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Privileged scaffolds turning green(er) - flow chemistry approaches *vs* traditional challenges

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ABSTRACT

Privileged scaffolds as starting points toward biologically active molecules represent a neuralgic point in drug discovery. The ability of synthetic chemists concerned with their generation should be flanked by robust technologies enabling the efficient synthesis and decoration of large libraries for extensive screenings and for scale-up processes. The use of continuous flow chemistry in the pharmaceutical chemistry sector may lead to facilitated scaffold generation, and furthermore to the implementation of more efficient multistep transformations observing upcoming socio-economic boundary conditions requiring green and sustainable processes.

This review discusses the use of flow chemistry applied to the synthesis of privileged scaffolds, considering also sustainability and green chemistry aspects. Flow protocols are discussed in a unified fashion such to facilitate effective comparison between chemical approaches and chosen technical solutions. The review also offers an authors' perspective on potential future directions in the field.

KEYWORDS

privileged scaffolds
flow chemistry
green chemistry
heterocycles
sustainable medicinal chemistry

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1 INTRODUCTION

1.1 Privileged scaffolds – what and why?

The first decade of the 20th century saw the ground-breaking contribution of Emil Fischer and Paul Ehrlich, who set the bases for modern medicinal chemistry by introducing vital concepts for the design of new chemical entities endowed with biological activity. First of all, the notions of ligand-receptor complementarity and molecular recognition paved the way to the rational design of new drugs, while the concept of selectivity towards a target helped unveiling critical molecular determinants for the modulation of drug efficacy and safety.[1-3] In 1958, Daniel Koshland with his induced fit theory expanded the lock-and-key principle initially proposed by Fischer for ligand-target interaction, thus providing a crucial addendum in the elucidation of the complex cross-talk between a biologically active molecule and its target.

The term 'privileged structures' was coined in 1988 by Evans to describe simple structural templates containing common features which are embedded in several bioactive compounds, with distinct therapeutic uses, and serving as ligands for a diverse array of receptors.[4-7] The judicious structural decoration of these structures could then provide a fruitful way to conceive novel receptor ligands and to fine-tune their potency and selectivity towards a given target. Over the years, this first definition increasingly widened in its use and acquired different meanings as well as a good number of synonymous, often flanking the progress of medicinal chemistry techniques. Therefore terms like 'molecular framework', 'molecular template', 'chemotype', 'substructure', 'molecular fragment', and 'molecular scaffold', arose hand in hand with the growing implementation of molecular docking and structure-, ligand- and fragment-based drug design techniques. [8]

If we go back for a moment to the lock-and-key theory, we can envision a privileged scaffold as a master key, a sort of *passe-partout* which gives access to several biological targets. Of course, this versatile character should not be seen as something odd or random, but rather as a direct and logical consequence of a few key concepts which apply to the majority of the biological targets.[9] The compelling reality is that, although in the human body roughly 19,000 genes code for proteins, research still focuses mainly on only about 2000 proteins and - surprisingly or not - they are not that different. In more detail, this means that fold families are highly conserved, structural motifs are re-used and that, basically, there are only limited ways for a protein to form a hole (binding site) and to exist in balanced conformational states. This is particularly true for G-protein coupled receptors, but the concept works quite well also for a variety of other biological targets. Several structural motifs labelled as privileged scaffolds are largely represented in naturally derived compounds. For examples alkaloids with distinctive pharmacological activities preferentially display heterocycles such as quinolines, isoquinolines, pyrrolidines, indoles and a variety of their combinations. Other widely common nature-inspired templates include isoflavones, coumarins and chalcones. Among synthetic drugs, five and six membered nitrogen-, oxygen- and sulphur-containing heterocycles as well as their fused derivatives represent a large slice of privileged scaffolds and they are present, with a huge variety of decorations, in the large majority of blockbuster drugs.[10]

It is then clear that the use of privileged scaffolds as starting points for the development of new biologically active chemical entities can represent a useful and robust tool for impacting the drug discovery process. A properly designed scaffold modification and decoration for these key substructures could help identifying not only novel therapeutics but also useful chemical probes for the study of critical disease pathways. In this context, the ability of synthetic and medicinal chemists should be flanked by robust technologies enabling the efficient synthesis of large libraries for extensive screenings, through phenotypic or biochemical assays, but also the scale-up of key intermediates or active ingredients.

1.2 Flow chemistry principles as enabling tool for green and sustainable medicinal chemistry

The concepts of ‘flow chemistry’ and ‘green and/or sustainable chemistry’ do not mandatorily have to go together, nor does the application of the first concept guarantees compliance with the second. Equally well can a perfectly green and sustainable reaction be done in conventional batch mode. The two concepts, emerging more or less in parallel fashion since the beginning of this century, can be very well complementary though, when the synthetic problem is faced considering the potentials and limitations of both concepts,[11] looking for the synergy that can eventually be exploited. These potential synergies have been discussed in great detail in the past years in several, also critical reviewing articles.[12-18]

Neither application of flow chemistry concepts nor the sustainability of a synthetic approach has to be connected to major investments. In terms of fundamentally necessary equipment for flow chemistry, comparably inexpensive syringe or HPLC pumps can be used to effectuate flow into and through a reactor. Reagents and reagent solutions can be - but do not need to be - loaded in sample loops, just as analyte solutions are prepared for injection into the system in analytical or better preparative HPLC analysis. The simplest reactor setup consists of a chemically inert tubing system, made up from polyether ether ketone (PEEK), polytetrafluoro ethylene (PTFE), polyfluoroacetate (PFA), copper, palladium alloys, stainless steel or Hastelloy. An already more specialised, nevertheless not too expensive tubular reactor is found in form of microfluidic chips, often made out of laboratory glass. While such tubular reactors are suitable for homogeneous reactions, heterogeneous conditions can be handled in column reactors, principally comparable to chromatography columns, which are placed in-line the flow of reagents after being filled with appropriate polymer-supported reagents or heterogeneous catalyst systems. Mixing of reagents, present most likely in form of streams of their solutions in the solvent of choice can be achieved using simple T-pieces, or using mixing devices with dedicated geometries for difficult cases like biphasic mixtures.

Specific synthetic needs, also associated with the preparation of active pharmaceutical ingredients, may lead to the implementation of more complex set-ups suitable for hosting multistep transformations in so-called telescoped reaction sequences.[19] Set-ups can be varied to allow for reagent recycling, in-line purification and selective capture and release protocols suitable for product isolation and by-product elimination, etc. All of these devices can help minimise solvent usage, reagent waste and manual handling of materials. Eventually necessary intermediate work-ups and/or an up-concentration of product-containing streams in line can be realised using hands-on solutions or specialised equipment. Adding additional levels of complexity to the basic flow set-ups, for example in form of in-line monitoring tools such as UV, FT-IR, RI or mass flow detectors, and computer-assisted, feed-back regulated pump controls can be used to maximise efficiency and efficacy of the flow set-up, rendering the flow process more sustainable and eventually green(er). As said introductory, connections between the fields of green and sustainable chemistry and flow chemistry have been subject to discussions since the two areas started emerging more or less in parallel in the late 1990s/early 2000s.[12-14, 16-18, 20, 21] The extensive research in the field of flow chemistry over the two decades since then, both in academia and industry, has by and large opened and mapped the field,[11, 22-25] indicating that synergy-generating possibilities involving flow methodologies are best brought into practice when using flow chemistry in a thoughtful, clever, if not wit way, also in fruitful combination with conventional batch transformations.

The use of flow chemistry for synthesising privileged scaffolds, and thus eventually fostering sustainability and environmental compatibility in the pharmaceutical chemistry sector comes in light of the above discussed aspects just naturally. The review thus lists and discusses, rather from an applicant than an experienced developer point of view, the use of flow chemistry in this context, also with respect to whether it is convenient and/or advantageous. This article also offers an updated[24] state-of-the art picture, implicitly bringing to light still unexplored chemical space, in terms of less investigated privileged scaffolds and/or heterocyclic moieties under continuous flow settings. Moreover, during this journey through heterogeneous research reports, a unified, homogenised symbol language was elaborated for both technical elements needed for flow chemistry and the description of reagent-related details and starting materials, in order not only to facilitate reading but also to allow an easier and effective comparison between chemical approaches, methodologies and outcomes. The review closes with an outlook on the potential future directions that emerge from the applicant point of view in light of the currently fast changing boundary conditions under which organic chemistry needs to deliver.

2 DISCUSSION

2.1 Preface: Flow equipment – from the absolutely necessary to the technological state-of-the-art

Unlike traditional chemistry, flow chemistry suffers quietly from a myriad of ways representing fundamental elements such as pumps and reactors. Research groups entering the field from the engineering side often use the unified engineering symbol language to describe key flow elements within their articles. Chemists entering the field often use a more figurative symbol language. This language developed naturally alongside with the field with particularities typical for the various leading schools and groups, but still fails after 20 years to arrive at a proper merging towards a uniformly accepted and applied form. From an applicant point of view, this 'mix of styles' represents only a time-consuming and at times misleading element. We thus propose *via* the schemes in this work a unified, homogenised symbol language for both technical elements needed for flow chemistry and the description of reagent stream compositions, such as to facilitate understanding with respect to original publications especially for less or un-experienced readers, that might find a solid ground to start from also in excellent, dedicated recent articles.[11, 26] This step toward uniformity also aims at enabling effortless comparability between different works and allowing identification of the equipment that would be really necessary to use an existing flow synthesis of a privileged scaffold as starting point for novel and innovative research. The proposed uniform(ed) symbol-language to be used throughout the text is shown in Figure 1. It was mainly inspired by the one developed on-the-go by Ley and co-workers when the field started growing seriously in the mid-2000s with some seminal works[27, 28] emerging from an eventually necessarily preceding more established use of solid-supported reagents only by the beginning of the century.[29-36]

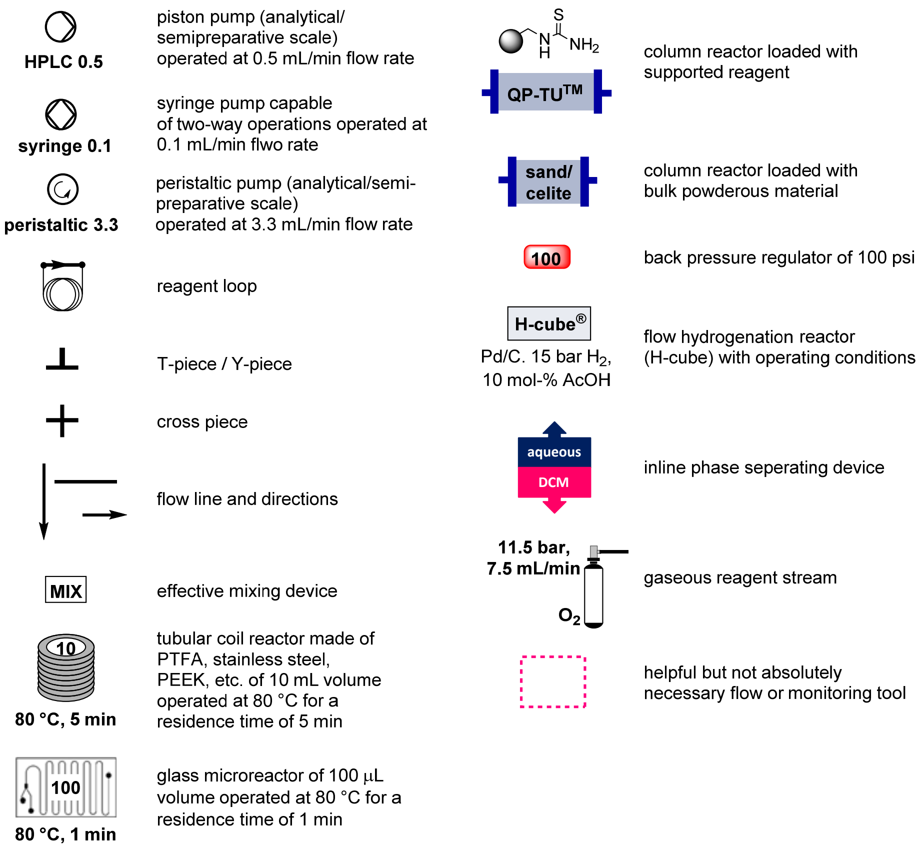
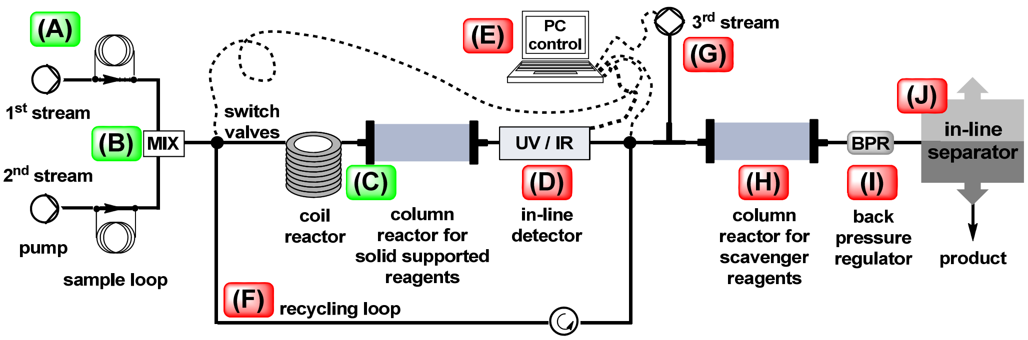


Figure 1: Unified symbol language used in tables and schemes throughout the manuscript for the most common components of flow chemistry set-ups at laboratory scales.

The last months have demonstrated that mankind does not have any more the luxury to play; global problems require global answers, also in terms of basic research, including chemical research with pharmaceutical perspectives. Flow chemistry is an enabling tool in this area, and it is time to abolish eventually existing artificial boundaries that prevent innovative synthesis also in different economic realities. In this sense, for selected works representing well the various aspects of the flow chemistry world, detailed flow schemes are shown applying the proposed unified symbol language shown in Figure 1. The few cases in which more particular reactors are employed are nevertheless highlighted as such, with the intent to encourage the development of individual hands-on solutions by pointing out these cases. The idea is to encourage laboratories concerned with synthesis around the globe to use ‘flow chemistry’ as a useful tool, rather than seeing flow processes as a nice but complex ornament to synthetic organic chemistry protocols. Flow chemistry owns a real potential to enrich the synthetic playground potentially offering several advantages to chemical processes as summarised in Figure 2.



(A) Enhanced process saftey by containment of potentially hazardous substances

(B) Simple T-pieces, or enhanced mixing possible using mixing chips with dedicated flow patterns

(C) Reactors for effective and uniform heat transfers; column reactors for in-line work-ups

(D) In-line monitoring of product formation for process optimisation

(E) Computer-assisted, eventually detector feedback-triggered control of valves and pumps for optimum processing and advanced control of stoichiometries of 3rd streams, or for 24/7 processing and monitoring

(F) Re-circulating reacgents for optimising process efficacy / product formation

(G) Additional reactant streams for multi-step processing

(H) Column reactors for housing scavenger reagents for in-line work-ups

(I) Back pressure regulator for augmenting process parameter options

(J) In-line separation of liquid phases, or in-line removal of solvents for continuous processing

Figure 2: Basic (green) and more advanced (green and red) flow chemistry set-ups.

For the advantages potentially offered, flow chemical applications have become part of the standard repertoire of many synthesis laboratories both in academic and industrial environments. Importantly, using the tool ‘flow chemistry’ is not connected to the presence of, or access to more or less dedicated flow reactor equipment. Often, a standard HPLC set-up can be requalified. The amount of literature has reached the significant critical mass that permits the interested practicing synthetic chemist to find hints for practical solutions of real problems or even hands-on procedures of how to face common issues, as this review intends to convey.

2.2 Privileged scaffolds realised in flow

2.2.1 Azetidines

Azetidines represent an important class of aza-heterocycles characterised by a high stability combined with molecular rigidity. This highly geometrically configured structure is very useful for exploring chemical space which makes azetidine ring a major privileged scaffold in the design of small active molecules.[37, 38] Azetidine-based templates are present in chemical analogues to several naturally occurring compounds and in several pharmaceuticals (*e. g.*, cobimetinib, delafloxacin, and penaresidin).[39, 40] The β-lactam ring, the azetidin-2-one, is embedded in several antimicrobial, antitumor and anti-Parkinson agents.[41]

The first published examples of flow chemistry applied to azetidin-2-one synthesis emerged in 2010, when Konopelski and co-workers reported the synthesis of an enantiomerically pure *trans*-β-lactam from an α-amino acid.[42] Using enantiomerically pure α-diazo-*N*-methoxy-*N*-methyl-ketoamide in an intramolecular Wolff rearrangement, enantiomerically pure β-lactam was obtained in a fluorescent light continuous flow photolysis performed in a tubular reactor (Table 1, entry 1).

Table 1: Azetidines in flow.

Entry	**Approach**	**Starting compound(s)**	**Reactor** [a]	**Structural scope**	**Yields [%]**	**Comments**	**Ref / year**
1	intramolecular Wolff rearrangement		, hν [b]		91	1 compound in flow, derivatisation options presented	42 / 2010
2	Norrish-Yang reaction		, hν [b]		28-85	36 compounds, limitations when using aliphatic ketones	43 / 2019
3	Staudinger synthesis with *in-situ*-generated ketenes				61 - 98	15 compounds, in-line FT-IR monitoring prior to 3rd stream addition, no info on eventual Zn leaching	44 / 2015
4	Staudinger synthesis with *in-situ*-generated ketenes				56	1 compound, FT-IR in-line monitoring, single product only	45 / 2015
5	[derivatisation]	**7-ACA**			81[c]	**7-ACA** derivatisation to cefotaxime, only toluenesulfonic acid as by-product	46 / 2018
6	[derivatisation]	**7-ACA**			85	**7-ACA** derivatisation to **TACA** on multi-gram scale	47 / 2019

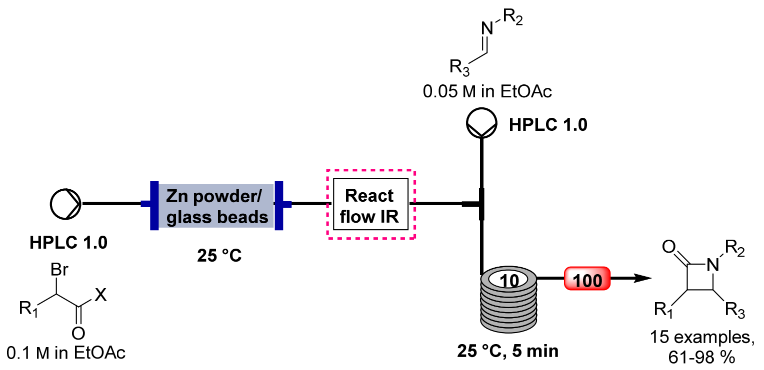
a: For reactor types, refer to Figure 1.

b: Photochemical reaction.

c: HPLC yield (isolation not reported).

Baxendale and colleagues reported in 2019 a different photochemical flow-synthesis of 3-hydroxyazetidines,[43] applying the Norrish-Yang reaction,[48] which involves intermolecular cyclisation of the excited state of a 2-amino ketone (Table 1, entry 2). Applying a coil reactor irradiated using a low-pressure mercury lamp, it was also possible to obtain an extended and uniform incident photon flow, avoiding unwanted heating effects. A library of 36 compounds was realised with this approach, in which steric effects rather than electronic effects were found to control achievable yields. 3-(4-chlorophenyl)-1-tosylazetidin-3-ol was used for product formation on a 100 mmol scale using the optimised set-up, providing 20.3 g (60%) of the target azetidine prior to purification in a single continuous run of 11.5 hours of processing.

Hafner and Ley reported the generation of reactive ketenes *in situ*, upon zinc-mediated dehalogenation of α-bromoacyl halides, in a continuous flow set-up that allowed their subsequent Staudinger reaction with imines in a [2 + 2] cycloaddition in diethyl ether or ethyl acetate (Scheme 1) (Table 1, entry 3).[44] An in-line FT-IR monitoring of the reaction was realised using a dedicated ReactIR flow cell to monitor intermediate ketene formation prior to addition of imines *via* a third stream. This in-line monitoring was not used, however, to precisely control stoichiometries of the added imines. A library of 15 β-lactam motifs with moderate to high yields was realised using this set-up; higher yields derived from benzylideneanilines as the starting material. Noteworthy, the flow chemistry protocol allowed for product formation in cases in which standard batch procedures reportedly failed.



Scheme 1: Flow synthesis of azetidinones using *in situ*-generated ketenes according to Hafner and Ley.[44]

A Staudinger protocol was also envisaged by Karlsson *et al.* to develop a large-scale pathway to a melanin concentrating hormone receptor 1 (MHC$_1$) antagonist in a convergent synthesis comprising four building blocks, one of which is an azetidine (Table 1, entry 4).[45] In this case, the i*n situ* ketene formation was achieved using a concentrated acid, starting form tetrahydrofuran-3-carbonyl chloride, in the presence of benzylmethanimine and using *N*-methylpiperidine as the base. Unlike in the Staudinger approach discussed above, the three reactants were mixed in a four-way valve directly, indicating as such an alternative, easier version and the facultative nature of controlling ketene formation. The desired lactam was isolated employing approx. 1 minute residence time. The effective yield of 56% is only moderate, however, and it is not evident whether this is due to set-up or the short reaction times.

Beside these works targeting the generation of the azetidine motif, two flow approaches involving the derivatization of specific azetidine motifs were reported, as part of large scale production of actives. These two approaches are listed here since they apply slightly different processing or reactor approaches.

Starting from advanced 7-aminocephalosporanic acid (**7-ACA)** building block, Bayer and Gröger presented in 2018 a batch-flow process towards cefotaxime, using 4-toluenesulfonyl chloride as a coupling reagent, such as to facilitate product purification (Table 1, entry 5).[46] The optimised batch-flow process saw the combination in flow of a mixture of (*Z*)-(2-aminothiazol-4-yl)-methoxyiminoacetic acid, trimethylamine and tosyl chloride in dimethylacetamide, stirred prior to the flow step in batch mode for 1 hour at -15 °C, with a mixture of 7-ACA and trimethylamine in methanol kept at 0 °C. After 1 minute in the tubular reactor held at –10 °C, target cefotaxime is obtained in 81% productive conversion after aqueous work-up. An isolated yield is not reported. The authors state that the batch-flow system delivered a space-time yield of approx. 3000 kg m^{-3} h^{-1} for cefotaxime, being thus approx. 400 times higher than the space-time yield achievable with a batch process.

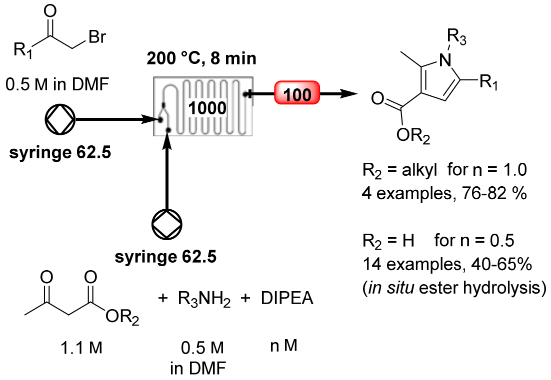
The synthesis of the antibiotic precursor thiazolyl-7-aminocephalosporanic acid (**TACA**) in a micro-structured flow system was also developed by Bayer and co-workers (Table 1, entry 6).[47] In batch mode, the synthesis is performed at 60 °C for 1 hour. The flow synthesis in microreactors has been designed to ensure high heat transfer capacities, short heating times and short residence times, all factors identified as crucial in light of the fact that both starting material and target compound are known to be heat sensitive. Using DoE-optimised parameters, **TACA** was obtained in 85% yield starting from **7-ACA** and methylmercaptothiazolyl acid. The flow synthesis allows for production of 440 kg of **TACA**, representing a 130-fold increase in the space-time yield.

2.2.2 Pyrroles

The pyrrole moiety is found in a wide range of biologically active natural products and pharmaceutically active agents. Pyrroles are connected to antibacterial, antiviral, anti-inflammatory, anticancer and antioxidant activities.[49, 50]

In 2010, Cosford *et coll.* developed a continuous flow Hantzsch synthesis of pyrrole-3-carboxylic acids and corresponding amides starting from *tert*-butyl acetoacetates, amines and α –bromoketones (Scheme 2)

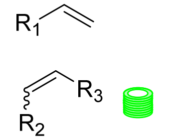
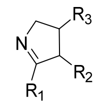
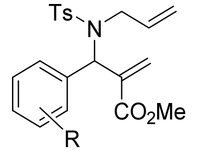
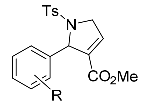
(Table 2, entry 1).[51] Different β–ketoesters were mixed with benzylamine and DIPEA in DMF, to be joined with a stream of α-bromoacetophenone to give the corresponding pyrrole derivatives. The HBr formed in stoichiometric amounts in the Hantzsch reaction was quenched by the DIPEA inserted right from the beginning. 4 compounds were obtained using this methodology. When *tert*-butyl esters were used as β–ketoesters for the reaction, the HBr could be utilised for effectuating a hydrolysis to yield the corresponding acids a**s** final products (Scheme 2) (Table 2, entry 2). Alternating the structure of the primary amine gave six additional, *N*-substituted pyrroles in good yields for isolated and purified products (Table 2, entry 3), underlining as such a remarkable robustness of the flow Hantzsch protocol towards variations in reactants. It was also possible to provide *N*-unsubstituted pyrrole 3-acids in this flow set-up starting from *tert*-butyl 3-aminobut-2-enoate/DIPEA mixed together with α -bromoacetophenone in DMF (Table 2, entry 4). The scale-up potential of the flow process was demonstrated synthesizing 850 mg of 1-benzyl-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid in 2.5 h.[51]



Scheme 2: Hantzsch pyrrole synthesis in flow as proposed by Cosford *et coll.*[51]

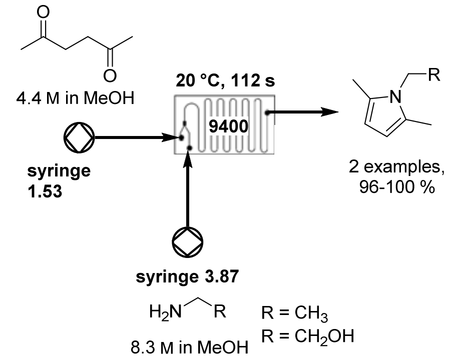
Table 2: Pyrroles and dihydropyrroles in flow.

Entry	Approach	Starting compound(s)	Reactor [a]	Structural scope	Yields [%]	Comments	Ref / year
1	Hantzsch synthesis				76-82	4 compounds	51 / 2010
2	Hantzsch synthesis				40-65	8 compounds	51 / 2010
3	Hantzsch synthesis				40-62	6 compounds	51 / 2010
4	Hantzsch synthesis				48-62	4 compounds	51 / 2010
5	Paal-Knorr cyclo-condensation				96-99	2 compounds, high excess of amine, no information about its potential recovery and reuse	52 / 2011
6	Paal-Knorr cyclo-condensation		, tube-in-tube		33-100	10 compounds	53 / 2012
7	Michael-addition followed by cyclisation-& aromatisation				70-71	2 compounds, no yield improvement with respect to batch	54 / 2015

8	[2+3] cycloaddition		 $h\nu$ [b],		35-83	8 compounds, azirines possible using the same set-up	55 / 2013
9	ring-closing metathesis				52-92	7 compounds, one scale-up	56 / 2017

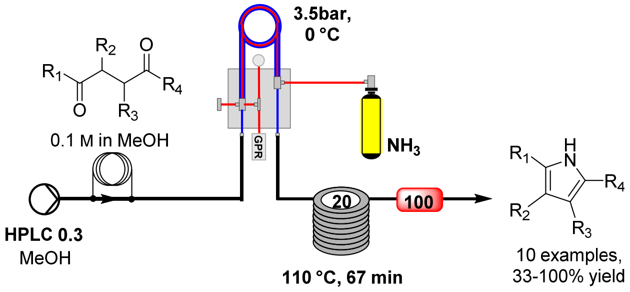
a: For reactor types, refer to Figure 1.
b: Photochemical reaction.

