Antibiotic Synthesis in Flow Mode

Subjects: Green & Sustainable Science & Technology

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Continuous-flow chemistry has become a mainstream process and a notable trend among emerging technologies for drug synthesis. It is routinely used in academic and industrial laboratories to generate a wide variety of molecules and building blocks. The advantages it provides, in terms of safety, speed, cost efficiency and small-equipment footprint compared to analog batch processes, have been known for some time. What has become even more important is its compliance with the quality objectives that are required by drug-development protocols that integrate inline analysis and purification tools. There can be no doubt that worldwide government agencies have strongly encouraged the study and implementation of this innovative, sustainable and environmentally friendly technology.

flow chemistry antibiotics continuous process drug synthesis

1. Cefotaxime

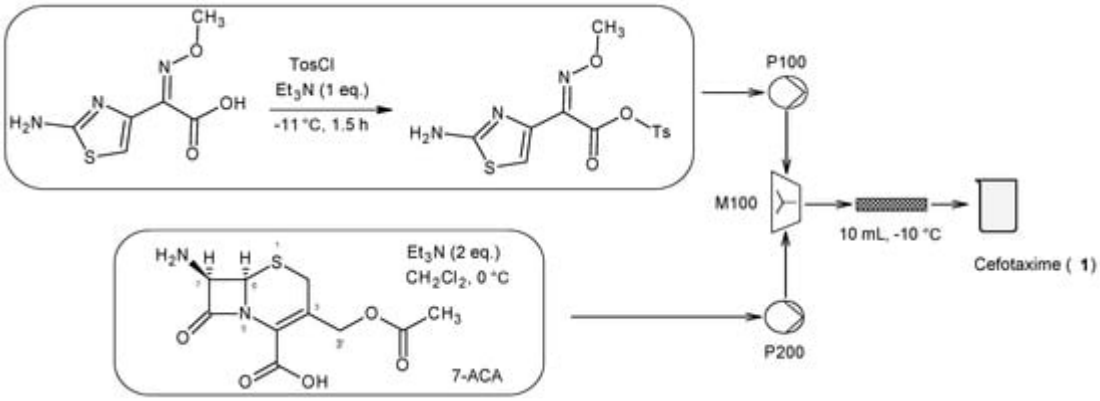
Cefotaxime (**1**) is a β-lactam antibiotic classified as a third-generation cephalosporin, was first synthesized in 1976 and was commercialized by 1980 under the brand name Claforan™. It was approved by the FDA to treat Gram-positive, Gram-negative and anaerobic bacteria.

Its broad-spectrum activity is useful in treating complicated urinary-tract infections, lower-respiratory-tract infections, bacteremia, meningitis, uncomplicated gonorrhea, skin and soft-tissue infections, and obstetric and gynecological infections. Its activity takes place via linkage to the penicillin-binding proteins (PBPs) via its β-lactam ring and by inhibiting the transpeptidation step in the peptidoglycan cell wall. It appears on the World Health Organization's List of Essential Medicines and is available for intramuscular and intravenous administration. It is distributed in powder form in 500 mg, 1 g, 2 g and 10 g vials or in a premixed solution for injection of 1 g and 2 g [1][2][3][4][5][6][7].

The processes to produce cephalosporins, including cefotaxime (**1**), were developed over thirty years ago and persist to this day. In the current context, which is characterized by strict concerns over worker safety and respect for environmental and energy savings, flow chemistry represents an attractive option for the synthesis of these drugs [8][9].

Pieper et al. have published an interesting study on the synthesis of this β-lactam antibiotic in flow mode and have made comparisons to batch mode [10]. The synthesis involved the amidation step between 7-aminocephalosporanic

acid (7-ACA) and (Z)-(2-aminothiazol-4-yl)-methoxyimino acetic acid under activation by 4-toluenesulfonyl chloride, as represented in Scheme 1.



Scheme 1. Cefotaxime (**1**) flow synthesis inspired by Ref. [10].

In this system, 7-ACA was dissolved and stored in dichloromethane with triethylamine at 0 °C in a vessel. In another vessel, the mixed anhydride suspension was formed in dimethylacetamide (DMAc) at −11 °C. This vessel was constantly stirred to avoid sedimentation and was stored for a maximum of 1 h to respect the stable hold time. Peristaltic pumps (P100 and P200) transported the raw-material solution to the Y-shaped polypropylene mixer (M100) in flow towards the reactor. The flow reactor was a fluorinated ethylene propylene (FEP) tube of 10 mL with an inner diameter of 4 mm that was submerged in butyl glycol, used as a cooling material. The cooling batch was tempered with a cooling jacket through which butyl glycol was constantly pumped. The flow rate was set up at 5 mL/min to prevent sedimentation effects that may arise from the insoluble mixed anhydride. The output was collected in a vessel so that the product could be analyzed in solution.

