Life Cycle Assessment of an Enzymatic Ibuprofen Production Process with Automatic Recycling and Purification

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Abstract

In this study, the environmental impact of three ibuprofen production routes, namely the BHC, the Bogdan, and the newly developed enzymatic synthetic routes (modified Bogdan process), are assessed and compared by the application of life cycle assessment (LCA). Based on the data obtained through literature and laboratory-based experiments, a pilot-scale production with a capacity of 500 g/day of ibuprofen was simulated to generate inventory data for the LCA study, using Aspen Plus V11®. The well-established BHC process was chosen as the benchmark to quantify the operational and environmental benefits of the innovative enzymatic Bogdan flow synthetic process. The comparison highlights the benefit of adopting the modified Bogdan synthesis route via an enzymatic catalyst. Results show that a general reduction of environmental impact is achievable across the whole set of impact categories of the analysis, and the magnitude of such reduction depends on the efficiency of recycling in the production system. Considering a 50% efficiency of recycling, the modified Bogdan system achieves lower environmental impacts in some impact categories like Acidification, Ecotoxicity of freshwater, Human toxicity, Particulate matter, and Resource depletion (mineral, fossils, renewables), whilst having higher impacts on the rest of the impact categories. Yet, the new process proposed here scores better environmental performances in all the impact categories when the enzyme recycling is close to 100% which is promising for future technology development.

Keywords: *Ibuprofen; Life Cycle Assessment; Bogdan Flow Process; Enzyme; Aspen Simulation*

1. Introduction

Ibuprofen is one of the most active ingredients used in many painkiller drugs [1]. The first ibuprofen was invented, patented, and manufactured by Stewart Adams at Boots UK Limited and was initially marketed as Brufen, which was probably the largest chemical enterprise at that time [2]. Originally, the synthesis of ibuprofen followed a six-step time-consuming process while the overall atom efficiency was just around 40% [3]. It means that approximately 60% of the mass of the feedstock materials was eventually sent to waste. Up until the point when the patent expired (in the middle of the 1980s), this conventional synthesis route was the only choice for the manufacture of commercial ibuprofen. Considering today's worldwide consumption of ibuprofen, approximately 20,000 tonnes of waste would be generated annually if the drug was still produced using the original route [4].

In the early 1990s, the synthetic route was, for the first time, redesigned by the BHC company (now is part of BASF) in light of the application of the 12 principles of green chemistry (see Figure 1) [5]. The most significant improvement of this greener route is the modification of the first synthetic step

where the same chemical transformation is observed, but the reactions are conducted in different ways. To reduce the generation of waste, aluminium trichloride, which was used in excess in the original route and largely ended up in the waste stream, is replaced by hydrofluoric acid to promote the reaction. Since hydrofluoric acid is used as a catalyst, only a small amount is required while it can also be recycled at the end of the process. The new synthesis strategy offers a great chance to eliminate solid waste and makes the process greener in terms of environmental impacts.

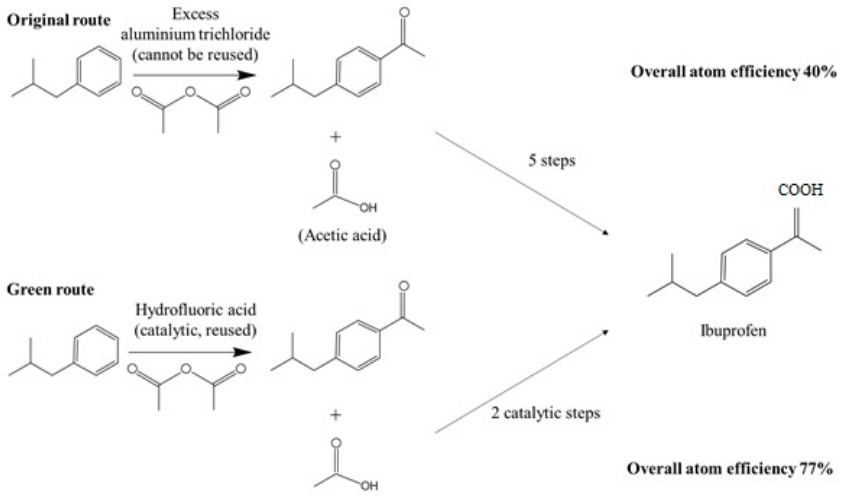

Figure 1. *The traditional synthetic route of ibuprofen vs. the greener route*

In 2009, a continuous-flow synthesis process was introduced by Bogdan et al. to synthesize ibuprofen in three steps without the need for intermediates purification [6]. The authors reported that up to 9 mg/min crude ibuprofen could be synthesized through this method, using a 0.5 m tubing reactor and five syringe pumps [6]. Additionally, the efficiency of the process and product yield could also be improved by utilizing parallel reactors, increasing the reactor length, or using alternative pumps. The advantage of using those continuous-flow reactors is achieved through precise temperature control of both process steps and exotherms. Although ibuprofen could be synthesized in a shorter time, several toxic chemicals are still utilized in large amounts, causing concern in terms of environmental impact and health safety.

Recently, an entirely new reactor and processing concept were proposed in the One-Flow EU project, to develop and explore in a bionic manner soft-matter compartmentalized processing systems [7]. One of those concepts is the 'Functional Solvent-enabled Factory'; representing a multi-phase system which (by virtue of solvent modeling) can be so fine-tuned that ideally pure product result (automatically) and the reactant and catalyst are recycled in their own phases (www.one-flow.org). We have recently reported the proof of concept through a de-esterification reaction using lipase as an enzyme and ionic liquids to uptake the low-polar reactant (ester) as a highly pure product and facilitating downstream processing, while water taking up the polar products (i.e. acid, alcohol, etc.) for recycling [7]. In light of the green chemistry approach, we are developing a new synthetic route for ibuprofen in which the toxic solvent, methanol, was replaced by a greener reagent which is water. To this end, we propose to modify the third step of the synthetic route proposed by Bogdan *et. al.*, the saponification reaction, by using an enzyme catalyst [8] in the presence of buffer and ionic liquid to enable the de-esterification reaction.

Although the experiments have been successful at the laboratory scale, to plan the further steps of our technology development, it is crucial to consider a holistic assessment to evaluate the environmental impact of the newly developed synthetic route in comparison to the existing synthetic routes which are the BHC and the Bogdan's. In this context, Life Cycle Assessment (LCA) is a powerful tool that allows systematically determining all inputs (i.e. substrates, reactants, utilities, etc.) and outputs (i.e. global warming, waste generations, etc.) as well as the related potential environmental impacts of

the pharmaceutical products [9]. Importantly, LCA is internationally accepted as a standard method to evaluate the environmental impact of a chemical or pharmaceutical process by the International Organization for Standardization (ISO) [10]. There are four phases included in an LCA study, according to the ISO 14040 and 14044 [11, 12], which are:

1) Goal and scope: clarifying the aim of the LCA study while defining important parameters such as the limitations, system boundaries, and functional unit, etc.
2) Life cycle inventory (LCI): generating and collecting relevant data on both qualification and quantification of the inputs/outputs within the defined system boundaries.
3) Life cycle impact assessment: assessing the potential environmental impacts of a process or a product based on LCI data with or without the assistance of software.
4) Interpretation: providing recommendations by analyzing and interpreting results obtained through the life cycle inventory and life cycle impact assessment within the goal and scope of the study.

Although ibuprofen is a popular pharmaceutical drug, there are only a few LCA studies that reported its environmental impacts as a single product [12], not as a whole synthetic route. It is important to include the environmental impacts of a process as one of the decision-making criteria and the application of LCA is always highlighted. Therefore, the present study aims to redesign the ibuprofen synthetic route; this attempt is based on flow chemistry considerations as well as input from the LCA, consisting of a comprehensive evaluation of the environmental performances of the synthesis routes under life cycle analysis. The assessment provides a snapshot of the environmental impacts of these production systems, in the form of comparative analysis, and investigates the causes behind such impacts, thus offering a practical basis to plan the further steps of our technology development.

2. Methodology

In this section, we report a description of the approach followed in the LCA analysis. Specifically, the Life Cycle Inventory, which describes the boundaries of the assessment, the source of LCA data, as well as the choice of the functional unit. This is followed by the Life Cycle Impact Assessment, which outlines the methodology used to translate the data of the life cycle inventory into the environmental impact and the software adopted for the model; furthermore, the environmental criteria (impact categories) considered in the analysis are introduced and explained. The methodology applied for this study is presented in Figure S1 (see supporting information).

2.2.1. Life Cycle Inventory (LCI)

The life cycle inventory quantifies the inputs and outputs of the system under analysis. Specifically, LCI tracks all energy and material streams throughout the life cycle of the target system. The information generated in this phase is used as a basis to calculate the environmental impacts; thus, the maximum data quality achievable is required to minimise the uncertainties of the results as underlined in previous works [13, 14]. To this end, the three processes under analysis were simulated with Aspen Plus V11®, taking into account all the reaction steps involved in the different syntheses comprising the peripheral equipment involved for heating and separation.