In 2011, Nieuwland *et al.* reported the pyrrole synthesis according to Paal-Knorr (Scheme 3) (Table 2, entry 5).[52] During the Paal-Knorr cyclocondensation of 1,4-diketones with amines, strongly exothermic reactions are often encountered, especially when working with higher concentrations to achieve higher space-time yields. Using a flow chemistry protocol allowing for effective heat exchanges was thus seen as a means to eliminate this intrinsic draw-back. Conditions were optimised using a DoE approach, accounting for substrate specificities using a microfluidic reactor chip. For realizing a flow process yielding gram amounts of product, instead of re-optimising parameters, the single microfluidic reactor was replaced with micro-structured reactor chips of slightly higher volumes, but more interestingly, also arranged in a parallel fashion. Analytically pure simple *N*-hydroxymethyl-substituted pyrrole was obtained at 56 g/h. Unfortunately, the paper does not report details regarding the purity of the compounds.



Scheme 3: Paal-Knorr cyclocondensation in flow as proposed by Nieuwland *et al.*[52]

Another chemically interesting, very simple flow-Paal-Knorr approach to pyrroles was published by Cranwell *et al.* in 2012, starting from 1,4-diketones and gaseous ammonia using an innovative tube-in-tube reactor (Scheme 4) (Table 2, entry 6).[53] The ammonia, flowing through the inner tube, permeates the tubing wall and enters the organic phase flowing in the outer tube, reaching thus the 1,4-diketone for pyrrole formation. The study confirmed the intuitively expectable strong dependence of the ammonia uptake of the organic phase on the solvent and the operation temperature. Using MeOH as greener solvent, the set-up could be used to produce ten differently substituted pyrroles in variable yields after column chromatographic purification. The lowest yield (33%) was obtained for a sample generated starting from a diketone carrying both a bulky and an electron-withdrawing substituent. Despite the simple, very atom economic approach, significant side-product formation was reported for some cases, hinting at the difficult to control reactivity of the gaseous reagent.



Scheme 4: Paal-Knorr cyclocondensation in flow using gaseous ammonia proposed by Cranwell *et al.*[53]

In 2015, Palmieri and Ballini developed in their group a flow route to alkyl pyrrole 2-carboxylates starting from β-nitroacrylates and primary amines and working in 2-MeTHF as green solvent (Table 2, entry 7).[54] In a tubular reactor held at room temperature the Michael addition was first realised; subsequent acetal opening and cyclisation/aromatisation were achieved *via* heterogeneous acid catalysis in a column reactor held at 60 °C and filled with Amberlyst 15 (A-15), a resin that proofed very versatile in a series of formations of heterocycles, both as reagent and as in-line scavenger (*vide infra*). Products were isolated in approx. 70% yield. Unfortunately, only two examples were reported using the flow process, while the overall synthetic approach was validated in batch with twelve realised products that were purified by conventional column chromatography.

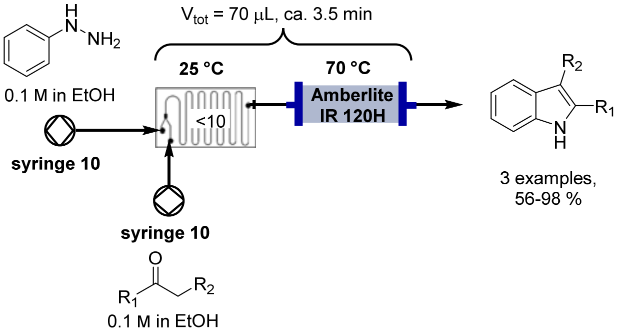
Cludius-Brandt *et al.* demonstrated the applicability of photochemical flow chemistry to the formation of dihydropyrroles through the [2+3] cycloaddition from aromatic vinyl azides and activated alkenes (Table 2, entry 8).[55] The authors reported in a previous work on the synthesis of vinyl azides under flow conditions, starting from corresponding alkenes and the solid-phase bound iodine azide transfer reagent, followed by elimination with DBU.[57] Starting from these flow-generated vinyl azides, azirines were obtained under both, thermal or photochemical conditions in flow, using DCM or toluene as solvent, respectively. Using optimised photochemical conditions, 8 dihydropyrrole derivatives were synthesised, highlighting the insensitivity of the reaction protocol to changes in substitution patterns, with a noteworthy exception in the case of a pyridyl substituent. The authors state that crude products were purified by column chromatography only when necessary, hinting thus at the clean chemical conversion in the flow approach.

In 2017, Drop *et al.* reported on a still rather unconventional synthetic approach to aromatic heterocycles: a ring-closing metathesis in continuous flow mode aimed at the synthesis of 2,5-dihydro-1*H*-pyrrole-3-carboxylates, using commercially available homogeneous ruthenium metathesis catalysts and working in green DMC as solvent (Table 2, entry 9).[56] After 5 minutes at 110 °C, or in 1 minute at 120 °C, methyl 2-(2-nitrophenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate was isolated in 83% yield. A library of 7 compounds was synthesised in this mode in moderate to excellent yields, although typical secondary products like degradation or coupling products could not be identified. Nonetheless, the study shows that flow chemistry set-ups are not only compatible with metathesis reactions, but that they hold the potential to overall improve the performance of metathesis reactions.

2.2.3 Indoles and carbazoles

Indoles are among the most important bioactive heterocyclic structures, being naturally presenting tryptophan and the related neurotransmitter serotonin. Indole alkaloids represent one of the largest classes of nitrogen-containing secondary metabolites, containing indole and/or indoline substructures. They are widely found in plants, bacteria, fungi and animals. The indole scaffold has been referred to as a "privileged scaffold" due to its capacity to interact with a diverse range of receptors, such as dopamine, serotononin and sigma receptors with high affinity. Indole-based compounds have shown anti-inflammatory, antihypertensive anti-tumour, anti-HIV, and antimigraine activities.[58] As one might expect, most of the flow-based approaches to indoles are based on the classical Fischer indole synthesis; only few differentiating innovative approaches can be found. A very recent dedicated review summarises the flow-based indole synthesis efforts in greater detail, so that only a few selected examples are discussed in here.[59]

A flow chemistry implementation for the Fischer indole synthesis was published in 2010 by Watts *et coll.*[60] Two versions were presented: in an entirely solution-based mode (Table 3, entry 1), substrates were dissolved in glacial acetic acid as green solvent, adding 10% sulfuric acid (v / v) as the catalyst. This approach allowed for short reaction times, minimizing thus tubing length, and hence back pressure and likeliness of blockages that were encountered in initial trials. The use of the highly protic solvent system allowed further reduction of the temperature to 105 °C. While the use of acetic acid was thus beneficial for the reaction as such, it was envisaged to cause problems in eventually telescoped reactions. It was therefore substituted in a fully optimised approach by Amberlyst IR-120H as a heterogeneous acid catalyst (Scheme 5) (Table 3, entry 2), working in ethanol as green solvent. The reaction temperature in this second mode could be lowered once more to 70 °C. The flow of the output solution was acid-free, and the product was collected in ice water from which it precipitated, avoiding further work up. Only conversions to a mini-library of 3 compounds are given, isolated yields have not been reported for any of the flow reactions, unfortunately.



Scheme 5: Fischer indole synthesis in flow as proposed by Watts *et coll.*[60]

Table 3: Indoles and carbazoles in flow.

Entry	Approach	Starting compound(s)	Reactor [a]	Structural scope	Yields [%]	Comments	Ref / year
1	Fischer indole synthesis				52-96[d]	4 compounds, solutions only, higher T necessary	60 / 2010
2	Fischer indole synthesis				56-98[d]	4 compounds, Amberlyst catalyst, T as low as 70 °C,	60 / 2010
3	Fischer indole synthesis				41	1 compound, no strong acids necessary	61 / 2013
4	Fischer indole synthesis		, MW[b]		78	1 compound	62 / 2017
5	Fischer indole synthesis				66	1 compound, questionable improvement with respect to conventional solution synthesis; DCM required for IL recovery	63 / 2017
6	Fischer indole synthesis				38-82	10 compounds, indole formation coupled to thiazole formation (Table 17)	64 / 2012
7	Reissert indole synthesis				41-96	9 compounds flow hydrogenation, scale-up demonstrated	65 / 2011

8	Hemetsberger-Knittel synthesis				70-96	4 compounds, only 2-substituted products reported	66 / 2013
9	Cadogan–Sundberg - type synthesis				40-90	16 compounds	67 / 2017
10	reductive cyclisation				82-91	1 compound, auxin mimic, synthesis on larger scale with appropriate reactors, including oxadiazol	68 / 2017
11	Heumann indole process				48-90	6 compounds	69 / 2019
12	Fischer indole synthesis				92-97	6 compounds	70 / 2016
13	photo-chemistry, Suzuki coupling		hv[c]		41-74	8 compounds, clausine C derivatives	71 / 2015

a: For reactor type acronyms, refer to Figure 1

b: Microwave reaction.

c: Photochemical reaction.

d: Conversion yields (HPLC).

In 2013, Kappe and co-workers adapted the Fischer indole synthesis of 7-ethyltryptophol (**7-ET**) under flow conditions in laboratory scale (Table 3, entry 3). They were inspired by a work on a kilogram scale reported in 2011 by Su and co-workers.[61] Combining a solution of hydrazine hydrochloride and stoichiometric 2,3-dihydrofuran in MeOH/H_2O 2/1 for 3 minutes at 150 °C in a stainless steel tubular reactor produced 41% of **7-ET** after off-line extraction and chromatographic purification to 92%. Despite the rather low yield, this synthesis benefits from mild reaction conditions.

The synthesis of **7-ET** was once more targeted by Xu *et al.*, who designed a continuous flow microwave-assisted Fischer indole protocol (Table 3, entry 4) in green solvents.[62] Optimal microwave conditions were found with 1300 W at 180 °C. A solution of 2-ethylphenylhydrazine hydrochloride, 0.14 M in H_2O/ethylene glycol and a solution of 4-hydroxybutanal, 0.13 M in H_2O, both preheated to 80 °C, were mixed and passed on into a first coil reactor that was placed in the microwave; the exiting stream was allowed to cool down in a dedicated cooling reactor. By applying a complete flow rate of 200 μL/min, **7-ET** was obtained in 78% yield after a simple off-line extraction process. The short time of microwave heating, *i.e.*, 20 s, and cooling, just 10 s, avoided the formation of by-products despite the high temperatures. The paper does not describe the outcome of the reaction in case conventional heating is used instead of MW heating; it is thus not possible to judge whether the short reaction times are really a benefit resulting from the combination of MW and flow.

Yu *et al.* developed 2017 a continuous-flow Fischer indole synthesis of 3-methylindole in ionic liquid (IL) 1-ethyl-3-methylimidazolium tetrafluoroborate ([emim]TFB) (Table 3, entry 5).[63] By using zinc chloride as Lewis acid catalyst, the product was obtained in low yield and with several by-products in batch. For the flow approach, a solution of phenylhydrazine and a solution of propanal, both 2 M in [emim]TFB, were pumped in the first reactor at 60 °C, with 3.0 mL/min respectively, before mixing in, *via* third stream, a solution of $ZnCl_2$ in IL. The mix was led into a coil reactor heated to 200 °C. After cooling, dilution with water and extraction with toluene, 3-methylindole was obtained in 4 minutes in 80% yield of purified product (95.3% yield for 96% pure crude product). Although the IL is claimed to be recovered to 85%, the necessity and/or the benefits of its use in this context needs to be carefully examined. ILs are not automatically green, as numerous studies showed more or less explicitly in recent years.[72, 73] Also from an equipment point of view, the use of ILs for flow chemistry should be more challenging due to their intrinsic viscosity profiles and eventual corrosive character. Moreover, DCM had to be used as solvent for ensuring functional IL recovery.

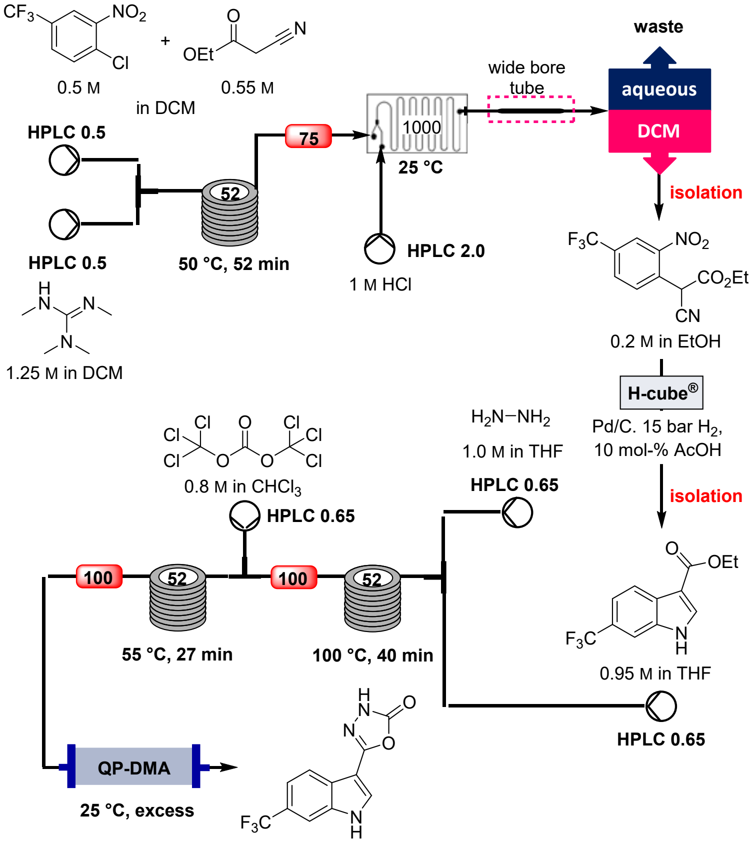
Cosford's group used the stoichiometric amount of HBr generated in their flow process to thiazoles (*vide infra*, Table 17, entry 2) for triggering indole cyclisation (Table 3, entry 6).[64] The thiazole derivative generated in the first step was mixed with a hydrazine chloride in DMF in a 1000 μL microreactor at 200 °C for 10 minutes (*vide infra*, Scheme 29). A total of 10 examples were realised including the thiazole generation step in yields between 38% and 82%.

Colombo *et al.* studied in 2011 the Reissert indole synthesis using continuous-flow hydrogenations (Table 3, entry 7).[65] In batch, the reduction of *o*-nitrophenylpyruvate needs approx. 7 hours with a disappointing 88% yield, mainly due to a secondary reaction pathway involving a *N*-hydroxyindole intermediate undergoing reduction at a much slower rate. A pilot study involving the synthesis of ethyl-1*H*-indole-2-carboxylate, using the commercially available hydrogenation reactor H-cube, provided 93% yield after 8 minutes, using 1 bar of hydrogen in an equimolar mixture of EtOH and EtOAc at 20 °C over 10% Pd/C as catalyst. The faster reaction rate in flow could be ascribed to the larger quantity of heterogeneous catalyst provided in form of the H-cube cartridges with respect to typical batch conditions. 9 compounds were synthesised this method and a full conversion was obtained for a scale-up delivering 11.1 g of indole with a mass return of 96%. The 88% purity after solvent evaporation is still not fully satisfactory and the authors do not specify if the reduced purity can be again ascribed to the secondary pathway mentioned above or to specific scaled flow-related reasons.

Jones, in 2013, reported a continuous flow version of the Hemetsberger-Knittel synthesis of indoles (Table 3, entry 8), *i.e.*, starting from azidocinnamates.[66] Good yields after chromatographic purification were obtained for 4 examples in a microfluidic reactor at 165 ºC. Relatively green xylene was used as solvent. Yields in flow were comparable to those obtained in batch, but reaction times could be shortened by a factor 12.

Kappe and co-workers reported in 2017 a reductive and continuous cyclisation of various *o*-vinylnitrobenzene motifs, in form of cinnamyl esters and stilbenes, into indoles using carbon monoxide as a terminal reductant (Table 3, entry 9).[67] The carbon monoxide reduces an initially employed palladium(II) catalyst almost instantly *in situ* to palladium(0), which settles on the inner tubing walls of the utilised flow microreactor. The optimised reaction mixture contained 2 mol% $Pd(OAc)_2$, 4 mol% of phenanthroline and 40 mol% of tributylamine in MeCN as the solvent. 16 *o*-vinylnitrobenzene motifs were converted into the corresponding indoles within 15-30 minutes reaction times and variable yields. In case of stilbenes, the conversion was found to depend on the electron density of the double bond employed; high conversions were obtained for deactivated stilbenes. The stereochemistry of the alkene was found to have negligible effect on the reaction rates.

Always in 2017, a flow-based transformation was used by Baumann *et al.* for the production of an auxin mimic-based herbicide, 5-(6-(trifluoromethyl)-1*H*-indol-3-yl)-1,3,4-oxadiazol-2(3*H*)-one (Scheme 6) (Table 3, entry 10).[68] A 3.75 M solution of 1,1,3,3-tetramethylguanidine (fully interchangeable with DBU) and a 1.65 M solution of ethyl cyanoacetate in EtOAc were reacted initially, before being mixed, *via* a third stream, with a 1.5 M solution of 2-chloro-4-trifluoronitrobenzene. While a typical coil reactor was principally usable for this transformation, larger scales were realised in an agitating cell reactor (ACR) that was chosen to avoid solubility problems that could be encountered in a typical coil reactor when using higher concentrations. To facilitate quenching and work up in flow, a static mixing element was added at the confluence point with an aqueous solution of 2 M HCl (6 mL / min) in the more robust scale-up version. The evaporation of the solvent gave the product with a yield of 94%-96%. The crude product was diluted in EtOH (0.2 M) and subjected to a subsequent reductive cyclisation using an H-cube equipped with a 10% Pd/C catalyst. While conversions were quantitative at lower flow rates without any further additives, 10 mol-% acetic acid were needed to ensure clean product formation at large throughputs with comparable performance parameters. Subsequently, a 0.95 M THF solution of the realised ethyl 6-(trifluoromethyl)-1*H*-indole-3-carboxylate as combined with a 1.0 M hydrazine solution in THF and directed in a coil reactor at 100 °C to furnish an acylhydrazine that is ultimately mixed with an additional stream containing 1,1'-carbonyldiimidazole (CDI) in THF or triphosgene in $CHCl_3$ in a second flow coil for oxadiazole formation (*vide infra*, Table 16, entry 4). Passing the crude product through a quadrapure-sulfonic acid (QP-SA)-filled washing cartridge in case of CDI or polymeric *N*,*N*-dimethylbenzylamine (QP-DMA) in case of triphosgene yielded 82% and 91%, respectively, of the target compound. The fully optimised and telescoped sequence, employing dedicated reactors for work on larger scale, saw for the necessary four steps a production rate of 3.4 g/h. Given that the first intermediate has been isolated anyway, the presented in-line work-up including the phase-separation using a wider bore tube, that could equally well be imagined to be a small diameter column reactor, could eventually be omitted and done traditionally off-line.



Scheme 6: Synthesis of indole-based auxin mimic-based herbicide in flow, showing reactors reportedly used for initial screenings of conditions. Synthesis of the 2-cyano-2-phenyl acetate intermediate is realised using the initial, easier to realise coil reactor-containing set-up. The fully optimised synthesis was realised with reactor systems developed for larger scale production.[68]

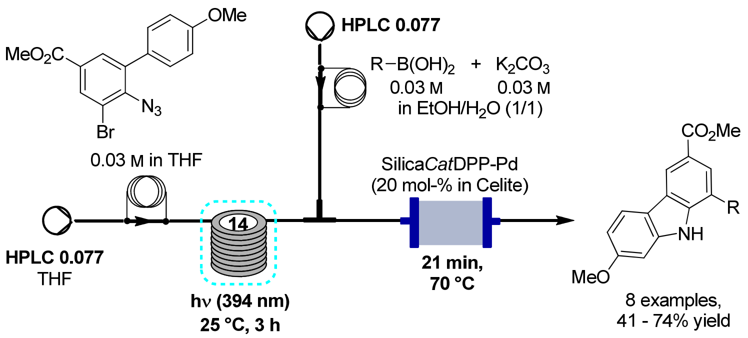
In 2019, Crifar *et al.* developed a continuous flow approach for the Heumann indole process (Table 3, entry 11),[69] which in batch requires long reaction times and high temperatures. In flow mode, solutions of the aniline and methyl bromoacetate in DMF were introduced into a tubular reactor at 110 °C, to give *N*-arylglycinate quantitatively after 90 minutes. Flow hydrolysis of the ester using NaOH in MeOH at 60 °C yielded in 15 minutes the free *N*-arylglycine quantitatively, isolated *via* a simple off-line work up. The amino acid was then subjected to Heumann cyclisation conditions with excess acetic anhydride and triethylamine in EtOAc for other 15 minutes in a tubular reactor held at 130 °C. A selection of

6 *N*-arylglycinates were converted into the corresponding indoles in shorter times with respect to the batch counterpart and more than two-fold improved yields without the need for additional purification.

Bosch and co-workers developed 2016 a green flow synthesis of pyrido[2,3-a]carbazoles, using Amberlyst IR 120 H as column-based heterogeneous catalyst to trigger a Fischer-type reaction (Table 3, entry 12).[70] The residence time for ideal space-time yields was optimised using methanolic solutions of diverse phenylhydrazines and cyclohexanone. A library of 6 examples was realised providing carbazole derivatives in high yields. The purity is not described in detail as such, but it can be assumed to be > 90% based on available NMR spectra. In batch, the preparation of pyridocarbazoles by Fischer's reaction displayed different stereochemical outcomes, depending on the use of phenylhydrazine or its hydrochloride salt, since in the latter case an initial isomerisation occurs through an opening in form of a retro-*aza*-Michael reaction, followed by a new ring closure. Interestingly, when using the flow process, such isomerisation has not been observed using either phenylhydrazine or its hydrochloride salt, suggesting an overall superior reactivity control in flow.

Collins published in 2018 two different two step-sequences yielding derivatives of the natural product clausine C (Scheme 7) (Table 3, entry 13) that was found to have antibacterial properties.[71] Rather than starting from clausine C, suitable precursors were directly transformed in clausine C derivatives using either a combination of a photochemical step and a thermally heated Suzuki coupling, or two orthogonal photochemical transformations, in which the second one consists of a light-triggered nickel-catalysed coupling. The presented protocols allowed synthesis of eight derivatives via the combination of photochemistry and Suzuki coupling, and one derivative using the doubled photochemical activation. Scheme 7 details the flow set-up for generating clausine C-derivatives using the combination of light and

Pd-catalysed transformations, starting from tailor-made azide-substituted biaryls. Compounds were obtained in moderate to good yields after column chromatographic purification.

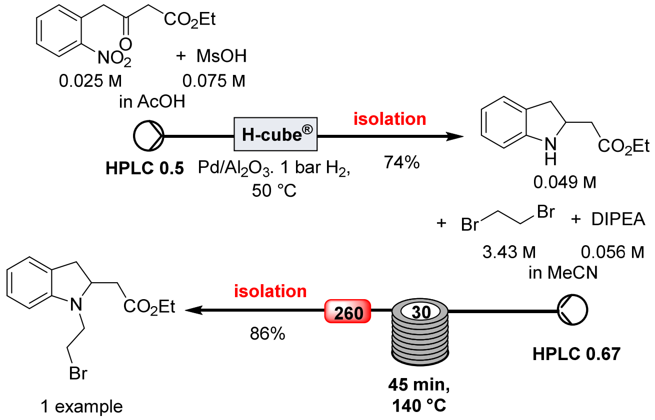


Scheme 7: Syntheses of clausine C derivatives in flow.[71]

2.2.4 Indolines and indolinones

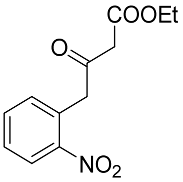
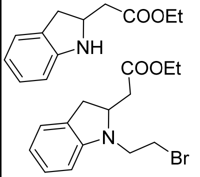
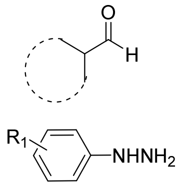
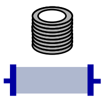
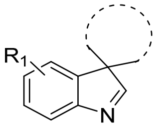
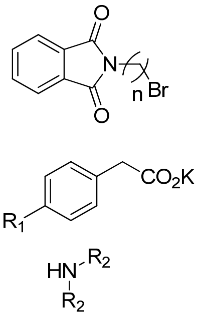
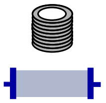
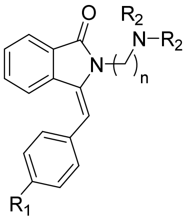
Indolines are interesting aromatic bicyclic heterocycles and are considered privileged scaffolds in pharmaceutical chemistry based on their manifold activities on different biological targets. Several indolines have been evaluated as 5-HT$_2$C receptor agonists for the treatment of obesity, as apoptosis protein inhibitors, histone deacetylase and monoacylglycerol acyltransferase-2 inhibitors. Some indolines derivatives have been found to show very good FXa inhibitory activities, and to bind progesterone receptors.[74-77] Indoline synthesis may present several hurdles, mainly related to challenging reduction as *N*-unprotected indoles often requiring harsh reaction conditions, or chemical instability as in the case of an indolenine precursor.[78]

A two-step flow process was devised by Örkényi *et al.* to synthesise indoline derivatives *via* reductive cyclisation reactions and *N*-alkylations (Scheme 8) (Table 4, entry 1), avoiding isolation of the indole intermediate.[79] Initial reductive cyclisation was achieved using an H-cube, employing atmospheric hydrogen pressure over a palladium catalyst supported by aluminium oxide, using AcOH as green solvent. An excess of methanesulfonic acid was present as a catalyst for facilitating cyclisation at 50 °C. The *N*-alkylation step with 1,2-dibromoethane, a known carcinogenic reagent, poses several challenges when performed in batch. The homogeneous *N*-alkylation route in flow used DIPEA as base and seven equivalents of 1,2-dibromoethane for achieving product formation with a conversion rate of 95% and a selectivity of 91% in less than 30 minutes. Seven equivalents of alkylating agent seem rather high, but the optimised batch process as well as flow protocols employing polymer-supported DMAP as heterogeneous base required at least 30 equivalents. The productivity of the flow reaction system was overall 200 times higher than that of the batch reaction on identical scale. Unfortunately, however, an isolated yield for the single realised product has not been reported.



Scheme 8: Flow photosynthesis of indolines according to Örkényi *et al.*[79]

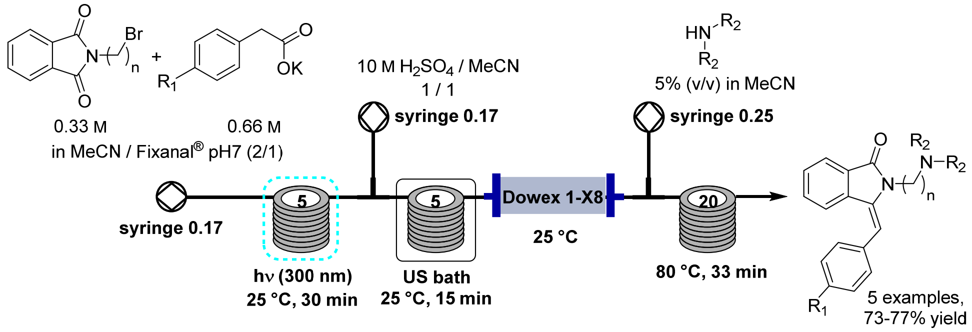
Table 4: Indolines and isoindolinones in flow.

