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Efficient Green Synthesis of Biologically Active Benzimidazole Derivatives for Pharmaceutical Applications

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Abstract: Benzimidazole is a bicyclic heterocyclic compound composed of a benzene ring fused with the imidazole ring. It is a versatile scaffold with various applications, particularly in medicinal chemistry, due to its diverse pharmacological activities. Benzimidazole derivatives are used in the treatment of a wide range of disorders, including cancer and helminthiasis. They have favourable properties like high stability, bioavailability, and significant biological activity. The Conventional ways of synthesizing Benzimidazole lead to toxic effects, use harmful solvents, and need a lot of heat and time. Green chemistry avoids all these Consequences, which leads to an eco-friendly and long-lasting way to make Benzimidazole derivatives. This process uses deep eutectic Solvents and microwave irradiation as an alternative, so for this we used a novel type-III eutectic mixture of Choline chloride & o-phenylenediamine, which acts as both reagent and solvent. Along with this, microwave irradiation is used, which in turn saves time and energy. The DES was used in the ratio of 1:1 molar Concentration, and it was created by direct heating without the use of any catalysts or harmful chemical solvents. Benzaldehyde was used in this condensation process as an aldehyde component. This approach follows the twelve principles of green chemistry, which have multiple uses like Safety, Scalability, and environmental impact. Overall, the process gives us a quick, Safe, and eco-friendly way to synthesise benzimidazole derivatives where they can be used in research and health care purposes. Benzimidazole contains antibacterial, antiviral, anti-inflammatory, anticancer properties. Due to its heterocyclic structure, it holds a great place in the pharmaceutical Industry.

Index Terms - Benzimidazole, Green chemistry, deep eutectic mixture, microwave irradiation, choline chloride, o-phenylenediamine, scalability.

1. INTRODUCTION

1.1. Green Chemistry

Paul Anastas and John Warner are the founders of green chemistry. Paul Anastas was a chemist and known for developing the 12 principles of green chemistry. John Paul Warner was also a chemist and co-author of the book "Green Chemistry". In 1991, they both began developing the principles of green chemistry, and in 1998, their book Green Chemistry: Theory and practice was published, simply introducing the concept to the scientific community. Green chemistry is often referred to as sustainable chemistry, clean chemistry, or benign chemistry. The rapidly increasing pharmaceutical and other industries contribute to the beneficial expansion and evaluation of the medicine and health care sectors[1].

The phrase "green" or "sustainable" chemistry refers to the development of chemical products and procedures that reduce or eliminate the usage and production of dangerous materials. It involves minimizing or doing away with the use of hazardous materials in chemical reactions, as well as minimizing hazardous and toxic intermediates and products. It is a new area of chemistry that incorporates ecological perspectives[2]. Green chemistry is crucial to pharmaceutical synthesis because it tackles the environmental issues related to drug

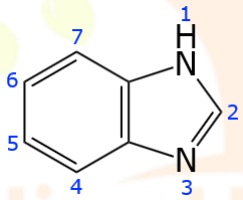
production. Several guidelines for the creation, advancement, and application of sustainable chemical processes are included[3].

These guidelines promote waste avoidance over cleanup, atom economy maximization in synthetic processes, renewable feedstock prioritization, safer chemical design to minimize toxicity while maintaining functionality, energy efficiency optimization to minimize environmental impact, avoidance of needless derivatization, preference for catalytic reagents over stoichiometric ones, design of products for post-use degradation into harmless substances to prevent environmental accumulation, and development of real-time analytical methodologies for in-process monitoring and control[4]. One of the biggest industries in the world for chemical manufacture is the pharmaceutical sector, which produces a wide range of life-saving drugs. Traditional pharmaceutical synthesis techniques, however, frequently produce a lot of waste, use dangerous compounds, and require a lot of solvents. This strategy is bad for the environment and for people's health[5]. These issues can be resolved by green chemistry, which offers sustainable substitutes that lessen their negative effects on the environment without sacrificing the effectiveness and quality of medicinal products. Several-step organic synthesis procedures using a range of reagents, solvents, and catalysts are commonly used in traditional pharmaceutical synthesis[6].