The chosen Functional Unit (FU) for this study is 1t of ibuprofen. As a reference line, the global ibuprofen production is almost 45,000t per year. The choice of 1t as a representative mass quantity enables the readability of the results and makes it easier to be compared with previous studies reported in the literature. The FU serves the purpose of normalizing the LCI data and environmental impacts, in accordance with ISO 14040 [15]. The data for the LCI is calculated through Aspen simulations for each operational unit involved in the synthesis of Ibuprofen.

As reported in the ISO 14040, the system boundary describes the set of activities that take part in the life cycle of the system under analysis, in this case, the production of ibuprofen. System boundaries are subdivided into the foreground and background systems (Figure 2). The foreground system accounts for the operations occurring in the production phase: reaction steps, heating generation,

and recovery and separation. The background system embraces the activities that satellite around the synthesis such as electricity production, waste disposal, and chemical production. Each process is built in the model by compiling the material and energy balance occurring in them through the standardised approach indicated in the ISO 14040 [15].

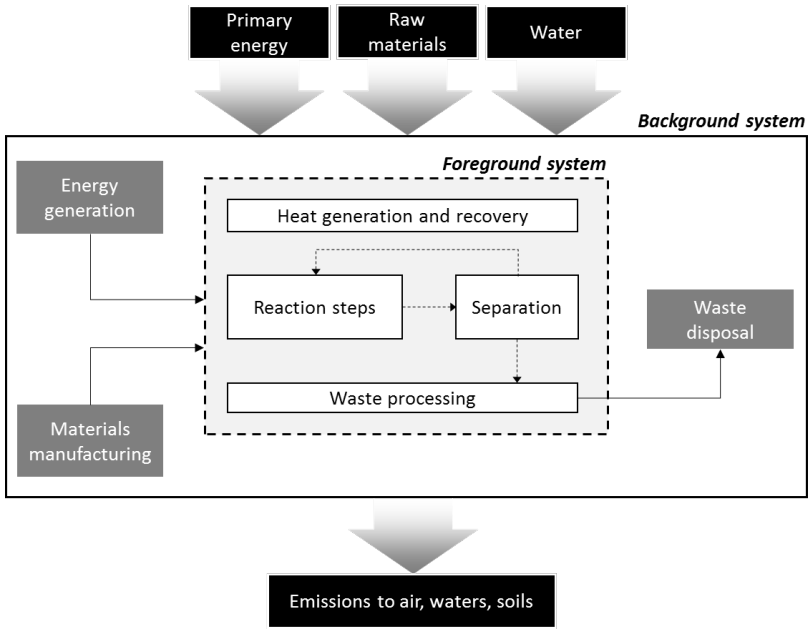

Figure 2. System boundaries: foreground and background systems

The functional unit and the system boundaries defined are the same for each one of the different synthesis methods under analysis, in order to assure a coherent comparison. For data gaps, allocation, and uncertainty, we have provided the information in the supporting information.

To provide data for the LCA study, three synthetic scenarios are considered including the BHC ibuprofen synthetic route, the Bogdan synthetic route, and the enzymatic-catalyst synthetic route which was modified base on the Bogdan process. A pilot-scale production with a capacity of 500 g/day of ibuprofen is simulated based on the data obtained from the literature review (the BHC and the Bogdan synthetic routes) and laboratory-based experiment (the newly proposed enzymatic-catalyst synthetic route).

Throughout the process simulation using Aspen Plus V11, the following assumptions have been made to reflect the availability of data.

- Peng-Robinson cubic equation of state was adopted since it can accurately predict the critical and supercritical states when used for phase equilibrium calculation and has good applicability to the non-ideal systems.
- The choice of reactors is based on the data collected from both literature review and laboratory-based experiments. Plug flow reactor (PFR) was used for the three steps of the Bogdan process while both PFR and Stoichiometric were applied in the case of BHC and modified Bogdan synthetic routes.
- The separation of the products in the three synthetic routes is mainly based on extraction and phase (organic/adequate) separation, so a simple component separator based on specified flows or split fractions was applied.
- Since the purpose of using Aspen Plus is to generate the data for LCA within the boundaries of the study, a simple heat exchanger is utilised in Aspen Plus.

- Providing that we only consider a plant capacity of 500g/day, pumps and stirrers are eliminated at this stage yet they will be further investigated in a larger scale simulation in the future.
- For the process simulation of IL-based process, the IL is defined as a pseudo-component by specifying its molecular weight, density, normal boiling point, critical properties, etc. This component definition approach for modeling the IL-involved process has been introduced in previous studies [16, 17]

2.2.1.1. Scenario 1: The BHC Synthesis

The three-step green synthetic route of ibuprofen developed by BHC is shown in Figure 3. One of the most significant of this process is to use HF as a reagent and also a catalyst [18]. This allows the reduction of chemical use as well as solid waste generation since HF could be recycled and reused for the next batch.

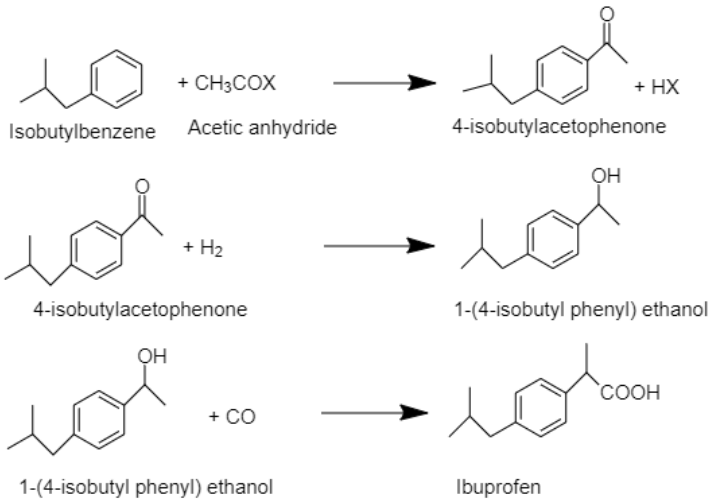

Figure 3. BHC ibuprofen synthetic route

However, despite the significant improvement in terms of green chemistry, there's room to improve the BHC process since ibuprofen synthesized using this route will take up to 9 hours which is a time and energy-consuming process. The specification of the BHC route and its experimental data applied for process simulation are presented in Table 1 [19].

Table 1. Reaction specifications and experimental data of the BHC synthetic route

Reaction information	**Friedel Crafts (batch)**	**Friedel Crafts (flow)**	**Hydrogenation**	**Carbonylation**
Reaction	Isobutylbenzene + acetic anhydride ⇨ 4-isobutyl-acetophenone + acetic acid	Isobutylbenzene + acetylating agent (AcF+AcAc) ⇨ 4-iso-butylacetophenone + acetic acid	4 isobutylacetophenone + H2 ⇨ isobutyl phenyl ethanol	isobutyl phenyl ethanol + CO ⇨ ibuprofen
Composition (reactants, in moles)	1:2	1:2	1:1	1:1
Reagent	HF	HF	-	-
Catalyst	HF	HF	Raney Nickel	Pd
By products	2-isobutylacetophenone; acetic acid; acetyl fluoride		Isobutyl ethyl benzene	Isobutyl styrene (IBS); 1-(4-isobutylphenyl)-ethyl chloride; 3-(4' isobutyl phenyl) propionic acid

Reaction Conditions				
Temperature	80°C	60-70°C	70°C	130°C
Pressure	10 atm	10 atm	6.89 atm	165 atm
Time	3 hr	2 hr	3 hr	2.6 hr
Catalyst amount	50eq.HF	50eq. HF	0.3eq. Raney Nickel	0.007 mol% PdCl2, ligand: 0.08 mol% PPh3
Solvent amount	50eq.HF	50eq. HF	-	-
Type of data				
Conversion	85%	77%	>99%	99%
Selectivity (main Product; by-products)	81%	100%	98.5%; 1.5% (by product)	96.6%; 1.0%; 0.00%; 0.8%
Yield	-	77%	-	-
Experimental	Starting and endpoints	Starting and endpoints	Starting and endpoints	Starting and endpoints
Model	No	No	Yes (parameter estimation is needed)	Yes (parameter estimation is needed)

2.2.1.2. Scenario 2: Bogdan Process in Flow

In 2009, Bogdan et al. proposed a continuous-flow synthesis of ibuprofen, consists of three reactive steps which are (1) Friedel Crafts acylation of IBB with propionic acid, (2) aryl migration using trimethyl orthoformate, and (3) saponification step to produce the ibuprofen salt [6]. Figure 4 shows the synthetic route developed by Bogan et al. [6]. Through the application of a flow reactor, this process has successfully reduced the reaction time from 9 hours to only 15 mins. Yet the use of toxic solvents, such as methanol, appears to be a problem in terms of well-being and environmental impacts.