Entry	Approach	Starting compound(s)	Reactor [a]	Structural scope	Yields [%]	Comments	Ref / year
1	reductive cyclisation reactions + *N*-alkylation		 H-cube		95[d]	1 compound, H-cube for reduction, rapid depletion of actives in column	79 / 2017
2	interrupted Fischer indoline synthesis, *via* indolenine intermediates				43-76	9 compounds	80 / 2020
3	flow photo-synthesis, dehydration, S_N		 hν [b], US [c]		73-77	5 compounds, sonication	81 / 2019

a: For reactor type acronyms, refer to Figure 1.
b: Photochemical step.
c: US – ultrasound bath.
d: Conversion yield.

An interrupted Fischer indole synthesis was used by Alfano *et al.* to produce, *via* (spiro)indolenines, (spiro)indolines in segmented continuous flow mode (Table 4, entry 2).[80] The newly developed method allowed straightforward reaction channelling towards the formation of the indolenines, thus reducing the competitive formation of side products. Indolenines could be readily reduced in a heterogeneous in-line reaction with sodium borohydride to furnish indolines. Ethanol could be used as green solvent for the synthesis. 9 examples were realised with isolated yields up to 76%. The set-up reduced also drastically the amount of solvent and time, *i.e.*, 30 minutes instead of 5 hours, needed compared to a conventional batch procedure.

A photochemical flow-synthesis of *N*-diaminoalkylated 3-arylmethylene-2,3-dihydro-1*H*-isoindolin-1-ones was realised by Oelgemöller *et al.*, telescoping several steps in flow using acetonitrile as solvent suitable to support each transformation (Scheme 9) (Table 4, entry 3).[81] *N*- (bromoalkyl) phthalimides and arylacetate (2 equiv.) were pumped into a capillary photoreactor with a flow rate allowing for 30 minutes photodecarboxylation. A 1:1 mixture of aqueous sulfuric acid (10 M) and acetonitrile was then added *via* a third stream, to induce dehydration within a tubular reactor immersed in an ultrasonic bath. Direct telescoping of the reaction mixture into a column reactor containing strongly basic Dowex 1-X8 ion exchange resin neutralised any excess of acid, before the amine was introduced into the reagent flow to perform the nucleophilic substitution at 80 °C in a last tubular reactor. Compared to the original three-step batch synthesis, the single-flow protocol produced improved the space-time yield from 50% to 77%.



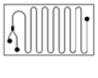
Scheme 9: Flow photosynthesis of isoindolinones as presented by Oelgemöller *et al.*[81]

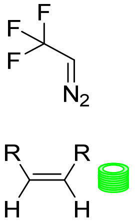
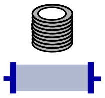
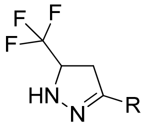
2.2.5 Pyrazoles and pyrazolines

Pyrazoles are reported to possess a wide range of biological activities such as antibacterial, anti-fungal, anti-tubercular, anticancer, and anti-viral. Moreover, pyrazole derivatives have been found to behave as angiotensin converting enzyme (ACE) inhibitors, vasodilators, neuroprotective agents, tyrosine-kinase-inhibitors, and cannabinoid-receptor antagonists. Several marketed drugs contain a pyrazole core, *i.e.*, rimonabant, sulfaphenazole, sildenafil and crizotinib. Many pyrazole derivatives have already found their application as nonsteroidal anti-inflammatory drugs, including lonazolac, celecoxib, deracoxib and mepirizole.[82] Pyrazolines, their reduced counterparts, also represent key structural templates for medicinally relevant compounds, including antifungal, anticonvulsivant, and antitumor, antibacterial and antiinflammatory agents.[83]

One of the first efforts concerning the flow synthesis of pyrazoles dates back to 2007 and was realised by Smith *et al.*, who developed a new approach to obtain 5-amino-4-cyanopyrazoles using a flow microwave set-up (Table 5, entry 1).[84] The authors used standard PTFE tubing, wrapped around a central Teflon core, to realise a tubular reactor inside a laboratory microwave not especially designed for hosting flow chemistry. A series of aryl hydrazines and ethoxymetylene malononitrile dissolved in methanol were mixed before entering into the microwave flow reactor coil to react at temperatures of 100-120 °C during residence times between 1 and 4 minutes. The output stream was passed through a first column reactor filled with benzyl amine resin as scavenger for unreacted reagents, and a second column reactor containing activated carbon to remove further impurities. A library of 14 compounds was synthesised in purities that were generally reported to be > 95% after solvent evaporation.

Table 5: Pyrazoles and pyrazolines in flow.

Entry	**Approach**	**Starting compound(s)**	**Reactor** ^{a}	**Structural scope**	**Yields[%]**	**Comments**	**Ref / year**
1	cyclo-condensation		MW ^{b}		62-96	14 compounds, in-line purification protocol	84 / 2007
2	condensation between hydrazines and *in situ* generated ynones				60-71	3 compounds	85/ 2010
3	cyclo-condensation				69	1 compound, in-line FT-IR monitoring for third stream optimisation, vitamin C as reducing agent	86 / 2016
4	*in situ* diazotation, reduction, hydrolysis, and cyclo-condensation				13-76	17 compounds, in-line FT-IR monitoring for third stream optimisation	86 / 2016
5	[3+2] cycloaddition, *in situ* diazotation				48-99	21 compounds, downstream processing steps suitable for telescoping proposed	87 / 2017
6	[3+2] cycloaddition between hydrazines and *in situ* generated vinyliden β-keto esters				62-67 (62-82^{c})	13 compounds, montmorillonite catalyst; only 3 isolated compounds	88 / 2019
7	[3+2] cycloaddition between hydrazines and *in situ* generated ynones		[MIX], 		20-74 (59-77^{c})	15 compounds (19 ynones), overall reaction time < 1 min	89 / 2019

8	[2+3] cycloadditions				59-82	6 compounds	87 / 2017

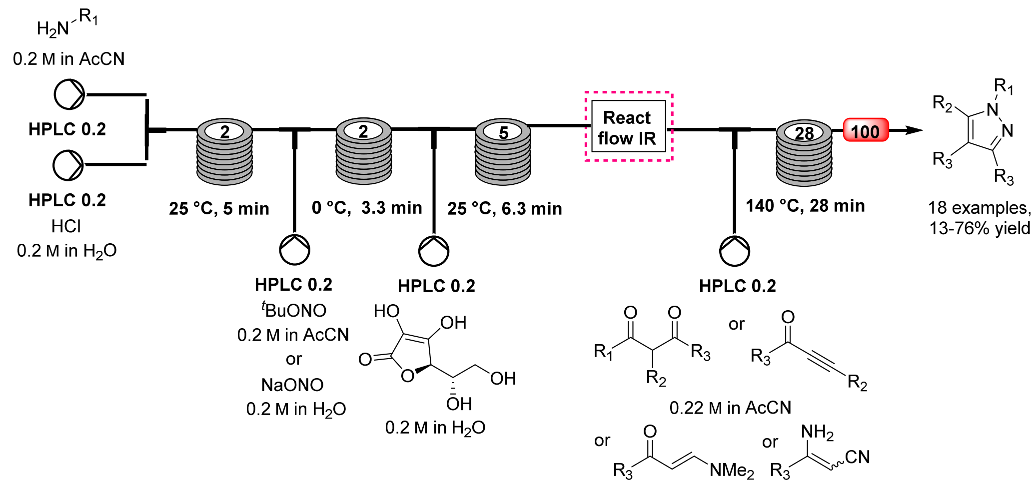
a: For reactor type acronyms, refer to Figure 1.
b: MW – microwave oven.
c: Conversion yields.

Schou, Sedelmeier and Baxendale in Ley's group published in 2010 a paper on the formation of various heterocycles in flow based on an *in situ* ynone generation (Table 5, entry 2).[85] Ynones were formed from acyl chlorides and terminal alkynes in the presence of catalytic amounts of $Pd(OAc)_2$ and DIPEA in DCM in a tubular reactor. Their immediate subsequent reaction to heterocycles was made possible by a three step in-line purification protocol using a series of three column reactors, filled with $CaCO_3$, polymer-supported sulfonic acid (QP-SA) and polymer-supported thiourea (QP-TU), respectively. When isolated, ynones were obtained sufficiently pure for further reactions in 49-94% yield after simple solvent evaporation.

In a telescoped approach, the flow-born ynones were reacted directly, *i.e.*, prior to the in-line purification sequence, in another tubular reactor with various hydrazine derivatives (Table 5, entry 2), added *via* a third stream, to yield pyrazoles in flow, which could be purified in-line using the same sequence of scavengers as described above. Nine pyrazoles in yields between 53% and 86% were obtained in high purity after solvent removal.

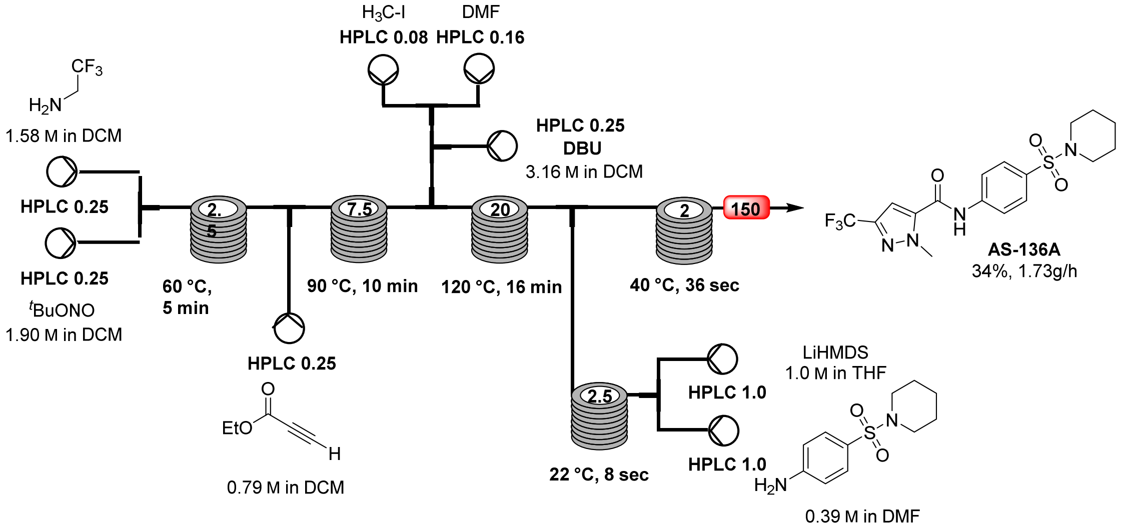
Poh *et al.* in 2016 reported on two continuous flow syntheses of pyrazole derivatives starting from anilines (Table 5, entry 3).[86] In a first approach, a metal-free amine-redox process in MeCN was used to furnish a hydrazine derivative that subsequently cyclocondensed after hydrolysis. L-ascorbic acid served as reducing agent. An in-line FT-IR-analysis tool was used both for monitoring the presence of carbonyl stretching and for controlling on the basis of the signal intensity the flow rate of the third stream containing the pentan-2,4-dione and hydrochloric acid, such as to allow for maintaining precise stoichiometry in order to reduce formation of byproducts. During 35 minutes in a second reactor coil held at 140 °C, 3,5-dimethyl-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole was obtained in 69% on a 0.8 mmol scale with respect to the diazonium salt. Unfortunately, the flow set-up was used for the production of only this single compound, whose purity as crude product was not stated.

The second telescoped flow process reported in the same work involved diazonium salts produced *in situ* from anilines, avoiding isolation of the dangerous intermediates (Scheme 10) (Table 5, entry 4).[86] A flow diazotisation step using a chloride salt of an aniline and *tert*-butyl nitrite (*t*BuONO) was performed. For the telescoped reduction step, *L*-ascorbic acid was used again as green reducing agent. Monitoring of the reduction and concomitant acquisition of the flow profile exiting the third reactor coil was achieved once more using the in-line ReactIR technology; signal feedback allowed, as in the first case, controlled addition of pentan-2,4-dione to effectuate the hydrolysis and cyclocondensation very efficiently. After 2 hours of reaction time at 140 °C, 69% of product was obtained. A library of 13 compounds was synthesised, changing starting anilines and 1,3-dicarbonyl compounds. Further four compounds were realised starting from aniline derivatives to yield pyrazole analogues of celecoxib, with yields of around 45%. The advanced control offered by the in-line monitoring contributes to both syntheses presented by Poh *et al.* most likely to an advanced productivity in terms of reduction of both byproducts and unreacted reagents. No information is provided, however, regarding the purity of the crude products in comparison to a purity obtained without (such unfortunately rather costly) in-line control.



Scheme 10: Telescoped flow process yielding pyrazoles as proposed by Poh *et al.*[86] *N.B:* The shown telescoped synthesis made use of the in-line FT-IR only for monitoring purposes during the steady state production, addition of the 1,3-dicarbponyl component was not controlled based on acquired signal intensity as it was done in non-telescoped version at smaller scales. The FT-IR tool has therefore been labelled as not strictly necessary here.

Britton and Jamison developed in 2017 a continuous flow synthesis for pyrazoles and pyrazolines decorated with CF_2H or CF_3-moieties at C-3, compounds common to agrochemicals and pharmaceuticals (Table 5, entry 5).[87] A first reactor allows for diazotation of 2,2-difluoroethan-1-amine or 2,2,2-trifluoroethan-1-amine using *t*BuONO in DCM at 60 °C in the presence of catalytic amounts of AcOH. Substituted alkynes were added *via* a third stream to react with the *in situ*-generated fluorinated diazomethane derivatives. A library of 15 3-substituted pyrazoles was synthesised starting from differently substituted alkynes with yields ranging from 48% to 99%. Alkynes with steric hindrance provided the lowest yields. Adjusting temperature and reaction time, a second library of additional six 2,2,2-trifluoromethyl-pyrazoles on the basis of different terminal arylalkynes is reported, with yield between 53% and 93%. A realised scale up provided ethyl 3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate with 2.16 g/h and 87% yield. In addition, several modules that allowed downstream functionalisation, were presented to reach pharmaceutical and agrochemical products. Such downstream functionalisation steps have not been reported in a telescoped approach though, but were demonstrated as add-on functionalisation after intermediate isolation of pyrazoles synthesised as described above. In-line purification protocols have not been developed in course with this downstream processing tool-kit. The consequences of missing in-line purifications were observed in a nevertheless remarkable telescoped multistep approach to AS-136A (Scheme 11), an anti-measles pharmaceutical, which was obtained with 1.73 g/h efficacy in 34% yield and a purity of 72% without final purification. The decreased yield in comparison to a non-telescoped flow approach that saw isolation and purification of intermediates and gave 75% of the product with an impressive reported purity of 99%, could be traced back to non-reactive reagent or by-product that need to be carried through the synthesis. Furthermore, some technical issues were encountered reducing especially the effectiveness of the initial pyrazole formation (75%-87% compared to 99%), as uneven fluid delivery observed at high back pressures.



Scheme 11: Flow synthesis of flow synthesis of pyrazoles as proposed by Jamison *et coll.*[87]

While the batch-typical use of Ag_2O and NaOAc could be avoided, leading to an economically more viable approach, the use of DCM as solvent remains a bottleneck. The study is informative also from a non-chemical point of view, since it openly discusses some practical problems eventually encountered with reactor components.

The basic set-up used for the production of pyrazoles reported by Britton and colleagues as discussed above could be used by the same group for the flow-synthesis of pyrazolines (Table 5, entry 8).[87]

Kobayashi *et coll.* presented recently a flow synthesis to pyrazoles starting from a nickel-montmorillonite-catalysed vinylidation of 1,3-dicarbonyl compounds *via* orthoester condensation in the presence of acetic acid anhydride (Table 5, entry 6).[88] The heterogeneous catalyst was loaded into a column reactor held at 90 °C, and condensation was achieved in the additional presence of acetic acid anhydride at lower flow rates of 0.1 mL/min in DCE as solvent. 13 compounds could be realised with conversions between 72% and 97% conversions. The crude products could be directly used for the generation of pyrazoles in a homogeneous [3+2]-reaction at –20 °C in flow, mixing them with alkyl- and arylhydrazines. THF was used as non-green solvent for this step. Yields were determined *via* ^{1}H NMR for a library of thirteen compounds, including the pyrazole core of active bixafen that formed in high regioselectivities; some isolated yields were reported in the range of 65%.

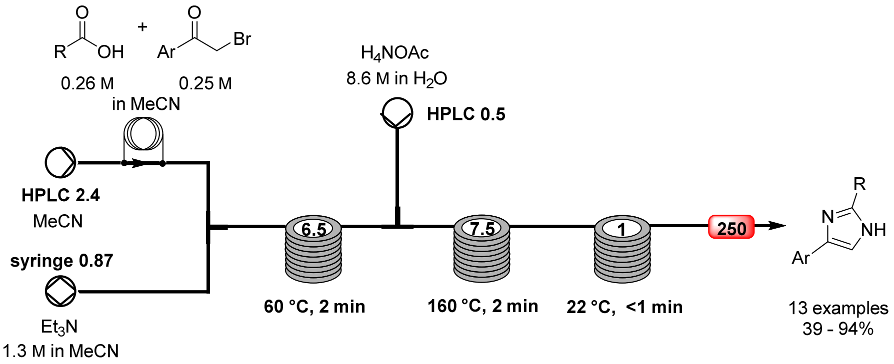
THF was also used by Lin *et coll.* for their 2019 flow pyrazole formation *via* classical [2+3]-cycloaddition on the basis of *in situ*-generated ynones (Table 5, entry 7).[89] A microfluidic set-up with dedicating mixing devices for stream combinations were used. In a first reaction, terminal alkynes were lithiated by *n*-butyllithium at 20 °C in THF, using high flow rates of 6.4 mL/min. After approx. 2.5 seconds, the anion was combined, again in a dedicated mixing device, with a third stream of acyl chlorides, again at 20 °C with high overall flow rate of 9.4 mL/min. Ynone formation proceeded in 2.5 seconds. This approach generated 19 ynones in isolated yields between 40% and 93% after work-up and purification. The ynone formation could be telescoped to pyrazole formation by adding a fourth stream that delivered the hydrazines to the stream of ynones through a mixing device. Cycloaddition took place then in approx. eleven seconds at 70 °C. A library of 15 pyrazoles was realised in variable yields after work-up and purification; lower yields were generally observed for *N*-phenylhydrazine-derived examples.

The study is impressive in terms of the minimum time needed for the overall process that properly benefits from the use of the dedicated equipment. The synthesis as such, in light of other reports discussed in here, seems possible also using simpler T-pieces for mixing, for example, but would probably take longer and require good temperature control for assuring more of less adiabatic processes at least for the lithiation step to avoid excessive by-product formation.

2.2.6 Imidazoles and benzimidazole-derivatives

The imidazole ring is found in important natural products, including purine, histamine, histidine, and nucleic acids. Imidazole derivatives have been reported to possess a broad spectrum of biological activities, including antibacterial, anticancer, antitubercular, antifungal, analgesic, and anti-HIV activities.[90] Their benzimidazole analogues are equally active, with reported antioxidant, antibacterial, antituberculosis, antifungal, anti-inflammatory and anticonvulsant activities.[91] Benzimidazol-2-one also represents a privileged azaheterocyclic scaffold in medicinal chemistry, since benzimidazolone-based templates are embedded in a significant number of active pharmaceutical ingredients, including flibanserin, domperidone, and sumanirole.[92, 93] An effectively scalable high-quality synthesis of these molecules thus has significant impact in medicinal studies.

In 2015, Carneiro *et al.* developed a continuous flow synthesis of 1*H*-4-substituted imidazoles starting from α-bromoacetophenones and carboxylic acids (Scheme 12) (Table 6, entry 1).[94] This work followed by and large a route published by May *et al.* in 2012,[95] in which an α-bromoketone was converted into the corresponding amine by a nucleophilic substitution with sodium azide, subsequent reduction of the azide with triphenylphosphine, acetylation of the resulting amine and ammonium acetate-catalysed formation of imidazole. A solution of α-bromoacetophenone and *N*-Boc-L-proline was mixed with a solution of Et_3N and passed through a tubular reactor at 60 °C to form first the α-acyloxy ketone, that was subsequently reacted with aqueous NH_4OAc, added *via* a third stream, at 160 °C for 5 minutes in a tubular reactor. Through an acidic work up effectuated offline, *tert*-butyl (*S*)-2-(4-phenyl-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate was obtained in 81%. Interestingly, this yield was reported to be 10% lower than the one achieved in the corresponding batch process; however, no potential reasons are discussed. The total reaction time in the reactor was 4 minutes, realizing 0.15 g/min of product in a reactor with a total residence volume of approx. 14 mL. The protocol was applied to 13 imidazole derivatives; notably, it also proved to be useful for the synthesis of the symmetric central unit of daclatasvir an inhibitor of the viral phosphoprotein NS5A, which was produced here in 71% yield allowing with a drastic improvement of the space-time yield.[96]



Scheme 12: Flow synthesis of 1*H*-4-substituted imidazoles by Carneiro *et al*.[94]

Table 6: Imidazoles and benzimidazoles in flow.

Entry	**Approach**	**Starting compound(s)**	**Reactor** [a]	**Structural scope**	**Yields [%]**	**Comments**	**Ref / year**
1	cyclocondensation of *in situ*-generated acyloxy ketones				39-94	13 compounds, telescoped reaction	94 / 2015
2	cyclo-condensation				80-95	16 compounds, rather high T, 10-fold excess of NH_4OAc	97 / 2010
3	cyclo-condensation for imidazole motif				20-59	12 compounds	98 / 2017
4	cyclocarbonylation				98	1 compound, very high T asking for stainless steel reactor; in-line UV detector	99 / 2019

a: For reactor type acronyms, refer to Figure 1.

Jia *et coll.* presented in 2010 a simple route to imidazoles starting from symmetrically substituted 1,2-diketones and aldehydes in the presence of an excess of ammonium acetate (Table 6, entry 2).[97] The reactions took place in a microreactor at 180° C, using acetic acid as solvent. 16 compounds were realised, with rather high isolated yields between 80% and 95%.

Cosford in 2017 presented an extensive work regarding the flow synthesis of oxadiazoles with different substitution patterns (*vide infra*, Table 16, entries 2 and 3).[98] Among these patterns was also an imidazolyl group. The imidazole-motif was realised combining in a microreactor a solution of pyridin-2-amine and 3-bromo-2-oxopropanoic acid in DMA at 100 °C, to obtain imidazo[1,2-a]pyridine-2- carboxylic acid in approx. 30 minutes. This acid was then used for oxadiazole formation as described below.

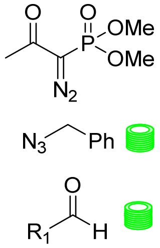
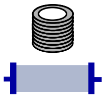
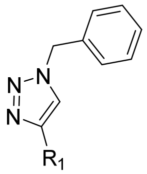
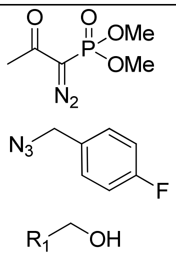
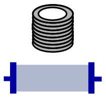
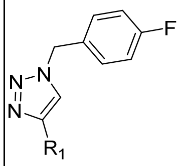
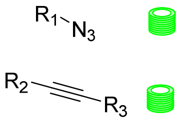
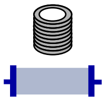
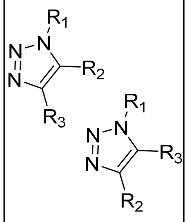
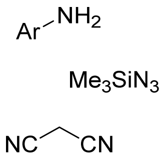
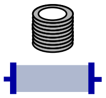
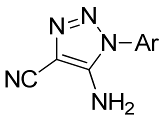
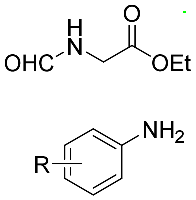
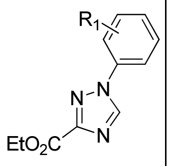
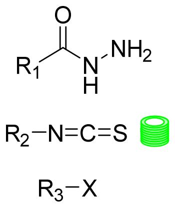
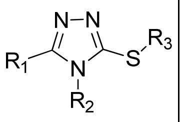
The benzimidazol-2-one motif was targeted 2019 by Mostarda *et al*. employing a CDI-promoted cyclocarbonylation of *o*-phenylenediamine (Table 6, entry 4).[99] Starting from an existing synthesis in batch,[100] the developed flow process used medium concentrated solutions of *o*-phenylenediamine in THF and CDI in a 7/3 (v/v) mixture of THF and PEG^{300}, to ensure solubility during the reaction. The high operating temperatures (210 °C) justify the choice of a tubular stainless-steel reactor. Product formation and purity were monitored by an in-line UV detector, indicating high purities of generated products (> 95%) under optimised conditions. The developed protocol has been successfully applied to the multigram flow synthesis of the *N*-(2-chlorobenzyl)-5-cyan-benzimidazol-2-one, a key intermediate for the preparation of new anti-inflammatory drugs, especially as inhibitors of the FLAP enzyme, essential in the synthesis of leukotrienes. The flow synthesis of benzimidazol-2-one clearly outperformed the batch synthesis: reaction time decreased from 16 hours in batch to 33 minutes of residence time in the reactor, the yield increased from 40% in batch to 98% in flow.

2.2.7 Triazoles

Triazoles play an important role as motif in active ingredients in pharmaceuticals and agrochemicals. This privileged scaffold has been reported to be part of structures that possess wide variety of biological activity, such as anti-fungal, antibacterial, antitubercular, anti-inflammatory, analgesic, anticancer and antiviral.[101, 102] Notably, 1,2,3-triazoles are crucial scaffolds for 'click chemistry' applications through straightforward azide-alkyne cycloadditions, following the principles introduced by Sharpless in 2001 for the rapid preparation of large libraries of compounds for drug discovery purposes. Flow synthesis routes to triazoles have recently been reviewed in a dedicated article.[103]

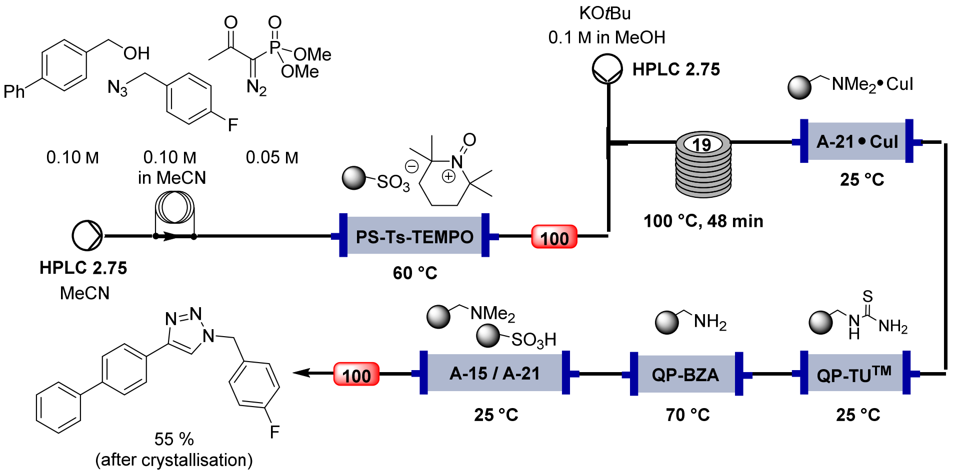
Ley *et coll.* demonstrated the importance of immobilised reagents and scavenger resins in the continuous multicomponent flow synthesis of 1,2,3-triazoles, allowing for isolation of products without further work-up or purification (Table 7, entry 1).[104] A solution of aldehyde, Ohira-Bestmann-reagent and azide in MeCN was mixed with potassium *tert*-butoxide in methanol and passed into a reactor coil at 100 °C. After a residence time of 30 minutes, the stream containing the flow-born alkyne necessary for the [3+2] reaction towards the triazole unit, was directed through a series of scavenger (A-15) columns: quadrapure-benzylamine (QP-BZA) resin was used at 70 °C to remove the excess aldehyde, Amberlist-15 sulfonic acid served to remove the base, and Amberlist-21 (A-21) dimethyl amine then removed any acidic material. Noteworthy, the use of the two polymer-supported reagents A-21 and A-15 allowed for a mixing of both acid and base scavenger in a single column and thus a double purification in a single passage. The purified stream was then passed through a column containing a copper(I) as catalyst enabling the [3+2]-cycloaddition on A-21 resin as support material. Leached metal catalyst could be effectively removed from the triazole-containing stream using quadrapure-thiourea (QP-TU). Two triazoles products were realised with this fully telescoped set-up, and isolated after simple crystallisation in moderate yields.

