



Review on Recent Advances in Green Synthesis of Benzimidazole Derivatives: Sustainable Synthetic Strategies and Biological Applications

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ARTICLE INFO	ABSTRACT
Article history: Received – 02 October 2021 Received in revised form – 22 November 2021 Accepted – 23 November 2021 Available online – 03 December 2021	Benzimidazole is an important nitrogen-containing fused heterocyclic scaffold that has attracted considerable attention in organic, medicinal and pharmaceutical chemistry because of its structural versatility and broad biological properties. The benzimidazole nucleus is present in numerous biologically active molecules and has been associated with antimicrobial, antiviral, anticancer, anti-inflammatory, antitubercular, antiparasitic and other pharmacological activities [1–4]. Conventional approaches for the preparation of benzimidazole derivatives frequently involve hazardous organic solvents, corrosive reagents, prolonged heating and tedious purification procedures. These limitations have stimulated the development of sustainable synthetic methodologies based on the principles of green chemistry. Recent research has demonstrated that solvent-free reactions, mechanochemistry, microwave irradiation, ultrasound-assisted synthesis, deep eutectic solvents, ionic liquids, recyclable heterogeneous catalysts and metal-free catalytic systems can provide efficient routes to structurally diverse benzimidazole derivatives [5–9]. Mechanochemical synthesis is particularly attractive because it can substantially reduce solvent consumption, reaction time and energy requirements. Similarly, deep eutectic solvents provide alternative reaction media with potential advantages in recyclability and reduced environmental impact [10,11]. The biological importance of benzimidazole derivatives has also encouraged extensive structure–activity relationship investigations and the development of hybrid molecules containing additional pharmacophores [2,12]. This review summarizes recent advances in sustainable synthesis of benzimidazole derivatives, focusing on reaction strategies, catalysts, green solvents, mechanochemical approaches, characterization, biological applications and structure–activity relationships. Future opportunities and challenges associated with the development of environmentally responsible benzimidazole-based molecules are also discussed.
Keywords: Benzimidazole; Green chemistry; Sustainable synthesis; Mechanochemistry; Deep eutectic solvents; Microwave synthesis; Biological activity; Heterocyclic chemistry; Medicinal chemistry.	

1. Introduction:

Heterocyclic compounds constitute one of the most important classes of molecules in modern organic and medicinal chemistry. Nitrogen-containing heterocycles are particularly significant because they are present in numerous natural products, pharmaceutical agents and biologically active molecules. Among these, benzimidazole represents a privileged heterocyclic scaffold with extensive applications in medicinal chemistry and drug discovery [1,3].

Benzimidazole consists of a benzene ring fused with an imidazole ring containing two nitrogen atoms. Its electronic characteristics, hydrogen-bonding ability, aromaticity and capacity for substitution at different positions provide considerable structural flexibility. These properties enable benzimidazole derivatives to interact with diverse biological targets, including enzymes, receptors, nucleic acids and other biomolecular systems [2,4].

A wide variety of pharmacological properties have been reported for benzimidazole derivatives, including antimicrobial, antiviral, antifungal, anticancer, anti-inflammatory, antitubercular, antiprotozoal, antihypertensive and antidiabetic activities [1,2]. The broad biological profile of this scaffold has therefore made it an

important structural component in medicinal chemistry research. However, conventional organic synthesis can generate considerable quantities of waste and may require volatile organic solvents, toxic reagents, elevated temperatures and lengthy reaction procedures. The pharmaceutical and fine-chemical industries have consequently increased their interest in sustainable approaches that minimize environmental impact while maintaining synthetic efficiency [5].

Green chemistry provides an important framework for addressing these challenges. In recent years, sustainable approaches to benzimidazole synthesis have included solvent-free reactions, microwave irradiation, ultrasound, mechanochemistry, water-based procedures, ionic liquids, deep eutectic solvents and recyclable catalysts [6–11]. Recent reviews specifically identify these strategies as important directions in contemporary benzimidazole chemistry.

2. Chemical Structure and Importance of Benzimidazole:

Benzimidazole is an aromatic bicyclic nitrogen heterocycle formed by fusion of benzene and imidazole rings. The presence of

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two nitrogen atoms gives the molecule distinctive electronic and acid–base properties.