With this methodology, cefotaxime (**1**) was generated at a yield of 80.9% to 7-ACA, working at −10 °C and using a residence time of 1 min. Higher reaction temperature (+20 °C) led to higher 7-ACA conversion, but lower product yield because of the degradation of the cephalosporin nucleus. Higher residence times decreased 7-ACA conversion and, consequently, cefotaxime (**1**) yield. This methodology allowed much shorter reaction times (1 min) to be used, compared to the 30 min needed in the batch synthesis. Furthermore, a more convenient temperature (−10 °C), than the −30 °C used for batch mode, is possible, providing a further advantage in energy savings and costs. The space-time yield was nearly 400 times higher than when the reaction is performed in a reactor vessel and efficient heat distribution corroborated the technology's safety.

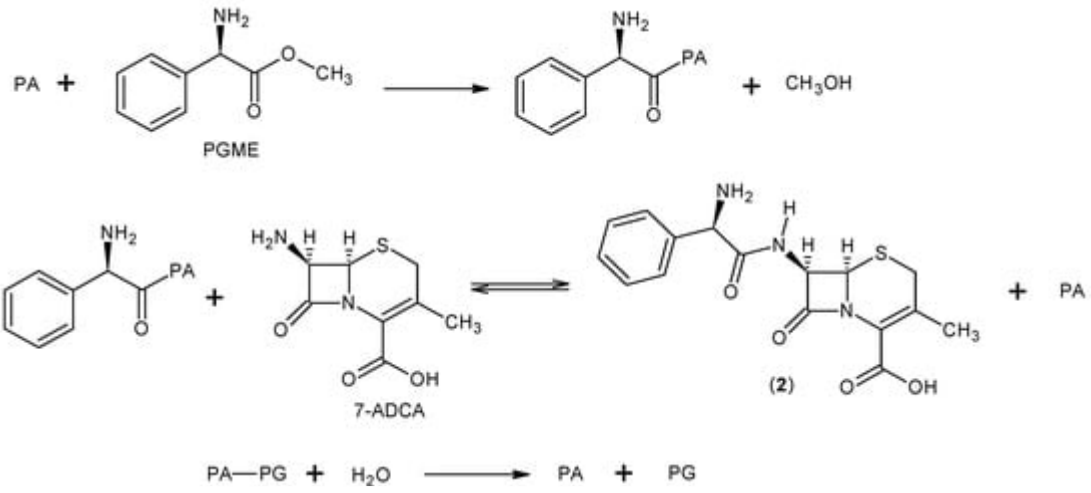
This result clearly shows the attractive features that the flow process possesses compared to the analogous batch route, although the yield was slightly lower. In order to boost productivity and overcome this shortcoming, the authors have proposed operating several identical systems in parallel [11], which would consolidate the great capabilities of flow chemistry.

2. Cephalexin

Cephalexin (**2**) is one of the most widely prescribed β-lactam antibiotics in the United States of America, with more than 7 million prescriptions being made in 2020 [12][13]. It is a first-generation cephalosporin discovered in 1967 and marketed under the brand names Keflex™ and Ceporex™ since 1969. It is used against Gram-positive and some Gram-negative bacteria, particularly *E. coli*, *Proteus mirabilis* and *Klebsiella pneumoniae*. It is administered orally as either 250 mg or 500 mg capsules to treat urinary-tract and respiratory infections. It appears on the World Health Organization's List of Essential Medicines [7][14][15][16][17][18][19].

Vobeckà et al. have reported a continuous-flow process for the production of cephalexin (**6**), with excellent outcomes [20]. The product was synthesized from phenylglycine methyl ester (PGME) and 7-aminodesacetoxycephalosporanic acid (7-ADCA) using penicillin acylase (PA) as the enzyme in a kinetic regime. This regime was necessary to achieve a high cephalexin (**2**) yield in a water medium, as this is difficult to achieve in the thermodynamic process.

As depicted in Scheme 2, the authors employed apparatus that is characterized by an aqueous two-phase system (ATPS) that forms two phases in the flow reactor, which acts as a reaction-separation environment. This system, used in a microfluidic arrangement, guaranteed the in situ extraction of cephalexin (**2**), as well as facilitating enzyme recycling, the addition of fresh reactants and the presence of a uniform reaction mixture. The ATPS consisted of 15 wt% of polyethylene glycol (PEG), with molecular weight ranging from 2000 g mol^{-1} to 4000 g mol^{-1}, 12 wt% of phosphates, to ensure pH = 7.0, and 73 wt% of water. This composition granted cephalexin (**2**) high affinity to the top phase, which split from the PA-containing bottom phase. The reaction mixture contained PGME and 7-ADCA, in a molar ratio of 3:1, which dissolved in ATPS at concentrations of 150 mM and 50 mM, respectively. The free enzyme in water had a concentration of 10 µL for 1 mL of reaction mixture and an activity of 2.88 kU mL^{-1}. The reaction temperature was set to 30 °C by immersing the flow reactor in a water bath.



