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Sustainable and solvent-free synthesis of molecules of pharmaceutical importance by ball milling

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The solvent-free mechanochemical reactions under ball milling have emerged as a promising alternative to traditional solution-based chemistry. This approach not only eliminates the necessity for large quantities of solvents and minimizes waste production, but it also facilitates a unique reaction environment that enables strategies, reactions, and compound syntheses that are typically unattainable in solution. This solvent-less synthetic strategy under ball-milling has been well employed in synthetic organic chemistry in accessing various potential organic molecules including pharmaceutically important molecules and pharmaceuticals or drug-molecules. This review highlights the potential of ball milling in the synthesis of pharmaceutically important classes of molecules without using any solvent (solvent-free conditions).

1. Introduction

The advancement of chemical syntheses through organic transformations is readily apparent while examining the progress in the discovery of new pharmaceuticals, agrochemicals, and essential materials, all of which are fundamental components of contemporary human existence.[1] However, one of the primary concerns associated with traditional chemical synthesis is the requirement of hazardous and toxic organic solvents, which results in substantial environmental impact and pollution.[2] The chemical technology that has overcome this issue in organic synthesis is ball-milling or mechanochemistry, and thus, it has become a unique and sustainable tool for synthesizing chemicals without using a hazardous solvent.[3] A reaction under ball milling or a mechanochemical reaction can be characterized as a "chemical transformation" that is facilitated by the absorption of mechanical energy, which may occur through mechanisms such as compression, shear, or friction.[4] Mechanochemical reactions are carried out by grinding reactants using various ball-milling devices such as vibrating (VBM), planetary (PBM), tumbler ball-mill, or single-screw devices (SSD) (Fig. 1). The International Union of Pure and Applied Chemistry (IUPAC)

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has recognized mechanochemistry as one of the ten transformative technologies of our time.[5] Despite its historical roots spanning millennia, mechanochemical reactions were largely overlooked by chemists throughout the 20th century. In contemporary practice, mechanochemistry is regarded as a highly effective approach within the framework of Green Chemistry, as it could completely eliminate the need for solvents.[6] Nevertheless, the lack of bulk solvents introduces novel synthetic possibilities, including enhanced selectivity, rapid reaction rates, and quantitative yields. This is further complemented by the reduction in extensive post-reaction processing and the potential to access intriguing molecules and materials.

In recent decades, health-related challenges have received considerable focus, leading to a profound evolution within the pharmaceutical sector, and due to the globally growing concerns about pollution and global warming, the synthesis of pharmaceuticals or pharmaceutically relevant molecules under solvent-free conditions is highly desirable in the context of Green Chemistry.

In contemporary research, a well-established application of modern mechanochemistry is prominently observed in the field of medicinal chemistry, referred to as ''medicinal mechanochemistry.'' This discipline focuses on the synthesis of active pharmaceutical ingredients (APIs) and relevant pharmaceutical fragments and functionalities through mechanochemical methods, aiming to minimize environmental impact.[7] Numerous sophisticated mechanosynthetic approaches for the production of APIs have been developed, including teriflunomide (used in multiple sclerosis treatment),[8] ftivazide (an anti-tuberculosis agent),[9] axitinib (for renal cell carcinoma),[10] nitrofurantoin (an antibacterial drug), and dantrolene (a skeletal muscle relaxant),[11] pioneered by researchers such as Lamaty, Baltas, Su, Colacino, and others. Notably, the pure *E*-isomer of nitrofurantoin, predominantly in amorphous forms, demonstrated significantly improved bioavailability and drug dissolution rates, achievable within 45 minutes of continuous milling, thereby highlighting the benefits of medicinal mechanochemistry. In this study, we summarize the solvent-free synthesis of pharmaceutically important molecules under ball milling, highlighting its advantages over conventional or traditional approaches.

2. Synthesis of pharmaceutically relevant molecules

2.1 Organochalcogenides

Organochalcogenides are molecules that bear at least one carbon–chalcogen bond and are biologically important due to their antioxidant, anticancer, and antimicrobial activities. These compounds, especially those containing sulfur (S) and selenium (Se), can modulate oxidative stress by scavenging reactive oxygen species (ROS) and enhancing cellular defence mechanisms.[12] Their diverse biological roles make them valuable in therapeutic development for conditions related to oxidative damage and infections.[13] Ebselen **1** is a Se-containing marketed drug used for its antioxidant and anti-inflammatory activities (Fig. 2).[14]

In 2013, Ranu *et al.* developed a metal-, reagent- and solvent-free, cost-effective synthetic methodology under ball milling to synthesize a pharmaceutically important class of molecules, *i.e.*, diorganyl disulfides (**6**), from thiols (**5**) using recyclable neutral alumina as a grinding auxiliary (Scheme 1).[15] The substrate scope of the reaction was very broad, including aryl,

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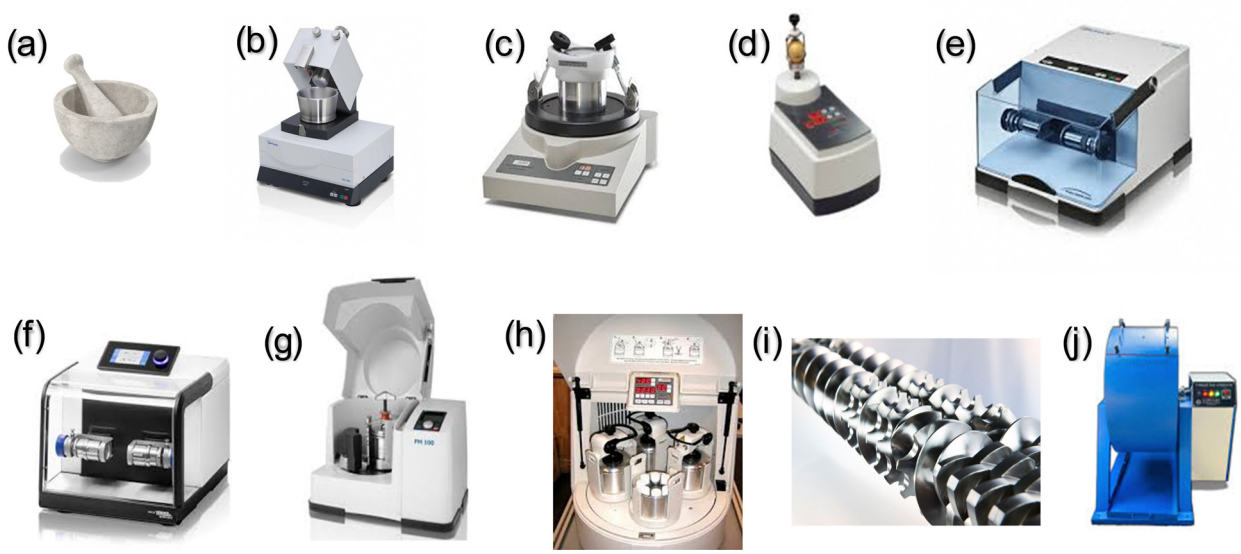


Fig. 1 Typical grinding and milling equipment: (a) mortar and pestle, (b) Retsch automated mortar, (c) Fritsch vibrational mill, (d) Fritsch vertical shaker mill, (e) Retsch vibrational ball mill, (f) Retsch vibrational ball mill with controlled temperature (cryomill), (g) Retsch planetary ball mill, (h) multiple-sample mill (automaxion), (i) twin-screw used for continuous mechanochemical extrusion, and (j) tumbler ball-mill.

heteroaryl, and alkyl thiols, thus furnishing a wide variety of disulfides, all in excellent yields (95–99%, average yield = 96.8%) within a short time (15–30 min). Notably, the synthesis of several pharmaceutically important disulfides, having *in vitro* anti-leishmanicidal activities (**6n–6q**) and also antibacterial activities (**6m**) against Gram-positive and Gram-negative strains, was achieved in excellent yields under ball-milling. The reaction was equally effective for both electron-withdrawing and electron-donating groups to afford the corresponding products. Interestingly, in the presence of another oxidizable functional group, $-CH_2OH$ (**6h**), only the thiol (–SH) functional group underwent chemoselective oxidation to furnish the corresponding disulfides. The grinding auxiliary, neutral alumina, was recovered after the reaction just by simply washing it with ethanol, followed by acetone, and finally drying it in an oven at 80 °C for 3 h. The excellent yields of the products with a very short reaction time make this solvent-free method superior to other conventional chemical methods.[16] Moreover, the recovery and reusability of the grinding auxiliary made the mechanochemical process more sustainable. C–H activation by ball milling is an innovative and mechanochemically-driven method for the direct functionalization of carbon–hydrogen (C–H) bonds, one of the most abundant and inert bonds in organic molecules.[17] This technique utilizes the mechanical force generated by milling balls to promote chemical reactions, eliminating the need for solvents and reducing reaction times. Ball milling induces energy-efficient activation of C–H bonds, enabling the formation of new carbon–carbon or carbon–heteroatom bonds. This environmentally friendly approach offers advantages like improved sustainability, scalability, and reduced by-product formation, making it an attractive alternative for synthetic transformations in modern organic chemistry.

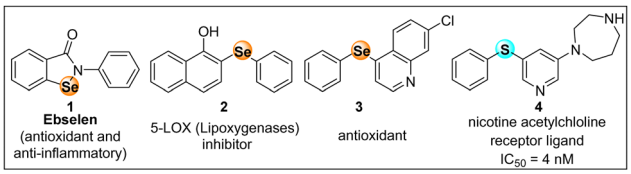
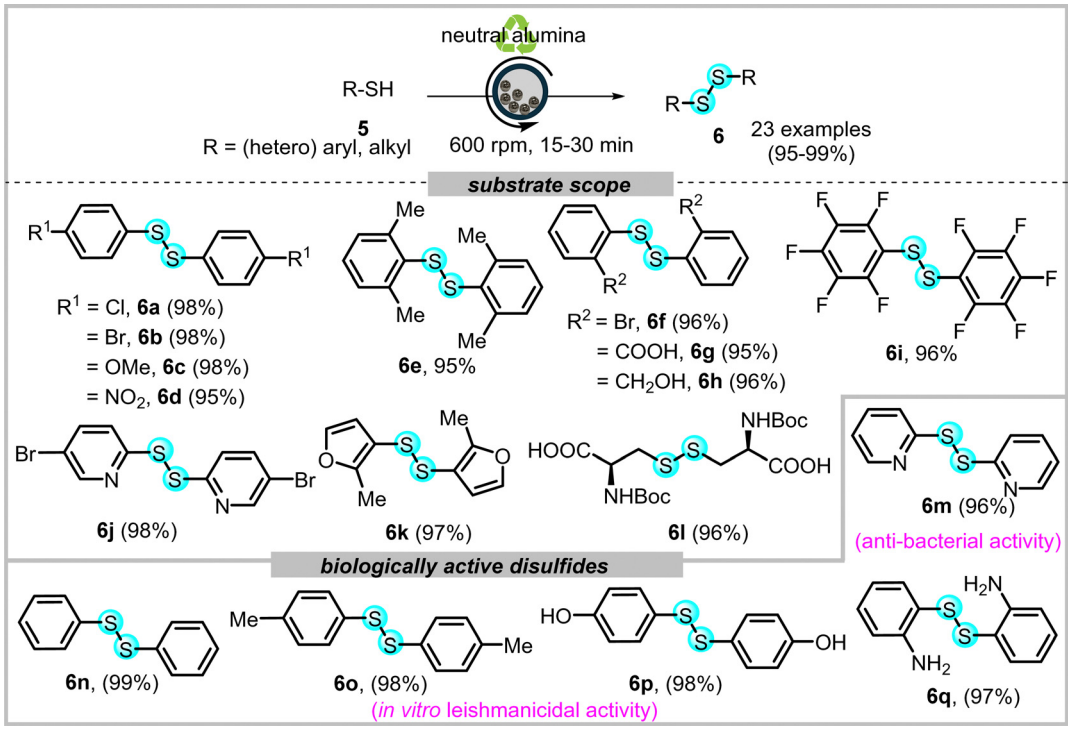


Fig. 2 Examples of S- and Se-containing drug molecules.

