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This is the author's manuscript

Original Citation:

Availability:

This version is available http://hdl.handle.net/2318/1766772 since 2021-01-14T12:13:15Z

Published version:

DOI:10.2174/1381612826999201116163951

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08 November 2026

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This is the author's final version of the contribution published as:

[Green Enabling Technologies for Competitive Synthesis of Pharmaceutical Lead Compounds, Silvia Tagliapietra, Arianna Binello, Fabio Bucciol, Vladimir Trukhan, Mariachiara Colia, Giancarlo Cravotto, Current Pharmaceutical Design, 26, 44, **2020**, 5700 – 5712. DOI: 10.2174/1381612826999201116163951]

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Green Enabling Technologies for Competitive Synthesis of Pharmaceutical lead Compounds

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Abstract.
Combinations of different technologies are at the heart of the development and implementation of new, innovative processes and approaches for Industry 4.0 in the field of medicinal chemistry and drug discovery. Process intensification and advances in high-throughput synthetic techniques can dramatically improve reaction rates in processes for which slow kinetics represent a bottleneck. Easier access to target-based chemical library collections offers wider access to new leads for drug development. Green enabling technologies are a reliable ally for the design of environmentally friendly synthetic processes and more highly competitive pharmaceutical production. Mechanochemistry, microwaves, ultrasound and flow chemistry are mature techniques that can boast drug synthesis when properly integrated in the production chain. In this review we selected examples from the literature of the last 5 years related to medicinal chemistry.

Keywords: Enabling Technologies; Pharmaceutical Compounds; Process Intensification; High-throughput synthesis; Mechanochemistry; Microwaves; Ultrasound; Flow chemistry.

1. Introduction

Improvements in human health are closely related to the design and development of new pharmaceutical compounds, and therefore also to the driving forward of innovation in synthetic protocols. Current research and production strategies are too often confined to traditional, linear thought patterns. The worldwide demand for lower-priced high quality drugs poses an increasing challenge for the development of high-yield manufacturing routes that minimize waste generation. The design of green, efficient and cost competitive industrial pharma processes is mandatory. Nevertheless, organic synthesis follows traditional protocols developed in round-bottomed flasks, closed vessels and test tubes that are then scaled up to standard batch reactors. Pharmaceutical-compound synthetic pathways can therefore be affected by long reaction times, poor yields and negative environmental impact. Fine chemicals and active pharmaceutical ingredients (APIs) often require several reaction steps, meaning that process intensification to improve reaction kinetics is mandatory both for economic and ecological reasons. New technologies are rapidly evolving because the complexity of drug structures drives the demand from the pharma industry for highly efficient, safer and ecologically friendly alternatives to traditional chemistry. The continuous-flow micro- and meso-reactor synthesis of APIs and their intermediates, which can combine a total synthesis into a single reaction stream, is one of these promising new technologies [1, 2].
In order to achieve this goal, new Pharma Industry 4.0 approaches that exploit combinations of technologies are being developed and implemented in the field of pharmaceutical process development. The so called “fourth industrial revolution” is based on cyber-physical systems that create intelligent networks along the value chain able to optimize synthetic processes by connecting cascade reactors by continuous physico-chemical parameters monitoring and even predicting solutions in case of unforeseen events.

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Over the last decade, several reviews and books have reported the advances in synthetic technologies in medicinal chemistry, with a number of interesting case studies, and the role of high-throughput chemistry in lead discovery has also been highlighted [3-5]. The optimization of new, greener, safer and high-performance strategies is one of the major challenges in pharmaceutical R&D, but can enable efficient access to complex molecular architectures [6, 7]. Slow chemical reactions, solid reagents and the difficult mixing of slurries all require more effective mass and heat transfer techniques to enable continuous manufacturing modes to be used [8]. The challenge of innovation involves competitiveness, product quality, economic demands and all of the complex aspects that are involved in the chain of pharmaceutical production, from laboratory (nano and micro) scale to industrial production. One of these emerging non-conventional techniques is the use of mechanical forces, which can be traced back to ancient times with mortar and pestle and were originally considered to be too expensive for practical use. This technique is now growing in use because of the availability of reactors, on milligram to multi-kilo scales [9]. Besides ball milling, solventless and solid-state reactions have also become increasingly popular and appealing options that can be carried out in reactive twin-extruders and via dielectric heating [10]. We are ever more frequently witnessing new ways of considering chemical synthesis for the production of complex bioactive compounds [11]. The development of new synthetic technologies also includes the generation of fewer by-products and easier workup procedures that, for example, can avoid chromatographic purification, and this is especially true for process scale-up. Several works have shown that activation by microwaves and ultrasound, as well as flow chemistry can all lead to considerable reductions in reaction times, which can range from several hours to a few minutes. Furthermore, although photochemical reactions are carried out under conventional conditions, this kind of activation allows poorly reactive substrates to be transformed. Substrates that are poorly-reactive under refluxing conditions can be activated by microwave heating or mechanochemical grinding, in both cases solventless (or almost), and can even result in changes in the selectivity of reaction mechanisms [12]. Acoustic and hydrodynamic cavitation can significantly promote synthetic procedures via the generation of transient radical species [13].

We are also currently observing the development of fully automated systems that can provide increases in efficiency and often in sustainability. For example, flow synthetic methodologies can be combined with microwave irradiation, ultrasound, photochemistry, supported reagents and catalysts, as well as with inductive heating, plasma and electrochemistry. It is worth remembering that the pharmaceutical industry has the peculiarity of operating at multiple production scales. If small-scale reactions are performed at the early stage of development, and a full-scale process is needed for commercial production steps, an intermediate phase, in which syntheses from hundreds of grams to kilograms of active molecules is used for both preclinical and clinical trials, is essential. The main drivers for small-scale and pilot production are the speed of R&D processes, and the avoidance of scale-up issues, whereas, for large-scale production, gains in yield and safety are among the main priorities when choosing microreactor technology. *The European Roadmap for Process Intensification* was followed [14] when applications of promising tools for the small-scale pharmaceutical manufacturing of active pharmaceutical ingredients (API) were summarized by Mitic and Gernaey [15], who focused on microwave radiation, microreactors, ultrasound and meso-scale tubular reactors; technologies that can be applied independently and combined with each other or even with catalysts. In this overview, we underline the considerable space for expansion that is present in the field of process intensification.

This review is focused on the very recent advances about the use of enabling green technologies in intensified synthetic protocols applied to APIs preparation. In particular, main characteristics of flow-chemistry, mechanochemistry, microwave irradiation and ultrasound activation will be discussed with regards to some peculiar examples.

2. Mechanochemical methods

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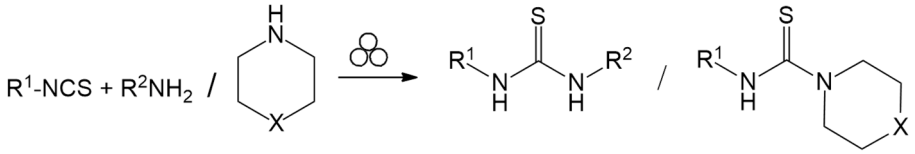
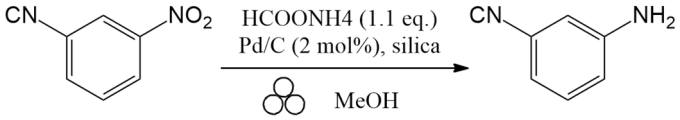
Mechanochemical reactions are “induced by the input of mechanical energy”, which is commonly generated by shock or friction between different surfaces, leading to the breaking and forming of covalent and supramolecular bonds [16]. Although initially faced with some reluctance, this technique is currently emerging and various synthetic applications highlight the advantages, first of which are the solvent-free conditions, either with solids (dry milling) or solid/liquid reagents (wet milling). Components of solid reacting mixtures interact each other by intimal diffusion and localized melting-point depression generated by impacts and frictions promoting intermolecular bonds formation and condensations that takes place in the resulting eutectic phase.
Vibratory and planetary ball mills are the most common devises with jars from 25 mL to 25 L. Ball size and number, reagent amounts, time and frequency can all be adapted for each specific reaction in order to provide a highly concentrated mixture and excellent mass transfer. High yields and simplified purification steps can be achieved together with low environmental impact. Eccentric vibratory ball mills can be easily scaled up. A vibrating unit is connected to a grinding chamber that is *displaced* from its centre of gravity; kilograms of products can be obtained in a 5-300 L grinding vessel. Continuous working can be achieved using a reactive extrusion process, in which a barrel containing one or two twin-screws allows the reagents to be mixed and carried from one end to the other. The products can either be recovered or re-injected into the cavity in order to obtain gram or kilogram amounts [17]. In 2017, Štrukil reviewed the latest developments in the synthesis of ureas, thioureas and guanidines by mechanochemical routes, and highlighted the improved yields and the lack of side reactions. This was a method of choice for click reactions applied in the preparation of pharmaceutical intermediates [18]. The mechanochemical synthesis of symmetrical and non-symmetrical *N,N′*-disubstituted thioureas from aromatic and aliphatic amines and aromatic isothiocyanates is an example of quantitative conversion. The combination of an electron-withdrawing group, in the amine (lower nucleophilicity), and an electron-donating group, in the isothiocyanate (lower electrophilicity), led to prolonged grinding times [19] (Scheme 1).