The study's goal is to investigate how green chemistry may effectively address environmental issues related to pharmaceutical manufacturing. The concepts and applications of green chemistry will be examined, with a focus on developing eco-friendly processes for pharmaceutical production. The review will also feature a case study and illustration of a successful pharmaceutical synthesis that makes use of green chemistry principles. It will also examine the potential contributions of green chemistry to the growth, difficulties, and future paths of the pharmaceutical sector.

1.2. Benzimidazole scaffolds:

Benzimidazole is one of the types of heterocyclic aromatic compounds. It is a privileged structure in medicinal chemistry and a significant pharmacophore. The synthesis of imidazole and benzene results in this bicyclic molecule. There is currently a variety of options with a wide range of pharmacological qualities. As an axial ligand for cobalt in vitamin B1, N-ribosyl-dimethyl benzimidazole is the most abundant benzimidazole chemical found in nature[7].

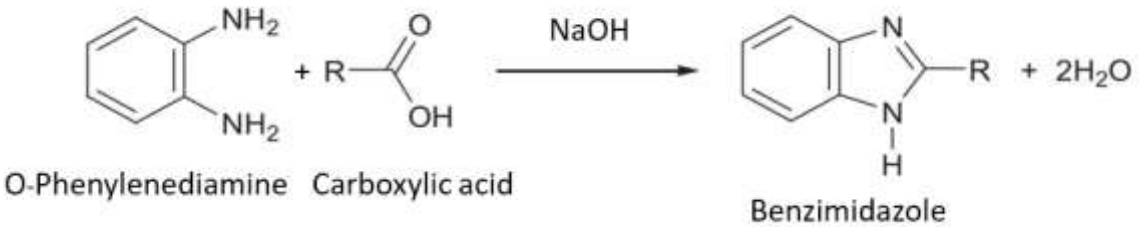


1H-BENZIMIDAZOLE

2. Traditional synthesis of benzimidazole:

2.1.By reaction with carboxylic acids:

O-phenylenediamines react easily with most carboxylic acids to produce 2-substituted benzimidazoles, typically in extremely high yields, according to a review of the literature. Heating the reactants together in a sealed tube, under reflux, or at a high temperature are the most common methods for carrying out the reaction.



O-Phenylenediamine Carboxylic acid Benzimidazole

2.1.1. Drawbacks of the traditional synthesis of benzimidazole:

Although classical synthetic techniques are reliable, they have two significant drawbacks. These processes have long durations, low yields, and severe conditions, which can cause unwanted side reactions and

degradation of sensitive functional groups[8]. Since these techniques rely on non-renewable solvents and chemicals, we now know that they also pose safety and environmental risks. Additionally, scaling up traditional methods can be problematic and hinder their use in larger-scale sustained commercial synthesis[9]. To avoid these consequences, moving to the conventional approaches (green approach) is determined as safe and eco-friendly.

2.2.Conventional Approach

2.2.1. Microwave Irradiation:

In recent years, high-speed microwave synthesis has garnered a lot of interest[10]. As a new enabling tool for drug discovery and development, microwave irradiation has gained popularity in the academic and pharmaceutical sectors for application in chemical synthesis[11].

Microwave radiation refers to electromagnetic radiation that occurs between 0.3 and 300 GHz. To avoid interference with cellular phone and telecommunications frequencies, all microwave ovens in homes and microwave reactors used specifically for chemical synthesis run at 2.45 GHz, or 12.24 cm in wavelength. The microwave photon's energy of 0.0016 eV in this frequency range is below both Brownian motion and the energy required to break covalent bonds. Consequently, microwaves cannot cause chemical reactions[12].[13]

The synthesis of benzimidazole derivatives using microwave assistance is a major development in organic chemistry that provides a more effective and environmentally friendly process. By using microwave irradiation, this method reduces reaction times, accelerates chemical processes, and increases yields above and beyond what is possible with conventional heating. Under microwave conditions, ortho-phenylenediamines are usually condensed with carboxylic acids or aldehydes, frequently without solvents or with green solvents. Early research has demonstrated that synthesis using solid supports and microwave energy may be accomplished, resulting in rapid cyclization and fewer byproducts. This approach is a desirable choice for researchers creating novel benzimidazole compounds with a range of biological activities since it not only increases the efficiency of the synthetic process but also complies with green chemistry principles by using less energy and hazardous waste[14].