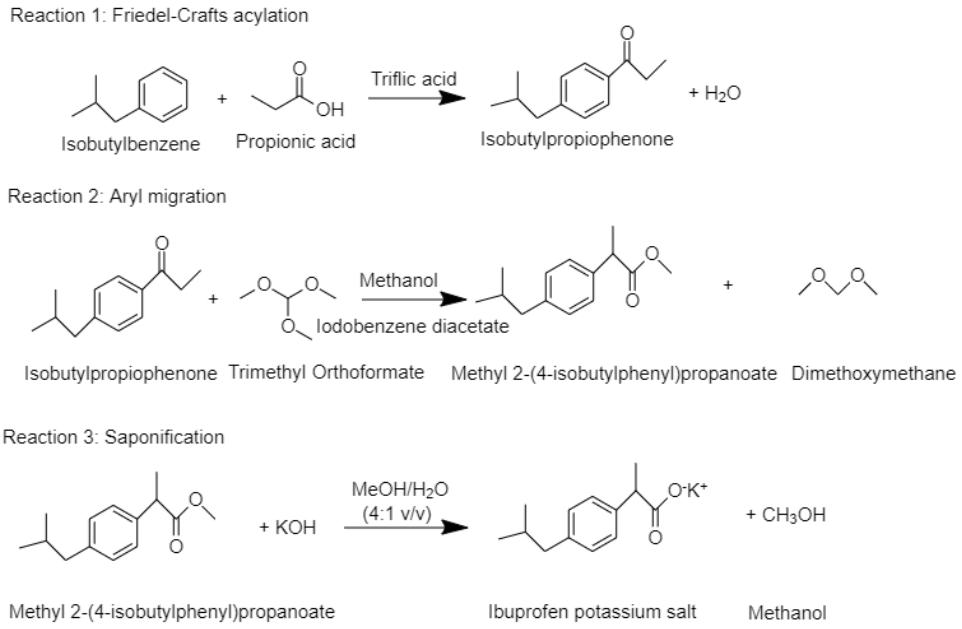

Figure 4. Bogdan reaction pathway for ibuprofen synthesis

The reaction specifications and experimental data for the Bogdan synthetic route are given in Table 2 [6, 19].

Table 2 *Reaction specifications and experimental data of the Bogdan synthetic route*

Reaction information	Friedel Crafts (flow)	Aryl Migration (flow)	Saponification (flow)
Reaction	Isobutylbenzene + Propionic acid → 4'-Isobutylpropiophenone +water	4'-Isobutylpropio-phenone + trimethyl orthoformate → Methyl-2-(4-isobutyl-phenyl)propanoate + dimethoxymethane	Methyl-2-(4-isobutyl-phenyl)propanoate + KOH → Ibuprofen-K+ + methanol
Composition (Reactant A: Reactant B, in moles eq.)	1:1	1:4	1:2
Solvent	-	MeOH	MeOH/H2O
Catalyst	Triflic acid	1 eq. Iodobenzene diacetate	-
Acid/Base	5eq. Triflic acid	5eq. Triflic acid	-
Reaction Conditions			
Temperature	150°C	50°C	65°C
Pressure	1 atm	1 atm	1 atm
Time	10 min	2 min	3 min
Catalyst	Triflic acid	Iodobenzene diacetate	-
Solvent amount	-	32eq. MeOH	MeOH/H2O (4:1v/v)
Conversion	92%	98%	99%

2.2.1.3. Scenario 3: Modified Bogdan Process with Last Enzymatic Step

Enzymatic esterifications are seen as a green route avoiding the harsh acidic and basic reagents commonly used in the synthesis of esters from alcohols and acids [20, 21]. The same argument holds for the reverse reaction, which is enzymatic esterification. Accordingly and taking the first two reactions of Bogdan's pathway as are, it is proposed in this research work to change the last third step toward an enzymatic reaction, replacing the consumed basic reactant KOH with a recoverable enzyme catalyst, see Figure 5. This reduces the process mass in the last step, avoids the use of a reactant with a considerable economic backpack, and uses water instead of an organic solvent. The Amano Lipase will be used as a catalyst. We want to test the greenness of a second new process concept, which is the use of the functional solvent-enabled factory, avoiding additional measures for the recovery of the enzyme and eliminating (in an ideal case) all processes and equipment for product purification. Therefore, an ionic liquid will also be introduced. The use of the ionic liquid itself creates additional environmental impact, yet if it functions well it can reduce also the burden by reusing the enzyme and helping to save purification equipment and related process mass.

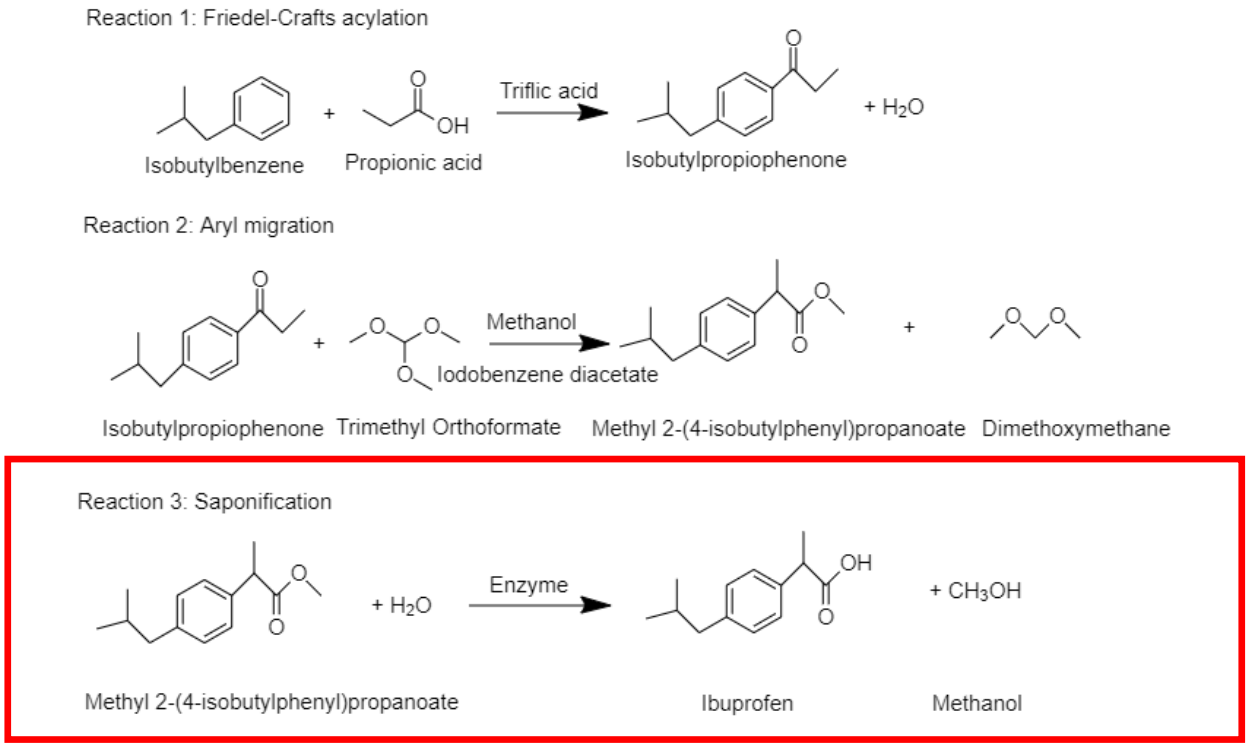

Figure 5. New proposed the last step for the Bogdan process

The third reaction is favourably carried out in segmented flow by contacting two immiscible feed solutions in a T- or Y piece to form regular, alternate slugs. Water and the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate [BMIM][PF6] carry the enzyme Amano lipase and the product from reaction 2 of the Bogdan process. The ester hydrolysis is thus a liquid-liquid reaction, likely to be interface-driven. Micro-flow processing ensures large specific interfaces and high mass transfer coefficients. The reaction solution splits into the aqueous phase and the organic phase, and ibuprofen dissolves preferably in the organic phase, which allows for facile separation from the ionic liquid, see Figure 6. This process is expected more energy and cost-efficient than Bogdan's pathway as investments are required for the separation of ibuprofen [22].

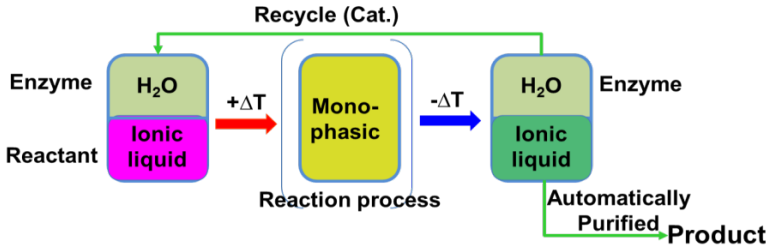

Figure 6. Functional solvents: Automatic reaction/separation replacing respective equipment

To obtain the data for LCA analysis, three enzymes were utilised as the catalyst for the saponification reaction, including commercially available powder *Amano lipase* from Sigma Aldrich, a solution of pure *Mycobacterium smegmatis* (MsAcT) enzyme from TU Delft [23, 24], and *Amano lipase PS* from Enginzyme. *Amano lipase* from Sigma Aldrich was the main enzyme that was utilised to investigate the optimal conditions. Experiments under the optimal conditions were then conducted with *Mycobacterium smegmatis* enzyme from TU Delft and *Amano lipase* from EnginZyme for comparison purposes. Results show that the maximum yield of ibuprofen obtained is 70% in the case of the *Amano lipase* from Sigma Aldrich while 57% and 48% product yields respectively were observed for experiments that utilised *Mycobacterium smegmatis* enzyme from TU Delft and *Amano lipase* from EnginZyme.