Scheme 1. Mechanochemical preparation of *N,N′*-disubstituted thioureas.

Štrukil *et al.* have shown that the efficient catalytic transfer hydrogenation of aromatic nitro compounds can be efficiently carried out using readily available ammonium formate (hydrogen donor) and Pd/C in a ball mill [20] (Scheme 2).



Scheme 2. Mechanochemical hydrogenation of nitroarenes in the presence of ammonium formate.

The simple synthetic protocol tolerates a variety of functional groups, including amino, hydroxyl, carboxyl, carbamate, α,β-unsaturated carbonyl, amide, imide, urea, acetyl and fused heterocycles, such as pyridine. Lower yields were found in the presence of halogen or *O*-benzyl substituents, while polyaromatic substrates were not suitable.
The mechanochemical approach has also been used for the two-step synthesis of common drugs, such as procainamide and paracetamol, both on milligram and gram scale (Scheme 3).

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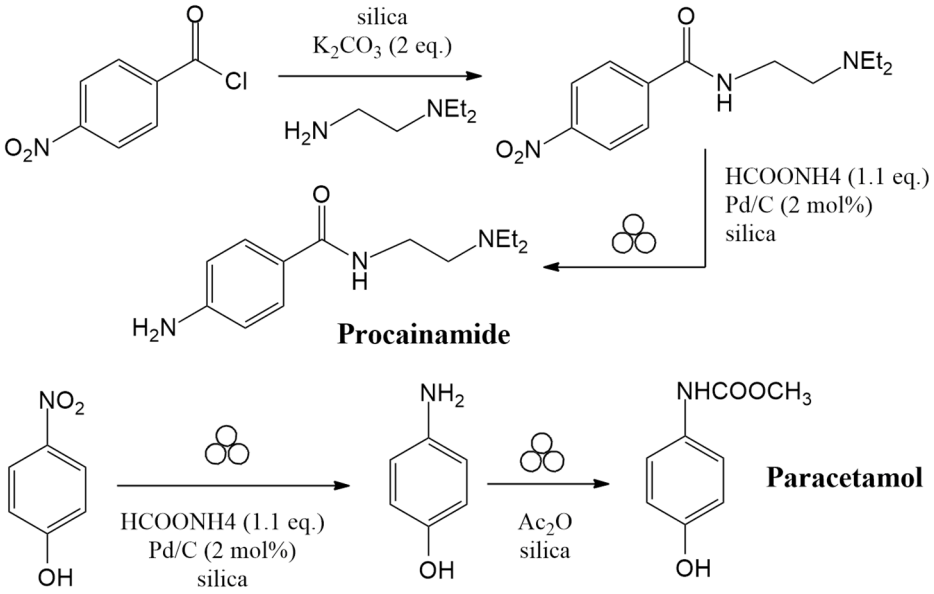


Scheme 3. Mechanochemical synthesis of procainamide and paracetamol, both up to 1g scale.

Colacino *et al.* have highlighted advances in "medicinal mechanochemistry" by investigating the preparation of two important APIs: nitrofurantoin and dantrolene (fig. 1), an efficient antibacterial agent, and an efficient skeletal muscle myorelaxant, respectively. Nowadays dantrolene is only clinically available for the treatment of malignant hyperthermia and is a substrate for a breast cancer resistant protein [21].

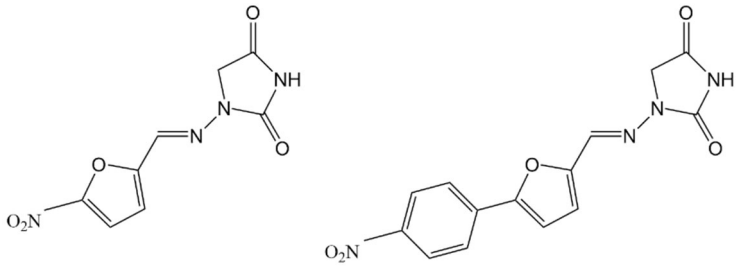
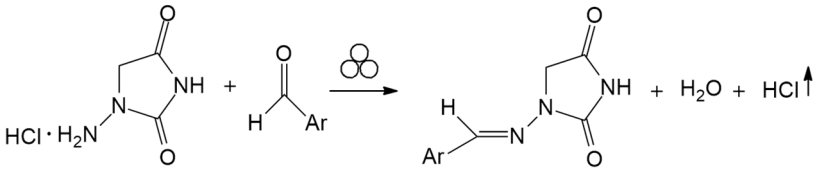


Figure 1. Chemical structures of nitrofurantoin and dantrolene.

Nitrofurantoin is usually prepared in solution via a condensation reaction between 1-aminohydantoin (up to 10 equivalents) and 5-nitro-2-furancarboxaldehyde diethyl acetal in DMF using 30% HCl in large excess or furfural, followed by an aqueous nitration reaction in a sulfonitric mixture. In the case of dantrolene, the condensation reaction leading to the hydrazone occurs in the presence of 5-(4-nitrophenyl)-2-furfural, under similar reaction conditions (Scheme 4).



Scheme 4. General scheme for the mechanochemical synthesis of nitrofurantoin and dantrolene.

The authors observed that the mechanochemical preparation of arylhydrazones had never been extended to the preparation of nitrofurantoin or dantrolene. Equimolar amounts of 1-aminohydantoin hydrochloride and 5-nitro-2-furfural were milled at 30 Hz in a 5 mL stainless steel jar without any special precaution. The conversion of the reactants was quantitative after 30 minutes and no other optimization studies were necessary on this first trial on a small reaction scale (0.84 mmol).

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Nitrofurantoin was then recovered in a 85% yield after work up in water. The results were replicated on a larger scale both in a planetary ball mill (13.2 mmol) and a SPEX mill (6.6 mmol SPEX Mill 8000, characterized by angular harmonic displacement in the vertical plane and synchronous rotation in the equatorial plane). The latter gave better results with a yield of up to 95%. The incomplete conversion of the substrates, even after prolonged milling (up to 6 hours), was observed when agate jars were used instead of zirconium oxide jars, confirming the importance of the hardness and density of the material in the activation process. In solution, the formation of arylhydrazones requires an acidic environment to ensure complete conversion of the product. We can therefore speculate that the reactions carried out in the ZrO jar were able to take advantage of the catalytic effect of this material (Lewis acid).

Silicon-derivatized hydantoin and urea scaffolds obtained from amino acid derivatives have been used to prepare functionalized bridged silsesquioxane nanospheres via a mechanochemical sol−gel procedure [22]. The biohybrid nanospheres easily open new perspectives and development for the synthesis of bridged silsesquioxane nanoparticles with desirable chemical functionalities to control the properties of nanoparticles designed for various advanced applications, such as chromatography, catalysis and biotechnologies (fig. 2).