2.2.2. Deep Eutectic Mixture:

Deep eutectic mixtures (DEMs) combine hydrogen bond acceptors (HBAs) and hydrogen bond donors (HBDs) to create a solvent with a lower melting point than its components[15].[16][17]The formation of a deep eutectic mixture is significantly influenced by the interaction between the HBD and HBA. The intricate hydrogen bonding network created by these interactions lowers the mixture's melting point. This melting point depression is caused by the following primary mechanisms:

Hydrogen Bonding: The crystal lattice structure is upset by the hydrogen bonds that form between the HBDs (like urea and glycerol) and HBAs (like quaternary ammonium salts), which causes a liquid state at a lower temperature. The liquid phase is stabilized and the mixture is prevented from hardening at room temperature because to this crucial interaction[18][19][20].

Electrostatic Interactions: In certain DEMs, particularly those involving ionic chemicals such as choline chloride, electrostatic interactions between ions help to maintain the stability of the eutectic mixture by lowering the melting point and preventing crystallization[21].

Vander Waals forces: These forces help to sustain the liquid state at lower temperatures and contribute to the overall interaction within the mixture, while being weaker than hydrogen bonds and electrostatic interactions[22][23] DEMs can be classified based on the type of HBAs and HBDs used.

Type I: A mixture of salts and donors of hydrogen bonds (such as urea and choline chloride), frequently utilized in general solvent applications[24][25][26].

Type II: Metal salt and HBD combinations that are helpful in electrochemical and catalytic processes.[27]

Type III: Contains complicated donors or non-ionic chemicals with a range of characteristics for specialized uses.[28]

using a novel type III eutectic mixture of Choline Chloride and O-Phenylenediamine, which is in the ratio of 1:1 molar concentration, and it was created by using direct heat without any catalyst or harmful chemical solvents, which is considered to be the green synthesis approach.

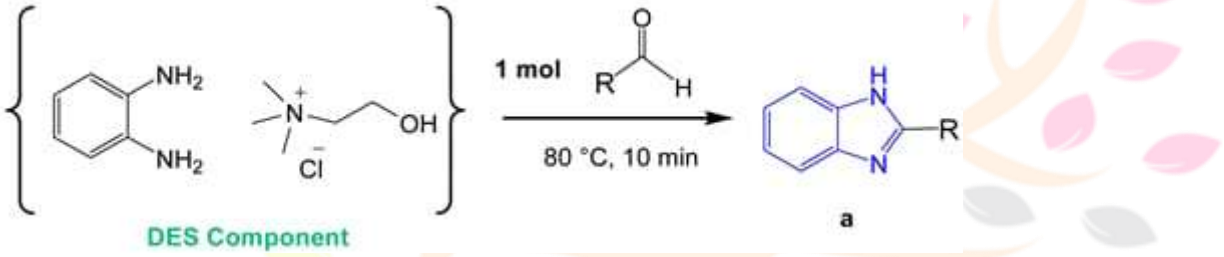
3. Procedure

The following process was employed to prepare ChCl:o–PDA (1:1) DES:

In a round-bottom flask, o-phenylenediamine (5.40 g, 50 mmol) and choline chloride (6.98 g, 50 mmol) were combined in an inert environment. The mixture was kept under a microwave apparatus, and it was set at 2.45GHz. After this, a clear yellow liquid was obtained.

