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Microwave *vs* Ultrasound *vs* Mechanochemical Activation in Heterocycle Synthesis: A Narrative Review

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ABSTRACT

Heterocycles are among the most important structural units in medicines, and their synthesis is increasingly judged by speed, selectivity, energy use and waste as well as yield. Microwave (MW), ultrasonic (US) and mechanochemical activation are the three best-known alternatives to conventional heating, but they act through different physical mechanisms and are usually described in separate literatures. This narrative review compares them for heterocycle synthesis. Microwave heating couples an oscillating electric field to polar molecules and ions, so its performance depends on the dielectric properties of the medium, and in the cases tested the benefits are explained by rapid, controlled heating rather than special field effects. Ultrasound works through acoustic cavitation, which creates transient hot spots, shock waves and intense mixing, and is particularly relevant to heterogeneous systems. Mechanochemistry replaces the solvent with mechanical energy delivered in ball mills or extruders, can change reaction time and selectivity, and has been taken to continuous, solvent-free manufacture of drug substances. Few studies compare all three methods directly. In the available comparisons on quinazolinone scaffolds, mechanochemical activation gave the highest yield ranges and microwave activation the lowest, but these results are specific to one family of compounds, to deep eutectic solvents, and to the conditions used. We present a mechanistic comparison, representative heterocycle syntheses, a practical selection guide and a checklist for fair benchmarking. No method is universally superior; the choice depends on phase behaviour, solubility, thermal stability, scale and sustainability goals.

Key words: Heterocycles; microwave-assisted synthesis; ultrasound; sonochemistry; mechanochemistry; ball milling; green chemistry.

1. Introduction

Heterocyclic rings are central to medicinal chemistry. An analysis of U.S. FDA-approved drugs found that 59% of unique small-molecule drugs contained a nitrogen heterocycle [1], and a later update showed that 82% of the 321 new small-molecule drugs approved between 2013 and 2023 contained at least one [2]. Efficient and sustainable routes to heterocycles therefore matter well beyond academic synthesis.

Conventional heating in refluxing solvent is slow, energy-inefficient and solvent-intensive. Sustainability is commonly measured by the E factor (mass of waste per mass of product), whose ideal value is zero and which for pharmaceutical manufacture lies between 25 and above 100 [3]. Three non-classical techniques have been promoted to improve on conventional heating: microwave irradiation, ultrasound and mechanochemistry. Each has its own reviews, enthusiasts and claims, yet they are rarely compared under matched conditions. This article reviews how each works, what it has delivered for heterocycle synthesis, where direct comparisons exist, and how a chemist might choose between them.

2. How the Three Methods Deliver Energy

The three techniques differ in the form of energy and in where it is deposited (Figure 1 and Table 1). Microwave irradiation heats a medium through its interaction with an oscillating electromagnetic field [4]. Ultrasound transfers acoustic energy into a liquid, where cavitation concentrates it in microscopic hot spots [5,6]. Mechanochemistry delivers mechanical energy directly to solid reactants through impact and shear [7,8].

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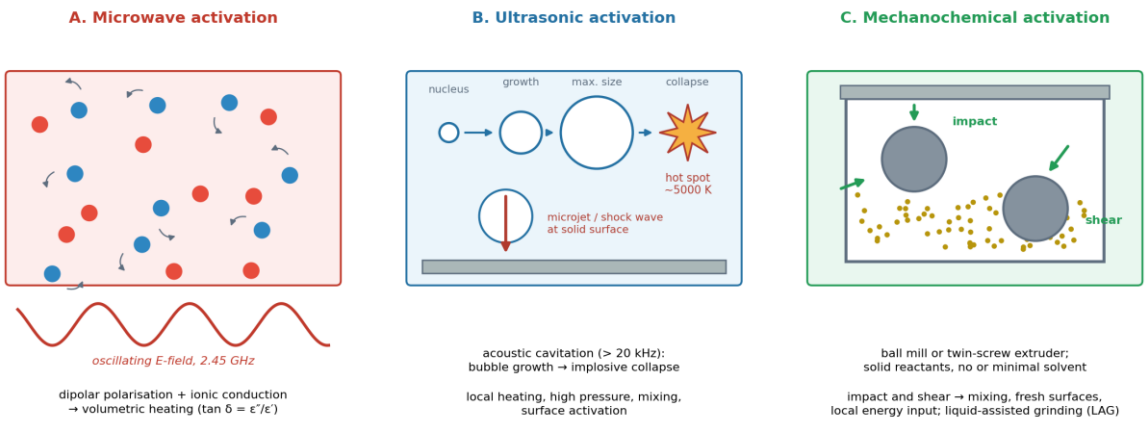

