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Comprehensive Review on Solvent-Free Multicomponent Strategies for Sustainable Synthesis of Heterocyclic Schiff Bases

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Abstract

A successful and environmentally friendly method in contemporary organic chemistry is the solvent-free multi-component reaction (MCR) for synthesizing heterocyclic Schiff bases. This method simplifies synthesis processes, improves atom economy, and uses less solvent, all of which are components of green chemistry. High functional variety and operational convenience are provided by multi-component reactions, which allow the quick synthesis of complex heterocyclic frameworks from simple precursors in a one-pot process. In addition to lowering reaction time and energy consumption, solvent-free conditions increase product yield and purity. Heterocyclic Schiff bases synthesized through this route exhibit a wide range of applications, including anti-microbial, anti-cancer, anti-oxidant and catalytic properties. This review highlights recent advancement, challenges and opportunities in solvent – free MCRs for the sustainable synthesis of heterocyclic Schiff bases, emphasizing their growing significance in pharmaceutical and material sciences.

Keywords: Schiff bases; Green chemistry; Multicomponent reactions; Solvent-free synthesis;heterocyclic Schiff bases; Sustainable synthesis

1. Introduction

Because of its enormous significance to life, the chemistry of organic synthesis garners special attention in science. The vast range of structures needed to support biological systems is perfectly matched to the incredibly flexible bonding at carbon. One of the most significant and practical areas of chemistry is organic synthesis, which primarily entails the formation and breaking of carbon–carbon (C–C) and carbon–heteroatom (C–X) bonds.

It has become extremely challenging to keep up with the research being reported in this field because to the exponential rise of the literature on multicomponent reactions (MCRs) over the past ten years, as well as the massive expansion of the literature on MCRs conducted without the use of solvents .[1,2]

1.1. Schiff bases

The German chemist Hugo Schiff, who was the first to characterize the results of the reaction between primary amines and carbonyl compounds in 1864, is the source of the term Schiff's base.[3]

The diversity of schiff bases, a broad class of compounds distinguished by the presence of a double bond connecting carbon and nitrogen atoms, is produced by the numerous ways in which a range of alkyl or aryl substituents can be combined.

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These kinds of compounds can be created in a lab or discovered in nature. Chemical compounds [imines] with a hyrocarbyl group on the nitrogen atom (R2C=NR'(R' ≠ H)) are known as Schiff bases .[4]

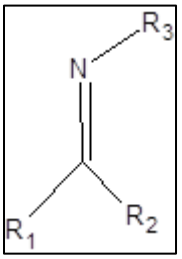


Figure 1 General mechanism for the formation of schiff bases via condensation of primary amines with carbonyl compounds under solvent -free conditions

2. Importance of heterocyclic schiff bases

Schiff base are important scaffolds in drug development. They are characterized by different synthetic schemes by both the aromatic and aliphatic chains. A large number of drugs are designed through the heterocyclic schiff base moieties. Biological importance: antimicrobial, anticonvulsant, analgesic, antioxidant, antimalarial, anti-inflammatory, anticancer, antidiabetic properties.

2.1. Principles of green chemistry

The twelve guiding principles of green chemistry are designed to reduce or eliminate hazardous materials from the synthesis, manufacturing, and use of chemical products. This, in turn, aims to reduce or eliminate the use of materials that are harmful to the environment and human health. The term "green chemistry" was initially coined in the early 1990s.[5]The Green Chemistry Institute was created in 1997.

The first volume of the reputable Royal Society of Chemistry's green chemistry journal was published in 1999.[6]

Predicated on twelve principles that seek to limit or remove hazardous compounds from the synthesis, manufacture, and usage of chemical products, and therefore the use of materials that are harmful to the environment and human health. Its foundation is the creation or replication of molecules, reaction materials, and procedures that are safer for the environment and human health.[7]

3. Definition of multi component reaction (MCR)

Compared to stepwise sequential methods to complicated and valuable compounds, multicomponent reactions which fall between one- and two-component and polymerization reactions offer a variety of useful conceptual and synthetic advantages.

