Review

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Posted Date: 28 October 2025

doi: 10.20944/preprints202510.2097.v1

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 doi:10.20944/preprints202510.2097.v1

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Green Synthetic Strategies in the Design of Bioactive Heterocycles for Neglected Tropical Disease Drug Discovery

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Abstract

Neglected tropical diseases (NTDs) remain a significant global health burden, exacerbated by the ongoing climate emergency, which alters disease distribution and increases vulnerability in affected populations. The urgent need for novel therapeutics demands innovative approaches in drug discovery, with heterocyclic compounds serving as versatile scaffolds due to their diverse electronic and structural properties that enable potent biological activity. This review highlights the integration of green chemistry principles in the synthesis of bioactive heterocyclic scaffolds for NTD drug development. Key sustainable methodologies are discussed, including microwave-assisted solvent-free and green-solvent reactions, ultrasound-assisted synthesis, mechanochemical one-pot multistep strategies, and the use of ionic liquids and deep eutectic solvents as environmentally benign catalysts and reaction media. By focusing on these approaches, the review emphasizes how green synthetic strategies can accelerate the development of pharmacologically relevant heterocycles while minimizing environmental impact, resource consumption, and hazardous waste generation.

Keywords: neglected tropical diseases; heterocyclic compounds; green chemistry; sustainable synthesis

1. Introduction

The accelerating climate crisis has emerged as one of the greatest challenges to global health in the 21st century, exacerbating pre-existing social and economic inequalities while reshaping the epidemiological landscape of infectious diseases [1–3]. Extreme weather events, rising global temperatures, and shifting rainfall patterns have expanded the geographical range of vectors and pathogens, directly influencing the transmission dynamics of Neglected Tropical Diseases (NTDs) [2,4,5]. Affecting more than one billion people worldwide, primarily in low- and middle-income countries, NTDs Symbolize the intersection between environmental vulnerability and health inequity [1,2].

Given this scenario, there is an urgent need for novel chemotherapeutic agents capable of addressing the persistent burden of NTDs under changing climatic conditions. Heterocyclic compounds represent a cornerstone in the discovery and optimization of bioactive molecules, functioning as versatile drug-like scaffolds with diverse electronic and structural properties that facilitate molecular recognition and biological activity [6,7]. Their synthetic flexibility, capacity for electronic modulation, and prevalence in natural products make them indispensable tools in the design of new therapeutics targeting parasitic and viral pathogens.

This review highlights recent advances in the green synthesis of bioactive heterocyclic scaffolds with potential activity against NTDs, emphasizing accessible and low-cost synthetic methodologies suitable for the early stages of the hit-to-lead process. By integrating efficiency, sustainability, and

 doi:10.20944/preprints202510.2097.v1

affordability, these approaches support innovative yet practical pathways for drug discovery in resource-limited settings most affected by NTDs.

2. Neglected Tropical Diseases and the Climate Emergency

Neglected Tropical Diseases (NTDs) represent a group of diseases that primarily affect low-resource countries in the Global South, mainly in tropical and subtropical areas of the globe, though some have a much wider geographic distribution. Collectively, these diseases affect over one billion people worldwide, incurring devastating health, economic, and social consequences [1]. Furthermore, the same communities disproportionately burdened by NTDs are also disproportionately affected by climate change [2].

While numerous biological, environmental, ecological, and socioeconomic factors influence the incidence and emergence of NTDs, it is possible to distill this complexity into a basic concept: the proliferation of these diseases depends on the interaction between pathogens and human hosts, specifically, the virulence of the former and the susceptibility of the latter [3].

Climate factors such as temperature and precipitation, exacerbated by global warming, generate heatwaves and floods that modify the habitats and reproductive cycles of NTD vectors. These changes contribute to population displacement and infrastructural damage, exposing communities to higher risks of infection through increased contact with contaminated water and closer proximity to wildlife. Such conditions facilitate transmission and emergence of vector-borne diseases [2,4].

Additionally, climate change creates new breeding grounds for vectors, accelerates their life cycles, extends transmission seasons, and enhances pathogen virulence. Simultaneously, populations affected by extreme climate events show reduced resilience to infections, as thermal stress and rapid temperature shifts can impair immune function and physiological adaptation [5]. Vulnerable populations are often forced to live in unsafe environments, increasing exposure to pathogens and reducing access to healthcare services [3].

In Brazil, for example, the increasing frequency of summer heatwaves correlates with a year-long rise in dengue incidence due to the accelerated reproduction of mosquitoes. Elevated temperatures have also led to the appearance of dengue outbreaks in previously unaffected high-altitude regions, indicating a geographic expansion of endemic transmission [8].

