

Environmentally Benign Synthesis of Benzimidazoles: Progress and Prospects

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Abstract: *The increasing presence of chemical substances in our environment poses a significant challenge, as many of these compounds are non-degradable and contribute to pollution. These persistent pollutants disrupt the ecosystem, leading to environmental instability and potential health risks. To address this issue at its source rather than merely mitigating its effects, the concept of Green Chemistry (GC) was introduced. GC focuses on designing chemical products and processes that minimize or eliminate the use and generation of hazardous substances. In recent years, heterocyclic compounds have gained prominence due to their diverse pharmacological properties. Among them, benzimidazole, an aromatic heterocyclic compound, holds great significance in medicinal chemistry. It exhibits a wide range of therapeutic activities, including analgesic, anti-inflammatory, antiulcer, antihypertensive, antibacterial, antiviral, antifungal, anticancer, and antihistaminic properties. Given its medicinal importance, the synthesis of benzimidazole derivatives has become a key area of research for synthetic chemists. Traditional methods for synthesizing benzimidazoles often require prolonged heating, intricate apparatus setups, and costly procedures that contribute to environmental pollution. In contrast, green synthetic approaches offer eco-friendly alternatives that are cost-effective, energy-efficient, and sustainable. This review highlights various green methodologies for synthesizing substituted benzimidazoles, emphasizing their advantages over conventional techniques in terms of efficiency, simplicity, and environmental safety.*

Keywords: Environmentally Benign Synthesis of Benzimidazoles: Progress and Prospects

I. INTRODUCTION

Green Chemistry (GC) is a transformative approach to chemical research and industrial processes, emphasizing the development and application of environmentally friendly methods. It focuses on designing chemical products and processes that minimize or eliminate the use and generation of hazardous substances, thereby reducing environmental impact and promoting sustainability. The foundation of Green Chemistry lies in thoughtful design, considering not only the final product but also the manufacturing processes and their potential effects on human health and the environment. Key factors such as the selection of raw materials, reaction efficiency, and waste prevention play a crucial role in ensuring a safer and more sustainable chemical industry. Since the early 1990s, Green Chemistry has gained global recognition, leading to the establishment of guidelines and research priorities aimed at reducing environmental hazards associated with traditional chemical practices. Various international initiatives have been undertaken to integrate these principles into industrial applications, emphasizing both economic feasibility and long-term sustainability. The development of Green Chemistry continues to shape the future of chemical research, driving innovation toward safer, cleaner, and more efficient chemical processes.



II. FOCUSED AREAS UNDER GREEN CHEMISTRY PRINCIPLES

Utilization of Alternative Feedstocks

Significant advancements have been made in the field of Green Chemistry, with a strong emphasis on replacing conventional raw materials with sustainable alternatives. The transition from fossil fuel-based feedstocks to renewable resources is crucial for ensuring long-term environmental and economic sustainability. The chemical industry must prioritize the use of raw materials that are not only renewable but also safer for both workers and the environment. By adopting bio-based and less hazardous feedstocks, industries can reduce their ecological footprint while promoting safer and more efficient chemical processes.

Use of Less Hazardous Reagents

Extensive data are available on the toxicological and environmental impacts of many chemicals widely used in industrial processes. To enhance safety and sustainability, chemists should prioritize the use of less hazardous raw materials and reagents in chemical synthesis. When faced with challenges in achieving this, alternative strategies such as reducing the number of harmful compounds or modifying reaction conditions should be considered. The adoption of catalysts and innovative synthetic techniques can further minimize risks while improving efficiency.

Integration of Natural Processes: Biocatalytic Techniques

Advancements in biosynthetic methods over the past decade have led to the development of highly selective, energy-efficient, and environmentally friendly processes. These biocatalytic techniques operate under mild conditions, such as lower temperatures and reduced energy consumption, while delivering high yields and minimizing toxicity. Green Chemistry research has played a key role in replacing traditional methods with novel catalytic approaches that generate fewer waste products, contributing to a more sustainable chemical industry.