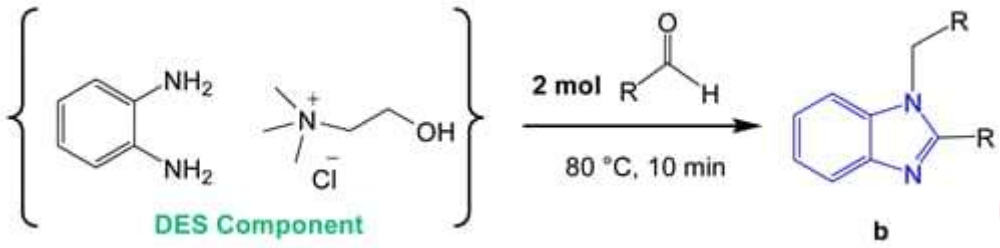
3.1.Synthesis of 2-substituted benzimidazole using a deep eutectic mixture:

While being stirred magnetically, 1 mmol of benzaldehyde was added to 1 mL of the Choline chloride and o-phenylenediamine (1:1) eutectic mixture. At 80°C, the resultant mixture was stirred for 8–10 minutes. Using HPLC, the reaction was tracked. 2ml of water was added after this. Ethyl acetate was then used to extract the resultant aqueous suspension (3 × 2 mL). To produce mono substituted benzimidazole, the organic phases were dried over sodium sulphate and then evaporated under low pressure[29].



3.2.Synthesis of 1,2-substituted benzimidazole using a deep eutectic mixture:

While being stirred magnetically, 2 mmol of benzaldehyde was added to 1 mL of the Choline chloride and o-phenylenediamine (1:1) eutectic mixture. At 80°C, the resultant mixture was stirred for 8–10 minutes. Using HPLC, the reaction was tracked. 2ml of water was added after this. Ethyl acetate was then used to extract the resultant aqueous suspension (3 × 2 mL). To produce 1,2-disubstituted benzimidazole, the organic phases were dried over sodium sulphate and then evaporated under low pressure[30].

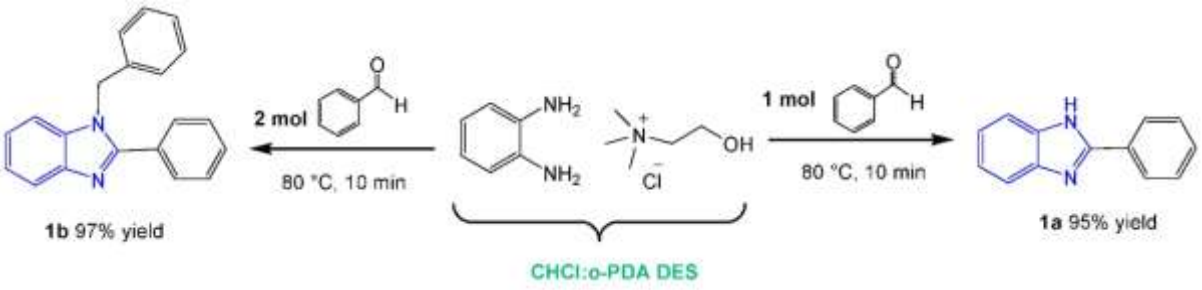


3.2.1. Reaction Observations:

After the completion of two reactions

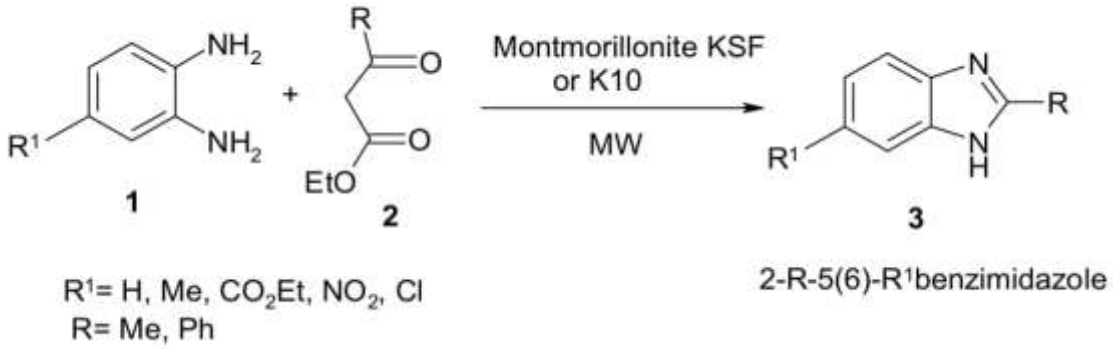
In the case of mono-substituted benzimidazole(1 mmol), the yield obtained was 95%.