The reaction specifications and experimental data for the Bogdan synthetic route are given as follows in Table 3 [6, 19].

Table 3 *Reaction specifications and experimental data of the proposed enzymatic synthetic route*

Reaction information	**Friedel Crafts (flow)**	**Aryl Migration (flow)**	**Saponification (flow)**
Reaction	Isobutylbenzene + Propionic acid → 4'-Isobutylpropiophenone +water	4'-Isobutylpropiophenone + trimethyl orthoformate → Methyl-2-(4-isobutylphenyl)propanoate + Dimethoxymethane	Methyl-2-(4-isobutylphenyl)propanoate + H_2O → Ibuprofen + methanol
Composition (Reactant A/B, in moles eq.)	1:1	1:4	1:2
Solvent	-	MeOH	[BMIM][PF6]/Phosphate buffer solution
Catalyst	Triflic acid	Iodobenzene diacetate	Amano lipase from Pseudomonas fluorescens
Acid/Base	5eq. Triflic acid	5eq. Triflic acid	-
Reaction Conditions			
Temperature	150°C	50°C	50°C
Pressure	1 atm	1 atm	1 atm
Time	10 min	2 min	3 min
Catalyst type	Triflic acid	Iodobenzene diacetate	Methyl-2-(4-isobutylphenyl)propanoate/Enzyme
Solvent amount	-	32eq. MeOH	Methyl-2-(4-isobutylphenyl)propanoate/Water = 3:1
Conversion	92%	98%	70%

2.2.2. Life Cycle Impact Assessment (LCIA)

The environmental impacts are calculated through the LCIA method 'ILCD/PEF recommendation 1.09'; this method has been used intensively in the last few years and has received a large consensus in the field of work of LCA [25]. The applied ILCD/PEF recommended impact assessment method, midpoint, v.1.09 considers all of the environmental impact categories while important impact categories relevant to the goal and scope of a study can be selected [26]. The quantitative modelling of the environmental impact is centred at a mid-point in the cause-effect chain, hence limiting the uncertainties of the results that would stem from speculating on the end-effects on the environment. The environmental impact is calculated for different impact categories, which cover a broad set of consequences on the environment. These are reported in Table S5 of the supporting information.

The software adopted for the LCA model is GaBi ts 8.7 (SP36). Processes and materials used in the model come from the databases professional + extensions (II, VI, IX, XVII) and Ecoinvent 3.6 (integrated SP36): the dataset complies with the ISO 14044 [27], ISO 14064 [28] and ISO 14025 [29] standards and up to date. All the results reported in this work refer to 1 ton of ibuprofen – the chosen FU.

3. LCA Results and Discussion

The LCA results are organized in three sections – inventory data analysis, comparative analysis, and hotspot analysis – that offer a different angle on the environmental performances of the systems under analysis.

3.1. Inventory data analysis

The three above-mentioned scenarios 1, 2, and 3 were simulated with Aspen Plus v11® to generate the LCI data for LCA.

3.1.1. Scenario 1: The BHC process

Figure 7 shows the schematic flowchart of the BHC process while the process input and output of each corresponding step are presented in Table 4.

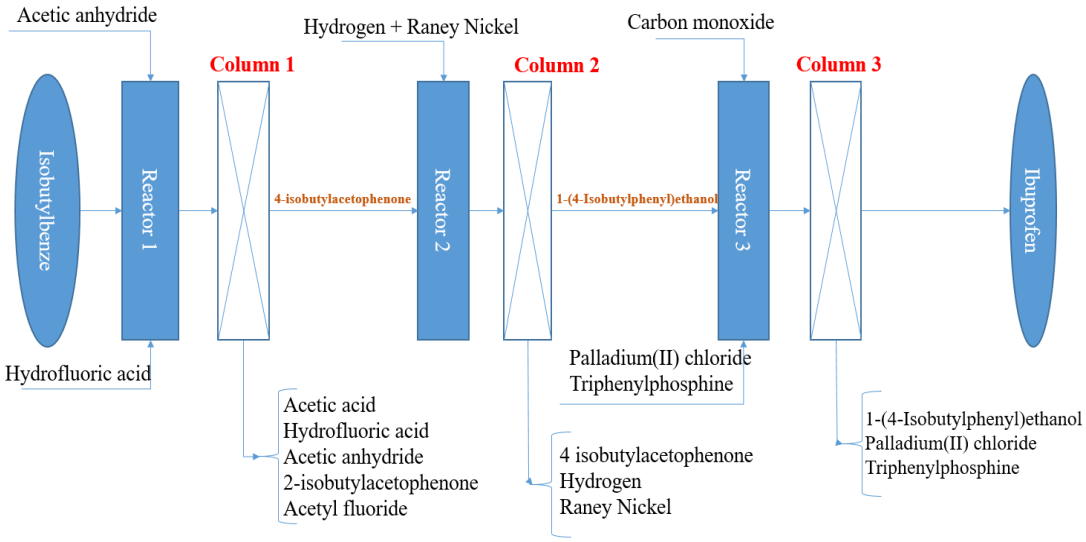

Figure 7. Schematic flowchart of the BHC ibuprofen production process.

Table 4 *Process input and output of the BHC synthetic route obtained through simulation*

Friedel-Crafts Acylation (Reactor 1)			
Input		**Output**	
Components	**Mass flow, g/day**	**Components**	**Mass flow, g/day**
Isobutylbenze	460	4-Isobutylacetophenone	483.3
Acetic anhydride	689.18	Acetic acid	164.7
Hydrofluoric acid	3377.04	Hydrofluoric acid	3377.0
		Acetic anhydride	409.3
		2-isobutylacetophenone	79.5
		Acetyl fluoride	12.5
Hydrogenation (Reactor 2)			
Input		**Output**	
Components	**Mass flow, g/day**	**Components**	**Mass flow, g/day**
4 isobutylacetophenone	483.255	1-(4-Isobutylphenyl)ethanol	488.6
Hydrogen	10.4	4-isobutylacetophenone	0.2
Raney Nickel	25.7	Hydrogen	4.9
		Raney Nickel	25.7

Carbonylation (Reactor 3)			
Input		**Output**	
Components	**Mass flow, g/day**	**Components**	**Mass flow, g/day**
1-(4-Isobutylphenyl)ethanol	488.56	Ibuprofen	494.9
Carbon monoxide	67.2	1-(4-Isobutylphenyl)ethanol	60.9
Palladium(II) chloride	0.34	Palladium(II) chloride	0.3
Triphenylphosphine	0.58	Triphenylphosphine	0.6

To generate the inventory data for LCA, the energy consumption of each piece of equipment used in the process is required. Table 5 shows the energy demanded by the BHC process obtained through process simulation using the literature-reported data.

Table 5 *Equipment energy consumption of the BHC process obtained through simulation*

Equipment	**Code**	**Heat duty, kW**
Heat exchanger 1	H1	0.001076
Heat exchanger 2	H2	0.001076
Heat exchanger 3	H3	0.000528
Heat exchanger 4	H4	0.000674
Heat exchanger 5	H5	0.001347
Heat exchanger 6	H6	0.00143
Flow reactor 1	R-1	0.001604
Flow reactor 2	R-2	0.002083
Flow reactor 3	R-3	0.001036
Separation column 1	SEP-1	0.003885
Separation column 2	SEP-2	0.000019
Separation column 3	SEP-3	0.000016

3.1.2. Scenario 2: The Bogdan Process

The innovative flow synthetic route proposed by Bogdan et al. is shown in Figure 8. In this process, there is no intermediate separation but only one separation column was utilised at the end of the process.

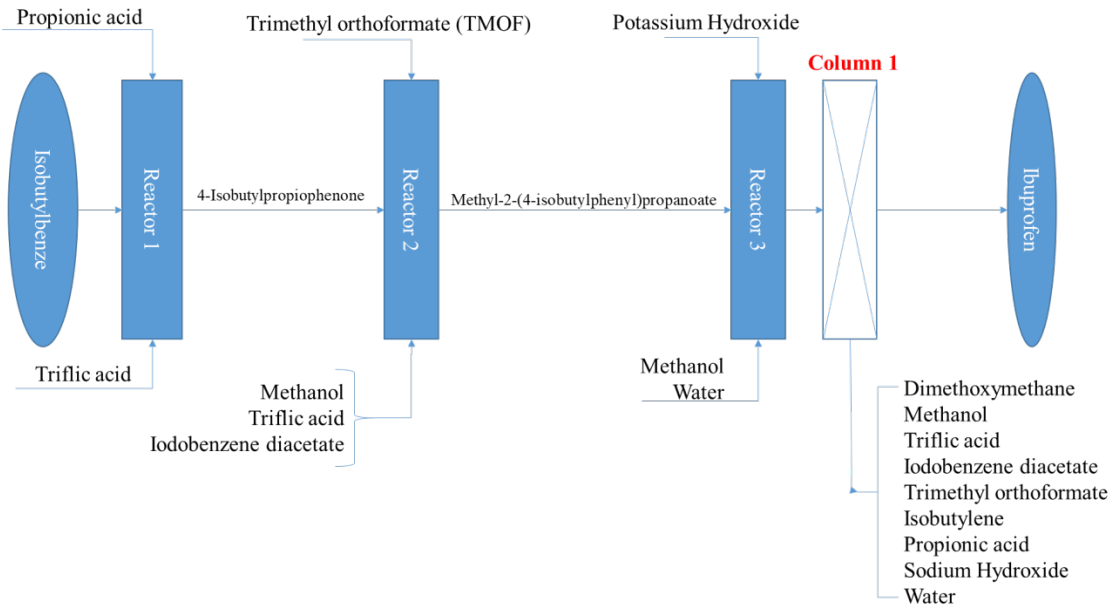

Figure 8. Schematic flowchart of the Bogdan ibuprofen production process.

