoxy)-hydrido-borate(III)] reagent.

The main benefit of this step is that no carcinogenic 1,2-dibromoethane was necessary; furthermore, when adopting all development until the intermediate **6**, the cost of the synthesis was managed to be reduced by 77% as compared to the original synthetic route. (All reactions were scaled-up to multi kg scale and financial analyses were made by Dr. András Páhi from the Laboratory of Process Development, Gedeon Richter Ltd.)

3.2. New continuous flow final-product purification method using centrifugal partition chromatography (CPC)

The target molecule, 4-fluoro-2-(morpholin-4-yl)aniline (**65a**), which is a key intermediate in the synthesis of bioactive carbazoles,[7] was synthesized in a nucleophilic aromatic substitution (S_NAr) reaction[8] of 2,4-difluoronitrobenzene (**61**) with morpholine (**62**) followed by heterogeneous catalytic hydrogenation (**Fig 3.4.**).



	Conv.	65a	65b	65c	others
Composition[a]	100	81.5	5.4	12.3	0.8
Deviation	0	1.8	0.3	1.4	0.8

[a] Calculated by GCMS measurements; average of 12 measurements over a 30 h period of time.

Figure 3.4. Continuous-flow S_NAr reaction of 2,4-difluoronitrobenzene (**61**) with morpholine (**62**) followed by a heterogeneous continuous hydrogenation of the nitro compounds (**63a-c**) to the corresponding anilines (**65a-c**), using a loop reactor and the H-Cube Pro™ device.

First, an adequate BLS was developed through extensive experimentation to differentiate between regioisomers (**65a,b**) that are similar in every physicochemical property, including p*K*a (see **Table 3.6.**). The mixture of *n*-hexane (*n*-Hex) / *tert*-butyl methyl ether (MTBE) / EtOH / water system in a volumetric ratio of 1/1/1/1 gave ideal partition

coefficients ($K_{U/L}$) for anilines **65a-c** (**Table 3.6.**) and exhibited a short settling time of 16 s (See SI of [9]).

Table 3.6. Measured physicochemical parameters of anilines **65a-c**.

Entry	Parameter	65a	65b	65c
1	$K_{U/L}$[a]	1.86	0.49	0.24
2	p*K*a[b]	4.08±0.015	4.06±0.029	4.76±0.023

[a] The partition coefficients ($K_{U/L}$) were determined by GCMS measurements in the biphasic solvent system of *n*-Hex/MTBE/EtOH/H_2O=1/1/1/1 v/v ratio. ($K_{U/L}$ = peak area of the compound in the upper phase divided by the peak area of the compound in the lower phase). [b] pK_a values were determined by UV-spectrophotometric titrations (See SI of [9]).

Employing the chosen BLS in the initial batch-wise CPC experiments performed on a 100 mL capacity column (Armen SCPC-100+1000-B apparatus with SpotPrepII system, now Gilson) showed practically baseline separation for the product both in AM and DM. The operating conditions on the equilibrated column were the following: 5-10 mL sample injection, mobile phase flow rate of 5 mL min^{-1} and a rotation speed of 2000 rpm. Owing to the distinctively higher partition coefficient of the desired product (**65a**) as compared to the by-products (**65b,c**), the product eluted first in AM (the upper phase is the mobile phase) and it eluted last in DM (the lower phase is the mobile phase), which is ideal for our purification purposes.

Using these optimized conditions without modification, an MDM method was developed to achieve quasi-continuous purification. After the column had been equilibrated and the first sample injection took place, the by-products (**65b, c**) were simply washed out from the column in DM. Next, the sample solution was injected into the column again, and finally the product from both injections was eluted and collected in AM. This process could be repeatedly reversed several times, without post-washing and equilibration of the column between cycles. The efficiency and recovery were not affected as compared to the single AM and DM separation. In this way a stable, uninterrupted MDM CPC separation could be conducted for more than 5 h. The purity of the product was more than 99.9% (GCMS) and the recovery of **65a** was 91%.

In order to connect the reaction stream with the purification unit it was essential to automate the sample intake, which was enabled by the SpotPrepII device's magnetic valves that can be programmed. Due to the increased dead volume before the column, a prolonged elution time was necessary in AM to achieve the same recovery.