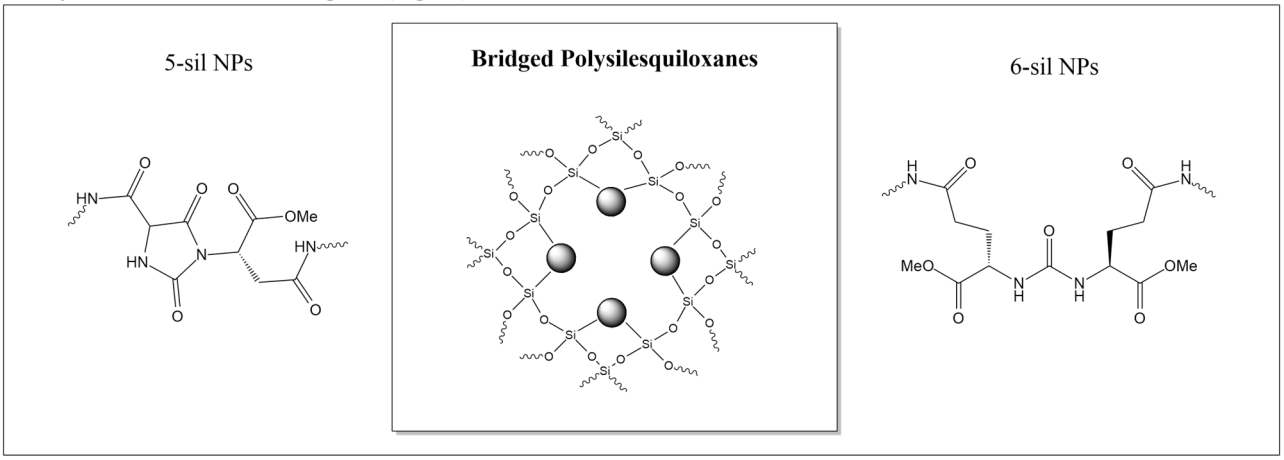
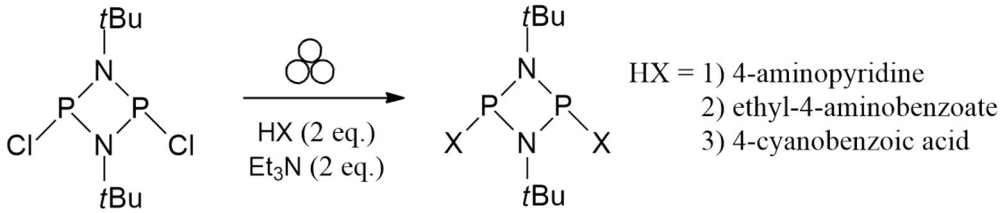


Figure 2. Mechanochemical preparation of bridged silsesquioxane nanospheres.

Garcia *et al*. have reported the mechanochemical synthesis of cyclophosphazane compounds [23], and showed its advantages via comparisons with traditional, time-consuming syntheses under reflux overnight. Three hours of grinding in a planetary ball mill (30 Hz loaded with 10 mm stainless steel balls) were sufficient to produce the target compound, as shown by the $^{31}P\{1H\}$ nuclear magnetic resonance spectrum of the crude sample (Scheme 5).



Scheme 5. Mechanochemical synthesis of cyclophosphazane derivatives.

The mechanochemical procedure used functionalised organic acids to exclusively provide the acyclic cyclodiphosphazane *cis,* which is most thermodynamically stable conformation. The same protocol can be used for the preparation of macrocycles that contain large cavities for coordination and supramolecular derivatives (Scheme 6).

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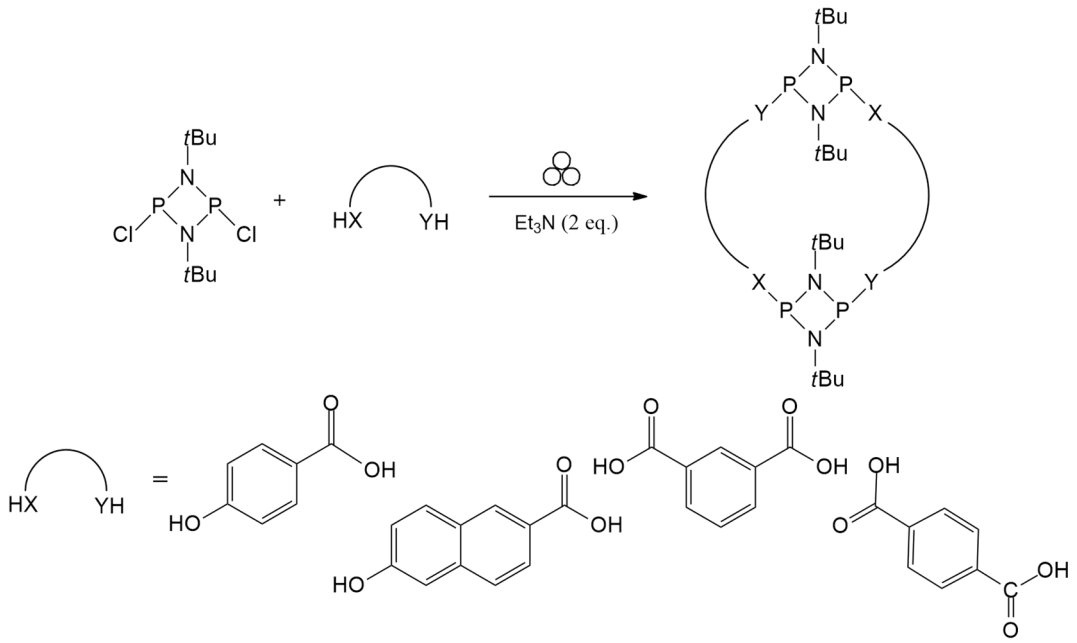
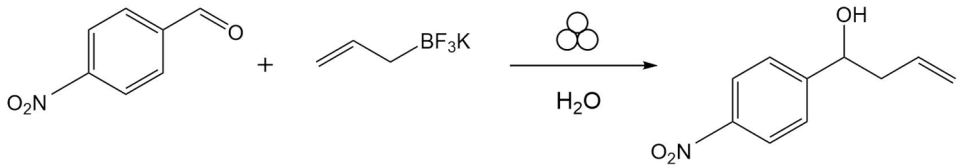


Scheme 6. Mechanochemical procedure for the preparation of macrocyclic phosphazanes.

The allylation of aromatic and aliphatic carbonyl compounds by potassium allyltrifluoroborate in the presence of water to activate the allylation agent is an interesting mechanochemical green procedure [24]. This efficient and fast allylation may find applications in the synthesis of several pharmaceutical intermediates. The allylation of a series of substituted benzaldehydes demonstrates the deleterious effect of electron-donor substituents. Furthermore, the physical state of the reagent becomes decisive in the mechanochemical process; liquid substrates give, in fact, low allylation yields even in the presence of the grinding auxiliary (Scheme 7).



Scheme 7. Mechanochemical allylation of aromatic carbonyl compounds.

Results have been replicated using different equipment (Planetary and Specs mills), showing that, as expected, lower mechanical energy conditions (polymer jar and glass beads) increase the allylation selectivity of aldehydes compared to ketones, in particular when the milling time and the presence/absence of catalyst are controlled.

Ethionamide (ETH) is a second-line drug for the treatment of tuberculosis (fig. 3). De melo *et al.* have developed a green supramolecular synthetic protocol for the production of novel solid forms of ETH [25].

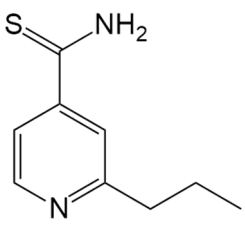


Figure 3. Ethionamide structure.

Several different polymorphs and assemblies have been observed in the crystals of ETH maleate, oxalate and saccharinate (monohydrate), which were obtained from slow solvent evaporation. ETH maleate and ETH oxalate crystals are dominated by a cyclic tetramer arrangement in which two ETH^+

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cations are alternately linked to two counterions. ETH saccharinate, in turn, assembles in discrete 1-D tapes that are alternated with water molecules. The authors investigated a mechanochemical route with the aim of improving the preparation of ETH salt with a scalable and environmentally friendly methodology. ETH maleate gave the best results. Although ETH maleate is thermodynamically less stable than ETH, equilibrium solubility studies show that ETH maleate exhibits high solubility in purified water and in acid media (fig. 4). This feature enabled higher concentrations of the API to be produced to improve the treatment of tuberculosis.