Scheme 2. Enzymatic cephalexin (**2**) synthesis reaction scheme.

Specifically, the reactants were dosed from the vessel (d) into the microcapillary reactor, (b), which has an inner diameter of 0.8 mm and a length of 87 cm, via a three-way PEEK connector (a). The PA was pumped from the recycle-system vessel (e) into the reactor. The flow rate was set to the value that provided a residence time of 20

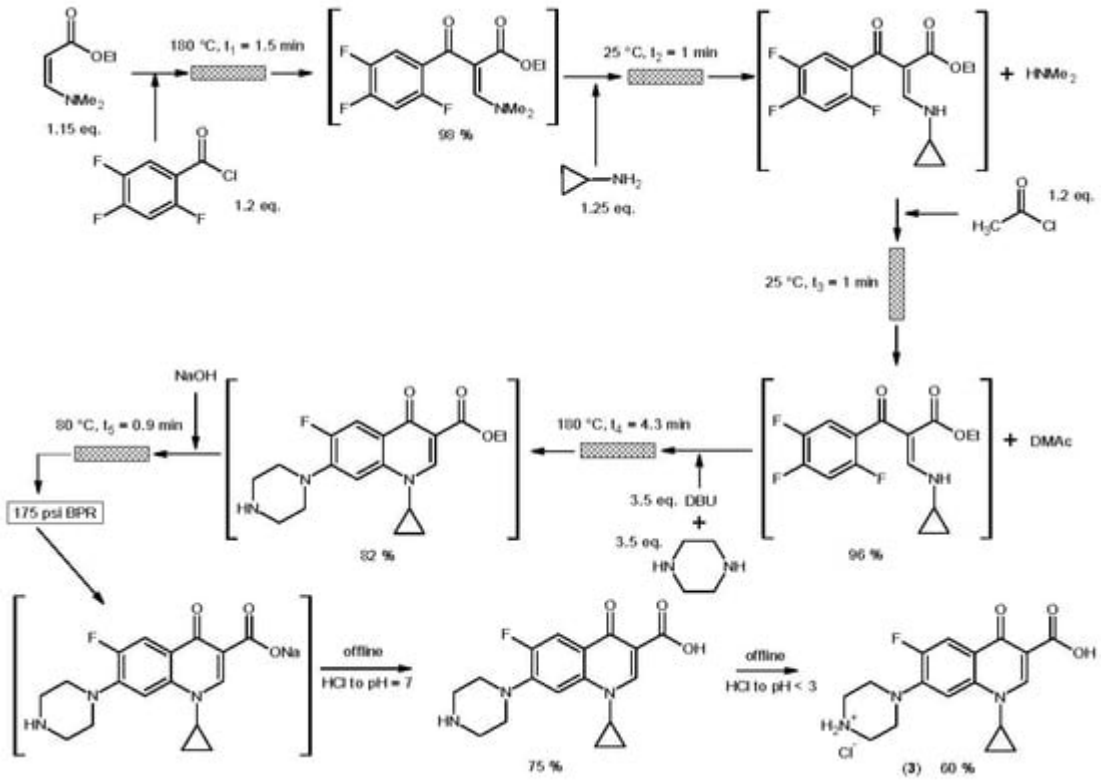
min. The phases were separated in a gravity settler (c) that was placed at the reactor outlet and was made of a 10 mL plastic syringe, without a vertically positioned piston and with the needle oriented downwards. Filter paper was placed at the bottom of this settler for the continuous removal of any precipitated phenylglycine (PG). The top phase was withdrawn from the top part of the settler (c) by a peristaltic pump (g) and collected in a product vessel (f). The bottom phase was pumped from the settler (c) through the filter paper into the reservoir (e), with continuously stirred enzyme recycling. To avoid PG clogging in the reaction mixture, the authors added a microdialyzer (h), operating in counter-current flow, that was closed from both sides using ad hoc made Plexiglas ports (k). In this way, the enzyme solution was restored fresh to the reservoir (e). The dialysate solution was collected in a waste reservoir (i), while a fresh phase was pumped from the reservoir (j) into the intertubing of the microdialyzer to clean the enzyme solution.

Using this integrated microfluidic platform, the authors obtained a cephalexin (**2**) yield of 80%, with respect to 7-ADCA, whereas the yield in batch mode was 75% under the same conditions. In addition, this technology was able to operate continuously, generating new C-N bonds, for at least 5 h. The optimization of reaction conditions, performed first in batch mode and then in flow mode, was fundamental to the success of this approach.