In 2020, Ranu's group reported a C–H chalcogenetion that leveraged mechanochemical techniques, specifically ball milling, to promote the reaction between bicyclic arenes (**7**) (such as naphthalene derivatives) and diaryl dichalcogenides (**8**), *i.e.*, disulfides or diselenides (Scheme 2).[18] The reaction occurred in the absence of solvents, ligands, metals, or oxidants, making it a greener approach. The key to the method's success was the use of basic alumina (washed with 15% KOH solution and dried) as a grinding auxiliary, which served as a solid surface for the reaction, facilitating the formation of the desired C–X bonds (X = S and Se) under milling conditions with 5 balls and 600 rotations per minute (rpm). The process accelerated the reaction, significantly reducing the reaction time compared to conventional methods and providing high yields of the desired products. The arenes and dichalcogenides' flexibility enabled the synthesis of diverse naphthyl chalcogenides. Specifically, the electron donating group substituted 2-naphthols showed greater reactivity than that of the electron-withdrawing group substituted ones. Heterocyclic disulfides (**9m** and **9o**) and diselenides (**9n** and **9p**) participated efficiently in these conditions. This reaction worked smoothly with different selenium sources, *i.e.* phenyl selenium chloride/bromide/cyanide (**10** and **12**) under ball-milling to produce 1-(phenylselanyl)naphthalen-2-ol (**11** and **13**) in high yields. After completion of the reaction, the reaction mixture absorbed in alumina was directly employed in column chromatography to get the pure product. This purification procedure eliminated the requirement of substantial amounts of organic solvents for the



Scheme 1 Solvent-free synthesis of disulfides from thiols *via* aerobic oxidation under ball milling.

workup process, and the organic solvent was required only for column chromatography. The reaction was proposed to proceed *via* the formation of intermediate **A** and **B** to furnish the desired product.

In 2013, Ranu *et al.* revealed a green synthetic method, free of metals and solvents, for the synthesis of valuable organochalcogenides (**15**) *via* C–X (X = S, Se, and Te) bond-forming cross-coupling reactions between aryldiazonium tetrafluoroborates (**14**) and diorganyl dichalcogenides (**8**) using neutral alumina as a grinding auxiliary and KOH under ball milling (Scheme 3).[19] All the reactions were completed within 15–20 minutes with the help of mechanochemical grinding of six balls at a speed of 600 rpm at room temperature. Under the ideal mechanochemical conditions, a wide variety of organosulfides, selenides, and tellurides were produced in moderate to good yields and with wide functional group tolerance. Electron-donating groups (Me, OMe) as well as electron withdrawing groups (CF_3, CN, COMe, CO_2Me, NO_2) and halogen (Br, Cl) substituted aryl diazonium compounds underwent the cross-coupling reaction with different di(hetero)aryl disulfides, dialkyl sulfides, diphenyl diselenide, and diphenyl ditelluride to afford the desired organochalcogenides (**15**) in good yields.

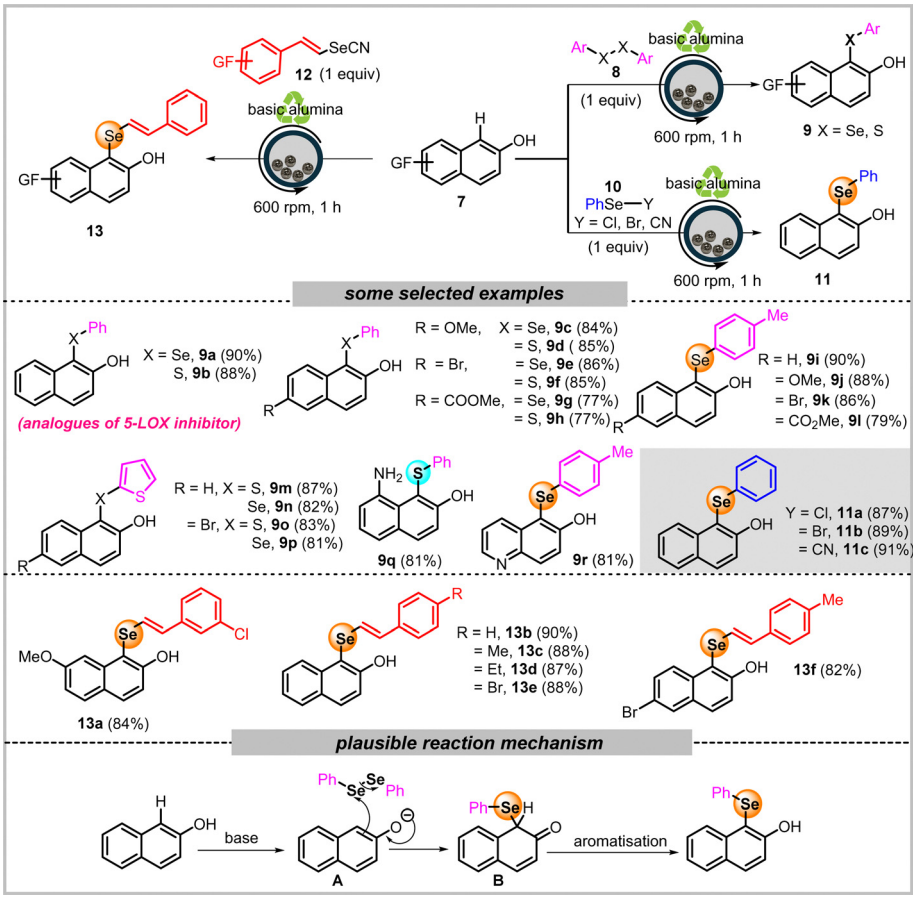
2.2 Coumarins

Coumarin is a pharmaceutically important naturally occurring compound with a wide range of applications in medicine, as well as in agriculture and the fragrance industry. It is naturally found in plants like tonka beans, lavender, and cinnamon, which have been used for centuries in traditional medicine. Their chemical structure allows for easy modification, leading to various therapeutic applications. Coumarins also exhibit other therapeutic properties, including anticancer, antiviral, antibacterial, anti-inflammatory, and antioxidant activities.[20] Its diverse biological properties and structural versatility have made it a focal point in drug discovery and chemical synthesis. Some well-known coumarin-containing drugs are warfarin (**16**) (anticoagulant), scopoletin (**17**) (anti-inflammatory), and hymecromone (**18**), a choleretic and antispasmodic agent (Fig. 3).

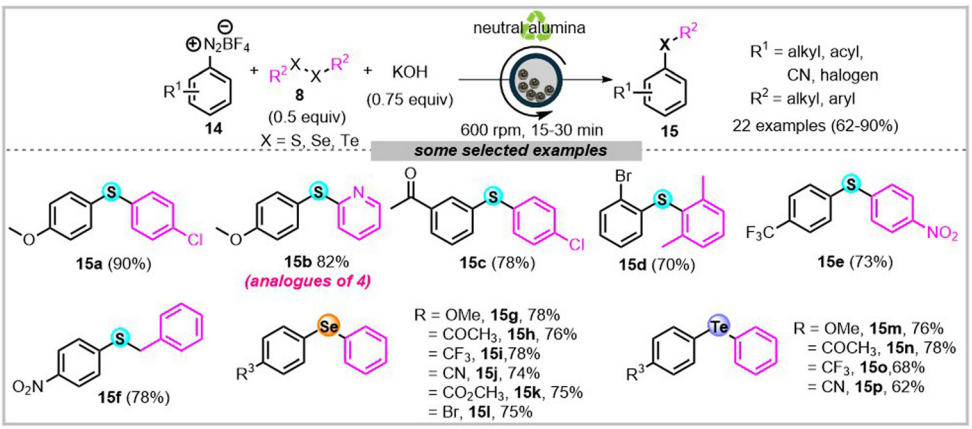
In 2022, Ranu *et al.* developed a mechanochemical Pechmann condensation reaction to access coumarins (**21**) and annulated pyrano[2,3-*f*] and [3,2-*f*]indoles (**23**).[21] In this reaction, phenol derivatives (**19** and **22**) were subjected to milling with β-ketoesters (**20**) at ambient temperature, employing methanesulfonic acid as a mild catalyst, in a stainless-steel jar using ten 5 mm stainless steel balls (Scheme 4). Notably, the reaction progressed smoothly without any grinding auxiliary such as silica or alumina. Specifically, 1*H*-indol-5-ol and 1*H*-indol-6-ol reacted with β-ketoesters in the same conditions to furnish the expected products, *i.e.* pyranoand [2,3-*f*] and [3,2-*f*] indoles (**23**) with good yields (Scheme 5). The key advantages of this approach include high yields, scalability, short reaction times, and the elimination of hazardous solvents or acids. The procedure avoids traditional purification methods like column chromatography and demonstrates a lower environmental impact, as indicated by high EcoScale metrics (>80) and a low *E*-factor (0.67 for **21a**). This method excels the traditional Pechmann condensation by improving both yield and regioselectivity.

2.3 Pyrimidine

In pharmaceuticals, pyrimidine derivatives help in developing antiviral, anticancer, and antimicrobial drugs. Compounds like 5-fluorouracil (**24**) (an anti-cancer agent) and zidovudine (**25**)



Scheme 2 C–H chalcogenetion of bicyclic arenes under solvent-less ball-milling conditions.



Scheme 3 Solvent-free synthesis of unsymmetrical diaryl chalcogenides under ball-milling.

(an anti-viral agent) showcase the role of pyrimidines in interrupting cellular processes like DNA synthesis, which makes them effective in treating diseases (Fig. 4).[22] From a synthetic perspective, pyrimidines are valued for their structural versatility and reactivity, particularly at the C-4 and C-5 positions. This enables the creation of a wide array of functionalized molecules, making pyrimidines a vital scaffold in drug discovery.

Due to multiple reactive sites, the regioselective C–H functionalization of pyrimidine and pyridine rings is challenging. The Yu group developed a solvent-free, mechanochemical Minisci-type regioselective C–H alkylation of pyrimidines and pyridines, particularly at the C-4 position, mediated by Mg(0) by using alkyl bromides or chlorides as the alkylating agents to furnish 4-alkyl pyrimidines and 4-alkyl pyridines (**30**) (Scheme 6).[23]

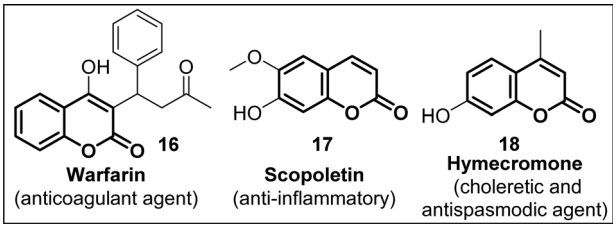
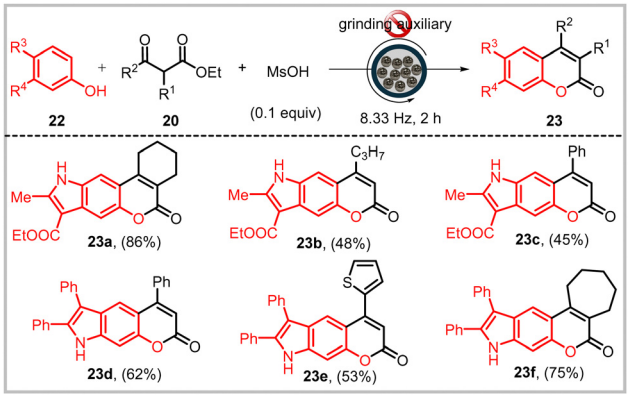


Fig. 3 Examples of pharmaceutically important coumarin derivatives.