In the case of 1,2-disubstituted benzimidazole(2 mmol), the yield obtained was 97%.

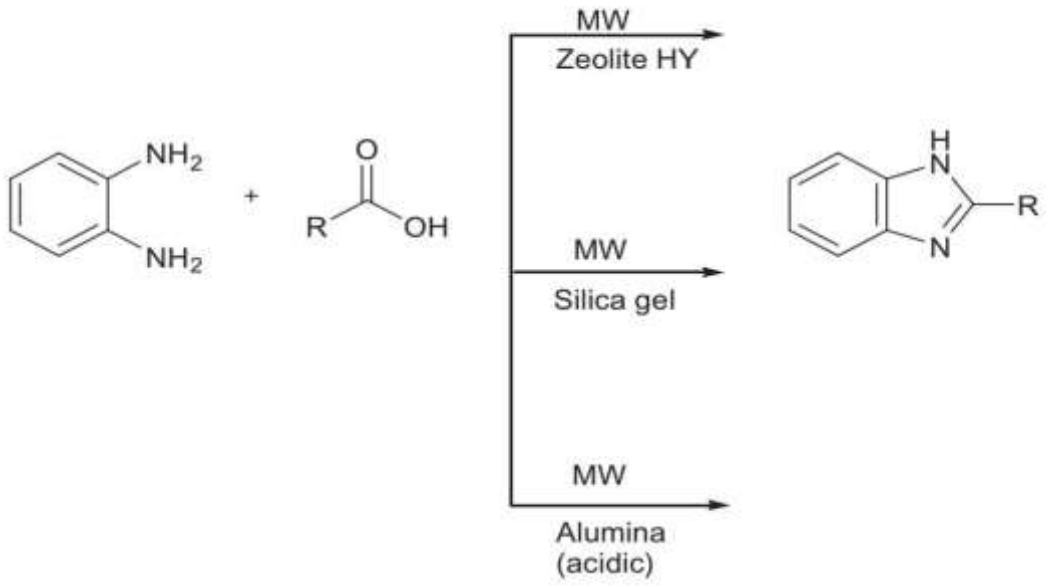


3.3.Synthesis of benzimidazole by using microwave irradiation

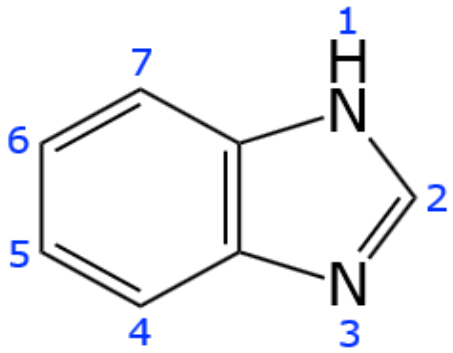
The first benzimidazole synthesis using a microwave was documented by Bougrin and Soufaoui in 1995[31]. On solid mineral supports in dry medium, they have reported a benzimidazole synthesis technique that uses 1,2-diaminobenzene or 4-substituted-1,2-diaminobenzene and ethyl acetoacetate or ethyl benzoylacetate under microwave irradiation in home ovens.



Saberi recently reported synthesizing 2-benzimidazoles without the need fot solvents and under microwave irradiation, using alumina, silica gel, and zeolite HY as catalysts. A mortar was used to thoroughly mix 50 mg of alumina, silica gel, or zeolite with 2 mmol of o-phenylenediamine and 2 mmol of aromatic, aliphatic, and heterocyclic carboxylic substances. Next, the reaction mixture was exposed to 160–560 W of radiation for 5–9 minutes in a home microwave oven[32].