3. Ciprofloxacin Hydrochloride

Ciprofloxacin hydrochloride (**3**) is an antibiotic agent in the fluoroquinolone class that is used to treat bacterial infections caused by Gram-negative bacteria, such as urinary-tract infections and pneumonia. It is also used against sexually transmitted infections (gonorrhea and chancroid) and lower-respiratory-tract infections. It was patented in 1983 by Bayer and approved in 1987 by the FDA. It was marketed with the brand name Cipro™ and reached a sales peak of USD 2 billion in 2001. It appears on the World Health Organization's List of Essential Medicines [7][21][22][23][24][25][26][27].

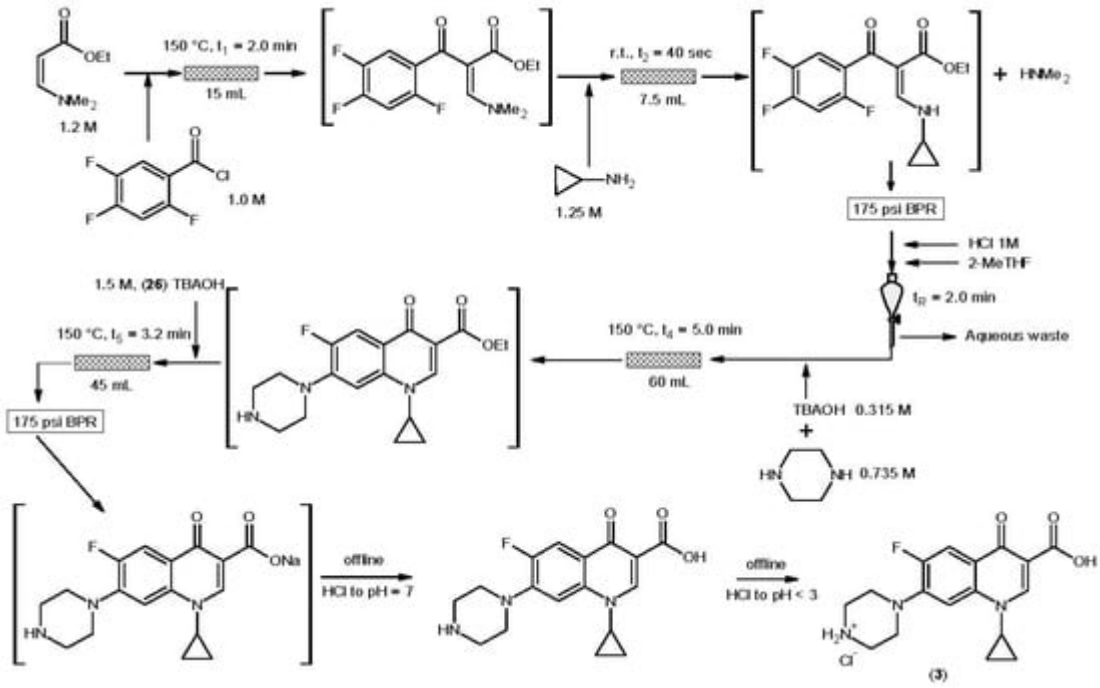
First, Lin and coworkers and, secondly, Armstrong et al. demonstrated, in two different manuscripts, an effective strategy for the total synthesis of ciprofloxacin hydrochloride (**3**) in flow mode [28][29]. In 2017, Lin et al. [28] applied flow-chemistry concepts to all six chemical reactions as they developed a telescopic process in five flow reactors (Scheme 3). They obtained ciprofloxacin hydrochloride (**3**) in a 60% overall yield, whereas the yield was 49% in the Bayer batch process. This result was achieved in a total residence time of only 9 min, whereas more than 24 h is required in batch mode, making this one of the longest linear sequences without the flow being interrupted in any workup.



Scheme 3. Continuous total synthesis of ciprofloxacin hydrochloride (**3**) by Lin [28].

Starting from 2,4,5-trifluorobenzoyl chloride and ethyl-3-(dimethylamino)acrylate, they optimized all of the reaction parameters to perform the process while reducing time and waste. Notably, inline acylation with acetyl chloride in the third flow reactor allowed the dimethylamine byproduct to be converted into dimethylacetamide (DMAc), thus overcoming the low-yield problem in the fourth step [30]. To avoid intermediate clogging at the inlet stream of the fifth flow reactor, the authors warmed the solution, due to its low solubility, to continue the synthesis.

In 2021, inspired by Lin's work and by Massachusetts Institute of Technology (MIT) researchers [31][32][33][34], Armstrong and coworkers developed a ciprofloxacin flow synthesis with an industrial perspective (Scheme 4). They scaled-up the process 1.5-to-2-fold to obtain enough crude product for 1000 tablets in 24 h. They demonstrated high reproducibility and robustness, providing concrete improvements to previous works, as they continuously ran the first three steps for 22 h and the last two steps for 10 h.