Table 7: Triazoles in flow.

Entry	Approach	Starting compound(s)	Reactor [a]	Structural scope	Yields [%]	Comments	Ref / year
1	[3+2] cycloaddition				62, 69	2 compounds, in-line purification	104 / 2009
2	[3+2] cycloaddition				55	1 compound, heterogeneous in-line oxidation, extensive in-line purification	104 / 2009
3	[3+2] cycloaddition				21-98	21 compounds, high pressures in-line scavenging of leached copper	105 / 2014
4	[3+2] cycloaddition, *in situ* azide formation				53-85	13 compounds, in-line purification, fully automated library generation	106 / 2011
5	[3+2] cycloaddition, *in situ* isocyanide formation and diazotization				53-71	8 compounds	107 / 2015
6	[3+2] cycloaddition				12-94	18 compounds, scale-up demonstrated	108 / 2017

a: For reactor type acronyms, refer to Figure 1.

As a further development, the same paper describes the extension of the flow process to an additional oxidation step, such as to allow starting from alcohols instead of aldehydes (Scheme 13) (Table 7, entry 2). To this end, in a single show case only though, activated alcohol biphenyl-4-ylmethanol, Ohira-Bestmann reagent and 1-(azidomethyl)-4-fluorobenzene in MeCN were first passed through a column filled with PS-TsO-TEMPO, held at 60 °C, to oxidise the alcohol *in situ*. The output stream was the directly mixed with potassium *tert*-butoxide in methanol, and this mixture entered as before a reactor coil heated to 100 °C to trigger the Seyferth-Gilbert homologation. After a residence time of 48 minutes, the cycloaddition was achieved by directly passing the stream through a column containing, as before, A-21-CuI. Unlike in the initial set-up, all necessary purifications were achieved by a series of four columns containing the scavengers used before, *i.e.*, QP-TU, QP-BZA, A-15 and A-21. Applying all purifications in series at the end holds the advantage that the plug of reactants entering into the metal-catalyst containing column is less dispersed, guaranteeing hence a higher concentration of the two reactants for the cycloaddition step. It is needless to say that such a change of positioning of the scavengers is possible only in case the chemistries applied before are robust enough/indifferent enough to an increasing amount of impurities. The triazole 4-([1,1'-biphenyl]-4-yl)-1-(4-fluorobenzyl)-1*H*-1,2,3-triazole was obtained in 55% yield after crystallisation.



Scheme 13: Flow synthesis of triazoles by Ley *et al.*[104]

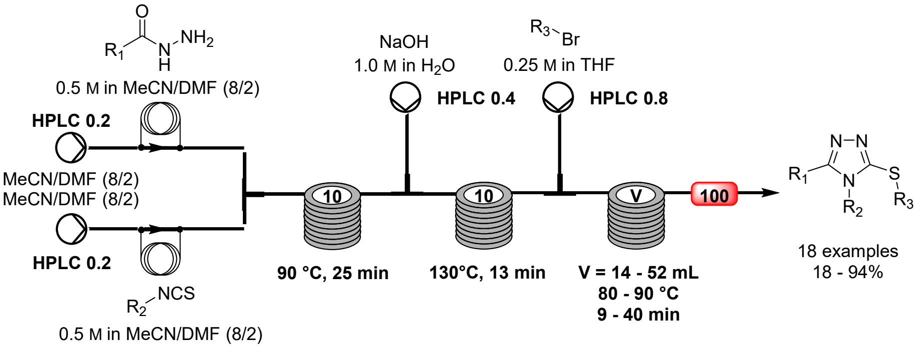
Fülöp *et coll.* tested a bimetallic catalyst system made from copper and iron in [3+2]-cycloaddition reactions between alkynes and azides (Table 7, entry 3).[105] The catalyst, comprising copper nanoparticles deposited on an iron core, was placed in a stainless steel column reactor. Using DCM as solvent, reactions took then place at ambient temperature and 100 bar. Depending on the nature and reactivity of the tested reaction partners, catalytic amounts of DIPEA or acetic acid were added. Eventually leached copper particles could be removed from the exiting stream using a column containing porous iron. The set-up hosted a wide range of substitution patterns. Isolated yields for 21 realised products raged from 21% to 98%. Products were reported to be sufficiently pure without additional purifications.

In 2011, Smith *et al.* developed an automated multistep flow synthesis of 5-amino-4-cyano-1,2,3-triazoles from aryl azides and malononitrile (Table 7, entry 4).[106] Arylamine/trimethylsilyl azide in a 1:1 mixture in MeCN, and *t*BuONO in MeCN were passed through a reactor coil heated to 60 °C, such as to maintain a residence time of 50 minutes, followed by a column reactor containing again the aforementioned A-15/A-21 in-line purification mix, to give aryl azides in decent purity. In order to react the exiting azide stream, an immobilised malononitrile was used, realised by simply generating the corresponding anion using a strong base on polymeric support for creating a polymeric malononitrile salt. This salt reacted readily at 60 °C with the azides to give the target triazole motifs. Some triazoles were found to stick in anionic form on the column themselves, and malononitrile in MeCN was used in these cases to conveniently release these triazoles from the resin while regenerating the column at the same time. This procedure allowed for reuse of the column in six consecutive reactions. The ‘solvent’ malononitrile was recovered using a conventional rotary evaporator, to generate 5-amino-4-cyano-1,2,3-triazoles with >90% purity. The synthetic approach was used to demonstrate the automation potential connected to continuous flow chemistry processing. A library of 13 compounds on the basis of this multistep flow process was successfully realised in a fully automated fashion, conducting up to six sequential reactions over 55 hours with no manual input in satisfying to good yields and high purities of generally >90% for all compounds.

Noteworthy exceptions were found when reacting *para*-methoxy and *para*-nitroanilines, which required modifications in the work-up procedure due to the physicochemical properties of the products: evaporation of malononitrile could be substituted with an in-line purification using polymer-supported 1,5,6-triazabicyclo[4.4.0]dec-5-ene polystyrene (PS-TBD).

Relying as well on a [3+2] cycloaddition approach, Baxendale's team devised a telescoped and convergent multistep flow synthesis of 1,2,4-triazoles based on the *in situ* generation of ethyl isocyanoacetate (Table 7, entry 5).[107] A solution of a mixture of *N*-formylglycine, DIPEA, DMAP (1:2:0.3) in DCM, was mixed with a solution of triphosgene as dehydrating agent in DCM and passed through a coil reactor. After a residence time of 20 minutes, ethylisocyanoacetate formed almost quantitatively at room temperature. In parallel, aryl diazonium salts were formed *in situ*. Using equal flow rates and timing, the two streams transporting the *in situ*-generated reagents could be united in flow to pass through a third reactor coil for initial mixing. The stream was then diluted with EtOH to assure sufficient ulterior mixing with a fourth steam of aqueous potassium carbonate. Mixing of the difficult solvent mixture was additionally forced using a static mixer before cyclisation was achieved in an ulterior reactor coil at 75 °C over 52 minutes. The methodology was successfully applied to 8 1,2,4-triazole derivatives, providing products in good yields and high purity grade after solvent evaporation and trituration.

In 2017, Damião *et al.* synthesised substituted 3-thio-1,2,4-triazoles in a linear telescoped three-step continuous flow process starting from hydrazides, isothiocyanates and alkyl/aryl halides (Scheme 14) (Table 7, entry 6).[108] A solution of phenylhydrazide in MeCN/DMF (8:2) was initially mixed with a solution of phenylisothiocyanate in the same solvent system. The newly generated thiosemicarbazides were mixed with an aqueous solution of NaOH added *via* a third stream, allowing the cyclisation in a tubular reactor at 130 °C in 38 minutes. The final step consisted in an *S*-alkylation with benzyl bromide, dissolved in THF, *via* a fourth stream. To explore the scope of this approach, different alkyl/aryl hydrazides, isothiocyanates and alkyl/benzyl halides were tested, and a library of 18 compounds was synthesised, with variable yields and in less than one hour per compound. A scale-up for the production of 3-(benzylthio)-4,5-diphenyl-4*H*-1,2,4-triazole was demonstrated, with reduced concentrations of the hydrazide and the isothiocyanate, and increased temperature of the first reactor to 100 °C, furnishing 3.5 grams *i.e.*, 93% yield, after off-line purification within 3 hours.



Scheme 14: Telescoped flow sequence for production of substituted 3-thio-1,2,4-triazoles developed by Damião *et al.*[108]

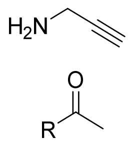
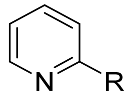
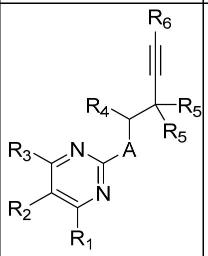
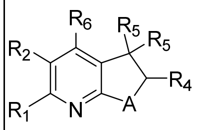
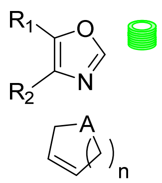
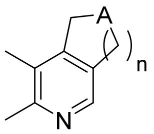
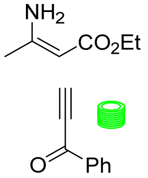
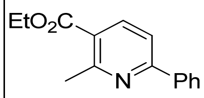
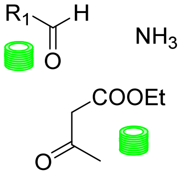
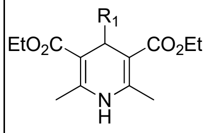
2.2.8 Pyridines and dihydropyridines

Pyridines derivatives display a wide range of biological activities, including antimicrobial, antiviral, antioxidant, antidiabetic, anticancer, antimalarial and anti-inflammatory properties.[109, 110] Their partially reduced dihydropyridine derivative (DHPs) show relevant important as well, being embedded in the structures of medicinally relevant agents against cardiovascular diseases, thrombosis and atherogenesis.[110]

In 2009, Abahmane *et al.* reported a two-step flow synthesis generating α-substituted pyridines starting from methyl ketones and propargylamines; both initial imine/enamine formation as well as finalizing cyclisation were catalysed by heterogeneous catalysts that were placed in microchannels (Table 8, entry

1).[111] This design allowed for an effective mixing directly in the channels housing the densely packed catalyst bed. This design represents an interesting merger/hybrid of a very long column and a tubular reactor, and as such an innovative reactor design that could nevertheless be eventually reproduced using non-standard flow chemistry equipment. Initial condensation was achieved using montmorillonite as catalyst in the presence of molecular sieves. Full conversions were obtained at exact stoichiometric amounts of reactants. In case of aromatic ketones, two-fold excess of propargylamine and higher temperatures, *i.e.*, 125 °C were needed to achieve similar condensation efficiency in 20 minutes. The oxidative cyclisation was achieved using gold nanoparticles sputtered on alumina particles as capillary-based catalyst. A slight excess of oxygen was introduced in form of compressed air into the system. Cyclisation was achieved at 125 °C within 20 seconds. Although isolated yields are not reported, excellent conversions were obtained for the 3 proposed examples, with a substantial improvement in space-time yields with respect to the batch counterpart.

Table 8: Pyridines and dihydropyridines.

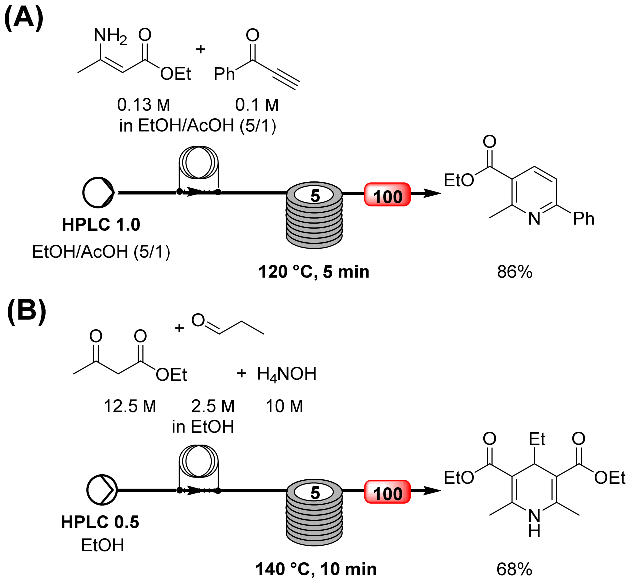
Entry	Approach	Starting compound(s)	Reactor [a]	Structural scope	Yields [%]	Comments	Ref / year
1	condensation, cyclisation, oxidation		 HC [b]		94-100 [c]	3 compounds, catalyst filled in tubings instead of columns	111 / 2009
2	inverse-electron-demand hetero-Diels–Alder				16-95	21 compounds, very high temperatures needed	112 / 2012
3	Kondrat'eva reaction				11-76	12 compounds, very high temperatures needed	113 / 2013
4	Bohlmann and Rahtz pyridine synthesis		 MW [b]		76[c] (w/ MW), 86[c] (w/o MW)	1 compound, necessity of MW not clear	114 / 2013
5	4-component Hantzsch dihydro-pyridine (DHP) synthesis		 MW [b]		43-85	3 compounds	114 / 2013

a: For reactor type acronyms, refer to Figure 1.
b: HC – heterogeneous catalysis.
c: Conversion yield.

In 2012, Martin *et coll.* developed synthesis for annulated pyridines *via* intramolecular inverse-electron-demand hetero-Diels-Alder reactions in flow (Table 8, entry 2).[112] Solution of pyrimidine alkynes as starting material in toluene containing 1% (v/v) pentan-3-one were pumped through a stainless steel coil reactor that was heated to 310 °C, using a conventional GC oven as a reliable method to reach the required extreme operational temperature exceeding the typical temperature range achievable by standard convection-based flow reactors. The solvent was kept in liquid phase by means of a 750 psi back pressure regulator. Starting from various pyrimidine alkynes, the authors generated a library of 21 annulated pyridines in 30 minutes reactions with variable results in terms of isolated yields of purified products. As a general trend, lower yields were observed in case of electron richer pyrimidine moieties.

Martin and Britton *et coll.* could use the above described stainless steel tubular reactor within the GC-oven for effectuating the production of annulated pyridines *via* an inverse-electron-demand Kondrat'eva reaction in flow (Table 8, entry 3).[113] Consequently, starting solutions consisted of a mixture of dienophile and phenyloxazole in toluene. Optimised reactions conditions required heating of the coil reactor to 230 °C and allowing for a residence time of 1 hour. The alkene had to be used in a ten-fold excess though for optimum results. Also in this case, the outcome for the 13 examples reported in terms of isolated yields of purified materials strongly relied upon the electronic situation of the starting materials. No information regarding the potential recovery of the starting material is made, nor whether the excess is necessary for compensating background polymerisation of starting material.

Bagley *et al.* developed in 2013 a continuous flow synthesis of pyridines and dihydropyridines (Scheme 15A) (Table 8, entry 4).[114] Applying a Bohlmann and Rahtz synthesis of pyridines, *i.e.*, starting from enamine and an ethinyl carbonyl compound. A coil reactor was used through which the compound mixture passed during 5 minutes, furnishing the product in a yield of 86%. This yield was significantly higher than that obtained when the set-up was changed using a MW-induced heating. On the basis of the single compound described one would have to state that MW-heating was ineffective; it can neither be excluded, however, that the practical realisation of the MW-heating, *i.e.*, using a bed of sand through which the reaction mixture passes, prevented better results in this case (*vide infra*).



Scheme 15: Bohlmann and Rahtz (A) synthesis of pyridines and 4-component Hantzsch synthesis of DHPs in flow as indicated by Bagley *et al.*[114] The presence of the sample loops and the back pressure regulator have been assumed, in light of a lack of specification, based on the flow instrument and conditions used.

A 4-component Hantzsch DHP synthesis is similar to the Bohlmann-Rahtz reaction, and the above developed flow process could consequently be adopted for DHP syntheses (Scheme 15B, Table 8, entry 5). A solution of ammonium hydroxide, benzaldehyde or propionaldehyde and acetoacetate in EtOH was passed over a timeframe of 10 minutes into a reactor coil held at 140 °C, to give, *via* a rate-limiting *in situ* enamine generation, diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate in 43% yield, and diethyl 4-ethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate in 68% yield. When the 4-component Hantzsch reaction was realised in the presence of MW-heating to 120 °C in the microwave flow reactor (*side supra*, preceding paragraph), diethyl 2,6-dimethyl-4-(phenylethynyl)-1,4-dihydropyridine-3,5-dicarboxylate was obtained in 85% yield. Interestingly hence, in this case, MW heating led to a superior result.

2.2.9 Pyrimidines, pyrimidinones and dihydropyrimidones

The pyrimidine ring is present in thymine, cytosine, and uracil, which are among the key building blocks of nucleic acids DNA and/or RNA. Other naturally occurring compounds display a pyrimidine unit in their structure, such as thiamine, and alloxan. The pyrimidine substructure and its fused derivatives are embedded in a wide range of drug candidates, including anticancer and anticonvulsant agents, antivirals, antibacterials and antibiotics. Moreover, several marketed drugs feature a pyrimidine scaffold, *i.e.*, 5-fluorouracil, idoxuridine, zidovudine, trimethoprim, sulphadoxin, prazosin, and phenobarbitone, among others.[115]

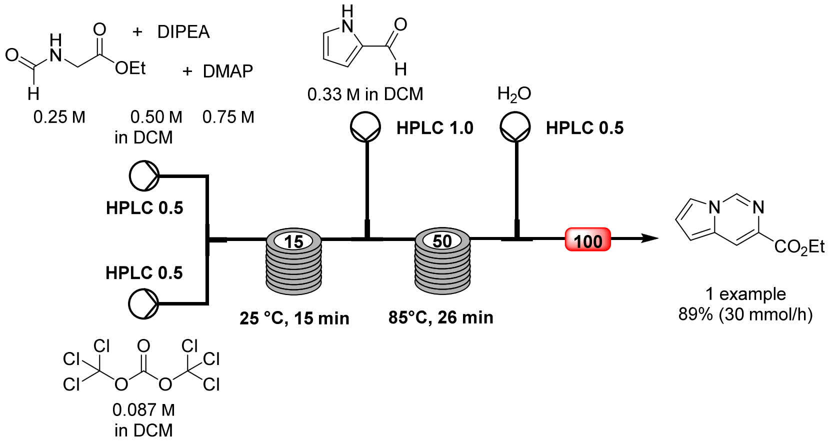
In their aforementioned (*vide supra*, Table 5, entry 2) paper on ynones as starting point for the formation of various heterocycles,[85] Baxendale et al. reported also a pyrimidine-structures (Table 9, entry 1). Two *in-situ*-generated ynones were reacted with benzamidines in a tubular reactor to furnish two phenyl-substituted pyrimidines in 67% and 60% yield. Using slightly harsher conditions, reaction with guanidine hydrochloride was possible, yielding an amine-substituted pyrimidine in 71%. Preparation of pyrimidines was achieved in DCM.

Table 9: Pyrimidines, pyrimidinones and dihydropyrimidinones in flow.

Entry	**Approach**	**Starting compound(s)**	**Reactor** [a]	**Structural scope**	**Yields [%]**	**Comments**	**Ref / year**
1	condensation between amidines with *in situ* generated ynones				60-71	3 compounds	85 / 2010
2	*in situ* generation of ethyl isocyanoacetate for cyclisation				85	1 compound, scale-up demonstrated	107 / 2015
3	*retro*-Diels-Alder				30-97	6 compounds	116, 117 / 2018
4	cyclocondensation for thiazole, then Biginelli reaction				39-46 for DHPM	8 Biginelli products in telescoped manner using third stream, connected to thiazole formation (Table 17)	118 / 2011

a: For reactor type acronyms, refer to Figure 1.

Bauman *et al.* reported the telescoped synthesis of pyrrolo-[1,2-c]pyrimidines in 2015 (Scheme 16) (Table 9, entry 2), based on *in situ*-generated ethyl isocyanoacetate once more (*vide supra*, Table 7, entry 4).[107] Combination of the *in situ*-generated isocyanoacetate with a third stream containing pyrrole-2-carboxaldehyde and piperidine in DCM in a coil reactor at 85 °C for 26 minutes provided the target pyrrolo-[1,2-c]pyrimidine in 85% isolable yield and with useful purity without the need for off-line purification (>95%). Only one compound was realised *via* this route unfortunately, but a scale-up experiment demonstrated that in 8 hours of continuous run, the reactor set-up delivers ~30 g of product.



Scheme 16: Synthesis of pyrrolo-[1,2-c]pyrimidines in flow by Baumann *et al.*[107]

Pyrimidinone is an important privileged scaffold, present in the structures of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Pyrimidinone-based nucleosides play a key role in drug discovery as anticancer, antifungal, antiallergic and antihistaminic and antiviral agents.[119] Over years, Biginelli type dihydropyrimidones have also received growing attention due to the interesting pharmacological profiles associated with this scaffold. Particularly, dihydropirimidinone-based compounds were recently developed as anti-inflammatory, antimicrobial, antiviral and anticancer agents, among others.[120]

The *retro*-Diels-Alder reaction is a privileged strategy for the synthesis of pyrimidinone scaffolds that was consequently chosen in 2018 by Nekkaa *et al.* who reported in two publications the flow-based synthesis of pyrrolopyrimidinone, pyrimidoisoindole, and spiropyrimidinone derivatives through continuous flow enantiodivergent and enantiocontrolled *retro*-Diels-Alder reactions (Table 9, entry 3).[116, 117] Starting from different fused tricyclic or tetracyclic precursors, which can partly be realised in a flow format (*vide infra*), a library of 11 pyrimidinones was obtained. The excellent isolated yields for the proposed examples were considerably higher than the ones obtained with 'conventional' MW-assisted batch synthesis routes by the same group as cited in the paper. Fine-tuning the conditions for the thermally-driven *retro*-Diels-Alder process resulted in residence times between 10-30 minutes, and temperatures ranging from 120 °C to 250 °C. The choice of solvent not only relied upon compatibility with the required temperatures, but also on the solubility of the starting materials, so that best options were represented by MeCN, toluene and MeOH. The purity is not described in detail as such, but it can be assumed to be > 90% based on available NMR spectra. The weak point of the as such elegant *retro*-Diels Alder approach is the inevitable complexity of the starting materials.

Pagano *et al.* in 2011, synthesised thiazole-containing dihydropyrimidinones (DHPMs) in flow (Table 9, entry 4).[118] Flow-born thiazoles (*vide infra*, Table 17, entry 1) produced in a reactor chip in 3.75 minutes were mixed with 3-hydroxybenzaldehyde and urea, *via* addition of a third stream, and reacted in a glass reactor heated to 200 °C to give DHPMs. After residence times of 10 minutes, a library of 8 compounds was realised in yields of approx. 45%. In light of the reported yields for the initial thiazole step, it was possible to establish that the following Biginelli reaction itself proceeded actually in approx. 70% yield.

2.2.10 Quinolines, isoquinolines and tetrahydroquinolines

Quinoline is an extremely versatile bicyclic scaffold with huge therapeutic potential. Quinoline ring has a primary role as privileged scaffold owing to its presence as substructure of several agents of choice for the treatment of various diseases, particularly cancer and malaria. Moreover, quinoline-based compounds exhibit a broad spectrum of antimicrobial, anti-inflammatory, and antidiabetic activities.[121, 122]

Biological activities and target specificities of quinoline derivatives are strongly dependent on the nature and position of the substitution pattern on the quinoline ring, which is also associated to a variety of different chemistries. Qi *et al*. presented in 2018 a flow protocol on the fluorine-mediated regioselective chlorination of quinolines and isoquinolines (Table 10, entry 1).[123] Differently substituted quinolines were reacted in a microfluidic chip in MeCN at 80 °C in the presence of Selectfluor with various chlorinating agents. Best results were obtained for 1,3-dichloro-5,5-dimethylhydantoin as chlorine source. Space-time yields drastically improved and isolated yields ranged from moderate to high. Tested quinoline substitution patterns included alkyl groups, bromine, chlorine, nitro- and methoxy-groups and esters. The method could be applied also for the chlorination of isoquinolines, with similar results (Table 10, entry 2).

Table 10: Quinolines, isoquinolines and tetrahydroquinolines in flow.

Entry	Approach	Starting compound(s)	Reactor [a]	Structural scope	Yields [%]	Comments	Ref / year
1	Selectfluor-mediated chlorination				45-83	15 compounds	123 / 2018
2	Selectfluor-mediated chlorination				traces - 90	6 compounds	123 / 2018
3	1,4-dipolar cycloaddition				21-91	16 compounds	124 / 2012
4	Povarov multi component reaction				12-84	22 compounds	125 / 2016

a: For reactor type acronyms, refer to Figure 1.

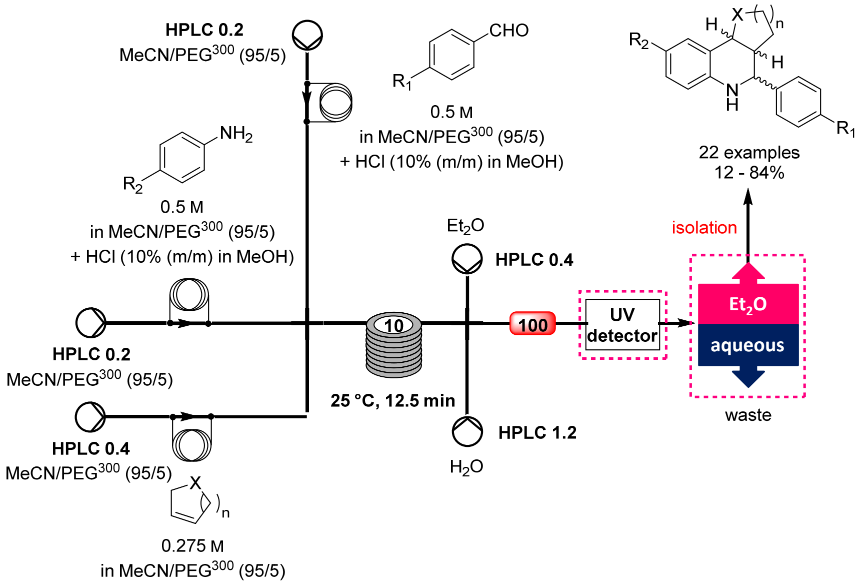
Isoquinoline derivatives find many applications as antimalarial, anti-HIV, antitumor, antimicrobial, antibacterial and anti-Parkinson's disease agents. Isoquinolines are key building blocks of different natural alkaloids in plants, always used by humans as active compounds in traditional medicine. In this context, fused isoquinolines are particularly appealing, and many synthetic efforts have been devoted to their preparation in recent years.[126-128]

Lei *et al* combined the advantages of a multicomponent synthesis with those of a continuous flow approach, to carry out a 1,4-dipolar cycloaddition reaction that provides isoquinoline derivatisation (Table 10, entry 3).[124] In batch, this reaction leads to the formation of several by-products and thus to low efficiency. In a relatively green flow process, a solution of isoquinoline in MeCN could be mixed with a solution of acetyl-enedicarboxylate and 2,2,2-trifluoro-1-phenylethanone in 10% excess in MeCN in a tubular reactor at 50 °C by means of a syringe pump with a very low flow rate of 4 µL/min, assuring a residence time of 60 minutes. Despite the long reaction time, collateral products are not formed in flow mode. This hints at the fact that the efficient mixing of the reagents as guaranteed in the tube reactor is a key advantage. However, this has not been explicitly shown or verified. The synthesis has not been tried on a larger scale. A library of 17 compounds was synthesised under optimised conditions, with yields varying as function of starting material characteristics with activated alkynes providing much higher yields with respect to less activated counterparts, with the best yield obtained when the benzaldehyde component was activated with a strong electron withdrawing nitro group (91%). Starting from ketones as the dipolarophiles did not lead to the corresponding products in the presented flow mode.