In the first step, isobutyl benzene is mixed with propanoic acid. The mixture is then diluted with triflic acid and enters the 1st reactor where the reaction happens at around 150 °C. The purpose of this first step is to convert isobutylbenzene to 1-(4-isobutylphenyl)propan-1-one (intermediate 2) through the Friedel–Crafts acylation. The outlet stream is then cooled to 0°C before mixing, also at 0°C, with the mixture of diacetoxyiodobenzene and trimethyl orthoformate in methanol. Next, the stream is brought into the 2nd reactor where the intermediate 2 is transferred to methyl 2-(4-isobutylphenyl)propanoate (intermediate 3) via the diacetoxyiodobenzene -mediated 1,2-aryl migration at 50 °C, using trimethyl orthoformate again as the catalyst. The products will be then mixed with a solution that includes potassium hydroxide dissolved in a mixture of methanol and water before feeding into the 3rd reactor where the intermediate 3 is saponified to form ibuprofen salt. The significant improvement of this process is that the time and energy-consuming separation and purification in the batch process can be effectively replaced by a continuous final separation. It is assumed that the product obtained through the 3rd reactor is entirely acidified to achieve a potassium-free acid form of ibuprofen and avoid the formation of the salt which is unable to use for pharmaceutical formulations [6].

Table 6 shows the process input and output of the Bogdan process obtained through Aspen Plus. The main products of each stage are highlighted in blue.

Table 6 *Process input and output of the Bogdan synthetic route obtained through simulation*

Process input and output

Friedel-Crafts Acylation (Reactor 1)			
Input		**Output**	
Components	**Mass flow, g/day**	**Components**	**Mass flow, g/day**
Isobutylbenzene	277	**4-Isobutylpropiophenone (4-IBPP)**	386.0
Propionic acid	152.9	Water	36.6
Triflic acid	309.8	Triflic acid	309.8

		Isobutylbenze	4.7
		Propionic acid	2.6
Hydrogenation (Reactor 2)			
Input		**Output**	
Components	**Mass flow, g/day**	**Components**	**Mass flow, g/day**
Trimethyl orthoformate (TMOF)	219	Dimethoxymethane	154.3
Methanol	1764.2	Methanol	1764.2
Triflic acid	1694.7	Triflic acid	1694.7
Iodobenzene diacetate	555.6	Iodobenzene diacetate	555.6
		Trimethyl orthoformate (TMOF)	3.8
Carbonylation (Reactor 3)			
Input		**Output**	
Components	**Mass flow, g/day**	**Components**	**Mass flow, g/day**
Methyl-2-(4-isobutylphenyl)propanoate	446.9	**Ibuprofen**	495.7
Potassium hydroxide	1175.2	Sodium hydroxide	1061.4
Methanol	6389.1	Methanol	6454.1
Water	1283.8	Water	1283.8

The energy consumption of equipment used in the Bogdan process is shown in Table 7. The data then was used as the inventory data for LCA analysis.

Table 7 *Equipment energy consumption of the Bogdan process obtained through simulation*

Equipment energy consumption

Equipment	Code	Heat duty, kW
Heat exchanger 1	H1	-0.002038203
Heat exchanger 2	H2	-0.001570048
Heat exchanger 3	E3H3	0.008547978
Flow reactor 1	PFR-1	0.004509297
Flow reactor 2	PFR-2	0.004722757
Flow reactor 3	PFR-3	0.011492787
Separation column 1	SEP-1	-0.00093496

3.1.3. Scenario 3: The Bogdan process with the last enzymatic step

The proposed enzymatic synthetic route is shown in Figure 9. As previously mentioned, the last step of the Bogdan process was modified to replace methanol with greener chemicals, water, and *Amano lipase*.

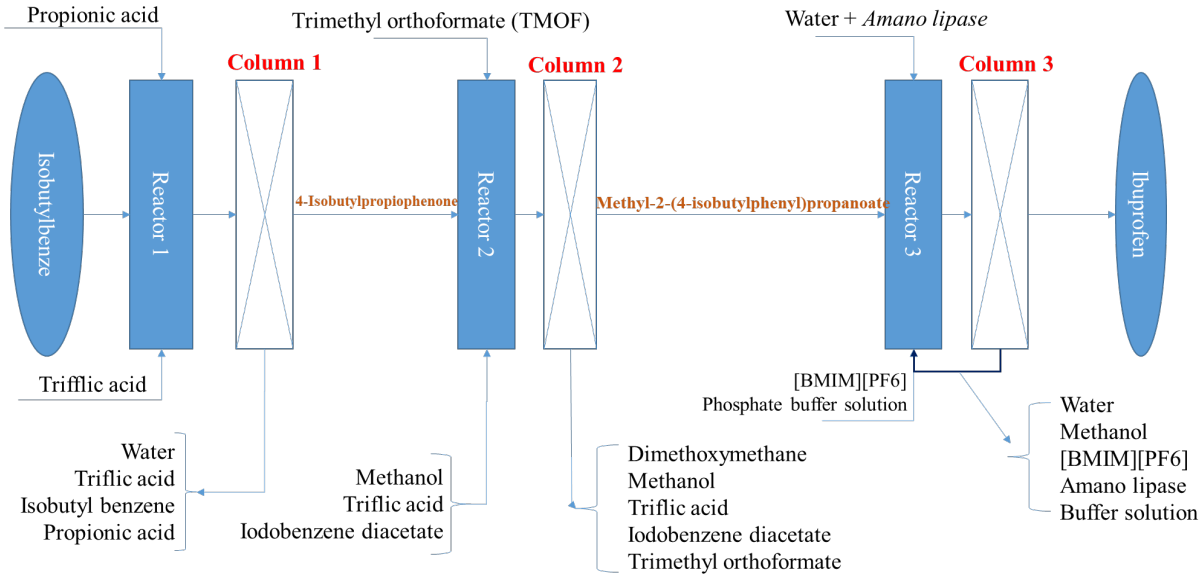

Figure 9. Schematic flowchart of the enzymatic ibuprofen production process

Table 8 shows the process input and output generated by Aspen Plus based on both literature data and experimental results. Our experimental study shows that using water and enzymatic catalyst could achieve up to 70% product yield of ibuprofen. A technical paper is under preparation for publication.

Table 8 *Process input and output of the enzymatic synthetic route obtained through simulation*

Friedel-Crafts Acylation (Reactor 1)			
Input		**Output**	
Components	**Mass flow, g/day**	**Components**	**Mass flow, g/day**
Isobutylbenze	392.2	**4-Isobutylpropiophenone (4-IBPP)**	542.7
Propionic acid	216.43	Water	51.4
Triflic acid	438.54	Triflic acid	438.5
		Isobutyl benzene	9.4
		Propionic acid	5.2
Hydrogenation (Reactor 2)			
Input		**Output**	
Components	**Mass flow, g/day**	**Components**	**Mass flow, g/day**
4 isobutylacetophenone	542.65	**Methyl-2-(4-isobutylphenyl)propanoate**	628.5

Trimethyl orthoformate (TMOF)	1141.3	Dimethoxymethane	217.1
Methanol	995.2	Methanol	995.2
Triflic acid	2017.3	Triflic acid	2017.3
Iodobenzene diacetate	661.30	Iodobenzene diacetate	661.3
		Trimethyl orthoformate (TMOF)	838.4

Carbonylation (Reactor 3)

Input		**Output**	
Components	**Mass flow, g/day**	**Components**	**Mass flow, g/day**
Methyl-2-(4-isobutylphenyl)propanoate	628.47	**Ibuprofen**	541.4
Water	167.8	Water	120.6
Ionic liquid [BMIM][PF6]	4554.1	Ionic liquid [BMIM][PF6]	4554.1
Amano lipase from Pseudomonas fluorescens	62.85	Amano lipase	62.9
Phosphate buffer solution 0.05 M	874.8	Phosphate buffer solution	874.8
		Methanol	84.0
		Methyl-2-(4-isobutylphenyl)propanoate	50.3

Similar to the BHC and Bogdan processes, the energy consumption of equipment used in the enzymatic synthetic route is reported in Table 9.

