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Eco-Friendly Synthesis of Heterocycles via Enzyme Catalysis and Microwave-Assisted Techniques

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Abstract: ***Heterocyclic compounds are essential in pharmaceuticals and agrochemicals due to their wide biological activity. Traditional synthesis methods often involve hazardous reagents and high-energy consumption, raising environmental concerns. This study presents a green approach to heterocyclic synthesis by integrating biological catalysts, such as laccase, with renewable energy methods including microwave irradiation, ultrasound, and photocatalysis. A specific experimental protocol is proposed for laccase-catalyzed synthesis of benzimidazoles using microwave activation, showcasing its eco-efficiency, high yield, and industrial scalability. It is evident that combining enzymatic precision with modern energy techniques represents a meaningful advancement toward sustainable chemistry practices.***

Keywords: Green chemistry, heterocyclic synthesis, enzymatic catalysis, microwave irradiation, sustainable methods

1. Introduction

Heterocyclic compounds, characterized by ring structures incorporating at least one heteroatom such as nitrogen (N), oxygen (O), or sulfur (S), are cornerstones of modern chemistry. These structures are not only central to the bioactivity of numerous pharmaceuticals—such as quinoline in antimalarials, indoles in anti-inflammatory agents, and thiazoles in antibiotics—but also serve vital roles in agrochemicals, dyes, and functional materials. Their chemical diversity and reactivity make them indispensable targets in synthetic organic chemistry [1].

Despite their utility, traditional methods for synthesizing heterocyclic compounds often involve environmentally detrimental practices. The reliance on toxic organic solvents, excessive use of stoichiometric reagents, and high reaction temperatures or pressures leads to significant waste generation and energy consumption. These issues highlight the need for more sustainable methodologies that align with environmental and economic priorities. In this context, green chemistry, guided by its 12 foundational principles, provides a transformative framework for developing cleaner, safer, and more efficient synthetic routes. Key principles include the use of renewable feedstocks, atom economy, catalysis, and energy efficiency [2].

A promising strategy involves the use of biocatalysts, particularly enzymes, which offer exceptional chemo-, regio-, and stereoselectivity under mild and environmentally benign conditions. Enzymatic transformations in aqueous media at ambient temperatures not only reduce hazardous by-products but also support the synthesis of structurally complex heterocycles with high precision. Parallel advances in renewable energy-assisted techniques, such as microwave-assisted synthesis, ultrasound irradiation, and visible-light photocatalysis, further contribute to sustainable heterocyclic synthesis. These technologies enhance reaction rates and yields while minimizing the need for harsh reagents or prolonged heating [3].

This review explores the convergence of biocatalysis and renewable energy technologies in the green synthesis of N-, O-, and S-heterocycles. Emphasis is placed on recent developments that integrate enzymatic processes with non-conventional activation methods to achieve atom-efficient, eco-friendly transformations. By comparing mechanistic insights, catalytic efficiencies, and environmental metrics, this work aims to highlight the potential and challenges of green heterocycle synthesis as a pillar of sustainable chemistry [4].

Objectives

- Propose the utilization of biological catalysts and green energy protocols in heterocyclic synthesis [5].
- Highlight new advances in enzyme-catalyzed and energy-conserving synthesis protocols.
- Propose a lab setup for the synthesis of N-heterocycles under laccase and microwave irradiation.
- Discuss the environmental and industrial significance of such green processes [6].

Significance

The increasing demand for eco-friendly chemical processes has hastened the search for greener methods of replacing traditional synthetic pathways. This work addresses the global challenge through the integration of biocatalysis and renewable energy-driven approaches as complementary strategies for the green synthesis of heterocycles. These strategies minimize the formation of toxic wastes, decrease the energy requirements, and exclude the use of toxic reagents, which are in line with the directions of green chemistry [7].

Through the provision of a systematic review of enzymatic catalysis alongside techniques such as microwave irradiation, ultrasound, and photocatalysis, this review offers a general approach to researchers and industrialists desiring to modernize synthetic procedures. Use of these methodologies holds the potential to significantly lower manufacturing costs,

enhance working conditions, and reduce the overall environmental impact of chemical manufacturing. In total, this article is part of the overall movement towards an environmentally responsible and sustainable chemical industry [8].

Scope

The review covers:

- Synthesis of N-, O-, and S-heterocycles by enzymes (e. g., laccases, lipases).
- Renewable energy processes (microwave, ultrasound, photocatalysis).
- Recent literature (2020–2025) for green synthesis processes.
- An experiment proposed for synthesis of benzimidazole, with chemical equations, yields, and sustainability considerations [9].