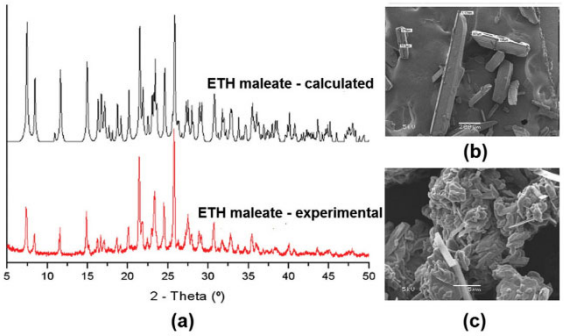

Figure 4. ETH maleate "conventional *vs* mechanochemical" methods. (a) Experimental and calculated powder XRD pattern of ETH maleate. SEM images of (b) ETH standard, (c) ETH by ball milling [ref. 25].

3. Microwave-assisted synthesis

Automated sequential library synthesis is a fundamental tool in drug discovery. The selection of new lead compounds requires integrated robotic systems to assist with fast analytical monitoring and biological screening. In this context, microwave-assisted synthesis can provide substantially higher synthetic throughput. Heating by means of microwave energy strongly differs from conductive heating mechanisms being the former based on the direct transfer of electromagnetic energy (of frequency and wavelengths comprised in the ranges 0.3-300 GHz and 1-0.001 m, respectively) into the reaction mixture, which in turns dissipates the absorbed energy into heat, according to its electric, dielectric and magnetic properties. This means a unique selectivity, thus favouring fast heating of the of the reaction mixture and in particular of the heterogeneous catalyst, rather than the reactor walls or other components. A dramatic reduction in reaction times and solvent amounts can be translated into yield increases and energy savings, while avoiding side reactions and product degradation. Microwave-assisted heating technology, also indicated as dielectric heating, demonstrated at different scales the ability to provide the reactants with a more narrowly distributed amount of energy with respect to less selective conventional heating techniques [26]. Pressure-resistant reactors and sealed tubes enable processes to be intensified as multiple reactions can be performed simultaneously and pressure can be built up during the course of a reaction [27]. The challenging scale-up of microwave methods can be approached using larger batch systems, or, even better, with multimode flow reactors [28]. Alkynes are a versatile class of compounds that are used by the pharmaceutical and fine-chemicals industries, in particular in the synthesis of lipophilic vitamins via alkyne semi-hydrogenation. An efficient protocol for microwave-assisted alkyne semi-hydrogenation under heterogeneous catalysis in a continuous flow microwave reactor has recently been reported [29]. This safe technology allows reactions to be scaled-up from gram to kilogram scale in industrial pilot reactors working in flow-mode.

An improved multistep procedure for the generation of a key intermediate in Lanabecestat synthesis (Synonyms: AZD3293, LY3314814 by Astra-Zeneca and Lilly), a potent inhibitor of the beta-site amyloid precursor protein–cleaving enzyme 1 (BACE1), has been described by Znidar *et al.* [30]. A previous patent described a complicated six-day synthetic process with several work-up steps [31]. Multistep synthesis in continuous systems, equipped with enabling technologies, can provide strong

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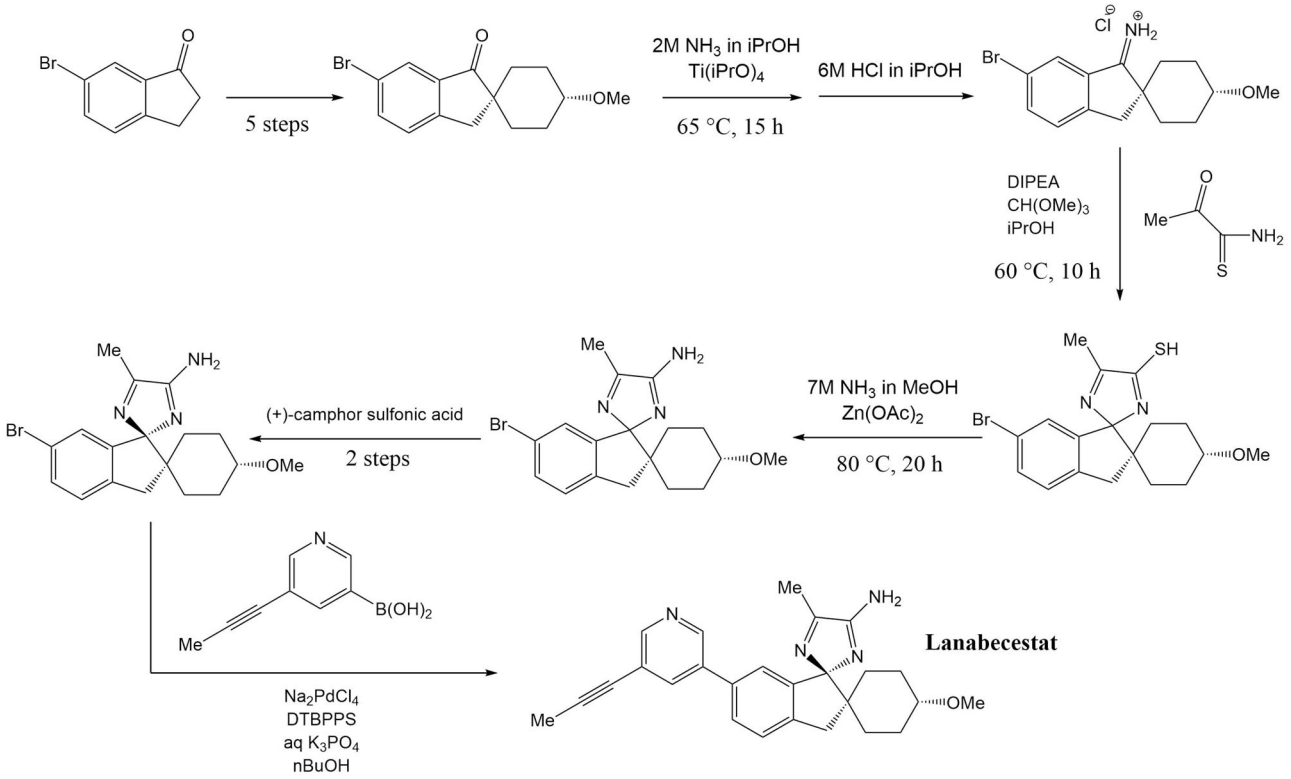
process intensification [32]. The semi-integrated procedure to intensify the multistep synthesis of the aminoimidazole intermediate (6) has been developed within the Lanabecestat synthetic route (Scheme 8), reducing the technical complexity of the process with relevant economic and environmental benefits.



Scheme 8. Improved synthetic route of Lanabecestat.

Although the attempt to integrate all these reaction steps into a one-pot procedure was not fully achieved, the aminolysis of mercaptoimidazole (5) to give (6) was carried out in an almost quantitative yield (96% yield, >99% purity) in the presence of $Zn(OAc)_2$, and ammonia in methanol under dielectric heating (150 °C).

Due to their important pharmacological activity, thiadiazoles and their derivatives have been considered by Dwivedi *et al.* in a review that, among other methodologies, emphasized their microwave-assisted synthesis. Combined irradiation with microwave and ultrasound was able to further improve reaction rates and yields [33].

4. Ultrasound-assisted synthesis

Ultrasound waves (US), with frequencies ranging from 16 kHz to 200 kHz, produce a pressure variation in a liquid, generating gas bubbles that grow, oscillate and finally implode to give rise to the phenomenon of acoustic cavitation. This cavitational collapse produces high-energy micro-environments that can significantly promote chemical reactions. The derived mechanical and chemical effects are transformed into the energy upon which sonochemistry is based, initiating reaction pathways that avoid the addition of phase transfer agents [34]. Although the intensity of cavitation is decreased when solvents with high vapour pressure are used, sonochemical reactions generally occur at room temperature. Synergic effects have been reported upon the combination of ultrasound and microwaves either in sequence or simultaneously [35]. Ultrasound-assisted organic synthesis is a new path towards greener and cost-effective procedures with constant catalyst activation. Sonochemical conditions enable efficient catalysis in water or biphasic aqueous systems,

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overcoming the solubility limits of reagents and reactants [36]. In figure 5, four different ultrasonic probes for sonochemical reactions are depicted schematically.