Figure 1. Mechanisms of the three activation methods: (A). Microwave heating through dipolar polarisation and ionic conduction [4]; (B). Acoustic cavitation: bubble growth, implosive collapse and hot-spot formation, with microjets at solid surfaces [5,6]; (C). Mechanochemical activation by impact and shear in a mill [7,8].

Table 1. Comparison of microwave, ultrasonic and mechanochemical activation.

Feature	Microwave	Ultrasound	Mechanochemistry
Energy input	Electromagnetic field (typically 2.45 GHz) couples with polar molecules and ions [4,9]	Acoustic waves (> 20 kHz) create cavitation bubbles whose collapse forms hot spots [5,6]	Mechanical impact and shear in ball mills or extruders [7,8]
Medium required	Microwave-absorbing medium, or a passive heating element [9,10]	A liquid, including liquid–solid slurries [5]	None or minimal liquid (liquid-assisted grinding) [7]
Main mode of action	Rapid volumetric heating; in tested cases, enhancements were explained by thermal effects [11–13]	Local extreme conditions, mixing and surface activation; mechanical effects in heterogeneous reactions [5,14]	Mixing, mass transfer and fresh surfaces; can alter reaction time and selectivity [8,15]
Scale-up route	Larger batches or translation to continuous flow [16]	Large-scale cavitational applications reviewed [14]	Twin-screw extrusion for continuous synthesis [17]
Monitoring and control	On-line temperature, pressure and power control in dedicated reactors [12]	Interpretation of cavitational effects and the role of the acoustic field has pitfalls [6]	In situ synchrotron X-ray diffraction has been used [15]
Key limitation	Sealed-vessel batch scale; yields fell and by-products formed at 180 °C and 20 bar in one test reaction [12]	Mechanistic interpretation can be difficult [6]	Mechanisms remain elusive; mixing and mass transfer influence outcomes [8]

3. Microwave Activation

3.1 Principles

The use of microwave ovens to accelerate organic reactions was first reported in 1986 [18,19]. Today dedicated reactors with temperature and pressure control have replaced domestic ovens, and the technique is credited with cutting reaction times from days and hours to minutes and seconds [4]. Heating arises mainly from dipolar polarisation and ionic conduction, and a solvent's ability to convert microwave energy into heat is expressed by its loss tangent, $\tan \delta = \varepsilon''/\varepsilon'$ [9,20]. Solvents are grouped as high ($\tan \delta > 0.5$), medium (0.1–0.5) or low (< 0.1) absorbers [9]. Ethylene glycol, ethanol and DMSO heat very rapidly, whereas toluene, hexane and dichloromethane barely respond (Figure 2). Low-absorbing mixtures can be heated by adding a passive heating element or a polar co-solvent [10].