The process leveraged the mechanochemical activation of magnesium, allowing alkyl radicals to be generated from the halides (**29**) under solvent-free conditions, offering a greener alternative to traditional methodologies that rely on harsh solvents and heating conditions. The developed method featured a broad substrate scope for both the alkyl halide (**29**) and pyrimidine ring (**28**) and pyridine. Among all primary, secondary, and tertiary alkyl halides, the yield was much higher for tertiary halides. The electron-rich pyrimidines, bearing an electron-donating group, showcased a higher yield than that of electron-poor pyrimidines, bearing an electron-withdrawing group. The method was equally effective for the pyridines, furnishing a couple of 4-alkylated pyridines (**30w–30z**). Interestingly, when the 4-position of the pyridine ring was blocked, the reaction took place at the 2-position of the pyridine ring to furnish 2,4-disubstituted pyridine (**30z**). Notably, the developed solvent-free, mechanochemical method was utilized in synthesizing an FDA-approved antimalarial drug, pyrimethamine (**33**), from 5-(4-chlorophenyl)pyridine-2,4-diamine (**31**) and EtBr (**32**) in 48% overall yield.

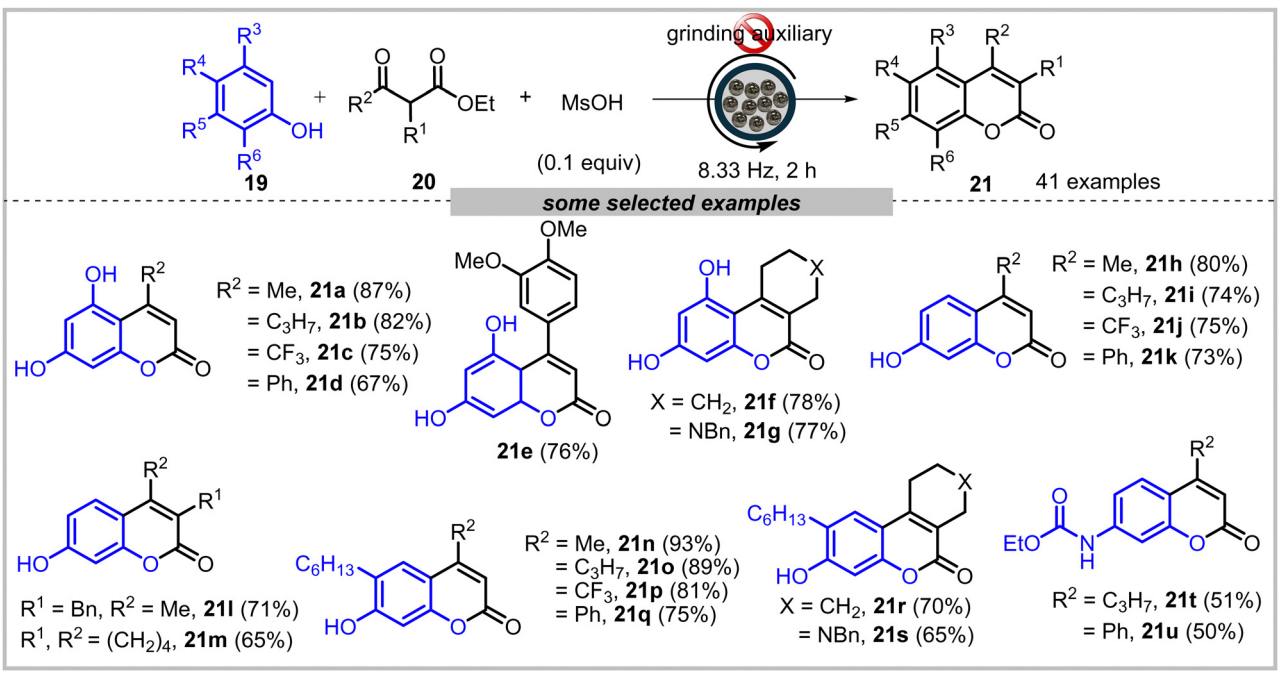
2.4 Quinoxalin-2(1*H*)-ones

Quinoxalin-2(1*H*) is a fused bicyclic ring that consists of a benzene ring and a pyrazine ring and provides a versatile framework for interactions with biological targets. These pharmaceutically active cores are very important in medicinal chemistry due to their wide range of biological activities, such as anticancer, antimalarial (**34**), anti-inflammatory, and antidiabetic activity, which makes them valuable scaffolds in drug development (Fig. 5).[24]



Scheme 5 Solvent-free synthesis of annulated pyrano[2,3-*f*] and [3,2-*f*]indoles.

In 2023, Yuan *et al.* reported a solvent-free mechanochemical piezochemically driven $BaTiO_3$-catalyzed decarboxylative coupling of quinoxalin-2(1*H*)-ones (**38**) using $NH_4S_2O_8$ as an oxidant and $NaHCO_3$ as a base to furnish C3-acylated quinoxalin-2(1*H*)-ones (**40**).[25] The ball milling mediated synthesis gives good to excellent yields for any type of quinoxalin-2(1*H*)-one containing substrate and the yields were much better for benzoyl radical than acyl radical. This method was applicable to other N-containing heterocycles (**40r–40s**). This method leveraged the mechanochemical agitation of $BaTiO_3$, which



Scheme 4 Solvent-free coumarin synthesis *via* Pechmann condensation under ball-milling.

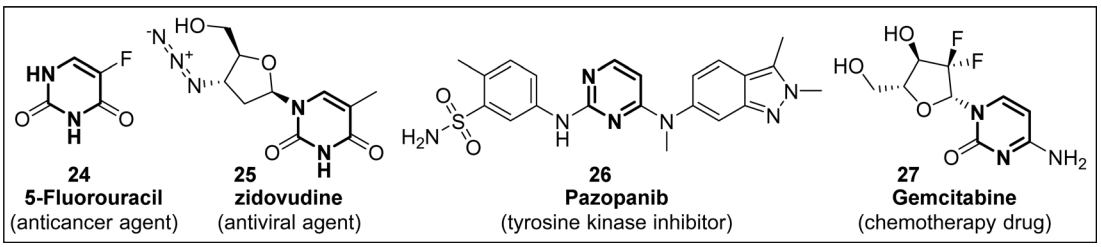
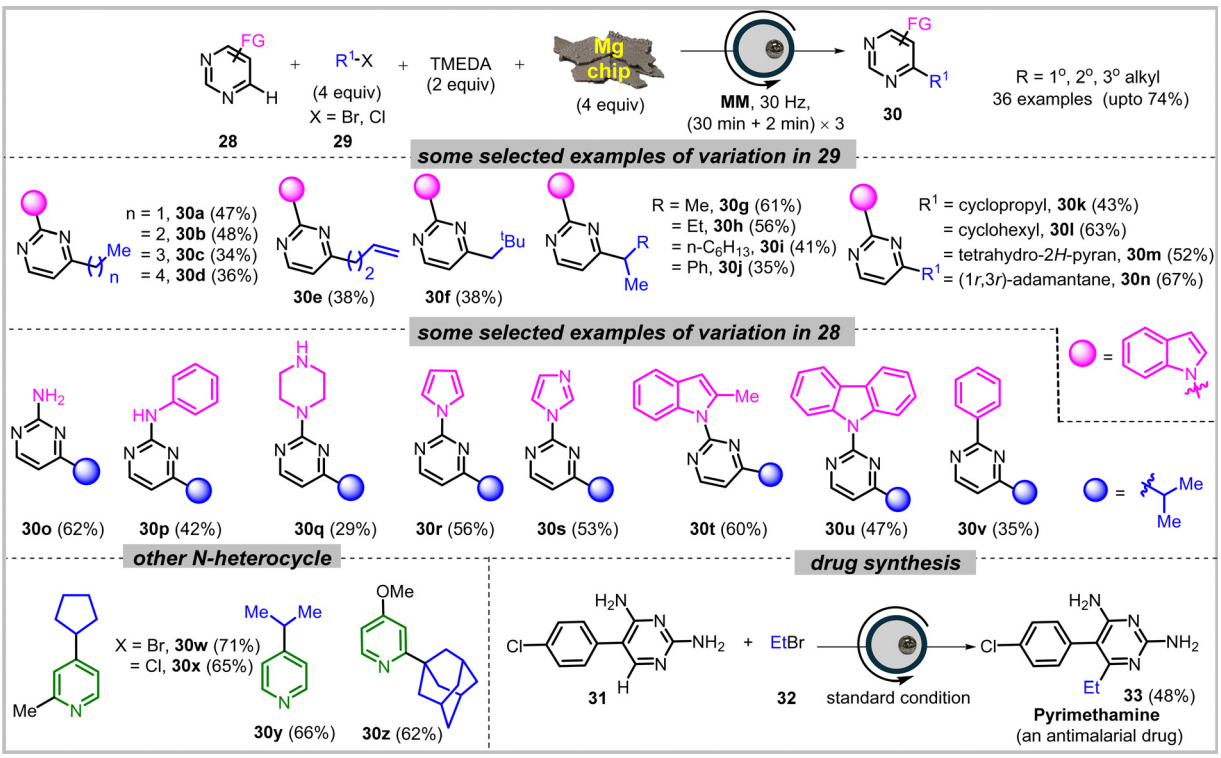


Fig. 4 Some examples of pharmaceutically active pyrimidine derivatives.



Scheme 6 Solvent-free mechanochemical synthesis of 4-alkylpyrimidines under ball-milling.

converts mechanical energy into electrical energy, leading to single electron transfer and formation of the acyl radical (Scheme 7). The piezoelectric material was recovered from the reaction mixture by simply washing and drying and was further used for the same reaction for up to three cycles (Scheme 8). In this mechanochemical method, initially, highly polarised $BaTiO_3$ particles were generated, which helped (**39**) to undergo decarboxylation to furnish radical **C**. Later, **C** reacted with (**38**)

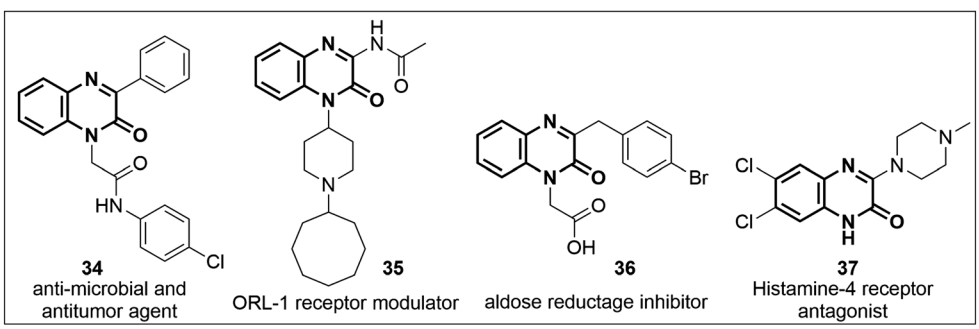
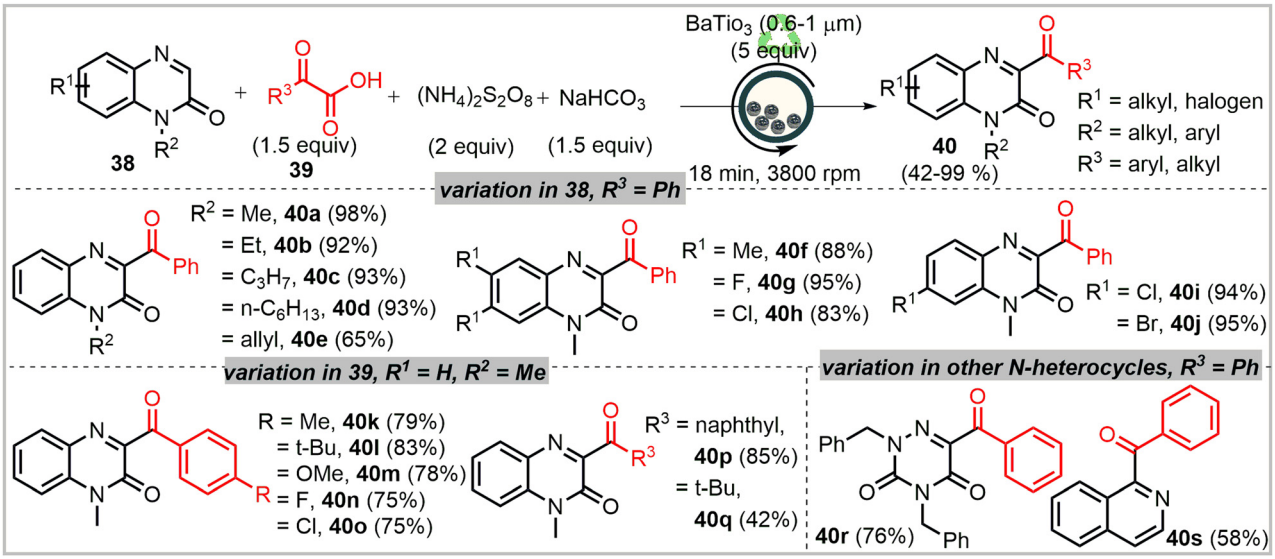


Fig. 5 Examples of drug molecules containing a quinoxaline moiety.