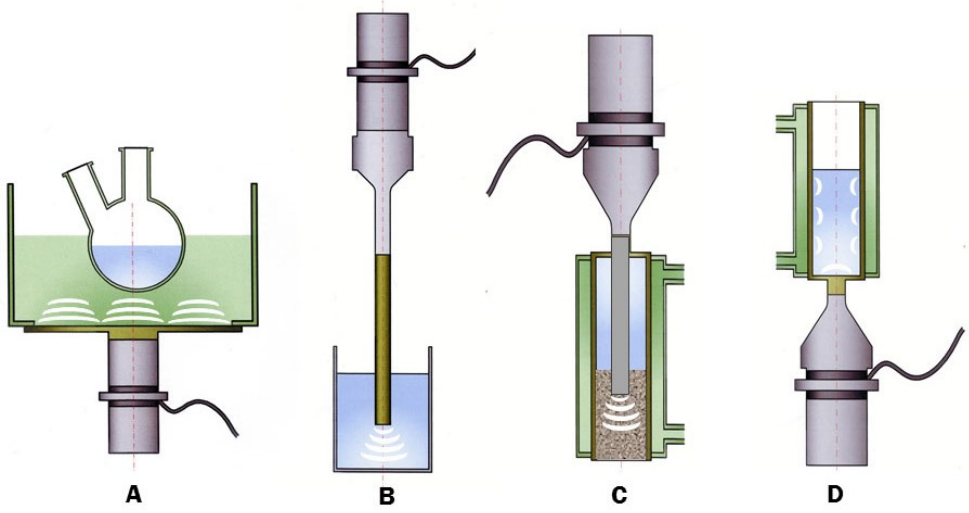
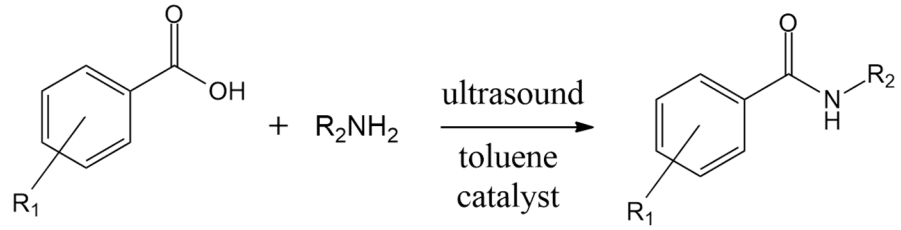


Figure 5. High-power ultrasonic probes: A. Bath, B. Immersion horn, C. Pressure resistant reactor, D. Cup horn (cavitating tube).

Besides outstanding mass transfer and mechanochemical effects, the formation of highly reactive, intermediate radical species can initiate mechanistic paths that do not occur under classical conditions.

Recently, new hybrid flow-reactors that bear a supported catalyst have combined ultrasound and photochemistry in microfluidic systems. Photocatalysis and sonochemistry can give rise to a synergistic effect that can be exploited by pharmaceutical industries, and a systematic overview about the use of these technologies for developing microreactors, together with their applications, has been reported by Pradhan *et al.* [37].

The amide group is crucial in API structures; it is present in about 65% of drug molecules. Amides are also used as an intermediate product in the synthesis of therapeutic agents. These compounds are usually produced from the reaction between carboxylic acids and amines at high temperature (180 °C), but this is incompatible with most functionalized molecules. Furthermore, the activation of carboxylic acids in acid chloride form, anhydrides or esters requires a separate step, and this protocol suffers from low atom economy. The activation of carboxylic acids with coupling agents is also complicated by the presence of collateral products that can make the recovery of the final amide difficult. The recent developments in catalysis, the use of ionic liquids, has become an active area of research. A green and highly efficient synthesis of benzamide derivatives that proceeds via the one-pot condensation of benzoic acids and amines in the presence of a green reusable and highly efficient solid catalyst (diatomite earth@IL/$ZrCl_4$) under ultrasound irradiation has been reported [38] (Scheme 9). Anilines with electron-donating groups on the phenyl ring and aromatic acids with electron-withdrawing groups showed higher yields of products. Moreover, aliphatic amines (and aliphatic acids) are more active than aromatic types. The separated catalyst was reused five times and the product yields only reduced to a small extent at each cycle.



Scheme 9. Sonochemical preparation of amides.

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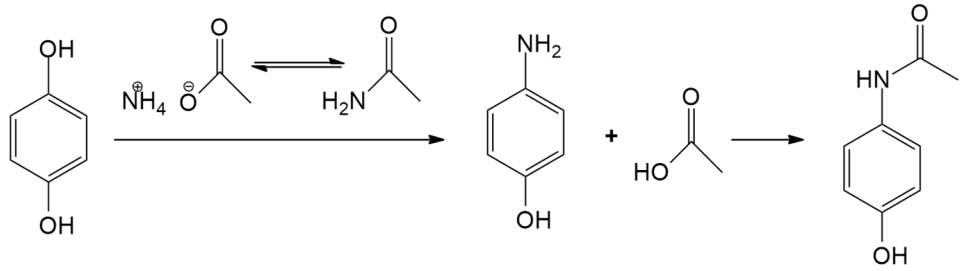
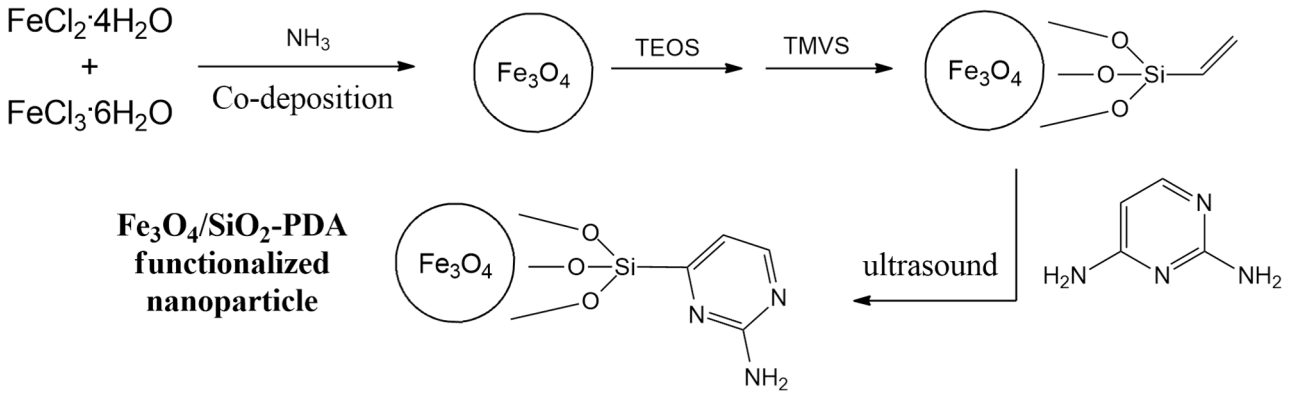
Paracetamol (acetaminophen) is one of the most frequently used analgesic and antipyretic drug. A sonochemical synthesis from hydroquinone and ammonium acetate (amidating agent) in solvent-free condition has recently been reported [39]. After parameter optimization, an overall yield of almost 58% was obtained after 150 min (22 kHz ultrasonic bath, at 60 °C). This is favourable compared to the conventional process, which is carried out at high reaction temperature (heating at 220 °C for 15 h). The reaction mechanism for the conversion of hydroquinone (HQ) to acetyl para aminophenol (APAP) is illustrated in Scheme 10. The reaction of HQ with ammonium acetate possibly progressed through the formation of para-aminophenol (PAP) as an intermediate, which further directly acetylated to APAP, producing two water molecules as side products (Scheme 10).



Scheme 10. Sonochemical preparation of acetyl *p*-aminophenol.

Dihydropyridine (DHP) derivatives are an important API scaffold, and are widely used as calcium channel blockers for the treatment of hypertension. Several DHP derivatives, such as Amlodipine, Aranidipine and Barnidipine, are typically prepared via multicomponent reactions. The preparation of pyrimidine-2,4-diamine-functionalised silica-coated magnetic nanoparticles (Fe_3O_4/SiO_2-PDA NPs), as an efficient co-catalyst for the synthesis of 1,4-dihydropyridine (1,4-DHP) derivatives, via three different methods (heating under reflux, microwave or ultrasound irradiation) has recently been reported [40] (Scheme 11). For this purpose, magnetic iron oxide nanoparticles (Fe_3O_4 NPs) were fabricated and suitably coated by a silica network (SiO_2) and trimethoxy vinylsilane (TMVS). Their surfaces were then well functionalized via a [4+2]-cycloaddition reaction with pyrimidine-2,4-diamine (PDA) to act as the main active sites that catalyze the main reaction.