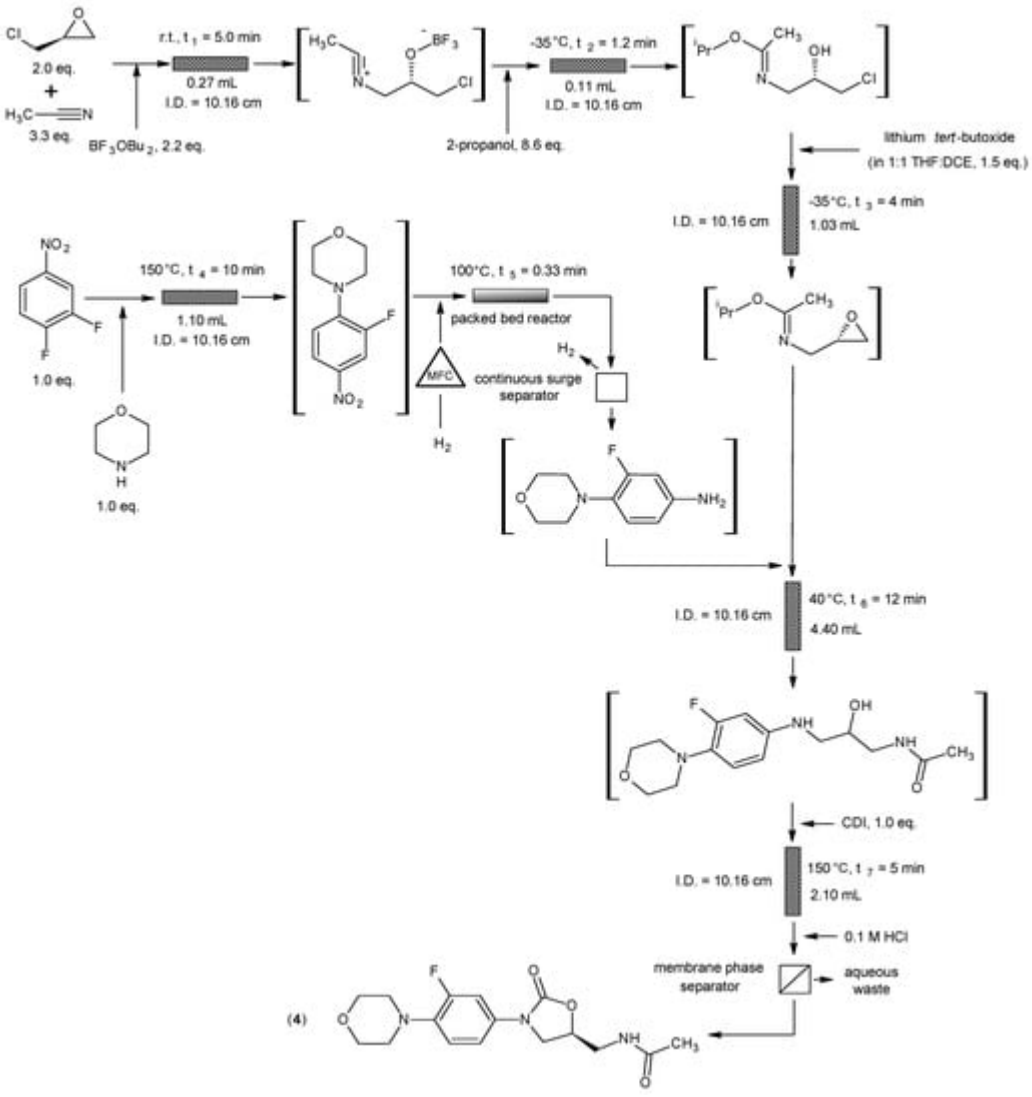
Scheme 4. Continuous total synthesis of ciprofloxacin hydrochloride (**3**) by Armstrong [29].

The authors determined and optimized operating and stoichiometric parameters with DOE in order to minimize impurities and increase step yields. They implemented continuous liquid–liquid extraction (CLLE) to remove dimethylamine without using acetyl chloride as a catching agent, meaning that the number of reactions could be reduced from five to four. This operation increased the concentration of the second intermediate in the organic stream and enabled the use of 2-methyltetrahydrofuran as a green solvent. The selected solvent system, with 1 M hydrochloric acid, was operated at a 5:2:3 ratio for the aqueous solution–organic/solution–reaction stream. 1,8-Diazabicyclo [5.4.0]undec-7-ene (DBU) was replaced with tetrabutylammonium hydroxide (TBAOH), meaning that blockages in the lines and the formation of impurities were avoided. The finalized process conditions afforded a yield of 91 ± 2% for the first two steps, providing the second intermediate with a purity of 95 ± 1% by area percent via liquid chromatography (LCAP). The CLLE efficiency was calculated to be 88 ± 2% for the rich solution and the final two steps afforded a yield of 90 ± 2% of ciprofloxacin via LCAP. The overall production was 700 g/24 h, meeting the project's goals.