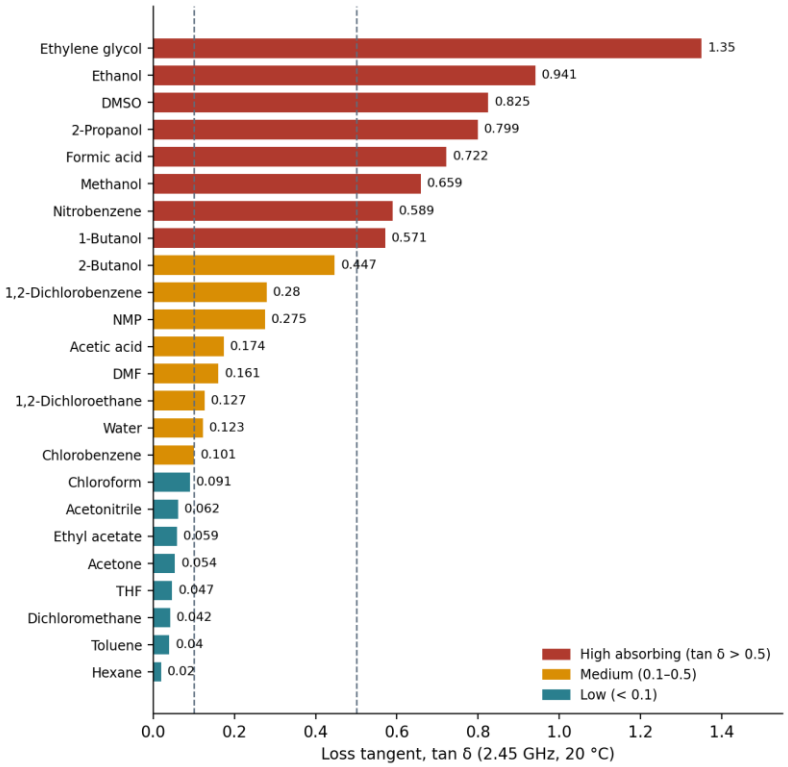

Figure 2. Loss tangents (tan δ) of common solvents at 2.45 GHz and 20 °C, plotted from the values tabulated in refs [4,9]. Dashed lines mark the conventional boundaries between high, medium and low microwave absorbers.

3.2 Thermal versus non-thermal effects

Whether microwaves do anything beyond heating has been debated for decades [11]. The microwave-mediated Biginelli reaction is an instructive case. When it was re-examined in a reactor with on-line temperature, pressure and power control, reactions in ethanol at atmospheric pressure showed no rate or yield increase relative to conventional heating at the same temperature. Increases seen on superheating were attributed to a thermal (kinetic) effect, and enhancements in open vessels were attributed to solvent-free conditions rather than to microwaves themselves. Under sealed conditions at 180 °C and 20 bar, yields fell and by-products formed [12]. Experiments in silicon carbide vials, which are heated by microwaves but shield the contents from the field, gave almost identical results to ordinary vials in 18 reactions for which microwave enhancements had been claimed [13]. The practical lesson is that the main benefit of microwave heating is rapid, uniform and controllable heating to temperatures above the solvent boiling point, and that fair comparisons must be made at identical, measured temperatures.

3.3 Heterocycle synthesis and scale-up

Microwave-assisted routes to heterocycles are extensively documented, and monographs devote a full chapter to heterocycle synthesis [10]. The Biginelli dihydropyrimidinone synthesis (Figure 3A) remains the standard example [12]. Work from our laboratory gave novel pyrano[2,3-d]pyrimidine-2,4,7-triones in 90–97% yield by a K_2CO_3-catalysed (10 mol%) three-component reaction of an aromatic aldehyde, Meldrum's acid and barbituric acid under microwave irradiation [21]. Other microwave work from our laboratory includes the Amberlite IR-120-catalysed rapid synthesis of 2-aryl-benzimidazoles [22] and the molecular iodine-catalysed, solvent-free one-pot synthesis of 5-arylmethylidene-2-phenyloxazol-4-ones (azalactones) [23]. The principal limitation is scale: batch microwave reactors are small, and one response has been to translate optimised high-temperature batch conditions into continuous-flow reactors, the "microwave-to-flow" approach [16].

4. Ultrasonic Activation

4.1 Principles

Ultrasound (> 20 kHz) acts through cavitation, in which voids form when a liquid undergoes a sufficient pressure drop [6]. Acoustic cavitation is the formation, growth and implosive collapse of bubbles in a

liquid, and the collapse creates hot spots with temperatures of the order of 5000 K, pressures of hundreds of atmospheres and lifetimes of microseconds [5,24]. In liquid–solid slurries, shock waves produce high-velocity interparticle collisions and clean, highly reactive metal surfaces [5]. In organic synthesis, ultrasound can therefore enhance mechanical effects in heterogeneous processes and can also induce new reactivity [14]. The bulk liquid remains much cooler than the hot spots, which is why many ultrasonic reactions are run near ambient temperature.

4.2 Heterocycle synthesis and limitations

Ultrasound-assisted one-pot multicomponent reactions have been widely applied to biologically relevant heterocycles [25]. Its advantages lie in simple equipment, mild bulk temperature and suitability for heterogeneous mixtures, including those containing metals or solid catalysts [5,14]. The main difficulty is interpretation: the literature contains considerable misunderstanding about cavitational effects and the actual role of the acoustic field [6]. Results depend on solvent, vessel and acoustic parameters that are often under-reported, and scale-up requires specialised reactor design [14].