Use of Alternative Solvents

For decades, polychlorinated and aromatic solvents have been widely used in synthetic organic chemistry, particularly for extractions. However, due to their harmful effects, solvents such as carbon tetrachloride (CCl_4) have been banned, while others face strict regulations. In response, chemists have shifted toward using low-toxicity solvents that can be recycled or decomposed at high temperatures, reducing environmental and health hazards. The chemical industry, guided by Green Chemistry (GC) principles, continues to invest in developing safer solvents that pose minimal risks to workers and can degrade more easily under natural conditions.

Designing Safer Chemicals and Products

Advancements in analytical methods and toxicological testing have significantly improved the understanding of chemical toxicity and its underlying mechanisms. The use of **Quantitative Structure-Activity Relationships (QSAR)** allows for faster assessments of toxicity, carcinogenicity, and other hazardous effects of newly synthesized compounds. By integrating GC principles, modern chemical products are designed to be less toxic and more environmentally friendly. Industrial chemists have refined synthetic processes to incorporate renewable raw materials, operate at lower temperatures, conserve energy, reduce waste, and utilize safer alternative solvents, ultimately promoting a more sustainable approach to chemical manufacturing.

Developing Alternative Reaction Conditions

Innovative and environmentally friendly reaction techniques have been developed to enhance product formation, conserve energy, and minimize waste. Green Chemistry promotes the adoption of alternative methods such as photochemical reactions, microwave (MW)-assisted synthesis, and other sustainable techniques. These approaches not only improve reaction efficiency but also reduce the environmental footprint associated with conventional chemical processes.



III. MINIMIZING ENERGY CONSUMPTION

Reducing energy consumption is a key objective in Green Chemistry, particularly in light of climate change and increasing environmental concerns. The chemical industry has made significant efforts to optimize synthetic processes by lowering reaction temperatures, reducing the number of reaction steps, and improving overall efficiency. Green Chemistry research is continuously focused on minimizing energy use at every stage of manufacturing, ensuring more sustainable industrial processes with lower waste generation and reduced environmental impact.

In 1990, Paul Anastas and John Warner defined Green Chemistry as “*The design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances.*” As human society faces critical environmental challenges—including ozone depletion, air pollution, climate change, soil and water contamination, acid rain, and hazardous waste accumulation—Green Chemistry provides a sustainable approach to addressing these issues.

Anastas and Warner introduced the **Twelve Principles of Green Chemistry**, which serve as the foundation for environmentally responsible chemical practices. These principles were first published in their book *Green Chemistry: Theory and Practice* in 1998. Their contributions continue to shape the field, and both have served on the California Green Chemistry Science Advisory Panel, advocating for the integration of sustainable practices in the chemical industry.

The 12 Principles of Green Chemistry

1. **Waste Prevention:** Focus on preventing waste generation rather than treating or disposing of it after production.
2. **Maximizing Atom Economy:** Ensure that all materials used in the manufacturing process are incorporated into the final product, minimizing waste.
3. **Safer Synthesis Methods:** Use synthetic techniques that produce minimal or no toxic substances, ensuring safety for both humans and the environment.
4. **Designing Safer Chemicals:** Develop chemical products with reduced toxicity while maintaining their desired functionality.
5. **Reducing Solvents and Auxiliary Substances:** Minimize or eliminate the use of solvents and additional substances whenever possible.
6. **Energy Efficiency:** Optimize processes to operate at ambient temperature and pressure, reducing energy consumption and environmental impact.
7. **Utilizing Renewable Feedstocks:** Prioritize the use of renewable raw materials over depletable resources.
8. **Recycling Chemical Intermediates:** Reuse intermediates and blocking agents to minimize waste generation.
9. **Catalysis Over Stoichiometric Reagents:** Employ catalysts that facilitate multiple reaction cycles rather than inefficient reagents.
10. **Design for Degradation:** Ensure that chemical products break down into harmless substances in the environment after use.
11. **Real-Time Pollution Prevention:** Develop and implement analytical techniques for continuous monitoring and control of hazardous substances.
12. **Enhancing Chemical Safety:** Choose chemicals with minimal risks of accidents, explosions, and fires to ensure workplace and environmental safety.