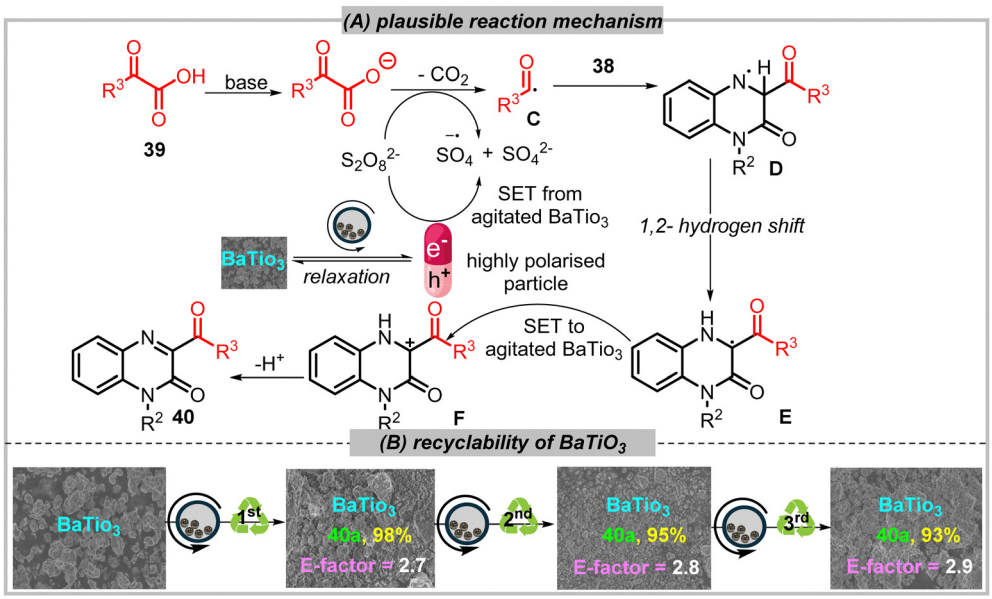
Scheme 7 Solvent-free, piezocatalyzed decarboxylative acylation of quinoxalin-2(1*H*)-ones under ball-milling.

to furnish intermediate **D**, which further underwent a 1,2-H shift to furnish intermediate **E**, followed by a single electron transfer (SET) mechanism to afford intermediate **F**. Finally, it underwent oxidation to furnish the desired product (**40**). The advantages of this method were shorter reaction time, solvent-free reaction, broad substrate scope, simpler work-up procedure, less *E*-factor (2.8 for **40a**), and gram-scale synthesis, which led to practical applications in the chemical and pharmaceutical industry.

2.5 1,2,3,4-Tetrahydroisoquinoline

The tetrahydroisoquinoline unit is a crucial structural motif found in many biologically active natural products and pharmaceutical compounds. It plays a significant role in drug discovery due to its resemblance to neurotransmitters and its presence in alkaloids. Its derivatives exhibit anticancer, anti-inflammatory, and antimicrobial activities, broadening its therapeutic potential. Some drugs containing 1,2,3,4-tetrahydroisoquinoline are mentioned below (**41–43**) (Fig. 6).[26]

The active enantiomer of the vital antiparasitic medication praziquantel, known as levo-praziquantel (*R*-PZQ), is mainly used to treat schistosomiasis, a neglected tropical illness that affects millions of people worldwide. Praziquantel is a racemic combination that comes in both *R*- and *S*-forms, although the therapeutic effects are attributed to the *R*-enantiomer. The production of pure *R*-PZQ improves its effectiveness, lessens its negative effects, and enables more accurate dosing. Its potential to enhance parasite infection therapies makes it



Scheme 8 (A) Proposed mechanism for decarboxylative acylation of quinoxaline. (B) Recycling efficiency of the piezocatalyst, $BaTiO_3$.

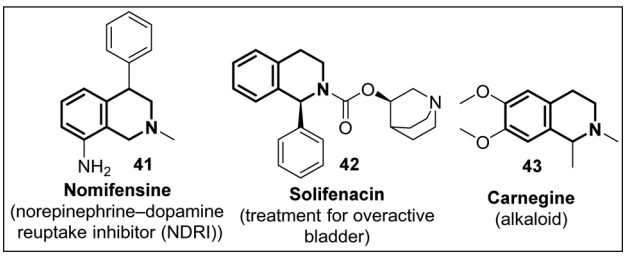


Fig. 6 Examples of 1,2,3,4-tetrahydroisoquinoline containing biologically active molecules.

significant, supporting international efforts to promote public health.[27]

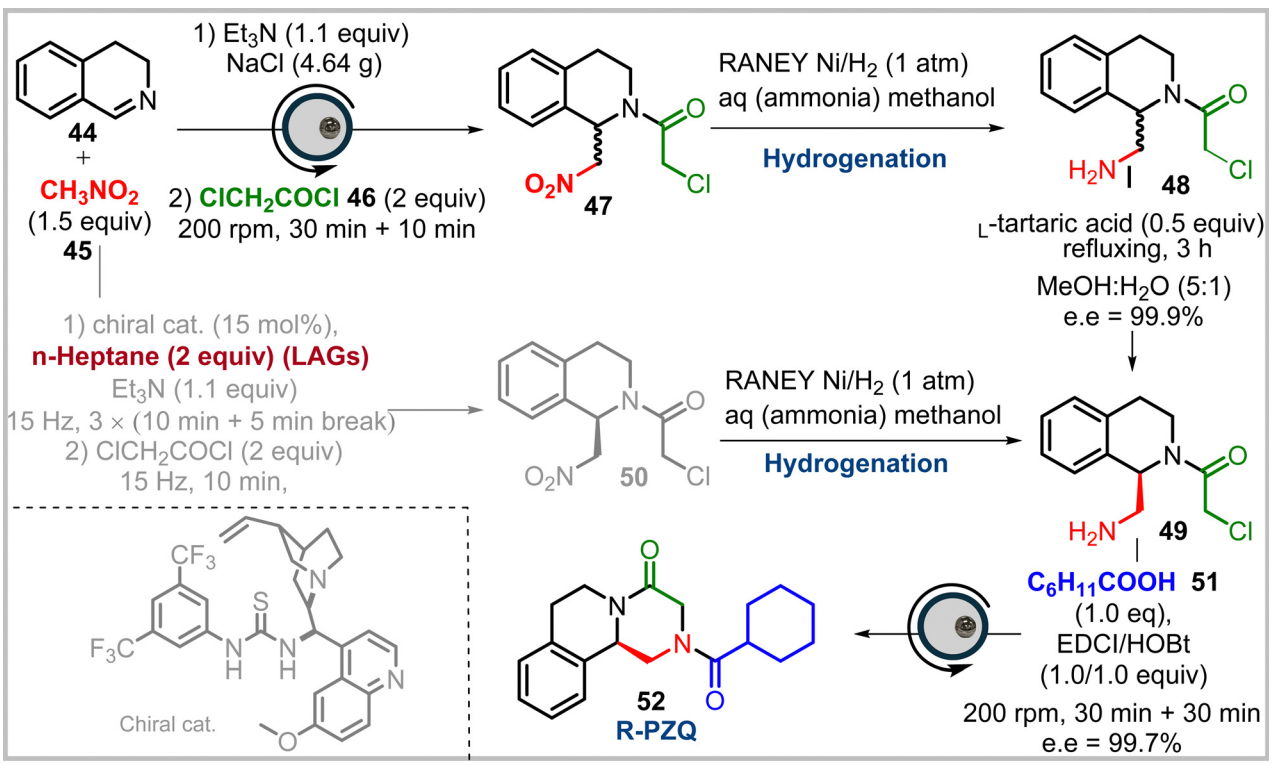
In 2021, Yu *et al.* reported two synthetic routes for preparing levo-praziquantel (*R*-PZQ), an enantiomer of the antiparasitic drug praziquantel (Scheme 9).[28] The first route (path-A) involves a mechanochemical solvent-free aza-Henry/acylation reaction, followed by hydrogenation and chiral resolution using L-tartaric acid.

The second method (path-B) uses enantioselective synthesis without toxic solvents. In the path-A route, the intermediate (**47**) was synthesized under solvent-free ball milling conditions using nitromethane (**45**), chloroacetyl chloride (**46**), and triethylamine as the preferred organic base and NaCl as the grinding auxiliary. The reaction was completed within 40 minutes, and after completion of the reaction, the organic part was washed off with ethyl acetate and NaCl was recovered and reused for up to 3 cycles. After that, (**47**) was subjected to reduction in the presence of RANEY® Ni and hydrogen to furnish 1-aminomethyl tetrahydroisoquinoline (**48**) in 75% yield. Subsequently, chiral resolution of (**48**) was done with the help of L-tartaric acid to get the *R*-isomer.