The benzimidazole nucleus can undergo functionalization at several positions, particularly at the N-1 and C-2 positions and on the benzene ring, especially C-5 and C-6. Variation in these positions allows researchers to modify lipophilicity, electronic properties, hydrogen bonding, steric characteristics and biological activity [2, 12].

Substitution at different positions can therefore significantly alter the biological profile of the resulting molecule. Studies of benzimidazole derivatives have demonstrated that appropriately selected electron-donating and electron-withdrawing groups can influence target binding and biological potency [12].

The versatility of this scaffold explains its continued importance in pharmaceutical chemistry and in the development of new antimicrobial and anticancer candidates. A 2026 review further emphasizes that structural modification of benzimidazole can generate derivatives with anticancer, antiviral, antimalarial, antimicrobial and anti-inflammatory properties.

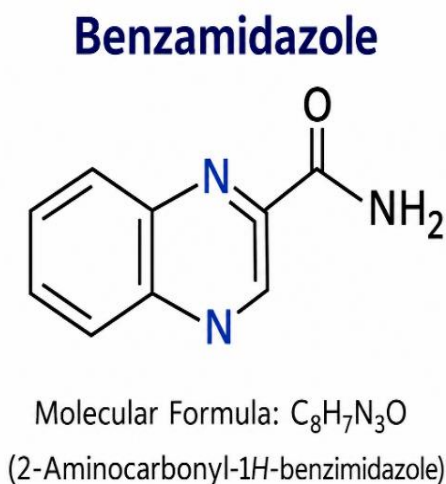


Fig-1 Chemical structure of Benzimidazole

3. Limitations of Conventional Benzimidazole Synthesis:

Traditional methods for benzimidazole synthesis commonly involve condensation of o-phenylenediamine with aldehydes, ketones, carboxylic acids or their derivatives. Depending on the reaction, oxidizing agents, Lewis acids, mineral acids or transition-metal catalysts may be employed [5, 7].

Although these procedures can provide good yields, several limitations remain:

- Use of volatile organic solvents
- High reaction temperatures
- Long reaction times
- Generation of chemical waste
- Difficult purification
- Use of corrosive acids or bases
- High energy consumption
- Limited catalyst recyclability

These drawbacks have encouraged the development of environmentally benign alternatives.

The objective of green synthesis is not simply to increase product yield; rather, it is to minimize waste, reduce hazardous

substances, and improve atom economy and lower energy consumption while maintaining synthetic performance.

4. Green Chemistry Approaches to Benzimidazole Synthesis:

Table 1. Conventional and Green Approaches for Benzimidazole Synthesis

S. No.	Synthetic approach	Typical reaction feature	Major advantage	Green chemistry benefit
1	Conventional heating	Organic solvent + heating	Simple and established	Limited
2	Solvent-free synthesis	No reaction solvent	Less waste	High
3	Microwave-assisted synthesis	Rapid dielectric heating	Short reaction time	Energy/time saving
4	Ultrasound-assisted synthesis	Acoustic cavitation	Mild conditions	Reduced energy/reaction time
5	Mechanochemical synthesis	Grinding/milling	Minimal solvent	Excellent solvent reduction
6	Deep eutectic solvent	DES as reaction medium/catalyst	Reusable medium	Low volatility and recyclability
7	Ionic-liquid catalysis	Ionic liquid as catalyst/medium	Catalyst recovery possible	Reduced VOC use
8	Heterogeneous catalysis	Solid/recoverable catalyst	Easy separation	Catalyst recycling
9	Metal-free catalysis	Organic/acid/base catalyst	Avoids metal contamination	Cleaner pharmaceutical synthesis
10	Nanocatalytic synthesis	Metal/metal-oxide nanoparticles	High catalytic activity	Potentially recyclable catalyst

Source: Compiled from reported green synthetic approaches [5–17].