The tetrahydroquinoline ring system is a privileged scaffold exhibiting a broad spectrum of biological activity. Substituted tetrahydroquinolines have a wide range of pharmacological activity, such as anti-arrhythmic, anti-HIV, antibacterial, antifungal, and anticancer. Also, immunosuppressants and ligands for 5-HT$_{1A}$, NMDA and cannabinoid receptors are based on this motif. The tetrahydroquinoline substructure is also is found in numerous bioactive natural products, like benzastatins C and D, isolated from Streptomyces, or galipinine and cuspareine, isolated from *Galipea officinalis*.[129]

The Povarov reaction is one of the key strategies to afford the tetrahydroquinoline template, and the main features and application of this protocol in batch mode for the synthesis of medicinally relevant compounds have been recently reviewed.[130]

In 2016, Gioiello *et coll.* reported a Povarov multicomponent reaction yielding tetrahydroquinoline compounds in flow mode, which behaved in preliminary *in vitro* assays as ligands of G-protein-coupled oestrogen receptor (GPER) 1 (Scheme 17) (Table 10, entry 4).[125]



Scheme 17: Povarov multicomponent flow synthesis of tetrahydroquinolines by Gioiello *et coll.*[125]

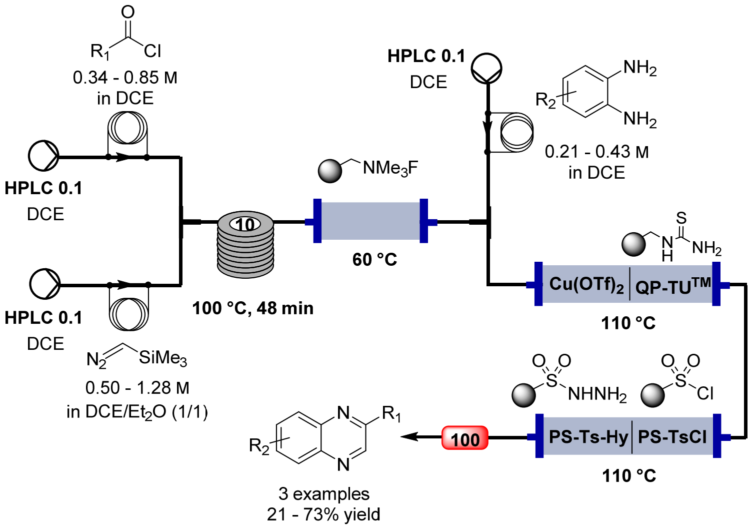
Using 5% (v/v) of PEG^{300} in MeCN as optimised solvent system that prevents effectively precipitation of eventually formed aniline salts, a solution of a substituted *p*-benzaldehyde in the presence of 10 wt% HCl in MeOH, a second solution of one equivalent of aniline and a third solution of 1.1 equivalents of different dienophiles were mixed and passed into the reactor coil at room temperature. After a residence time of 13 minutes in the reaction coil, followed by simultaneous addition of streams of water and diethyl ether as part of a semi in-line work up, the product heterocycles were isolated from the organic phase off-line. A library of 22 tetrahydroquinolines was obtained, in racemic form, but diastereomerically pure in *cis*/*trans* geometry, in yields between 12% and 84%. A correlation between the diastereoselectivity and chosen dienophile showed that dihydropyran gave the highest *trans*-yield, while *cis* outcome was favoured with five-membered dienophiles. Diastereoselectivity was found to be enhanced in the presence of groups that withdraw electron density from the amine component.

2.2.11 Quinoxalines, quinoxanilones and riboflavin

Quinoxaline-based heterocycles exhibit a broad variety of medicinal chemistry applications. Suitably functionalised quinoxalines have been described as promising antibacterial, antifungal, anti-inflammatory, anticancer, anti-tubercular and antineoplastic agents.[131, 132] Quinoxalinones are also useful drug discovery templates, being incorporated in potent anti-inflammatory and anticancer agents. Moreover, some quinoxalinone derivatives have shown good inhibitory activity against HIV-1 related lymphoma and as protein kinase inhibitors.[133]

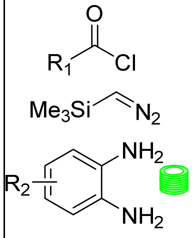
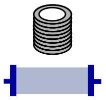
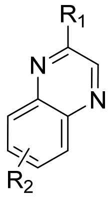
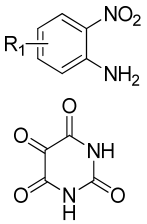
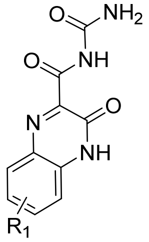
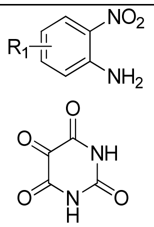
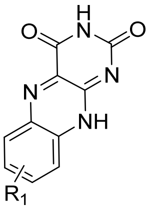
In 2010, Martin *et al.* developed a continuous flow synthesis, including in-line work-up, of quinoxalines based on a coupling of diazoketones with 1,2-diaminobenzene derivatives (Table 11, entry 1).[134] The authors developed a strategy for producing diazoketones just before their use in a first step in flow of a multistep flow procedure. A solution of the suitable acyl chloride in THF:MeCN (1:1) and a solution of trimethylsilyl diazomethane in Et_2O:THF:MeCN (5:7:1) were mixed and passed through a coil reactor for 25 minutes, before entering in a glass cartridge containing PS-fluoride. A library of 10 aliphatic and aromatic diazoketones was implemented with yields ranging from 46% to 98% and high purity >95%, in less than 1 hours, compared to 24-90 hours necessary in batch. The obtained diazoketone, re-dissolved in DCE, was mixed with different 1,2-diaminobenzene derivatives dissolved in DCE, and passed into a glass column containing $Cu(OTf)_2$ and PS-thiourea at 110 °C to catch any dissolved metal salts. The stream passed subsequently into a double cartridge system designed for purifying the formed products: a column containing PS-tosyl chloride was used to remove unreacted diamine, and a cartridge column containing PS-tosylhydrazine served for scavenging residual diazoketone. A library of 21 quinoxalines was realised; compounds were obtained as single regioisomer or 1:1 ratio of the two regioisomers when using unsymmetrical phenylendiamines. Purities were found to exceed 95%, thanks to the efficient in-line purification protocol, while yields ranged from 30% to 96%. The lowest yield was registered in the presence of two electron donors which activated the aromatic system. It was possible to telescope the reactions to achieve a full flow synthesis without intermediate isolation of any toxic material (Scheme

18). A solution of acyl chloride in DCE and $TMSCHN_2$ in Et_2O/DCE 1:0.6 was passed through a 5 to 10 mL coil reactor at room temperature for 25 to 50 minutes of residence time, accounting for differences in reactivity. The diazoketone-containing stream was mixed with substituted diamine, using a third stream, and passed through the four-cartridge system for effectuating the copper-catalysed addition reaction and achieving the in-line work-up. 3 quinoxalines were generated using this full flow protocol, with yields between 21% and 73%.



Scheme 18: Martin's flow synthesis of quinoxalines. $Cu(OTf)_2$ was mixed with Celite as excipient.[134]

Table 11: Quinoxalines, quinoxalinones and riboflavin in flow.

Entry	Approach	Starting compound(s)	Reactor [a]	Structural scope	Yields [%]	Comments	Ref / year
1	coupling of *in situ* generated diazoketones with 1,2-diaminobenzene				30-96	21 compounds, 3 in telescoped approach with in-line work-ups and purification	134 / 2010
2	*in situ* preparation of 1,2-diamino benzene		 H-cube		4-98	9 compounds	135 / 2014
3	*in situ* preparation of 1,2-diamino benzene		 H-cube		26-97	8 riboflavine analogues	135 / 2014

a: For reactor type acronyms, refer to Figure 1.

The synthesis of, amongst others, quinoxalinones through flow-based hydrogenations, starting from 1,2-diaminobenzenes and alloxanes was reported in 2014 by Baumann *et al.* (Table 11, entry 2).[135] Unstable and toxic 1,2-diaminobenzenes were prepared *in situ* starting from 2-nitroanilines. Various 2-nitroanilines, dissolved in EtOAc/MeOH (3/1) were pumped through an H-cube-based cartridge containing Pd/C or PtO_2 as catalyst at 45 °C and a flow rate of 0.85 mL/min. The obtained 1,2-diaminobenzenes were mixed with alloxane in a stirred vial for 10 hours at room temperature. A library of 9 quinoxalinones was realised, with yields ranging from 4% to 98%, with interesting exceptions for two examples containing two bromide residues on the aromatic ring.

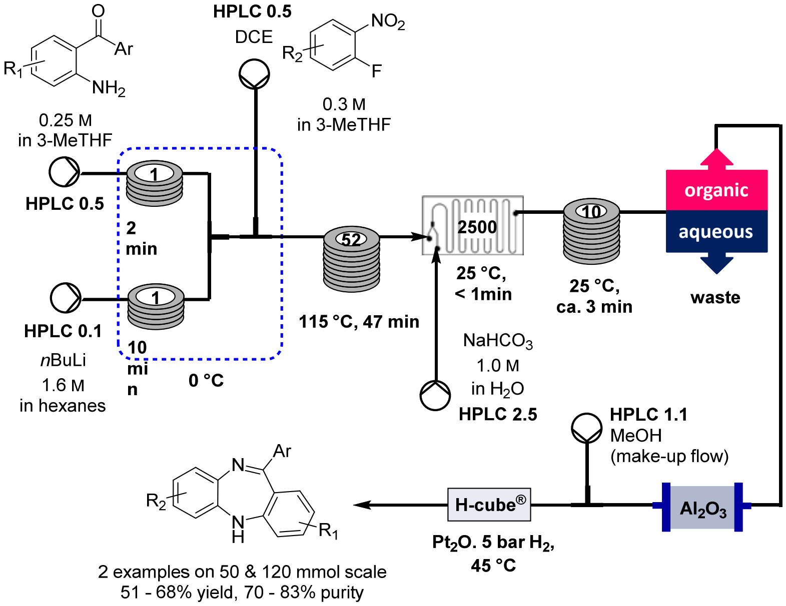
Riboflavin, known as vitamin B_2, is found in food or taken as a dietary supplement. This vitamin is an essential component of two major coenzymes, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). Riboflavine and its analogues have displayed interesting therapeutic potential over years, including anti-inflammatory, antihyperalgesic, anticancer and antimalarial activities.[136]

The synthesis of riboflavine derivatives was reported by Baumann *et al.* together with the above described procedure for the quinoxalinone-based scaffolds (Table 11, entry 3), using similar chemistries for initial 1,2-diaminobenzene formation.[135] The second step was realised in a stirred vessel mixing the diamines with alloxane dissolved in methanol containing HCl for 10 hours at room temperature. A library of 8 compounds was isolated in variable yields, strongly related to the substitution patterns of 1,2-diamminobenzenes, with the dibromoaniline once more providing the lowest yield.

2.2.12 Benzodiazepines

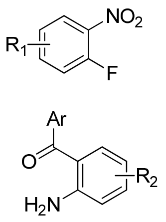
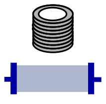
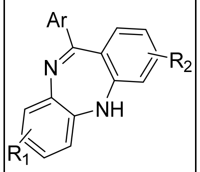
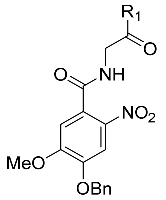
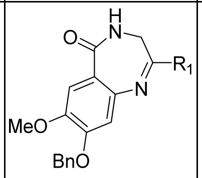
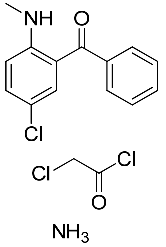
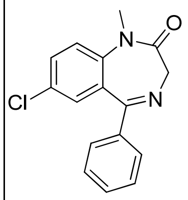
The benzodiazepine (BDZ) motif is an important, privileged scaffold with anxiolytic, hypnotic and anticonvulsant activities. BDZs are very often used also in the therapy of insomnia, of epileptic conditions, as well as with pre-anaesthetic purposes.[137] Dibenzodiazepines are instead very common structural templates for atypical antipsychotic drugs, useful for the treatment of schizophrenia.[138] Despite the broad therapeutic applications of these scaffolds very little progress has been made towards the development of improved or innovative synthetic procedures.

Always in their multi-scaffold publication of 2014, Baumann *et al*. developed a continuous multistep synthesis to dibenzodiazepines starting from 2-amino-benzophenones and 2-fluoronitroarenes, using *n*-BuLi in flow (Scheme 19) (Table 12, entry 1).[135] A solution of 2-aminobenzophenone in green 3-MeTHF and a solution of *n*-BuLi in hexane were precooled in flow before being united in the reaction loop to obtain deprotonation in around 1 minute. To the stream containing the generated nucleophile was then mixed, *via* a third stream, a solution of 2-fluoronitroarene in 3-MeTHF, and the resulting reaction mixture was passed through a heated reactor coil for promoting the S_N^{Ar}. For combining this first sequence with the necessary hydrogenation step in a continuous flow mode, an aqueous work-up in flow was realised by addition of a bicarbonate solution to the product stream and effective mixing using a microchip in line. Continuous extraction using a continuous separation tank was employed to avoid interruption of the flow process: overflowing organic layer was dried by passing through an exchangeable oven-dried alumina column. Dilution of the exiting stream with a carrier stream of MeOH completed the preparations for the reduction in flow over a PtO_2 catalyst effectuated in an H-cube model MIDI™, developed for larger scale purposes. The reaction was performed on two different scales using the fully continuous mode; on a 50 mmol scale, for example, a yield of 68% was obtained, with product purity reaching 83%. The technically most difficult part of this synthesis is the in-line work-up/solvent switch. An intermediate, more traditional isolation of the intermediate could represent a ‘lower-tech’ version.



Scheme 19: Flow synthesis of dibenzodiazepines proposed by Baumann *et al.*[135]

Table 12: Benzodiazepines and dibenzodiazepines in flow.

Entry	**Approach**	**Starting compound(s)**	**Reactor** [a]	**Structural scope**	**Yields [%]**	**Comments**	**Ref / year**
1	S_N^{Ar} followed by reduction		 H-cube		51, 68	2 compounds, telescoped approach with third stream and in-line work-up; purities of 69% and 83%, scale-up realised	135 / 2014
2	reduction of nitrobenzamides for cyclisation		 H-cube		92-94	3 compounds, scale-up realised	139 / 2015
3	acetylation followed by condensation				100[c]	1 compound	140 / 2017

a: For reactor type acronyms, refer to Figure 1.

c: Conversion yield.

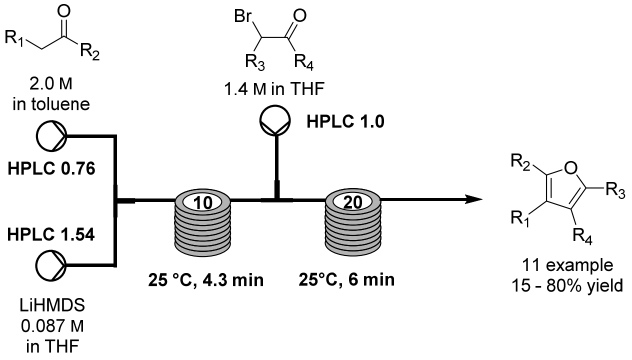
Reduction was also the main step in the development of a continuous flow process by Viviano *et al.* for the synthesis of 1,4-benzodiazepin-5-ones based on the flow reduction of nitrobenzamides that were obtained in a preceding step using conventional batch methods (Table 12, entry 2).[139] Either catalytic hydrogenation or metal-mediated non-catalytic reduction, carried out on different substituted 2-nitrobenzamides were unsatisfactory in batch settings. Optimal conditions in flow included ruthenium as catalyst, for being selective for the hydrogenation of 2-nitrobenzamide when dissolved in THF, using 50 bar of hydrogen pressure at 80 °C. The protocol was applied on 3 compounds providing products in high yield without purification. A realised scale-up produced 1.3 g of the target compound 8-(benzyloxy)-7-methoxy-2-phenyl-3,4-dihydro-5*H*-benzo[e][1,4]diazepin-5-one.

Ewan *et al* demonstrated the continuous synthesis of diazepam in two steps in a microfluidic flow reactor (Table 12, entry 3).[140] The synthesis involved the use of two sequential microfluidic chips, which allowed precise control of temperature and reaction times in the range of a few seconds. A first chip combined 5-chloro-2-(methylamino) benzophenone and bromoacetyl chloride, respectively, in a 1:2 ratio for *N*-acylation. The product-containing stream was diluted with methanol for subsequent addition of ammonia in methanol to provide diazepam. Yields were determined using an ESI-MS-based quantitation method. Using bromoacetyl chloride in a toluene/methanol solvent system, product formation is reported to be quantitative. Especially for the very short reaction times, this study is very interesting, theoretically. Only one example is described, for which unfortunately no isolated yield is reported; the study was mainly focusing on mechanistic insights for reactor development.

2.2.13 Furans and benzofurans

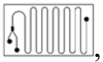
Furan is considered a privileged scaffold in drug discovery, since a variety of furan-based drug-like compound have been shown to possess antibacterial, antiviral, anti-inflammatory, antifungal, anticancer, and antihyperglycemic activities. Moreover, being the most reactive of the 5-membered heterocycles, furan also represents a convenient handle for the preparation of more complex heterocyclic systems, trough cycloaddition reactions and multiple possibilities for ring expansion.[141]

York reported an interesting continuous flow process for the synthesis of annulated and polysubstituted furans *via* carbanions (Scheme 20) (Table 13, entry 1).[142] A solution of ketone in toluene was brought in contact with a solution of LiHMDS in THF and reacted in a 10 mL reaction loop for ca. 4 minutes at 22 ºC to allow for complete formation of the enolate, which was combined with a solution of the αhaloketone in THF *via* a third stream set-up prior to entering in a 20 mL tubular reactor held at room temperature, to obtain furan rings in approx. 10 minutes total reaction time. The yields of 11 synthesised compounds significantly varied depending on the nature of the starting material and with 2-bromo-1-phenylpropan-1-one and cyclohexanone producing generally higher yields; the reaction did not take place starting from an aldehyde. Although batch to flow transition demonstrated beneficial in terms of yield, chromatographic purification was still necessary to obtain acceptable purity grades.



Scheme 20: Furans in flow developed by York *et al.*[142]

Table 13: Furans and benzofurans in flow.

Entry	**Approach**	**Starting compound(s)**	**Reactor** [a]	**Structural scope**	**Yields [%]**	**Comments**	**Ref / year**
1	*in situ* enolate formation, cyclisation				15-80	11 compounds	142 / 2011
2	dehydration		tube-in-tube, ring magnets		82-99	4 compounds, telescoping demonstrated, purity up to 98%, magnetic catalyst beads	143 / 2015
3	Suzuki cross-coupling				82-96	7 compounds from aryl bromides, 6 compounds from aryl chlorides	144 / 2014
4	etherification, cyclisation				4-69	3 compounds	145 / 2015
5	electro-chemical oxidative cyclisation		, EC [b]		50-87 (X= I) 65-81 (X=Br) 64, 60 (X=H)	11 compounds for X = I, 4 compounds for X = Br, 2 compounds for X = H, realised by induced dehalogenation during cyclisation	146 / 2020

a: For reactor type acronyms, refer to Figure 1.

b: Electrochemical reaction using a platinum cathode and carbon anode.

In a work that is intriguing more with respect to the used reactor technology than with respect to the actual chemistry, Jeong *et al.* reported in 2015 a continuous microfluidic flow system involving an innovative way to incorporate a heterogeneous two-phase catalytic process for the conversion of fructose into various furan motifs (Table 13, entry 2).[143] The flow set up consists of two capillary microreactor units: the first comprised a sulfonic acid-functionalised silica coating of the internal wall of a capillary tubing. This reactor was used to dehydrate fructose producing 5-hydroxymethylfurfural (HMF) at 150 °C in 6 minutes with a yield of 99%. The resulting HMF was further transformed into the second reactor type to achieve either a decarbonylation, an etherification, an oxidation or a hydrogenolysis. To these aims, the second reactor incorporated in one version a magnetic bead-based catalyst system in combination with reduced graphene oxide or silicate matrices on the internal tubing wall, with the magnetic catalyst beads held in place by an external magnetic field. This version was used for production of decarbonylated and etherified derivatives. Oxidative and reductive conversions were achieved using a ternary phase reaction, realised by a tube-in-tube reactor as used in other studies before (*vide supra*, Table 2, entry 6), positioning a gas permeable membrane inside the magnetised catalyst-containing tube. Oxidation saw the use of salen-based catalyst and oxygen, reduction Ru or Cu on magnetised beads on a nitrogen-doped reduced graphene oxide matrix in the presence of hydrogen. The purity of the 2 compounds generated in the binary phase reactions was of yields of 94% and 99%, while for the ternary phase reaction slightly lower yield were registered, namely 82% for the oxidation process and 90% for the hydrogenolysis. The temperature employed ranged between 70 °C and 150 °C for residence times of 6-60 minutes. Telescoping of the two steps was demonstrated for the production of dimethylfuran.

In 2014, Gordon *et coll.* designed a new continuous flow approach to obtain furan-based biaryls through Suzuki cross-coupling reactions using 2-boro-substituted furans and immobilised palladium as catalyst (Table 13, entry 3).[144] A 0.05 M solution of equimolar amounts of aryl bromide and 5-formyl-2-furanylboronic acid, as well as a rather large excess of tetrabutylammonium fluoride (3.2 equiv.) in

MeOH was passed through an immobilised palladium catalyst CatCart^{TM} FC1032^{TM} fitted in an X-cube, *i.e.*, a reactor originally tailor-made for high pressure-high temperature reactions, at a temperature of 120 °C for a total of 2 hours, realised in form of a looped set-up (compare example Figure 2). After off-line workup, the desired products were isolated in yields between 82% and 92%. A library of 7 compounds was synthesised starting from activated or neutral aryl bromides. In order to generate products from deactivated aryl bromides and aryl chlorides, tetrabutylammonium acetate was used in combination with polymer-supported $PdCl_2(PPh_3)_2$, allowing for the synthesis of a library of other 6 compounds. Unfortunately, with the more activated *bis*-triphenyl-phosphine palladium, a high quantity of homo-coupled product was observed as well.

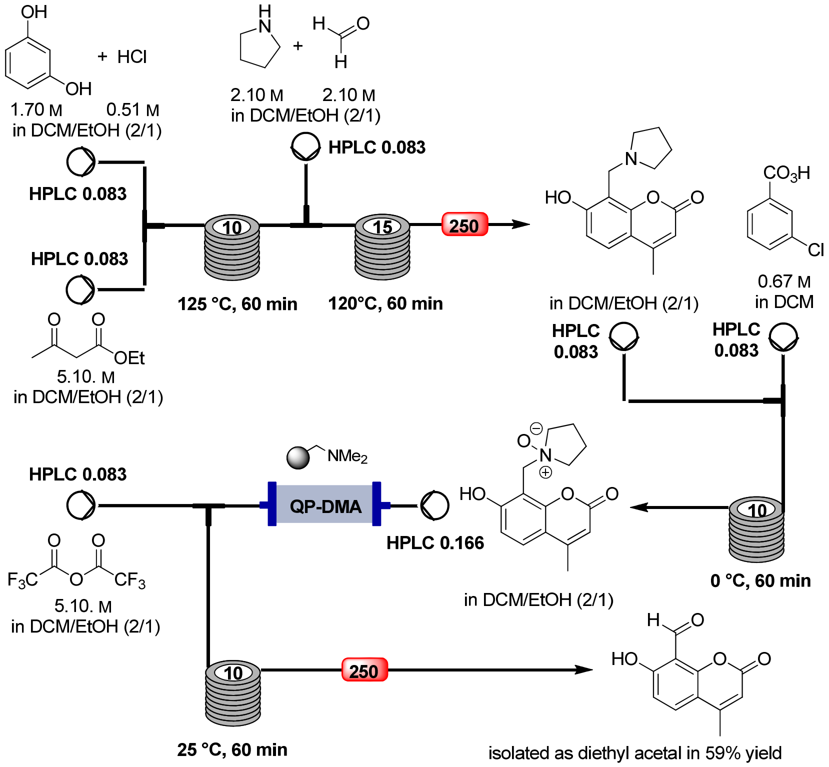
Túrós and his group developed a general protocol to benzothiazoles (*vide infra*, Table 17, entry 6), and in course of this work, a two-step flow process to benzofurans was devised as well (Table 13, entry 4).[145] In a first step, a solution of nitro-substituted salicylaldehyde or *ortho*-hydroxylated acetophenone in DMF was etherified adding a stream of α-brominated ethyl acetate in DMF at 100 °C for 25 minutes in a microfluidic chip. The isolated product was subsequently dissolved in EtOH and combined with a stream of Verkade's base in EtOH in a second microfluidic reactor chip such as to induce benzofuran formation at 100 °C within 5 minutes. The protocol provided variable yields of purified products for the 3 selected benzofuran derivatives, although it is interesting to evidence an opposite trend compared to previous batch results. The in 4% isolated 3-nitro-derivative gave 57% in batch; on the other hand, the yield of the 5-nitro-derivative was three times higher in flow than in batch.

Very recently, in 2020, Guo *et coll.* succeeded in combining the advantages of flow chemistry in microreactor chips with those of electrochemical transformations to a green synthesis of benzofurans and benzothiophenes (Table 13, entry 5).[146] Placing the microfluidic channelling between a platinum cathode and a carbon anode, allowing contact of the solution to the electrodes, benzofurans were generated starting from variously substituted 2-alkynylanisoles and potassium halides as electrolytes dissolved together in an acetonitrile-water mixture. Under standard conditions, the halide entered the benzofurans at position 3, leading to 11 iodinated and 4 brominated species in moderate to high yields. Changing slightly the standard electrochemical parameters, dehalogenation could be achieved in case of potassium iodide as electrolyte, leading to non-halogenated derivatives.

2.2.14 Coumarins

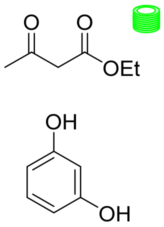
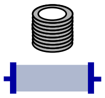
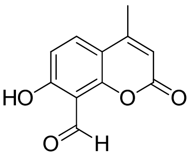
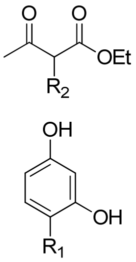
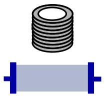
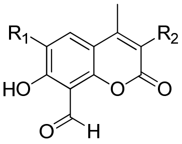
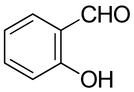
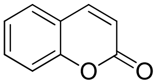
Coumarins, also known as benzopyrones, are heterocyclic compounds that are found in many plants as secondary metabolites produced for plant defence against microbial attacks and fungi. They are hence also intrinsically pharmacologically active, with their substructures embedded in anti-tumour, anti-coagulant, anti-inflammatory, anti-oxidant, anti-HIV and anti-bacterial agents.[147, 148]

In 2012, Zak *et al.* developed a synthesis of differently substituted coumarin-8-carbaldehydes *via* two noteworthy approaches realised in two different continuous flow processes, both starting from resorcinol and β-keto esters.[149] One approach could be practically realised as a single telescoped flow sequence using DCM as solvent (Table 14, entry 1). The telescoped sequence (Scheme 21) commenced reacting resorcinol and 30 mol% concentrated HCl in a DCM-EtOH solvent system in a reactor coil at 125 °C for 1 hour to achieve a Pechmann condensation. A subsequent Mannich aminoalkylation could be realised in sequence, reacting the Pechmann product with paraformaldehyde and pyrrolidine, added *via* a third stream, in a second reactor coil, held at 120 °C, for 1 hour. The amine could then directly be transformed in flow at low temperatures in 30 minutes to the *N*-oxide using *m*-CPBA. The crude product was directly passed through a column reactor containing polymer-supported amine in form of QP-DMA as scavenger for residual peracid to achieve as such a rough in-line purification before mixing with trifluoroacetic anhydride in DCM for 1 hour at room temperature to enable the Polonovski reaction. The crude product was collected in 1 M aqueous HCl for a concluding off-line extraction for product isolation. This telescoped process furnished 7-hydroxy-4-methyl-2-oxo-2*H*-chromene-8-carbaldehyde in 47% overall yield, with >95% purity as determined by LC-MS and NMR analysis. Analyses of the various single steps revealed that the oxidation was the lowest yielding one, with 82%; the other three steps were found to proceed with yields exceeding 90%. A greener approach using acetic acid as solvent was possible up to the *N*-oxide formation, while the following Polonovski step, although tolerating the EtOH in the DCM-based approach, proofed incompatible with the presence of high amounts of protic solvent.