Scheme 11. Synthesis of pyrimidine-2,4-diamine (PDA) functionalized silica-coated magnetic nanoparticles.

The same catalyst and method gave the diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate in high yield (90%) in only 20 min.

5. Flow chemistry and combined techniques

Chemical engineers have always investigated technologies that can improve the efficiency and safety of industrial syntheses. The transition from batch- to continuous-flow synthetic processes is one of

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the more relevant advances expected in the pharmaceutical industry. The high level of complexity and functionalisation in APIs generally means that syntheses require a large number of steps with work-up and purification, affecting the overall yield [41]. The industrial exploitation of flow chemistry began in the 1930s when the company Dipharma (Italy) started the production of nitroglycerin in flow-mode, resulting in a much more efficient and safer process [42]. Although the setup of continuous-flow synthetic procedures of complex chemical architectures is not a trivial task [43], an economic analysis of continuous processes in comparison to equivalent processes in batch-mode has highlighted that large savings (up to 40%) can be achieved [44].

Micro-reaction technology involves a continuous flow process and microfluidic chemistry, which is provided by the unique physical and chemical interactions of particles. Microreactors have very small diameter channels (less than 1 mm), with an inlet and an outlet, in which a reaction can take place under controlled conditions in the continuous flow path [45]. This simple and fast technology allows reagents to be continuously pumped into a microsystem, products are steadily collected with high selectivity, and the generation of side products can be minimized. Glass and silicon have been commonly used in microfluidics, but polymeric materials are now gaining increased attention because of the need to have available materials with enhanced properties. Improvements in reaction kinetics can be pursued thanks to mass-transfer enhancements, while the possibility of working under pressure in controlled conditions, with superheated solvents above their boiling points, allows conditions similar to those of sealed microwave reactors to be reproduced [46]. Rapid reagent mixing occurs, improving reaction selectivity with precise stoichiometric control, avoiding the critical control of exothermic reactions [47]. The system is extremely versatile, and fully automated continuous processes can be achieved and equipped with: HPLC or peristaltic pumps for the pumping device; different interchangeable reaction modules, such as reactor coils and microfluidic chips, even with integrated heating; columns packed with purification phases or heterogeneous reagents. Appropriate modules allow low-temperature reactions to be performed, and automated reagent samplers or fraction collectors can be added and controlled via software. Additional operations, such as workup, quenching, purification, crystallization and drying can also be fully performed in a continuous process [48].

The reaction volume of these systems can be increased either by scaling channel width and length, or by arranging a reasonable number of microchannels/microreactors in parallel [49]. Ramanjaneyulu *et al.* have reported an integrated multistep flow processes for a gas–liquid binary phase in modified polydimethylsiloxane microreactors. Ultrafast organic synthesis in a polyimide chip reactor was also covered, thus providing an outlook for integrated and automated flow chemistry that may be useful in drug development [50]. An entirely integrated manufacturing plant, working in continuous-flow, has been described for the synthesis of Aliskiren hemifumarate (Scheme 12, compound **6**) [51]. Starting from the intermediate (1) (Scheme 12), the procedure involves two synthetic steps, including workup and purification, that allows the active pharmaceutical **6** to be crystallised. Despite disturbance to the process, high yields (90−95%) were obtained under closed-loop control.

The aminolysis reaction of lactone (1) has been run solvent-free in molten conditions at high temperature. The yield of the amide intermediate (4) was maximized (90%), while the handing of a solid and long residence times were avoided.

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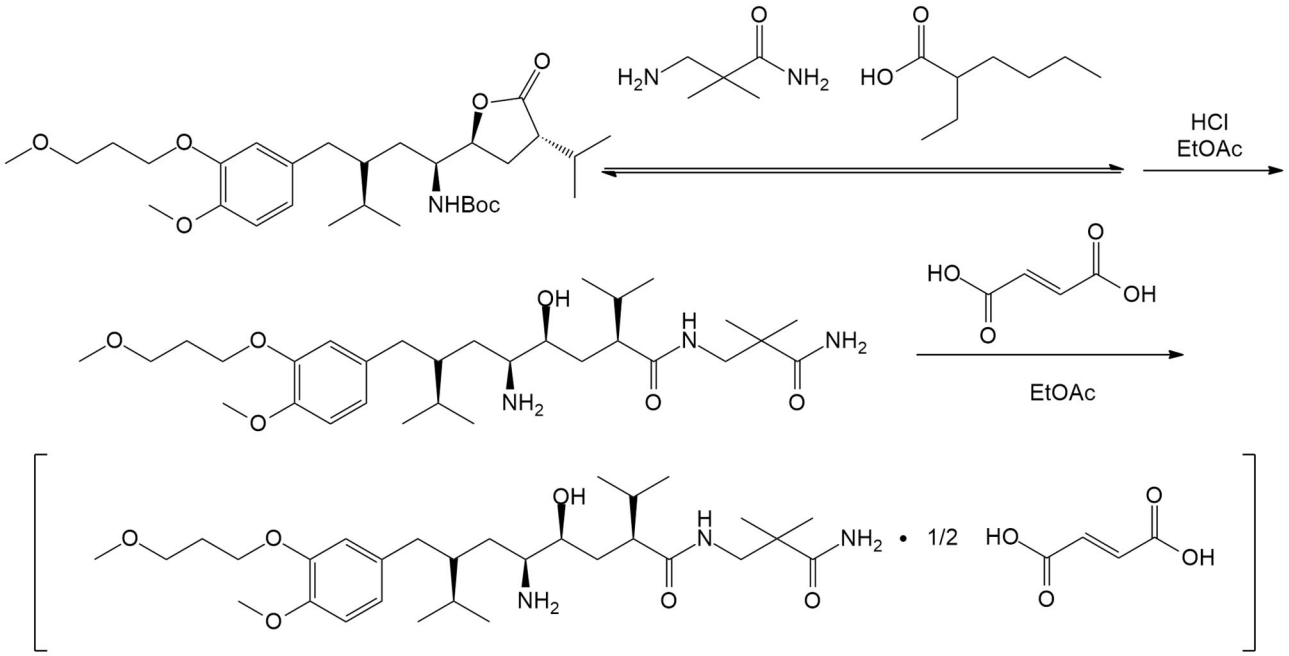

Scheme 12. Continuous-flow process for the synthesis of Aliskiren hemifumarate (6).

Continuous-flow methods can be monitored online using gas-chromatography, IR or UV spectroscopy [52, 53]. Tube-in-tube systems permit the use of gases, and photochemical reactors with different wavelengths can be adapted to different target applications [54]. In-line purification can therefore be included in the API-preparation process. Different approaches and synthetic strategies for the continuous-flow multistep synthesis of API intermediates have recently been reviewed with the aim of reducing the gap between academic research and pharmaceutical manufacturing [55]. Moreover, stereoselective organocatalysis under continuous flow conditions for chiral drug synthesis was highlighted. When flow reactions were carried out with heterogeneous catalysts, an increased process efficiency was observed, together with easier product recovery.

A continuous flow system that involves columns packed with heterogeneous catalysts has been employed in API preparation, showing that multistep chemical transformations can smoothly proceed without the isolation of intermediates and the separation of by-/co-products and catalysts [56]. Following the retrosynthesis depicted in Scheme 13, the anti-inflammatory drug Rolipram (**1**) was enantioselectively achieved on a gram scale. In particular, eight steps of chemical transformations were carried out using commercially available starting materials **2**, **3**, **5**, H_2, H_2O and several columns containing heterogeneous chiral and achiral catalysts (fig. 6).