4.3 Ultrasound-assisted syntheses from the author's laboratory

Our laboratory at Bangalore University has contributed several ultrasound-assisted multicomponent syntheses of heterocycles, mostly in aqueous media. These include the glycine-catalysed synthesis of 2-amino-4H-chromenes in water under sonic conditions [26], the iodine-catalysed synthesis of novel 2-amino-3-cyano-4H-pyrans [27], and the meglumine-catalysed one-pot three-component synthesis of novel pyridylpiperazines in water [28]. In a further example, polysubstituted 1,4-dihydropyridines were obtained by a copper(I) iodide-catalysed one-pot four-component cyclocondensation of aromatic aldehydes, malononitrile, acetylenedicarboxylates and arylamines in aqueous medium under ultrasound, with shorter reaction time, excellent yields, milder conditions and product isolation by precipitation reported relative to earlier methods [29]. What these studies share is water or an aqueous medium, simple or no catalysts, multicomponent assembly and easy isolation, which is the heterogeneous, mild-temperature setting in which ultrasound is most naturally applied (Section 4.1). More recently, new hydrazino-thiazole (isatin–thiazole) derivatives were prepared catalyst-free in water under ultrasonication and evaluated for antioxidant activity [30]. A related guanidine·HCl-catalysed one-pot three-component route to spiro chromeno-pyrimidine and spiro pyrano-pyrimidine-indolinone derivatives was also developed, with anticancer evaluation against CA-46 Burkitt's lymphoma cells [31]. Matched comparisons of these scaffolds against microwave and mechanochemical activation would be a natural extension of this work.

5. Mechanochemical Activation

5.1 Principles

Mechanochemical synthesis means reactions conducted by grinding solid reactants together with no or minimal solvent [7]. Solvent-free reactions between solids were demonstrated by Toda in the 1980s and 1990s, although some involved grinding followed by heating and may have proceeded through molten phases [7]. Modern work uses ball mills and, increasingly, extruders; the mixer mill suits gram-scale laboratory work, and extruders offer a route to larger scales [8]. Small amounts of liquid can be added in liquid-assisted grinding, and the milling variables (frequency, jar and ball material, filling) all influence the outcome [8,32].

The mechanisms are still not well understood [8]. Real-time synchrotron X-ray diffraction of milling reactions showed that mechanochemistry is highly dynamic, with rates comparable to or greater than those in solution [15]. Comparisons with solution reactions suggest that grinding can shorten reaction times, change selectivity and, in some cases, give products not accessible in solution [8].

5.2 Heterocycles, drug substances and scale-up

Ball milling has been used to prepare pyrroles, indoles, pyrazoles, imidazoles and benzimidazoles, and has been described as economical and eco-friendly but still under-represented in the knowledge of organic chemists [33]. A notable example is the preparation of the hydantoin-based drugs nitrofurantoin and dantrolene by stoichiometric ball milling of 1-aminohydantoin hydrochloride with aldehydes, which gave the more stable E-isomers selectively, in high yield, without solvent, base or post-reaction work-up (Figure 3C) [32]. The same hydrazone drugs have since been made by continuous twin-screw extrusion with minimal or no solvent [17], and a cradle-to-gate life-cycle assessment for nitrofurantoin

indicated cost, sustainability and operational advantages for extrusion over the conventional solvent-based batch route [34]. Mechanochemistry, including reactive extrusion, was included in IUPAC's first list of emerging technologies in chemistry [35].

Our own mechanochemical work includes the *p*-toluenesulfonic acid-catalysed synthesis of bis(indolyl)methanes by the grindstone method [36] and a solvent-free mechanochemical synthesis of 3-amino-2,4-dicarbonitrile-5-methylbiphenyls [37]. The latter builds a carbocyclic rather than heterocyclic ring, but it illustrates the same solvent-free, grinding-based multicomponent strategy.

6. Representative Heterocycle Syntheses

Figure 3 shows three reactions that illustrate the three methods: the Biginelli synthesis of dihydropyrimidinones under microwave heating [12], the condensation of 3-amino-2-methylquinazolin-4(3H)-one with aldehydes under all three activation modes [38], and the mechanochemical synthesis of nitrofurantoin [32]. Table 2 summarises these and related studies.