4. Structural activity relationship of benzimidazole:



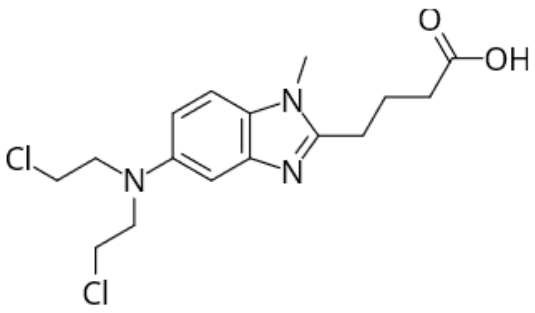
The presence of an electron-withdrawing group on the benzimidazole ring at C-5,6,7 Positions enhances the anti-microbial activity, while the presence of electron-releasing atoms or groups decreases it, according to the SAR studies. Particularly, compounds that had a nitro group in either position 5 or position 7 of the benzimidazole core were much more effective against B.subtilis, MRSA (Methicillin-Resistant Staphylococcus Aureus), and S.aureus. The antibacterial activity was lost when the nitro group at position 7 was changed to an amine group. Increased activity in MRSA and B.subtilis was largely dependent on the location and substitution of a third atom or group in the nitro-substituted benzimidazole. Benzimidazole that has a nitro group at position 5 and either chlorine or bromine atoms at position 4 demonstrated the strongest antibacterial activity. The nitro group is very important in enhancing the anti-microbial activity against the Gram-positive bacteria. Changing the atoms or groups in the benzimidazole ring did not significantly stop E.fecalis from growing[33, 34]. According to the SAR analysis, the benzimidazole molecule's action against Gram-positive bacteria is significantly influenced by the acidity of its hydrogen atoms 1 and 1'[35]. The NH group at the first position of benzimidazole shows anti-inflammatory activity. However, benzimidazole's C5 demonstrated significant inhibition when –CH3 or –NO2 were substituted, whereas –OCHF2 did not exhibit a favourable inhibitory effect[36]. Benzimidazole's C5 substitution is essential for its anti-inflammatory and [CDK] Cyclin Dependent Kinase inhibitory properties. A molecule with a nitro group at C5 shows strong action against CDK1 and CDK5 enzymes. On the other hand, the anti-inflammatory and CDK-inhibitory properties were eliminated when an amino or methyl group was added at position C5[37–40]. A study reported that benzimidazole linked to oxadiazole via a thioacetamide linker exhibited strong anti-inflammatory activity. When a hydroxy group was added to the phenyl ring in the ortho position, there was a decrease in activity. The thioacetamide linker, on the other hand, is necessary for anti-inflammatory action[41]. Non-substituted benzimidazoles were demonstrated to be less effective than the substituted compounds, whereas different substituents in the aromatic ring did not produce much inhibition.

4.1.Pharmacological diversity of benzimidazole:

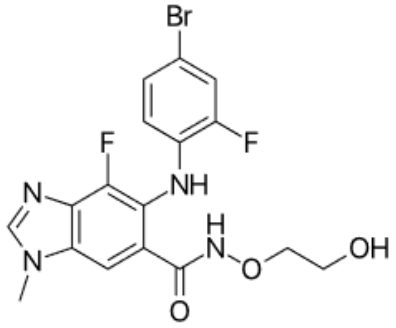
Because of their many pharmacological characteristics, benzimidazoles are a significant class of chemicals with a variety of therapeutic applications. This section discusses the various roles and consequences that they have.

4.2.Anti-cancer properties:

Because of their potential as effective anticancer medications, benzimidazole is an interesting oncology choice. Their unique contributions to cancer treatment are examined in this part, along with recent clinical uses and an emphasis on the fundamental mechanisms behind their anticancer effect.