In order to match the composition of the sample intake of the CPC separation with the output of the continuous-flow reactor, the EtOH solution of the product was mixed with the other components of the chosen BLS. After phase separation using a separatory funnel, the upper and lower phase of the resulting biphasic mixture was separately introduced according to the program (see SI of [9]) into the CPC device (**Fig 3.5A.**). The phase separation unit served as a buffer flask and also allowed the escape of the excess hydrogen from the reduction step (which would otherwise be forcing out the liquid from the CPC column). In order to reach an overall continuous operation, the total inlet throughput of the reaction stream and the other components of the sample solution into the buffer flask must be equal or larger than the throughput of the outlet in a certain period of time. For this purpose the elution times (both in AM and DM), the time and flow rate of the sample intakes, the flow rates of the reaction stream and the other components of the sample solution, and their volume contraction factor were considered.

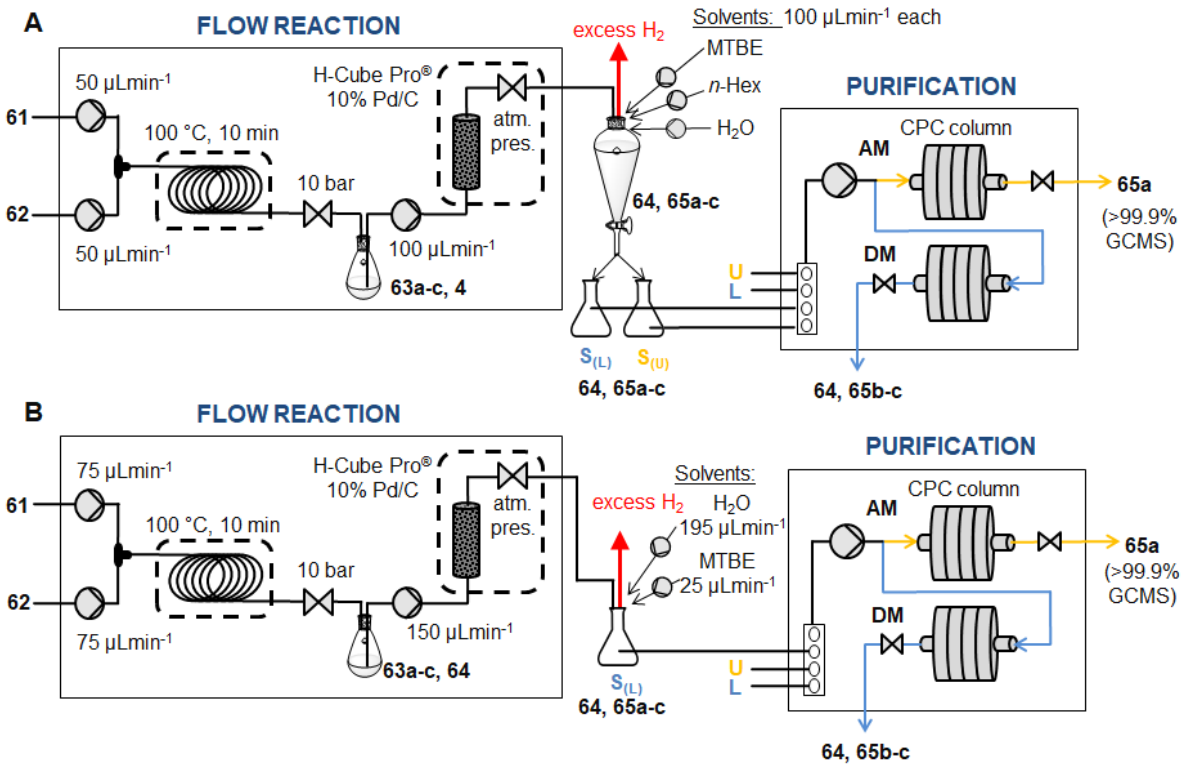


Figure 3.5. Flow chart of the two-step synthesis followed by a quasi-continuous MDM CPC purification, using: **A**, two-phase sample intake or **B**, one-phase sample intake. U: Upper phase of the chosen BLS, L: Lower phase of the chosen BLS; $S_{(L)}$: Sample solution in lower phase, $S_{(u)}$: Sample solution in upper phase.

