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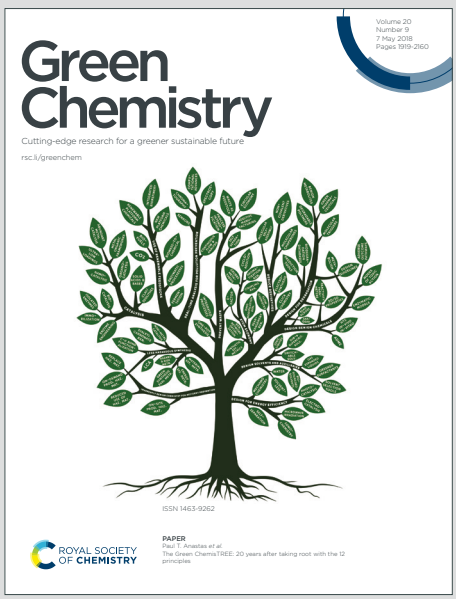

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1. The present review comparatively discusses progress in E-factor, Reaction Mass Efficiency, Space-Time-Yield, and solvent management between the batch and flow approaches to the synthesis of API.

2. The topic is of high interest because it tackles a problem never covered by other contributions that assumes importance for further green development, whether through better batch processes or innovative flow approaches.

3. Future development of the present review should also include energetic, techno-economic, and Life Cycle Assessment analyses in the comparison to provide deeper insight into this matter.

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# Sailing the Stormy Seas of Sustainability: Flow vs. Batch in API Synthesis

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Given the numerous improvements in the flow synthesis of Active Pharmaceutical Ingredients (APIs), this approach has garnered significant attention both from academia and industry. Flow chemistry can indeed shorten synthesis steps and/or reaction time, increase productivity, and generally lead to the creation of new intellectual property. Compared with batch processes, continuous-flow protocols may also facilitate solvent utilisation and often eliminate the need for intermediate isolation, thereby reducing process waste. These features naturally suggest improved sustainability, though it is often expressed more qualitatively than quantitatively. Herein, we systematically compared batch and flow methods for API synthesis. The comparison is based on multiple levels of quantification, including mass-related green metrics (E-factor and unified RME), solvent safety and hazards, as well as space-time-yield, offering a quantitative insight into this subject.

## 1. Introduction

The synthesis of active pharmaceutical ingredients (APIs) aims to balance high quality and high productivity, thereby maximising the yield of the final target compounds.[1] Only over the last three decades, a growing interest has led to the inclusion of additional factors in this balance: the minimisation of waste production,[2] aligned with global awareness of pollution and climate issues.[3] In this context, continuous flow manufacturing of APIs has rapidly expanded due to its ability to meet the needs for high yield, high reproducibility, and cost, space, waste, and hazard reduction.[4] Flow chemistry is no longer considered an 'exotic' way to run chemical reactions.[5] More than a decade after the first pioneering examples, this approach is now recognised by regulatory authorities as compatible with Good Manufacturing Practice (GMP) types of industrial production.[6]

As a further indication of its pivotal role in research and development (R&D), the tutorial aspects, applications, and emerging technologies of flow chemistry,[7] as well as its sustainability solutions and challenges, have been reviewed, shaping the sector's present and future directions.[8] Although numerous studies have highlighted the benefits of the flow approach regarding chemical efficiency, productivity, and techno-economic factors,[8b] there are still some relevant gaps for the accurate measuring of its overall sustainability advantages.

It is widely assumed that performing reactions in flow is generally more convenient and efficient than batch . This is primarily attributable to enhanced control of the main reaction parameters (temperature and pressure) and variables such as mass and heat transfer, reactant mixing, intrinsic safety, and greater contact between reactants and the catalyst. However, sustainability is not a general concept; it is specific, and therefore, there is no technology or approach that is intrinsically green. Labelling a process or technology as 'green' in the absence of quantitative mass metrics and qualitative assessment of procedure benignity and safety may be superficial.

In this context, the use of appropriate green metrics and indicators that can effectively communicate the sustainability improvements provided through flow approaches is pivotal.[9] Environmental factor (E-factor), Process Mass Intensity (PMI), and Reaction Mass Efficiency (RME) are straightforward and intuitive mass-related metrics that can be calculated from detailed experimental procedures. Other indicators, such as Andraos's safety hazard (SHI) and benign index (BI) or similar calculations, are also valuable tools for gaining a more precise, context-specific understanding of a process's sustainability.[10] Importantly, the comparison must allow an intuitive recognition of advantages from non-specialised readers.

At the same time, the comparison should include all necessary details for experts, enabling them to analyse the data and identify trends in the procedures examined.


**Figure 1.** The aim of this review is to compare batch-patented synthesis to available flow synthetic approaches.

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Electronic Supplementary Information (ESI) available

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While flow chemistry can be a more productive and sustainable option compared to batch conditions, this is true only when the process is deliberately designed and developed with these goals in mind. In contrast, batch processes implemented in the pharmaceutical industry are inherently advantageous, as they reliably generate profit for the company. Within this framework, the space–time yield (STY) provides a quantitative, practical metric for assessing and comparing productivity and efficiency across different processing strategies. This is defined as the product amount per unit reactor volume over time. This tool can also help predict the product's economic value by correlating process efficiency with reactor size.[11]

Finally, another key consideration is related to the use of solvents, both as reaction and purification/extraction media. As is well known, solvents constitute a significant mass fraction in most chemical processes, including industrial ones.[12] Thus, it is crucial to evaluate their sustainability profile and potential hazards to operators and the ecosystem.[13] Solvent selection guides are commonly used for this purpose.[14] Additionally, the mass percentage of solvents (aqueous, organic, and eventually halogenated) used, which must be disposed of, can give a rough idea of process costs, regardless of the raw materials or catalysts eventually employed,[15,16]

By combining and measuring all these aspects, it is possible to compare which process is more environmentally sustainable and which delivers the best value in terms of yield relative to the time and space used.

The twofold aim of this review is to address the gap in the literature on quantitative sustainable improvements of flow protocols for API synthesis. While critically comparing the environmental benefits of flow conditions with those of batch processes (Figure 1). With this intention, we aim to provide a standardized, multi-criteria comparison between batch and flow approaches, enabling clearer, more transferable insights for industry.

The review covers 10 examples of largely produced API (Figure 2). The case studies discussed herein were selected based on three criteria.

First, they represent a diverse array of reaction manifolds and levels of route complexity, encompassing both standard unit operations and less common synthetic routes. Second, the selection comprises widely manufactured molecules (preferably listed in the WHO essential medicines list) to ensure as much information as possible on their production. Finally, the examples were filtered from a larger initial pool based on the richness of data availability. The final selection includes only the APIs for which the reported experimental procedures provided sufficient detail to perform the accurate comparative calculations presented in this study.

The review considers E-factor and Reaction Mass Efficiency, safety hazards, and benign Index of solvents used as reaction media and during work-up, the total amount of organic solvent used, the total amount of aqueous solution, reaction time, and space-time yield. Temperature data has been excluded from the assessment as temperature analysis is part of a broader sector, energy costs and consumption, which is outside the scope of this work, but warrants a separate discussion.

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# Journal Name

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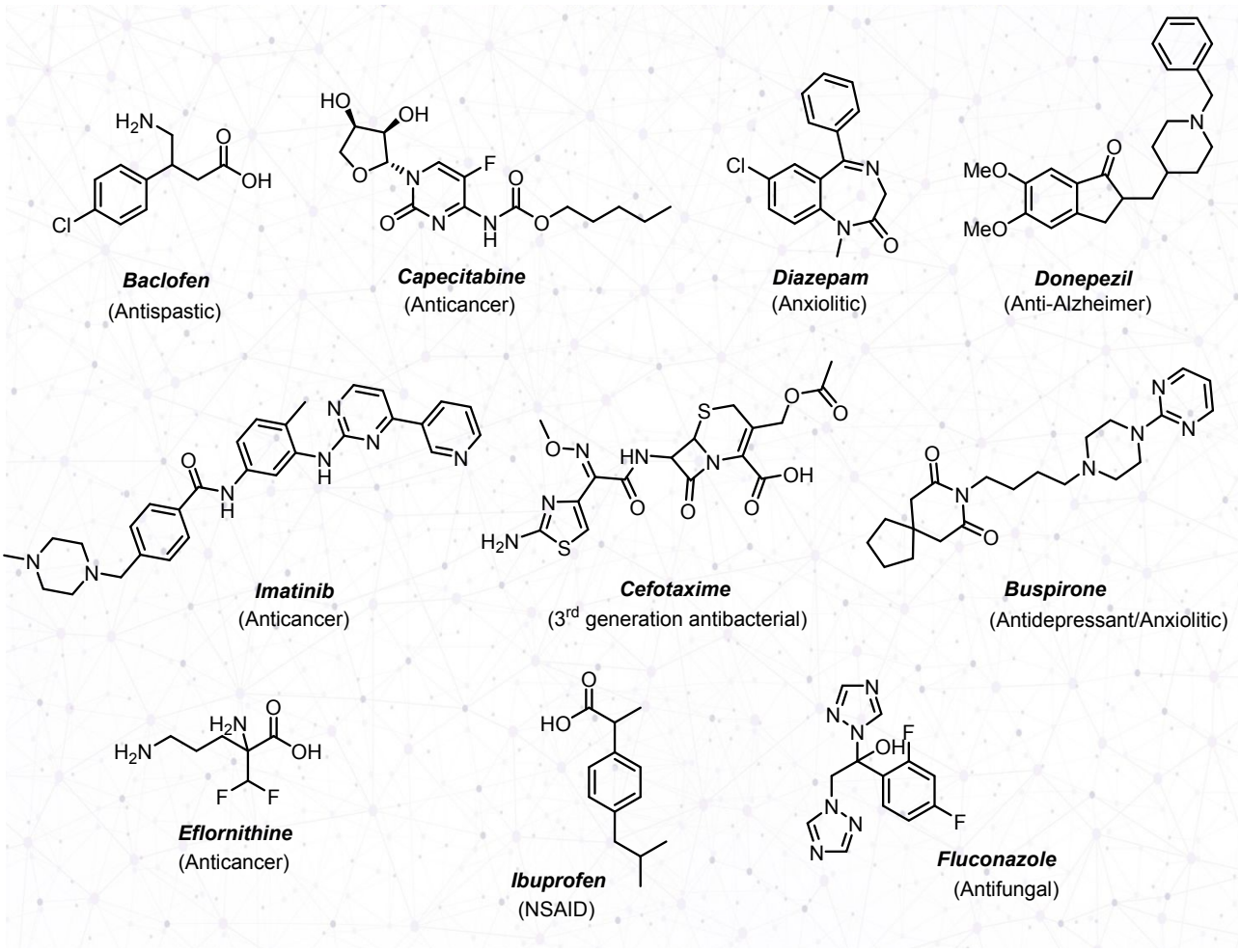


**Figure 2.** APIs discussed in the present review

### 2. Methodology of comparison

As outlined in Figure 3, the comparison is based on E-factor, RME, STY, and on the safety and environmental score associated with the reaction and work-up solvents.