3. Heterocycles in the Development of New Treatments for NTDs

Heterocycles are cyclic compounds whose ring structures contain two or more different atoms. They represent one of the most structurally diverse classes of organic molecules, a diversity attributable to the wide range of possible ring sizes, fused systems, aromatic characteristics, and heteroatom compositions, most commonly nitrogen, oxygen, and sulfur [6,9,10].

Heterocycles play a crucial role in medicinal chemistry as bioisosteres and structural scaffolds, enabling the incorporation of multiple functional groups during the drug design and optimization process. Their ring systems profoundly influence molecular shape, electrostatics, and biological activity. Consequently, heterocycles are fundamental components of natural products such as nucleic acids, amino acids, carbohydrates, vitamins, and alkaloids, all of which are integral to metabolism across living organisms [6,7].

More than 90% of newly approved drugs contain at least one heterocyclic moiety, and over 85% of known bioactive compounds are based on heterocyclic scaffolds [9,11]. These structures exhibit essential physicochemical properties, including electron-donating and -withdrawing behavior, hydrogen-bonding capabilities, and participation in π–π interactions with biological targets [6].

In chemotherapy for NTDs, the importance of heterocycles is evident. Established treatments rely heavily on such frameworks, as in the case of benznidazole and nifurtimox for Chagas disease, paromomycin for cutaneous leishmaniasis, and praziquantel for schistosomiasis.

Furthermore, heterocyclic cores have guided the development of new drug candidates, serving as the foundational scaffolds in hit-to-lead processes. Fused five- and six-membered systems such as

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benzimidazoles, benzoxazoles, benzothiazoles, and indoles have demonstrated notable bioactivity against pathogens responsible for dengue virus [12–16], *Trypanosoma cruzi* [17–22], *Leishmania* spp. [22–25], and *Schistosoma* spp. [26–29]. The ability to chemically combine a wide variety of moieties with different substituents to generate these rings is crucial for the synthetic relevance of these systems in the early stages of drug development. Five-membered ring systems continue to attract considerable interest among medicinal chemists due to their distinctive geometries and electrostatic properties. Nitrogen-containing rings, including 1,2,3-triazoles and 1,2,4-triazoles, serve as pharmacophoric moieties or linker structures, and numerous studies have highlighted their utility against neglected tropical diseases (NTDs) [30–41]. Pyrazoles, an emerging scaffold, have increasingly appeared in newly approved drugs over the past decade [42], whereas oxadiazoles offer a versatile platform for addressing diverse challenges in drug development [11]. Collectively, these heterocycles have been demonstrated to play a critical role in drug discovery and optimization.

Altogether, these heterocyclic frameworks have demonstrated significant pharmacological potential against multiple NTD targets.

4. Green Chemistry Principles

Although heterocycles offer considerable advantages in drug discovery, their conventional synthesis often involves hazardous conditions, such as the use of toxic solvents, heavy-metal catalysts, strong acids or bases, and high temperatures, that raise environmental and safety concerns [43–47]. Therefore, implementing green chemistry methodologies is essential for advancing the development of sustainable pharmaceuticals.

Green chemistry can be defined as the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances [48]. It does not represent a new discipline, but rather an evolution of existing chemical practices guided by environmental responsibility and process efficiency [49].

Formal recognition of green chemistry as a scientific approach emerged in 1998 with the publication of the *Twelve Principles of Green Chemistry* by Paul T. Anastas and John C. Warner [50]. These principles aim to prevent pollution at the source rather than manage waste post-production.

The principles include:

1. Waste Prevention: It is better to prevent waste from being created in the first place than to treat or clean it up later [51]. The use of solvents, catalysts, and auxiliaries in a chemical reaction, as well as handling solvents for separation and purification steps, must be reconsidered. Strategies such as solvent-free reactions and one-pot multi-step synthesis fulfill this principle [50].
2. Atom Economy: Synthetic methodologies must be optimized to achieve the maximum incorporation of all starting materials into the final product [51]. This minimizes byproduct formation, reduces the environmental burden, aims for "more from less," incorporates the total value of materials, and reduces costs [49]. Chemical transformations like cycloadditions, molecular rearrangements, and isomerizations are intrinsically atom-economical since 100% of the atoms in the reactants remain in the desired product. Similarly, Multicomponent Reactions (MCRs) are atom-economical [50].
3. Less Hazardous Chemical Synthesis: Synthetic procedures should, wherever feasible, be designed to utilize and generate materials exhibiting little or no toxicity to human health and the environment [51]. Non-hazardous materials and processes reduce the risk of exposure, release, explosions, and fires, improve worker safety, and reduce costs related to special control measures [49].
4. Designing Safer Chemicals: Chemical products should be engineered to deliver their required function while simultaneously minimizing inherent toxicity [51]. A "safe chemical" has reduced toxicity to humans and does not persist or bioaccumulate in the environment. A huge

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push in this direction has been given by computer-aided drug discovery, which can now efficiently provide researchers with predicted ADME-Tox data. However, ecotoxicity has not yet received similar significant attention. Drugs for human use are primarily introduced into the environment as unmetabolized drugs and/or their metabolites through effluent discharge, while unused drugs may come from sources like hospitals, households, and the pharmaceutical industry. Thus, a structured implementation of in silico methods for ecotoxicological assessment is highly needed for designing and synthesizing pharmaceuticals that prevent environmental risk [50].