The whole system (two-step reaction and purification) could be continuously operated, the isolated yield, purity and productivity values were satisfactory (**Table 3.1.** Entry 1). In order to increase the productivity by increasing the sample solution concentration and its throughput, a one-phase sample intake method was developed (**Fig 3.5B.**). The sample solution was prepared as a single-phase mixture of the reaction stream in EtOH combined with MTBE and water using two additional pumps (195/25/150 μL min^{-1} of flow rates of H_2O/MTBE/EtOH, respectively), in a composition that corresponds to the lower phase of the BLS (ratios were determined using GC-FID or ^1H NMR for the organic compounds and Karl-Fischer titration for the water content, See SI of [9]). The more concentrated sample solution and the higher throughput of the reaction stream gave a productivity that was 60% higher (**Table 3.1.** Entry 2) than that of the two-phase sample intake method.

Table 3.1. Results obtained in the coupled system of the two-step synthesis with purification.

Entry	**Sample intake method**	**Yield[a] (%)**	**Purity[b] (%)**	**Productivity[c] ($g•h^{-1}$ L^{-1})**
1	Two-phase [d]	57	> 99.9	1.44
2	One-phase [e]	59	> 99.9	2.27

[a] Isolated yield for the overall two synthetic steps followed by the quasi-continuous purification. [b] Measured by GCMS. [c] Mass of the pure product divided by the time of the process and the volume of the column. [d] Scheme of the process shown in FIG 3.14A. [e] Scheme of the process shown in FIG 3.14B.

In summary, we have developed a system for the multistep continuous-flow synthesis and purification of a complex reaction mixture, utilizing quasi-continuous multiple dual-mode centrifugal partition chromatography that can be operated in a truly continuous manner by using buffer flasks and a few pumps (See SI of [9]) and by synchronizing the flow reaction with the purification. The productivity increased significantly by the one-phase intake of the sample solution.

Throughput could be easily elevated by scaling up the column capacity or by converting to a true moving bed system via introducing the sample solution continuously into the intermediate point of the column (e.g. between two columns).

This system is the very first continuous-flow adsorbent-free final-product purification technique, and should have a wide applicability in the synthesis of APIs or its intermediates.

Thesis Findings

1. New, flow chemical syntheses of melanin-concentrating hormone receptor 1 (MCHr1) antagonists with a 1*H*,2*H*,3*H*,4*H*,5*H*-[1,4]diazepino[1,7-*a*]indole scaffold were developed. Flow chemistry proved to be a valuable technique in certain reactions to improve the synthesis of indoline derivatives by making the optimisation safer, faster, more economical and more environmentally friendly as compared to the batchwise methods. References: [I][III][IV]

2. A novel, consecutive heterogeneous catalytic hydrogenation reaction was developed with continuous-flow hydrogenation reactor (H-Cube^{TM} and H-Cube Pro^{TM}) using palladium on charcoal and methanesulfonic acid catalyst in acetic acid for the synthesis of ethyl 2-(2,3-dihydro-1*H*-indol-2-yl)acetate (**6**) from ethyl 4-(2-nitrophenyl)-3-oxobutanoate (**29**) through ethyl 2-(1*H*-indol-2-yl)acetate (**21**). Based on the literature overview, this is the first time that an *N*-unprotected indole derivative was formed *in situ* and selectively reduced further to form the corresponding indoline derivatives in palladium catalysed atmospheric pressure catalytic hydrogenation, which is ideal for scaled-up reaction and gave higher yield than any known two-step synthesis. References: [I][III][IV]

3. A purpose-built flow reactor and design of experiments were applied first for the optimisation of *N*-alkylation reaction of ethyl 2-(2,3-dihydro-1*H*-indol-2-yl)acetate (**5**) with the carcinogenic and bivalent 1,2-dibromoethane to form ethyl 2-[1-(2-bromoethyl)-2,3-dihydro-1*H*-indol-2-yl]acetate (**6**) was also optimised. Using the optimal set of parameters allowed us to decrease the excess of the reagent almost to tenth. Moreover, a nearly complete conversion was achieved under a fraction of the original reaction time. The productivity of the flow reactor system is ca. 200-times better as compared to the batch reaction conducted in the same volume of reactor. References: [I][III][IV]