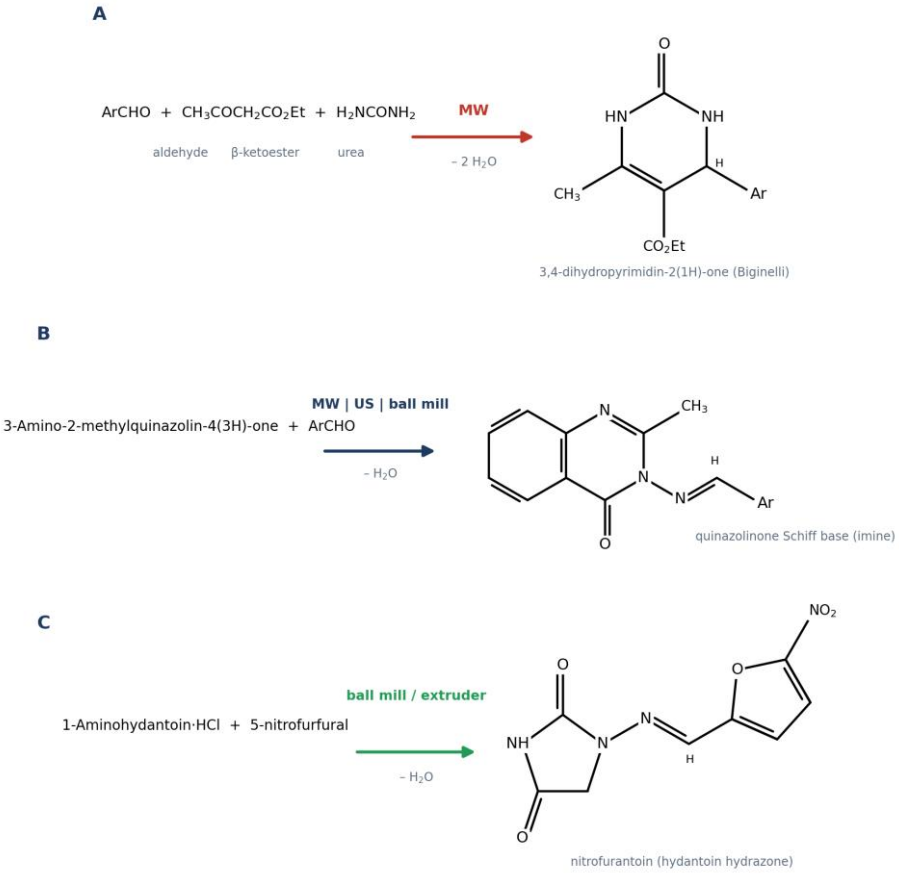

Figure 3. Representative heterocycle syntheses: (A). Biginelli condensation under microwave heating [12]; (B). Condensation of 3-amino-2-methylquinazolin-4(3*H*)-one with benzaldehydes under microwave, ultrasonic and mechanochemical conditions [38]; (C). Mechanochemical synthesis of nitrofurantoin [17,32]. Ar = aryl.

Table 2. Representative studies of heterocycle synthesis under microwave, ultrasonic and mechanochemical activation.