4.1. Solvent-Free Synthesis

Solvent-free reactions are among the simplest approaches to sustainable organic synthesis. Elimination of the reaction solvent can substantially reduce solvent waste and simplify product isolation. Mechanochemical solvent-free synthesis of benzimidazoles has received considerable attention. Agarwal and co-workers developed a mechanochemical method using aromatic aldehydes and o-phenylenediamine in the presence of urea nitrate. The reaction occurred under solvent-free conditions at room temperature and generated 1,2-disubstituted benzimidazoles within a very short reaction time. Reported yields were 92–99%, with favourable green chemistry parameters including high atom economy and reaction mass efficiency [13].

Such approaches demonstrate that efficient benzimidazole synthesis does not necessarily require conventional solvent-based heating table-1.

5. Mechanochemical Synthesis:

Mechanochemistry involves chemical transformations induced by mechanical energy, commonly through grinding, milling or related processes. It has emerged as an important strategy for reducing solvent consumption and improving the sustainability of organic synthesis.

Zhang et al. reported a mortar–pestle grinding procedure for the synthesis of benzimidazoles using aldehydes and o-

phenylenediamine in the presence of acetic acid. The condensation–cyclization sequence afforded benzimidazole products in yields of up to 97% [14].

A more recent study reported the use of an ionic liquid, [EMIM] AlCl₄, as catalyst in a mechanochemically assisted synthesis. The reaction employed ethanol as an environmentally preferable solvent together with grinding in a mortar and pestle, giving benzimidazole derivatives with attractive yields and relatively short reaction times [15].

Mechanochemical synthesis offers several advantages:

1. Reduced solvent consumption
2. Lower energy requirements
3. Short reaction times
4. Simple experimental setup
5. Potential scalability
6. Reduced waste generation

Therefore, mechanochemistry represents an important component of sustainable benzimidazole chemistry.

6. Deep Eutectic Solvents in Benzimidazole Synthesis:

Deep eutectic solvents (DESs) have emerged as alternative reaction media because they can be prepared relatively simply from suitable components and can possess low volatility and useful catalytic properties.

A notable approach involved the synthesis of benzimidazole derivatives using DES as both reaction medium and reagent. The method employed o-phenylenediamine and aldehydes and avoided the use of an additional external solvent [10].

More recently, Zr- and Ce-based deep eutectic solvents were investigated for benzimidazole synthesis. Among the systems examined, a ZrOCl₂·8H₂O/urea-based DES showed particularly promising catalytic activity for the synthesis of 2-substituted benzimidazoles. The reported methodology combined good conversion, straightforward catalyst preparation, organic-solvent-free conditions and catalyst reusability [11].

The use of DES can therefore address several green chemistry objectives simultaneously.

7. Microwave-Assisted Synthesis:

Microwave irradiation has become an important tool in modern synthetic chemistry because it can provide rapid and relatively uniform heating.

Compared with conventional heating, microwave-assisted synthesis can substantially shorten reaction times and sometimes improve yields and selectivity. Microwave methods have been explored for the preparation of various nitrogen-containing heterocycles, including benzimidazole derivatives [5,16].

The major advantages include:

- Rapid heating
- Reduced reaction time
- Potential improvement in yield
- Lower energy consumption
- Convenient reaction monitoring

Microwave-assisted approaches are therefore particularly valuable when rapid library synthesis of structurally diverse benzimidazole derivatives is required.

8. Ultrasound-Assisted Synthesis:

Ultrasound irradiation provides another alternative energy source for organic synthesis. Acoustic cavitation generated by ultrasound can enhance mixing and mass transfer and may accelerate chemical transformations.

For benzimidazole synthesis, ultrasound-assisted methods can potentially reduce reaction times and enable reactions under milder conditions. Such approaches are consistent with the broader movement toward energy-efficient heterocyclic synthesis [5,8].

However, the environmental benefit should be evaluated comprehensively because the electricity requirement of ultrasonic equipment, solvent use and catalyst recovery can influence the overall sustainability of the process.

9. Ionic Liquids as Catalysts and Reaction Media:

Ionic liquids are salts with melting points generally below conventional temperatures and have been explored extensively as alternative reaction media and catalysts.