5. Safer Solvents and Auxiliaries: The utilization of auxiliary substances, such as solvents and separation agents, should be eliminated whenever possible; if required, they must be innocuous [51]. Minimizing solvent usage leads to decreased solvent waste and a lower environmental impact [49]. Green chemistry promotes the use of safer alternatives, such as water or bio-based solvents, and the development of environmentally friendly and non-volatile solvents. In this respect, Ionic Liquids (ILs) are non-volatile, with thermal stability over 350 °C, minimize evaporation and environmental release, and are non-explosive, easy to handle, thermally robust, and recyclable [50].
6. Design for Energy Efficiency: The energetic demands of chemical processes must be acknowledged for their environmental and economic consequences and should be rigorously minimized. Where feasible, synthetic methods ought to be executed at ambient temperature and pressure [51]. This reduces the environmental burden related to power generation, increases efficiency, shortens processes, and reduces costs [49]. Strategies to reduce energy consumption and solvent use include microwave (MW)-assisted chemistry and mechanochemistry (where chemical reactions are initiated by mechanical energy at room temperature with minimized solvent use), as many of these techniques employ solvent-free methodologies [50].
7. Use of Renewable Feedstocks: A raw material or feedstock should be renewable rather than non-renewable whenever technically and economically feasible [51]. The production of bioactive compounds from agricultural and food waste holds immense promise within the framework of a circular economy perspective, as these materials represent an almost inexhaustible source of high-value-added molecules [50].
8. Reduce Derivatives: Unnecessary derivatization (e.g., the use of protecting or blocking groups) should be minimized or completely eliminated, as these steps necessitate additional reagents and generate waste [51]. Each additional synthetic step consumes resources and contributes to waste. By optimizing synthetic routes, chemists can increase overall process efficiency. Solvent-free, one-pot, and multicomponent procedures, flow chemistry, and computational approaches play a pivotal role in reducing the number of steps and chemical derivatives [50].
9. Catalysis: Catalysts should be employed over stoichiometric reagents to minimize waste, as they are effective in small amounts and capable of repeated transformations [51]. Modern synthetic chemistry is increasingly leveraging highly efficient and environmentally benign tools, such as metathesis, biocatalysis, and photocatalysis. Catalysis is a central pillar of green chemistry, facilitating milder reaction conditions, significantly lowering energy requirements, and enhancing reaction selectivity. Furthermore, catalysts are often more sustainable than stoichiometric reagents, making them crucial for the efficient synthesis of Active Pharmaceutical Ingredients (APIs) and other bioactive compounds [50].

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10. Design for Degradation: Chemical products should be intentionally designed to degrade into innocuous substances after use, thereby preventing environmental persistence [51]. Knowledge regarding the biodegradation of human and veterinary pharmaceuticals (and their metabolites) remains limited, particularly concerning their effects on ecological processes driven by microorganisms. Nonetheless, the focus of current research includes investigating the toxicity in terrestrial and aquatic environments, especially the chronic ecotoxicological impact on non-target species such as invertebrates, plants, and algae [50].
11. Real-Time Analysis for Pollution Prevention: To ensure pollution prevention, robust analytical techniques must be developed that allow for the real-time, in-process control of chemical reactions before hazardous materials can form [51]. The principles of Real-Time Analysis for Pollution Prevention (RTAP) can be applied throughout the drug discovery and production pipeline to proactively identify and mitigate potential sources of pollution or environmental damage. This approach underscores the crucial shift from reactive strategies to proactive pollution prevention measures [50].
12. Inherently Safer Chemistry for Accident Prevention: Chemical processes should be inherently designed to use and handle materials in a manner that drastically minimizes the risk of chemical accidents, such as explosions, fires, and uncontrolled releases [51]. The principle of Inherently Safer Chemistry (ISC) promotes the use of processes designed to minimize the risk and severity of chemical accidents. This focus on hazard minimization is central to creating a more robust chemical industry. Accordingly, maximizing operational simplicity is essential in all fields as it directly reduces the overall potential for accidents [50].