E-factor, RME, and STY were calculated using the following equations:

$$E-factor = \frac{mass\ of\ all\ reagent\ and\ solvents - mass\ of\ recovered\ materials}{mass\ of\ product}$$

$$RME = \frac{1}{1 + E-factor} * 100$$

$$STY = \frac{mass\ of\ product}{reactor\ volume * reaction\ time}$$

To compute the solvent score, 36 common solvents were used (See Electronic Supplementary Information for a detailed description). The 36 solvents were selected based on two criteria: 1) including all solvents necessary to discuss the API examples presented in the text, and 2) including solvents already listed in the CHEM21 solvent selection guide. Solvents (present in the CHEM21 list) that were omitted were excluded because essential information required to calculate the indices, such as Henry's law constants or toxicity data, was unavailable. For each solvent, the omega (Ω) values are calculated using

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Andraos's indexes, considering the environmental (BAP, BCP, INHTP, INGTP, GWP, SFP, CPP) and safety/hazard (FP, CGP, CLP, OELP, RPP) potentials.[10] Based on Ω values, the 36 solvents were ordered, ranked, and normalised against water (baseline score = 1). For each synthetic sequence, the normalised BI and SHI scores for all reaction and work-up solvents were assigned and summed independently to provide the final score. A simplified graphical description of this procedure is given in Figure 3, and a more detailed (normalisation, aggregation, justification, and use) explanation is provided in the Electronic Supplementary Information.

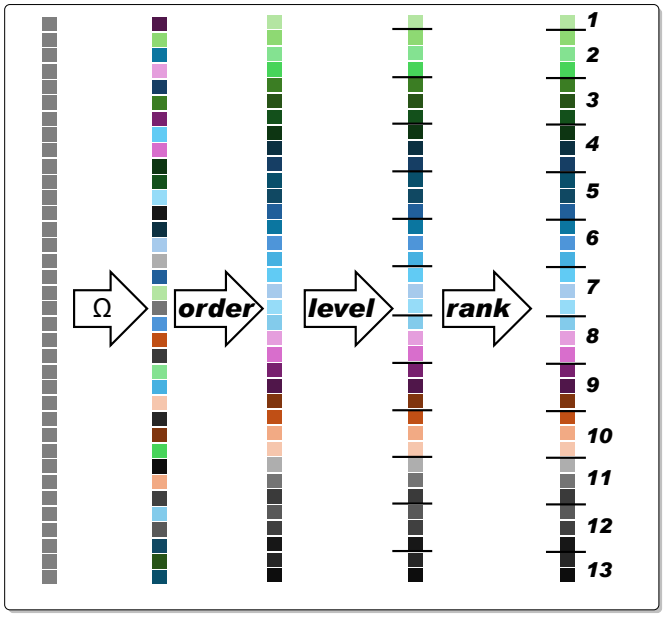



**Figure 3.** Normalization process of BI and SHI indices.

We referred to these rankings as the benign index (BI) and the safety/hazard index (SHI).

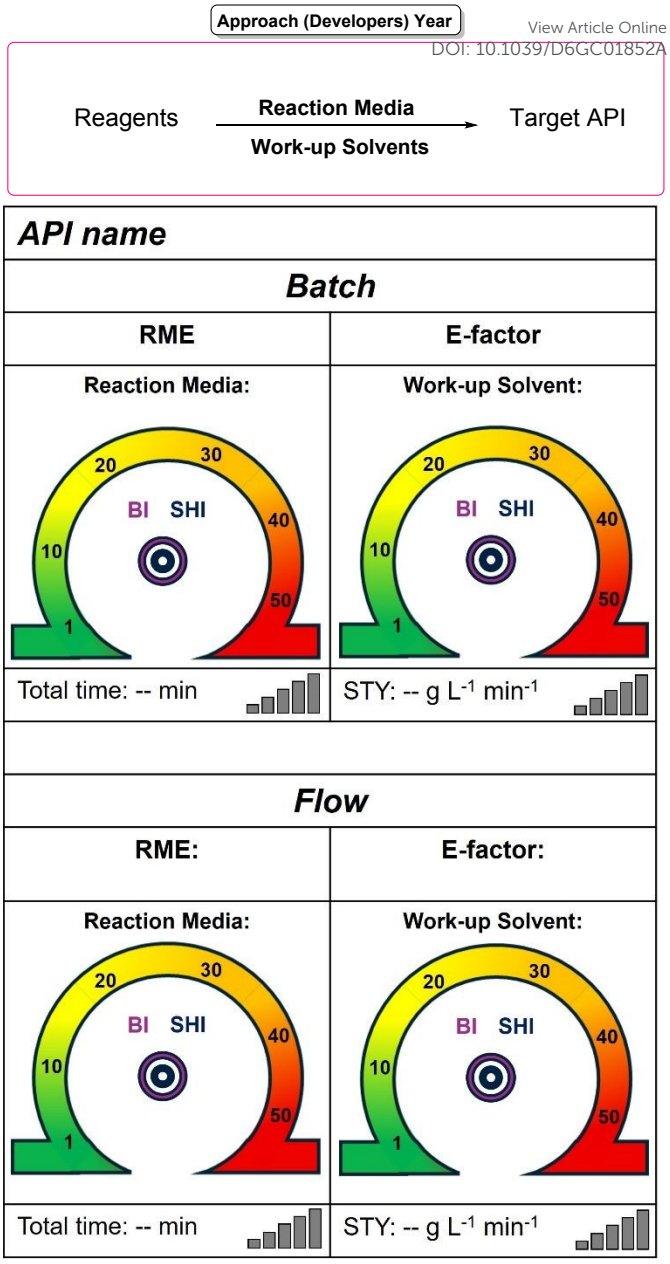



**Figure 4.** Summary of the schematic visualization of the results reported

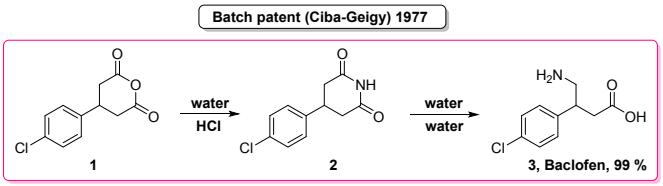
For any API synthesis analysed, the solvent ranks associated with the different solvents used (as reaction media or in the work-up operations) are summed and reported as a gradient graphical output (Figure 4). This process, therefore, accounts for the quality of each solvent and for the amount of the different solvents used in the synthesis. It is worth noting that some examples compare reported routes to the same API rather than direct batch/flow versions of the same synthetic sequence.

A final table summarises the BI and SHI data, along with the percentages of organic, aqueous, and halogenated solvents used.

Importantly, in the following discussion, the schemes related to the synthesis path show only the solvents used at each step, as outlined in Figure 3. All other information can be found in the references cited throughout the text.

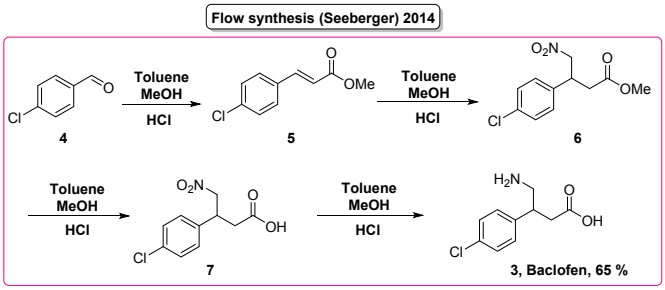
## 3. Results of the comparison and discussion

### 3.1 Baclofen




**Scheme 1.** Patented Baclofen synthesis.

Baclofen was initially synthesised industrially by Ciba-Geigy (now Novartis) and was approved for marketing in 1977.[17] From 2023, it has been available as a generic medication. Baclofen is primarily used to treat spinal and spastic conditions, mainly resulting from multiple sclerosis. It is increasingly used off-label to treat various disorders, including musculoskeletal pain, gastroesophageal reflux disease, and alcohol use disorder.[18] The patented synthesis route[19] (Scheme 1) for Baclofen begins with a glutaric acid derivative **1**, which undergoes imide formation in the presence of concentrated aqueous ammonia, followed by ring opening via hydrolysis to produce Baclofen **3**. In 2014, Seeberger (Scheme 2) and colleagues developed an assembly system for the multistep synthesis of various drugs and synthesized Baclofen via a four-step telescoping process in continuous flow.[20] Their strategy begins with 4-chlorobenzaldehyde **4**, which reacts with a phosphate carbanion solution to form an acrylate ester derivative **5**. This is followed by nitromethane addition to the double bond, ester hydrolysis, and nitro group reduction, ultimately yielding Baclofen **3**.




**Scheme 2.** Flow synthesis of Baclofen from Seeberger.

Apart from differences in the synthetic routes, the two processes mainly vary in solvent usage. In the batch protocol, this resulted in a Reaction Mass Efficiency (RME) of 36% and 8% for the two steps, with E-factors of 1.77 and 12.08. Meanwhile, the flow protocol achieved an RME of 0.4 and an E-factor of 234.95. The patented batch procedure uses only water as the reaction medium (with ammonia in the first step) under highly concentrated conditions (2.2-1 M). In contrast, the flow method primarily uses a 4:1 toluene-methanol mixture at 0.5 M. Consistent with the impact of concentration, despite the significantly shorter total reaction time in flow (160 minutes versus 540 minutes in batch), the resulting STY is not substantially different between the two methods. The evaluation indicates that the batch protocol still provides a greener approach to synthesizing Baclofen.

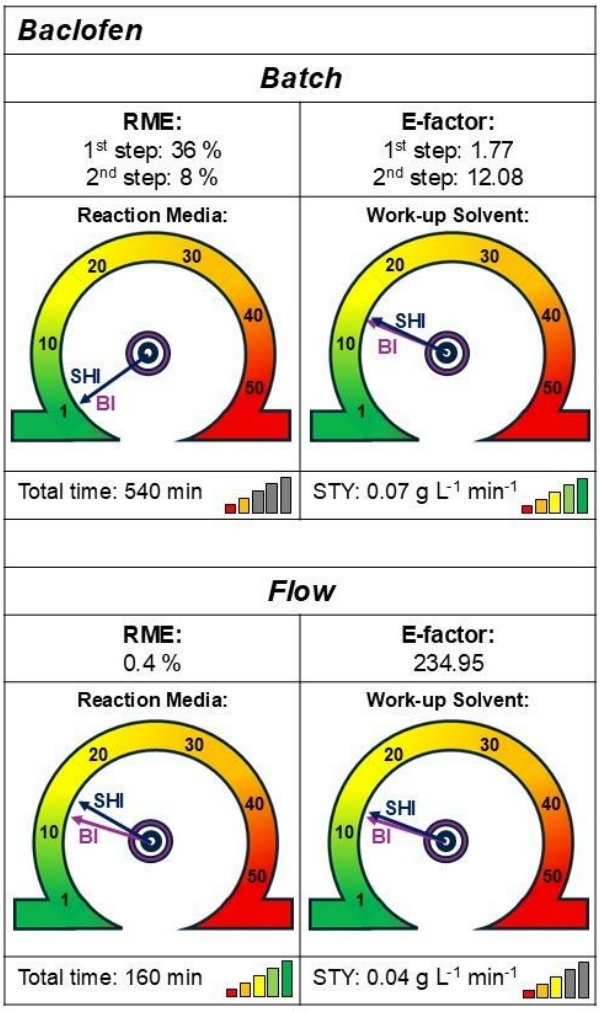
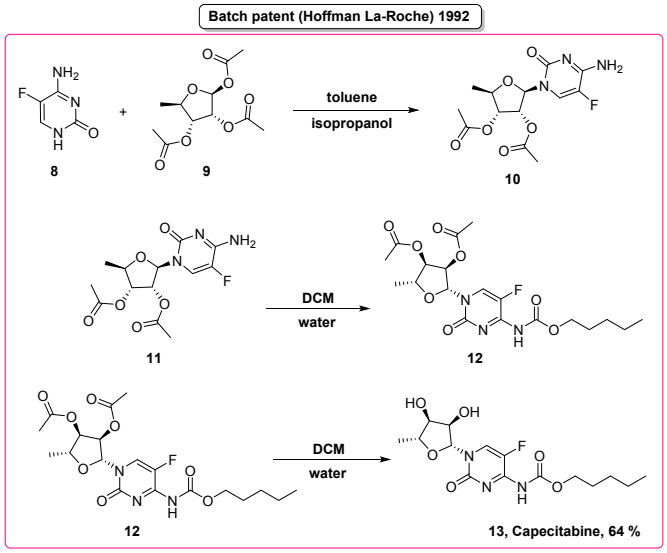