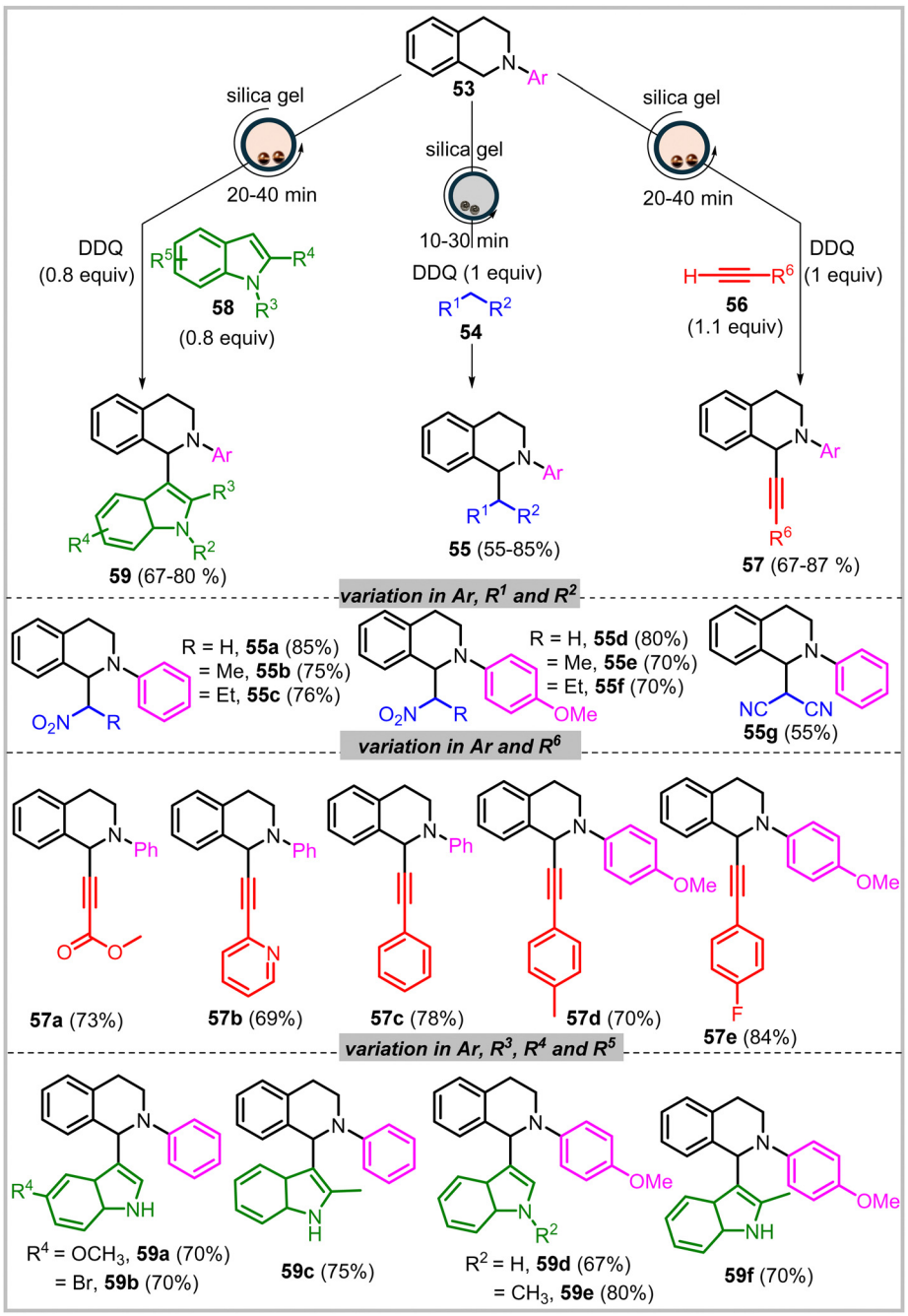
Eventually, compound (**49**) underwent ring-closing and acylation reactions under ball milling conditions in the presence of EDCI/HOBt and cyclohexane carboxylic acid (**51**) to furnish *R*-PZQ (**52**) in high yield. The methods were scalable up to 50 mmol scale, environmentally friendly, and delivered excellent enantiopurity (>99%). This study offers environment-friendly, scalable alternatives for the synthesis of *R*-PZQ, contributing to sustainable pharmaceutical manufacturing.

In 2011, Jiang *et al.* developed a DDQ-mediated mechanochemical cross-dehydrogenative coupling (CDC) reaction involving tetrahydroisoquinolines (**53**) and three different types of pronucleophile, including nitroalkanes (**54**), alkynes (**56**), and indoles (**58**) under solvent-free conditions by ball milling to furnish (**55**), (**57**), and (**59**) (Scheme 10).[29] For nitroalkane and malononitrile, C_{sp^3}–H functionalization adjacent to the N-atom proceeded smoothly under metal-free conditions using silica gel as an auxiliary and stainless-steel balls for milling. For alkyne and indoles, copper balls were used instead of any other additional catalyst, which played the role of both catalyst and milling balls. Electron-rich isoquinolines reacted smoothly under the standard conditions. For electron-rich alkynes and indoles, the yields of the reactions were comparatively high.

The main advantages of the reaction were short reaction time (not more than 40 min), solvent-free conditions, no requirement of any additional catalyst, broad substrate scope,



Scheme 9 Solvent-free mechanochemical enantioselective synthesis of levo-praziquantel (*R*-PZQ).



Scheme 10 Solvent-free synthesis of functionalized tetrahydroisoquinolines under high-speed ball-milling.

and good to excellent yield. The reaction was equally effective for gram-scale synthesis.

2.6 Amides

Amides are essential in biology as they form peptide bonds, the backbone of proteins, providing structural stability and functionality. They are crucial in drug molecules for enhancing stability, bioavailability, and target binding. Amides also play important roles in neurotransmission and lipid metabolism and are key components of many antibiotics (**61**, **62**). Their biocompatibility makes them valuable units in biomaterials and medical applications. Some biologically active drug molecules containing amide linkage are shown in Fig. 7.[30]

In 2021, Browne *et al.* developed a metal-free, solvent-free mechanochemical direct amination of esters by ball milling (Scheme 11).[31] In this procedure, an amine (**65**), an ester (**64**), and a stoichiometric amount of base, *i.e.*, KO^{t}Bu, were mixed in a ball mill jar for 1 h to furnish the desired amide (**66**). Following the reported protocol, a wide variety of amides were synthesized. Both the electron-donating and electron-withdrawing group substituted (hetero)aromatic and aliphatic esters efficiently participated in the reaction. The primary,

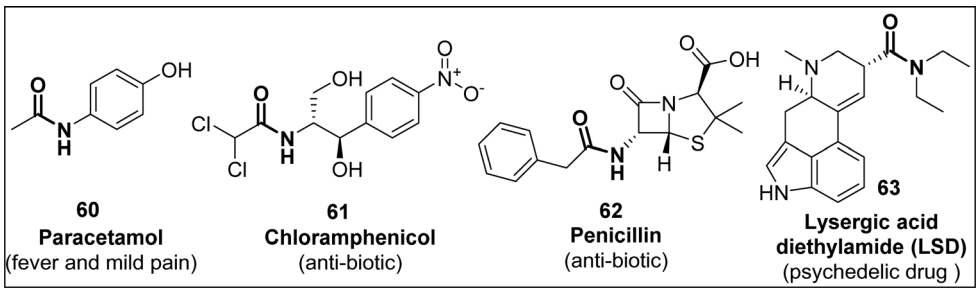
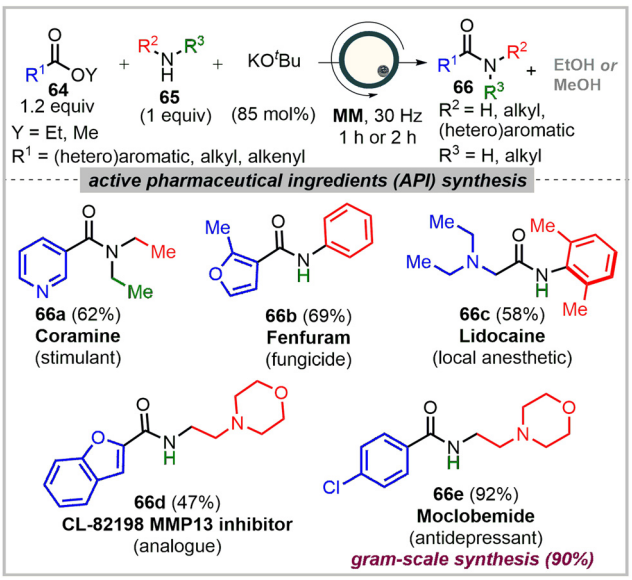


Fig. 7 Examples of drug molecules bearing an amide functional group.



Scheme 11 Amidation of esters *via* solvent-free ball-milling.

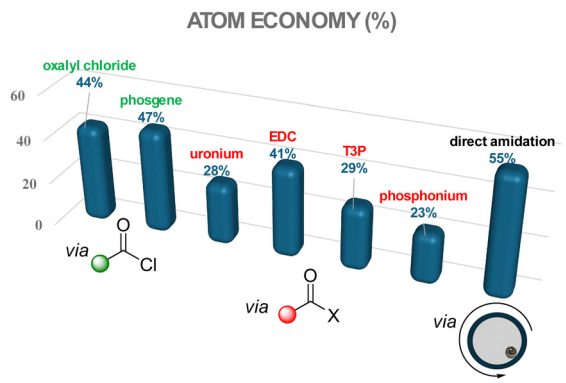


Fig. 8 Comparison of atom economy between the conventional methods and ball milling.

secondary, and tertiary amines also reacted with the esters under ball milling conditions to furnish the desired amides.

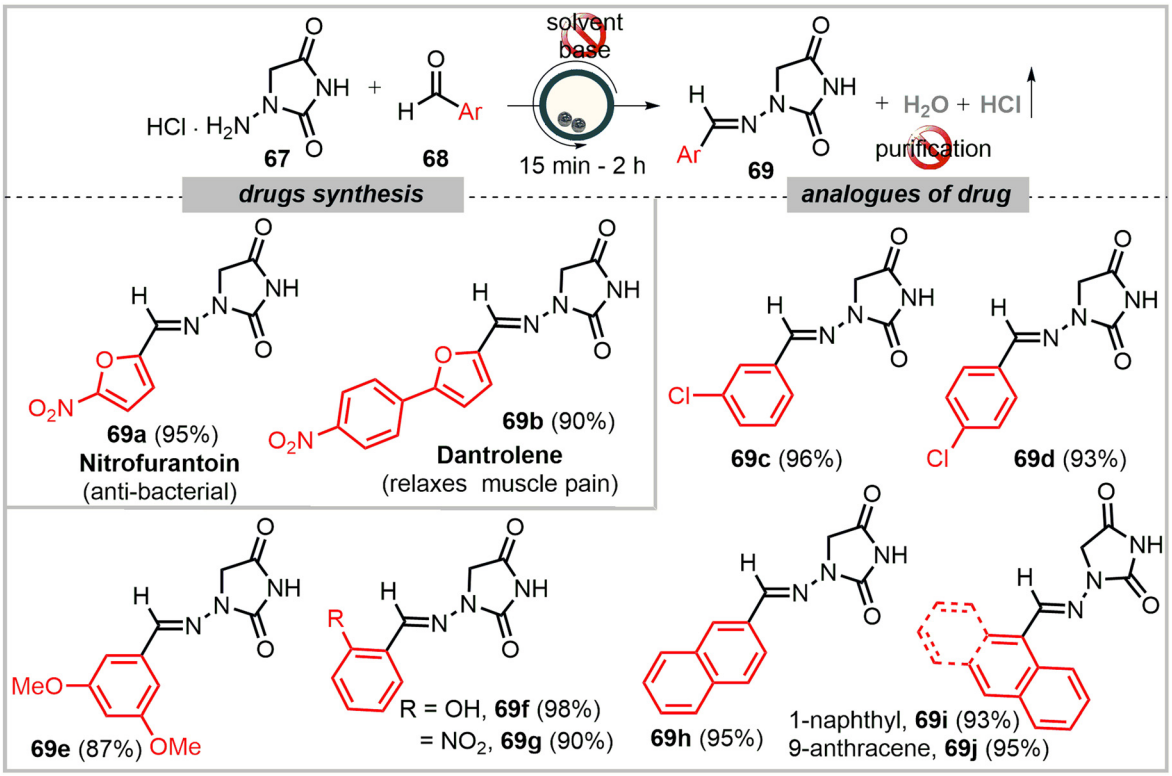
The reaction was equally effective for the synthesis of active pharmaceutical ingredients (APIs) and agrochemicals, *i.e.*, moclobemide coramine (stimulant, **66a**), fenfuram (fungicide, **66b**), lidocaine (anaesthetic, **66c**), an analogue of CL-82198, an MMP13 inhibitor (**66d**), and the gram-scale synthesis of moclobemide (an antidepressant drug, **66e**). Notably, the ball-milling technique was found to offer direct amidation reaction with a much better atom-economy as compared to other conventional methods (Fig. 8).