Following the discussion of the 12 principles of green chemistry, the subsequent section illustrates examples of heterocyclic scaffold syntheses with potential applications in the treatment of neglected tropical diseases, emphasizing how these principles can inform the design of more sustainable and efficient synthetic strategies.

5. Heterocyclic Scaffolds for NTD Drug Discovery: Green Synthetic Approaches

Given this significance, the development of concise, efficient, and environmentally conscious synthetic strategies is essential, not only to facilitate the production of these heterocycles on a larger scale but also to minimize chemical waste and enhance overall sustainability. Figure 1 illustrates representative structures of these heterocyclic cores, emphasizing their role in biologically active compounds.

5.1. Microwave-Assisted Sustainable Synthesis: Solvent-Free and Green-Solvent Pathways

Microwave-assisted organic synthesis (MAOS) has become an established strategy for the preparation of bioactive compounds, providing both synthetic and environmental benefits. Unlike conventional heating, microwave irradiation delivers rapid and homogeneous energy directly to the reaction medium, often leading to marked reductions in reaction times, from hours to minutes, while improving yields and reproducibility [52–55].

A key advantage of this approach is its strong adherence to the principles of green chemistry. Microwave-driven protocols frequently operate under solvent-free conditions or employ benign media such as water or bio-derived solvents. These features contribute to a substantial decrease in the use of volatile organic solvents, thereby minimizing the generation of hazardous waste. The shortened reaction periods also reduce energy consumption and, consequently, the overall environmental footprint of the synthetic process [52–55].

Moreover, microwave irradiation often enhances reaction selectivity and suppresses the formation of undesired by-products. This results in cleaner crude products that require less

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demanding downstream purification, further reducing waste streams and process costs. These attributes make MAOS particularly attractive for the sustainable synthesis of pharmacologically relevant scaffolds, including heteroaromatic cores such as benzimidazoles, benzothiazoles, indoles, and other heterocycles that are commonly found in clinically important drugs.

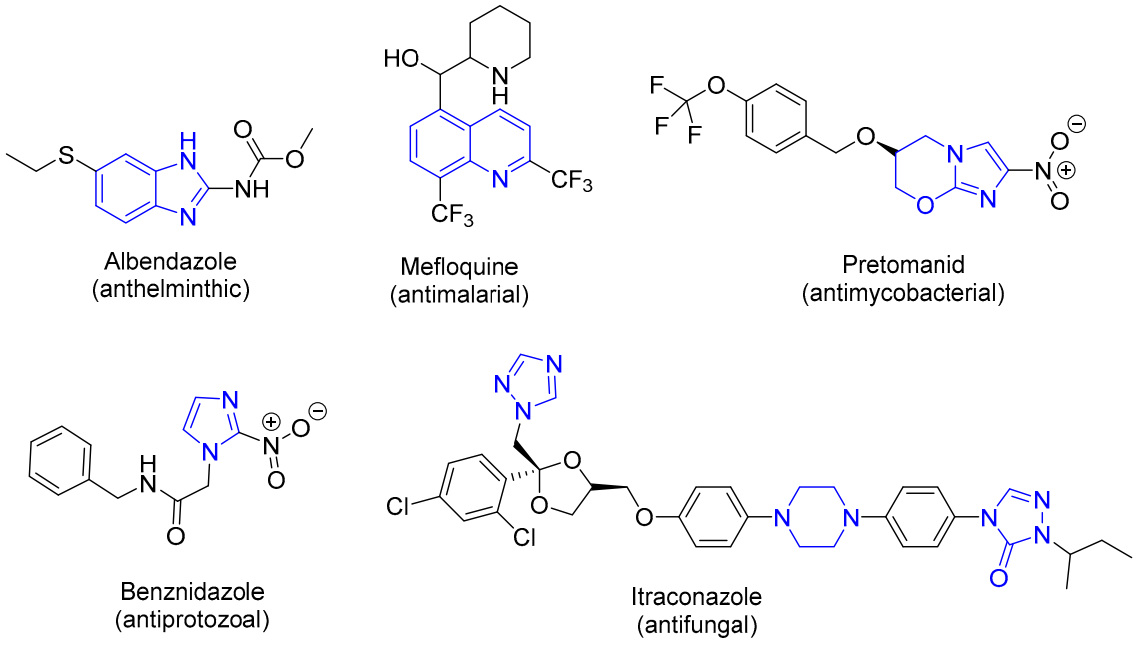

Figure 1. Representative heterocyclic drugs employed in the treatment of neglected diseases, with the heterocyclic ring shown in blue.