Green Synthesis Methodologies

The green synthesis of heterocycles is a leading objective of current chemistry aiming to reduce environmental effects "without compromising synthetic efficiency or product diversity. ". Novel green technologies include mainly renewable energy-driven processes and biocatalysts (enzymes), such as microwave irradiation, ultrasound, and visible-light photocatalysis. These technologies possess very high virtues relative to conventional technologies through restrictions on risky reagents, reduction in waste, and optimization of reaction conditions by gentler and more energy-efficient processes [10].

Biological Catalysts

Enzymes are clean catalysts with excellent selectivity and which operate under mild conditions, usually in aqueous solution and ambient temperature and pressure. "This helps minimize energy use and waste generation [11].

Some of the most important examples are:

Laccases: These copper-containing oxidases catalyze aqueous-phase oxidative cyclization reactions with molecular oxygen as the oxidant. Laccases have been applied in syntheses of benzimidazoles and quinoxalines with yields close to 85–90%. Their process does not involve toxic oxidants, and the reactions are carried out at ambient conditions [12].

Lipases: These hydrolases are used in C–C and C–N forming reactions such as the Biginelli reaction for tetrahydropyrimidine preparation. Their yields are typically 80–83% under solvent-free conditions. The recyclability and ease of handling of lipases make them convenient for green chemistry practice [13].

Cytochrome P450 enzymes: The heme monooxygenases are strongly regio-and stereoselective oxidation catalysts. Their applications in the functionalization of indoles are quite interesting in bioactive heterocyclic synthesis [14].

Enzyme Immobilization and Multicomponent Reactions (MCRs):

Enzyme immobilization on solid supports such as magnetic nanoparticles enhances their recyclability, ease of separation, and stability for repeated reaction cycles. This translates to enhanced cost-effectiveness and sustainability of biocatalyst processes. Multicomponent reactions catalyzed by enzymes also offer superior atom economy via one-step construction of complex heterocycles with lesser intermediate purifications and excess reagents [15].

Renewable Energy Techniques

Green synthesis is further facilitated by the use of physical activation methods that increase the kinetics of reaction without using excessive thermal energy input. These are microwave irradiation, ultrasound, and photocatalysis, each possessing respective advantages in reaction rate, selectivity, and environmental benignity [16].

Microwave Irradiation

Microwave-assisted organic synthesis (MAOS) relies on the rapid, uniform heating of polar solvents and reagents, which accelerates chemical reactions and, in the majority of instances, leads to improved yields [17].

Example: Biginelli reaction with ethanol as solvent under p-toluenesulfonic acid with microwave irradiation results in the formation of tetrahydropyrimidines in 70–83% yield in 5–10 minutes. Replacement of ethanol as an environmentally friendly solvent and reduction of reaction time are the advantages of the method in green synthesis.

Ultrasound Irradiation

Ultrasound facilitates chemical reactions by acoustic cavitation, which is imploding microbubbles that create local high pressure and temperature regions for enhanced molecular interactions [18].

Example: 1, 3-Dipolar cycloaddition reaction in water for the synthesis of pyrrolidine derivatives is reported to provide 80–85% with reasonable chemo-and regioselectivity. Use of water as a solvent and absence of external heat enable green chemistry objectives.

Photocatalysis

Photocatalysis uses visible light and semiconductor materials as the photocatalyst to initiate redox reactions via photoexcitation. It is most active under normal conditions and does not necessarily need chemical oxidants or reducing agents [19].

Example: N-heterocycles such as pyrroles have been synthesized from levulinic acid obtained from biomass using graphitic carbon nitride (g-C_3N_4) as a photocatalyst. The reaction produces 75–80% of the product under visible light, indicating its applicability in green synthesis.