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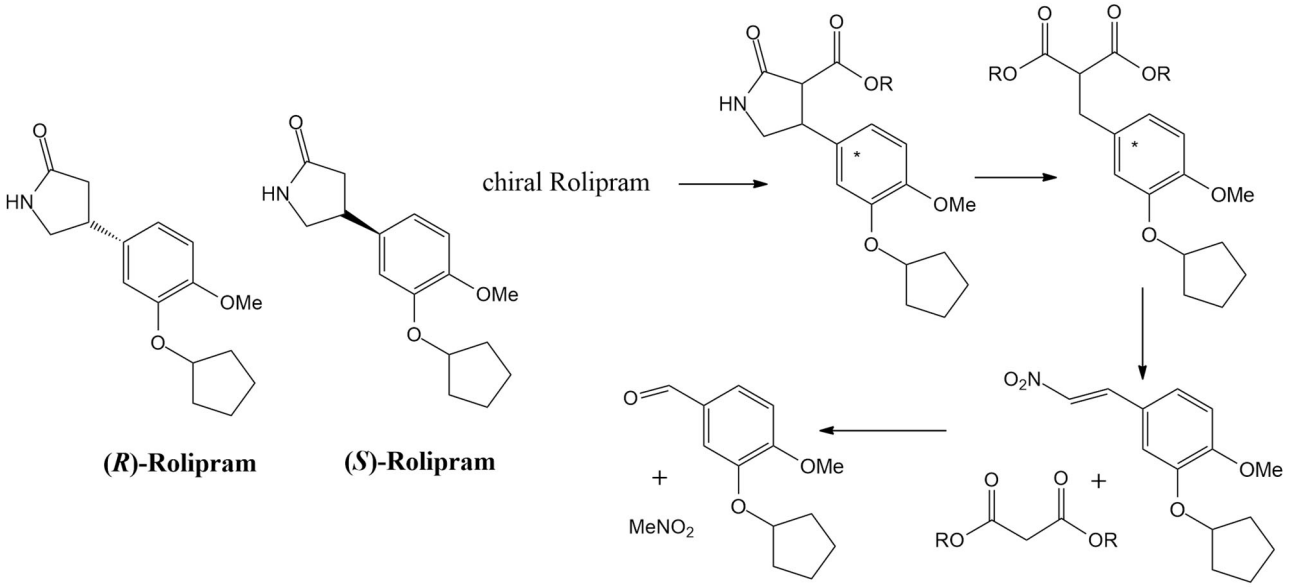

Scheme 13. Retrosynthetic analysis for (*R*)- and (*S*)-Rolipram.

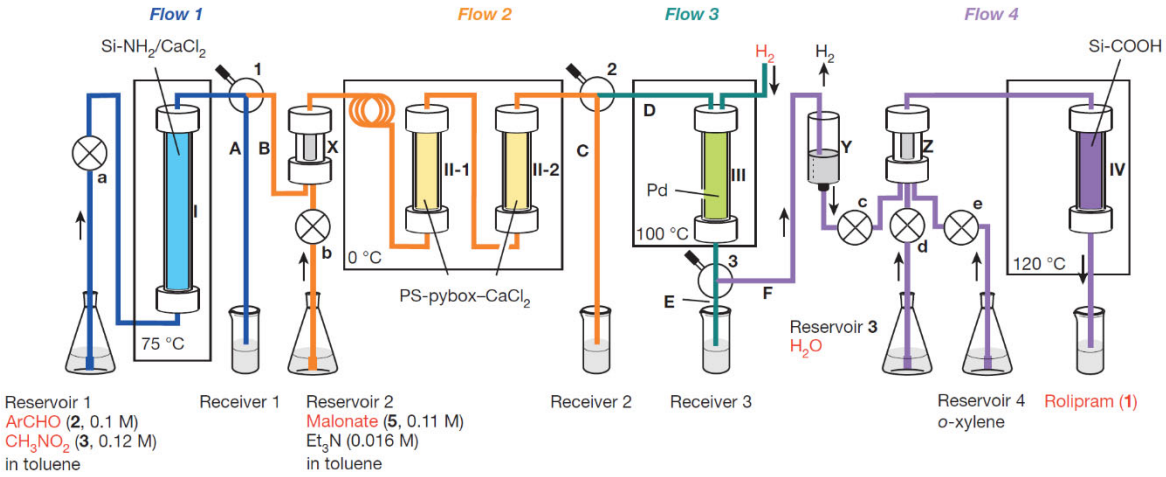

Figure 6. Synthesis of (R)- and (S)-Rolipram: diagram of the series of flow reactors. Red text indicates starting materials and products. Structures labelled a, b, c, d and e are pumps; those labelled A, B, C, D, E and F are flow lines. X is MS 4A; Y is Amberlyst 15 Dry; Z is Celite.

The simple replacement of a column packed with a chiral heterogeneous catalyst (column II filled with PS-(S)-pybox-calcium chloride) with another containing the opposing enantiomer (column II' filled with PS-(R)-pybox-calcium chloride), allows both (S)- and (R)-Rolipram to be recovered, with a 50% yield from compound **2** and a 96% enantiomeric excess. The same flow system was used to obtain (R)-Phenibut, another drug belonging to the GABA family, from benzaldehyde using a slightly modified flow system.

The synthetic pathway for Pregabalin (Scheme 14), a γ-amino acid derivative used for the treatment of nervous system disorders, involves the use of toxic substances, such as cyanide sources and Raney nickel [57]. A continuous-flow method has been reported by Ishitani *et al.* [58]. The authors employed heterogeneous catalysts at each stage of the synthetic procedure that affords the γ-lactam (Scheme 14), involving: Knoevenagel reaction of isovaleraldehyde with methyl malonate; Michael 1,4-addition of nitromethane to alkylidenemalonate; reduction of the nitro group and intramolecular cyclization. An improvement in the lifetime of the entire flow system was observed when the length of the column reactor used in the second step, which contains the ion-exchange resin, was increased from 10 to 30 cm. This approach allowed the precursor of Pregabalin to be smoothly produced, and yields of 75–100 % were maintained for about 45h. The space-time yield was found to be 52.2 g/L.

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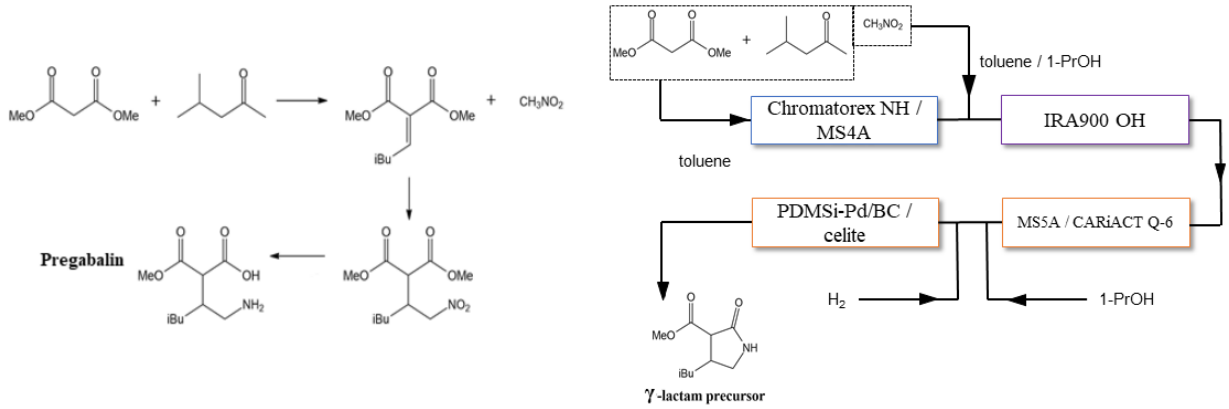

Scheme 14. Synthetic route to Pregabalin (sx) and the three-step sequential-flow synthesis with heterogeneous catalysts of its precursor γ-lactam (dx).

Finally, the hydrolysis of γ-lactam, performed by heating in hydrochloric acid followed by neutralisation, produced the desired drug Pregabalin.

Despite the wide range of applications reported, the commercialisation of microfluidic systems is still limited [59]. Although the *in situ* preparation of highly reactive compounds is convenient, small amounts of unexpected precipitation or crystallisation can lead to reactor clogging [60]. Direct or indirect sonication and suitable fluid laminar speeds may overcome these troubles. In order to coat nanoparticles in the inner walls of a fluoropolymer, commercial ZnO nanoparticles and fluorinated ethylene propylene have been chosen, and modified microtubes, obtained thanks to the physical changes that occur during irradiation in a low energy ultrasonic bath, were used as photocatalytic microreactors for the conversion of aromatic alcohols to aldehydes [61].