Representative example of microwave-assisted protocols for the synthesis of heterocyclic frameworks, which constitute key structural motifs in numerous approved pharmaceuticals as well as in experimental compounds under investigation for the treatment of neglected tropical diseases (NTDs), is presented as follows.

Bandyopadhyay and colleagues (2017) described the synthesis of benzimidazole derivatives using a simple and eco-friendly method, affording compounds with promising activity against Chagas disease and leishmaniasis. Their approach employs bismuth nitrate pentahydrate as a Lewis acid catalyst in aqueous medium under microwave irradiation (Figure 2), offering several advantages, including mild reaction conditions, high atom economy, ease of product isolation, and minimal waste generation, thus representing a valuable green protocol for this class of heterocycles. Initially, the authors evaluated which catalyst would be the most effective for the reaction (BiI_3, $BiBr_3$, $BiCl_3$, $Bi(OTf)_3$, $BiO_5(OH)_9(NO_3)_3$, $Bi(NO_3)_3{\cdot}5H_2O$) in comparison with the reaction carried out without a catalyst. A significant increase in yield was observed when $Bi(NO_3)_3{\cdot}5H_2O$ was used as the catalyst (81% yield) compared to the reaction without a catalyst (37%). Continuing the optimization of the reaction conditions, the reaction was then tested in different solvents, using bismuth nitrate pentahydrate as the catalyst in all cases. The solvents evaluated were tetrahydrofuran, ethanol, methanol, DMSO, acetonitrile, dichloromethane, toluene, and water, including a neat condition. Fortuitously, the best solvent was water (89% yield), which is consistent with the principles of green chemistry. Finally, the authors evaluated the optimal amount of catalyst to be used in the reaction, achieving the highest yield (94%) when bismuth nitrate pentahydrate was employed at a concentration of 5 mol% [22].

This case study illustrates how microwave irradiation not only accelerates and simplifies synthetic routes but also contributes to the discovery of bioactive molecules with significant therapeutic potential.

Numerous other examples of microwave-assisted protocols for the synthesis of heterocyclic scaffolds are reported in the literature [22,56–60], further highlighting the versatility of this approach.

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Overall, microwave irradiation represents a promising and sustainable technique aligned with the principles of green chemistry, offering significant potential for the efficient development of bioactive compounds.

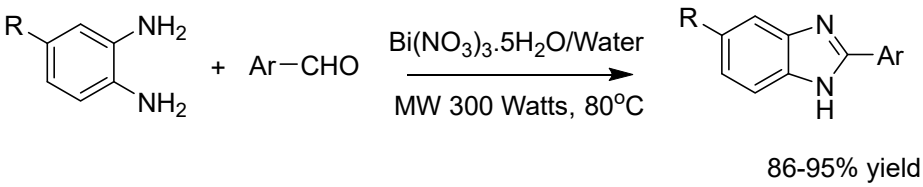

Figure 2. General scheme for the synthesis of benzimidazoles using microwave irradiation and bismuth nitrate pentahydrate–catalyzed reaction [22].

5.2. Ultrasound as a Green Tool for the Synthesis of Heterocyclic Scaffolds

Ultrasound-assisted reactions have emerged as a valuable tool in green chemistry due to their ability to accelerate chemical transformations under milder reaction conditions. The fundamental principle behind sonochemistry is the phenomenon of acoustic cavitation, which involves the formation, growth, and implosive collapse of microscopic bubbles in a liquid medium. This collapse generates localized hotspots with transiently high temperatures and pressures, as well as intense micro-mixing, thereby enhancing reaction rates and yields without the need for harsh reagents or excessive heating. These features make ultrasound an attractive and environmentally friendly alternative for the synthesis of heterocyclic compounds, contributing to more sustainable and energy-efficient chemical processes [55,61,62].

Rock et al. (2021) reported the synthesis of a series of benzopyrazines with leishmanicidal and trypanocidal activity using an ultrasound-assisted, environmentally friendly methodology that eliminates the need for catalysts, supports, additives, or hazardous solvents. According to the authors, this is the first example of benzopyrazine synthesis under such conditions, showing very promising results. The benzopyrazine derivatives were obtained in high yields (above 92%) within a short reaction time (~3 minutes) using water as the solvent. Variation of the substituents R_1, R_2, and R_3 (Figure 3) did not significantly affect the reaction progress, indicating that the method exhibits high applicability for the synthesis of a wide range of benzopyrazine derivatives [63].

