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Green Synthesis: Mechanical Activation and Multicomponent Reactions
Síntesis verde: activación mecánica y reacciones multicomponentes

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ABSTRACT

The need for sustainable development in materials technology is becoming increasingly urgent due to the environmental impact largely generated by human activity. One promising way to mitigate this impact is through green syntheses that use alternative energy sources, such as mechanical milling. This method promotes chemical reactions through the mechanical treatment of materials. It is classified either as tribochemical or mechanochemical, depending on whether it acts on all states of aggregation or only on solids, respectively. These techniques offer sustainable options by minimizing both toxic byproducts and energy consumption, and promote waste prevention or reduction. Likewise, the multicomponent reactions, which allow the synthesis of complex molecules in a single step, are addressed. These reactions are especially valuable in pharmaceutical chemistry, as they facilitate the production of compounds with medicinal properties and contribute to greater structural diversity. This paper presents a review of the topics above, analyzing their definition, development, past, current, and future applications, as well as the advantages offered by the synergy between multicomponent reactions and mechanical milling.

Keywords: Green chemistry; Mechanochemical synthesis; Multicomponent reactions; Tribochemical processes; Solvent-free synthesis.

RESUMEN

La necesidad de un desarrollo sostenible en la tecnología de materiales es cada vez más urgente debido al impacto ambiental generado en gran medida por la actividad humana. Una forma prometedora de mitigar este impacto es mediante síntesis ecológicas que empleen fuentes de energía alternativas, como la molienda mecánica. Este método promueve reacciones químicas a través del tratamiento mecánico de los materiales, y se clasifica como triboquímica o mecanoquímica, según actúe en todos los estados de agregación o únicamente en sólidos, respectivamente. Estas técnicas ofrecen opciones sostenibles al minimizar tanto los subproductos tóxicos como el consumo energético, y fomentan la prevención o reducción de residuos. Asimismo, se abordan las reacciones multicomponente, que permiten la síntesis de moléculas complejas en un solo paso. Estas reacciones son especialmente valiosas en la química farmacéutica, ya que facilitan la obtención de compuestos con propiedades medicinales y contribuyen a una mayor diversidad estructural. Este artículo presenta una revisión de los temas mencionados, analizando su definición, desarrollo, aplicaciones pasadas, actuales y futuras, así como las ventajas que ofrece la sinergia entre las reacciones multicomponente y la molienda mecánica.

Palabras clave: Proceso triboquímico; Química Verde; Reacciones multicomponentes; Síntesis mecanoquímica; Síntesis sin disolvente.

INTRODUCTION

Scientific research reveals that humans have inhabited this planet for millions of years. The development of science and technology over time has generated significant environmental changes. As a result of the expansion and development of human activity, essential resources such as soil, air, and water have been consumed excessively, without considering future needs (Colborn *et al*. 1966; Pyykkönen & De Beukelaer, 2025).

Now, it is necessary to take advantage of the experience of past generations to define the planet´s future positively. Therefore, this generation must define a better future for life on the planet. The need for sustainable development is urgent due to the effects of pollution, caused mainly by human activity. Thus, it is essential to maintain or improve the quality of life by developing new materials for emerging technologies, aimed at a more environmentally friendly synthesis. For this reason, synthesis methods that use clean energy or "green synthesis" are gaining relevance. These methods harness the properties of matter to obtain the desired structures sustainably.

This article aims to critically analyze the intersection between mechanical activation—particularly tribochemistry—and multicomponent reactions (MCRs) as strategies aligned with the principles of green chemistry (Table 1).

MATERIALS AND METHODS

This review focuses on recent developments and relevant case studies, emphasizing both the practical applications and theoretical implications of these techniques in sustainable chemical synthesis. The methodology employed is that of a narrative review, integrating sources selected through thematic relevance, peer-reviewed credibility, and publication recency (primarily from 2010 onwards). Particular emphasis was placed on articles addressing experimental advances, mechanistic perspectives, and scalability in pharmaceutical and materials synthesis.

Non-peer-reviewed sources, theses, and academic repositories were excluded unless they provided foundational historical context or were cited in indexed journals.