**Figure 5.** Sustainability Comparison for the synthesis of Baclofen.

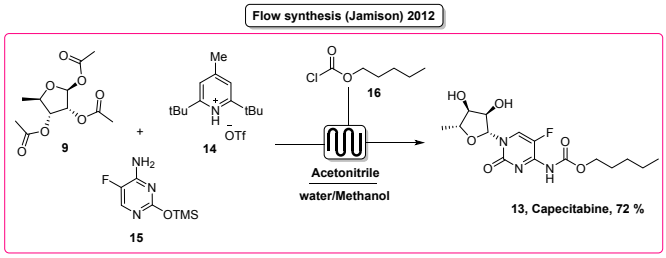
### 3.2 Capecitabine

Capecitabine, patented by Hoffmann-La Roche in 1992,[21] is a widely used anticancer medication for treating a broad range of cancers, including breast, gastric, and colorectal cancers.[22] Due to its widespread use, Capecitabine is listed as an essential medicine by the World Health Organisation (WHO). In its patented synthesis (Scheme 3), Capecitabine is derived from the initial glycosylation of 5-fluorouracil **8** in the presence of tin chloride, followed by carbamoylation to install the pentyl moiety **12** and deprotection of the acetyl groups, to afford the title compound **13**.




**Scheme 3.** Patented batch synthesis of Capecitabine.

Flow synthesis of Caecitabine was developed by Jamison's research group in 2012 (Scheme 4) via a Bronsted-acid-catalyzed glycosylation reaction.[23] The flow synthesis integrated three steps into a single flow setup with a total reaction time of only 52 minutes.




**Scheme 4.** Jamison flow synthesis of Capecitabine

The whole flow synthesis benefits from the catalytic use of a pyridinium triflate derivative **14** as a Brønsted acid, enabling a smooth and fast glycosylation reaction. The following steps mirror the sequence outlined in the patent but are executed more rapidly and efficiently using a continuous-flow apparatus. From a sustainability perspective, the patented batch synthesis is superior in terms of RME (4.6%) and E-factor (20.75). In contrast, the use of two reaction media (toluene and DCM) compromises the environmental and safety profile compared to the flow synthesis, which utilises only acetonitrile throughout. The flow process significantly outperforms the batch in terms of STY (2.55 g $L^{-1}$ $min^{-1}$ versus 0.13 g $L^{-1}$ $min^{-1}$). In summary, although the two processes are roughly comparable in overall sustainability, the flow process unsurprisingly demonstrates higher productivity in a reduced reaction time and without solvent switching.

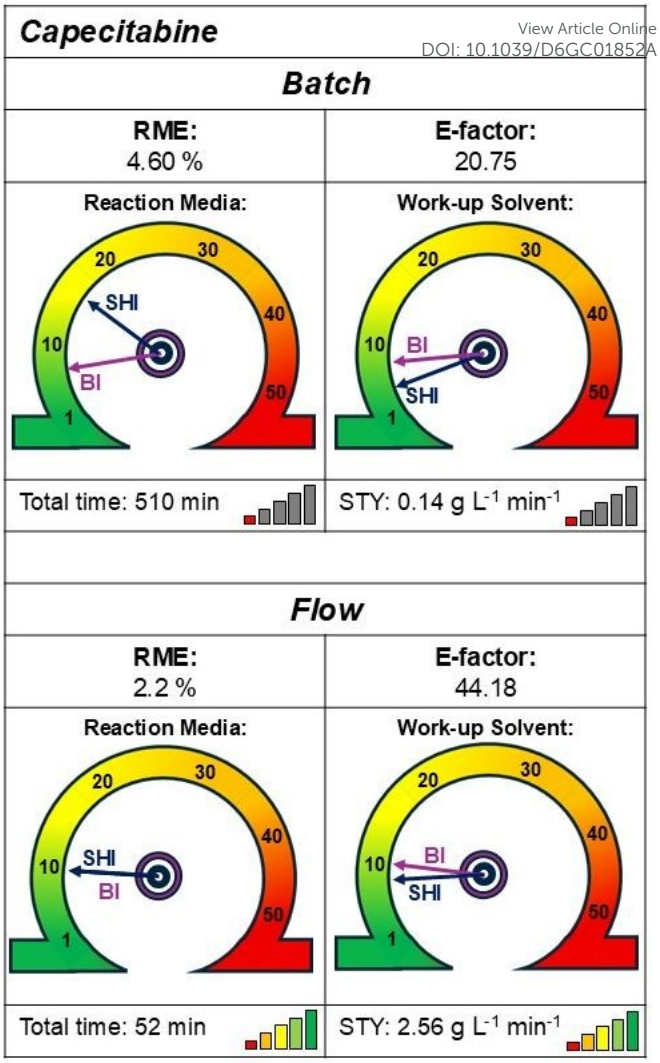
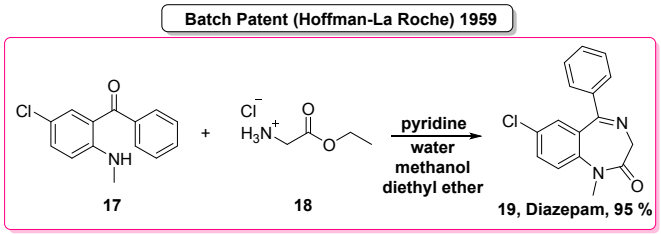



**Figure 6.** Sustainability comparison for the synthesis of Capecitabine.

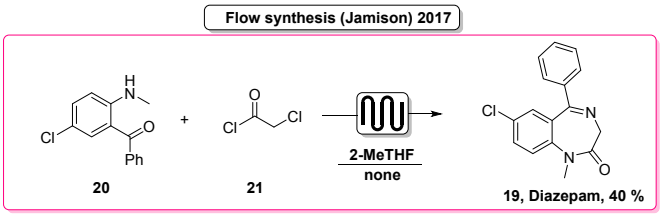
### 3.3 Diazepam

Diazepam is probably the most famous anxiolytic drug,[24] which is also used for a variety of other nervous and muscular disorders. Since its patent by Hoffman-La Roche in 1959,[25] Diazepam has gained increasing success as a medication, earning its inclusion on the World Health Organization's list of essential medicines. The Hoffmann-La Roche batch synthesis (Scheme 5) is a straightforward process that relies on the intramolecular acylation of a secondary amine in a benzophenone derivative **17**, followed by cyclization, yielding the product **19** in almost quantitative yield.



**Scheme 5.** Batch-patented synthesis of Diazepam

In 2017, Jamison,[26] aiming to reduce the waste associated with the current batch synthesis of Diazepam, reported a continuous flow strategy (Scheme 6) that relies on the same sequence (acylation/cyclization), while optimizing both the reaction medium in terms of quality (2-MeTHF) and quantity (highly concentrated conditions) and the work-up strategy.




**Scheme 6.** Flow Jamison's synthesis of Diazepam

By comparing the two approaches, even though La-Roche synthesis has an acceptable E-factor (42.68), Jamison flow synthesis nearly halved it (E-factor: 17.65), with an RME of 5.4%. More importantly, Jamison's synthesis achieved a STY of 9.6 g $L^{-1}$ $min^{-1}$ by miniaturizing the flow apparatus, thereby accelerating the synthesis (total reaction time: 28 min). Moreover, by an environmental and safety point of view, batch synthesis is negatively affected by the use of pyridine employed as reaction medium. This factor is clearly outweighed by the utilization of the alternative and biomass-derived 2-MeTHF used under flow conditions.

Considering the isolation procedure, Diazepam was obtained in flow by filtration through activated charcoal, followed by automated flash chromatography. This process is not included in the sustainability assessment because it concerns only small samples collected by the authors. Even treating this last aspect as unknown, the flow synthesis, designed to reduce cost while enhancing sustainability, achieved its goal. It is also worth noting that, beyond miniaturizing the system under flow conditions, the main improvement in Jamison's synthesis is attributed to using more concentrated conditions with a safer solvent (2-Me-THF) compared to the batch approach.

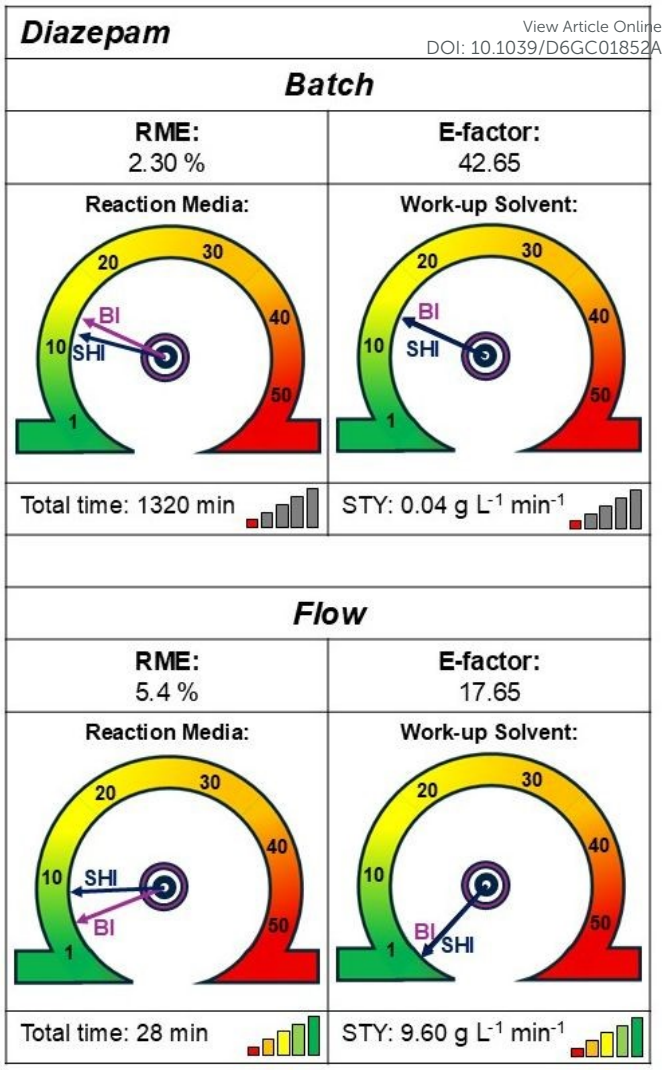



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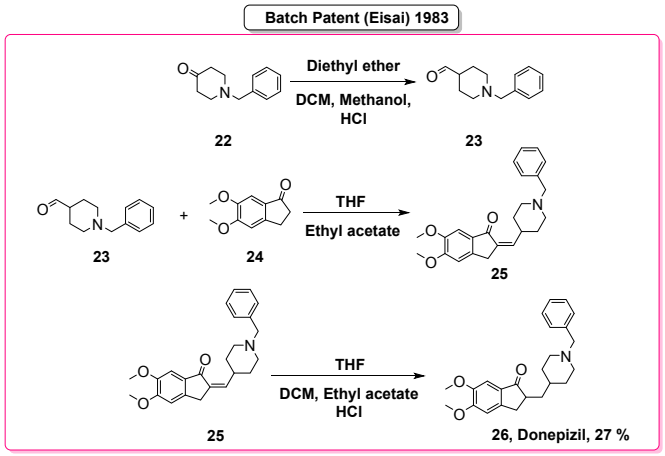
**Figure 7.** Sustainability Comparison for the synthesis of Diazepam.