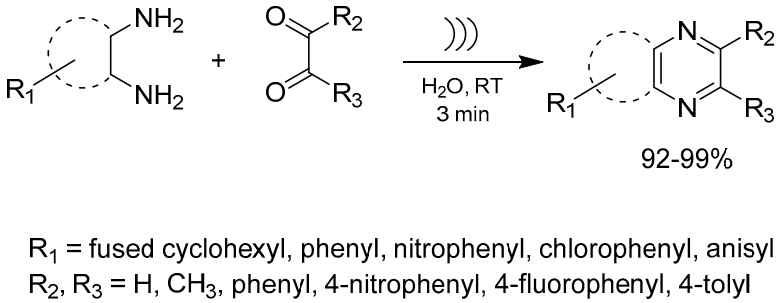

Figure 3. General Synthetic Route for the Ultrasound-Assisted Preparation of Benzopyrazine Derivatives.

5.3. Mechanochemical Advances Enabling One-Pot Multistep Organic Synthesis

Mechanochemistry has emerged as a powerful and sustainable alternative to traditional solution-based synthesis, providing an efficient route for the preparation of structurally complex and biologically active compounds. In mechanochemical reactions, mechanical energy, typically applied by ball milling or grinding, replaces conventional heating or solvent-mediated activation, enabling chemical transformations to occur under solvent-free or minimal-solvent conditions. This

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significantly reduces the generation of hazardous waste and the environmental footprint of synthetic processes [64–66].

The integration of mechanochemical methods with one-pot multistep strategies represents an important advance in sustainable synthesis. Such approaches allow consecutive transformations to occur in a single vessel, minimizing purification steps, improving atom economy, and reducing energy consumption. These advantages are particularly relevant for the synthesis of heterocyclic compounds, which constitute key structural motifs in numerous active molecules with potential applications in the treatment of neglected tropical diseases [64].

Quinoline-containing drugs are widely used in the treatment of several neglected diseases, such as malaria (quinine, quinidine, chloroquine, mefloquine, primaquine, etc.), tuberculosis (bedaquiline), and fungal or protozoal infections (clioquinol). Moreover, the presence of quinoline rings in the structure of antiviral agents such as saquinavir and indinavir suggests that quinoline derivatives may also display activity against a broad spectrum of viral infections, including those caused by Zika virus, enteroviruses, herpesvirus, Ebola virus, MERS-CoV and SARS-CoV [67].

Given the broad pharmacological relevance of the quinoline scaffold, the development of efficient and sustainable synthetic methodologies for its construction is of great importance. A relevant example of the application of mechanochemical one-pot multistep synthesis for the preparation of quinoline derivatives was described by Tan et al. (2017). In this work, 2,4-diphenylquinolines were synthesized through a solvent-free multicomponent strategy using aniline derivatives, benzaldehydes, and phenylacetylenes. The reaction was carried out in the presence of $FeCl_3$ as a Lewis acid catalyst under ball milling conditions. To standardize the methodology, different Lewis acids were initially tested as catalysts ($ZnCl_2$, $AlCl_3$, $FeCl_3$, and $BF_3{\cdot}OEt_2$), with $FeCl_3$ being selected as the most efficient. The influence of different substituents on the benzaldehyde, phenylacetylene, and aniline reagents was also investigated. Electron-donating substituents on the aniline moiety and electron-withdrawing substituents on the aldehyde or phenylacetylene components led to better yields. The reaction time was 2 hours, and the product was easily isolated by washing the reaction mixture with a dilute hydrochloric acid solution, without the need for further purification. The general reaction scheme is shown in Figure 4 [68].

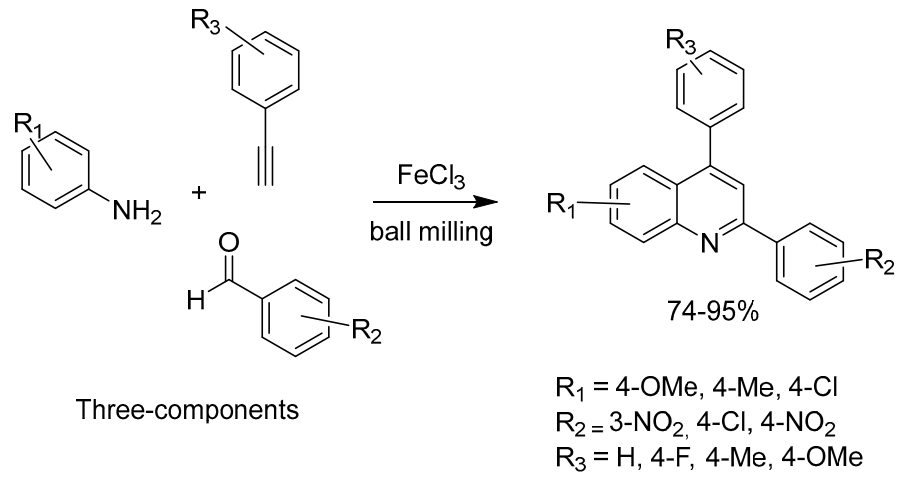

Figure 4. General scheme for the synthesis of 2,4-diphenylquinolines via a three-component reaction under ball-milling conditions [68].