4. A novel continuous-flow final product purification technique was developed by coupling a multistep flow reaction with centrifugal partition chromatography (CPC) and the target compound, 4-fluoro-2-(morpholin-4-yl)aniline (**65a**), was continuously manufactured in the purity over 99.9% (GC-MS). The complex reaction mixture that was separated with the multiple dual-mode CPC technique, was synthesised in a nucleophilic aromatic substitution (S_NAr) reaction of 2,4-difluoronitrobenzene (**61**) with morpholine (**62**) followed by heterogeneous catalytic hydrogenation. Applying a two-phase sample intake method for the

feed of the CPC device, 67% of isolated yield was achieved for the two synthetic steps and the purification. References: [II][III]

5. It was invented that the productivity of the continuous-flow final product purification with centrifugal partition chromatography (CPC) coupled to a multistep flow synthesis can be increased by applying a so-called one-phase sample intake methodology for feeding the CPC device. It was shown that the target compound 4-fluoro-2-(morpholin-4-yl)aniline (**65a**), could be manufactured with higher productivity (by almost 60%) as compared to the two-phase sample intake, which involved the mixing of the sole lower phase of the biphasic liquid system suitable for the separation. References: [II][III]

Publications

In journals with impact factor
Publications on which thesis findings are based:

I.[6] **R. Örkényi,*** Gy. Beke, E. Riethmüller, Z. Szakács, J. Kóti, F. Faigl, J. Éles, I. Greiner: Environment-Friendly Synthesis of Indoline Derivatives Using Flow Chemistry Techniques; *Eur. J. Org. Chem.* **2017**, *44*, 6525–6532. IF (2017) = **2.882**. Ref: 1 (Scopus), [ÖR: 100%]

II.[9] **R. Örkényi,*** J. Éles, F. Faigl, P. Vincze, A. Prechl, Z. Szakács, J. Kóti, I. Greiner*: Continuous Synthesis and Purification by Coupling a Multistep Flow Reaction with Centrifugal Partition Chromatography; *Angew. Chem. Int. Ed.* **2017**, *56*, 30, 8742–8745.; *Angew. Chem.* **2017**, *129*, 30, 8868–8871. IF (2017) = **12.102**. Ref: 12 (Scopus), [ÖR: 95%]

III.[2] P. Bana,* **R. Örkényi**, K. Lövei, Á. Lakó, Gy. I. Túrós, J. Éles, F. Faigl, I. Greiner: The route from problem to solution in multistep continuous flow synthesis of pharmaceutical compounds; *Bioorg. Med. Chem.* **2017**, *25*, 6180–6189. IF (2017) = **2.881**. Ref: 22 (Scopus), [ÖR: 20%]

IV.[10] K. Lövei,* P. Bana, **R. Örkényi**, Gy. I. Túrós, J. Éles, Z. Novák, F. Faigl: Continuous flow synthesis of heterocyclic scaffolds; Design principles of multistep systems – A review; *Chimica Oggi – Chemistry Today* **2016**, *34*, 4, 18–21. IF (2016) = **0.597**. Ref: 1 (Scopus), [ÖR: 10%]

Further, related publications:

V.[11] A. Balogh,* A. Domokos, B. Farkas, A. Farkas, Z. Rapi, D. Kiss, Z. Nyiri, Z. Eke, G. Szarka, **R. Örkényi**, B. Mátravölgyi, Gy. Marosi, Zs. K. Nagy,* *Chem. Eng. J.* **2018**, *350*, 290–299. IF (2017) = **6.735**. Ref: 15 (Scopus), [ÖR: 1%]

Further, not related publications:

VI.[12] V. Bódai,* L. Nagy-Győr, **R. Örkényi**, Zs. Molnár, Sz. Kohári, B. Erdélyi, Zs. Nagymáté, Cs. Romsics, Cs. Paizs, L. Poppe, G. Hornyánszky: *Wickerhamomyces subpelliculosus* as whole-cell biocatalyst for stereoselective bioreduction of ketones; *J. Mol. Catal. B: Enzym.* **2016**, *134*, 206–214. IF (2016) = **2.269**. Ref: 3 (Scopus), [ÖR: 5%]