Their low volatility and tunable physicochemical properties have encouraged their use in green organic synthesis. Benzimidazole synthesis using ionic-liquid catalysts has been reported under mechanochemical and solvent-assisted conditions [15].

10. Metal and Nano Catalyst-Assisted Green Synthesis:

Heterogeneous catalysts and metal nanoparticles have received increasing attention because of their high surface area, catalytic efficiency and potential for recovery.

Iron-based nano catalysts are particularly interesting because iron is relatively abundant and several iron-containing catalytic systems can provide efficient transformations under mild conditions. A review published in *Sustainable Chemistry and Pharmacy* highlighted the importance of iron nano catalysts for sustainable benzimidazole synthesis, emphasizing their catalytic efficiency, mild conditions and recyclability [17].

However, the use of nanomaterials requires careful consideration of:

- Nanoparticle toxicity
- Metal leaching
- Catalyst preparation
- Recovery efficiency
- Environmental persistence

Thus, catalyst recyclability and life-cycle assessment are important when claiming that a nano catalytic method is genuinely green.

11. Metal-Free Catalytic Approaches:

Metal-free catalysis is another important direction in sustainable benzimidazole chemistry. Avoidance of transition metals can reduce concerns related to metal contamination, catalyst recovery and pharmaceutical residual metals.

Organic acids, heterogeneous organic catalysts, solid-supported reagents and other metal-free systems have been investigated for condensation and cyclization reactions leading to benzimidazole derivatives [5,7].

The development of metal-free protocols is particularly relevant to pharmaceutical synthesis, where residual metal contamination can represent a significant concern.

12. General Synthetic Strategy:

One of the most common approaches to benzimidazole formation involves the reaction of *o*-phenylenediamine with aldehydes, followed by cyclization and oxidation.

A simplified reaction sequence can be represented as:

***o*-Phenylenediamine + Aldehyde → Schiff-base intermediate → Cyclization → Benzimidazole derivative**

The reaction may proceed through initial condensation between one amino group and the carbonyl group, followed by intramolecular cyclization and subsequent oxidation/dehydrogenation. The exact mechanism depends on the catalyst, oxidant, solvent and reaction conditions.

13. Effect of Substituents on Benzimidazole Synthesis:

Substituents present on aromatic aldehydes can strongly influence the reaction.

Electron-withdrawing groups such as:

- $-\text{NO}_2$, $-\text{CN}$, $-\text{CF}_3$, $-\text{Cl}$, $-\text{Br}$

can alter carbonyl electrophilicity and consequently influence condensation rates.

Electron-donating groups such as:

- $-\text{OH}$, $-\text{OCH}_3$, $-\text{CH}_3$

modify electronic density and can influence both synthetic behaviour and biological activity.

The final biological activity is determined not only by electronic effects but also by lipophilicity, steric effects, hydrogen bonding and molecular geometry [12].

14. Characterization of Benzimidazole Derivatives:

Proper structural characterization is essential for confirming the formation and purity of synthesized benzimidazole derivatives.

FT-IR Spectroscopy

FT-IR spectroscopy can provide information regarding characteristic functional groups and the benzimidazole ring system. Changes in N–H, C=N, C–N and aromatic C–C/C–H vibrations can support product identification.

^1H NMR Spectroscopy

^1H NMR is useful for confirming aromatic proton environments, N–H signals and substituent-specific resonances.

^{13}C NMR Spectroscopy

^{13}C NMR provides information about carbon environments within the fused heterocyclic system and substituent groups.

Mass Spectrometry

Mass spectrometry can be used to determine molecular mass and support molecular formula assignment.

Elemental Analysis

CHN analysis can further support the proposed molecular composition.

Modern characterization should ideally combine several analytical methods rather than relying on a single spectrum.

15. Biological Applications of Benzimidazole Derivatives

Benzimidazole derivatives are recognized as versatile pharmacophores with a broad biological profile [1–4].

A comprehensive review published in 2021 described antimicrobial, antiviral, anticancer, antihypertensive, antidiabetic and other activities of benzimidazole derivatives [1].

A 2026 review similarly summarizes recent biological studies involving anticancer, antiviral, antimalarial, antimicrobial and anti-inflammatory applications [3].