2.7 1-(Arylideneamino)imidazolidine-2,4-dione

In 2018, Fullenwarth *et al.* designed a mechanochemical solvent-free, base-free, and chromatography-free method to synthesize pharmaceutically active nitrofurantoin, dantrolene, and their derivatives (Scheme 12).[32] At first, 1-aminohydantoin·HCl (**67**) was treated with aldehydes (**68**) in the absence of base and solvent under ball milling conditions for 10–15 min to afford (**69**) in high yields (87–98%), selectively in the form of the *E*-isomer. Additionally, this methodology was employed in synthesizing two pharmaceutically important marketed drugs, *i.e.*, dantrolene and nitrofurantoin, as a practical application of the developed technology with an excellent yield of 95% and 90%, respectively. Notably, the by-products of the reaction were HCl and H_2O. Hence, adding water to the reaction mixture led to precipitation, followed by filtration and drying *in vacuo* over P_2O_5. So, pure products were obtained in powdered form without using a single drop of organic solvent, even for gram-scale synthesis. The main advantages of the reaction were mechanochemical ball milling assisted solvent-free, base, and metal-free synthesis, no requirement of any harsh conditions, the feasibility of gram scale synthesis, energy efficiency, and very low *E*-factor (0.29 and 0.30, for nitrofurantoin (**69a**) and dantrolene (**69b**) respectively) compared to conventional chemical methods (Fig. 9).

2.8 Isoxazolidine and isoxazoline

Isoxazolidines and isooxazolines are key heterocyclic scaffolds in medicinal chemistry due to their biological activity and stability. Isoxazolidines are used as intermediates in drug synthesis, and they exhibit antimicrobial, anti-parasitic, anticancer, antitumor, and antiviral properties. Isooxazolines are important in designing enzyme inhibitors and pesticides, with applications in agrochemicals and pharmaceuticals. Their unique ring structures provide rigidity and functionality for developing bioactive molecules. Some examples of isoxazolidine-based well-known drugs are fluralaner (marketed antiparasitic agent, **70**), acivicin (anti-tumour, **71**), and fluxametamide (pesticide, **72**) (Fig. 10).[33]



Scheme 12 Mechanochemical solvent-free synthesis of hydantoin-based active pharmaceutical ingredients: nitrofurantoin and dantrolene and their derivatives.

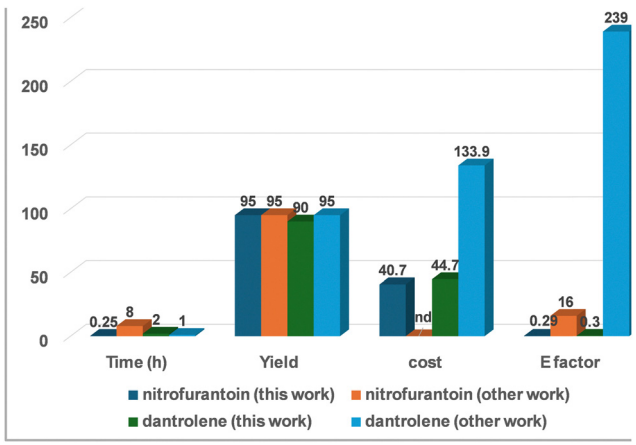


Fig. 9 Comparison of time, yield, cost, and *E*-factor between previous work and the present work for the synthesis of nitrofurantoin and dantrolene.

In 2019, Chakraborty developed a two-step solvent-free mechanochemical synthesis *via* ball milling to furnish isoxazolidine and isooxazoline (Scheme 13).[34] In the first step of the reaction, furfural (**73**) reacted with *N*-methylhydroxylamine hydrochloride (**74**) in the presence of base $NaHCO_3$ under solvent-free ball milling conditions to furnish *N*-methyl-*C*-(2-furyl) nitrone (**75**) within 1 h. Subsequently, (**75**) was subjected to 1,3-dipolar cycloaddition reaction with alkenes (**78**) and electron-deficient alkynes (**76**) to synthesize isoxazolidine (**79**) and isoxazoline (**77**) under solvent-free mechanochemical conditions. The main advantages of the reaction were solvent-free process, short time for completion of the reaction, and an environment-friendly protocol. Furthermore, the synthesized compounds were investigated for anticancer activity study against six human cancer cell lines, including HCT-8 (colon), NALM-6 (leukemia), PC-3 (prostrate), PANC-1 (liver), MDA-MB-231 (breast), and NCI-H23 (lung) using mytomycin, adriamycin, and 5-FU as a reference. Among them, compound (**77c**) showed the best anticancer activity against the NCI-H23 cell line with an IC_{50} value of 16.

2.9 *S*-Aryl dithiocarbamates

Dithiocarbamates are of much importance in pharmaceuticals due to their strong metal-chelating properties and ability to inhibit enzymes like metalloproteinases. They exhibit a wide range of biological activities, including antimicrobial, anticancer, and antiviral effects. Their versatile chemical structure makes them useful for developing drugs targeting various therapeutic pathways. Some examples of biologically active drugs containing a dithiocarbamate group are given in Fig. 11 (**80–83**).[35]

In 2013, Ranu *et al.* synthesized a series of *S*-aryl dithiocarbamates by reacting carbon disulfide, aryl diazonium fluoroborate, and an amine under solvent-free ball milling conditions (Scheme 14).[19] At first, CS_2 and amine reacted in solvent-free ball milling at 1–5 °C for 2 min using basic alumina as a grinding auxiliary to furnish the intermediate (**83**). Later, intermediate (**83**) is subjected to reaction with aryl diazonium fluoroborate under ball milling conditions using basic alumina as the grinding auxiliary to

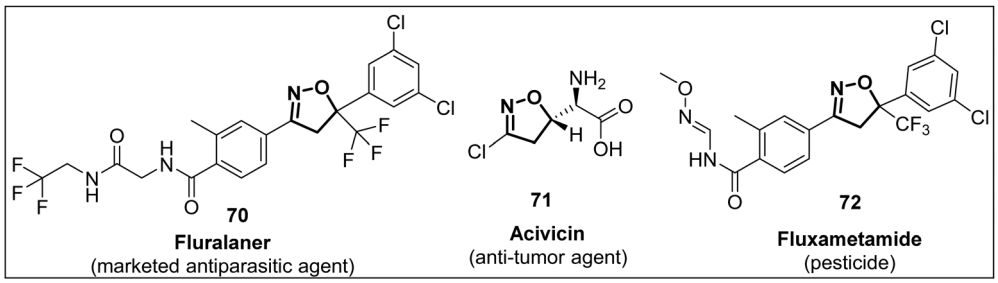
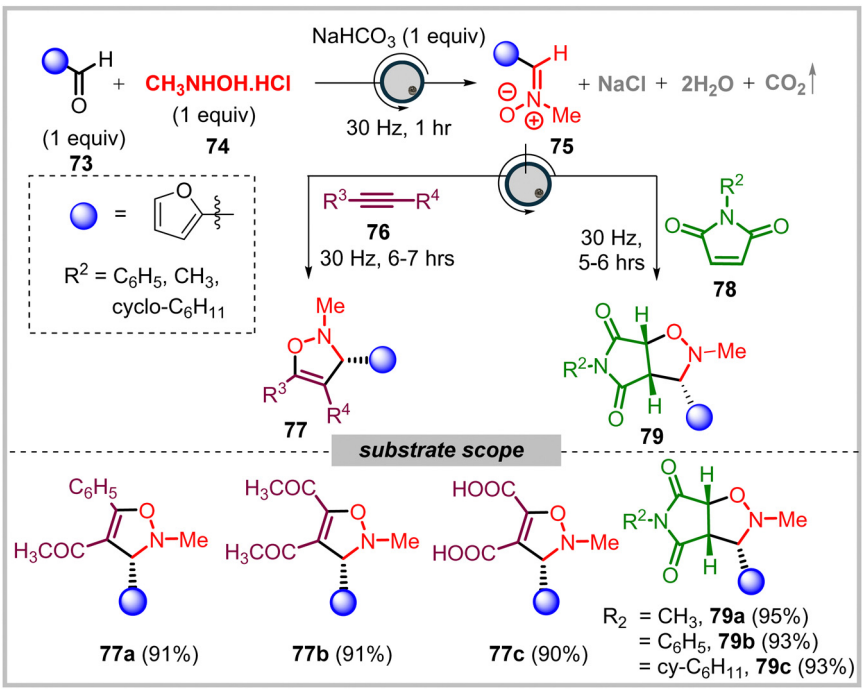


Fig. 10 Examples of biologically-active isoxazolidines.



Scheme 13 1,3-Dipolar cycloaddition of *N*-methyl-*C*-(2-furyl) nitrones under solvent-free ball milling.

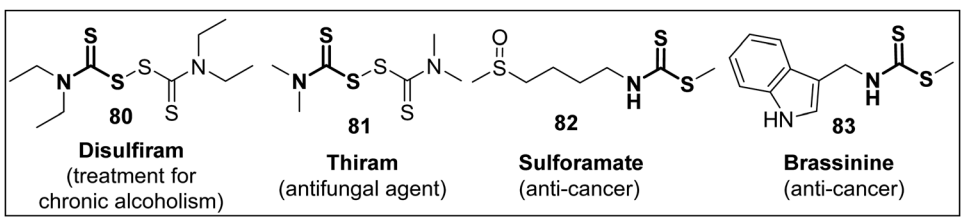
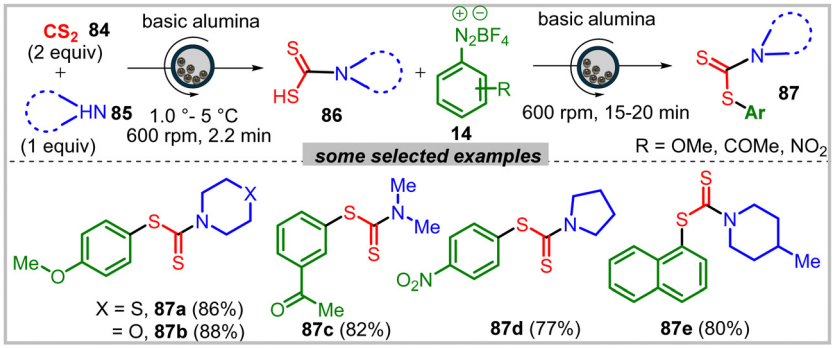


Fig. 11 Examples of pharmaceutically important dithiocarbamates.

afford the desired products (**87**) in good yields. In this case, acyclic amines like dimethyl amine and cyclic amines like thiomorpholine, morpholine, pyrrolidine, and piperidine reacted smoothly to furnish the desired product.

2.10 Imidazo[1,2-*a*]pyridines

Imidazo[1,2-*a*]pyridine is a valuable scaffold in pharmaceutical chemistry. The unique structure of imidazo[1,2-*a*]pyridines allows for strong interactions with biological targets, making them effective in drug design. Their versatility has led to the development of compounds with anticancer, antimicrobial, anti-inflammatory, and CNS-modulating properties, highlighting their importance in modern drug discovery. Some notable examples of imidazo[1,2-*a*]pyridine containing drugs are zolpidem (a widely prescribed sedative-hypnotic used for the short-term treatment of insomnia, **88**), alpidem (an anxiolytic drug used for



Scheme 14 Solvent-free synthesis of *S*-aryl dithiocarbamates by ball-milling.