RESULTS AND DISCUSSION

Research and Development

<u>Mechanochemistry (MCh).</u> This method uses a mechanochemical treatment that modifies the crystallinity of samples and increases their reactivity by exposing the reagents to solid-state mixing and grinding, which facilitates the reaction. Chemical reactions can be activated by alternative energy sources. Is believed to have its roots in prehistory, being applied to transform materials by friction, due to the lack of complete documentation (Takacs, 2013).

Table 1. The 12 principles of Green Chemistry. Based on the data presented in the Lancaster text (Lancaster, 2025).

#	Principle
1	Prevention - It is preferable to avoid the production of waste rather than to treat it once it has been formed.
2	Atom economy - Synthesis methods must maximize the incorporation of each material used in the process.
3	Safe chemical design - Chemicals should be designed to maintain efficacy while reducing toxicity.
4	Less hazardous synthesis - Synthesis methods should be designed to use and generate substances that have little or no toxicity, both for humans and the environment.
5	Safe solvents and auxiliary substances - Auxiliary materials (generally solvents, etc.) should be avoided if possible or replaced with substances that are nontoxic and have minimal environmental impact.
6	Design for energy efficiency - Energy requirements will be categorized by their environmental and economic impact, reducing them as much as possible. Methods should be carried out at ambient pressure and temperature.
7	Use of renewable raw materials - Raw materials should preferably be renewable rather than exhaustible, whenever technically and economically feasible.
8	Reduce derivatives - The formation of derivatives (protection/deprotection) should be avoided as much as possible.
9	Catalysis - Catalysts (as selective and reusable as possible) should be used instead of using reagents in stoichiometric quantities.
10	Design for degradation - Chemicals should be designed so that at the end of their function, they do not persist in the environment but are transformed into harmless degradation products.
11	Real-time analysis for pollution prevention - Analytical methodologies should be developed to allow real-time analysis and control of the process, before the formation of hazardous substances.
12	Inherently safe chemistry for accident prevention - Substances used in chemical processes should be selected to minimize the risk of chemical accidents, including fumes, explosions, and fires.

During this process, the reagent crystals are crushed and mixed, generating reactive conditions, involving a variety of reactions, including organic compounds for asymmetric synthesis (Figure 1), formation of materials, and drug production (Butyagin, 1971; Brindaban & Stolle, 2016; Wang, 2013).

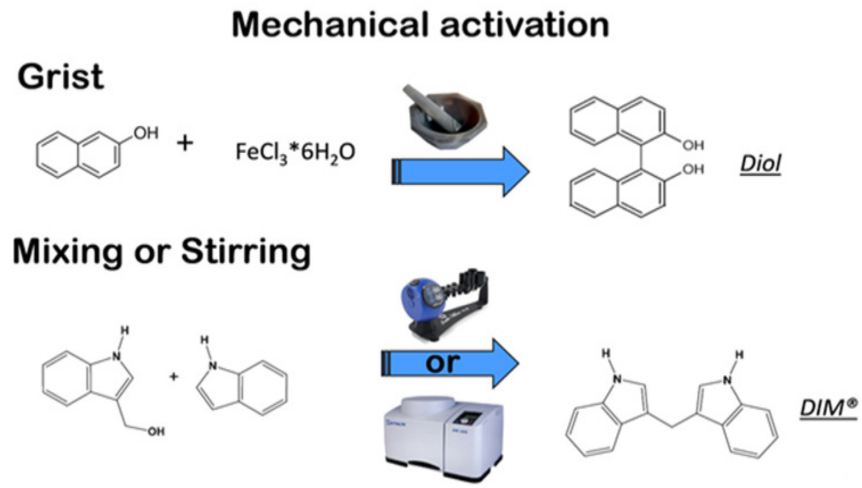

Figure 1. Production of [1,1'-binaphthalene]-2,2'-diol (diol) and 3,3-diindolylmethane (DIM®) by mechanochemical activation. For the Grist technique, the compounds involved are naphthol and iron trichloride hexahydrate. For the mixing or stirring technique, the reagents are indole-3-carbinol and indole. Image prepared based on World Wide Web pictures and relevant references on the subject (Wang, 2013; Fragoso-Medina *et al.* 2025).