Activation	Heterocycle or reaction	What the study showed	Ref.
Microwave	Biginelli dihydropyrimidinones	No rate or yield increase in ethanol at identical temperature; enhancements explained by superheating or solvent-free conditions; yields fell at 180 °C and 20 bar	[12]
Microwave	Heterocycles (general)	Heterocycle syntheses under microwave heating compiled in a dedicated chapter of a standard monograph	[10]
Ultrasound	One-pot multicomponent syntheses of biologically relevant heterocycles	Extensively reviewed; ultrasound applied to a wide range of heterocyclic targets	[25]
Microwave	2-Aryl-benzimidazoles; 5-arylmethylidene-2-phenyloxazol-4-ones (azalactones) (author's laboratory)	Amberlite IR-120-catalysed microwave synthesis of benzimidazoles; iodine-catalysed, solvent-free microwave synthesis of azalactones	[22,23]
Microwave	Pyrano[2,3-d]pyrimidine-2,4,7-triones (author's laboratory)	Three-component reaction of aldehyde, Meldrum's acid and barbituric acid with 10 mol% K_2CO_3 under microwave irradiation; yields 90–97%	[21]
Ultrasound	2-Amino-4H-chromenes, 2-amino-3-cyano-4H-pyrans, 1,4-dihydropyridines, pyridylpiperazines, hydrazino-thiazoles (author's laboratory)	Multicomponent syntheses in water or aqueous media under sonication; dihydropyridines by CuI catalysis with shorter time, excellent yields and isolation by precipitation; hydrazino-thiazoles catalyst-free in water	[26–30]
Grinding	Bis(indolyl)methanes; 3-amino-2,4-dicarbonitrile-5-methylbiphenyls (author's laboratory)	p-TSA-catalysed grindstone synthesis of bis(indolyl)methanes; solvent-free mechanochemical synthesis of a biphenyl carbonitrile (carbocycle)	[36,37]
Ball milling	Pyrroles, indoles, pyrazoles, imidazoles, benzimidazoles	Reviewed; ball milling described as economical and eco-friendly but under-represented	[33]
Ball milling	Hydantoin hydrazones (nitrofurantoin, dantrolene)	Solvent-, base- and waste-free milling; E-isomers selectively, high yield, no work-up	[32]
Extrusion	Nitrofurantoin, dantrolene	Continuous synthesis with minimal or no solvent; no post-synthetic work-up	[17]
MW, US and mechanochemical	Quinazolinone Schiff bases (27 compounds)	Yields 11–90% across the three methods; ethanol as solvent; no further purification	[38]
MW, US and stirring	2-Mercaptoquinazolin-4(3H)-ones in 20 choline chloride DESs (54 compounds)	ChCl:urea most effective; stirring and ultrasound 16–76% versus microwave 13–49%	[39]

7. What Direct Comparisons Show

Direct, matched comparisons are rare and most come from one group working on quinazolinones. In the first, 27 Schiff bases of 3-amino-2-methylquinazolin-4(3H)-one were prepared by microwave, ultrasonic and mechanochemical methods in ethanol, with yields of 11–90% and no further purification needed [38]. In the second, 54 substituted 2-mercaptoquinazolin-4(3H)-ones were made in choline chloride-based deep eutectic solvents (DESs); choline chloride:urea was the best solvent, stirring and ultrasonication gave higher yields (16–76%) than microwave heating (13–49%) [39]. The same group's doctoral thesis reports four-way comparisons for two compound classes, including mechanochemical synthesis, summarised in Figure 4 [40]. In both classes, mechanochemical yield ranges were the highest and microwave ranges the lowest.

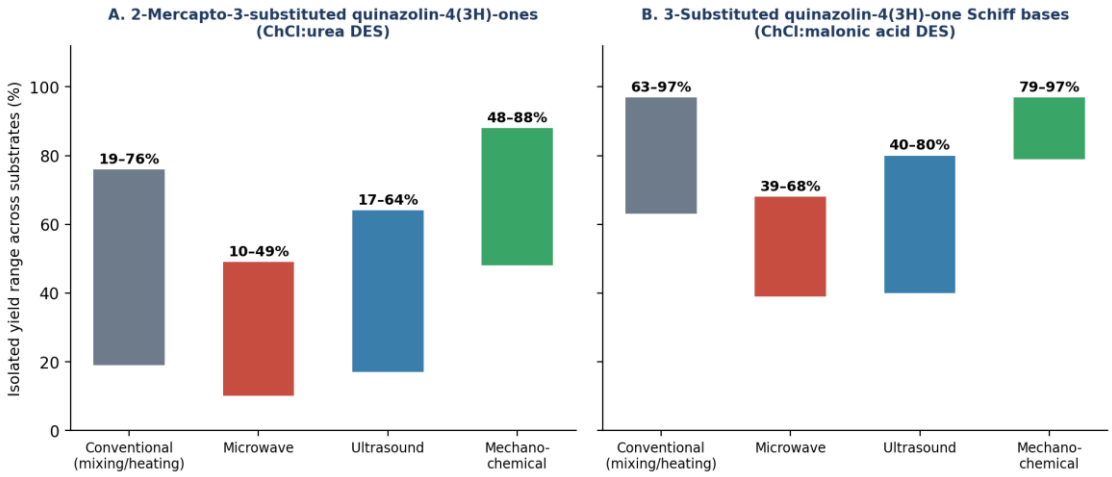

Figure 4. Isolated-yield ranges across substrates for two quinazolinone families prepared in deep eutectic solvents by conventional mixing or heating, microwave, ultrasonic and mechanochemical methods: (A). 2-Mercapto-3-substituted quinazolin-4(3*H*)-ones in Choline Chloride:urea. (B). 3-Substituted quinazolin-4(3*H*)-one Schiff bases in Choline Chloride:malonic acid. Ranges as reported in ref [40]; related published data in refs [38,39].