IV. BENZIMIDAZOLE DERIVATIVES

In recent years, there has been significant interest in the synthesis of heterocyclic compounds containing nitrogen (N), oxygen (O), and sulfur (S) due to their broad range of pharmacological activities. Researchers have explored various environmentally friendly synthetic approaches, including solvent-free reactions, immobilization of reactants on solid

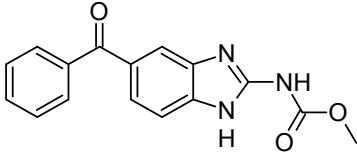
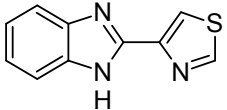
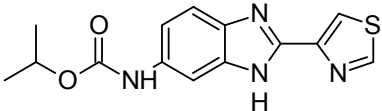
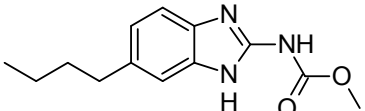
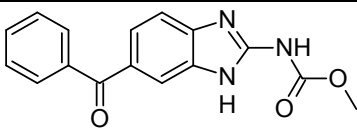
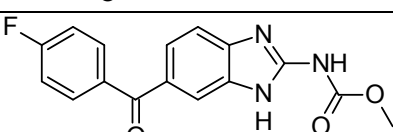
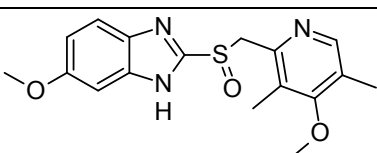


supports, microwave (MW) irradiation, the use of green catalysts, and eco-friendly solvents. Benzimidazole, a bicyclic heteroaromatic compound, holds a crucial place in medicinal chemistry as a **pharmacophore** and a **privileged structure** for drug development. Structurally, benzimidazole consists of a fused benzene (1) and imidazole (2) ring system, forming the benzimidazole core (3) (Scheme 1). Due to its versatile biological activities, the synthesis and functionalization of benzimidazole derivatives continue to be an area of active research in pharmaceutical and green chemistry.

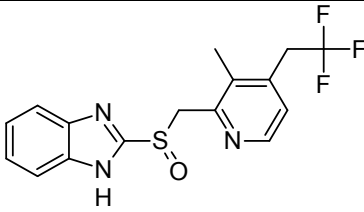
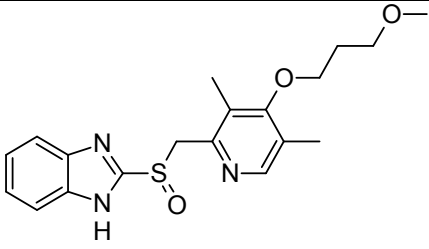
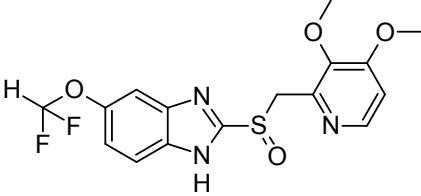
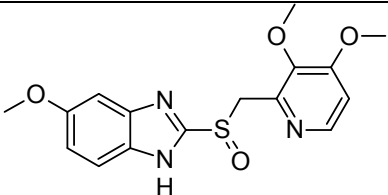
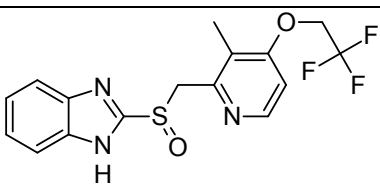
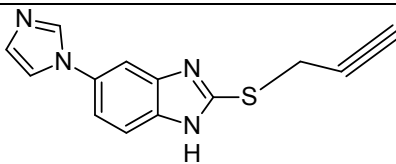
V. IMPORTANCE OF BENZIMIDAZOLE RING SYSTEM:

A wide range of Benzimidazole and their derivatives find uses in pharmaceutical and veterinary drugs showing therapeutic activities. Some of the commercially important Benzimidazole derivatives are listed below.