While the scientific study of MCh began in the 16th century, it was not systematically investigated until the end of the 19th century by Walthère Victor Spring (Schwers, 1912) and Mathew Carey Lea it (Takacs, 2004). In 1919, Wilhelm Ostwald, a chemist, introduced the term "mechanochemistry", defining it as the study of the relationship between mechanical and chemical energies (Ostwald & Drucker, 1919; Boldyreva, 2013; Geciauskaitė *et al*. 2017).

However, MCh gained recognition in conferences and symposia from the 1960s onwards. At the beginning of the 21st century, James & Friščić (2013) documented applications of MCh in the research field. In 2013, the Journal of Chemical Society Reviews highlighted its relevance with a concise summary of its diverse scope (Boldyreva, 2013; Braga *et al.* 2013; Takacs *et al.* 2013).

The functionalities and applications of MCh are shown in some reviews on the subject, such as the review on the challenges in waste management and treatment (Guo *et al*. 2010) or the mechanochemical destruction of halogenated persistent organic pollutants (Cagnetta *et al.* 2016). Some researchers have also worked on the synthesis of materials by MCh, such as solid-phase milling reactions, which highlight the importance of the reactants, the substrate, each metallic element in the reaction, and their structure. This information is key to understanding and estimating the solid-state reactions of the starting materials by MCh (Zhang & Saito, 2012). Particularly, a method for the synthesis of layered double hydroxides (LDH) is shown, which is well known from the classical method. However, it faces some challenges, such as the treatment of aqueous waste, high energy consumption, complex operation, etc. Furthermore, it requires materials for practical application as a heterogeneous catalyst for mechanochemical synthesis (Ralphs *et al*. 2013).

It is believed that the MCh method may have the potential to effectively overcome these difficulties and, in addition, synthesize several new types of LDH with further development (Qu *et al.* 2016). It is worth mentioning that, in recent years, MCh has made significant progress, reflected in a large number of publications (Adams *et al*. 2015; Lavalle *et al*. 2016; Takacs, 2018). Despite its ecological potential and industrial applicability, this research is still at an emerging stage compared to other traditional green synthesis methods.

Between Friction, Synthesis, and Sustainability.

Tribochemistry (TCh). Derived from the Greek *tribos* (meaning "to rub"), is an environmentally friendly synthesis technique that performs chemical reactions initiated by frictional contact between surfaces. While both terms, MCh and TCh, refer to the study of the chemical behavior of materials caused by friction between substances, it is essential to delineate their conceptual boundaries. A deeper analysis of the reaction phenomenon revealed that the term MCh works specifically in solid-state reactions, while the term TCh encompasses a broader range of systems, including liquids and gases (Guo *et al.* 2010). Clarifying this distinction is crucial to avoiding ambiguities, especially when addressing mechanical activation phenomena in complex technological environments.

In early literature, one of the first documented TCh reactions is the formation of mercury from ground cinnabar (HgS) using a bronze mortar, as described by Theophrastus of Ephesus (371–286 BC) (Takacs, 2000). The term "tribochemistry" was coined by the British scientist Peter Jost in 1966 in his report on the state of friction in mechanical systems (Jost, 1966; Maini *et al.* 2021; Marchini *et al.* 2022; Ciulli, 2019). This seminal report prompted studies of friction at several research centers in the United Kingdom, the United States, and Germany, which in turn generated a growing interest in line with the rapid technological advancements of society at that time.

According to data presented at the inaugural conference of the Symposium on Metallurgy and Tribology and the Biennial Meeting of the Royal Spanish Society of Physics and Chemistry held in Burgos in 1980, the study objective of tribology is the behavior of tribosystems (i.e., systems that operate employing friction) both in machine parts and in everyday objects, such as toothbrushes with toothpaste or razors (Rabinowicz, 1995; Martínez, 2002; Santa Marín & Toro Betancur, 2015).

Currently, tribology contributes to the development of various areas, such as design, solid mechanics, fluid mechanics, thermodynamics, lubrication, metallurgy, nanotechnology, and manufacturing of new materials (Meng *et al.* 2020; Arunprasad & Atkins, 2025).