4. Linezolid

Linezolid (**4**) is a synthetic oxazolidinone antimicrobial drug. It is indicated for use in Gram-positive infections and approved for the treatment of bacterial pneumonia, skin and skin-structure infections, and vancomycin-resistant enterococcal (VRE) infections. It represents the last line of defense against multi-drug-resistant Gram-positive bacteria. It was discovered and developed by Pfizer in the 1990s and approved by the FDA in April 2000. It is sold under the brand name Zyvox™ and appears on the World Health Organization's List of Essential Medicines [7][35][36][37][38][39][40][41].

Russell et al. have demonstrated an effective strategy for the synthesis of this drug in a completely continuous fashion [42]. This represents the highest number of reactions performed in sequential flow without the purification of intermediates and workup (Scheme 5). While the reported synthetic routes require several steps and rely on several organic chemistry manipulations, they were able to develop the synthesis so that it can be performed in only seven steps. They have slashed the total time from more than 60 h in batch mode to 27 min in flow mode. The E-factor calculated for this process was 25, whereas the average for chemical reactions is 3.57, and in the pharmaceutical industry, it ranges from 25 to 100. Linezolid (**4**) was obtained at a yield of 73%, which corresponds to a throughput of 816 mg h^{-1} [43][44][45][46].



Scheme 5. Seven-step linezolid (**4**) flow synthesis. I.D., inner diameter.

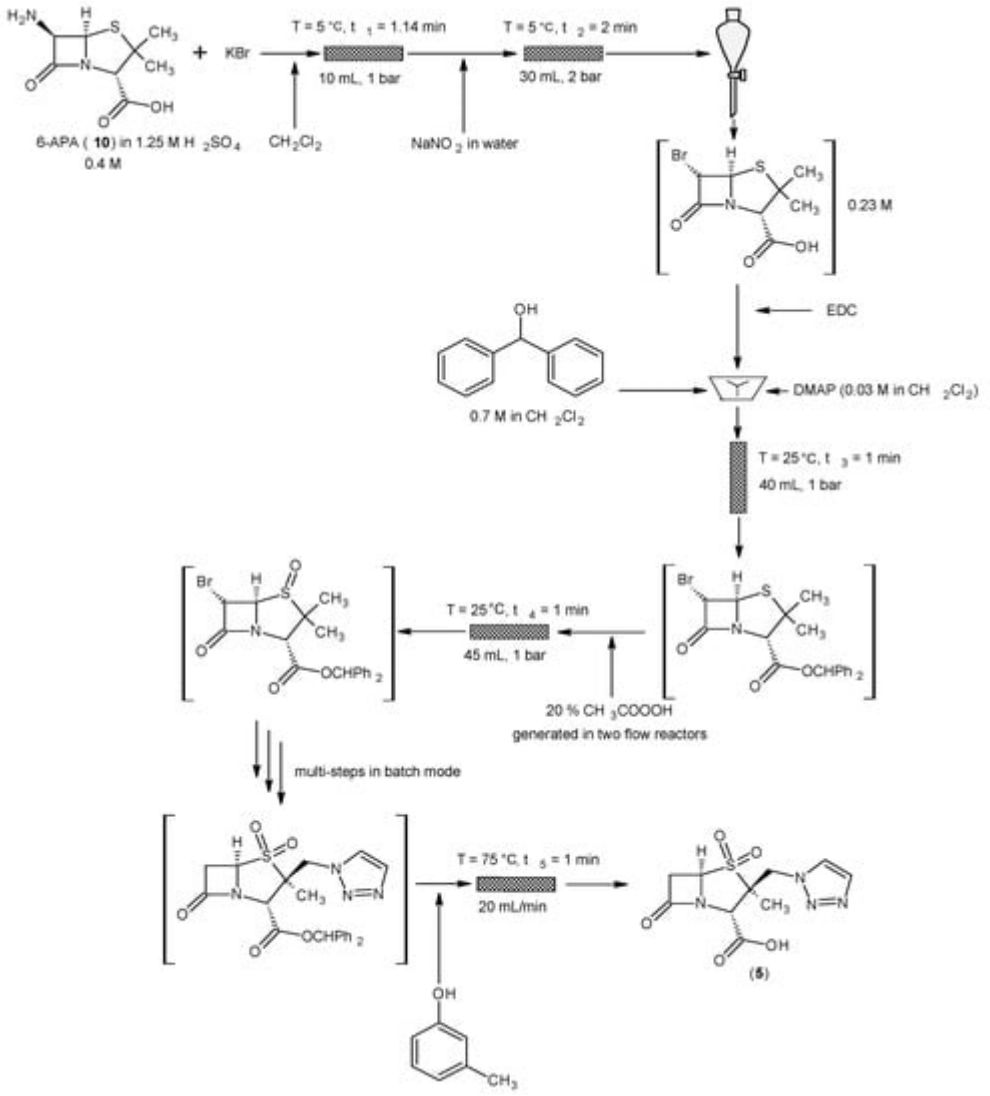
In the first step, the authors promoted a Ritter-type reaction between (+)-epichlorohydrin, acetonitrile and $BF_3{\cdot}OBu_2$ to obtain the nitrilium intermediate with a yield of 90%. 2-propanol was used to quench the Lewis acid in order to avoid clogging in the tubes and to generate the imidate intermediate. The epoxide intermediate was formed by treating the previous stream with lithium *tert*-butoxide in a 1:1 THF:1,2-dichloroethane (DCE) mixture. Overall, the residence time for these steps was 10.2 min. At this point, the authors focused on the nucleophilic aromatic