15.1. Antimicrobial Activity

Benzimidazole derivatives have been extensively investigated against Gram-positive and Gram-negative bacteria as well as pathogenic fungi.

Structural modifications at N-1, C-2 and C-5/C-6 can substantially affect antimicrobial potency.

A recent review covering 2018–2024 reported extensive investigation of benzimidazole derivatives against bacterial and fungal pathogens, including multidrug-resistant strains. It also emphasized the growing use of hybrid structures and structure–activity relationship studies [18].

15.2. Antiviral Activity

The benzimidazole scaffold has also demonstrated antiviral potential. Its ability to participate in hydrogen bonding and aromatic interactions makes it suitable for designing molecules capable of interacting with viral proteins and enzymes.

Benzimidazole-containing hybrid molecules, especially benzimidazole–triazole systems, have attracted attention in antiviral research. A systematic review reported that incorporation of a triazole ring into benzimidazole-based structures can improve biological properties in several systems [19].

However, antiviral activity should be interpreted carefully because in-vitro activity does not necessarily indicate clinical effectiveness.

16. Anticancer Activity:

Anticancer activity represents another major area of benzimidazole research. Benzimidazole derivatives have been investigated against different cancer cell lines and molecular targets. Reported mechanisms include interference with kinase signalling, microtubule function, DNA-related processes and cellular redox systems [3].

The electronic nature and position of substituents can strongly influence cytotoxic activity. Recent literature emphasizes the importance of systematic SAR studies to optimize potency, selectivity, solubility and pharmacokinetic properties.

17. Anti-inflammatory and Other Activities:

Additional biological activities reported for benzimidazole derivatives include:

- Anti-inflammatory activity
- Antitubercular activity
- Antimalarial activity
- Antiprotozoal activity
- Antidiabetic activity
- Antihypertensive activity
- Antioxidant activity

The broad pharmacological profile is one of the major reasons why benzimidazole remains an important scaffold in medicinal chemistry [1,2,4] table-2.

Table 2. Biological Activities Reported for Benzimidazole Derivatives

S. N.	Biological activity	Potential biological target/mechanism	Importance
1	Antibacterial	Bacterial enzymes/cellular processes	Development of new antibacterial agents
2	Antifungal	Fungal cellular/enzymatic targets	Antifungal drug discovery
3	Antiviral	Viral enzymes/proteins	Development of antiviral candidates
4	Anticancer	Kinases, tubulin, DNA-related pathways	Cancer drug discovery
5	Anti-inflammatory	Inflammatory mediators/enzymes	Development of anti-inflammatory agents
6	Antitubercular	Mycobacterial targets	Tuberculosis research
7	Antimalarial	Parasite-specific pathways	Antimalarial drug development
8	Antiprotazoal	Protozoal enzymes/metabolism	Treatment of parasitic infections
9	Antioxidant	Free-radical scavenging/redox pathways	Oxidative-stress-related research
10	Antidiabetic	Enzymes involved in glucose metabolism	Metabolic disease research

18. Benzimidazole-Based Hybrid Molecules:

Molecular hybridization is an important contemporary strategy in medicinal chemistry.

In this approach, the benzimidazole nucleus is combined with another pharmacologically relevant heterocycle or functional group.

Examples include:

- Benzimidazole–triazole hybrids
- Benzimidazole–pyridine hybrids
- Benzimidazole–coumarin hybrids
- Benzimidazole–thiazole hybrids
- Benzimidazole–indole hybrids

Benzimidazole–triazole hybrids have received particular attention because the additional heterocyclic ring can improve antimicrobial and antiviral properties. Reported SAR studies indicate that groups such as F, Cl, Br, CF₃, NO₂, CN, OH and OCH₃ can influence biological activity depending on their position and molecular environment [19].

19. Structure–Activity Relationship:

Structure–activity relationship analysis is essential for understanding how chemical modifications influence biological performance.

Important structural parameters include:

N-1 Substitution

N-1 substitution can alter lipophilicity, hydrogen-bonding behavior and molecular orientation.

C-2 Substitution

The C-2 position is highly useful for introducing aromatic, heteroaromatic and other pharmacophoric groups.