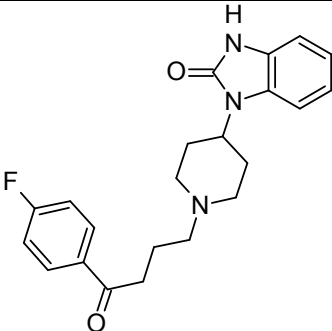
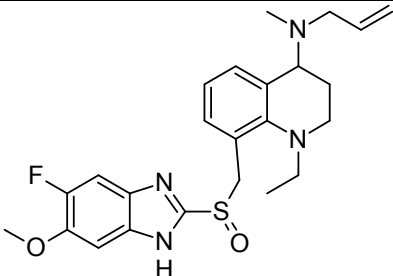
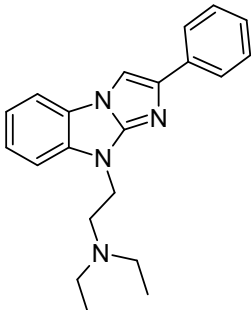
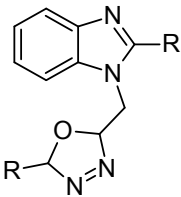
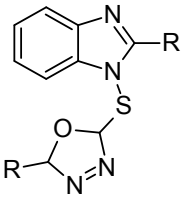
Table 1.

Sr. No	Trade Name	Structure	Activity
1	Mebendazole		Anthelmintic
2	Thiabendazole		Anthelmintic
3	Cambendazole		Anthelmintic
4	Parbendazole		Anthelmintic
5	Albendazole		Anthelmintic
6.	Flubenzadazole		Anthelmintic
7	Omeprazole		Anti-ulcer drugs

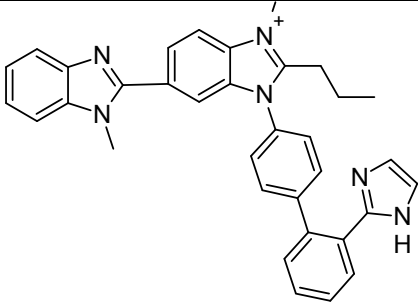
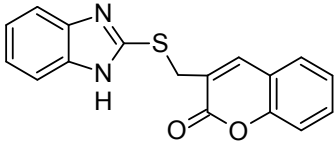
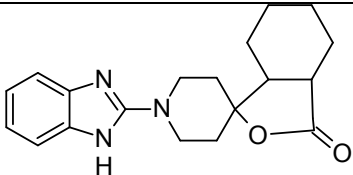
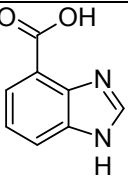
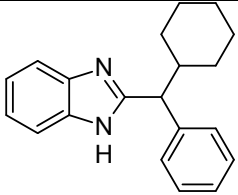
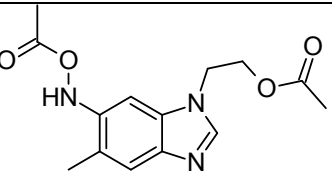
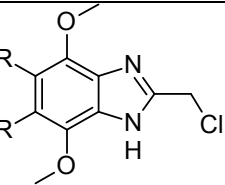


8	Lansaprazole		Anti-ulcer drugs
9	Rabeprazole		Anti-ulcer drugs
10	Pantoprazole		Anti-ulcer drugs
11	Esomeprazole		Anti-ulcer drugs
12	Triethoxy-pyridylBenzimidazole derivative		Anti-ulcer drugs
13	Thiophene derivatives of Benzimidazole		Anti-ulcer drugs