This research was conducted by the "Tribology and Surfaces Group" in Colombia, along with other teams specializing in "Advanced Materials and Energy." It is worth noting that, although the terms mechanochemistry (MCh) and tribochemistry (TCh) were used interchangeably at the 3rd Symposium on Triboemission and Tribochemistry held in Berlin, Germany, in 1971 (Bowden & Tabor, 2001), the Triboemission book was published later in 1987. This publication was developed by the Structural Unit of Tribology and Chemical Engineering of the Institute of Physical Chemistry "Rocasolano" (Arizmendi, 1987) to promote the concept of tribology as a multidisciplinary and multisectoral science and technology. It emphasized the integration of various fields, such as tribophysics and tribochemistry, highlighting their practical applications.

In order to correctly apply the revised terminology and take into account the information previously presented for MCh, and systems in general for TCh, a classification of mechanical activation based on the type of chemical system is proposed in Figure 2. This proposal arises from the information presented by Wang (2013).

Reactions are Activated by Mechanical Energy. Significant attention has been given to explain these reactions from the tribochemical process theoretical basis, presenting the facts considered most representative. However, theoretical development gained attention in the 20th century with models that proposed a hybrid static-dynamic framework to explain reactive zones under tribological sliding. This model offers a useful basis for distinguishing between regions where true tribochemical reactions occur and those with merely mechanical interaction.

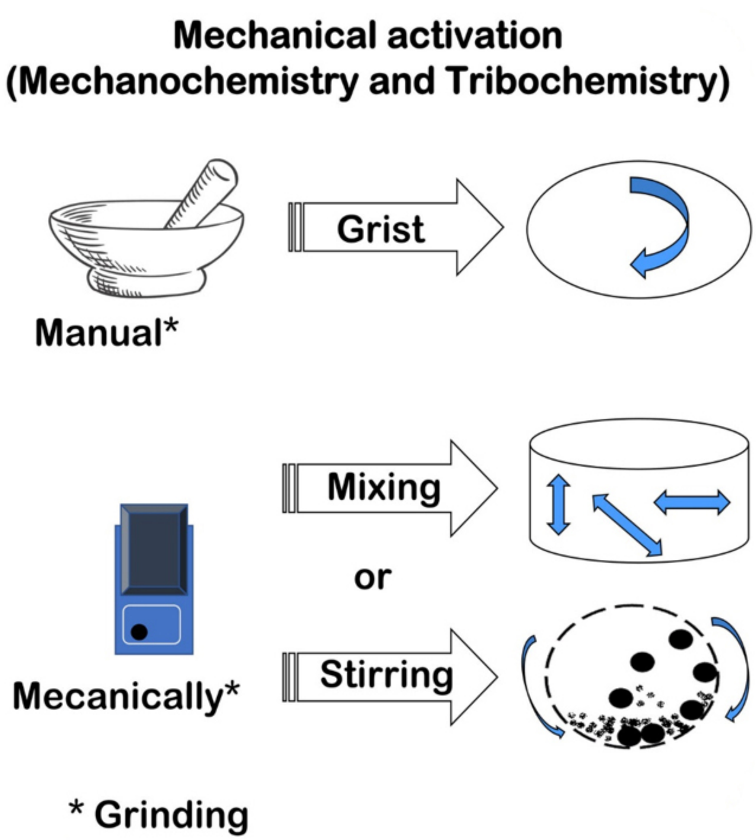

Figure 2. Proposed classification of mechanical activation. Images obtained from the World Wide Web and Microsoft Office LTSC Professional 2025.

In this proposal, the dynamic tribophysical processes that occur during friction were described as a function of the sliding position (Nakayama & Martin, 2006).

According to this model, the tribochemical process occurs in three regions:

1) Contact area: The mechanical energy applied during grinding breaks the crystalline structure, generating new surfaces.

2) Near the contact area: Considered the main region of tribomicroplasma formation, hot spots and triboemission, through which reactions occur.

3) Outside the contact area: Only static reactions occur in this area, without dynamic physical processes that generate significant tribochemical reactions. It includes worn surfaces far from the tribosystem´s contact zone.