Table 9 *Equipment energy consumption of the enzymatic process obtained through simulation*

Equipment energy consumption

Equipment	Code	Heat duty, kW
Heat exchanger 1	H1	0.001885336
Heat exchanger 2	H2	-0.001660049
Heat exchanger 3	H3	-0.000633844
Heat exchanger 4	H4	0.000219705
Heat exchanger 5	H5	0.004226038
Heat exchanger 6	H6	0.004856786
Flow reactor 1	PFR-1	0.004477326
Flow reactor 2	PFR-2	-2.63E-05
Flow reactor 3	PFR-3	-0.001488754
Separation column 1	SEP-1	-7.31E-05
Separation column 2	SEP-2	-0.000470412

3.1.4. Comparative analysis of the environmental impacts

The comparison of the environmental impacts of the selected ibuprofen production routes is shown in Figure 10. The graph refers to 1 ton of product. In this graph, the environmental impacts are presented through an internal normalisation based on the environmental impact of the BHC synthesis. The latter synthesis is used as a baseline to benchmark the environmental impacts of the Bogdan and modified Bogdan (enzymatic catalyst) synthesis routes.

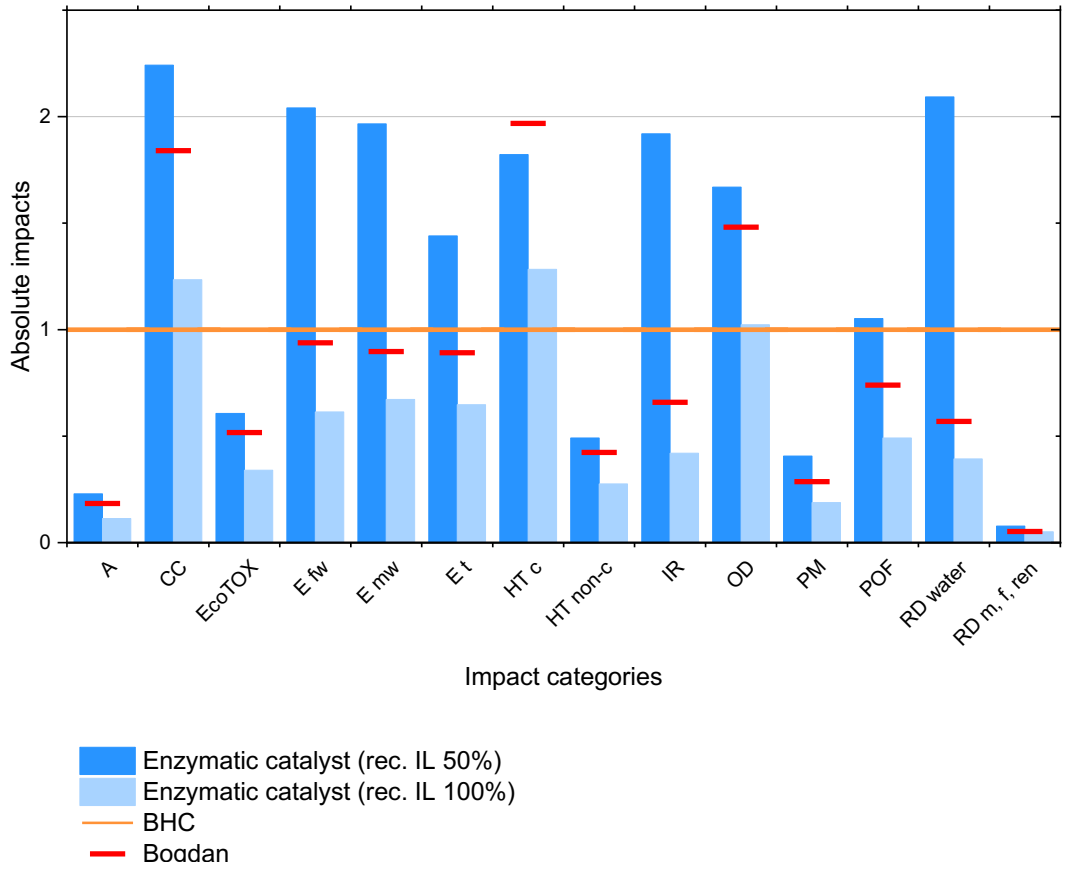

Figure. 10 Comparison of the environmental impacts of the selected synthesis routes for the production of ibuprofen.

The comparison highlights the benefit of adopting the modified Bogdan synthesis route via an enzymatic catalyst. In this scenario, a general reduction of environmental impact is achievable across the whole set of impact categories of the analysis, and the magnitude of such reduction depends on the efficiency of the recycling in the production system. When comparing the modified Bogdan process with the industrial BHC process, the results are mixed. Considering a 50% efficiency of recycling, the modified Bogdan system achieves lower environmental impacts in some impact categories like Acidification, Ecotoxicity of freshwater, Human toxicity, Particulate matter and Resource depletion (mineral, fossils, renewables), whilst having higher impacts on the rest of the impact categories. Yet, the new process proposed here scores better environmental performances in all the impact categories when the enzyme recycling is close to 100%. It is evident that the new flow chemistry process (Bogdan) is better than the industrial BHC process in all categories for this scenario; for several categories, the difference is very large (Acidification, Ecotoxicity of freshwater, Human Toxicity, Ionising radiation, Particulate matter, and Resource depletion). It can also be seen that the synthesis proposed in this paper can improve the Bogdan process substantially, provided that the enzyme recycling is of a high standard.

Table 10 *LCA results divided by impact category and synthesis method. Colour scale (green to red = increasing impact).*

Impact categories		BHC	Bogdan	Enzymatic catalyst (50% rec.)	Enzymatic catalyst (100% rec.)	comp. to BHC	comp. to Bogdan
A	[Mole of H+ eq.]	2.67	0.49	0.61	0.30	-89%	-38%
CC	[kg CO2 eq.]	0.59	1.08	1.32	0.72	23%	-33%
EcoTOX	[CTUe]	1.16	0.60	0.70	0.40	-66%	-34%
E fw	[kg P eq.]	0.36	0.33	0.73	0.22	-39%	-35%
E mw	[kg N eq.]	0.64	0.57	1.25	0.43	-33%	-25%
E t	[Mole of N eq.]	0.65	0.58	0.94	0.42	-35%	-27%
HT c	[CTUh]	0.62	1.23	1.14	0.80	28%	-35%
HT non-c	[CTUh]	4.06	1.72	2.00	1.12	-72%	-35%
IR	[kBq U235 eq.]	0.71	0.47	1.37	0.30	-58%	-36%
OD	[kg CFC-11 eq.]	0.65	0.96	1.08	0.66	2%	-31%
PM	[kg PM2.5 eq.]	1.47	0.42	0.60	0.28	-81%	-34%
POF	[kg NMVOC eq.]	0.36	0.26	0.37	0.17	-51%	-34%
RD water	[m^3 eq.]	0.85	0.48	1.78	0.33	-61%	-31%
RD m, f, ren	[kg Sb eq.]	5.56	0.29	0.43	0.28	-95%	-3%

In this scenario, the modified Bogdan impact would be around 30% or less of the industrial BHC process in almost all impact categories. This is depicted in Table 11.

Table 10 reports the absolute environmental impacts of the synthesis routes under analysis, expressed for different impact categories with their respective units listed in Table S5. Table 10 also quantifies the change (%) of environmental impact in the production via enzymatic catalyst (100% rec.) with respect to BHC and Bogdan syntheses. The results put in evidence the reduction of environmental impacts resulting from the modified Bogdan synthesis via enzymatic catalysts compared to industrial BHC and Bogdan syntheses. The reduction is considerable over the whole range of impact categories of the LCA analysis and it is quantified at -31% and -45% for BHC and standard Bogdan syntheses.

In the next section, the results of the hotspot analysis are outlined for the four scenarios considered in the comparative analysis, providing insight on the origin of the environmental impact across the life cycle steps of the Ibuprofen production system.

3.1.5. Hotspot analysis

The results shown in the previous section are analysed more in-depth through a hotspot analysis. This investigates the single activities in the life cycle of the production system of ibuprofen that primarily accounts for the environmental impact of the systems under analysis. As shown in Figure S1 (see supporting information), the system boundaries considered in this LCA study cover the full spectrum of activities involved directly in the production phase as well as those satellite activities (e.g production of precursors) that orbit around the production phase.

By quantifying each contribution to the overall impact, it is possible to identify the primary actors behind the environmental performances of the selected production systems. Furthermore, when cross-compared with the comparative analysis it is possible to capture the causes of a reduction or increase of the environmental impact in a specific impact category. Finally, the outcomes of the hotspot

analysis can be used to intervene in the process design of technology and use the latter results as inputs to the process development to improve the environmental performances.

In the next figures, codes are used in the legends (preceding the name of the activities) to indicate which synthesis step a given activity is linked to. The list of codes is reported in Table 11.

Table 11 *List of code names used in the hotspot analysis.*

Code	Location in the process flow diagram
R1	Reaction step 1
R2	Reaction step 2
R3	Reaction step 3
SC1	Separation column after reaction step 1
SC2	Separation column after reaction step 2
SC3	Separation column after reaction step 3
HE	Heat exchangers

In the BHC synthesis (Figure 11) the production of hydrofluoric acid and acetic anhydride has a strong impact on the overall environmental performance of this production system.