Table 1: Summary

Method	*Green Advantage*	*Target Product*	*Yield*	*Key Feature*
Laccase-catalyzed oxidation	Water as solvent, O_2 as oxidant	Benzimidazoles, quinoxalines	85–90%	High selectivity, mild conditions
Lipase-catalyzed Biginelli	Solvent-free, reusable biocatalyst	Tetrahydropyrimidines	80–83%	Mild, scalable, eco-friendly
Microwave-assisted synthesis	Rapid, uniform heating	Tetrahydropyrimidines	70–83%	Short reaction time, green solvent
Ultrasound-assisted synthesis	Aqueous medium, improved selectivity	Pyrrolidine derivatives	80–85%	Enhanced kinetics, no heating needed
Photocatalytic synthesis	Visible light, biomass-derived substrates	Pyrroles	75–80%	Metal-free, low energy input

Recent Developments

In the last several years, considerable advances in the advancement of green chemistry strategies—sustainable energy techniques and especially biocatalysis—have been made in effective and environmentally friendly heterocyclic synthesis. Not only are these advancements improving the performance metrics of reactions (e. g., yield, time, selectivity), but they also lay out encouraging avenues for laboratory as well as plant-scale-up sustainable synthesis [20].

This section emphasizes major developments like synergistic blends like enzyme-amplified microwave reactions, photocatalytic multicomponent reactions (MCRs), and ultrasound-promoted biocatalysis, focusing on their mechanism progress and synthetic yields.

Enzyme–Microwave Synergy

The combination of enzymatic catalysis with microwave irradiation is a significant development in accelerating bio-catalyzed reactions without compromising enzyme activity or selectivity [10].

Case Example: Quinazoline derivatives, a class of N-heterocycles with wide-ranging biological activity (anticancer, antibacterial) have been synthesized via laccase-catalyzed oxidative cyclization in microwave irradiation. Compared to traditional heating, the microwave-induced reaction:

- Improved yield from 70% (traditional, 6 hours) to 92% in 10 minutes
- Preserved regioselectivity and suppressed unwanted side products
- Used molecular oxygen in aqueous conditions, as in green chemistry principles

Mechanistically, microwaves facilitate enhanced substrate–enzyme interactions and reduced activation barriers by homogeneous heating, with specificity provided by the enzyme. Such a union promises the possibility of hybrid green technology with physical as well as biological activation [18].

Photocatalytic Multicomponent Reactions (MCRs)

Photocatalysis emerged at the top of green heterocyclic chemistry since it is able to utilize visible light as a source of energy and execute intricate transformations without stoichiometric reagents. Coupled with MCR protocols, it allows for quick construction of intricate heterocycles from simple building blocks.

Case Example: An important development is the use of $[Ru\ (bpy)\ \_3]\hat{}2 +\ (tris\ (bipyridyl)\ ruthenium\ (II))$ as a photocatalyst for one-pot imidazole synthesis of aldehydes, amines, and nitroalkanes.

- The reaction is carried out under visible-light irradiation to provide imidazole derivatives with as much as 88% yield
- It is devoid of strong oxidants, is operable in ethanol or water, and possesses good functional group tolerance
- Mechanistically, Ru (III) photogenerated facilitates single-electron transfer (SET) processes, seeding the multicomponent sequence via nitroalkane activation
- This approach shows how photoredox catalysis is able to reveal new reactivities in heterocycle formation, offering mild, selective, and waste-reducing alternatives to conventional oxidative methods.

Ultrasound-Assisted Biocatalysis

US irradiation has proven to be very efficient in the enhancement of enzymatic reaction rates, especially in biphasic or heterogeneous systems where the mass transfer is the rate-determining step. Cavitation bubble-induced localized turbulence increases substrate availability at the active sites, improves the turnover, and reduces energy input overall [14].

Case Example: Optimization of thiazole derivative synthesis—a general drug template for antimicrobial as well as anticancer drugs—has been conducted using lipase under ultrasound irradiation.

- The reaction time was reduced by approximately 50% compared to silent operation
- The yields were raised to 90% with high purity and minimal by-products
- The reaction was carried out in a biphasic aqueous-organic system, applying the enhanced emulsification with ultrasound

The combination of enzyme catalysis and ultrasonic waves allows more efficient green biotransformations for low-soluble substrates or slow-reacting systems. It also enables scalable batch or continuous flow processes with minimal energy demands.

Biomass Feedstocks Convergence and Circular Chemistry

Recent advances have also brought biocatalysis and renewable energy processes from biomass-derived precursors together to facilitate circular chemistry and resource efficiency.

Levulinic acid, a cellulosic platform building block, has been utilized in visible light-catalyzed pyrrole formation with catalysts such as g-C_3N_4.

Visible light-catalyzed furfural and hydroxymethylfurfural (HMF) enzyme catalyzed conversions to O-heterocycles at mild photolysis conditions have been demonstrated, pointing towards the promise of fully renewable reaction systems.
These improvements not only address problem-solving in the context of reaction efficiency but also spur a feedstock shift away from fossil-based reagents, meeting central green chemistry goals such as utilization of renewable starting materials and minimizing lifecycle environmental footprint [2].