The classification proposed in this model is based on the main function of the components in each region where the reaction occurs (Do & Friščić, 2017; Li & Szlufarska, 2021). Despite these theoretical models, a mechanistic understanding of TCh processes remains limited. Key parameters, such as energy thresholds for bond activation and associated electronic mechanisms, are not yet fully elucidated. Most studies focus on metallic or engineering materials, overlooking TCh's potential in organic or pharmaceutical synthesis, where reactive interfaces are more sensitive and structurally complex (Julien *et al.* 2017; Hwang *et al.* 2022). Experimentally, several critical variables impacting TCh reaction outcomes have been identified, including rotation frequency, milling media mass and composition, and ambient conditions (Rybkin, 2017; Spikes, 2018). Yet, reproducibility remains a significant challenge due to the intrinsic heterogeneity of tribological contacts. This methodological variability limits TCh's establishment as a predictive tool in synthetic chemistry.

The models proposed by Bowden, and refined by Nakayama & Martin, offer a useful basis for explaining the active zones where tribochemical reactions occur, but their experimental validation requires more sophisticated and specific techniques (Nakayama & Martin, 2006). New proposals for in situ monitoring using X-rays or surface spectroscopy represent key advances in overcoming the lack of dynamic information during the reaction process. From the experimental point of view, variables such as grinding frequency, size and composition of balls, and environmental humidity are determinants of yields and reproducibility (Pagola, 2023; Hergesell *et al.* 2024). The literature reviewed indicates that these conditions have been poorly systematized, which represents a gap for developing reliable methodologies.

Furthermore, the scarce application of TCh in the synthesis of organic or inorganic compounds (Ashok *et al*. 2025) stands out, where it could have a great impact, especially in multicomponent reactions aimed at bioactive compounds. It is proposed to explore this research line as an opportunity to diversify sustainable chemistry. The development of mechanical activation has advanced considerably thanks to the renewed interest in it as an environmentally friendly synthetic route. As a result, various applications that have inspired innovative methodologies to investigate reactions have emerged. These include, monitoring the progress of milling reactions by synchrotron powder X-ray diffraction (Friščić *et al*. 2013), or the development of a new in situ ball mill configuration, whose particular geometry allows a more detailed analysis of mechanochemical processes, expanding the scope of this technique (Ban *et al*. 2017).

Mechanical activation offers a wide range of opportunities in the development of different types of chemical synthesis reactions (Hernández & Boll 2017), such as active ingredient synthesis for pharmaceuticals (Tan *et al*. 2016). In particular, due to their nature, aliphatic or aromatic aldehydes are used as substrates, since the derived products usually exhibit biological activity. This sets the scene of TCh in the pharmaceutical industry, which has suitable manufacturing equipment for these purposes (Ruiz-Navas *et al*. 2000; Fuentes *et al*. 2014).

Regarding the tribochemistry phenomenon, there are a lot of publications discussing the various factors that influence the reactions carried out using this method. Some of these factors include the rotation frequency, which is decisive in modifying the yields and reaction times, and the control of the quantity, size, and composition of the balls. These variables mainly influence the kinetic energy of the reaction. Since its application reduces the need for manual procedures, this process provides several advantages, such as being safe, reduced by products, low production costs, etc. (Smalø *et al*. 2014; Quapp *et al*. 2017; Wan *et al*. 2017).

Critical Trend Analysis and Research Gaps in Tribochemistry

Tribochemistry is evolving from a primarily descriptive discipline to a more rational and design-oriented field. Current trends emphasize the development of in situ characterization tools, such as X-ray diffraction coupled to ball milling (Ban *et al.* 2017) or spectroscopic techniques synchronized with frictional events. These innovations allow real-time monitoring of reactive intermediates, expanding the possibilities for kinetic control of tribochemical processes.

Nonetheless, significant gaps remain in current research:

- Lack of advanced computational modeling tailored to TCh, integrating localized pressure effects and surface dynamics.

- Limited application in fine organic chemistry, particularly for the selective synthesis of bioactive compounds.

- Need for a standardized taxonomy to facilitate comparison of results across laboratories and process scales (bench to pilot plant).