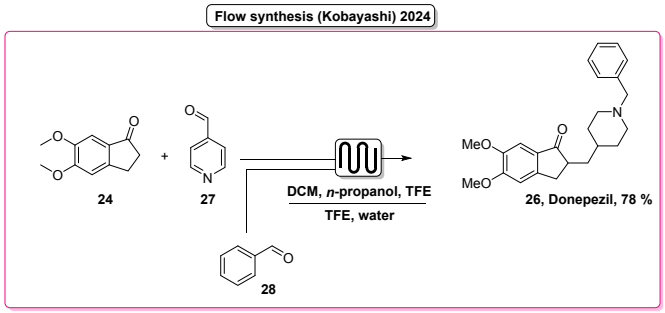
### 3.4 Donepezil

Donepezil was first synthesised in 1983 at Eisai Pharmaceutical Company in Japan by a team led by Hachiro Sugimoto.[27] It received approval in 1996 and became a leading treatment for Alzheimer's disease. Compared to most acetylcholinesterase inhibitors (AChEIs), Donepezil is a selective and reversible piperidine derivative that shows good performance in cognitive improvement, responder rates (40%–58%), dropout cases (5%–13%), and side effects (6%–13%) in Alzheimer related conditions.[28]




**Scheme 7.** Donepezil synthesis from Sugimoto at Eisai

Sugimoto's route (Scheme 7) to Donepezil starts with the synthesis of the piperidine aldehyde derivative **23**, followed by a cross-aldol addition with the indanone enolate **24** and subsequent hydrogenation to produce the target compound **26** (Donepezil) in three consecutive steps with yields of 54%, 62%, and 82%, respectively. In 2024, Kobayashi developed a continuous-flow assembly (Scheme 8) for the synthesis of Donepezil,[29] **26** utilising six heterogeneous catalysts. The Kobayashi synthesis of Donepezil differs conceptually from the Sugimoto synthesis, beginning with an initial condensation between indanone **24** and the pyridine aldehyde **27** catalysed by basic Amberlyst A26, followed by a Pd/C-catalysed double hydrogenation and a Pt/C-catalysed reductive benzylation sequence, resulting in a final Donepezil yield of 78% and a productivity of 6.1 g day$^{-1}$.




**Scheme 8.** Kobayashi flow synthesis of Donepezil.

The differences in the synthetic pathways reflect significant variations in sustainability. The Sugimoto pathway (in three steps) primarily uses ethereal solvents such as diethyl ether and tetrahydrofuran, which are not highly harmful to the environment, as reaction media. However, it employs hydrochloric acid, dichloromethane, ethyl acetate, and methanol in the workup procedures. This approach performs well in terms of reaction sustainability but is less effective in purification and final product recovery. The main reason for this scenario is the use of multiple solvents across various steps (five in total): DEE, THF, DCM, MEOH, and EtOAc. Conversely, the Kobayashi flow procedure utilises only three organic solvents (TFE, DCM, and n-PrOH) and water throughout the entire process, including both the reaction and the workup. Despite consistently lower BI and SHI values in the flow process, this results in better overall sustainability. Additionally, the Kobayashi process has a favourable E-factor and RME value (82.42 and 1.2%, respectively) and an excellent STY value (0.27 g L$^{-1}$ min$^{-1}$ ), compared to the Sugimoto process, which has an STY of 0.0006 g L$^{-1}$ min$^{-1}$. Overall, we can conclude that the flow synthesis of Donepezil developed by Kobayashi represents an advancement over the patented method, not only in technology but also in sustainability.

The differences between the E factor and STY not only reflect the choice between flow-based and batch synthesis but also the higher step integration and heterogeneous catalysis in flow-based synthesis design. The latter is an inherent advantage of a well-designed flow platform.

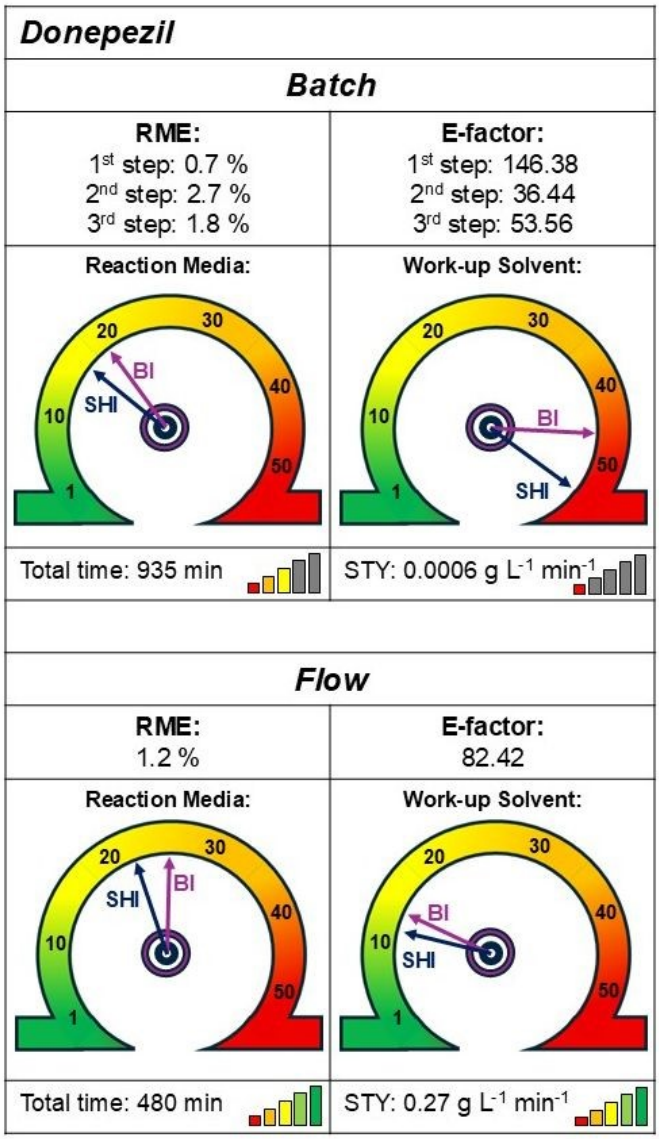
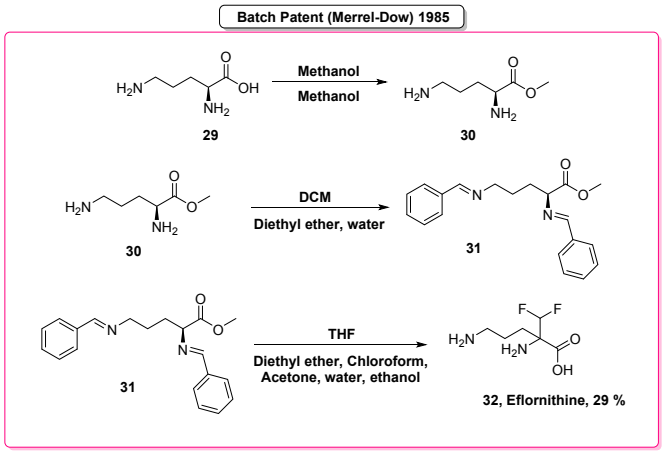



**Figure 8.** Sustainability Comparison for the synthesis of Donepezil.

### 3.5 Eflornithine

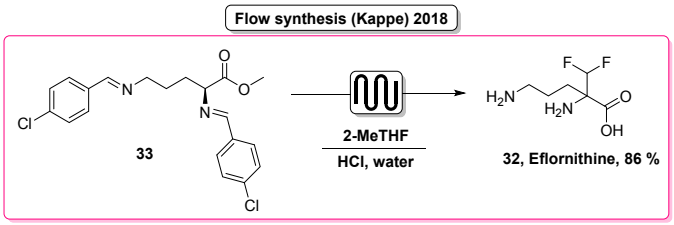
Eflornithine, also known as difluoromethylornithine, was studied during the 1970s and 1980s as a treatment for benign prostatic hypertrophy.[30] It acts as an inhibitor of ornithine decarboxylase, leading to the stopping of cellular division. Later, a biochemist named Cyrus Bacchi decided to explore its activity in a mouse model of trypanosomiasis. The dramatic results in mice led to early clinical studies, initially in Sudan. By 1985, the WHO, in collaboration with Merrell Dow Pharmaceuticals, the manufacturer of the drug, and local clinicians in Sudan, had organized more rigorously designed clinical trials. The clinical responses of some comatose sleeping sickness patients earned eflornithine the nickname, "the resurrection drug." Eflornithine is now used to treat both sleeping sickness and hirsutism in women. It is listed on the World Health Organisation's List of Essential Medicines, and the WHO provides Eflornithine free of charge in regions where sleeping sickness is prevalent.

The initial development of Eflornithine synthesis was carried out by Merrell-Dow (now Sanofi) through a three-step process starting from L-ornithine hydrochloride (Scheme 9).[31] The enantiopure amino acid **29** undergoes Fisher esterification with methanol, followed by a condensation with benzaldehyde to form the dibenzaldimine intermediate **31**. Ultimately, electrophilic α-difluoromethylation using chlorodifluoromethane and imine hydrolysis yields Eflornithine **32** in 37% yield (considering only the last step) and 29 % overall yield. In 2018, Kappe and colleagues developed a continuous-flow synthesis of Eflornithine (Scheme 10),[32] using gaseous fluoroform as a stepwise difluoromethyl source. The process begins with the substrate **33**, which is deprotonated with LiHMDS, then difluoromethylated and deprotected to produce Eflornithine in 86% yield, using only 2-MeTHF as the solvent and water with HCl for the work-up procedure.




**Scheme 9.** Eflornithine synthesis from Merrel Dow

Batch synthesis of Eflornithine, although it requires a large number of different organic solvents for reaction and work-up, is surprisingly efficient in terms of reaction mass efficiency and the E-factor. This is mainly true for the two initial steps, which have high yields (E-factor for the 1st step: 3.35; for the 2nd step: 9.70). In the third step, overall efficiency drops, as well as sustainability, because of the high amount of waste generated per kg of product (E-factor: 196.04). The situation becomes increasingly complex considering the benign and safety profile of the solvent used. The flow synthesis reported by Kappe, on the contrary, demonstrates high efficiency and overall good sustainability.




**Scheme 10.** Kappe flow synthesis of Eflornithine.

The use of a single solvent (2-MeTHF) throughout the flow process, together with high yield and reduced waste attributable to the use of gaseous fluoroform, results in an optimized E-factor of 16.27 (RME: 5.8%) and demonstrates excellent safety and environmental profiles for the solvents adopted in both reaction and work-up. The short reaction time of the flow synthesis also enabled an improved STY of 12.56 g $L^{-1}$ $min^{-1}$, which significantly surpasses the STY of the batch synthesis, which took approximately 40 hours to produce the same amount of Eflornithine.