5.4. Ionic Liquids as Catalysts in Green Chemistry Approaches

Ionic liquids (ILs) have emerged as versatile and environmentally friendly alternatives to conventional organic solvents and catalysts in modern synthetic chemistry. Defined as salts that remain liquid below 100 °C, ILs possess unique physicochemical properties such as negligible vapor pressure, high thermal stability, tunable polarity, and excellent solvating ability for both organic and

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inorganic compounds. These characteristics make them particularly attractive for promoting reactions under mild, solvent-free, or recyclable conditions, in line with the principles of green chemistry [69].

In the synthesis of heterocyclic compounds, ILs have been successfully employed, enhancing reaction rates, selectivity, and yields while minimizing waste generation. Imidazolium-, pyridinium-, and ammonium-based ionic liquids, in particular, have shown remarkable efficiency in multicomponent and one-pot reactions, often enabling metal-free or solvent-free protocols [70,71]

Several drugs used in the treatment of neglected diseases contain an imidazole ring in their molecular structure. Examples include metronidazole, employed in the treatment of *giardiasis* and *amebiasis*; fexinidazole, used for *human African trypanosomiasis* (HAT or sleeping sickness); luliconazole, an antifungal agent with potent activity in vitro against *Leishmania major* [72]; and benznidazole, used for the treatment of *Chagas disease*, among several others. In this context, the synthesis of imidazole derivatives using green chemistry approaches, particularly through the application of ionic liquids, becomes a subject of significant interest.

Shirole et al. (2016) described the synthesis of new 1,2,4,5-tetrasubstituted by combining key strategies for sustainable chemistry: a multicomponent reaction using the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF_4]) as a catalyst under microwave irradiation. For comparison purposes, the authors also carried out the same synthesis under conventional reflux conditions. The protocol involved a multicomponent reaction between benzil, various *para*-substituted anilines, 1-phenyl-3-p-tolyl-1*H*-pyrazole-4-carbaldehyde, and ammonium acetate under different conditions: (a) conventional reflux or microwave heating; (b) in the presence of *p*-toluenesulfonic acid, the ionic liquid [BMIM][BF_4], or without any catalyst; (c) using ethanol as solvent or under solvent-free conditions. Among the tested conditions, the one that provided the best results was microwave irradiation at 240 W, using the ionic liquid as catalyst under solvent-free conditions. Under these conditions, the reaction time ranged from 10 to 12 minutes, and the yields varied between 84% and 89% [73] (Figure 5).

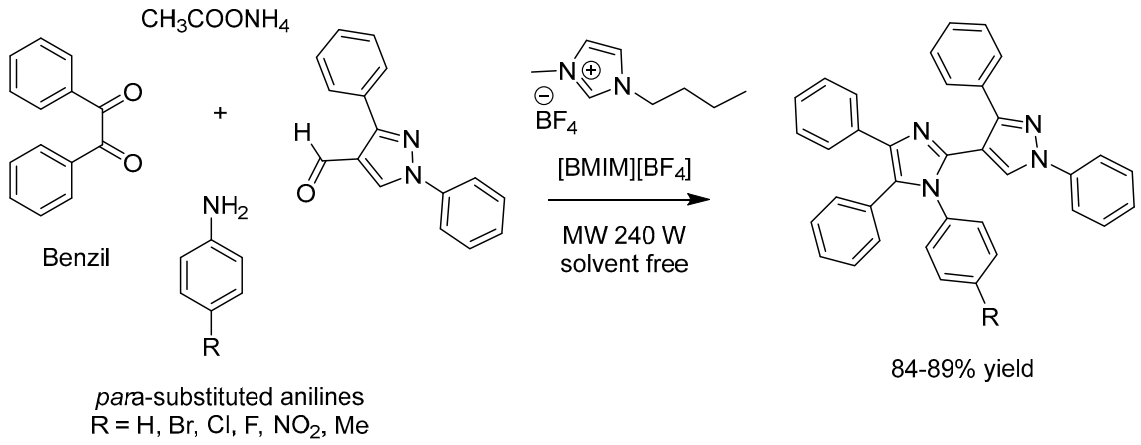

Figure 5. General synthesis of imidazole derivatives via a multicomponent reaction under microwave irradiation using [BMIM][BF_4] as catalyst [73].