- Underrepresentation in Latin American literature, despite potential in green mining, recycling, and sustainable manufacturing.

While TCh holds promise for reshaping industrial processes, its consolidation as a central methodology demands interdisciplinary efforts to close these gaps.

Discussion: Implications, Limitations, and Future Directions

Although less widely known than other green synthetic routes, tribochemical reactions offer compelling advantages: solvent elimination, lower waste generation, mild operational conditions, and improved handling safety. However, several key challenges persist:

- Methodological limitations, including a lack of standardized experimental protocols.

- Insufficient mechanistic insight, hindering controlled process scaling.

- Absence of regulatory frameworks for assessing environmental and safety impacts.

From a sustainability perspective, integrating TCh into pharmaceutical or advanced materials synthesis will require rethinking reactor design and fostering collaboration among chemistry, engineering, and materials science.

Proposed Future Research Directions (Do & Friščić, 2017; Julien *et al.* 2017; Li & Szlufarska, 2021; Hwang *et al.* 2022; Hergesell *et al.* 2024).

- Development of molecular simulations incorporating tribological dynamics.

- Application of tribochemistry in the synthesis of chiral and pharmacologically active compounds.

- Preparation of green-by-design protocols embedding TCh from the conceptual stage.

- Comparative evaluation of ecological footprints relative to other mechanochemical techniques.

Multicomponent Reactions (MCRs).

MCRs have several advantages, such as minimal component manipulation and a practical addition process. A multicomponent reaction (MCR) is defined as a process in which three or more components are combined in a single reaction and single vessel to produce a final product without the need for further additions, isolations, or manipulations (except for the final product isolation). In this type of reaction, practically all or most of the substrate and reagent atoms contribute to the target molecule.

Assigning an acronym to an MCR in a scientific protocol correctly identifies the multicomponent reaction being referred to and how many components are involved. It must be highlighted that the most common way of referring to them is in the English language.

The acronym for MCRs is typically formed using the initial of the researcher who first described the reaction, followed by a hyphen (-) and the letters "CR" to indicate that it is a multicomponent reaction. Some well-known MCR acronyms include U-4CR (Hooshmand & Zhang, 2023), H-4CR (Leonardi *et al.* 2018), SGT-4CR, B-3CR (Oliver, 2000) and Kamal-Qureshi (Fragoso-Medina *et al.* 2025), which involve either three or four components (Fragoso-Medina *et al.* 2025). Including the specific acronym of an MCR in a scientific protocol helps to identify the type of reaction and the number of components involved. Furthermore, there are cases where MCRs involve five components to efficiently produce complex molecules. Examples include the U-5CR reaction, which yields highly complex and diverse peptidyl ethers or structural analogues; the B-5CR reaction, producing functionalized dihydropyridines with significant structural diversity; and the Isatin–Amine–Malonate–Aldehyde–Isonitrile reaction, which generates bioactive oxyindole spironate compounds or polycyclic derivatives with high structural complexity and pharmacological potential (Elinson *et al.* 2016; Sun *et al.* 2017; Zhao & Zhao, 2023).

Advantages of MCRs

These types of reactions offer various advantages compared to classical or "traditional" synthesis (Salehi & Guo, 2004; Kashani *et al.* 2015; Sahoo *et al.* 2015; Jiang *et al.* 2019); some of which are highlighted below:

- They are distinguished by their elegant and simple execution.

- They exhibit high atom economy, since most or all of the reactant atoms contribute to the final product.

- The final product is obtained through a multi-step sequence with the formation of a single bond in each step.

- They allow for a higher yield of the final product.

- They facilitate quick and easy access to organic compounds with diverse structures in a simple procedure.

Given the above, the use of MCRs is currently being promoted to approach an ideal synthesis (Allen & Shonnard, 2002; Calvo-Flores, 2009; Li *et al.* 2009).

Some synthesis examples of medically applicable materials by combining ball mills and MCR.

It is worth mentioning that the quality of human life has improved since the beginning of the 20th century due to the systematic use of drugs.