substitution (S_NAr) between morpholine and 3,4-difluoronitrobenzene and on hydrogenation using a mass-flow controller (MFC) to obtain 3-fluoro-4-morpholinoaniline. They used the 1,4-dioxane and *N,N*-dimethylformamide solvent system to enhance the S_NAr rate, to solubilize all of the starting materials and byproducts and ensure good compatibility with the palladium packed bed. The hydrogenation reactor was a compact stainless steel packed bed of Pd(0) that was operated at 100 °C and 100 psi of back-pressure. After hydrogenation, the hydrogen-gas excess was removed through the continuous surge separator, and the aniline stream was introduced into the epoxide stream, giving the last intermediate without any additional activating agent. In the final step, linezolid (**4**) was generated by treating the stream with *N,N*-carbonyldiimidazole (CDI) and subsequent offline crystallization.

5. Tazobactam

Tazobactam (**5**) is a β-lactamase inhibitor used in combination with β-lactam antibiotics. It was first marketed in the USA in 1992 with piperacillin under the brand name Tazocin™. In recent years, tazobactam (**5**) has been studied in combination with other β-lactam drugs due to its low toxicity and strong activity in fighting antimicrobial resistance (AMR). It appears on the World Health Organization's List of Essential Medicines [7][47][48][49][50].

Zhou and coworkers have reported an interesting tazobactam (**5**) synthesis that works as a combination of continuous-flow and batch conditions [51]. Flow chemistry was implemented in the first three steps and in the final step, giving a total yield of 37.1%, whereas the yield was 30.1% in batch mode (Scheme 6). This synthetic route was safer and more efficient, as it provided a 7% reduction in process mass intensity (PMI) while maintaining high purity (99.8%).



Scheme 6. Tazobactam (**5**) synthesis under combined flow and batch conditions.