Scheme 21: Telescoped flow synthesis of coumarins presented by Zak *et al.*[149]

Table 14: Coumarins in flow.

Entry	Approach	Starting compound(s)	Reactor [a]	Structural scope	Yields [%]	Comments	Ref / year
1	Pechmann condensation, Mannich amino-alkylation, oxidation, Polonovski reaction				47	1 compound, telescoped sequence with in-line purifications, no solvent switch	149 / 2012
2	Coumarin formation as in entry 1, then modification of coumarins using Claisen rearrangement, elimination and oxidation				70-80 (Claisen), 100 (elimination), 89 (oxidation)	6 compounds (Claisen), 6 compounds (elimination), 1 compound (oxidation), partial telescoping, in-line work-up	149 / 2012
3	*O*-acetylation of salicylaldehyde and subsequent cyclisation				91[b]	1 compound, scale-up demonstrated; mechanistic study	150 / 2015

a: For reactor type acronyms, refer to Figure 1.

b: Conversion reported.

The second route (Table 14, entry 2) started from 7-hydroxycoumarin synthesised as described above and represents as such only decorations of the coumarin core.[149] The developed processes are nevertheless interesting, including in-line purifications and using different chemistries based on reagents whose toxicities could be well contained using the flow processes. Rather than a telescoped sequence, this second approach required isolation of intermediates due to necessary solvent switches.

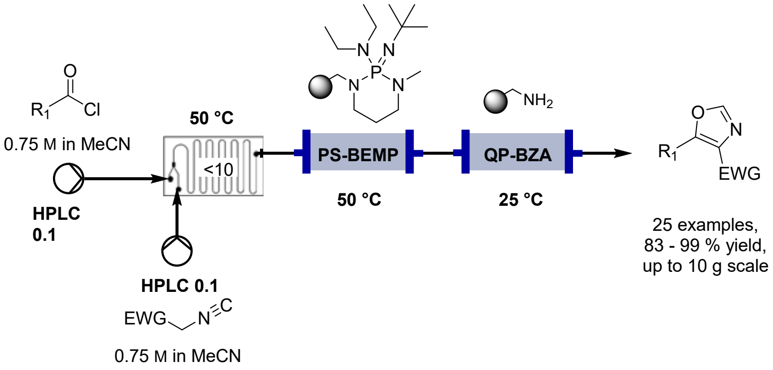
Similar to the idea in Smith's triazole approach (*vide supra*, Table 7, entry 3), using a solution of 7-hydroxycoumarin in NMP, column reactors filled with a carbonate resin were employed as solid support for catching 7-hydroxycoumarin in its reactive phenoxide form. The phenoxide was then washed off the resin again upon reaction with a stream of allyl bromide in NMP. An in-line purification of the exiting product stream from surplus allyl bromide could be realised placing a column filled with the polymer-supported amine QP-BZA, in-line. The allyl aryl ether stream was passed through a reactor coil held at 235 °C to trigger the Claisen rearrangement, forming 8-allyl coumarin derivatives that contained the C-6 regioisomer as by-product. The isomer mix could be trapped again in salt form on a scavenger resin comprised of supported tetraalkylammonium hydroxide such, as to allow for in-line purification by simple washings of this trapped form prior to simple TFA-assisted release or, as a variant, 7-*O*-alkylation using a solution of MeI in THF. Two products were isolated in overall yields between 70% and 80%. The next step consisted in passing the allylated hydroxycoumarins, dissolved in THF, through a column containing Felkin's iridium catalyst at 60 °C, in order to trigger the migration of the double-bond into the thermodynamically favourable position. After 47 minutes of reaction time, the corresponding (*E*)-alkenes were synthesised quantitatively. The desired *ortho*-formylated hydroxycoumarins were then obtained in a flow version of a conventional oxidative cleavage, employing polymer-supported osmium tetroxide-version OsEnCat, a polymer-supported periodate and a stoichiometric amount of *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant. In this case, in-line purification was achieved by sulfonic acid resin QP-SA to trap the formed amine. Oxidation reaction proceeded with 89% yield following solvent evaporation using the metal-based catalyst system. Scale-up, however, proofed very difficult with this system, so that the group developed an ozone-based alternative in flow. The alkene-containing solution was mixed with a continuous gas flow of ozone in oxygen and passed through a tubular reactor coil with a residence time of 75 seconds, before being collected in a nitrogen-covered purge vessel. A second pump was used to pass the purged solution through filled with polymer-supported thiourea. The final aldehyde was obtained with a yield of 92%. The total four-step synthesis provided 7-hydroxy-4-methyl-2-oxo-2*H*-chromene-8-carbaldehyde with a 51% yield after crystallisation.

In 2015, Li *et al.* developed a flow synthesis of coumarin *via* *O*-acetylation of salicylaldehyde and subsequent cyclisation, adopting as such an existing synthetic approach (Table 14, entry 3).[150] While for the batch process that motivated this study, a Perkin reaction was postulated, the authors found strong evidences that a different temperature profile might change the mechanism towards a sequence of *O*-acetylation followed by aldol condensation-type ring closure. Temperature screening indicated then that above 180 °C, (*E*)-3-(2-hydroxyphenyl)acrylic acid did not form and therefore the Perkin process did not occur. Based on the mechanistic insights, the optimised flow process involving *O*-acetylated salicylaldehyde started with its generation. A stream of potassium acetate, acetic anhydride and acetic acid was mixed with salicylaldehyde and pumped in a first 10 mL coil reactor held at 150 °C before being passed into a second 10 mL coil held at the optimum temperature of 240 °C, with the residence time of approx. 23 minutes for each step. The flow synthesis route provided coumarin in 91% conversion. While the mechanistic understanding was of only secondary importance for the desired net transformation, the study does highlight nevertheless the possibility to arrive at a better mechanistic understanding thanks to improved parameter control in flow processing, and hence at a more sustainable reaction planning.

2.2.15 Oxazoles and benzoxazoles

Oxazoles are an important class of five-membered aromatic heterocycles, considered a privileged scaffold in pharmaceutical chemistry. The oxazole moiety is prevalent in alkaloid natural products and in many synthetic active pharmaceutical ingredients. The wide range of biological activities of oxazoles includes antimicrobial, anticancer, antitubercular, anti-inflammatory, antidiabetic, antifungal, antiobesity, analgesic and antiviral.[151]

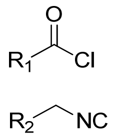
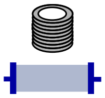
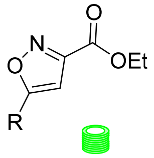
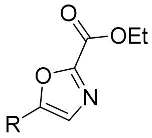
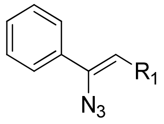
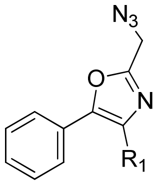
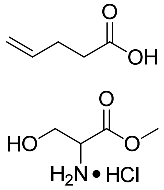
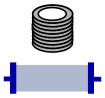
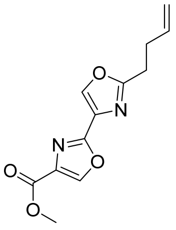
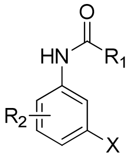
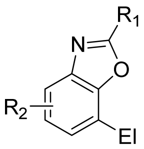
In 2006, Ley *et coll.* developed a continuous flow synthesis for 4,5-disubstituted oxazoles, starting from alkyl isocyanoacetates and acyl chlorides in a base-catalysed cyclisation reaction (Scheme 22) (Table 15, entry 1).[152] In an approach adhering to green practices, equimolar mixtures of ethyl isocyanoacetate and different acyl chlorides in MeCN were combined in a reactor chip, before entering a column reactor containing PS-BEMP, a polymeric version of 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine, for triggering cyclisation; a high-load of QP-BZA, placed in a second column reactor in-line functions as a scavenger to improve product purity. Using this simple set-up, a library of 25 4,5-disubstituted oxazoles was synthesised with high yields and affording up to 10 g of material in a scale-up demonstration. A library of 12 compounds was realised replacing ethyl isocyanoacetate with a tosyl or a phosphonate group providing good yields as well.

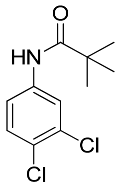
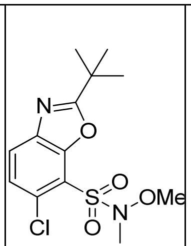
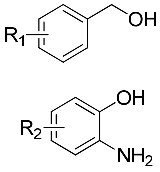
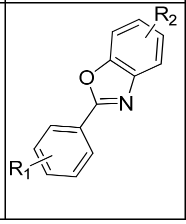


Scheme 22: General flow synthesis of 4,5-disubstituted oxazoles by Ley *et coll.*[152]

However, the use of the more sterically hindered phosphonate group causes issues which seem to be accentuated by the solid support. The column containing PS-BEMP needed to be heated to 85 °C to yield oxazoles effectively. Alternatively, 1 equivalent of BEMP, directly mixed in solution could be used. In the latter case, a cartridge of PS-sulfonic acid was inserted in the flow scheme for BEMP removal. 3 selected 4,5-dibustituted oxazoles were synthesised following this protocol, in around 85% yield and >95% purity according to NMR data, achieved solely using the in-line work-up and scavenging procedure.

Table 15: Oxazoles and benzoxazoles in flow.

Entry	Approach	Starting compound(s)	Reactor [a]	Structural scope	Yields [%]	Comments	Ref / year
1	condensation plus cyclisation				83-99 (isocyanoacetate), 81-94 (tosyl), 84-85 (phosphates)	25 compounds from isocyanoacetates, 9 compounds from tosyl, 3 compounds from phosphate, in-line purification, scale-up	152 / 2006
2	photo-isomerisation	 R = Ar or Het	 $h\nu$ [b]	 R = Ar or Het	24-81, 73-80 from hetero-aryls	15 compounds, plus 7 compounds from heteroaryls, scale-up realised	153 / 2020
3	*in situ* azirine formation plus cyclisation				50, 60, 78[c]	3 compounds	154 / 2018
4	oxazolines by cyclo-dehydration with DAST, aromatisation	 DAST, DBU, $BrCCl_3$			53 (7 steps)	bisoxazole core of *O*-methyl siphonazole and (−)-hennoxazole, telescoped	155 / 2011 156 / 2012
5	aniline lithiation, cyclisation and quenching with electrophile	 X = Cl or F		 El = electrophile	68-91	15 compounds, adiabatic flow set-up, scale-up demonstrated	157 / 2013

6	aniline lithiation, cyclisation and quenching with SO_2 for ultimate sulphonamide formation	 SO_2 SO_2Cl_2 NHMeOMe			65	1 compound, adiabatic flow set-up, scale-up demonstrated	158 / 2017
7	oxidative cyclisation using heterogeneous manganese catalysis				95-99	18 compounds, gas pressure for realising flow of reagents	159 / 2019

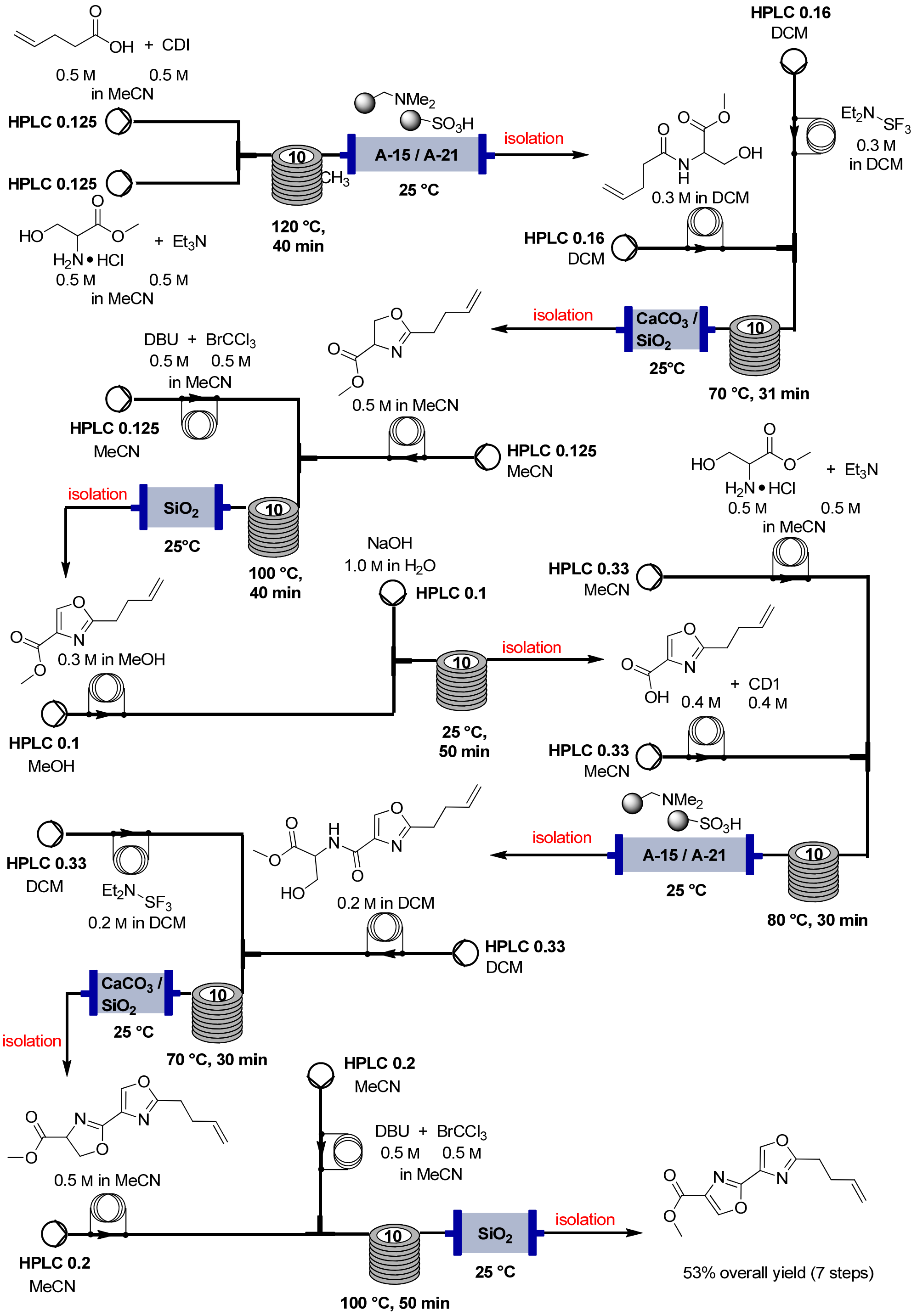
a: For reactor type acronyms, refer to Figure 1.
b: Photochemical step.
c: Conversion yield.

More recently, Baumann and Bracken reported a continuous flow photoisomerisation reaction converting isoxazoles (*vide infra*, Table 16, entry 2) into oxazoles (Table 15, entry 2).[153] Starting from acetophenones and diethyl oxalate dissolved in MeCN, substituted isoxazoles were obtained *via* two-step process in batch mode. A library of 15 isoxazoles was then converted in their oxazoles counterparts through the photochemical flow reaction in variable yields, with generally lower outcomes observed for electron poor compounds. Starting from ethyl 5-(4-methoxyphenyl)isoxazole-3-carboxylate, a realised scale up employing the same reaction conditions produced 1.5 g of the desired oxazole in 12 hours. A library of seven compounds starting from heteroaryls-substituted isoxazoles, *i.e.*, furans, thiophenes, indoles, or pyrroles, resulted in oxazoles in high yields of (73% to80%. The crude reaction products needed purification by silica column chromatography.

Another interesting example in which flow chemistry was used as the key step of oxazole synthesis was reported by Rossa *et al.* in 2018 (Table 15, entry 3).[154] After optimisation of stoichiometries, nature of base, reaction time, temperature, a continuous-flow synthesis enabled the authors to obtain 2-

(azidomethyl)oxazoles. A 0.5 M solution of vinyl azide in acetone was passed through a reaction loop at 150 °C to effectuate a thermolysis within 1 minute at approx. 17 bar. The obtained azirine, collected temporarily in an open vessel for allowing diffusion of nitrogen gas from the solution, was subsequently mixed with a stream of bromoacetyl bromide and reacted in a third reaction loop for 1 minutes at 30 °C. Two oxazoles were produced in this mode, in full conversion of the starting materials, but with only moderate purities (81% and 59%). Upon purification, the products decomposed, leading to low yields. Decomposition could be avoided by adding two additional streams, containing an aqueous solution of NaN_3 and DIPEA, respectively, to the stream containing crude product, such as to perform a nucleophilic substitution in flow. 3 products were obtained *via* this route in moderate yields.

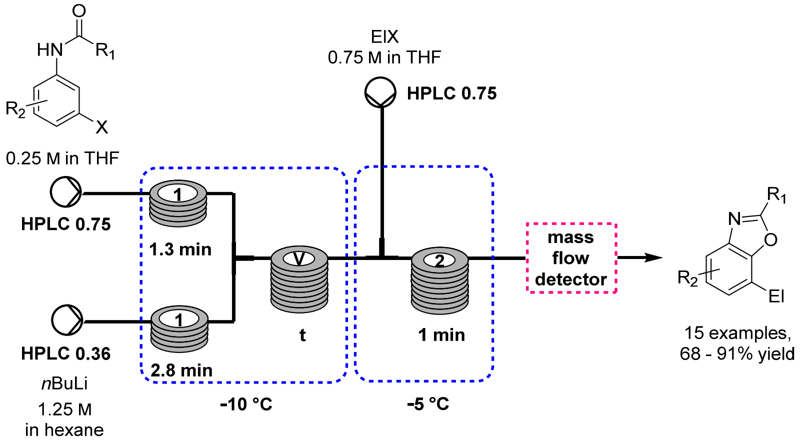
In 2011 and 2012 followed total synthesis papers by Ley's group detailing the generation of bisoxazole containing antiviral natural products *O*-methyl siphonazole[155] and (–)-hennoxazole[156] by an integrated batch-flow approach (Table 15, entry 4). Flow chemistry transformations were used for the synthesis of the bisoxazole core present in the natural products, as discussed in the following example on hennoxazole (Scheme 23). The telescoped sequence started from coupling of 5-pentenoic acid, *in situ* activated with CDI, and (±)-serine methyl ester in the presence of trimethylamine; the first oxazoline ring was then obtained by cyclodehydration employing diethylaminosulphur trifluoride (DAST). The excess of DAST necessary for the transformation and removal of generated HF was achieved in-line using a column filled with $CaCO_3/SiO_2$ as scavengers. Oxazoline was oxidised using $BrCCl_3$ in the presence of DBU to form the oxazole derivative, in which the ester was cleaved in basic medium yielding the corresponding acid. Applying again the oxazole-formation steps just described resulted in the desired bisoxazole core ester in 53% overall yield.



Scheme 23: Flow chemistry protocol to bisoxazole core motif in hennoxazole A. Steps shown represent the synthesis flow as described in the Supporting Information. The use of back pressure regulators is not detailed.[156]

Benzoxazoles represent an important class of privileged scaffold in pharmaceutical chemistry and have shown a wide range of biological activities such as antimycobacterial, antibacterial, anticancer, antifungal, antiparkinson and COX-2 inhibitor.[160-163]

Sedelmeier *et al*. reported a multiple flow process for highly functionalised benzoxazoles (Scheme 24) (Table 15, entry 5).[157] Starting from an existing batch procedure[164] the work represents one of the first uses of organolithium in flow. The flow set-up saw features like precooling of reagent streams and a Coriolis mass flow control unit for ensuring an adiabatic flow system in the production of higher quantities. The flow process started from a solution of an aniline derivative in THF and a solution of an excess of *n*-BuLi in hexane; both reactant streams were pre-cooled by means of passage through a cooled tubular reactor before being adiabatically mixed for aniline lithiation in a first tubular reactor over a course of 5 minutes at −10 °C.A higher concentrated solution of an excess of electrophile in THF, precooled as well, was then adiabatically added as third stream to quench the organolithium in a second tubular reactor within 60 seconds at −5 °C. To effectively remove the reaction heat generated upon mixing, and thus guaranteeing the adiabatic mixing, narrow hole metal T-pieces (Swagelok) were chosen. Substitutions with different electrophiles and different parts of aniline led to a library of 15 benzoxazoles with good to excellent yields and high purity following an aqueous work-up off-line. A scale-up was demonstrated generating 114 g of benzoxazole with a yield of 86% in a continuous process, in comparable yield and purity as for the small-scale flow reactions. No comments were made regarding eventual necessity to ‘dry’ the meso-scale reactor prior to using *n*-BuLi.,



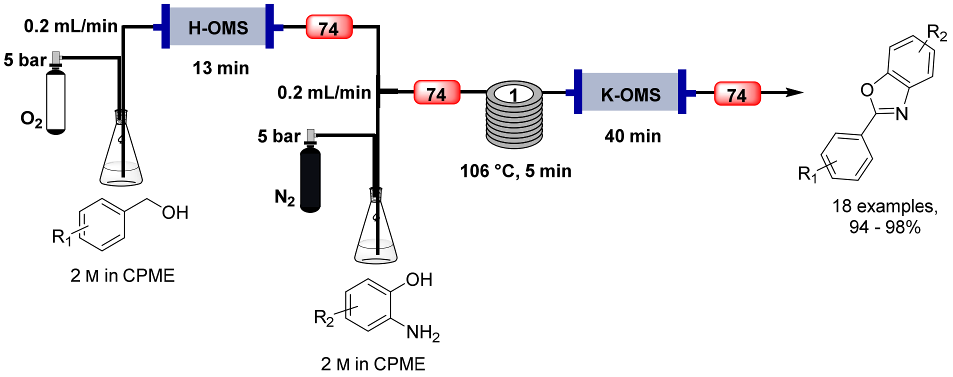
Scheme 24: Flow synthesis of benzoxazoles on large scale according to Sedelmeier *et al.*[157] Volumes (V) of the first coil reactor were chosen between 5.55 mL or 7.57 mL, causing residence times (t) of 300 - 500 seconds; ElX: electrophile.

In 2017, the same research team optimised this flow synthesis for the continuous production of a benzoxazole based pharmaceutical intermediate for a CXCR2 receptor antagonist candidate (Table 15, entry 6).[158] The reaction starts as before with the lithiation of the advanced aniline precursor; the aryllithium was then trapped by sulphur dioxide in THF. The resulting lithium sulphate was reacted with a solution of sulphuryl chloride in hexane provided off-line in the collection vessel, such as to provide a benzoxazole-based sulphonyl chloride. The flow configuration yielding the benzoxazole-based sulphonyl chlorides consisted in two tubular reactors for effectuating the reactions between pre-cooled reagents (*vide supra*); a 11 mL "division and recombine" reactor held at –20 °C was used for lithiation, allowing for reducing the residence time for *n*-BuLi from 4.5 to 1.9 minutes, obtaining 20 g more compound in 4 hours. Trapping with sulphur dioxide proceeded in a 9 mL tubular reactor immersed at 0 °C in an ultrasonic bath, necessary to avoid the precipitation/aggregation of solid products that could block the tube. Off-line generation of sulfonyl chlorides was achieved in hexane at 5 ºC. Sulphonamide formation was presented as a separate flow chemistry step.

Using after additional optimisations a mix of batch and flow reactions, 17 kg of the target benzoxazole with a 65% yield and with an overall cost reduction of around 35% was obtained. The purity of the compound was determined on a 5 kg scale and was as high as 99.8%. The fact that a mix of batch and flow was used reflects a careful evaluation of reactor performances. The study is thus a worthwhile 'real life' example for the fact that best solutions for complex problems more likely exist in form of mixed batch-flow synthesis, appreciating that flow chemistry is not always the panacea.

In 2019, Ferlin *et al.* developed a continuous multi-step flow process for the synthesis of 2-arylbenzoxazoles catalysed by heterogeneous manganese systems (Scheme 25) (Table 15 entry 7).[159] 2-arylbenzoxazoles were realised using octahedral manganese oxide molecular sieves (OMS) together with oxygen as the oxidant in cyclopentylmethyl ether (CPME). The interesting aspect of this approach is the fact that flow process could be realised using gas, *i.e.*, oxygen and nitrogen, for ensuring net mass transport. Initial oxidation of benzyl alcohol to benzaldehyde was realised in an acidic OMS (H-OMS)-filled column reactor, the flow of the solution was realised by the oxygen stream needed for oxidation. The exiting stream enters a T-piece, by which it is mixed with a nitrogen-pushed stream of *o*-aminophenol: imine formation proceeded without catalyst and furnished the starting point for the third step which involves oxidative cyclisation to provide 2-phenylbenzoxazole. Potassium-loaded OMS (K-OMS) was chosen as catalyst to this end. Under optimal conditions, a library of 18 compounds was generated with very high yields, among which the active pharmaceutical ingredient tafamidis with 92% yield. Unfortunately, the purity of the compounds is not explicitly described.

The process presented by Ferlin *et al.* represents principally an out-of-the-box example for a green and sustainable process: the use of CPME as green solvent and the possibility to use the oxygen gas not only for the benzaldehyde formation but also for the recovery of the catalyst and the generation of flow, in combination with nitrogen, comply with modern demands. With respect to the gas-based flow generation, it would be interesting, however, to analyse whether overall carbon footprint is lower compared to the use of conventional mechanical pumps.