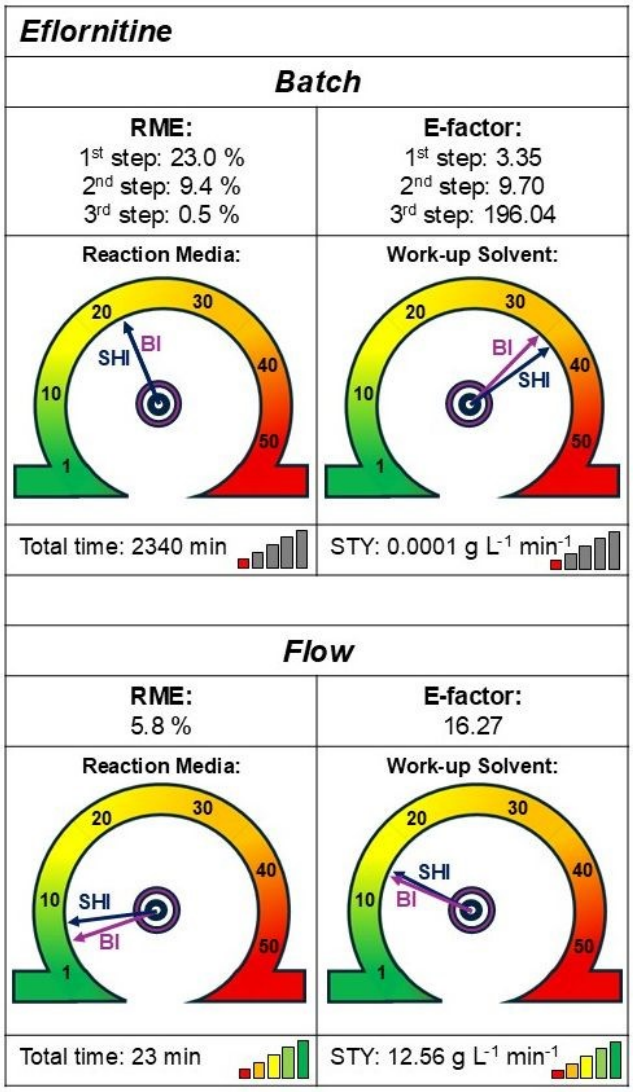
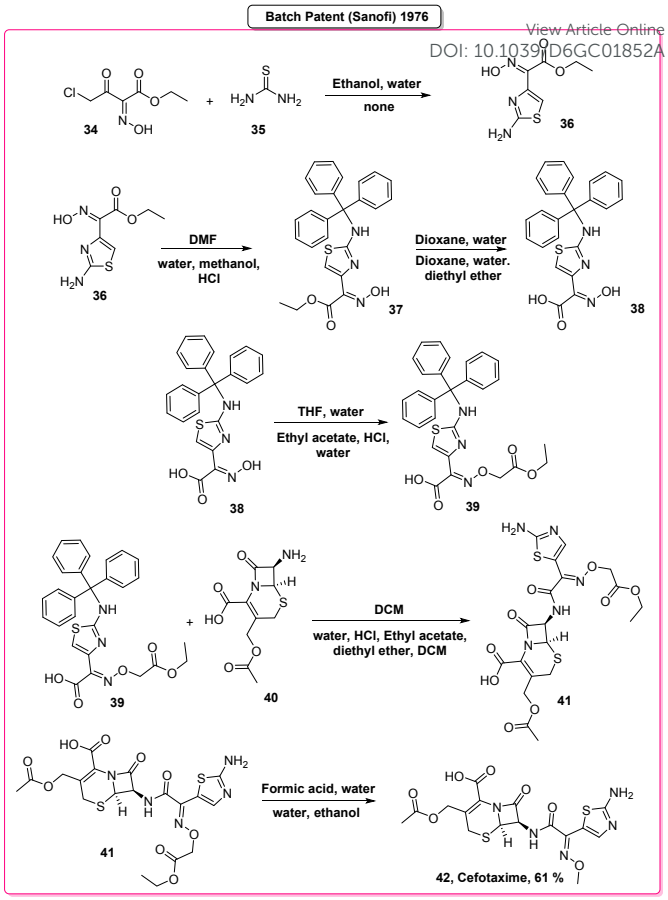



**Figure 9.** Sustainability Comparison for the synthesis of Eflornithine.

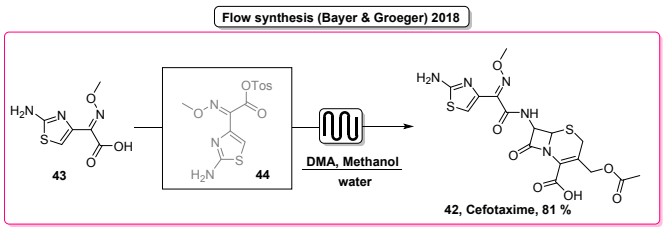
### 3.6 Cefotaxime

Cefotaxime is the first third-generation cephalosporin antibacterial drug to be marketed.[33] Cefotaxime is now available as a generic medication and is included on the WHO list of essential medicines. It was discovered and first synthesized in late 1976 by Sanofi through a complex six-step process (Scheme 11).[34] The synthesis begins with an intramolecular nucleophilic substitution to form the thiazole **36**, followed by amine protection using trityl chloride. The ester functionality is then hydrolysed to obtain the free acid **38**. The oxime functionality is subsequently O-alkylated rather than N-alkylated, using a strong base. The subsequent steps involve activating the free acid with DCC, followed by aminolysis with 7-aminocephalosporanic acid **40** to form the amide **41**. The synthesis ends with the deprotection of the trityl group on the amine, yielding Cefotaxime **42**.




**Scheme 11.** Cefotaxime batch synthesis from Sanofi

In 2018, Bayer and Groeger developed a continuous-flow synthesis (Scheme 12) of Cefotaxime that starts from a preformed thiazole 43,[35] which is activated with acid as a tosylate, followed by amide formation with 7-aminocephalosporanic acid **44**, yielding Cefotaxime with an overall yield of 81%. It is noteworthy that, here, the quantitative comparison and evaluation must account for the fact that the initially developed batch synthesis largely comprises the steps required for thiazole ring synthesis. On the other hand, using flow conditions enabled milder cooling (-30°C in batch versus -10°C) and simultaneously eliminated the need to protect the amine functionality on the thiazole scaffold.




**Scheme 12.** Bayer and Groeger flow synthesis of Cefotaxime

The first synthesis of Cefotaxime by Sanofi performs well overall in terms of RME and E-factor, with only the 4th (O-alkylation) and 5th (amidation) steps showing E-factors of 97-130. All other steps show E-factors below 48. Importantly, all six steps in the batch synthesis have RME values ranging from 14% to 0.8%. On

the other side, the flow process has an RME of 3.2% and an E-factor of 30.5. The main difference between the two processes, which makes the flow methodology preferable over batch synthesis, is the assessment in terms of safety/hazard, and the benignity of the solvents used in both processes. Batch synthesis is primarily influenced by the use of DMF (second step), dioxane (third step), and formic acid (sixth step), whereas flow synthesis benefits from using only water as the work-up solvent. Additionally, when comparing the STY of the two procedures, we see that although the total reaction times are not significantly different, the flow process has a value that is four orders of magnitude higher, indicating that the amount of Cefotaxime produced in a given volume is much greater than in batch synthesis. Importantly, in this example, even if overall sustainability favours the flow approach, it must be noted that improving the "greenness" of the protocol is driven more by chemical substitution of the reaction media and work-up solvent than by purely technological advances.

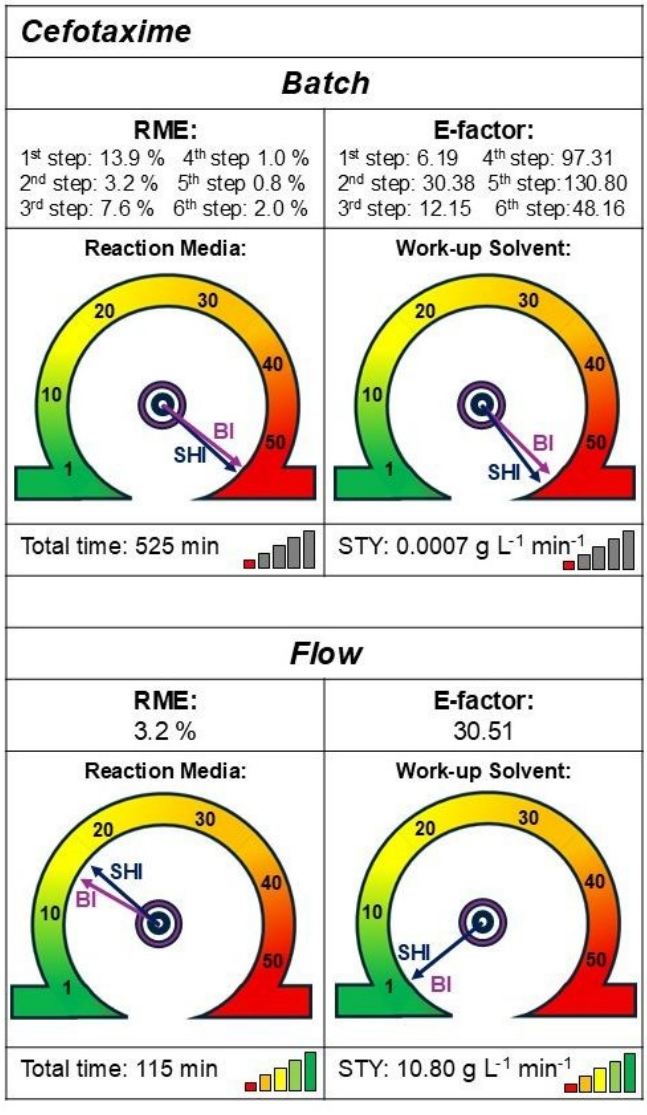
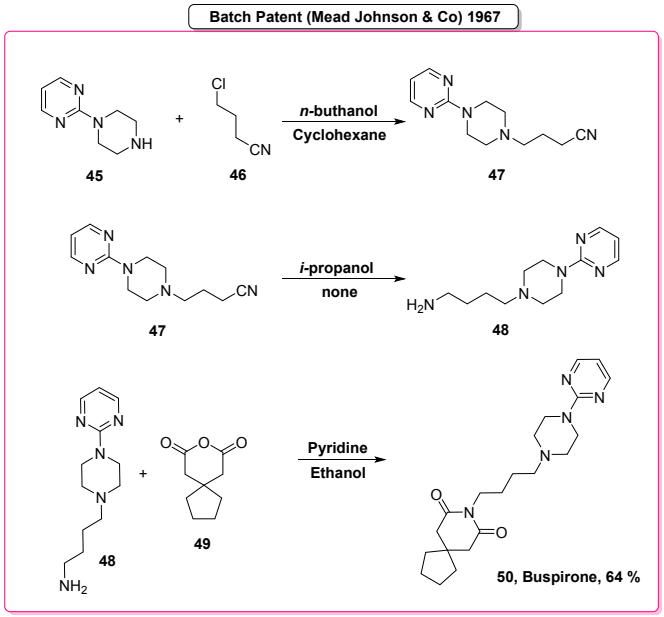



**Figure 10.** Sustainability Comparison for the synthesis of Cefotaxime.

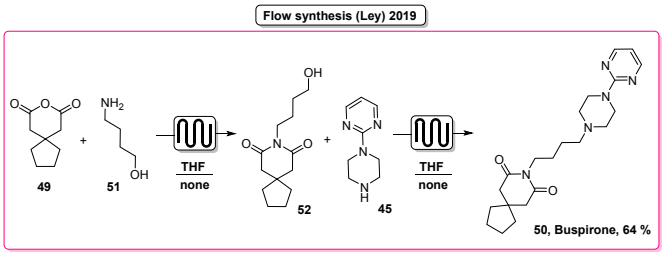
### 3.7 Buspirone

Buspirone was first developed by Mead Johnson & Company (a Johnson & Johnson co-founded individual project) in 1967.[36] Buspirone belongs to a unique class of azaspirones that combine antidepressant and anxiolytic effects in a single pharmaceutical ingredient.[37] It became very popular because it proved to have fewer common side effects with respect to other anxiolytic APIs, such as dependence. Although it was discovered in 1967, it was not approved for the U.S. market until 1986, and it remains among the most prescribed medications in the United States today. The initial synthesis of Buspirone (Scheme 13) relied on a three-step process: the first step is the N-alkylation of the pyrimidyl-piperazine scaffold **45** with the formation of an alkyl nitrile **47**; the nitrile is then reduced to the amine **48** using Raney-Nickel, and the final step involves a cyclocondensation with glutaric acid anhydride **49** to obtain the spiro compound Buspirone **50**. In 2019, Steven Ley developed a flow synthesis of Buspirone in two steps (Scheme 14):[38] the first involves an intramolecular amidation between glutaric anhydride **49** and aminobutanol **51**, and the second is a ruthenium-catalysed alcohol amination employing a borrowing hydrogen strategy that furnishes Buspirone.