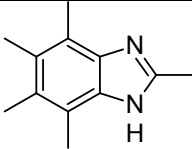
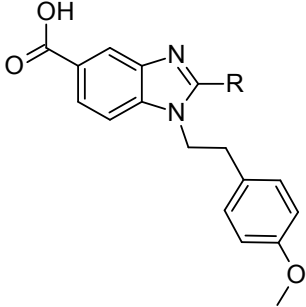
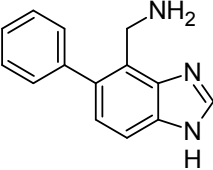
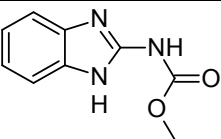
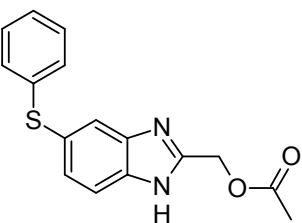
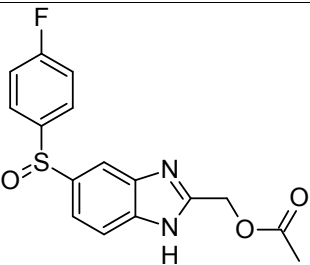
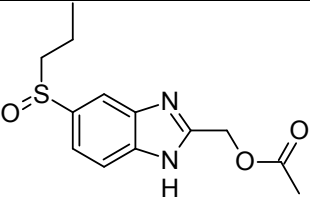


14	Droperidol		Anti-psychotic agents
15	Quinoline Benzimidazole Analog		Anti-psychotic agents
16	Imidazole derivative with Benzimidazole		Anti-psychotic agents
17	Oxazole derivative with Benzimidazole		Antimicrobial activity
18	Oxazole derivative with Benzimidazole and thio-linkage		Antimicrobial activity

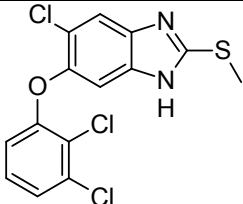


19	Bibenzoimidazole derivatives		Antagonist
20	Benzimidazole and coumarine derivative		Antiseptic virus c activity
21	Spiro compound of Benzimidazole		NPY N5 Receptor Antagonist
22	4-Carboxylic acid Benzimidazole		Selective 5 HT 4 Antagonist
23	Phenyl cyclohexyl derivative of Benzimidazole		Amp Activated protein kinase activator
24	Amide derivative of Benzimidazole		Anticancer activity
25	Substituted Benzimidazole		Anticancer activity



26	Alkyl substituted Benzimidazole		Antiamoebic activity
27	Benzyl substituted carboxyl Benzimidazole		Antilukemic activity
28	Phenyl amine derivative of Benzimidazole		Antidiabetic activity
29	Amide derivative of Benzimidazole		Cytocidal activity
30	Thioether derivatives of Benzimidazole		Nematicide and taeniacid
31	Oxfendazole		Roundworms and tapeworms
32	Ricobendazole		Anthelmintic

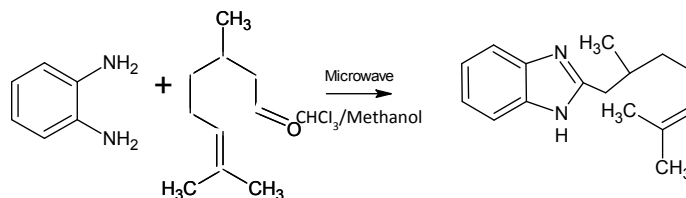


33	Triclabendazole		anthelmintic
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Despite the high efficiency of benzimidazole synthesis, many existing methods have limitations, including the need for elevated reaction temperatures, prolonged reaction times, toxic solvents, and expensive catalysts [17]. Therefore, the development of a **simple, mild, cost-effective, and environmentally friendly** approach for benzimidazole synthesis remains a key focus in research. Since the first reported applications of microwaves in synthetic chemistry in 1986, **microwave-assisted synthesis** has gained immense popularity, especially over the past two decades. This technique offers **significantly shorter reaction times, high product yields, and superior purity**, making it an attractive alternative to conventional methods. Numerous microwave-assisted strategies for benzimidazole synthesis have been developed to date. In this review, we explore various microwave-assisted methodologies for the efficient synthesis of benzimidazole derivatives, highlighting their advantages over traditional approaches.