VII.[13] N. Zs. Kiss, **R. Örkényi**, Z. Mucsi, Gy. Keglevich*: The Synthesis of 3-Phosphabicyclo[3.1.0]-hexane 3-Oxides and 1,2-Dihydrophosphinine 1-Oxides with Lipophilic P-Alkoxy Substituents by Ring Enlargement; *Heteroatom Chemistry* **2014**, *25*, 4, 265–273. IF (2014): **1.076**. Ref: 3 (Scopus), [ÖR: 30%]

(Sum of Impact Factors: **28.542)**

Oral presentations (in Hungarian):

VII. **Örkényi R.**, Faigl F., Éles J., Greiner I.: Folyamatos áramú tisztítási eljárások a gyógyszerhatóanyagok szintézisében – A centrifugális megoszlásos kromatográfia alkalmazása; *Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium 2017*.; Szeged, Magyarország, **2017. 09. 11-12.**

VIII. Túrós Gy. I., Éles J., Lövei K., Bana P., **Örkényi R.**, Lakó Á., Greiner I.: Áramlásos kémiai kutatások a Richterben. Legújabb eredmények; *Richter Gedeon Kutatási Fórum*, Herceghalom, Magyarország, **2015. 10. 4-6.**

IX. Túrós Gy. I., Éles J., Lövei K., Bana P., **Örkényi R.**, Greiner I.: Megvalósult és tervezett áramlásos kémiai kutatások a Richterben, Tapasztalatok és kihívások; *Richter Gedeon Kutatási Fórum*, Herceghalom, Magyarország, **2014. 10. 5-7.**

X. **Örkényi R.**: Az áramlásos kémia előnyei, egy gyógyszeripari példa környezetbarát szintézisút kidolgozására; *Fiatal Kutatók Fóruma*, Budapest, Magyarország,
2014. 11. 28.

Oral presentation (in English):

XI. **R. Örkényi**, F. Faigl, J. Éles, I. Greiner: Purification in Continuous Flow Manufacturing: The Use of Centrifugal Partition Chromatography; *6th Conference on Frontiers in Organic Synthesis Technology*; Budapest, Hungary, 18-20. 10. **2017.**

Poster presentations:
(Oral presentation in English before the Poster Committees)

XII. **R. Örkényi**, F. Faigl, J. Éles, I. Greiner: Purification in Continuous-Flow Manufacturing: The use of Centrifugal Partition Chromatography; *SPICA 2018 - 17th International Symposium on Preparative and Industrial Chromatography and Allied Techniques*; Darmstadt, Germany, **7-10. 10. 2018.** (First Place, Best Poster Presentation Award.)

XIII. **R. Örkényi**, F. Faigl, J. Éles, I. Greiner: Purification in Continuous-Flow Manufacturing: The use of Centrifugal Partition Chromatography; *PREP 2018 - 31st International Symposium on Preparative and Process Chromatography*, Baltimore, Maryland, USA, **8-11. 07. 2018.** (Second Place, Academic Best Poster Presentation Award.)

XIV. **R. Örkényi**, J. Éles, F. Faigl, P. Vincze, A. Prechl, I. Greiner: The use of multiple dual-mode centrifugal partition chromatography for the final purification of multistep continuous flow reaction; *Flow Chemistry Congress 2016*, Miami, Florida, USA,
1-2. 11. 2016. (First Place, Best Poster Presentation Award.)

XV. **R. Örkényi**, I. Greiner, F. Faigl, E. Riethmüller, Z. Szakács, J. Kóti, J. Éles: Synthesis of Indoline Derivatives by Flow Chemistry Techniques; *Symposium on Advances in Heterocyclic Organic Chemistry 2016;* Sheffield, UK, **1-2. 09. 2016.**

Other poster presentations:

XVI. **R. Örkényi**, J. Éles, F. Faigl, P. Vincze, A. Prechl, I. Greiner: Final product purification of a continuous flow multistep synthesis using multiple dual mode centrifugal partition chromatography; *Richter Gedeon Kutatási Fórum*, Herceghalom, Hungary, **2-4. 10. 2016.**

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