These data must be interpreted cautiously. They come from a single research group, two scaffolds and deep eutectic media; the bars show ranges over different substrates rather than paired comparisons; and they do not report time, energy or scale. Microwave heating under the conditions used was not optimised in the sense of a sealed-vessel, temperature-controlled study, so the results should not be read as showing that microwave synthesis is inherently less effective. They do show that, for solid-forming condensations in viscous media, mechanical activation can match or outperform both radiation-based methods, and that ultrasound can be competitive with conventional heating. Whether these trends hold for other heterocycles, for homogeneous reactions in microwave-absorbing solvents, or for larger scales is unknown.

8. Sustainability and Scale

Mass-based metrics such as the E factor and process mass intensity are useful but need to be supplemented by life-cycle assessment and economic metrics [3]. On these measures, solvent-free mechanochemistry is attractive because the solvent usually dominates the waste of conventional batch synthesis, and green metrics were calculated for the milling synthesis of nitrofurantoin and dantrolene [32]. The life-cycle assessment of nitrofurantoin supports an environmental advantage for extrusion [34]. Microwave and ultrasonic methods still use solvents, so their sustainability case rests on shorter times, lower bulk temperatures or milder conditions, and should be quantified by measuring energy consumption and waste rather than assumed. Continuous processing is the common route to scale for all three: flow reactors for microwave chemistry [16], large-scale cavitational reactors [14], and twin-screw extruders for mechanochemistry [17].

9. Choosing a Method

No method is best for every heterocycle. Figure 5 offers a practical decision aid based on the properties reviewed above: microwave heating suits reactions in polar, absorbing media or those limited by temperature, particularly when sealed-vessel superheating is useful [4,12]; ultrasound suits heterogeneous mixtures and reactions that benefit from surface activation at modest bulk temperature [5,14]; and mechanochemistry suits poorly soluble solids, solvent-free routes and processes aimed at continuous manufacture [7,17]. Because the available head-to-head data are limited [38,39], the most reliable approach is to test all feasible methods on a model reaction under matched, reported conditions.

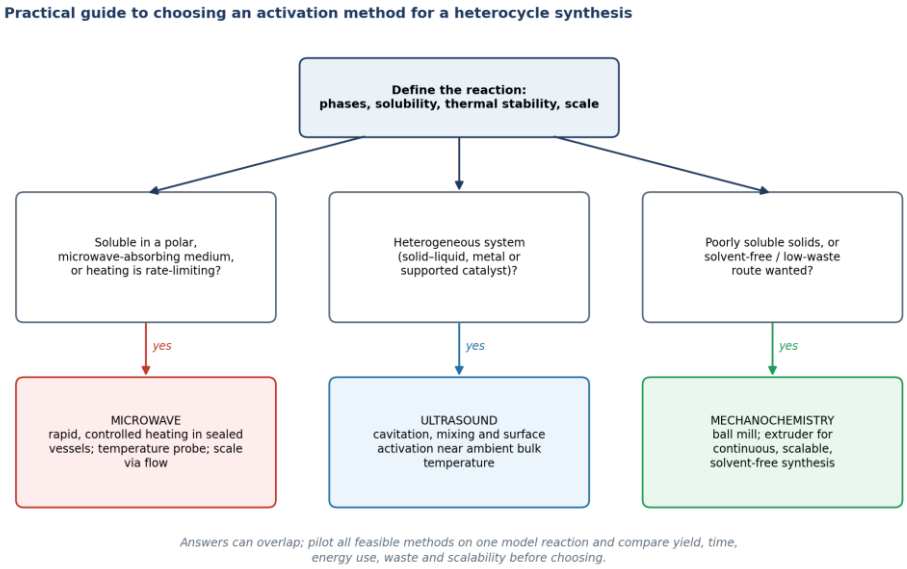

Figure 5. Decision guide for selecting an activation method. The guide is the author's synthesis of the properties summarised in Table 1 and refs [4,5,7,12,17].