The term "follow-on drugs" refers to pharmaceutical compounds that are introduced after the pioneer API, and usually present enhanced properties as regards dosage and side effects [62]. A machine-assisted approach to the synthesis of compounds can provide advantages, as the automation and robots minimise errors that may occur during repetitive operation. The synthetic process can be simplified through the integration of reaction steps and workup procedures, thus limiting handling operations.

Indole compounds are known for their biological effects, which are useful for the pharmaceutical industry [63, 64], and, although a broad range of syntheses have been reported, the most commonly used procedures are still based around the Fischer indole reaction [65]. A hybrid machine-assisted approach that includes a multistep continuous-flow processes plus automated robotic microwave reactors has been used for the rapid preparation of an indole library, including the generation and consumption of hazardous materials [66]. In particular, taking into account the key Fischer indole intermediate enhydrazines, the authors intended to use the hybrid machine to prepare and then consume diazonium salts, in order to obtain hydrazines on demand from their corresponding aniline input feeds (Scheme 15, Step 1). The obtained "masked hydrazines" directly feed into the second part of the machine, giving rise to expedited Fischer indole reactions with a range of carbonyl compounds using a robotic microwave reactor (Scheme 15). A series of vials were preloaded with the desired aldehydes or ketones, and then a stream of hydrazine was distributed before irradiation, producing 14 different indoles that were isolated with yields in a range from 24% to 74 %.

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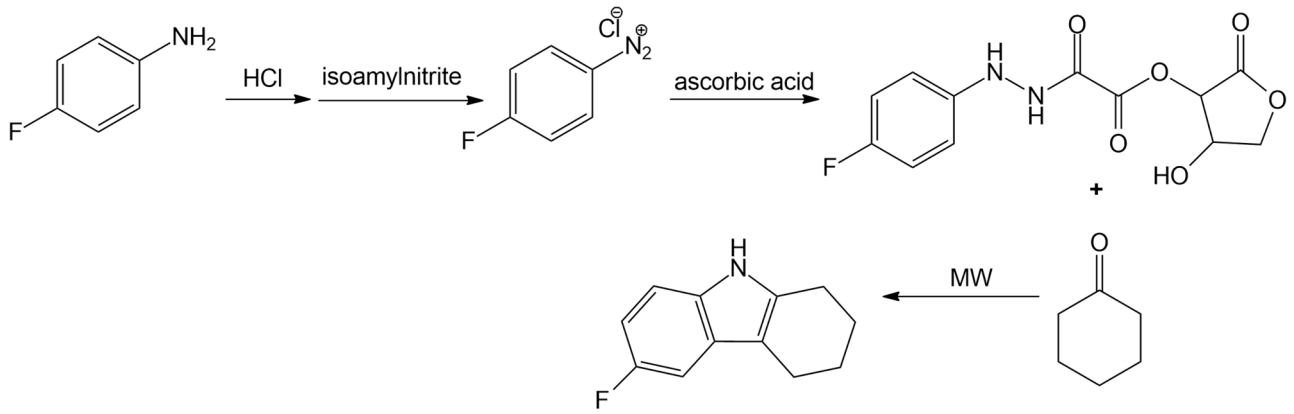
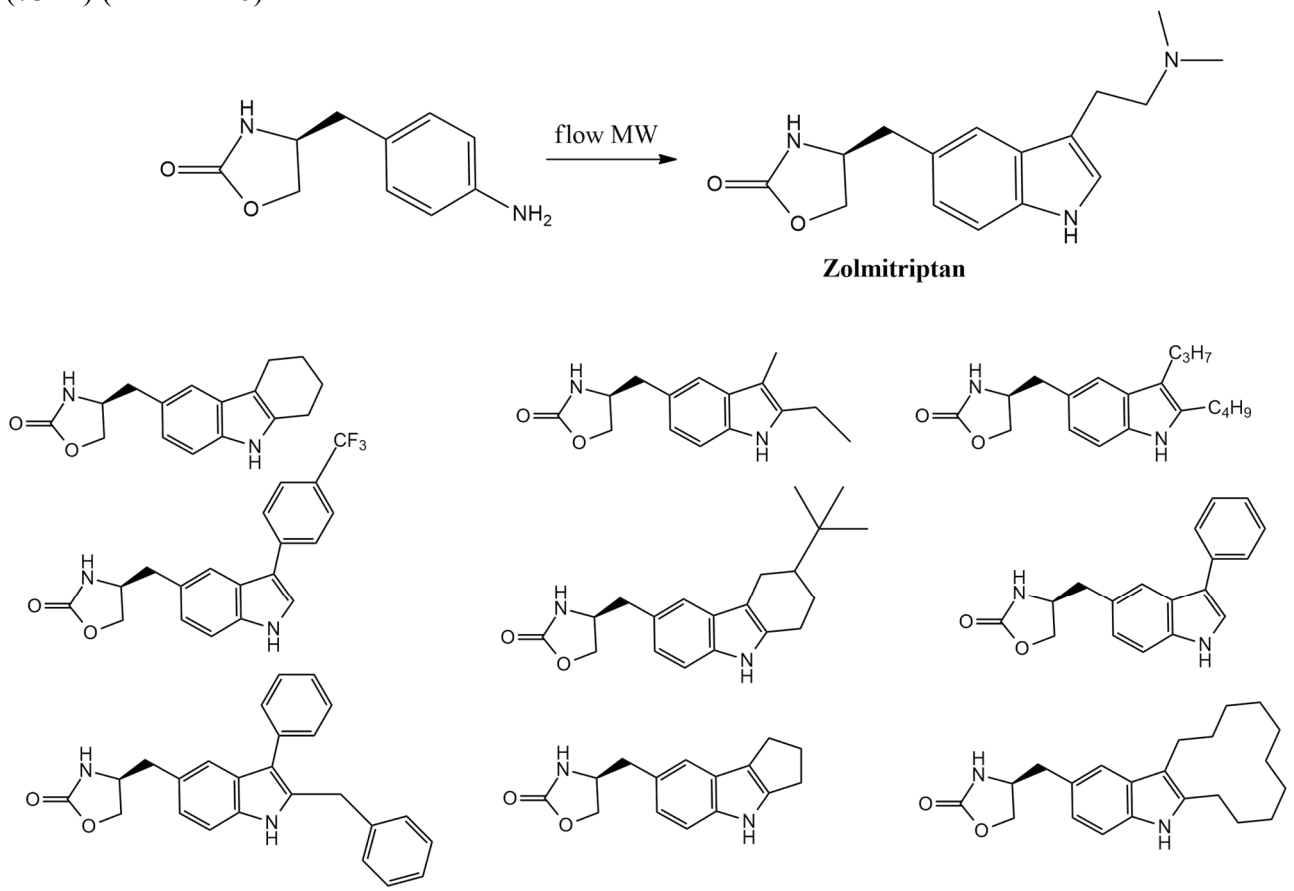


Scheme 15. Technologies combination in multistep synthetic flow process.

Moreover, the anti-migraine drug Zolmitriptan and its nine analogues were synthetized in good yield (73 %) (Scheme 16).



Scheme 16. Continuous flow Zolmitriptan synthesis and analogues.

Conclusion

Although the impressive process intensification of enabling technologies in chemical reactions has been well established, the techniques are mainly exploited in drug-discovery labs. The driving force of investment towards Industry 4.0 should bridge the technological gap between research and production. The examples reported in this review highlight how these advances can improve reaction yields while limiting impurities and side reactions, and how they thus help to answer the challenge of more highly competitive pharmaceutical lead-compound synthesis. Recent examples of multikilo scale applications could design semi-industrial production methods [67, 29]. The four evolutionary stage of pharma manufacturing is connecting cyber-physical systems with big data networks and

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cloud computing, with reactors parameters and in-line analytical monitoring, enabling higher productivity and product quality.

Consent for Publication

Not applicable.

Funding

None.

Conflict of Interest

The authors confirm that this article content has no conflict of interest.

Acknowledgements

None.

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