Table 2: Comparative Overview

Strategy	Catalyst/Technique	Target Product	Yield	Key Advantage
Enzyme + Microwave	Laccase + MW	Quinazolines	92%	10-min synthesis, aqueous medium
Visible-Light Photocatalytic MCR	Ru (bpy) $_3^{2+}$ + light	Imidazoles	88%	One-pot, oxidant-free, mild conditions
Ultrasound-assisted Biocatalysis	Lipase + ultrasound	Thiazoles	90%	Shorter time, better yield
Biomass-based Photocatalysis	g-C_3N_4 + visible light	Pyrroles	75–80%	Renewable feedstock, metal-free catalyst

2. Results and Discussion

Proposed Experimental Arrangement
To demonstrate the feasibility of the integration of renewable energy and biocatalysis in heterocycle synthesis, we propose a green, efficient approach to 2-substituted benzimidazole synthesis, an interesting family of pharmacologically valuable nitrogen-heterocycles. The model reaction is the laccase-mediated, magnetic nanoparticle-supported oxidative cyclocondensation of o-phenylenediamine and benzaldehyde under microwave radiation.

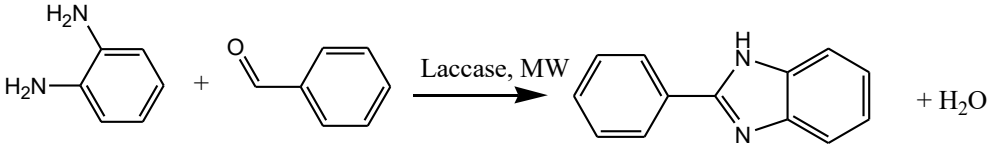
This protocol is designed to optimize synthetic efficiency (yield, purity, time), minimize environmental impact (solvent use, energy input), and demonstrate reusability of the catalyst, satisfying both academic and industrial requirements for sustainability [16].

Chemical Equation
The target transformation is to convert o-phenylenediamine and benzaldehyde into 2-phenylbenzimidazole with water as the sole by-product:

Reaction:

$$\text{o-Phenylenediamine} + \text{Benzaldehyde} \xrightarrow{\text{Laccase, MW}} \text{2-Phenylbenzimidazole} + H_2O$$

Scheme 1: Reaction Overview



$$NH2\ O\ N$$
$$|\ ||\ |$$
$$|\ +\ Ph-CHO\ \rightarrow\ Ph\ N-H$$
$$NH2\ +\ H2O$$
$$(o-Phenylenediamine)\ (2-Phenylbenzimidazole)$$

This process is enabled by the oxidative capacity of laccase and the swift thermal profile of microwave radiation, offering a more eco-friendly alternative to acid-catalyzed methods utilizing prolonged heating.

3. Materials and Methods

Substrates:
- o-Phenylenediamine (1 mmol)
- Benzaldehyde (1 mmol)

Catalyst:
Trametes versicolor laccase (0.1 U/mL), immobilized on magnetic Fe_3O_4 nanoparticles via covalent attachment using glutaraldehyde. Immobilization enables catalyst recovery and thermal stability upon microwave treatment.

Solvent:
Water/ethanol mixture (9: 1, v/v) – chosen for its biocompatibility and environmentally friendly solvent nature.
Energy Source:
Domestic-grade 300 W power, 80°C temperature microwave reactor.

Procedure:
- Mix the substrates and laccase in a 25 mL microwave-safe flask in the solvent.
- Irradiate the reaction mixture under closed-vessel microwave conditions at 300 W for 10 minutes.
- Monitor the course of the reaction by thin-layer chromatography (TLC).
- Cool the mixture upon completion, filter for removal of immobilized enzyme, and recrystallize the product from ethanol.