**Scheme 13.** Buspirone synthesis from Mead Johnson & Co

Regarding the mass-metric analysis of the two protocols, there were no critical differences between them, despite a divergent number of steps (3 in batch vs 2 in flow).



**Scheme 14.** Steven Ley's flow synthesis of Buspirone

The high RME across all steps in both procedures reflects the high overall yield of the two syntheses, as well as the conscious generation of waste. Additionally, the reaction media and work-up solvents were substantially similar, with only two aspects worth noting: the use of pyridine as the reaction medium in the third step worsens the overall evaluation of the batch synthesis. Meanwhile, since the Ley flow synthesis ends both steps with the final solvent evaporation (and chromatography, which cannot be quantified using our methodology), it is assumed to yield good results after any purification procedure (crystallisation/precipitation). Remarkable differences, however, were observed in both reaction time (1140 min for the batch synthesis versus 33 min for the flow synthesis) and particularly in STY, where the flow process resulted in approximately 2 orders of magnitude higher. Based on these considerations, it is reasonable to assign a higher rank to the flow process for the synthesis of Buspirone.

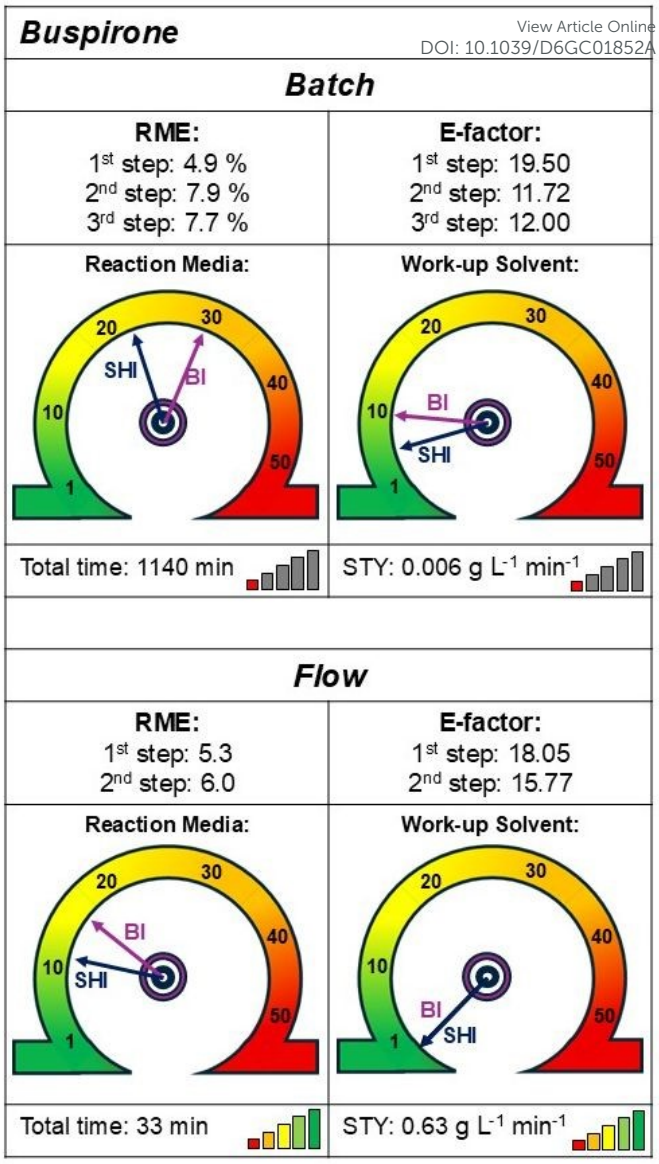
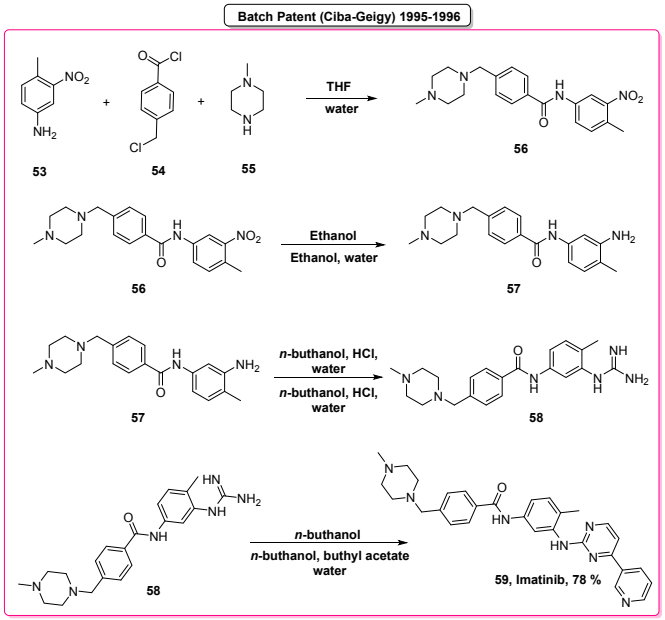



**Figure 11.** Sustainability Comparison for the synthesis of Buspirone.

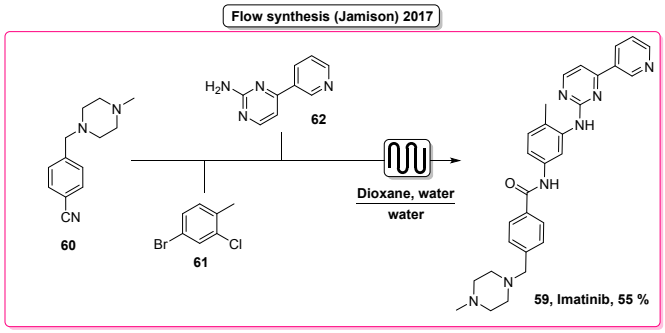
### 3.8 Imatinib

Imatinib is the best-known lead molecule developed through rational drug design following the discovery of the Philadelphia chromosome.[39] It was also known as a "magical bullet," as it revolutionized the treatment of chronic myeloid leukemia (CML) after its FDA approval in 2001. By 2017, it was available as a generic medication and was listed as an essential medicine by the WHO. Imatinib was discovered in the 1990s at Ciba-Geigy, shortly after the 1996 merger with Sandoz to form Novartis. The patented synthesis (Scheme 15) involves four concise steps.[40] In the first step, the substituted aniline **53** undergoes acylation followed by nucleophilic substitution to install the *N*-methylpiperazine **55** at the benzylic position. In the second and third steps, the nitro group on the aniline is hydrogenated (second step) and then converted to a guanidine **58** by the addition of cyanamide. The final step involves forming pyrimidine **59** via condensation of guanidine with a piperidine

enone. The entire synthesis is characterised by high yields at each step: 95%, 99%, 89%, and 93%, respectively. In 2019, Jamison and colleagues developed a modular flow synthesis of Imatinib in a continuous process (Scheme 16),[41] consisting of three consecutive steps—amidation, hydration, and C-N coupling—without isolating any intermediates, resulting in an overall yield of 55% Imatinib **59**.




**Scheme 15.** Imatinib synthesis from Ciba-Geigy




**Scheme 16.** Jamison flow synthesis of Imatinib

From a mass-metrics perspective, the two processes are very different. The patented batch synthesis offers a better profile despite involving four steps, each with intermediate and final product isolation and purification, resulting in E-factor values of 11.56, 13.50, 24.00, and 10.45. In contrast, although the flow protocol telescopes the three steps consecutively, it has an E-factor of 209.74. The primary reason for these differences is that the batch process operates under highly concentrated conditions, achieving very high yields at each step. The flow process, even under moderately concentrated conditions, yields a modest final yield of imatinib (55%). The situation changes significantly when the safety/hazard, and environmental profiles of the solvents used are taken into account. Jamison's synthesis avoids solvent switches and operates entirely in a dioxane/water mixture, using only water for work-up. On the contrary, the patented batch protocol utilises multiple solvents as reaction media and, during work-up, adds complexity and worsens the overall sustainability. Based on these evaluations, it is reasonable to consider the patented synthesis a good option only in terms of mass metrics, as it uses many solvents. In contrast, the flow setup is a better solution for solvent quality rather than quantity. Additionally, it is worth noting that the STY of the two processes differs by three orders of magnitude, with the flow process having the higher value. Both processes, in batch or in flow, have some pros and cons. This example shows that technological progress alone is not enough to achieve larger global sustainability or performance, if not accompanied by a concomitant 3evaluation of the materials and their amounts used in the optimisation.

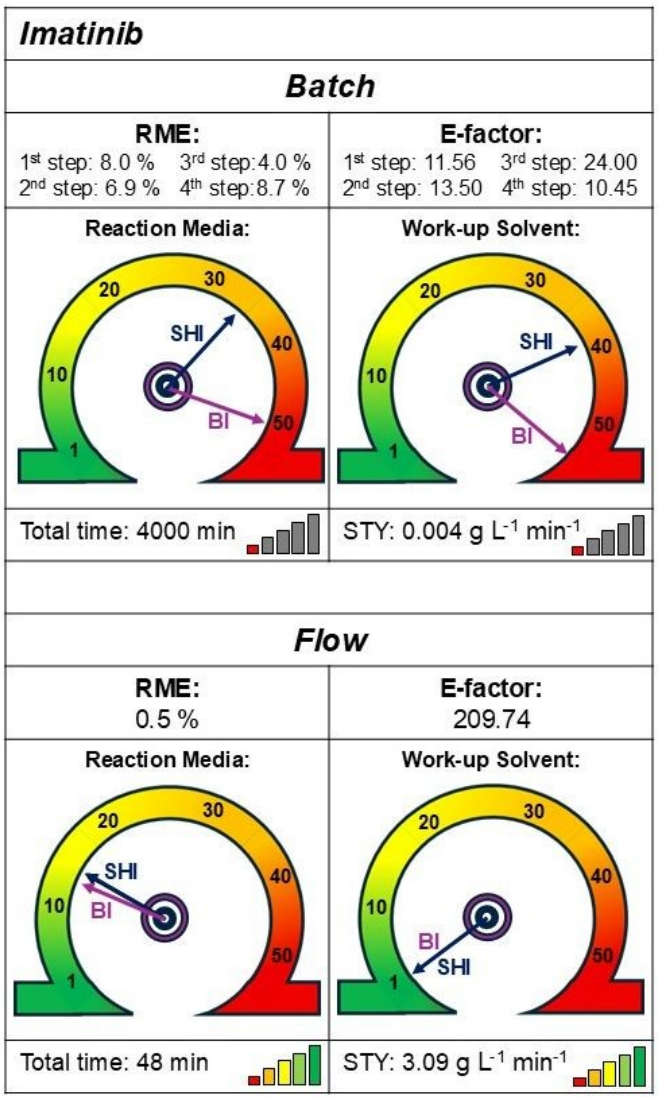
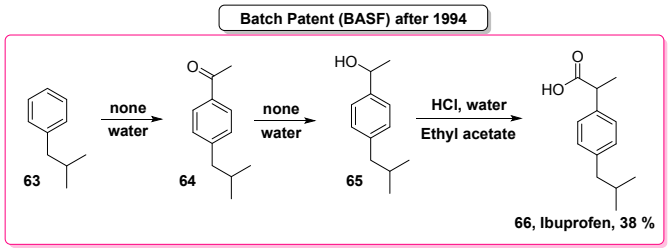