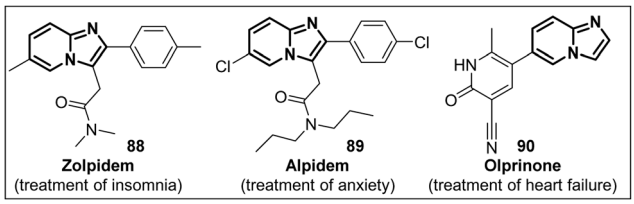


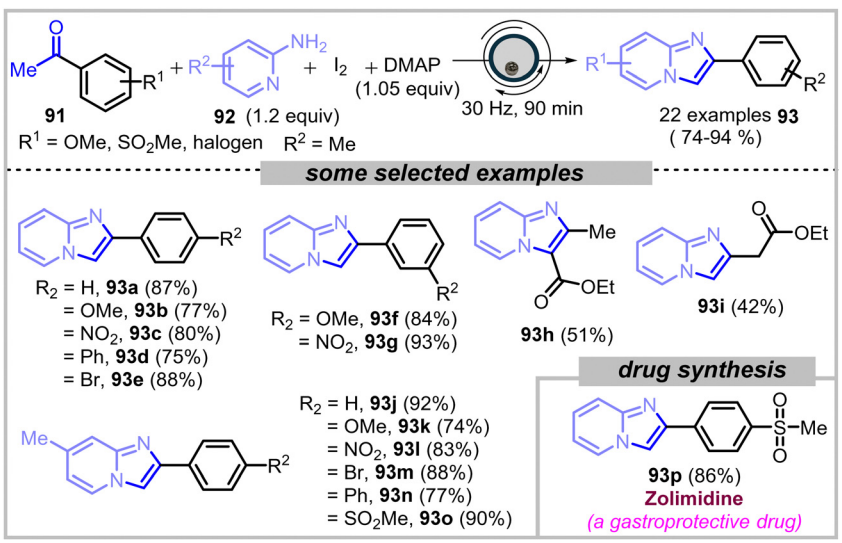
Fig. 12 Examples of pharmaceutically-active imidazo[1,2-*a*]pyridines.

the treatment of anxiety, **89**), and olprinone (a cardiotonic agent used for treating heart failure, **90**) (Fig. 12).[36]

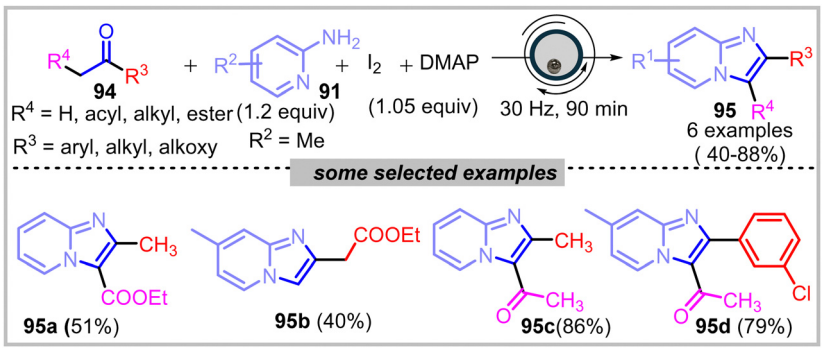
In 2016, Zhang *et al.* developed a solvent-free mechanochemical method to furnish pharmaceutically active imidazo[1,2-*a*]pyridines (Scheme 15).[37] In this I_2/DMAP promoted high-speed ball milling (HSBM) method, methyl ketones (**91**) or 1,3-dicarbonyl compounds (**94**) underwent cyclization with 2-aminopyridines in the absence of any solvent to synthesize imidazo[1,2-*a*]pyridines (**93** and **95**) within 90 min in excellent yields (Scheme 16). After completion of the reaction, the reaction mixture was washed with sodium thiosulphate solution, and the organic layer was extracted with ethyl acetate and subjected to column chromatography. Aromatic methyl ketones containing electron-withdrawing groups showcased higher yields than electron-donating groups containing aromatic methyl ketones. The reaction with 1,3-dicarbonyl compounds went smoothly following this method. As a practical application of this method, a pharmaceutically active marketed drug, zolimidine (**93p**) (a gastroprotective drug), was synthesized with 86% yield. The key advantages of the mechanochemical method were the broad substrate scope, high yields, good functional group tolerance, short reaction time, and no requirement for solvent and metal.

2.11 Isoxazoles and isoxazolines

Isoxazoles are of much significance in pharmaceutical chemistry due to their broad range of biological activities, including anticancer, anti-inflammatory, and antimicrobial properties. Their unique five-membered heterocyclic structure, containing both nitrogen and oxygen atoms, allows them to interact effectively with various biological targets. Isoxazole derivatives have been investigated for their potential as enzyme inhibitors and receptor modulators, making them promising candidates for drug development (Fig. 13) (**96–99**).



Scheme 15 Synthesis of 2-aryl-imidazo[1,2-*a*]pyridines from 2-aminopyridines and methyl ketones under HSBM.



Scheme 16 Synthesis of 2,3-disubstituted imidazo[1,2-*a*]pyridines from 2-aminopyridines and ketones under solvent-free HSBM.

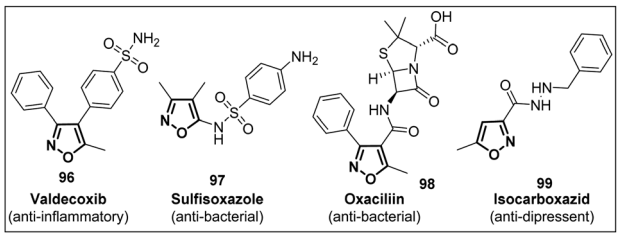
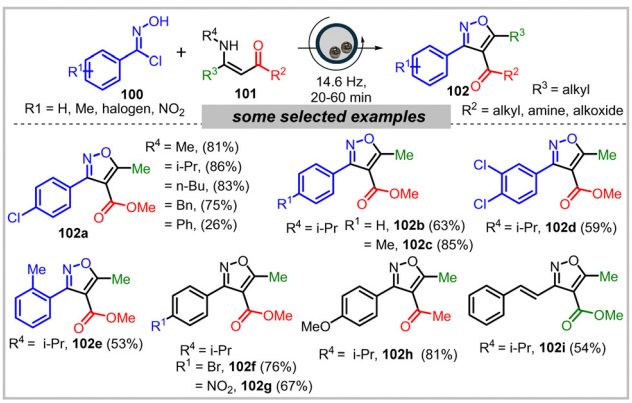
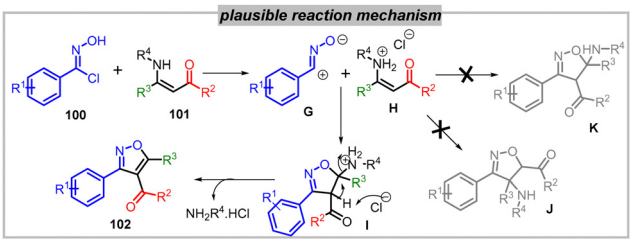


Fig. 13 Examples of isoxazole-based drug molecules.

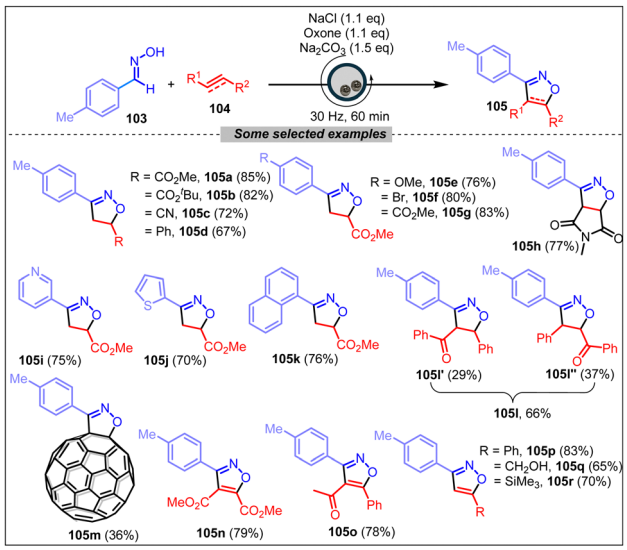


Scheme 17 Solvent-free synthesis of isoxazoles from *N*-hydroxybenzimidoyl chlorides and enamines under ball milling.

Additionally, their synthetic flexibility such as a weak N–O bond, favors the design of diverse bioactive molecules for



Scheme 18 Plausible reaction mechanism for the synthesis of isoxazoles under ball milling.



Scheme 19 Solvent-free synthesis of isoxazoles under ball milling.

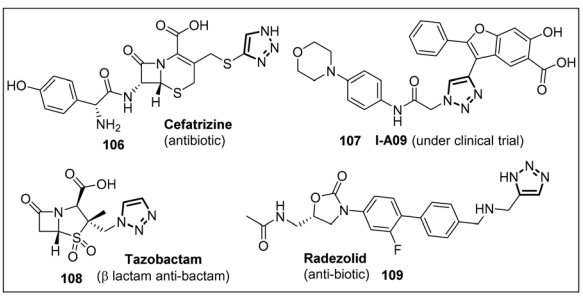
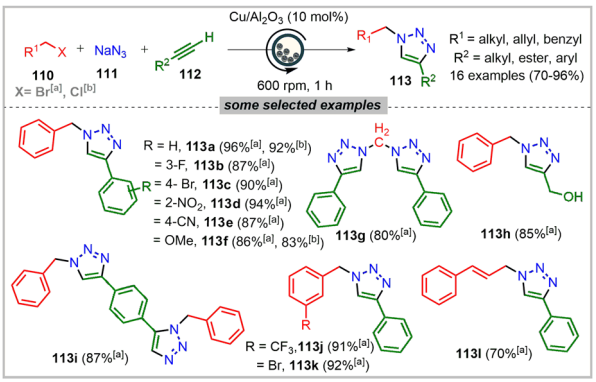


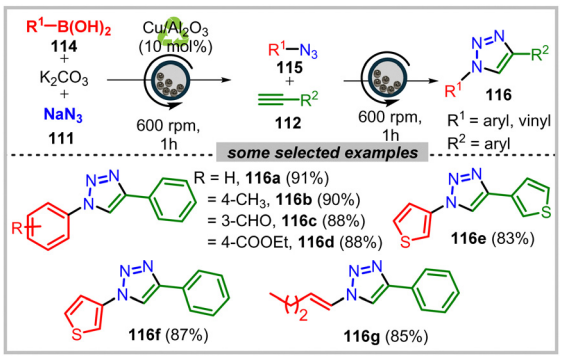
Fig. 14 Examples of drug molecules containing a 1,2,3-triazole unit.

therapeutic use. Some marketed drugs containing an isoxazole unit are valdecoxib (**96**) (anti-inflammatory drug), sulfisoxazole (**97**) (an antibacterial drug), oxacillin (**98**) (anti-bacterial drug), and isocarboxazid (**99**) (used in the treatment of depression) (Fig. 13).[38]

In 2018, Wang *et al.* developed a solvent-free, additive-free, highly regioselective mechanochemical, 1,3-dipolar cycloaddition



Scheme 20 Cu/Al_2O_3-catalysed, solvent-free, one-pot synthesis of 1,2,3-triazoles starting from alkyl halides, sodium azide, and alkynes under ball-milling.



Scheme 21 Cu/Al_2O_3-catalysed, solvent-free, one-pot synthesis of 1,2,3-triazoles starting from boronic acids, sodium azide, and alkynes under ball-milling.

reaction to furnish pharmaceutically active isoxazoles, including the analogues of oxacillin (**98**), a marketed antibacterial drug (Scheme 17).[39] *N*-Hydroxybenzimidoyl chlorides (**100**) reacted with enamino carbonyl compounds (**101**) under mechanochemical ball milling conditions, using stainless steel balls as a miller to furnish **102**. Electron-rich *N*-hydroxybenzimidoyl chlorides provided higher yields than electron-deficient *N*-hydroxybenzimidoyl chlorides. Initially, under the ball milling condition, *N*-hydroxybenzimidoyl chloride removed HCl and generated nitrile oxide **G**, which protonated the enamino carbonyl compound to generate **H**. Subsequently, **G** and **H** underwent regioselective 1,3 dipolar cycloaddition reaction to furnish intermediate **I** regioselectively (no trace of **J** and **K**). Finally, by the elimination of H_2O and ammonia from the intermediate **I**, the final product (**102**) was formed (Scheme 18). The key advantages of the reaction were milder reaction conditions, solvent-free operation, catalyst-free synthesis, higher yields, better selectivity, and broad substrate scope.