10. Challenges and Future Directions

The main obstacle to rational choice is the lack of standardised, matched comparisons. Temperature must be measured internally in microwave work, because apparent enhancements disappear when conventional controls are run at identical temperatures [12,13]. Ultrasonic studies must report acoustic parameters so that results can be reproduced [6]. Mechanochemical studies must report the mill, jar material and milling conditions, since these were varied in comparative experiments on nitrofurantoin [32]. Mechanistic understanding is weakest for mechanochemistry, where in situ monitoring is beginning to provide data [8,15]. Table 3 proposes a minimum reporting set for comparative studies.

Table 3. Suggested minimum information to report in comparative studies of activation methods (author's recommendation, drawing on refs [3,6,12,32]).

Item	Recommended reporting
All methods	Identical scale, concentration and stoichiometry; conventional control at the same measured temperature; time to completion; isolated yield; solvent and work-up mass; energy consumption; E factor [3]
Microwave	Reactor type, vessel (sealed or open), power, internal temperature and pressure and how they were measured [12]
Ultrasound	Frequency, probe or bath, applied power or intensity, duty cycle, bulk temperature and cooling, vessel geometry [6]
Mechanochemistry	Mill or extruder type, frequency or screw speed, jar and ball material, ball number and mass, filling, any liquid additive [32]

Future work should also extend ultrasound-assisted multicomponent syntheses developed in water, such as those from our laboratory [28,29], to matched microwave and mechanochemical comparisons. It should also test combinations, apply the same heterocyclic targets across all three methods at several scales, and extend the comparison from yield to energy and life-cycle impact.

11. Conclusions

Microwave, ultrasonic and mechanochemical activation offer genuine but different advantages for heterocycle synthesis. Microwave heating provides rapid, controllable heating whose benefits, in the cases tested, are thermal. Ultrasound provides localised cavitational energy and suits heterogeneous systems. Mechanochemistry removes the solvent, can change reaction outcomes and has reached continuous, scalable production of drug substances. Direct comparisons are few, and the available data from quinazolinone syntheses favour mechanochemistry for those substrates without establishing general superiority. Chemists should choose according to the physical properties of the reaction, verify claims against conventional controls at identical temperature, and report conditions in enough detail for fair comparison.

Declaration, Conflict of Interest, Funding and Other Statements

Use of Artificial Intelligence (AI): Artificial intelligence (AI) tools were used in preparing this narrative review to assist with organizing the subject matter, developing the manuscript structure, refining scientific explanations, and improving the clarity and presentation of the text. These tools supported the discussion of microwave-assisted, ultrasound-assisted, and mechanochemical approaches to heterocycle synthesis. The author is responsible for critically reviewing and verifying the scientific content, checking the accuracy of the cited literature and bibliographic information, evaluating the interpretation of reported findings, and ensuring the scientific integrity of the final manuscript. The author retains full responsibility for the content and conclusions presented in the review.

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Data Availability: No new datasets were generated or analyzed during the preparation of this review. The information discussed is based on previously published literature and other sources cited in the manuscript.

Author Note

The manuscript entitled *"Microwave vs Ultrasound vs Mechanochemical Activation in Heterocycle Synthesis: A Narrative Review"* provides a comparative overview of three approaches to reaction activation in modern synthetic chemistry. It discusses their underlying principles, applications in heterocycle synthesis, potential advantages, practical limitations, and relevance to efficient and more sustainable chemical synthesis.

The review examines how microwave irradiation, ultrasound-assisted reactions and mechanochemical activation may influence reaction time, energy requirements, reaction efficiency, selectivity, product yield, and solvent consumption. Particular attention is given to the synthesis of heterocyclic compounds of importance in medicinal chemistry, pharmaceutical research and other areas of chemical research. The comparative discussion aims to help researchers understand the suitability of each technique for different reaction systems and experimental conditions.

Artificial intelligence tools were used to assist in preparing and organizing the review and improving the presentation of the scientific discussion.

This article is intended for academic and educational purposes and is based on previously published research. It does not report new experimental results.

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