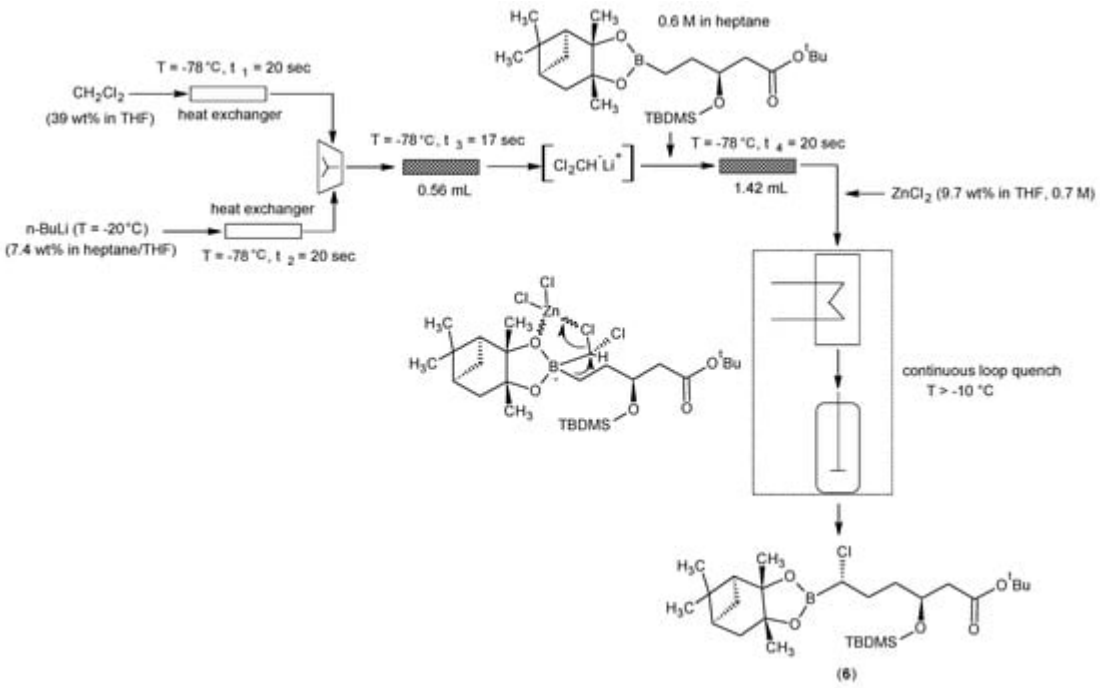
6. Key Vaborbactam Intermediate

Vaborbactam is part of the new generation of β-lactamase inhibitors, classified as a non-β-lactam β-lactamase inhibitor. It is a cyclic boronic acid that was discovered, in 2015, by Rempex Pharmaceuticals, which is a 'The Medicines Company' subsidiary and now part of Melinta Therapeutics. It is combined with meropenem for the treatment of complicated urinary-tract infections and pyelonephritis. It was approved by the FDA on 29 August 2017 and sold under the brand name Vabomere™. It acts against serine carbapenemase enzymes, including *Klebsiella pneumoniae carbapenemase* (KPC), boosting carbapenem action. This drug is administered via intravenous injection into a vein and appears on the World Health Organization's List of Essential Medicines [7][52][53][54][55][56][57][58].

Stueckler et al. have presented a flow approach for the synthesis of the key intermediate (**6**) of this inhibitor [59]. They moved the Matteson reaction from batch mode to flow mode while improving diastereoselectivity, purity, reproducibility, yield and productivity for the key intermediate (**6**). This flow system is currently applied in the

industrial-scale production of the intermediate under cGMP conditions, with several hundred kilograms being manufactured, and has been approved by FDA inspection.

In batch mode, the need to cool the process to −95 °C, the need to remove reaction heat, the high dilution and slow dosing protocols were impediments to commercial production. Moreover, byproduct formation, due to poor mixing, limited productivity. The authors overcame these issues using the patented flow technology depicted in Scheme 7 [60].

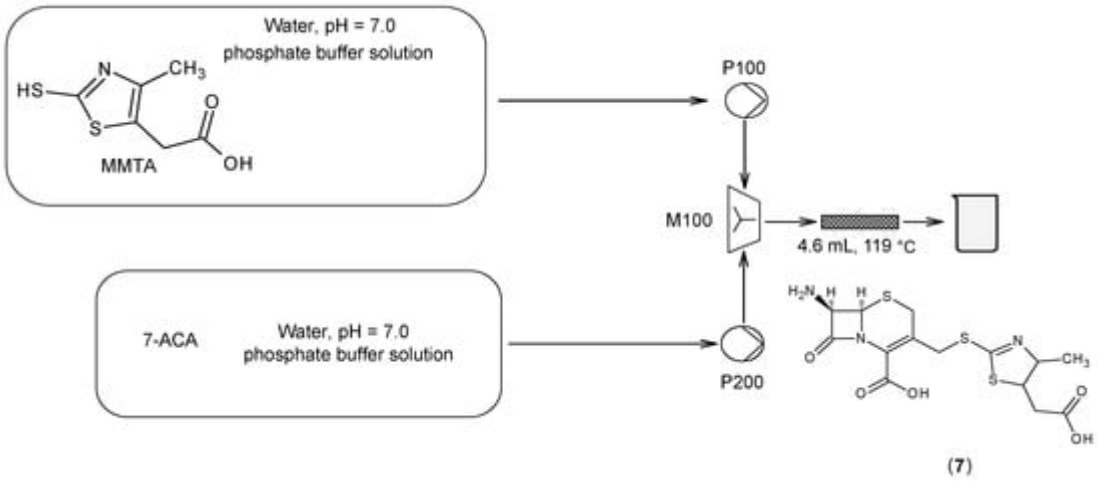


Scheme 7. Flow process for the Matteson reaction to manufacture the key vaborbactam intermediate (**6**).

7. Key Cefodizime Intermediate

Cefodizime is a third-generation cephalosporin with broad-spectrum activity against aerobic Gram-positive and Gram-negative bacteria. It is administered intravenously and intramuscularly to treat upper- and lower-respiratory-tract infections and urinary-tract infections. A single dose contains 1 g or 2 g of the drug, which is used for an average of 7-to-10 days. It is not currently approved by the FDA for use in the USA [61][62][63].

Wirth et al. have published an interesting manuscript for the continuous synthesis of thiazolyl-7-aminocephalosporanic acid (7-TACA, **7**) [64]; the key cefodizime intermediate. This involves a 3′-modification using methylmercaptothiazolyl acid (MMTA) on 7-ACA, the antibiotic's backbone, as depicted in Scheme 8.



Scheme 8. Flow synthesis of 7-TACA (**7**).

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