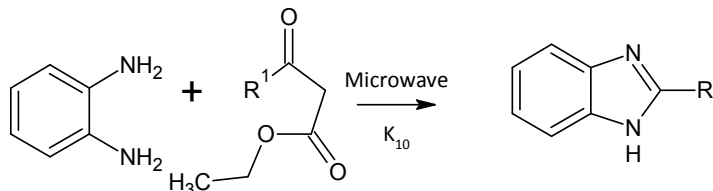
1] Dwi Sapri Ramadhan *et al*

The synthesis of benzimidazole derivatives can be efficiently achieved using **microwave irradiation**, utilizing **citronellal extracted from *Citrus hystrix* DC leaves** as a key reactant. This reaction is carried out in **water**, along with **o-phenylenediamine (OPDA)** and an **aromatic aldehyde**. The process has been explored using **methanol and dichloromethane** as solvents, with reaction times varying at **30, 40, 50, 60, and 70 minutes**. The molar ratio of **citronellal to 1,2-phenylenediamine is maintained at 1:1**, ensuring an optimal reaction environment for the formation of benzimidazole derivatives



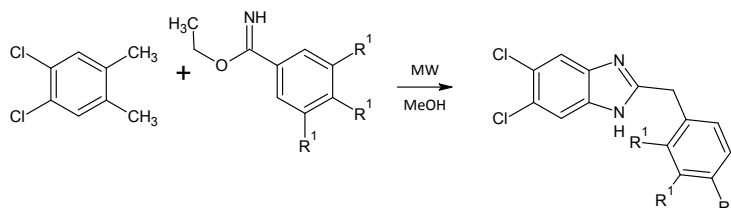
2] Bougrin Kand *et al*

Microwave-assisted synthesis of benzimidazole derivatives involves the reaction of **1,2-diaminobenzene or 4-substituted-1,2-diaminobenzene** with **ethyl acetoacetate or ethyl benzoylacetate** in a **solvent-free environment**. The reaction is carried out on **solid mineral supports or other suitable supports** under **microwave irradiation** using domestic microwave ovens. This method offers a **rapid, efficient, and eco-friendly** approach for the synthesis of benzimidazole derivatives, minimizing reaction time and reducing the need for harmful solvents [19].



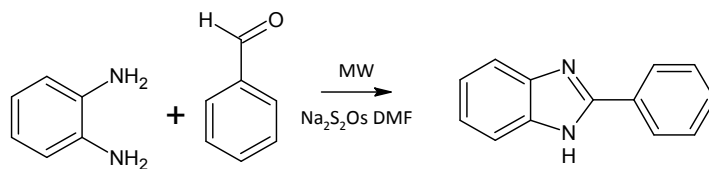
3] Emre Mentese *et al*

A straightforward and efficient protocol has been developed for the synthesis of **benzimidazoles**, achieving **high yields** within a **remarkably short reaction time** [20]. This method involves the reaction of **iminoester hydrochlorides of phenylacetic acid** with **4,5-dichloro-1,2-phenylenediamine or its derivatives** under **microwave irradiation**, providing a rapid and effective approach to benzimidazole synthesis.



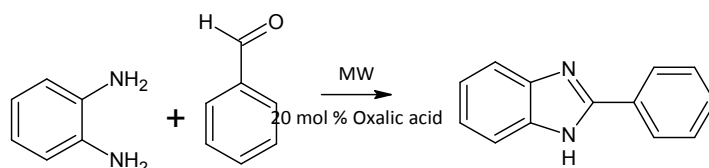
D. Secci *et al*

The synthesis of **1,2-diaryl-benzimidazole** and **2-aryl-1H-benzimidazole derivatives** has been successfully carried out using both **microwave irradiation** and **conventional heating methods**. However, **microwave-assisted synthesis** consistently resulted in **higher yields** and **significantly reduced reaction times** compared to traditional heating techniques [21].



5] Jyoti Pandey *et al*

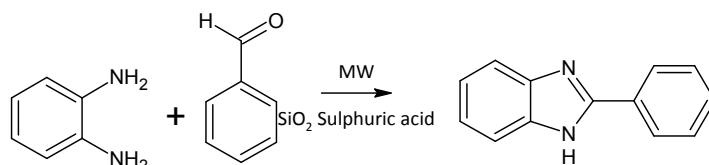
A **simple and efficient** one-pot microwave-assisted synthesis of **benzimidazoles** has been developed using **1,2-phenylenediamine** and **aromatic aldehydes**, with **oxalic acid** as a catalyst. This method offers several advantages, including the use of an **inexpensive and readily available catalyst**, **shorter reaction times**, **higher product yields**, and **easy isolation of the final compounds** [22].