Initially, their application was not scientific, but over time, it has evolved into a highly specialized development. However, this improvement in the quality of life may have had a negative environmental impact. It should be noted that the pharmaceutical industry is one of the biggest contributors to the generation of toxic waste, water pollution, and CO_2 emissions during its production processes, in addition to being an industry with enormous income. This makes it necessary to actively engage in the prevention of these effects. Currently, the "usual" pharmaceutical design process consists of several stages, in which only a few molecules are selected for further development, based on their properties (Marovac, 2001).

Some compounds with potential pharmaceutical applications, due to their diverse properties and biological effects, are obtained through multicomponent reactions (MCRs). Examples include Světlík-Goljer-Tureček, Hantzsch, and Biginelli compounds, which exhibit antioxidant, anti-arteriosclerotic, bronchodilator, antitumor, antidiabetic, neuroprotective, vasodilator, and calcium channel modulator activities, among others. Kamal-Qureshi type compounds, particularly DIM®, have been used to treat several cancer types and other diseases (Figure 3).

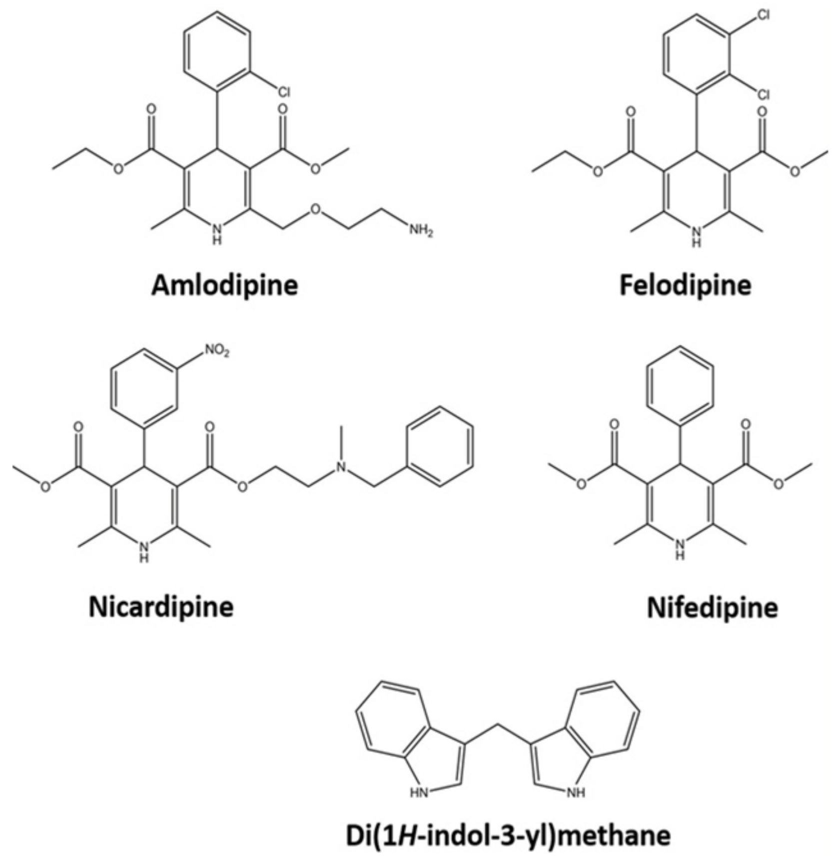

Figure 3. Commercial drugs and their structure that can be obtained from multicomponent reactions. Image made by Luna-Mora, R.A.

The increasing adoption of MCRs along with mechanical activation techniques, such as tribochemistry, marks a significant step toward environmentally responsible chemical processes. These methods not only reduce solvent use and toxic waste, but also enable the design of efficient one-pot syntheses of pharmacologically relevant compounds. However, widespread implementation requires overcoming technical challenges in scalability, reaction control, and real-time monitoring.

Therefore, future research should focus on standardizing protocols for tribochemical MCRs, particularly in pharmaceutical applications, and on developing in situ analytical tools that facilitate a deeper mechanistic understanding. The concepts explored in this review—especially tribochemistry—are still evolving in terms of their terminology and scientific adoption. For clarity and consistency in future discourse, it is recommended to reserve the term "tribochemistry" for transformations induced by frictional interactions in one or more phases, as opposed to conventional solid-state mechanochemistry.