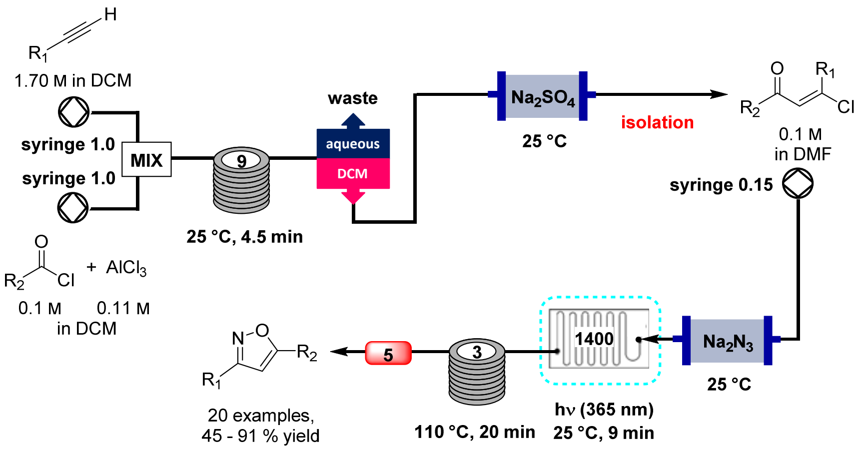


Scheme 25: Flow synthesis of benzoxazoles according to Ferlin *et al*. H-OMS – acidic octahedral manganese oxide molecular sieves, K-OMS – potassium-loaded octahedral manganese oxide molecular sieves.[159]

2.2.16 Isoxazoles

Isoxazole motifs exhibit a broad range of biological activities and they are embedded is several drugs displaying antimicrobial, analgesic, anti-inflammatory, antioxidant, anticancer, and antihypertensive activities. The isoxazole moiety is also contained in CNS-targeted drugs, including agents against schizophrenia, and bipolar disorders.[165] The isoxazole ring is also found in some herbicides. In nature, the isoxazole ring is present as structural motif in natural products like ibotenic acid and muscimol. Isoxazole-based scaffolds are relevant templates in medicinal chemistry due to their ability to establish hydrogen bonding interaction, displaying both N and O heteroatoms as suitable hydrogen bond acceptors, and electronic interactions of the aromatic moieties through their unsaturated five-membered ring. More interestingly, their incorporation in drug-like compounds may improve toxicity and pharmacokinetics profiles.[166]

Oh and co-workers developed a continuous flow synthesis of isoxazoles *via* vinyl azide intermediates starting from a Friedel−Crafts-like acylation of alkynes and photochemical cyclisation (Scheme 26).[167] Typical azide-related issues during synthesis could so be circumvented. Following some initial screening of conditions, a combined flow system was designed: starting from a 0.1 M solution of alkyne in DCM, an acyl chloride-$AlCl_3$-mix in DCM was added *via* an effective mixing device to form (*E*)-β-chlorovinyl species in flow. The product obtained was subjected to an in-line work-up, which was realised employing an in-line solvent separation in a simple Erlenmeyer flask, demonstrating that difficult in-line operations are principally possible using intuitive low-cost solutions. Upon isolation, the intermediate was re-dissolved in DMF, and passed through an HPLC column that was packed with sodium azide. The reaction mixture was then exposed to light emitted by a 365 LED while passing through a microreactor for 9 minutes. An ultimate heating of the mixture for 20 minutes followed.



Scheme 26: Isoxazoles in flow by Oh *et coll*. The phase separation was realised using a conventional, sealed Erlenmeyer flask.[167]

A library of 20 compounds was synthesised, with yields ranging between 45% and 91% after chromatographic purification; unfortunately, the purity of the crude products has not been reported. While elegantly resolving the issues connected with azide-based syntheses, the presented work is not sustainable or green: stoichiometric amounts of aluminium salt and DCM as solvent are unfortunately present as reminiscences of traditional chemistries.

2.2.17 Oxadiazoles

The oxadiazole-based scaffolds exhibit wide versatility for medicinal chemistry applications and they have been employed for the development of potent antitumor, anti-HIV, antimicrobial, anti-inflammatory, and antidiabetic agents.[168] Moreover, several receptor ligands are oxadiazole-based compounds, such as benzodiazepine receptor agonists, D_3 receptor ligands, monoaminoxidase B inhibitors and adenosine A_2B receptor antagonists, among many others.[169-172] Oxadiazoles may further impart improved metabolic stability, increased bioavailability and membrane permeability, and they are often utilised as suitable amide bioisosteres.[173] Although four possible regioisomers for oxadiazole exist, the 1,2,4- and 1,3,4-isomers are the most commonly employed in medicinal chemistry. Both of them reproduce the molecular planarity and dipole moment of an amide functionality, although with strategical variation in aromatic, electrostatic, and hydrogen-bonding character.

Cosford *et coll.* developed a multistep synthesis protocol that delivered 1,2,4-oxadiazoles, bis-substituted by arylnitriles *via* a single continuous sequence of microreactors generating *O*-acyl-amidoximes *in situ* (Table 16, entry 1).[174] A solution of arylnitrile in DMF and a solution of hydroxylamine hydrochloride and excess Hünig's base in DMF were combined for reaction in a coil reactor at 150 °C. After a residence time of 6 minutes, the reaction was quenched by drastic cooling before being combined at room temperature with a third stream of acyl chloride in DMF. This mixture is passed through a second coil reactor heated to 200 °C to finish the reaction. A focused library of 9 compounds was synthesised, confirming the applicability of the methodology to (hetero)aryl nitriles and both (hetero)aromatic and aliphatic acyl chlorides, with moderate yields following off-line purification by preparative HPLC. The scope of the methodology was additionally broadened through replacement of the acyl chlorides with succinic anhydride for the preparation of 3 examples of the corresponding 1,2,4-oxazolyl propanoic acids. In this case, the replacement of DMF with DMA as the solvent of choice was necessary in order to guarantee a comparable outcome and avoid partitioning of DMF in the reaction.

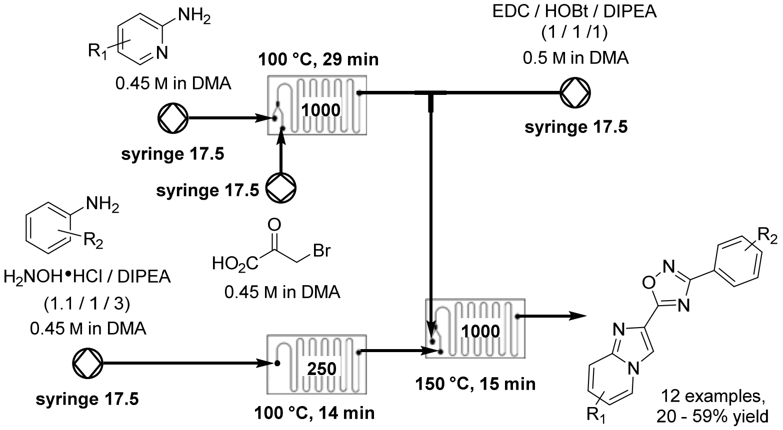
Table 16: Oxadiazoles in flow.

Entry	**Approach**	**Starting compound(s)**	**Reactor** [a]	**Structural scope**	**Yields [%]**	**Comments**	**Ref / year**
1	cyclisation of *in situ*-generated *O*-acyl amidoxime				45-61	9 compounds from acyl chlorides, 3 compounds from succinic anhydride	174 / 2008
2	cyclisation of *in situ*-generated *O*-acyl amidoxime				53-81	8 compounds	98 / 2017
3	cyclisation of *in situ*-generated *O*-acyl amidoxime				20-59	12 compounds	98 / 2017
4	coupling, cyclisation				82 (CDI) 91 (triphosgene)	1 compound	68 / 2017

a: For reactor type acronyms, refer to Figure 1.

The same research group then reported in 2017 a continuous-flow synthesis of highly functionalised oxadiazoles starting from arylnitriles and carboxylic acid derivatives in 2017 (Table 16, entry 2).[98] Again, DMA as solvent led to superior results when reacting a solution of arylnitrile, hydroxylamine hydrochloride and DIPEA (1.05:1:3) injected in a microreactor held at 100 °C. The after approx. 10 minutes of residence time exiting stream was combined with a second and third stream containing carboxylic acid/DIPEA (1:1) and EDC/HOBt/DIPEA (1:1:1), respectively, in a second microreactor held at 150 °C; chosen flow rates guaranteed a residence time of 15 minutes to achieve the desired cyclisation. A library of 8 compounds was synthesised using commercially available carboxylic acids.

In order to generate differently functionalised imidazo-oxadiazoles, a variation of the above protocol was presented using starting materials synthesised in flow (Scheme 27) (Table 16, entry 3).[98] This protocol started with the generation of imidazo[1,2-a]pyridine-2- carboxylic acid in flow, as briefly mentioned above (*vide supra*, Table 6, entry 3). The exiting stream was then combined first with a stream containing EDC / HOBt / DIPEA (1:1:1) as to set the scene for a 15 minutes reaction at 150 ºC with an amidoxime that is synthesised in flow as in the first approach in a 100 °C reactor. A library of 12 compounds was synthesised using this more flexible approach, although with generally lower yields. A scale up of this process was realised using larger reactors and six-fold higher flow rates, *i.e.*, 100 μL/min instead of 17.5 μL/min. Furthermore, a microfluidic liquid-liquid extraction module was incorporated in the process, working with toluene and water to remove the high boiling DMA at the end of the sequence. Oxadiazole derivatives were obtained in good yields with a production rate of ~ 0.5 g/h. One can argue that the flow set-up leads to an overall reduced consumption of the problematic solvents, and to an eventually higher efficiency of the route when compared to batch; a quantification of these aspects is, however, not possible on the basis of the accessible data.



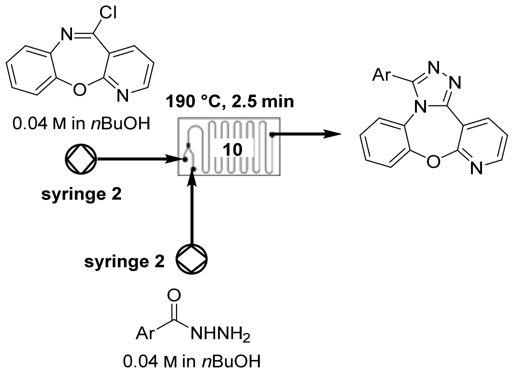
Scheme 27: Flow synthesis of imidazo-oxadiazoles according to Cosford *et coll.*[98]

An oxadiazole was also formed in flow during the above-discussed synthesis of herbicide 5-(6-(trifluoromethyl)-1*H*-indol-3-yl)-1,3,4-oxadiazol-2(3*H*)-one (Table 16, entry 4).[68] Ethyl 6-(trifluoromethyl)-1*H*-indole-3-carboxylate was combined with hydrazine in THF and directed in a coil reactor at 100 °C to furnish an acylhydrazine that is ultimately mixed with an additional stream containing CDI in THF in a second flow coil for oxadiazole formation on the previously generated indole scaffold (*vide supra*, Table 3, entry 10) after in-line purification and re-crystallisation in 82% yield. The process could be further optimised using triphosgene instead of CDI, requiring just an in-line purification using *N*,*N*-dimethylbenzylamine (QC-DMA) as polymeric basic scavenger (Scheme 6).

2.2.18 Benzoxazepines

Benzoxazepine-based compounds display different biological activities like anticonvulsant, antimicrobial and anticancer; besides, antipsychotic agents, calcium antagonists and neuroprotective compounds comprising benzoxazepine motifs have been reported.[175-178]

In 2017, Ranasinghe *et al*. developed a Pellizzari intramolecular cyclisation-based access towards fused triazolo-pyrido benzoxazepines comparing a flow and microwave-mediated route (Scheme 28).[179] The realised 1,2,4-triazolo-pyrido[2,3-b][1,5]benzoxazepines are structurally similar to known antipsychotics, such as loxapine and JL13, and could thus have a role in CNS disorders. 12 compounds were synthesised first in the MW-based batch approach in good yields between 54% and 98%. When a solution of 5-chlorobenzo[*b*]pyrido[3,2-f][1,4]oxazepine (0.04 M) and a solution of hydrazide (0.04 M) in *n*-BuOH were reacted in a tubular flow reactor for a residence time of 2.5 minutes at 190 °C, triazolo-pyrido benzoxepines were obtained in yields between 57% and 99%, as such comparable to batch, but indicating an increase in space-time yield. Since for this type of reaction only good mixing and effective heating are needed, as such both easily realisable in flow, this paper demonstrates once more that MW heating might be exchangeable with an effective conductive heating as possible in flow chemistry set-ups, especially in case of homogeneous reactions.



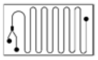
Scheme 28: Benzoxazepines in flow *via* Pellizzari intramolecular cyclisation as proposed by Ranasinghe *et al.*[179]

2.2.19 Thiazoles and benzothiazoles

Thiazoles are present in a broad range of biologically active small molecules and natural products, especially in marine organisms. Thiazoles, as well as their reduced counterparts and their fused derivatives, display antitumor, antihypertensive, antibacterial, antihypnotics, antiallergic, antischizophrenic, antithrombotic and antifungal activities.[180]

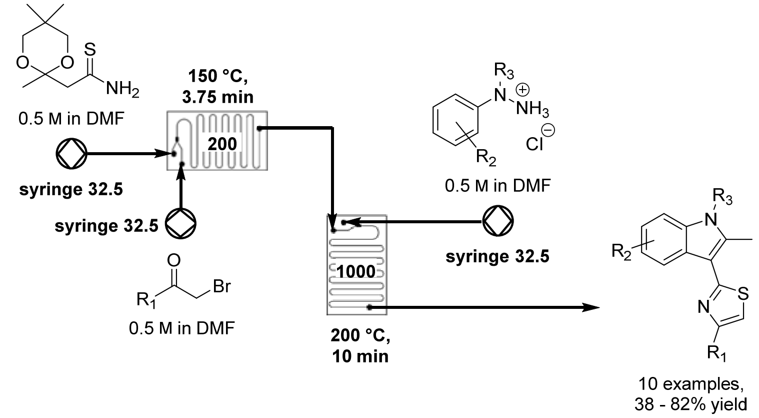
A flow approach towards thiazole motifs was published in 2011 by Pagano *et al.*, which reported a telescoped multistep continuous flow synthesis of 5-(thiazol-2-yl)-3,4-dihydropyrimidin-2(1*H*)-one (DHPM) derivatives (*vide supra*, Table 9 entry 4) (Table 17, entry 1).[118] Starting from ketal-protected thioamide and α-bromoacetophenone, a residence time of 5 minutes in a tubular reactor held at 150 °C furnished a library of 10 compounds isolated in moderate to excellent yields, with the best outcomes obtained when the α-bromoacetophenone component was activated with an electron-rich group. Molar equivalents of HBr and water are released *in situ* as by-products that could catalyse the Biginelli reaction, which was explored in this study to produce the DHPM scaffold of the target compounds as discussed before (*vide supra*, Table 9 entry 4). Products had to be purified chromatographically off-line. In terms of sustainability, the devised telescoped reaction sequence represents a nice example of how by-products can be used as catalysts in a subsequent step. From a green chemistry-point of view, the presented approach suffers from the use of DMF as solvent; no information regarding a screen aiming at the use of a greener solvent is reported.

Table 17: Thiazoles and benzothiazoles in flow.

Entry	Approach	Starting compound(s)	Reactor [a]	Structural scope	Yields [%]	Comments	Ref / year
1	cyclocondensation, then Biginelli reaction				49-91 (condensation), 39-46 for DHPMs	10 compounds, 8 Biginelli products in telescoped manner using third stream	118 / 2011
2	cyclocondensation, then Fischer indole synthesis				41-65 (unsubstituted hydrazines), 38-82 (substituted)	22 compounds	64 / 2012
3	copper-catalysed A^3 coupling reactions				27-93	15 compounds, flow synthesis allowed for products not accessible in batch	181 / 2017
4	condensations and α-brominations, cyclocondensation				89	1 example in telescoped sequence with high space-time yields	182 / 2018
5	oxidative cyclisation using heterogeneous manganese catalysis				95-99	1 compound, gas pressure for realising flow of reagents	159 / 2019
6	cyclocondensation		H-cube,		33-82	5 compounds, only one example using a telescoped approach	145 / 2015

a: For reactor type acronyms, refer to Figure 1.

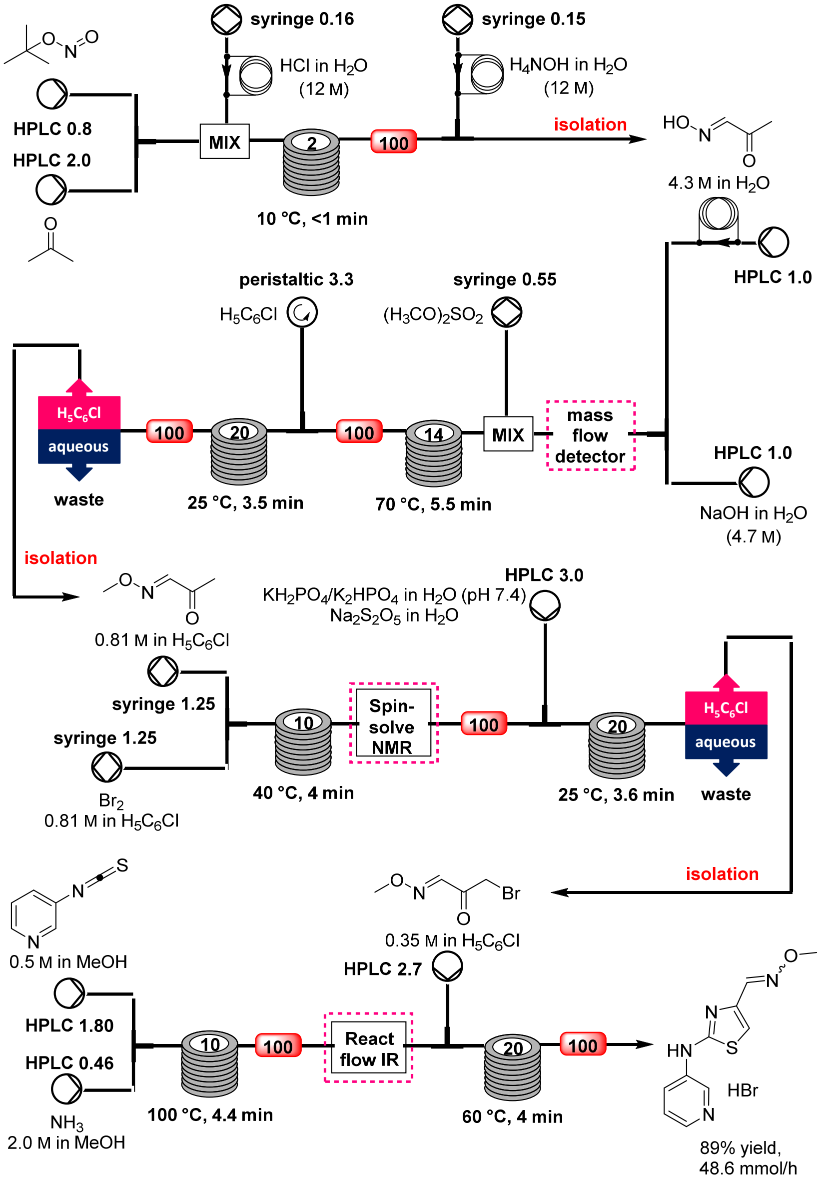
The group around Cosford reported also on a multistep continuous flow synthesis of 2-(1*H*-indol-3-yl)thiazole derivatives (*vide supra*, Table 3, entry 11) (Scheme 29) (Table 17, entry 2), choosing an overall very similar approach to the just discussed.[64] Aldehyde and urea used for synthetizing DHPM derivatives were replaced with hydrazine hydrochloride to provide indolyl-thiazole motifs. Starting from ketal-protected thioamide and different α-bromoketones, ketothiazoles were obtained after approx. 4 minutes at 150 °C in a glass reactor. The liberated HBr could be used as acid catalyst for the subsequent Fischer indole condensation, as discussed above (*vide supra*, Table 3, entry 11). A total of 12 indolylthiazoles were synthesised in moderate yields stating from unsubstituted hydrazines. An additional library of 10 compounds was then produced to explore substituted hydrazines (as hydrochloride salts or free base) and non-substituted ketothiazoles. A direct synthesis of free indolylthiazoles in flow was not achieved, due to an incompatibility of deprotection conditions with the flow set-up developed. Just as the preceding work, the major drawback of this work is once more the use of DMF as a master solvent.



Scheme 29: Flow synthesis of 2-(1*H*-indol-3-yl)thiazoles according to Cosford *et coll*.[64]

In 2017, Rassokhina *et al.* developed a synthesis in flow of imidazo[2,1-*b*]thiazoles *via* copper-catalysed A^3 coupling reactions, hence starting from a mixture of aldehyde, alkyne and amine (Table 17, entry 3).[181] Unfortunately, amines were reacted only off-line with aldehydes to form the necessary imine in a first step that could eventually be imagined to represent an initial step in a larger telescoped flow sequence (*vide infra*, Addendum). Imines were then used in a copper-catalysed cyclisation process in flow: for example, (*E*)-*N*-(benzo[*d*]thiazol-2-yl)-1-phenylmethanimine was mixed with propiolate in anisole just before the mixture was passed into a column reactor filled with CuI/SiO_2 in a 1:1 ratio, held at 200 °C , to obtain an imidazo[2,1-*b*]benzothiazole after 15-20 minutes of reaction time and 1.5-2 mL/min flow rate. Alternatively, CuI granules could be employed to obtain the thiazole derivatives. A library of 15 products was obtained, with generally higher yields with respect to batch counterparts performed within the same group. More importantly, use of the flow method allowed synthesis of thiazole derivatives that could not be obtained in batch in the group; these were isolated in flow in yields between 63% and 93%. Scaling possibilities using the developed flow process with CuI granules as catalyst were evidenced synthesizing methyl [6-(4-chlorophenyl)imidazo[2,1-*b*][1,3]thiazol-5-yl]- acetate in 1.8 g on 9 mmol scale, corresponding to a 65% yield, a value that corresponded to the ones reported for the smaller screening scale. A potential issue in this synthesis is the leaching of the copper catalyst. Unfortunately, the authors do not explicitly address this issue, which could, however, be tackled using an effective catching protocol with polymeric thiourea (QP-TU) as demonstrated by other studies (Table 7, entries 1 & 2).

In 2018, Godineau and Battilocchio reported a telescoped multistep synthesis of C_4 oxime-substituted thiazoles in continuous flow (Scheme 30) (Table 17, entry 4).[182] In batch, this synthesis required only a three-step sequence, but scale-up proofed to be difficult. In flow mode, a partly convergent, partly semi-telescoped way involving the use of elemental bromine was designed, primarily for increasing space-time yields. First, 2-oxapropanal oxime is synthesised in 88% yield and 94% purity by reacting *in-situ*-generated m\nitrosyl chloride with aqueous ammonia. A 4.3 M solution of this oxime in H_2O was then combined with a 4.7 M solution of aqueous NaOH, efficiently mixed with dimethyl sulphate introduced *via* third stream, and passed into reactor coil at 70 °C to finish methylation in 5 minutes. Chlorobenzene was then introduced into the flow system to allow for a liquid/liquid separation providing 73% of chlorobenzene-solubilised product collected in a reservoir, from which it was transferred into a tubular reactor held at 40 ºC after being mixed with a solution of elemental bromine in chlorobenzene. Semi-in-line work-up with aqueous phosphate buffer and sodium bisulfite yielded a diluted solution of 3-bromo-2-oxopropanal as instable reactant. This reactant was brought immediately in contact with 1-(pyridin-3-yl)thiourea, which in turn was synthesised in flow starting from a solution of isothiocyanate and one of ammonia. After mixing, the emulsion was passed through a reactor coil at 60 °C for a total residence time of 4 minutes to give the final product 2-(pyridin-3-ylamino)thiazole-4-carbaldehyde *O*-methyl oxime in 89% yield as a mixture of *E*/*Z* isomers. No information regarding the purity of the final product is given. The presented flow approach was capable of delivering 1.4 g of material in 1 hour, in its dissected version. The group used advanced, economically demanding in-line analysis tools for process monitoring, namely a flow FT-IR cell and a flow benchtop NMR. As in the other cases encountered in this review, that used advanced monitoring technologies, these are un-doubtfully helpful for optimisation, but eventually not absolutely necessary for net product generation. The overall process is difficult to be judged in terms of sustainability and green chemistry principles. Some of the steps inevitably generate stoichiometric amounts of byproducts that require removal in recurrent aqueous work-ups. Chlorobenzene as master solvent, however, represents a green choice in terms of chlorinated solvents that were needed for hosting the presented chemistries.



Scheme 30: Flow synthesis of 1-(pyridin-3-yl)thiazoles) by to Godineau and Battilocchio *et coll.*[182]

Benzothiazole is a privileged bicyclic ring system with anticancer, antimicrobial, antidiabetic, anticonvulsant, anti-inflammatory, antiviral and antitubercular activities.[183] In particular, 2-aminobenzothiazoles are broadly employed in drug discovery and development. Investigations into the preparation of 2-aminobenzothiazoles date back to early 1900s with the work of Hugerschoff, who found that an arylthiourea can be promptly cyclised with liquid bromine in chloroform to generate the corresponding 2-aminobenzothiazole. Although this reaction usually proceeds efficiently at room temperature, several drawbacks are associated with the handling of liquid bromine, and the risk of generating brominated side products.[184]

Ferlin's continuous multi-step flow process for the synthesis of 2-arylbenzoxazoles catalysed by heterogeneous manganese systems (*vide supra*, Scheme 25, Table 15 entry 7).[159] proofed principally robust enough to host also sulphur-containing substrates. This could be exploited for the synthesis of a 2-arylbenzothiazole in an otherwise unchanged set-up (Table 17, entry 5).

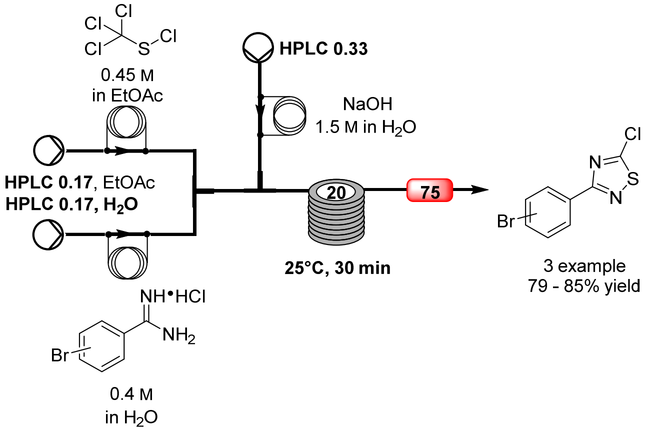
Lövei and co-authors developed a multistep continuous-flow process for generating condensed tricyclic benzothiazole derivatives, exhibiting furan-, thiophene- and pyrrole motifs (Table 17, entry 6).[145] Benzofurans (*vide supra,* Table 13, entry 4) and benzothiophenes were synthesised in flow in a first step, to be then condensed with NH_4SCN to form the target benzothiazoles; the two reactions have not been telescoped. Variable yields were obtained for a total of 5 examples, as such comparable to batch processes employing the same chemistries in the authors' laboratories. Higher yields were generally obtained for 2-hydroxy-5-nitrobenzaldehyde indicating the importance of the steric reasons for cyclisation, compared to the 3-nitro isomer in which the closure was less favourable.

With the application of a multistep flow protocol, ethyl 2-amino-6*H*-thiazolo[5,4-e]indole-7-carboxylate was synthesised without isolation of intermediate species and intermediate purification, handling the bromine step safely in flow. Starting from a 50 mM solution of ethyl 5-nitro-1*H*-indole-2-carboxylate in DMF that is pumped through a column filled with 10% Pd/C in the presence of 1 bar of hydrogen using the H-cube. The resulting amine was then mixed with 5 equiv. of NH_4SCN in 10 mL of DMF *via* the addition of a second stream. The mixture was reacted inside a PTFE coil reactor over 30 minutes at ambient temperature before it was brought in contact with 1.2 equivalents of bromine, dissolved in 20 mL of an equivolume mixture of DMF and NH_4Br-saturated MeOH, forcing the closure of the benzothiazole ring in a second PTFE coil reactor for 30 minutes at ambient temperature. The yield obtained for ethyl 2-amino-6*H*-thiazolo[5,4-e]indole-7-carboxylate in the telescopic reaction is 33% after recrystallization, with a 24 mg/h of productivity.