5.5. Deep Eutectic Solvents in Sustainable Heterocycle Synthesis

Deep eutectic solvents (DESs) have gained increasing attention as a new generation of environmentally benign media for organic synthesis. Formed by combining a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA), DESs exhibit a melting point significantly lower than that of their individual components, resulting in a liquid phase at or near room temperature. Compared to many conventional ionic liquids, DESs are typically easier to prepare, less expensive, and often biodegradable, which enhances their appeal for sustainable chemical processes [74].

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In heterocyclic synthesis, DESs have demonstrated remarkable versatility as solvents, catalysts, or co-catalysts, promoting various transformations such as condensation, cyclization, and multicomponent reactions under mild and often solvent-free conditions. Their tunable physicochemical properties and compatibility with both organic and inorganic substrates enable efficient reaction pathways with reduced environmental impact [75–77].

The benzothiazole ring represents a common heterocyclic framework found in a wide range of compounds, many of which exhibit notable biological activities, including antiparasitic and antiviral activities with potential applications in the treatment of neglected diseases [13,78–80]. An example of the synthesis of 2-phenylbenzothiazoles using a deep eutectic solvent (DES) was recently reported by Truong et al. (2024). The optimal reaction conditions were established by varying the catalysts and their ratios, as well as the solvent, temperature, reaction time, and sulfur concentration, which was used as the redox reagent in the condensation step. The DES catalyst selected after optimization was [CholineCl][Imidazole]$_2$, prepared from a mixture of choline chloride (CholineCl) and imidazole (IM) in different molar ratios. The hydrogen-bond interaction between CholineCl and IM leads to the formation of the DES (Figure 6) [75].

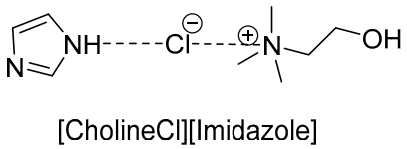

Figure 6. Proposed formation of a deep eutectic solvent (DES) between CholineCl and IM via hydrogen-bond interactions [75].

After evaluating the impact of different solvents on the synthesis (DMSO, DMF, 1,4-dioxane, sulfolane, and solvent-free conditions), the solvent-free condition was selected as the most suitable, as it provided the highest yield. Regarding the reaction times tested (1, 2, 4, 6, and 8 h), the yields tended to increase with longer reaction times, with the highest yield obtained after 6 hours, showing only a slight difference compared to 8 hours. The reaction was carried out at four different temperatures (80 °C, 100 °C, 120 °C, and 140 °C), and 120 °C was selected as the optimal temperature due to its most significant positive effect on the yield. The effect of catalyst loading (0.15 mol%, 0.25 mol%, 0.35 mol%, and 0.50 mol%) was also evaluated by comparing the results with the reaction carried out in the absence of a catalyst. It was demonstrated that the reaction does not proceed without the catalyst, and the optimal catalyst loading was determined to be 0.35 mol%. The sulfur concentration was varied from 1 to 5 mmol, with 2 mmol being selected as the optimal amount. The reaction scheme, including the reagents used during the optimization steps, is illustrated in Figure 7. After optimizing the conditions, the reaction was carried out with various aldehydes, leading to the formation of a wide range of benzothiazole derivatives, thereby confirming the scope of the synthesis. [75].

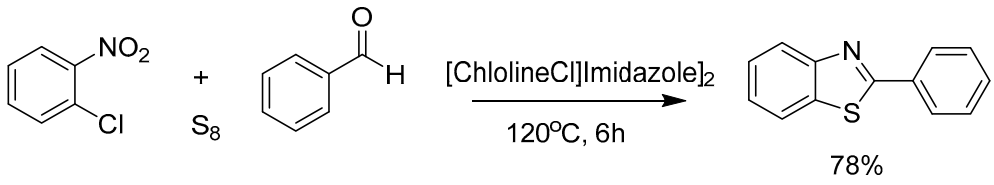

Figure 7. DES-mediated synthesis of a benzothiazole derivative under optimized conditions [75].

6. Conclusions

The synthesis of heterocyclic scaffolds under green chemistry paradigms offers a promising avenue for the discovery of new therapeutic agents against NTDs, particularly in the context of

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climate-driven shifts in disease burden. Sustainable methodologies, including microwave and ultrasound-assisted reactions, mechanochemical one-pot processes, and the application of ionic liquids and deep eutectic solvents, demonstrate that high-yielding, efficient, and environmentally responsible synthesis is feasible for complex bioactive molecules. By aligning medicinal chemistry innovation with ecological considerations, these approaches not only enhance the development of drug candidates for NTDs but also contribute to broader efforts toward climate-conscious pharmaceutical research, underscoring the critical role of green chemistry in the future of global health.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: During the preparation of this work, the authors used ChatGPT to assist with language editing. The authors have reviewed and revised all content and takes full responsibility for the published article.

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