**Figure 12.** Sustainability Comparison for the synthesis of imatinib.

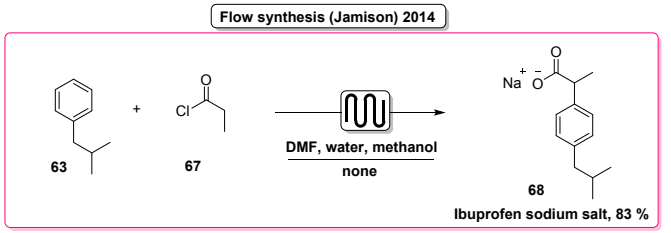
### 3.9 Ibuprofen

Ibuprofen, probably the most famous NSAID, was discovered at The Boots Pure Drug Company Ltd in Nottingham, United Kingdom, in 1961.[42] Interestingly, it was discovered even before the identification of prostaglandins in 1971 (the target of Ibuprofen). Initially developed to treat rheumatoid arthritis, it quickly became a common drug for various types of pain and has been added to the list of essential medicines (WHO). The patent synthesis used here is from BASF Corporation (Scheme 17), as the patent by Boots Pure Drug Co Ltd does not contain sufficient mass information to perform our calculations.[43]



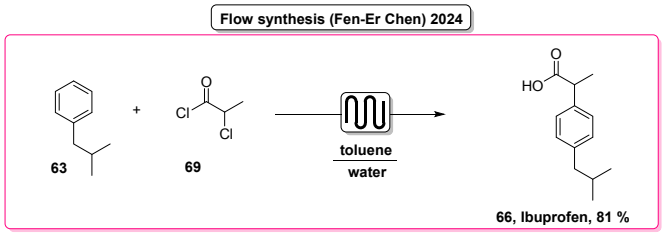

**Scheme 17.** Ibuprofen synthesis from BASF

Additionally, in 1994, Boots sold its prescription drug division to BASF, which also included the master files for ibuprofen. The batch synthesis consists of three steps: a Friedel-Crafts acylation, followed by Ni-Raney catalytic hydrogenation, and then a Pd-catalysed carbonylation to produce Ibuprofen **66**. Two flow syntheses are considered relevant here: the first, developed by Jamison at MIT in 2014 (Scheme 18), known as "Three-minute synthesis of Ibuprofen,"[44,] and the second, developed very recently in 2024 by Fen-Er Chen (Scheme 19).[45] The Jamison flow strategy closely resembles the initial Boots process, comprising a three-step sequence of Friedel-Craft acylation, oxidative aryl shift, and hydrolysis of the methyl ester to achieve Ibuprofen with a final yield of 83%. The Fen-Er Chen flow synthesis, on the other hand, is based on a single-flow platform integrating four steps: a Friedel-Kraft acylation, followed by Amberlyst-15 (acidic) catalysed synthesis of an acetal, then a zinc-catalyzed 1,2-migration of the aryl moiety, and finally, basic hydrolysis and acidification to yield ibuprofen in 81% yield %.




**Scheme 18.** Jamison flow synthesis of Ibuprofen

The three processes are not only synthetically similar but also closely related in their use of solvents as reaction media, and in their work-up procedures.




**Scheme 19.** Fen-Er Chen flow synthesis of Ibuprofen

Specifically, considering the impact associated to reaction media, the batch patented synthesis resulted the preferred since it uses neat starting materials in the whole procedure. This is followed by the Fen-Er Chen flow process (Flow 2), which uses neat starting materials and toluene, and then by the Jamison process (Flow 1), which utilises DMF and MeOH. Regarding work-up solvents, the least favourable is the patent synthesis, which uses ethyl acetate, whereas the two flow processes employ only water and are comparable in this aspect. In terms of mass metrics, all the investigated routes perform well, especially because of the high yields and the effective solvent management. The Fen-Er Chen flow process (Flow 2) has the poorest data, followed by the patent batch method, with the Jamison flow process (Flow 1) being almost comparable. In terms of STY performance, the Jamison flow synthesis stands out with a very high value, completing in three minutes, while the Fen-Er Chen flow synthesis and the patented one achieve values of 16.6 g $L^{-1}$ $min^{-1}$ and 0.08 g $L^{-1}$ $min^{-1}$, respectively. Based on these evaluations, the Jamison flow process can be regarded as the best method among those observed for synthesising Ibuprofen, as it provides extremely rapid access to Ibuprofen with high yield. Jamison's flow protocol is indeed a good balance, in which the slightly worse mass-metric values are more than compensated by the impressive performance resulting from technological advances.

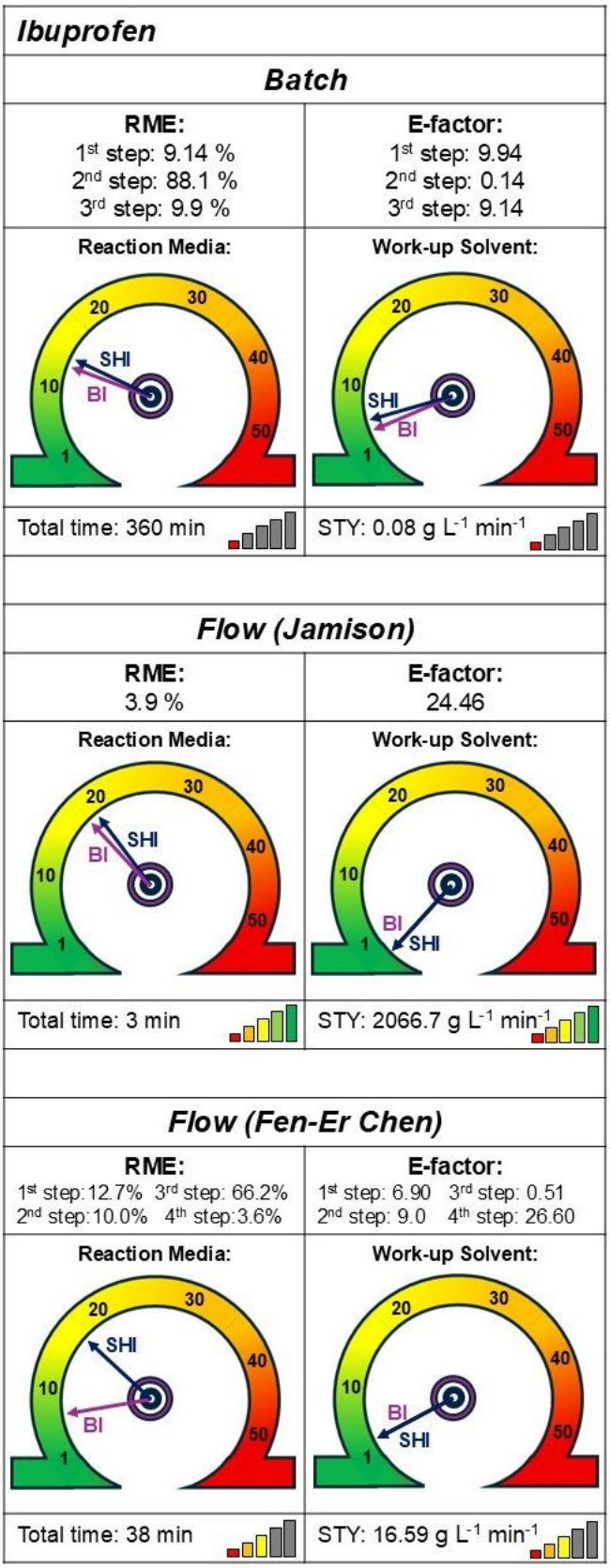
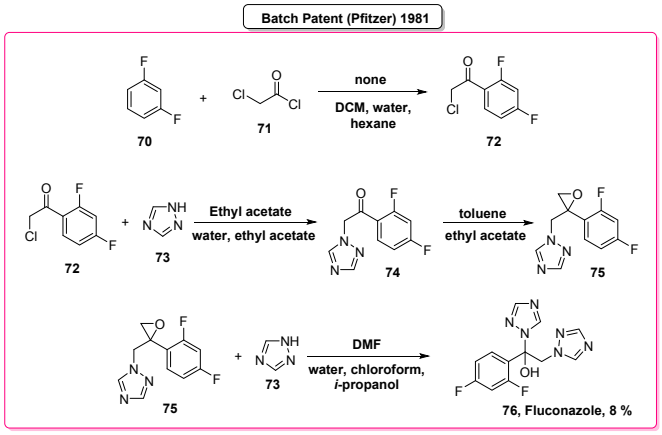



**Figure 13.** Sustainability Comparison for the synthesis of Ibuprofen.

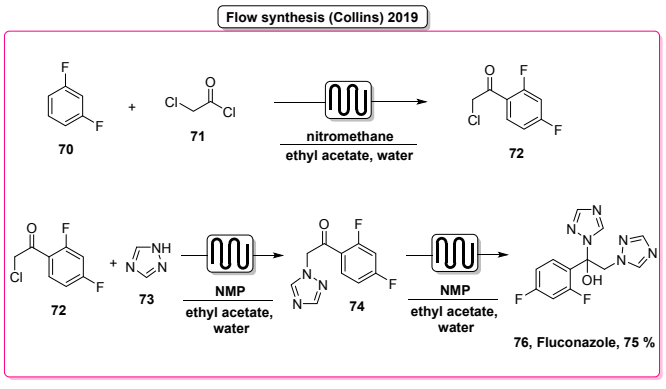
### 3.10 Fluconazole

Fluconazole, a triazole antifungal used in the treatment of various localised and disseminated mycoses, is the result of a research program initiated at Pfizer in 1978 aimed at developing a broad-spectrum antifungal agent.[46] Fluconazole was patented in 1981 and became commercially available a few years later.




**Scheme 20.** Fluconazole synthesis from Pfizer

Today, Fluconazole is a reliably used antifungal agent available in both intravenous and oral formulations, which can also be helpful in treating AIDS-related systemic fungal infections. For these reasons, Fluconazole is included on the WHO's List of Essential Medicines. The first patent by Pfizer describes the synthesis of Fluconazole in four steps (Scheme 20).[47] The synthesis begins with the Friedel-Crafts acylation of a difluorobenzene derivative **70**, followed by nucleophilic substitution with 1,2,4-triazoles **73**. The Corey-Chaykovsky reaction then yields an epoxide intermediate **75**, which undergoes nucleophilic ring opening. Finally, the second 1,2,4-triazole attacks the less substituted epoxide carbon to produce Fluconazole **76**. In 2019, Collins and co-workers developed a three-step flow synthesis of Fluconazole (Scheme 21),[48] which relies on a sequence like the batch synthesis: Friedel-Crafts acylation, nucleophilic substitution, and simultaneous O-alkylation and nucleophilic substitution. This flow synthesis was developed either step-by-step or in a continuous process, with the key difference being that, in the continuous flow method, acylation was not considered a step.