A synthetic process known as a multicomponent reaction (MCR) creates a new product by reacting three or more reactants in a single reaction vessel. MCRs typically incorporate most of the reactant atoms into the final product, generating minimal by-products. [1]

3.1. Benefits of multicomponent reactions

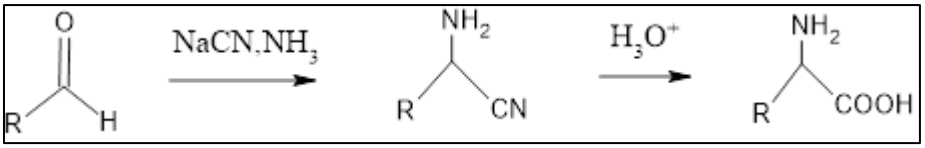
Multicomponent reactions offer significant advantages in organic synthesis, primarily due to their ability to create complex molecules in a single step, improving efficiency and reducing waste.

- Step economy and efficiency
- Atom economy
- Molecule diversity
- Green chemistry principles
- Applications in drug discovery

3.2. Types of multicomponent reactions

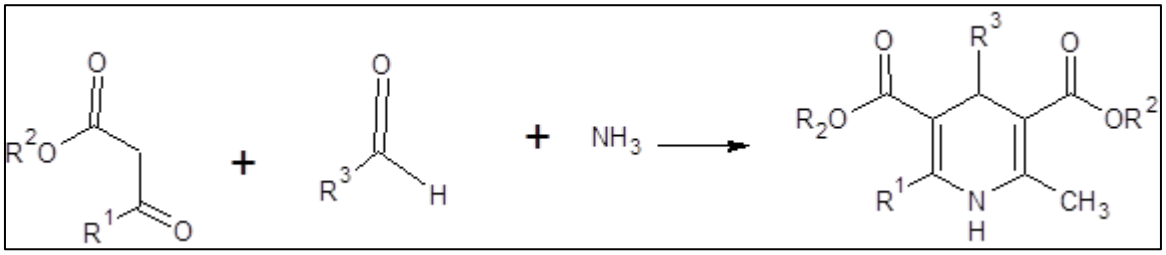
3.2.1. Strecker reaction[3cr]

The synthesis of α-amino acids is a well-known reaction that was first reported by A. Strecker in 1850.[8] The three substrates in this MCR reaction (aldehydes, hydrogen cyanide, and ammonia) are acknowledged as the first MCR in history.[8]



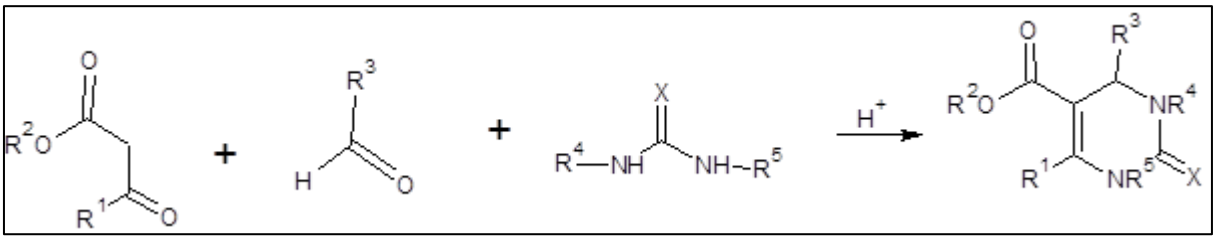
3.2.2. hantzsch dihydropyridine synthesis[3cr]:

The most well-known three-component MCR, which produces 1,4-dihydropyridine derivatives utilising β-keto esters, aldehydes, and ammonia, was first described by A. R. Hantzsch in 1881.[9] For instance, this reaction also produces "Nifedipine," a calcium channel blocker.[10]



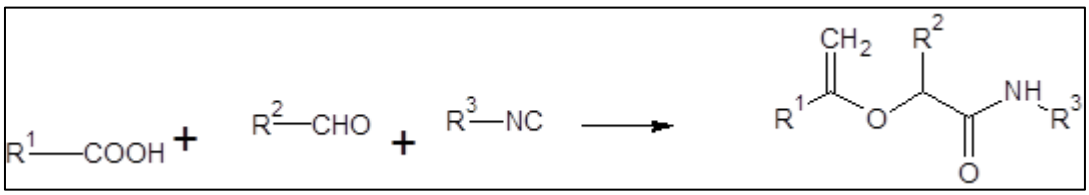
3.2.3. Biginelli reaction [3cr]:

In 1891, P. Biginelli, an Italian chemist, reported the three-component MCR that produced dihydropyrimidinone derivatives by utilising β-keto esters, such as ethyl 8 acetoacetate [A0649], aromatic aldehydes, such as benzaldehyde [B2379], and ureas (or thioureas) in the presence of an acid catalyst, such as Brönsted or Lewis acids.[11]Dihydropyrimidinones have received a lot of interest due to their diverse bioactivities, including antibacterial and anti-inflammatory properties. Several anti-tubercular medicines have been identified as examples of medications created by the reaction. [12]



3.2.4. Passerini reaction (3CR)

The three-component reaction that yields α-acyloxy amides utilising carboxylic acids, aldehydes, and isonitriles was reported by Italian chemist M. Passerini et al. in 1921.[13] Hulme et al. have described the library synthesis of new norstatine compounds with benzimidazole moieties, demonstrating the application of the Passerini reaction to pharmacological research.[14]



3.3. Solvent -free synthesis

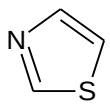
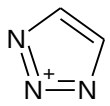
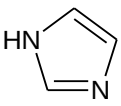
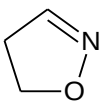
Chemical and medicinal chemists have become interested in chemical reactions that are conducted using green solvents or without conventional organic solvents due to growing concerns about the detrimental effects of organic solvents on the environment and human health. Interest in solvent-free MCRs has grown over the last ten years and now spans several sectors of the chemical industry. Solvent-free methods are used to modernize traditional procedures by making them safer, easier to conduct, and cleaner for economic and pollution prevention purposes.[15] There is an increasing need for chemical syntheses that are both efficient and clean.[16] Solvent-free conditions are gaining popularity among the suggested solutions, and it's sometimes asserted that the best solvent is none at all.[17]

3.3.1. Techniques used in solvent -free MCRs

- **1.Grinding (Mechanochemical Method):**
  - Procedure: A mortar-pestle or ball mill is used to grind the reactants (amine, aldehyde/ketone, and heterocyclic precursor) together.
  - Example: Consider the one-pot solid-state grinding of active methylene compounds, amines, and aldehydes to create heterocyclic Schiff bases.[18]
- **2. Microwave-Assisted Solvent-Free Synthesis:**
  - Procedure: In solvent-free conditions, the consumption of microwave irradiation improves overall reaction kinetics.
  - Example: Consider the synthesis of Schiff bases from heteroaryl aldehydes using a microwave.[19]
- **Ultrasound-Assisted Solvent-Free Method:**
  - Method: Using microwave irradiation enhances overall reaction kinetics when there is no solvent ✓ present.
  - Example: The microwave-assisted synthesis of Schiff bases from heteroaryl aldehydes.[20]
- **Thermal/Conventional Heating (One-Pot Solid-State):**
  - Method: Reactants are heated together without the use of a solvent, frequently with the use of solid supports such as silica or alumina or catalytic supports such as basic or acidic catalysts.
  - Example: Consider the straightforward synthesis of heterocyclic Schiff bases utilising aldehyde + amine + active heteroaryl precursor.[21]

3.4. Objectives of the Review

Table 1 Five membered ring

S.no	Compounds	Method	Catalyst	Time	Temperature	Yield
1.	Thiazole 	Grinding	None	10 mins	Room temperature	90%
2.	Pyrazole 	Solvent-free cyclization	Acetic acid	30 mins	120°C	85%
3.	Imidazole 	Multicomponent reaction (MCR)	ZnCl2	20 mins	100°C	88%
4.	Isoxazole 	1,3-Dipolar Cycloadditi on	None	1hour	80°C	82%
5.	Oxazole	Cyclodehydration of α-acylamino	POCl3	2hours	Reflux (110°C)	84%

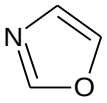
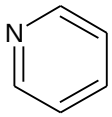
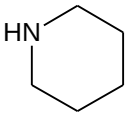
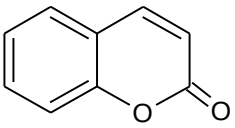
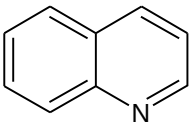
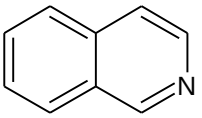
						

Table 2 six membered ring:

S.no	Compounds	Method	Catalyst	Time	Temperature	Yield
1.	Pyridine 	Grinding	L-proline	25 mins	80°C	88%
2.	Piperidine 	One pot heating	ZnCl2	30 mins	100°C	90%
3.	Coumarin 	Thermal grinding	Sulfamic acid	20 mins	90°C	94%
4.	Quinoline 	Mechanochemical	Nano TiO2	35 mins	100°C	85%
5.	Isoquinoline 	Dry heating	Amberlite IR-120	40 mins	80°C	82%

4. Synthesis of heterocyclic schiff bases via solvent -free multicomponent reactions

4.1. Thiazole:[22-24]

4.1.1. Starting materials

- α-haloketone (or α-haloester)
- Thioamide (or thiourea)
- Primary amine/aldehyde (for Schiff base formation)

4.1.2. Method

- One-pot grinding or heating under solvent-free conditions.

4.1.3. Mechanism:

- In situ formation of Schiff base from aldehyde + primary amine.
- Nucleophilic attack of thioamide/thiourea on α-haloketone.

Cyclization via intramolecular condensation → formation of thiazole ring.

4.1.4. Catalysts (optional):

Ionic liquids, silica-supported acids, or mechanochemical activation.

4.1.5. Example Reaction:

✓ Schiff base + thiosemicarbazide + α-bromoacetophenone → 2-aminothiazole derivative.

4.2. IMIDAZOLE:[25-26]

4.2.1. Starting materials:

- Benzil (1,2-diketone)
- Aldehyde (Ar–CHO)
- Ammonium acetate (NH_4OAc) or primary amine (for Schiff base formation)

4.2.2. Method:

One-pot, solvent-free grinding or heating.

4.2.3. Mechanism:

- Aldehyde + amine → Schiff base (imine).
- Schiff base condenses with benzil + NH_4OAc → diimine intermediate.
- Cyclization and aromatization → 2,4,5-trisubstituted imidazole.

4.2.4. Catalysts (optional):

- Solid acids (silica sulfuric acid, montmorillonite K-10).
- Ionic liquids or Lewis acids.

4.2.5. Example Reaction:

- Benzil + benzaldehyde + ammonium acetate → 2,4,5-triphenylimidazole.

4.2.6. Green Chemistry Benefits:

- No volatile organic solvent.
- Atom economy (all atoms incorporated into product).
- Easy workup (crude solid filtered/recrystallized).

4.3. QUINOLINE:[24,29]

4.3.1. Starting materials:

- Aromatic aldehyde (Ar–CHO)
- Amine → Schiff base (imine)
- Active methylene compound (β-ketoester, β-diketone, or malononitrile)

4.3.2. Method:

One-pot grinding or heating (90–130 °C) without solvent.

4.3.3. Mechanism:

- Formation of Schiff base (Aldehyde + Amine).
- Nucleophilic attack of β-ketoester/β-diketone on Schiff base.
- Intramolecular cyclization → quinoline nucleus.

Aromatization → stable quinoline derivative.

4.3.4. Catalysts (optional):

- Acidic solids (Montmorillonite K-10, silica sulfuric acid).

- Lewis acids ($FeCl_3$, $InCl_3$, $ZnCl_2$).
- Ionic liquids or mechanochemical activation.

4.3.5. Example Reaction:

✓ Aldehyde (benzaldehyde) + aniline → Schiff base.

4.3.6. Green Chemistry Benefits:

- No solvent → avoids VOCs.
- High atom economy.

4.4. ISOQUINOLINE:[28]

4.4.1. Starting materials:

- Aromatic aldehyde (Ar–CHO)
- β-phenylethylamine (Ar–CH_2CH_2–NH_2) or substituted aniline
- Solid acid catalyst (Montmorillonite K-10, silica-sulfuric acid, $ZnCl_2$, $FeCl_3$)

4.4.2. Method:

One-pot solvent-free grinding or heating (90–130 °C).

4.4.3. Mechanism:

- In situ Schiff base formation: Aldehyde + amine → imine (Schiff base).
- Cyclization: Intramolecular electrophilic substitution (Bischler–Napieralski or Pictet–Spengler type) → dihydroisoquinoline.
- Oxidation: Solid oxidant (MnO_2, I_2, DDQ) → aromatization → isoquinoline.

4.4.4. Example Reaction:

✓ Benzaldehyde + 2-phenylethylamine → Schiff base → (solid acid catalyst) → dihydroisoquinoline → (MnO_2 oxidation) → isoquinoline derivative.