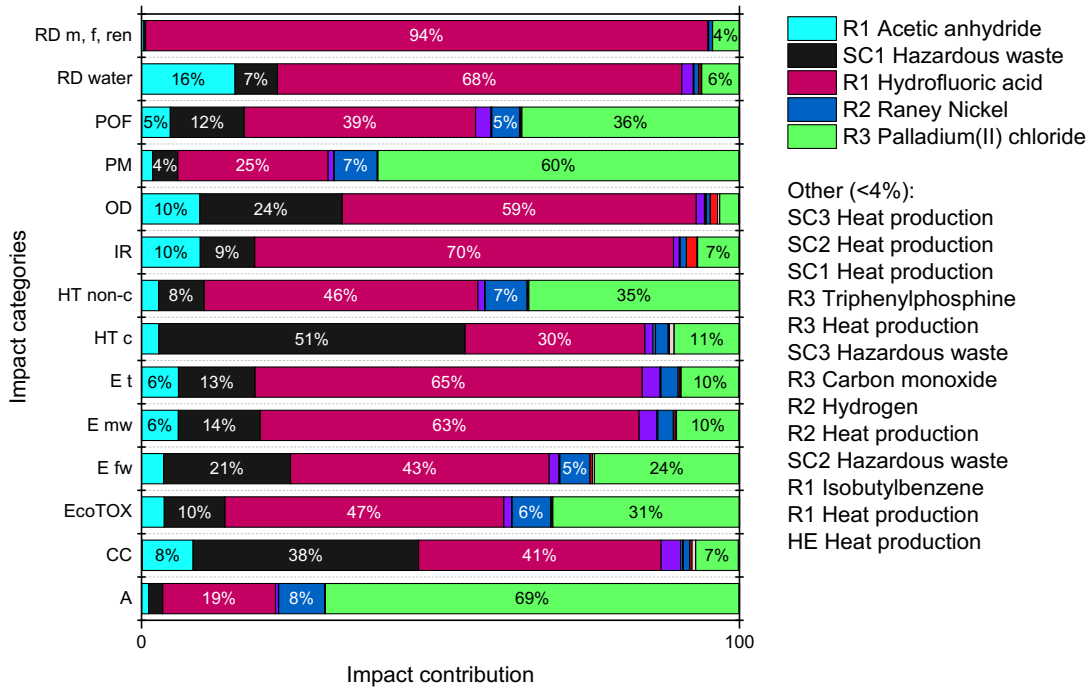

Figure 11. Contributions to the environmental impact of the BHC synthesis

The latter chemicals are both processed in high quantities in the first reaction step for the production of 4-isobutylacetophenone, thus also contributing to burden considerably the waste stream resulting from the first separation column. In particular, the production of hydrofluoric acid is of primary concern in the Resource depletion of minerals, fossil, and renewables. The production of palladium(II) chloride (processed in the third reactor) and Raney nickel (second reactor) take a considerable share of the impact in the impact categories Acidification and Particulate matter. The rest of the activities (listed under other in Figure 10) have a negligible effect on the overall environmental impact of the BHC synthesis.

With regards to the Bogdan synthesis (Figure 12), the waste treatment carries a large part of the environmental impact across all the impact categories.

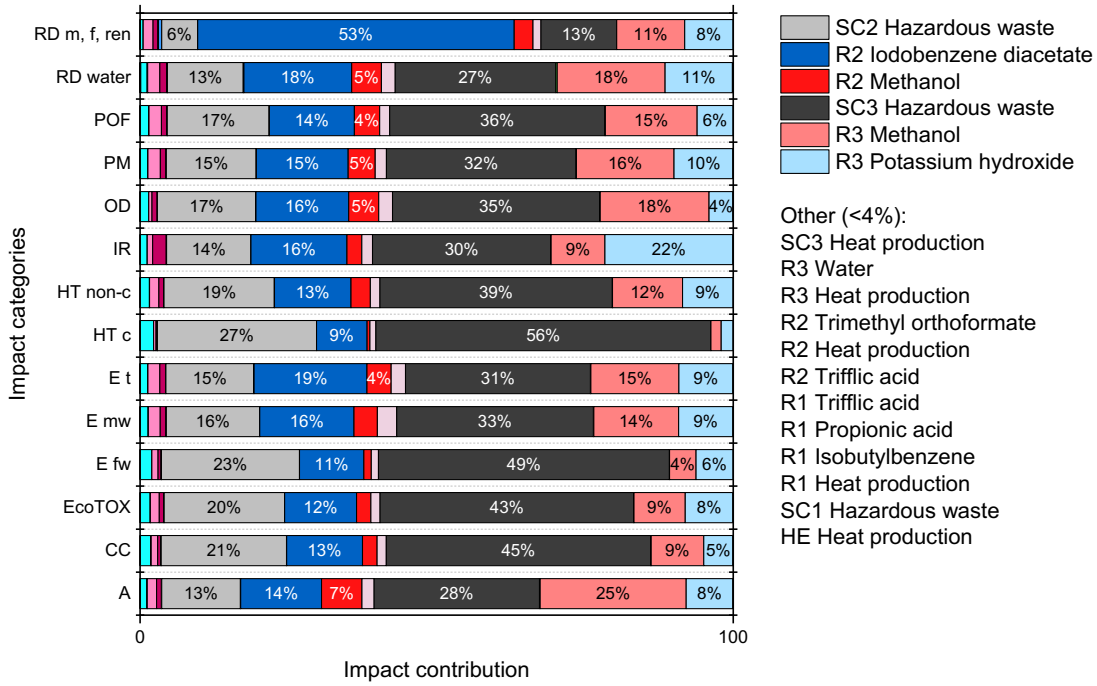

Figure 12. Contributions to the environmental impact of the Bogdan synthesis

To this end, the Bogdan synthesis resulted to be the one generating the highest volumes of waste presenting an E-factor $\left(\frac{\text{mass of total waste}}{\text{mass of product}}\right)$ of 27. Furthermore, the production of iodobenzene diacetate, methanol, and potassium hydroxide takes around 60% on average of the impact in all impact categories. These are processed in large volumes in the second and third reactors of the synthesis.

In the comparative analysis, the synthesis of ibuprofen via enzymatic catalyst showed great potential to enhance the environmental performances of the BHC and standard Bogdan syntheses. The advantages of adopting such a type of synthesis mainly consist in a low volume of hazardous waste generated, the possibility to recover ionic liquids from the effluents of the last step of the synthesis, and lower quantities of methanol processed. This emerges from Figure 13 and Figure 14 that report respectively the hotspot analysis for the enzymatic catalyst system under different recirculation efficiencies.

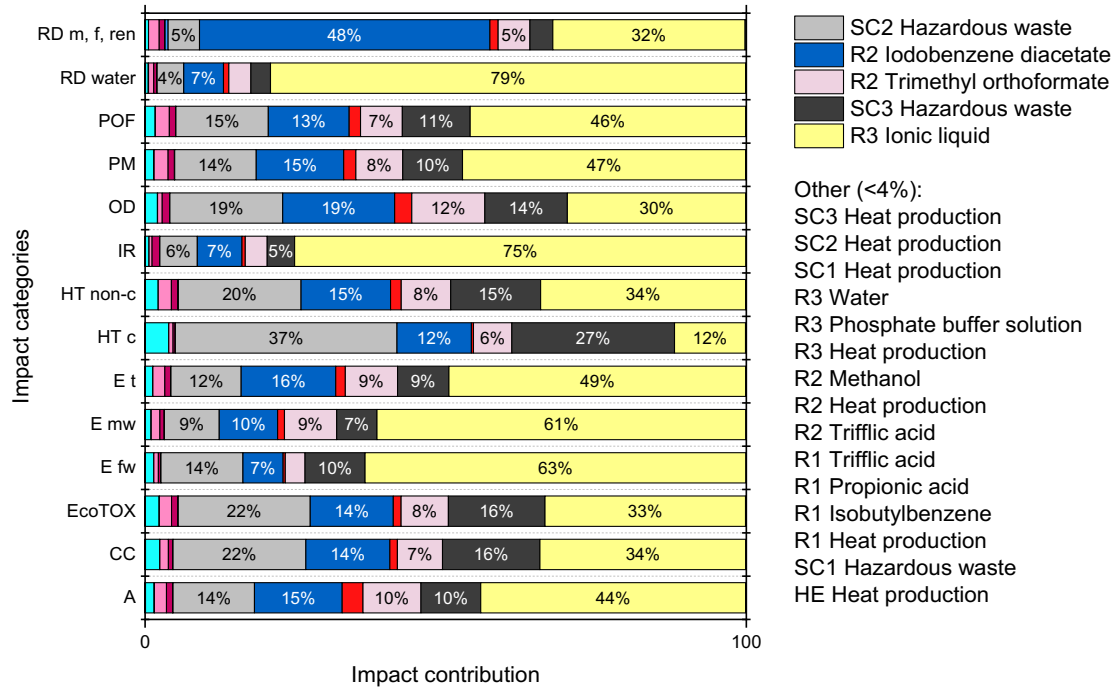

Figure 13. Contributions to the environmental impact of the synthesis of ibuprofen via the enzymatic catalyst: an efficiency of 50% is considered for the recirculation of IL.