**Scheme 21.** Collins flow synthesis of Fluconazole

**Figure 14.** Sustainability Comparison for the synthesis of Fluconazole.

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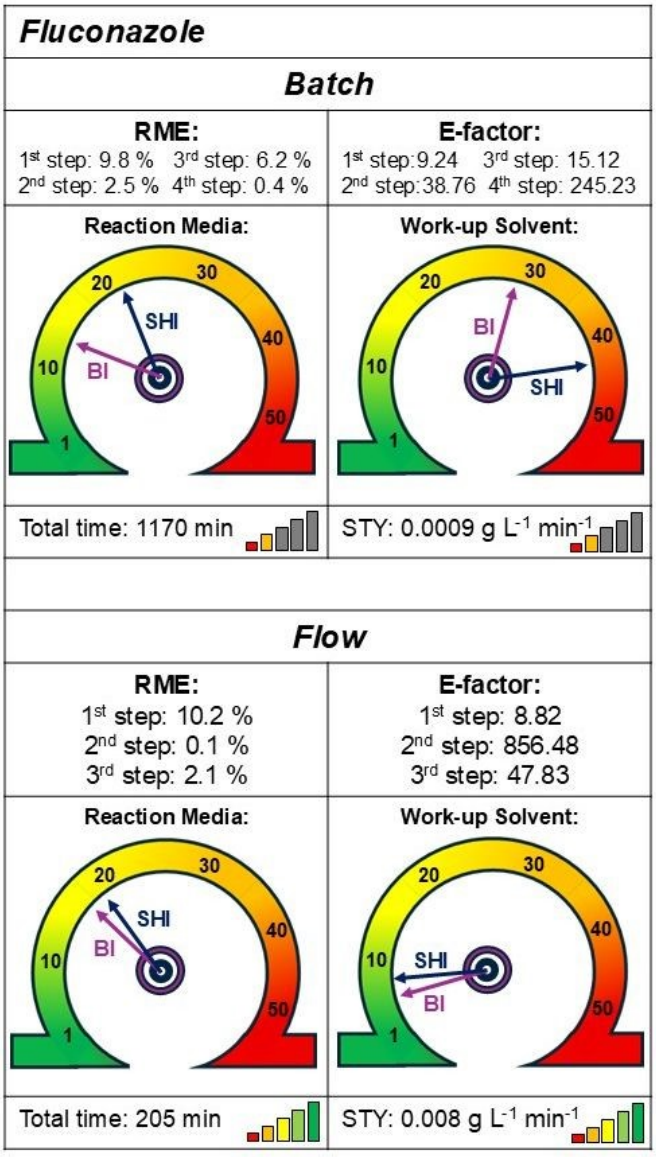
DOI: 10.1039/D6GC01852A

From a mass-metric point of view, the two mechanistically similar syntheses also yield comparable values. The Friedel-Crafts acylation performs slightly better in flow, while the first nucleophilic substitution (the Corey-Chaykovsky reaction in batch) has a less significant impact on the patent. Regarding environmental and safety aspects, the Pfizer route (batch) uses avoidable DMF and chloroform (as reaction and work-up solvent, respectively). In contrast, the flow protocol primarily relies on an NMP-water mixture as the reaction medium and water/ethyl acetate as the work-up solvents, thereby improving performance. Reaction times and yields are not significantly different; therefore, STY differs by only an order of magnitude between the two processes, with the flow procedure having the better value. In a crude comparison, the Pfizer synthesis is slightly preferred, as the mass metrics are better so far, with environmental indices similar between the two processes.




## Conclusions

In conclusion, after comparing the batch "standard" approaches with the flow procedure for the synthesis of some of the most widely produced APIs worldwide, using a multi-level analysis (mass metrics, solvent assessment, space/time/yield), the following conclusions summarise the most relevant and general information. Also, in some cases, different routes to APIs, are discussed as the direct comparison of the same process in batch or flow was not possible. Therefore, not all case studies are directly comparable in terms of route design and starting points. As outlined in Table 1, in most cases (7 out of 10 examples), the flow approaches showed a better overall assessment in terms of solvent utilisation.

At the same time, only in half of the examples (5 out of 10) flow mediated procedures resulted in a smaller production of waste, with lower E-factor and RME compared to batch processes. For flow chemistry to surpass batch processing in terms of E-factor, it must achieve higher concentrations, fewer solvent changes, and a more efficient integration of the purification procedures. Flow protocols, if properly designed including sustainability-data, benefit from an evident reduction in the number of steps and, consequently, are more efficient in terms of both mass metrics and qualitative nature of the solvents used for running the reactions and for the work-up procedures.

On the other hand, the batch procedures herein reviewed, developed mostly between the 1960s and 1980s, generally use lower-quality solvents and generally show acceptable (and, in certain cases, optimal) performance in mass metrics, probably due to economic considerations already considered for commercial routes.

As expected, STY is always better in flow, while in a few examples this difference is not as marked (Baclofen, Capecitabine, and Fluconazole), with differences of less than 2 orders of magnitude.

As a more general conclusion, we can state that to be truly more sustainable than batch protocols, flow approaches must be designed from several perspectives, trying to combine as much as possible the different shades of the term sustainability. Primarily, this can be done by using limited quantities of solvents (for example working under more concentrated conditions) and higher "quality" (safer, less impactful and in the appropriate cases, biomass derived) solvents.

Furthermore, this multi-compartment analysis shows that workup procedures performed on industrial processes are often (and, also reasonably) highly efficient in terms of material mass. In this context, the development of flow processes should also focus on improving the efficiency of downstream operations by leveraging modern tools and technologies.

As part of our detailed sustainability analysis, it should be noted that while mass (E-factor, RME) and productivity-based metrics (STY) provide a valuable framework for comparing batch and flow processes, they may highlight chemical and practical limitations. Specifically, E-factor and RME focus only on mass performances and do not account for waste quality (toxicity and

environmental persistence), or broader life-cycle impacts (LCI). Space-Time-Yield values indicate high productivity but do not account for energy consumption for heating/cooling or the risk of reactor clogging in continuous systems. Furthermore, solvent scores (SHI and BI) serve as useful indicators but often overlook the practical feasibility of solvent recovery and recycling.

The apparently variegated scenario is actually the proof that sustainability cannot be assessed by using a single metric or a specific feature. A multivariable approach is necessary, and scientists should get used to this reality and see it as richness rather than a burden of complexity. Future work should extend to more comprehensive analyses that include energy consumption across the production cycle and life-cycle assessment of the reagents and solvents used. This further analysis is strategic to individuate the most relevant areas where improvements can have a large impact.





**Table 1**. Aggregated BI and SHI values and liquid waste information.

| API | approach | (SHI+BI) | Advantages | Liquid waste | |
|---|---|---|---|---|---|
| | | | | Non halogenated | Halogenated |
| **Baclofen** | **Batch** | 31 | RME, E-factor, STY, Reaction Media | | 100 % (aqueous) |
| | **Flow** | 52 | Work-up Solvent | 46 % (organic). | 54 % (aqueous) |
| **Capecitabine** | **Batch** | 35 | RME, E-factor | 26 % (aqueous); 9 % organic | 65 % (organic) |
| | **Flow** | 36 | STY, Reaction Media, and Work-up Solvent | 44 % (aqueous); 56 % (organic) | |
| **Diazepam** | **Batch** | 51 | - | 32 % (aqueous); 68 % (organic) | |
| | **Flow** | 13 | RME, E-factor, STY, Reaction Media, and Work-up Solvent | 63 % (aqueous); 37 % (organic) | |
| **Donepezil** | **Batch** | 136 | Reaction Media | 20 % (aqueous); 40 % (organic) | 20 % (aqueous); 20 % (organic) |
| | **Flow** | 73 | RME, E-factor, STY, Work-up Solvent | | 100 % (organic) |
| **Eflornithine** | **Batch** | 115 | - | 13 % (aqueous); 69 % (organic) | 18 % (organic) |
| | **Flow** | 40 | RME, E-factor, STY, Reaction Media, and Work-up Solvent | 85 % (organic) | 15 % (aqueous) |
| **Cefotaxime** | **Batch** | 283 | - | 71 % (aqueous); 21 % (organic) | 8 % (organic) |
| | **Flow** | 34 | RME, E-factor, STY, Reaction Media, and Work-up Solvent | 55 % (aqueous); 45 % (organic) | |
| **Buspirone** | **Batch** | 69 | - | 100 % (organic) | |
| | **Flow** | 28 | RME, E-factor, STY, Reaction Media, and Work-up Solvent | 100 % (organic) | |
| **Imatinib** | **Batch** | 178 | RME, E-factor | 49 % (aqueous); 51 % (organic) | |
| | **Flow** | 29 | STY, Reaction Media, and Work-up Solvent | 64 % (aqueous); 36 % (organic) | |
| **Ibuprofen** | **Batch** | 36 | RME, E-factor | 55 % (aqueous); 45 % (organic) | |
| | **Flow (Jamison)** | 37 | STY, Work-up Solvent | 30 % (aqueous); 70 % (organic) | |
| | **Flow (Fen-Er Chen)** | 28 | Reaction Media | 100 % (organic) | |
| **Fluconazole** | **Batch** | 107 | RME, E-factor | 44 % (aqueous); 41 % (organic) | 15 % (organic) |
| | **Flow** | 49 | STY, Reaction Media, and Work-up Solvent | 64 % (aqueous); 36 % (organic) | |

SHI +BI column value represents the sum of the indices calculated for each example, combining the data for both the reaction mediua and the work-up solvents

## List of Abbreviations

2-MeTHF = 2-Methyl-tetrahydrofuran
ACN = Acetonitrile
AcOH = acetic acid
AcOH = Acetic Acid
BAP = Bioaccumulation potential
BCP = Bioconcentration potential
BI = Benign index
BuOAc = Butyl acetate
CGP = Corrosiveness potential as gas
CLP = Corrosiveness potential as liquid/solid
CPME =Cyclopenthyl methylether
CPP = Cancer potency potential
DCC = Dicyclohexylcarbodiimide
DCE= Dichloroethane
DCM = Dichloromethane
DEC = diethyl carbonate

DMA = Dimethyl acetamide
DME = Dimethoxyethane
DMF = N,N-dimethylformamide
DMSO = dimethyl sulfoxide
Et2O = Diethyl Ether
EtOAc = Ethyl acetate
EtOH = Ethanol
FP = Flammability potential
GWP = Global Warming po
HCl = Hydrochloric acid
INGTP = Ingestion toxicity potential
INHTP = Inhalation toxicity potential
iPOH = isopropanol
LiHMD = Lithium bis(trimethylsilyl)amide
MeOH = Methanol
MTBE = Methyl tert-butylether
nBuOH = n-buthanol
NMP = N-methyl-2-pirrolidone
OELP = Occupational exposure limit potential
RPP = Risk phrase potential
SFP = Smog formation potential
SHI = Safety/Hazard index
STY = Space Time Yield
t-BuOH = tert-buthanol
TFE = 2,2,2-trifluoroethanol
THF = Tetrahydrofuran

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

The European Union has partially funded this work under the program NextGenerationEU and the project National Innovation Ecosystem grant ECS00000041 – VITALITY. We acknowledge the Università degli Studi di Perugia and the MUR for their support.

## Notes and references

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View Article Online
DOI: 10.1039/D6GC01852A

The data supporting this article have been included as part of the Supplementary Information.





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