In 2022, the Wang group developed a mechanochemical, solvent-free synthetic strategy of [3+2] cyclo addition reaction (Scheme 19) under ball milling to access a wide variety of isoxazoles and isoxazolines.[40] In this reaction, alkenes or alkynes (**104**) reacted with nitrile oxide, generated *in situ* from

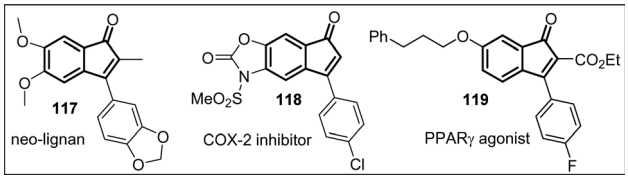
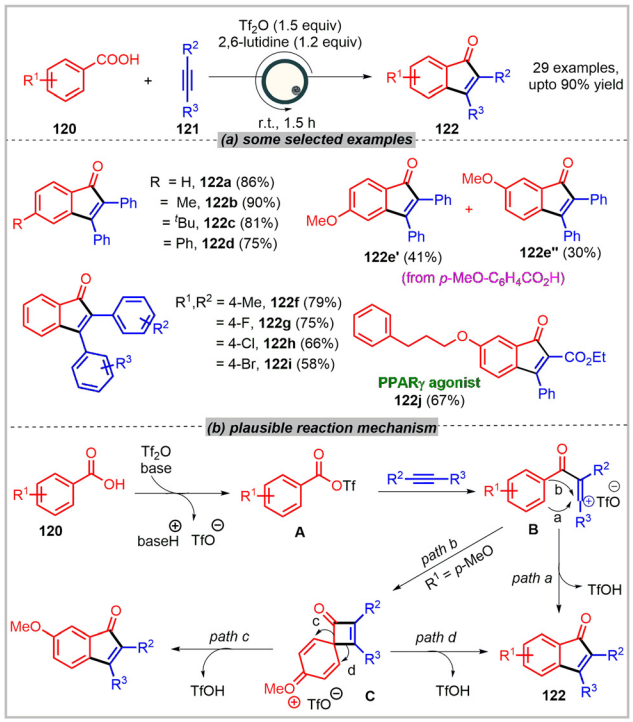


Fig. 15 Examples of pharmaceutically active molecules containing the indenone core.

aldoxime (**103**), in the presence of NaCl, oxone, and Na_2CO_3. The substrate scope of the reaction was very broad. The (hetero)aromatic (**105i** and **105j**) and aliphatic aldoximes, alkenes containing acrylate esters, acrylonitrile, *N*-methyl maleimide (**105h**), chalcone (**105l**), styrene, and fullerene (**105m**) participated in the reaction to afford a wide variety of isoxazolines in moderate to good yields (29–86%). Moreover, this ball milling strategy was compatible with various alkynes, including phenylacetylene (**105p**), and alkynes containing CH_2OH (**105q**), $SiMe_3$ (**105r**), $COCH_3$, and CO_2CH_3 functional groups to furnish the corresponding isoxazoles in moderate to good yields up to 83%. Ambient reaction conditions, remarkable functional group tolerance, and good yields of products made this solvent-free mechanochemical method have great potential in accessing pharmaceutically active isoxazolines.

2.12 1,2,3-Triazoles

1,2,3-Triazole is a crucial structural motif in biology due to its remarkable stability and bioisosteric properties, mimicking



Scheme 22 (a) Some selected examples for the solvent-free mechanochemical synthesis of pharmaceutically active indanones under ball milling, and (b) the plausible reaction mechanism.

peptide bonds and hydrogen bond interactions. It exhibits broad bioactivity, making it a key motif in drug design, including antimicrobial, antiviral, and anticancer agents (**106–109**) (Fig. 14). The ease of its synthesis *via* click chemistry enhances its use in bioconjugation, biomolecular probes and therapeutic agents. Additionally, triazole's resistance to metabolic degradation enhances its utility in developing stable, effective drugs.[41]

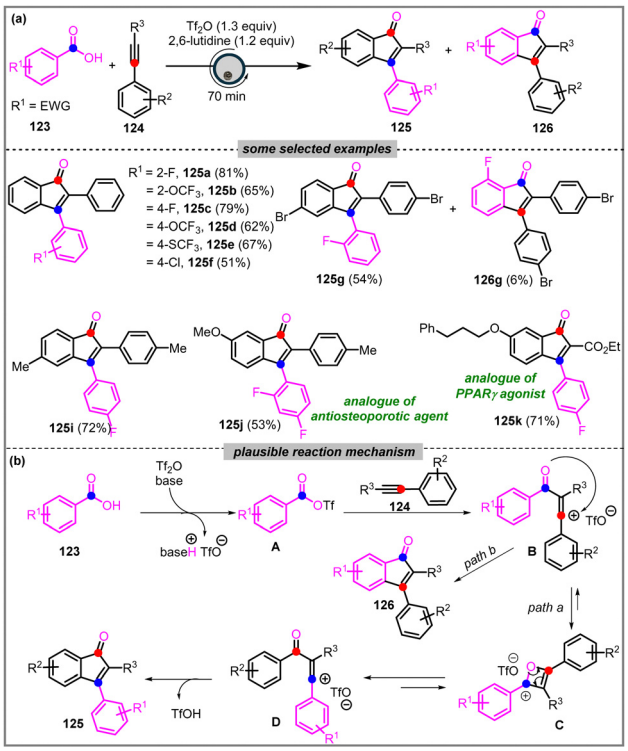
In 2013, Ranu *et al.* developed a solvent-free, cost-effective, and sustainable synthetic strategy of click-chemistry under ball milling for the chromatography-free synthesis of a pharmaceutically important class of molecules, *i.e.*, 1,2,3-triazoles (**113**), by a one-pot reaction of readily available alkynes, alkyl halides and sodium azide using a recyclable heterogeneous catalyst, Cu/Al_2O_3 (Scheme 20).[42] The substrate scope of the reaction was very broad. The aryl, heteroaryl, and alkyl-substituted alkynes and aliphatic halides, furnished a wide variety of disulfides in good yields (70–96%) within a short time (15–30 min). Notably, compounds (**113g**) and (**113i**) were synthesized following this method, starting from diiodomethane and 1,4-diethynylbenzene separately. The reaction was equally effective for one-pot synthesis starting from substituted boronic acid (**114**) to afford the corresponding products (Scheme 21). The catalyst, Cu/Al_2O_3, was reused for up to eight cycles and recovered after the reaction by simply washing it with ethanol, then acetone, and finally drying it in an oven. This solvent-free method is superior to other conventional chemical methods due to its excellent yield of products, no need of column chromatography for purification, use of no hazardous solvents, and very short reaction time. Moreover, the recovery and reusability of the catalyst made the mechanochemical process more relevant to use in pharmaceutical industries.

2.13 Indenones

Indenones are a class of compounds featuring a fused benzene and cyclopentenone structure, important for their versatile reactivity and biological activity. The electron-deficient nature of the cyclopentenone ring allows indenones to participate in diverse reactions, such as Michael additions, cycloadditions, and Diels–Alder reactions, enabling efficient formation of multiple bonds in a single step. They are often used in the synthesis of complex polycyclic frameworks and become essential intermediates in constructing molecular scaffolds for both natural products and synthetic compounds. Moreover, the core structure of indenones can be functionalized to enhance biological activity, offering potential leads in developing drugs for inflammatory, infectious, PPARγ agonist, malignant diseases, and antiosteoporotic agents. These properties make indenones important building blocks in medicinal chemistry, agrochemicals, and materials science (Fig. 15).[43]

In 2021, the Wang group developed a solvent-free, atom-economic, mechanochemical synthesis of pharmaceutically active indenones in the presence of aromatic carboxylic acid (**120**) and alkynes (**121**) using Tf_2O as an activating agent under ball milling conditions (Scheme 22).[44] At the initial step, the benzoyl triflate **A** was generated from benzoic acid (**120**) in the presence of a base and Tf_2O. Next, the *in situ* generated **A** reacted with the alkyne (**121**) to afford the vinyl cationic intermediate **B**. Finally, **B** underwent an intramolecular Friedel–Crafts acylation to afford the desired products (**122**) in moderate to good yields (41–90%). In the case of *p*-methoxy benzoic acid, vinyl cationic species **B** likely underwent the intramolecular 4-*exo-trig* dearomatization followed by spiro cyclization to furnish the spirocyclic cationic species **C**. Following this mechanochemical solvent-free method, a PPARγ agonist (**122**) was synthesized in one step. The mild reaction conditions, high efficiency, very low *E*-factor (2.8 kg waste per kg product formation) compared to other previously reported chemical methods, and practicability of scalability of the reaction made this a remarkable method for the synthesis of pharmaceutically active indenones.

The same group, in 2022, reported another metal- and solvent-free, mechanochemical synthesis of pharmaceutically active 3-arylindenones starting from an electron-withdrawing group containing benzoic acids (**123**) and alkynes (**124**) using Tf_2O as an activating reagent *via* an unprecedented aryl swapping under ball milling conditions (Scheme 23).[45] Like the previously discussed method, initially, the intermediate **A** is formed, which immediately reacted with the alkyne (**124**) to form the corresponding vinylic cation intermediate **B**; but as the benzoic acids (**123**) contain an electron-withdrawing group, intramolecular Friedel–Crafts acylation is quite unfavorable. Hence, **B** underwent an intramolecular 4-*endo-dig* cyclization to afford the intermediate **C**, followed by ring opening to realize



Scheme 23 (a) Solvent-free mechanochemical indanone synthesis *via* an unprecedented aryl migration under ball milling. (b) Plausible reaction mechanism for indanone synthesis.

the unprecedented aryl swapping, and thus afforded the highly reactive vinyl cationic species **D**. Finally, **D** underwent intramolecular Friedel–Crafts acylation with the more electron-rich aromatic ring to furnish the aryl migrated indenones (**125**) in moderate to good yields (54–81%). Following this metal-free and solvent-free method, an analogue of the anti-osteoporotic agent (**125j**) and a PPARγ agonist (**125k**) were synthesized with a good yield of 71% and 53%, respectively. The key advantages of the reaction were ambient reaction conditions, broad substrate scope, excellent regioselectivity, and feasibility of gram-scale synthesis.

3. Conclusions

Ball-milling has already emerged as a unique tool in carrying out useful and fundamental organic transformations under solvent-free sustainable conditions and it has been widely employed in recent times to access highly promising pharmaceutically important molecules, including drug molecules and APIs. The advantages associated with this technique over the conventional or traditional organic synthetic methods are (a) the non-requirement of hazardous and toxic solvents in the reaction, thus bringing a great extent of sustainability in organic synthesis, (b) the unique reactivity of substrates in certain cases, and (c) improved key green matrices such as atom-economy and *E*-factor and thus increasing the greenness of an organic reaction. Although several examples of the synthesis of pharmaceutically important classes of molecules, including drug molecules, are reported under solvent-free conditions by ball-milling, there are still some challenges associated with this area of research, such as (a) enabling those organic transformations where solvent plays some pivotal role in the reaction outcome, and (b) scalability of a reaction up to an industrial scale for the commercial production of drug-molecules or pharmaceuticals. Hence, future research should be more focused on these directions to overcome the limitations of solvent-free, ball-milling strategies in synthesizing more pharmaceutically active molecules, including life-saving drugs in a scalable and more sustainable manner.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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