4.4.5. Green Chemistry Features:

- No solvent (grinding/microwave).
- Recyclable catalysts.

5.PURINE:[23,27]

4.4.6. Starting materials:

- Aldehyde (Ar–CHO)
- Aminoazoles (e.g., 5-aminoimidazole, 3,5-diamino-1,2,4-triazole, guanidine derivatives)
- Active methylene compounds (β-diketones, formamides, urea/thiourea)

4.4.7. Method:

One-pot solvent-free grinding or thermal heating (80–120 °C).

4.4.8. Mechanism:

- Schiff base formation: Aldehyde + aminoazole → imine.
- Condensation/cyclization: Nucleophilic addition of active methylene compound → fused heterocyclic intermediate.
- Cyclodehydration & aromatization → purine nucleus.

4.4.9. Example Reaction:

- 5-aminoimidazole + formamide + aldehyde → Schiff base → cyclization (solid acid catalysis, solvent-free) → substituted purine derivative.

4.4.10. Green Chemistry Features:

- Solvent-free (grinding or microwave).
- High atom economy.

5. Applications of synthesized schiff bases:[30]

- **Medicinal and Pharmaceutical Applications:**
    - Antibacterial and antifungal: Schiff bases made from salicylaldehyde, vanillin, etc., exhibit activity against Candida albicans, Staphylococcus aureus, and E. coli;
    - Anticancer: Schiff base metal complexes, particularly Cu(II), Zn(II) and Pt(II) are tested for cytotoxicity against tumor cell lines;
    - Antioxidant: a number of Schiff bases scavenge free radicals and guard against oxidative stress;
    - anti-inflammatory: Schiff bases can occasionally mimic non-steroidal anti-inflammatory medications (NSAIDs).

- **Catalysis**
    - Schiff base-metal complexes act as catalysts in:
    - Epoxidation of alkenes
    - Oxidation of alcohols
    - Polymerization of lactides and olefins

- **Sensors and Analytical Applications**
    - Synthesized Schiff bases are employed in:
    - Colorimetric and fluorescent sensors for metal ions
    - ✓ Fe^{3+},
    - ✓ Cu^{2+},
    - ✓ Hg^{2+}.
    - pH indicators
- •Detection of biological molecules like amino acids or glucose

- **Polymeric and Material Applications:**
    - Schiff bases are used in:
    - Polymeric resins and coatings
    - Non-linear optical materials
    - Corrosion inhibitors in metals.

5.1. Challenges and limitations:

- **1.Heat and Mass Transfer Issues:**
    - It can be challenging to provide even heat distribution and efficient mixing without a solvent, particularly in large-scale operations.
    - Slower reactions or lower yields can result from poor reactant diffusion.
- **2.Limited Substrate Scope:**
    - For some reactants to react effectively or be stable, solvation is necessary. Their reactivity can drastically decrease in solvent-free environments.
    - Reactants that are very hygroscopic or volatile are more difficult to employ.
- **3.Difficulty in Monitoring and Controlling Reaction Progress:**
    - Real-time analysis (such as TLC, in-situ IR, or NMR monitoring) is made more difficult when a liquid medium is absent.

  - Without exact control, overheating or adverse reactions may happen.
- **4. Reaction Reproducibility:**
  - Physical elements that might significantly affect results and decrease reproducibility include humidity, solid reactant particle size, and mixing procedure. [31,32,33]

5.2. Future scope

Solvent-free multi-component reactions (MCRs) have emerged as a cornerstone of green and sustainable chemistry. Nonetheless, there are still a number of uncharted territories that present opportunities for further investigation. Important avenues for the future include:

- **1.Expansion to Complex Heterocycles:**

Future research can investigate the creation of solvent-free MCRs for the synthesis of more biologically active and varied heterocyclic frameworks, particularly fused systems and analogs of natural products.

- **2.Integration with Catalysis:**

Efficiency, selectivity, and atom economy can all be improved by combining solvent-free MCRs with green catalysts (such as enzymes, organocatalysts, and nanocatalysts).

- **3.Automation and Flow Chemistry Adaptation:**
  - High-throughput synthesis for drug discovery could be revolutionized by automating solvent-free MCRs with AI-guided platforms or continuous flow systems.
- **4.Environmental and Toxicological Assessments:**
- To confirm their green credentials, further research should include life cycle assessments (LCA), toxicity profiles, and biodegradability data for goods made with solvent-free MCRs.