C-5/C-6 Substitution

Modification of the fused benzene ring can alter electronic and physicochemical properties.

Electron-Withdrawing Groups

Halogens, nitro and cyano groups can influence molecular polarity, binding interactions and membrane permeability.

Electron-Donating Groups

Methoxy, hydroxyl and alkyl substituents may influence electron density and target interaction.

Recent literature confirms that systematic modification of these positions is an important strategy for optimizing biological activity [12,18].

20. Comparison of Conventional and Green Synthesis:

Parameter	Conventional synthesis	Green synthesis
Solvent	Often organic VOCs	Water, ethanol, DES, solvent-free
Energy	Conventional heating	Microwave/mechanoc hemical/ultrasound
Catalyst	Often non-recyclable	Recyclable/heterogeneous catalysts
Reaction time	Frequently longer	Often shorter
Waste	Relatively high	Reduced
Work-up	Often complicated	Frequently simplified
Environmental impact	Higher	Potentially lower
Scalability	Established	Requires further validation

Green approaches can therefore provide significant environmental benefits, but their sustainability must be assessed using quantitative parameters rather than yield alone

21. Green Chemistry Metrics:

Future research should report quantitative green chemistry parameters such as:

1. Atom economy
2. E-factor
3. Reaction mass efficiency
4. Process mass intensity
5. Energy consumption
6. Solvent intensity
7. Catalyst loading
8. Catalyst recyclability

For example, a mechanochemical benzimidazole synthesis using urea nitrate was reported with an E-factor of 0.11 and high atom economy and reaction mass efficiency, illustrating how quantitative metrics can demonstrate the sustainability of a synthetic procedure [13].

22. Advantages of Green Synthesis of Benzimidazoles:

The major advantages include:

1. Reduced use of hazardous solvents
2. Lower waste generation
3. Improved energy efficiency
4. Shorter reaction times
5. Potentially higher yields
6. Simplified purification
7. Catalyst recycling
8. Better alignment with sustainable pharmaceutical chemistry

9. Possibility of scale-up
10. Compatibility with modern medicinal chemistry

23. Limitations and Challenges:

Despite considerable progress, several challenges remain.

First, not every method described as “green” is necessarily environmentally benign. Some ionic liquids and nanomaterials may have toxicity or persistence concerns.

Second, many reported methods have been demonstrated only at laboratory scale. Their industrial applicability remains uncertain.

Third, catalyst recovery and recycling are sometimes insufficiently investigated.

Fourth, complete life-cycle assessment is rarely reported.

Finally, biological activity obtained in preliminary in-vitro experiments does not guarantee acceptable pharmacokinetics, selectivity or safety.

Therefore, future studies should combine synthetic efficiency with environmental, toxicological and pharmaceutical evaluation.

24. Conclusion:

Benzimidazole represents one of the most valuable nitrogen-containing heterocyclic scaffolds in modern organic and medicinal chemistry. Its structural versatility and broad biological profile have stimulated extensive research into the preparation and evaluation of new derivatives. Conventional synthetic methods, although effective, can suffer from limitations associated with hazardous solvents, energy consumption, waste generation and difficult purification.

Recent advances demonstrate that green approaches—including solvent-free synthesis, mechanochemistry, microwave irradiation, ultrasound, deep eutectic solvents, ionic liquids, recyclable catalysts and nano catalytic systems—can provide efficient alternatives to conventional procedures [5–18]. Particularly promising examples include mechanochemical synthesis at room temperature, DES-mediated synthesis under solvent-free conditions and recyclable catalytic systems.

At the same time, biological evaluation confirms that benzimidazole derivatives possess significant antimicrobial, antiviral, anticancer, anti-inflammatory and antiparasitic potential. Structural modification and molecular hybridization provide important tools for optimizing their biological properties [1–4,18,19].

The future of benzimidazole chemistry therefore lies in the integration of green synthetic methodology, quantitative sustainability metrics, advanced characterization, computational chemistry and biological evaluation. Such an integrated approach can contribute to the development of environmentally responsible and biologically effective benzimidazole-based molecules for pharmaceutical applications.

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