Overall, integrating tribochemistry into multicomponent reaction frameworks holds promise not only for sustainable synthesis, but also for advancing our theoretical and practical grasp of energy-activated processes. This positions the field as a frontier in green chemistry, where innovation aligns with environmental stewardship.

Additionally, tribochemistry is understood as the science of chemical reactions induced by friction at any stage, and represents a little explored field, but with great potential within green chemistry. Despite notable advances in instrumentation and theoretical understanding, important limitations persist in experimental standardization, predicting mechanisms, and their implementation in the synthesis of high-added-value organic compounds. As a summary, Table 2 below shows information in a more user-friendly manner.

Table 2. Relevance of cited references in the context of medical material synthesis via MCRs and tribochemistry.

Brief Description / Relevance in Context	Reference
Provides a global framework for understanding the environmental impact of industries, including the pharmaceutical sector, and the need for sustainable policies. Links economic development to environmental mitigation	(Davies & Warren, 2015)
Comprehensive review of natural products as primary sources of new drugs, supporting the rationale for using MCRs to generate bioactive derivatives	(Newman & Cragg. 2016)
Describes the conventional drug design process and its stages, serving as a baseline to propose greener approaches such as tribochemistry combined with MCRs	(Marovac, 2001)
Reviews recent progress in Hantzsch synthesis using nanocatalysts, illustrating MCR applications to pharmacologically active compounds	(Lavanya *et al.* 2024)
Highlights green synthetic strategies for dihydropyridines via sustainable MCRs, directly linked to tribochemical methods	(Sonali Anantha *et al.* 2021)
Presents examples of indole derivatives with anticancer potential, obtainable via MCRs	(Debnath *et al.* 2025)
Focuses on the versatility of indoles in medicinal chemistry, emphasizing their compatibility with multicomponent synthesis	(Babalola *et al.* 2025)
Describes synthesis and biological evaluation of functionalized indole derivatives, suitable for high-value pharmaceutical applications via MCRs	(Abdelhalim *et al.* 2025)
Discusses the molecular mechanisms of indole-3-carbinol and derivatives, illustrating MCR-accessible bioactive scaffolds	(Aggarwal & Ichikawa, 2005)
Explores the therapeutic potential of natural supplements (e.g., DIM®) in cancer treatment, linked to derivatives obtainable via MCRs	(Arellano Ortiz *et al.* 2013)
Demonstrates a rapid, efficient synthesis of bis(indolyl)methanes, exemplifying catalysis in multicomponent reactions	(Bandgar & Shaikh, 2003).
Reports green synthesis of DIM® and derivatives, illustrating sustainable approaches in MCR chemistry	(Pal *et al.* 2007)

CONCLUSIONS

Environmental impact and sustainable future: Both tribochemistry and mechanosynthesis offer clear advantages in reducing the ecological footprint of chemical synthesis by eliminating solvents, minimizing waste, and decreasing energy consumption compared to traditional routes. These attributes position these technologies as key tools for advancing more sustainable chemistry.

Current Advantages and Challenges: Tribochemistry enables the synthesis of organic compounds, pharmacologically active molecules, and high-value materials under mild conditions. However, it still faces inherent limitations, including process standardization, in-depth mechanistic understanding, and interlaboratory reproducibility.

Interdisciplinarity and Technological Advances: Progress in integrating in situ techniques to monitor tribochemical reactions, along with the emergence of molecular simulations incorporating tribological dynamics, represents crucial steps towards transforming tribochemistry from an empirically driven approach into a predictive and rational science.

Future outlook: See Meng *et al.* (2020), Pagola (2023), Arunprasad & Atkins (2025), and Hamza *et al.* (2025).

- Standardization of experimental protocols.
- Expansion of tribochemistry: applications beyond metallic materials towards fine and bioorganic synthesis, where multicomponent reactions and mechanical activation can have a greater impact.
- Interdisciplinary collaboration between chemistry, engineering, and materials science may establish tribochemistry as a strategic pillar of sustainable chemistry in the twenty-first century, supporting both product innovation and environmental protection.

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