6] B. Guruswamy *et al*

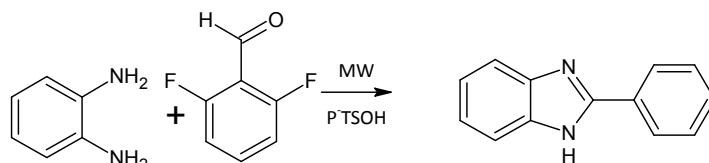
In this method, **o-phenylenediamine** and an **aromatic aldehyde** were placed on **H⁺SO₃-SiO₂** and transferred into a **microwave vial**. The vial was then **sealed and subjected to microwave irradiation at 80°C for 5 minutes**. Upon completion of the reaction, the product was **extracted and purified using column chromatography**, yielding the desired benzimidazole derivative efficiently [23].





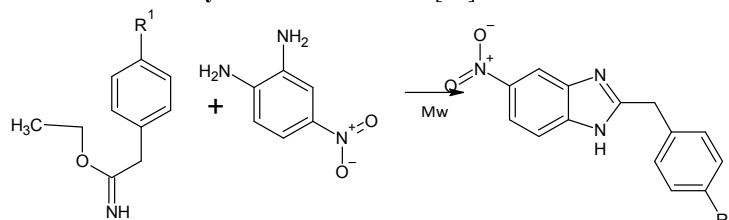
7] Angela Rao *et al*

Angela Rao *et al.* reported a reaction between **substituted aromatic aldehydes** and **o-phenylenediamine**, resulting in the efficient synthesis of benzimidazoles. This method is notable for its **high yields** and **significantly reduced reaction time** [24].



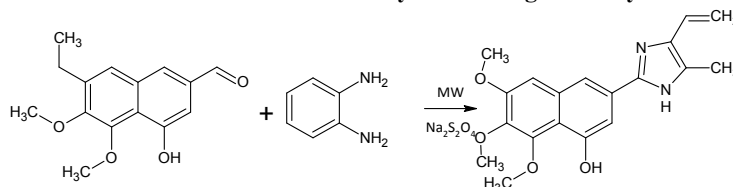
8] Fatih Yılmaz *et al*

The synthesis of **5-nitro-substituted benzimidazole** and **6-nitro-substituted benzimidazole derivatives** was achieved using **iminoester hydrochloride** and **4-nitro-o-phenylenediamine** under **microwave irradiation**. This approach resulted in **high yields** within a **remarkably short reaction time** [25].



9] Hue Thi Buu Bui *et al*

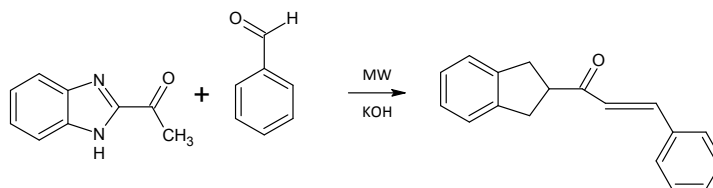
Novel **2-quinoliziny benzimidazole** and **2-naphthalyl benzimidazole derivatives**, featuring various **5- and 6-positioned substituents**, have been synthesized through the **condensation of 4-oxo-4H-quinolizinecarbaldehyde or naphthalenecarbaldehyde** with **substituted o-phenylenediamine**. This method operates at a **lower temperature** than conventional approaches and achieves **moderate to excellent yields** in a **significantly shorter reaction time** [26].



10] Janardan Singh Yadav *et al*

This method involves the **reaction of 2-acetyl benzimidazoles** with **substituted aldehydes** in **methanol**, using a **base catalyst** under **microwave irradiation**. The process is highly efficient, yielding **high product output** within a **short reaction time** [27].





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