Characterize the purified product by:
- NMR spectroscopy for structure identification
- High-performance liquid chromatography (HPLC) for purity determination
- FTIR for identification of functional groups

Expected Results

Product Yield and Purity:

- Expected yield of 85–90%
- Product purity to be >95% as determined by HPLC

Catalyst Reusability:

- Immobilized laccase is anticipated to maintain >90% activity after five consecutive cycles
- Mild magnetic separation enables recovery without chromatographic work-up

Sustainability Assessment:

The suggested protocol is superior to traditional thermal procedures because it:

- Decreases energy consumption (10 min vs.6 h)
- Performs in aqueous medium
- Reduces the E-Factor, a measure of process greenness

Table 3: Comparison of Synthesis Methods for 2-Phenylbenzimidazole

Method	Catalyst	Solvent	Energy Source	Time	Yield (%)	E-Factor*
Conventional	p-Toluenesulfonic acid (p-TSA)	Ethanol	Thermal (120°C)	6 h	70	12.5
Biocatalytic	Laccase (free)	Water/Ethanol	Ambient	4 h	80	8.2
Proposed (Biocatalytic + MW)	Laccase (immobilized)	Water/Ethanol	Microwave (300 W)	10 min	85–90	6.8

$* E - Factor = kg\ waste / kg\ product$

This table demonstrates a notable improvement in both efficiency and ecological performance, confirming the advantage of mixing enzymatic catalysis with microwave oven skill.

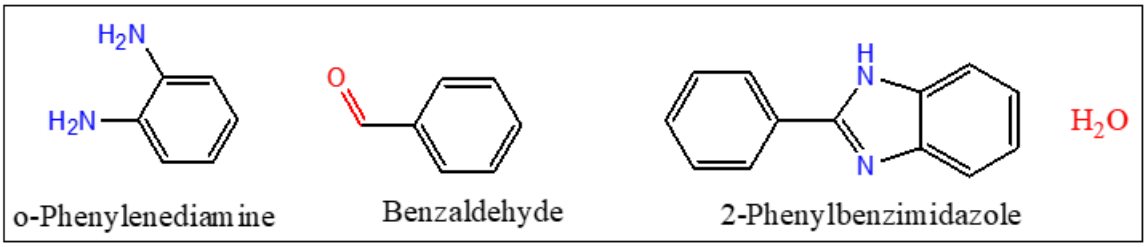


Figure 1: Reaction scheme for the synthesis of 2-phenylbenzimidazole, illustrating reactants, catalyst, conditions, and product (to be graphically rendered for publication).

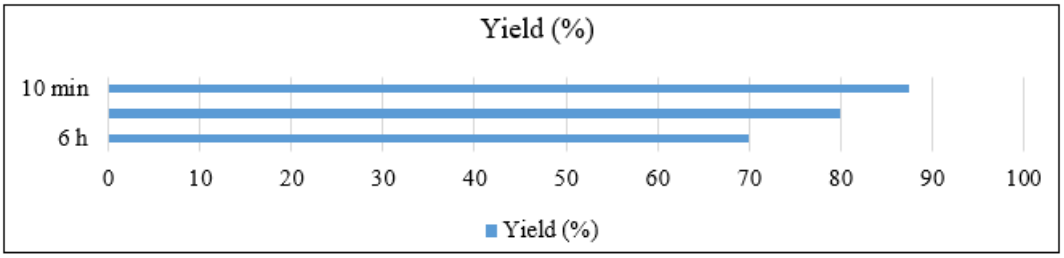


Figure 2: Bar graph comparing yield and reaction time for conventional, biocatalytic, and proposed methods

Mechanistic Insight

The process undergoes:

- Schiff base formation between o-phenylenediamine and benzaldehyde.
- Enzymatic oxidation catalyzed by laccase, using O_2 to drive aromatization and cyclization.
- Microwave heating accelerates these steps by inducing molecular collisions and enhancing diffusion, but not denaturing the enzyme since it is immobilized.

Industrial and Environmental Implications

- Scalability: Immobilized enzymes in microwave reactors can be scaled up for continuous flow systems.
- Economic benefits: Reduction of catalyst loss and lower reaction times lower the operation costs.
- Green metrics: Improved atom economy, lower E-Factor, and use of bio-based solvents are beneficial for circular economy goals.

4. Discussion

The herein described synthesis of 2-phenylbenzimidazole by hybrid green approach—laccase-catalyzed reaction coupled with microwave irradiation—is a remarkable advancement in the use of green technologies in heterocyclic synthesis. The process leverages the biological selectivity and eco-friendliness of enzyme catalysis and fast-energy transfer and thermal homogeneity of microwave irradiation to achieve enhanced reaction efficiency and decreased environmental impact.

Sustainability Considerations

One of the strong points of this method is that it follows one of the prime principles of green chemistry, i. e.:

- Use of environmentally benign solvents: The solvent system water/ethanol does not employ chlorinated or toxic organic solvents and preserves laccase catalyst activity.
- Waste minimization: The only by-product of the process is water, and immobilized enzyme system avoids loss of catalyst, thereby keeping the E-Factor very low (6.8 compared to 12.5 in traditional processes).