6. Predicted MCR combinations:

6.1. Computational Prediction of MCR Pathways:

- The prediction of possible MCRs in solvent-free environments by the combination of machine learning (ML) and quantum chemical computations (such as DFT).
- Creation of AI-based instruments to evaluate kinetics, thermodynamics, and chemical reactivity for appropriate MCR partners.

6.2. Library Design for Sustainable MCRs:

- Creating virtual libraries of solvent-free, environmentally safe MCRs for quick hit-to-lead detection in agricultural and pharmaceutical applications.
- In silico screening for combinations that produce analogues of natural products, peptidomimetics and heterocycles.

6.3. Mechanistic Studies and Reaction Pathway Mapping:

• Using sophisticated spectroscopy (such as in situ IR and solid-state NMR) and computational techniques to clarify the solid-state reaction processes in solvent-free systems.

• Software for reaction prediction, such as SynRoute, IBM RXN, or DeepChem, can aid in the mechanistic design of innovative MCRs.

6.4. Green Metrics & Process Optimization:

• E-factor, atom economy, and reaction mass efficiency are examples of green chemistry metrics that should be incorporated into future MCR investigations. [34]

• Utilizing Process Analytical Technology (PAT) and Design of Experiments (DoE) to maximize energy input (pulverization aided by microwave and ultrasound).

6.5. Predictive Combination of Bioactive Scaffolds:

• Using structure-activity relationship (SAR) prediction, creating MCRs that include several bioactive heterocycles (such as pyrazoles, imidazoles and thiazoles).

• Use in targeted scaffold synthesis for medication repurposing and personalized medicine.

7. Future Scope in Preclinical Applications:

7.1. Eco-friendly Synthesis of Lead Molecules:

Rapid synthesis of structurally varied libraries is made possible by solventfree MCRs, which is essential for early-stage high-throughput screening (HTS).

7.2. Pharmacophore Hybridization:

This is very helpful for multi-target drug design in the preclinical stage, particularly for conditions like diabetes, cancer, and neurodegenerative illnesses.

➢ Integration with AI & Automation:

When MCRs are combined with automated platforms and AI-driven molecular design, the scope is further expanded by facilitating the quick and scalable synthesis of drugs for preclinical pharmacokinetics (PK), ADME, and toxicity assessment.

C. Future Scope of Solvent-Free Reactors in MCRs:

- **.Sustainability and Green Chemistry:**
  - Reducing environmental and health risks by doing away with solvents is consistent with green chemistry concepts.
  - These techniques are perfect for the environmentally aware agricultural and pharmaceutical sectors due to their energy efficiency and atom economy.
- **Integration with Modern Technologies:**
  - In solvent-free environments, MCRs with ultrasonic enhancement and microwave assistance can significantly speed up reactions and increase yields.
  - Ball mill-based mechano chemistry provides accurate energy input and is industrially scalable.
- **Automation and Artificial Intelligence (AI):**
  - AI-guided optimization can predict optimal conditions for solvent-free MCRs, reducing trial-and-error in lab synthesis.
  - Smart reactors with in-line monitoring and real-time analysis can aid in the scale-up of complex reactions. [35]
- **Preclinical and Medicinal Applications:**
  - The potential for quicker drug candidate development with the use of quick, hygienic MCR procedures.
  - Heterocyclic scaffolds important for antiviral, antibacterial, and anticancer medicines are easily accessible thanks to solvent-free MCRs.[36]
- **Challenges and Research Needs:**
  - Material restrictions for temperature control and grinding machinery.
  - Reporting and comparing solvent-free procedures need to be standardized. [37]

8. Conclusion:

Solvent-free multicomponent reactions represent an efficient, sustainable, and environmentally friendly approach for the synthesis of heterocyclic Schiff bases. These strategies enhance atom economy, reduce reaction time, minimize hazardous solvent usage, and simplify purification processes while maintaining high product yields. The integration of green chemistry principles with multicomponent methodologies enables the rapid construction of structurally diverse and biologically significant heterocyclic frameworks. Overall, this study highlights the potential of solvent-free MCRs as a powerful tool for sustainable pharmaceutical and material synthesis, benefiting society by promoting eco-friendly chemical processes and paving the way for future innovations in green synthetic chemistry.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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