2.2.20 Thiadiazoles

The thiadiazole ring is an important privileged scaffold with broad-spectrum biological activity. Among the possible thiadiazole isoforms, the most investigated ones are the 1,2,4- and 1,3,4-thiadiazoles. The thiadiazole substructure plays a crucial role as bioisostere of pyrimidine and oxadiazole rings, therefore exhibiting a broad applicability in drug design. In particular, the presence of a sulphur atom imparts increased liposolubility and ability to cross biological membranes. The thiadiazole moiety is an essential constituent of some important synthetic drugs covering a wide spectrum of biological activities used in anticancer, anti-inflammatory, antitubercular, antibacterial, antifungal, antiviral, anticonvulsant, and antiparasitic applications.[185]

In 2017, Baumann and Baxendale developed a continuous flow synthesis of 1,2,4-thiadiazoles to avoid batch risks associated with the use of trichloromethane sulfenylchloride (Scheme 31).[186] A solution of hydrated benzamidine hydrochloride in aqueous NaOH was mixed with a solution of trichloromethane sulfenylchloride in EtOAc, before the principally biphasic flow entered in a tubular flow reactor kept at room temperature. After 5 minutes of residence time, during which the phases separated in distinguishable droplets, 5-chloro-1,2,4-thiadiazole was provided with 80% yield. Although the reaction proceeds well in 5 minutes, the formation of hazardous by-products could be completely avoided only by extending the reaction/residence time up to 30 minutes. A realised scale-up to 20 mmol yielded 3.25 g of the product corresponding to 83% yield.



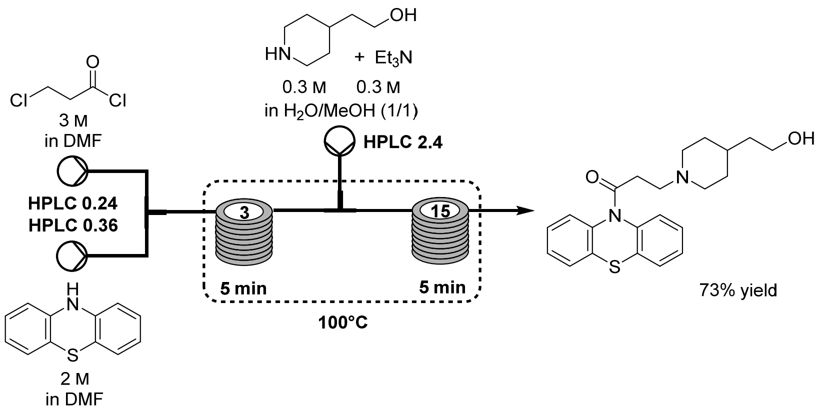
Scheme 31: Flow synthesis of bromo-substituted thiadiazole according to Baxendale *et coll.*[186] For the synthesis of non-brominated analogues, NaOH can be directly mixed with the hydrazone, omitting the third stream addition.

To extend the utility scope of 5-chloro-1,2,4-thiadiazoles, insertion of a bromide on the phenyl motif in different positions was considered useful. To produce such products in flow, the initial benzamidine hydrochloride was substituted with bromophenylamidine hydrochloride in water and sequestering of the acid by addition of aqueous NaOH *via* third stream only after the biphasic system had been generated upon reagent mixing. After 30 minutes of residence time, 3 bromo-containing products were obtained in 79-85% yield after chromatographic purification.

2.2.21 Phenotiazines

Phenothiazine is related to the thiazine-class of heterocyclic compounds which are the most widely used compounds in the treatment of major psychoses. Phenothiazine derivatives have been found to behave as potent dopaminergic, histaminergic, serotonergic, cholinergic and glutaminergic antagonists.[187] Moreover, some phenothiazine derivatives showed analgesic, diuretic, anti-microbial and anti-depressants effects.[188] Relevant is also their antitumor potential which is ascribable to several mechanisms, including an apoptosis-inducing effect, inhibition of efflux pumps, and inhibition of angiogenesis.[189, 190]

In 2019, Movsisyan *et al.* reported a proof-of-principle study on phenothiazine-derived antipsychotics, using a telescoped flow synthesis for the derivatisation of the phenothiazine core (Scheme 32).[191] A 3 M solution of 3-chloropropionyl chloride in DMF and a 2 M solution of 10*H*-phenothiazine in DMF were mixed and pumped through a coil reactor at 100 °C, with a residence time of 5 minutes, to give 3-chloro-1-(10*H*-phenothiazin-10-yl)propan-1-one in 97% conversion. The alkyl chloride underwent final nucleophilic substitution applying a third stream containing a solution of 4-piperidineethanol in DMF and triethylamine in H_2O/MeOH at 100 °C in 5 minutes. 3-(4-(2-hydroxyethyl)piperidin-1-yl)-1-(10*H*-phenothiazin-10-yl)propan-1-one was obtained in 73% yield, without the further need of purification. The obtained yield is significantly higher than the one obtained in batch mode for the same product, *i.e.*, 31%, involving also two purification steps, as demonstrated by the same group in an earlier study.[192] The flow process allowed for considerably shorter reaction times, *i.e.*, 10 minutes instead of 1 day, lower reaction temperatures, *i.e.*, 100 °C instead of 130 °C in batch, and optimisation of stoichiometries, such as to improve overall process performance.

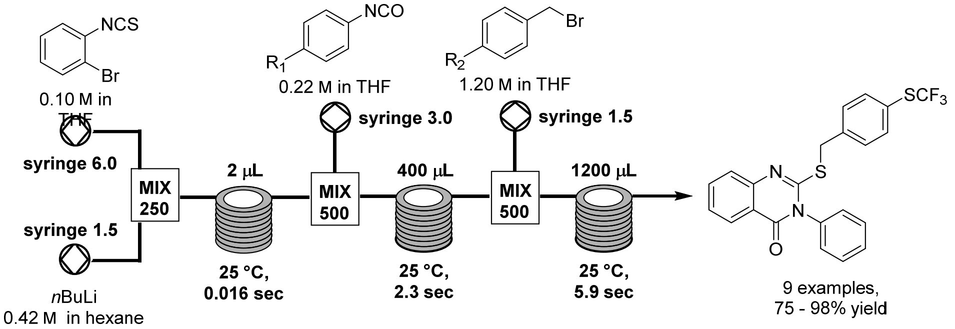


Scheme 32: Proof-of-principle study on phenothiazines in flow by Movsisyan *et al.*[191]

2.2.22 Thioquinazolinones

Quinazolinone derivatives represent a class of drugs with hypnotic and sedative function, such as afloqualone, cloroqualone, and diproqualone. Quinazolinone derivatives were additionally found to exhibit anti-inflammatory and antifungal properties.[193] *S*-functionalised thioquinazolinones have recently been reported as a new type of bioactive chemical structure with antiplatelet activity that prohibits platelet aggregation induced by arachidonic acid and collagen.[194]

The three step flow synthesis delivering these scaffolds, as demonstrated by Kim *et coll.* in 2015,[195] also on a gram scale, in microreactors (Scheme 33), commenced with a classic bromine-lithium exchange in THF. Using an unusually high total flow rate of 7.5 mL/min after mixing of *o*-bromophenyl isothiocyanate and *n*-BuLi at 25 ºC, allowed for flash chemistry conditions that helped maintaining control over selectivity by having residence times of only 16 milliseconds. Quench of the aryllithium was achieved by addition of phenyl isocyanate derivatives, delivering the *S*-lithiated thioquinazoline core that could be readily alkylated using various benzyl bromides. Overall yields obtained for the library of 9 compounds, each synthesised in seconds, ranged from 75% to 98% after recrystallization.



Scheme 33: Thioquinazolinones in flow according to Kim *et coll.*[195]

3 CONCLUSIONS AND OUTLOOK

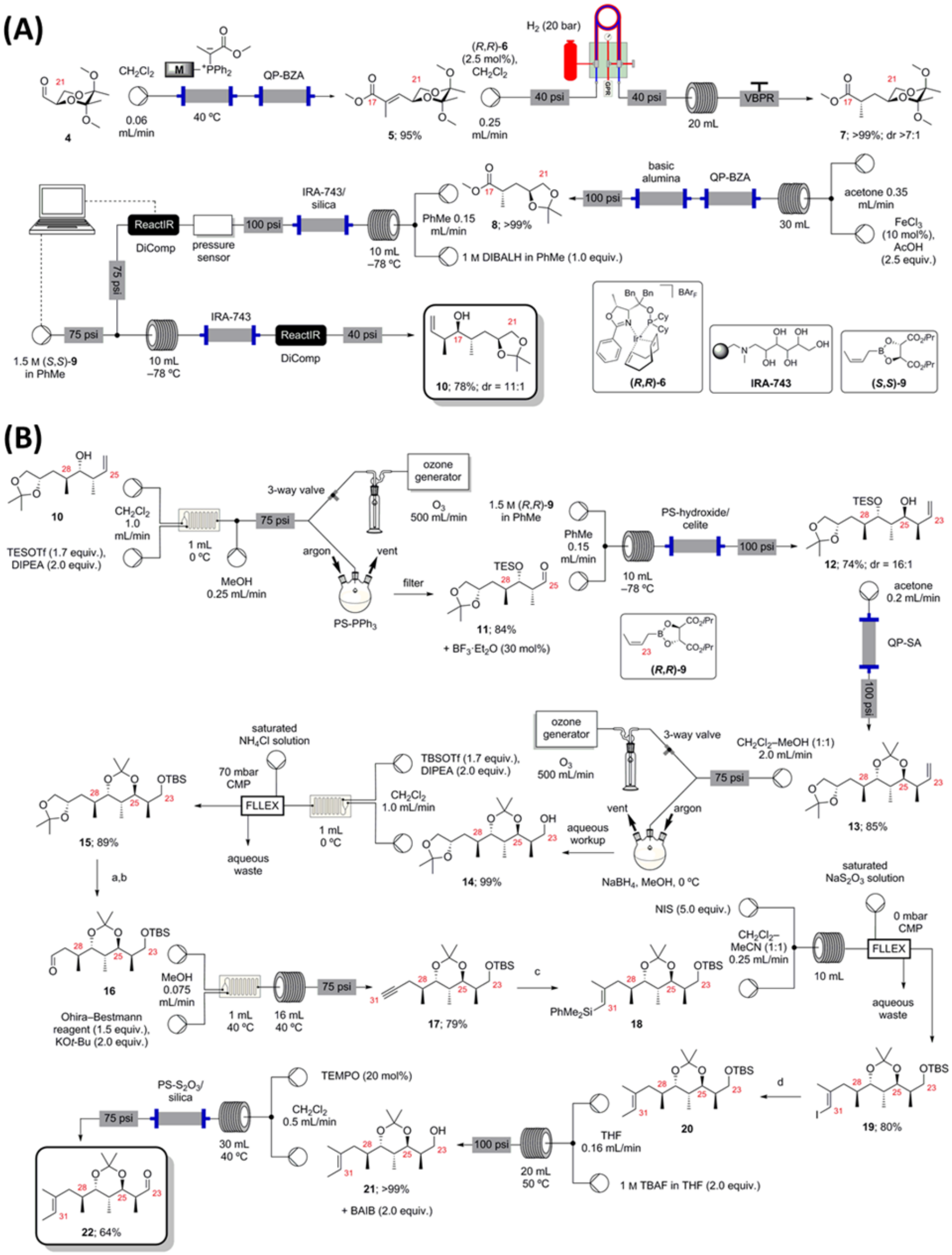
The scene seems set after nearly two decades of flow chemistry. The contributions and examples discussed within the present review demonstrate that practically all privileged scaffolds can be generated using flow chemistry approaches. Looking at the development of the field as a whole over the last 15 years, it is evident that the main developments and challenges shifted from the chemistry to the technology/engineering field. Felpin's self-optimising flow reactors[196] or Lin's three step pyrazole formation[89] and Kim's three step thioquinazolinone synthesis,[195] done each in less than 1 minute are probably to be seen as spearheads of novel and needed main directions in the field, also in the context of the new socio-economic settings that are drastically different from the ones in the early 2000's when the meso- and microscale flow chemistry field emerged.

On a more pharmaceutical point of view, the current huge potential in terms of high-throughput biochemical or phenotypic assays, justifies the increasing requirement for rapid and diversity-oriented library generation. Flow-based technologies may nicely boost the armamentarium towards quick hit compounds generation, and the work by Ley[85] that splits the stream containing the score scaffold in four for realising four different heterocycles in parallel is a well-fitting example. In this respect, also Cosford's contributions[64, 98] detailing the formation of a first heterocycle that gets subsequently decorated in a telescoped sequence by a second privileged motif, and Baumann's recent photoflow-induced isomerisation of isoxazoles to oxazoles,[153] represent additional seminal works towards diversity-oriented syntheses already more compliant with green and sustainable aspects.

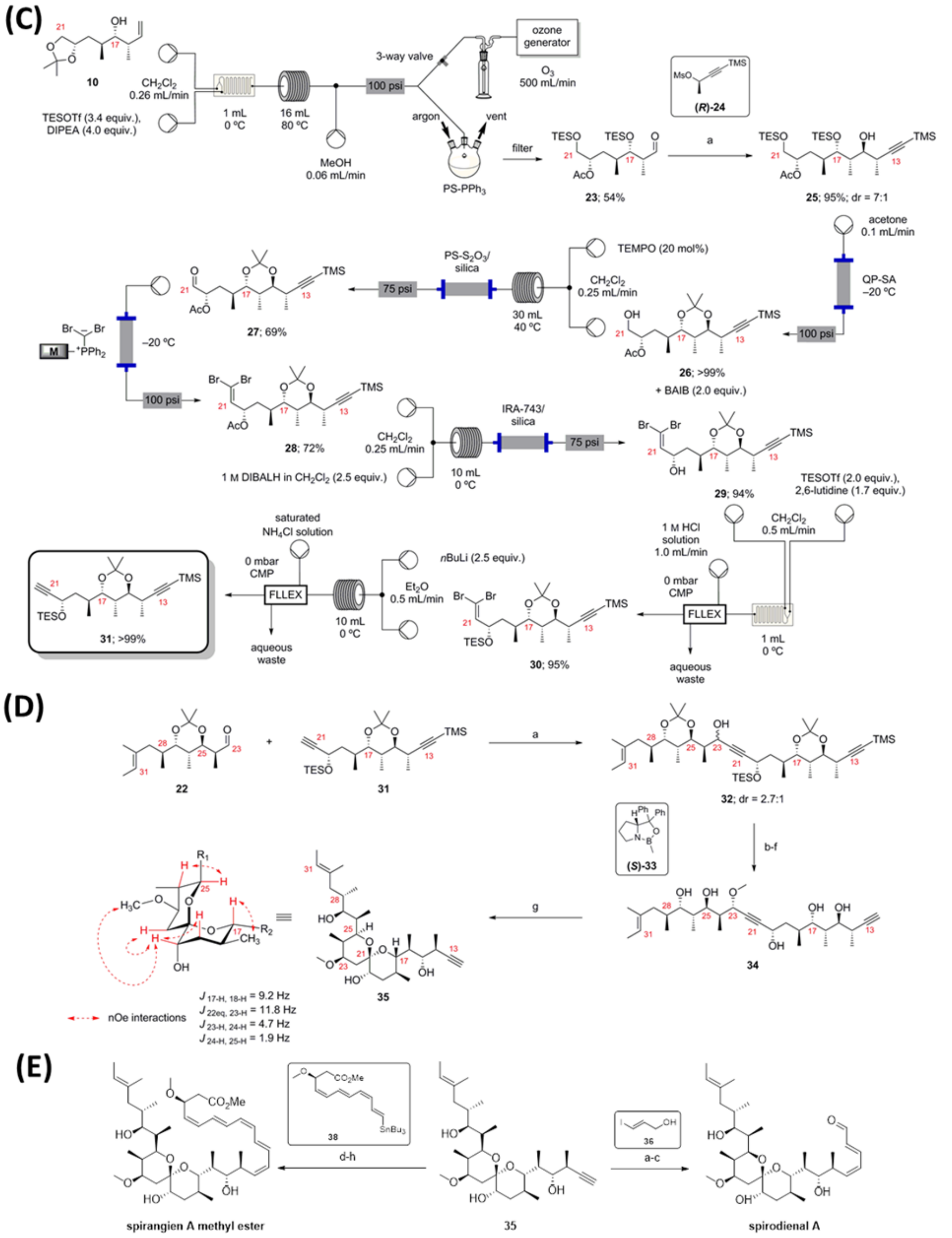
In terms of scaling up productions, the conventional approach of 'leaving running the reactor for a longer time' is eventually productive, but can be time-consuming, especially in cases of very low flow rates. Future efforts might thus want to take lessons from Nieuwland *et* al.[52] for realising scale-ups by parallelising flow paths. More convergent than just telescoped approaches as demonstrated by Karlsson *et al*.[45] on scale probably indicate as well valid options to a further advancement.

From an organic chemistry perspective, the challenges return, or persist, to be the basic evergreens, especially nowadays additionally flavoured by the finally pressing environmental concerns that cannot be negated any more. While most of the discussed synthesis managed to make progress, also significant, in terms of atom economy and reaction efficiency thanks to the control offered by flow chemistry, the widespread use of non-green solvents, such as DCM or DMF for ensuring solution, represents a persisting, notorious problem, like a reminiscence from older-fashioned batch syntheses and the inherent nature of heterocycles. Finding functional, efficient and maybe even elegant synthetic routes to new actives that comply with green chemistry principles and carbon footprint constraints, especially with respect to the solvent issue, is thus a crucial point awaiting true inputs.

Curiosity, hands-on mentality and a certain level of explorative spirit are needed, in close collaborations between chemistry and engineering, to make the most of this set scene in the very near future. The fact that flow approaches are not only enabling the field of syntheses of privileged heterocyclic scaffolds, but eventually help to also facilitate synthesis on scale of complex molecules, shall be shown, as a kind of additional incentive, by the last example touched: the total synthesis of natural spirocyclic polyketide spirangien A and its derivative spirodienal A using flow chemistry for the larger part. These two metabolites isolated from myxobacterium Sorangium cellulosum, strains So ce90 and KM0141, respectively[197, 198] showed activity against several yeasts and fungi. Traditional batch synthesis were realised for spirangien A[199] and its spiro core element.[200-202] The flow total synthesis, realised by Newton and Carter and their team in Ley's laboratory between 2008 and 2012,[203] with more than 50% of the steps in flow is still a benchmark, in both the field of flow chemistry technology development and flow chemistry application. The work shows that there is virtually no type of major chemistry left that has not been shown to be advantageously feasible in flow mode. The convergent synthesis consisted of a total of 41 steps, with 23 steps realised in flow for production of key building blocks (Scheme 34). A large number of steps were realised using cutting edge flow technologies that in part were specifically developed as new methods also in the context of the needs emerging from this total synthesis: automated reagent addition,[204] diastereoselective crotylations,[205] and diastereoselective reductions,[206] all of which iteratively and dramatically accelerating the parallel synthesis of main fragments in combination with parallel but independently emerging flow transformations beyond heterocycle formation. Scheme 34 shows the integrated flow/batch total synthesis as a whole. In the context of this review, a detailed discussion of the various steps and technologies shall be omitted; the Scheme demonstrates on its own the general range of applicability of flow chemistry.



Scheme 34-1: Total synthesis of spirangien in combined flow/batch mode.[203] (A) Flow synthesis of homoallylic alcohol **10**. M = monolith; QP = QuadraPure; BZA = benzylamine; psi = pounds per square inch; VBPR = variable back pressure regulator; DIBALH = diisobutylaluminium hydride; Cy = cyclohexyl; (B) Flow synthesis of aldehyde **22**. Reagents and conditions a) TMSOTf, DIPEA, CH_2Cl_2, 0 °C → RT, 89%; b) $NaIO_4$, THF–H_2O (1:1), RT, 95%; c) CuCN, $PhMe_2SiLi$, THF, 0 °C, then MeI, 0 °C, 90%; d) $PdCl_2(PPh_3)_2$, Me_2Zn, THF, RT, 82%. TESOTf = triethylsilyl trifluoromethanesulfonate; DIPEA = *N*,*N*-diisopropylethylamine; PS = polymer-supported; SA = sulfonic acid; TBS = *tert*-butyldimethylsilyl; FLLEX = flow liquid-liquid extractor; CMP = cross membrane pressure; NIS = *N*-iodosuccinimide; TBAF = tetrabutylammonium fluoride; BAIB = *bis*(acetoxy)iodobenzene; TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl.



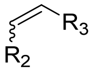
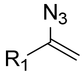
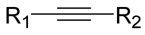
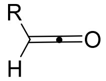
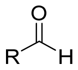
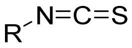
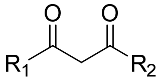
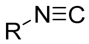
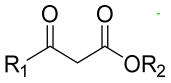
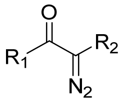
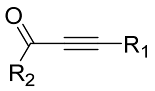
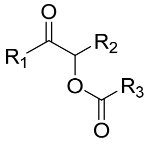
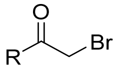
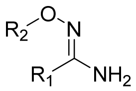
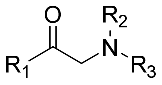
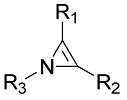
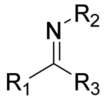
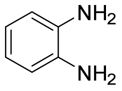
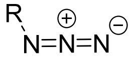
Scheme 34-2: Total synthesis of spirangien in combined flow/batch mode.[165] (C) Flow synthesis of *bis*-alkyne **31**. Reagents and conditions a) (*R*)-**24**, Pd(OAc)$_2$, PPh$_3$, Et$_2$Zn, THF, 0 °C → –78 °C → –20 °C → RT, 95%. Ms = methanesulfonate; TMS = trimethylsilyl; (D) Reagents and conditions a) **31**, *n*BuLi, THF, –78 °C, then **22**, –78 °C → RT, 87% (>99% brsm); b) MnO$_2$, CH$_2$Cl$_2$, RT, 97%; c) (*S*)-**33**, BH$_3$·Me$_2$S, THF, –30 °C, 91%; d) NaH, MeI, THF, 0 °C → RT, 99%; e) TBAF, THF, RT, >99%; f) QP-SA, MeOH, RT, >99%; g) AuCl, PPTS, CH$_2$Cl$_2$, –20 °C → RT, 30%. PPTS = pyridinium *p*-toluenesulfonate; (E) Reagents and conditions a) **36**, Pd(PPh$_3$)$_4$, CuI, Et$_3$N, PhH, RT, 90%; b) Zn(Cu/Ag), MeOH–H$_2$O–THF (1:1:1), 40 °C, 59%; c) MnO$_2$, CH$_2$Cl$_2$, RT, 84%; d) TESOTf, 2,6-lutidine, CH$_2$Cl$_2$, –78 °C → 0 °C, 59%; e) NIS, AgNO$_3$, acetone–DMF (5:1), RT, 49%; f) NBSH, Et$_3$N, *i*PrOH–THF (1:1), RT, 93%; g) CSA, MeOH, RT, 91%; h) **38**, Pd$_2$(dba)$_3$, AsPh$_3$, DMF–THF (4:1), RT, 43%. NBSH = 2-nitrobenzenesulfonylhydrazide; CSA = (±)-camphor-10-sulfonic acid; dba = dibenzylideneacetone.

4 ADDENDUM – UNSTABLE OR UNPLEASANT STARTING MATERIALS IN FLOW-MODE

The various privileged scaffolds discussed were realised starting from more or less reactive smaller building blocks that are typical for, if not characteristic within, the area of heterocycle formation. While such heterocycles, and hence their syntheses are of interest due to their role in actives, the generation of the starting materials, and here especially the 'real' starting materials is obviously a neuralgic point. Lots of groups work on the realisation of useful, interesting and eventually rather reactive starting materials in flow mode. Their contribution to the discussed topic is thus not to be underestimated. Some of the discussed scaffold syntheses do this starting material formation in flow in form of dedicated initial steps. In the various tables, little green coil reactor symbols indicate that the listed stable starting material can be realised in flow mode. Table 18 lists these starting materials again in a general fashion and gives exemplary additional references for their flow generation, allowing as such generally imagining longer telescoped flow chemical synthesis of privileged scaffolds starting from really simple precursors.

In case the starting materials for the heterocycle formation are either toxic and/or chemically not stable, their *in situ*-generation is a convenient entry into the synthesis. Table 18 lists thus also explicitly these reactive and/or toxic intermediates with additional references that exemplary detail their flow generation.

Table 18: Generation of reactive or instable (‘real’) starting materials in flow.

Entry	Starting material	Reference		Entry	Starting material	Reference
1	 alkenes	207-211		11	 vinyl azides	55
2	 alkynes	104		12	 ketenes	44, 45
3	 aldehydes	104, 212, 213		13	 isothiocyanates	214
4	 1,3-diketones	215		14	 isocyanates	107
5	 β-ketoesters	216		15	 diazo ketones	134
6	 ynones	85, 89		16	 acyloxy ketones	94
7	 α-halogenated carbonyls	217		17	 amidoxims	64, 118
8	 α-aminocarbonyls	218, 219		18	 azirines	55, 154
9	 imines	212, 220		19	 1,2-diaminobenzene	135
10	 azides	55, 106, 220				

ABBREVIATIONS

7-ACA, 7-aminocephalosporanic acid; A-15, Amberlist-15; A-21, Amberlist-21; ACE, angiotensin-converting enzyme; ACR, agitating cell reactor; BDZ, benzodiazepine; BEMP, 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine; CDI, 1,1'-carbonyldiimidazole; CNS, central nervous system**;** CPME, cyclopentylmethyl ether; CXCR2, CXC chemokine receptor 2; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCE, 1,2-dichloroethane; DCM, dichloromethane; DHP, dihydropyridine; DHPM, dihydropyrimidinone; DIPEA, *N*,*N*-diisopropylethylamine; DMA, *N*,*N*-dimethylacetamide; DMAP, 4-(dimethylamino) pyridine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; DOE, design of experiments; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; ESI-MS, electrospray ionisation-mass spectrometry; 7-ET, 7-ethyltryptophol; FAD, flavin adenine dinucleotide; FLAP, 5-lipoxygenase activating protein; FMN, flavin mononucleotide; FXa, activated blood coagulation factor X; FT-IR, Fourier-transform infrared spectroscopy; GPER, G-protein-coupled oestrogen receptor; HIV, human immunodeficiency virus; HMF, 5-hydroxymethylfurfural; HOBt, hydroxybenzotriazole; HPLC, high performance liquid chromatography; 5-HT_{2C}, 5-hydroxytryptamine; IL, ionic liquid; LC-MS, liquid chromatography-mass spectrometry; LED, light emitting diode; LiHMDS, lithium bis(trimethylsilyl)amide; MHC1, melanin concentrating hormonereceptor 1; *m*CPBA, *meta*-chloroperoxybenzoic acid; MRT, microreactors; MW, microwave; NMDA, *N*-methyl-D-aspartate; NMO, *N*-methylmorpholine *N*-oxide; NMP, *N*-methyl-2-pyrrolidone; NMR, nuclear magnetic resonance; NS5A, non-structural protein 5A; OMS, oxide molecular sieves; PEEK, polyether ether ketone; PEG300, polyethylene glycol with Mn = 300 Da; PFA, polyfluoroacetate; PS, polymer-supported; PTFE, polytetrafluoroethylene; QP-SA, quadrapure-sulfonic acid; QP-TU, quadrapure-thiourea; RI, refractive index; RNA, ribonucleic acid; S_N^{Ar}, nucleophilic aromatic substitution; SS, solid supported; TACA, thiazolyl-7-aminocephalosporanic acid; THF, tetrahydrofuran; US, ultrasound; UV, ultraviolet.

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Notes

The authors declare no conflicts of interest.

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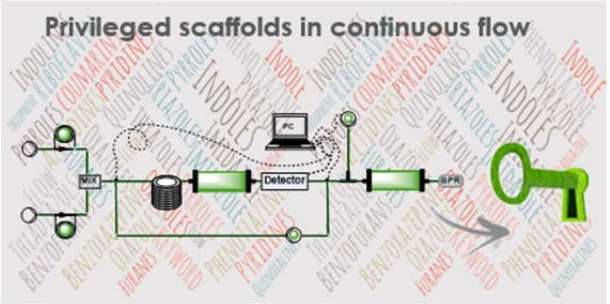

This review discusses the use of flow chemistry as versatile tool for the synthesis and derivatisation of privileged scaffolds, from a point of view of applicability, diversity-oriented synthesis, inherent sustainability and green chemistry aspects.