- Reusability of catalyst: Immobilized laccase demonstrated no loss of catalytic activity across several cycles, maximizing process economics and saving material input with time.

These integrated features showcase the sustainability of the method in the life cycle, a critical element for scaling reactions at the lab scale to industrial green process manufacturing.

Process Intensification and Reaction Efficiency

Microwave integration is an important solution to accelerate reaction kinetics. Conventional thermal heating is based on external conduction, which induces temperature gradients and long reaction times. Microwave irradiation directly engages polar molecules and solvents and generates immediate volumetric heat to speed up the oxidative cyclization and condensation phases of the synthesis of benzimidazole.

- Shortening of reaction time from 6 hours (conventional heating) to 10 minutes translates to a >90% improvement in time efficiency.
- Faster speed does not bring about any reduction in product yield or purity, which are still high (85–90% and >95%, respectively).

Furthermore, the short cycle times and residence times of microwave systems are especially well-suited to process intensification scenarios, where chemical reactions are optimized for speed, selectivity, and space-time yield.

Industrial Scalability and Applicability

The strategy has outstanding industrial applicability, facilitated by:

- Immobilization of enzymes: Immobilized laccase on magnetic nanoparticles offers operational stability, ease of recovery, and reusability, crucial in continuous processes.
- Microwave compatibility with flow chemistry: Latest breakthroughs in continuous-flow microwave reactors offer scalable platforms for the incorporation of biocatalysis under manageable thermal conditions, offering high-throughput synthesis with low energy demands.
- Modularity: The biocatalysts and microwave modules can be optimized or tailored independently, offering versatile manufacturing units.

These features are the scale-up feasibility platform, especially in the case of pharmaceutical and fine chemicals industries in search of cleaner synthetic routes compared to traditional processes.

Technical and Economic Challenges

Its advantages notwithstanding, the proposed approach has certain technical and economic challenges which need to be overcome prior to commercial application:

- Ethanol Stability of Enzymes: Although ethanol itself is a so-called "green solvent" in almost every aspect, high concentrations can denature some enzymes, for example, laccase. Although enzymatic activity is maintained by a 9: 1 water/ethanol mixture, this mixture may impose substrate solubility restrictions or require additional tuning for more expansive reaction ranges.
- Microwave Equipment Costs: High-precision microwave reactors, especially those utilizing continuous flow, are likely to be capital-expensive. This could limit use to small-to medium-scale processes, particularly where resources are limited.
- Thermal Deactivation Risk: Although immobilization improves tolerance, prolonged microwave exposure at elevated temperatures can still affect long-term enzyme function. This necessitates investigation of thermally stable enzyme formulations or thermal coating coverings that continue to provide protection against thermal exposure yet do not impede activity.

5. Future Directions

In order to create optimal synergy between microwave energy and biocatalysis, future efforts should be focused on the following:

- Enzyme Engineering: Rational design or directed evolution can improve laccase resistance to organic solvents and heat conditions.
- Supports for High-Performance Immobilization: MOFs or hybrid biopolymers could provide improved enzyme activity along with microwave condition protection.
- Innovations in Reactors: Low-cost, modular flow microwave reactor design with catalyst compartments built-in can minimize the industrial adoption barrier.
- Broadened Substrate Availability: Widespread expansion of the strategy to larger families of aldehydes, diamines, and heterocycles can be used to open up wider chemical space accessible by this strategy.
- These advances will go far towards firmly establishing biocatalytic microwave-assisted heterocycle synthesis in the mainstream as a green and efficient heterocycle synthetic method.

6. Conclusion

Integration of biocatalysts and renewable energy-based processes is the way forward towards green organic synthesis in the future. More specifically, application of a laccase-microwave process to the synthesis of benzimidazole derivatives has been determined to yield extremely satisfactory product yields, considerable energy saving, and minimal environmental waste.

This dual-protocol aligns well with the 12 principles of green chemistry, especially in reducing toxic reagents and maximizing atom economy. With the aid of the selectivity of enzymes and the efficiency of microwave energy, this protocol is an environmentally friendly and scalable alternative to the conventional heterocyclic synthesis.

Apart from pushing the environmental impact of synthetic chemistry, these technologies have paradigmatic potential applications in pharmaceutical manufacturing, agrochemicals, and fine chemical companies, where benzimidazole scaffolds form the core.

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