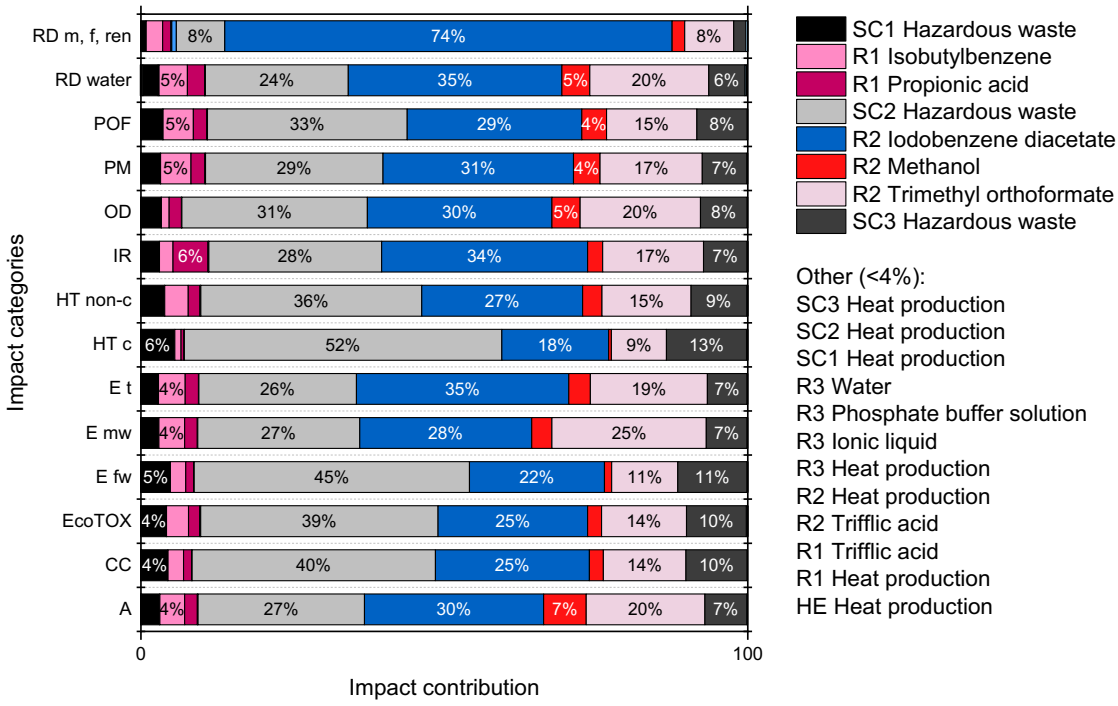

Figure 14. Contributions to the environmental impact of the synthesis of ibuprofen via the enzymatic catalyst: an efficiency of 100% is considered for the recirculation of IL.

When cross-compared with Figure 10 and Table 11, the results of the hotspot analysis indicate that the saving of environmental impact - which stems from adopting the Bogdan synthesis in combination with using an enzymatic catalyst synthesis in place of the BHC synthesis - arises from: the avoided use of hydrofluoric acid in the first reaction step, Raney nickel and palladium (II) chloride in

the last step of the synthesis, and from a contained amount of waste generated across the synthesis. In fact, the E-factor for the enzymatic-modified Bogdan synthesis (50% and 100% recycling scenarios) is respectively 15.5 and 11.3, as opposed to 8.4 of the BHC synthesis and 27 of the Bogdan synthesis. The difference in environmental impact between the Bogdan synthesis and the enzymatic-modified Bogdan synthesis shows that even a variation of one step in a multi-step synthesis can have considerable impact and that essentially is the mission of this research work.

As expected, an efficient recirculation of the IL processed in the synthesis would have beneficial effects on the environmental performance of the system, and inevitably is the environmental asset to guarantee when establishing such a biocatalytic route. The production of IL takes in fact a significant share of the impact in the modified Bogdan scenario and can only be justified when the system achieves a high efficiency of recycling. An efficient recycling system essentially diminishes that large share of environmental impact arising from the production of fresh IL, hence reducing significantly the overall impact of the production of ibuprofen.

The scenario with a 100% total recovery presents the best scenario in terms of environmental impacts within this study. However, it is necessary to assess the stability of the IL and the enzyme in the long term as well as the total recovery of the IL. The IL selected, 1-butyl-3-methylimidazolium hexafluorophosphate, was chosen due to its hydrophobicity [30]. However, its anion can be hydrolyzed under contact with moisture, and release HF or POF, which can damage glassware or steel equipment. This decomposition or degradation may be the result of the synthetic procedure selected. The hydrolytic decomposition can be hindered by the preparation by metathesis from a salt rather than an acid, and therefore avoid acid-catalyzed hydrolytic decomposition [31]. The toxicity of the ion is also of concern, which has an impact on its handling and the equipment selected for the process [31]. However, it was also found in Ranke et al. [32] that for C3MIM PF_6 up to C5MIM PF_6, the toxicity of the IL is lower than that of the anion itself. The cation and anion form an ion pair that reduces the toxicity of the ion.

In the case that the recovery of the IL is limited, the disposal of the IL needs to be assessed, or possible regeneration options [31]. Besides, other ILs could also be assessed for the reaction. These ILs, besides having the correct physicochemical properties, should comply with the concept of nontoxic pharmaceutically acceptable ions and GRAS (generally regarded as safe) [33]. Amon the nontoxic pharmaceutically acceptable anions includes inorganic anions are the following: Cl^-, Br^-, $SO4^{2-}$, $PO4^{3-}$, and NO^{3-} [31].

4. Conclusions

The present work offers an all-round analysis of the performances of different synthesis routes for the production of ibuprofen. The research focuses on a well-established industrial process (BHC) and a modern flow chemistry process (Bogdan), which is one of the most promising options – available today - in the context of continuous processing applied to pharmaceutical manufacturing which is supported by the industry and the legislative authority (Federal Drug and Food Administration, FDA). The replacement of the industrial BHC batch production route - awarded for its greenness as compared to the former Hoechst-route -with a flow chemistry route (Bogdan), results in significant environmental benefits; part is due to the advanced flow chemistry reaction performance and part of its accounts for the replacement of harsh chemicals by more environmentally-friendly ones.

The current trend in pharmaceutical production leans toward the adoption of bioprocesses [34]; hence we considered how the flow-Bogdan process can be ‘bio-reengineered’. In this context, the results of this work show that the mere change of one reaction steps in favour of biocatalysis can translate into considerable environmental benefits. The results of the LCA show in fact that such benefits regard the whole spectrum of impact categories of the assessment. The enhanced environmental performances primarily originate from the avoided use of hydrofluoric acid in the first reaction step, Raney nickel and palladium(II) chloride in the last step of the synthesis, and a contained amount of waste generated across

the synthesis; this translates into a low E-factor compared to the alternative Ibuprofen production routes. On the whole, the change of environmental performances between the Bogdan synthesis and the enzymatic-modified Bogdan synthesis testify that rethinking just one step in a multi-step synthesis can have a significant impact on the whole production system. The combination of bioprocesses and flow chemistry, inherently pursuing the idea of process simplification, can be a viable opportunity to increase sustainability in pharmaceutical production at all scales; starting from the early stages of technology development in R&D activities, and eventually at industrial scale.

While the best results were obtained for the commercial Sigma-Aldrich enzyme because of its highest yield, the other enzymes tested in this study have their advantages as well. The Enginzyme enzyme uses support to immobilize the enzyme and this supports facile recycling. The acyltransferase and perhydrolase from *Mycobacterium smegmatis* display the hydrolytic activities earlier described [24]. But with its narrow active side, it is less suitable for this reaction. We did not optimise the respective conditions for the enzymes, meaning there is room for further optimization.

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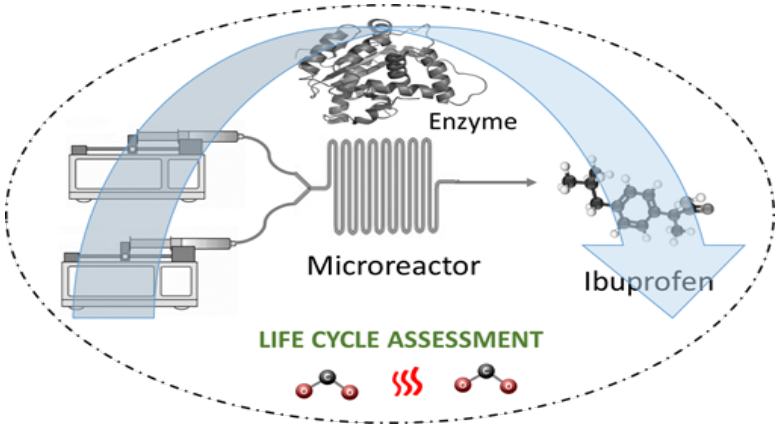

Life Cycle Assessment of a continuous flow ibuprofen production process with green chemistry approach