BENDAMUSTINE



BINIMETINIB

4.3.Anti-cancer activity mechanism:

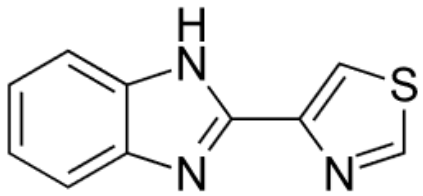
Benzimidazole compounds have a variety of anticancer properties that show they can target a broad range of disease markers. Certain chemicals interfere with the establishment of mitotic spindles and cause cell cycle arrest or death by altering the dynamics of microtubules. Some of these, such as angiogenesis, DNA repair, and proliferation, block essential enzymes or processes that lead to the development of cancer. A number of cancer types may be susceptible to benzimidazole's complex modes of action[42].

4.4.Anti-microbial properties:

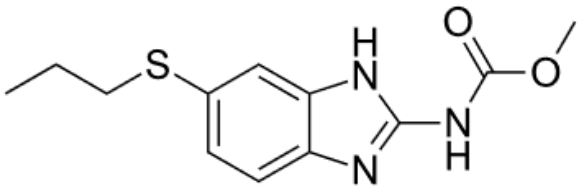
The remarkable effectiveness of benzimidazole as an antibacterial agent has demonstrated its strength and adaptability. The primary focus of this section is their functions in antibacterial, antifungal, and antiparasitic treatments[43].

4.5.Antibacterial activity:

There is potential for treating bacterial infections with certain benzimidazole compounds due to their robust antibacterial qualities. These chemicals prevent bacteria from growing and surviving by interfering with essential metabolic functions through interactions with important bacterial enzymes or cellular components. Benzimidazole-based antibacterial drugs have shown promise in treating a variety of illnesses, including those caused by gram-positive and gram-negative bacteria.



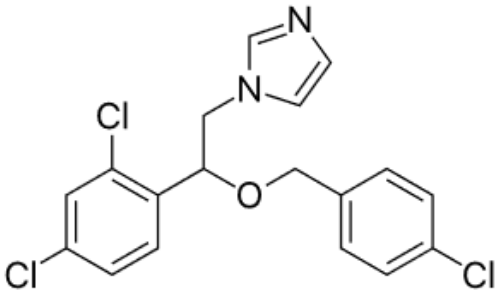
THIABENDAZOLE



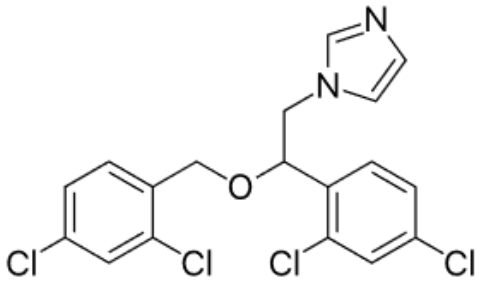
ALBENDAZOLE

4.6.Antifungal activity:

Benzimidazole has emerged as a drug in the antifungal drug sector that can treat fungal infections. Benzimidazole derivatives can have fungicidal or fungistatic effects on a variety of fungal species via changing fungal cell division, membrane integrity, or the synthesis of essential components. Their capacity to target both superficial and systemic fungal infections makes them useful tools in the creation of antifungal drugs[44].



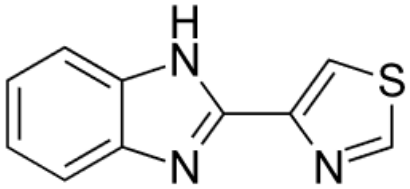
ECONAZOLE



MICONAZOLE

4.7.Antiparasitic activity:

Benzimidazole is a crucial part of antiparasitic medications, which provide effective solutions for a variety of parasitic illnesses. They impair parasites' capacity to divide cellularly and cause structural damage by interfering with their microtubule dynamics. Consequently, by successfully combating parasitic infections like nematodes and cestodes, benzimidazole derivatives contribute significantly to the global effort to manage parasitic disorders[45].



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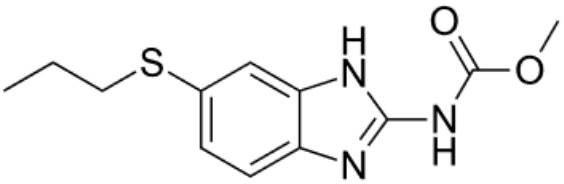
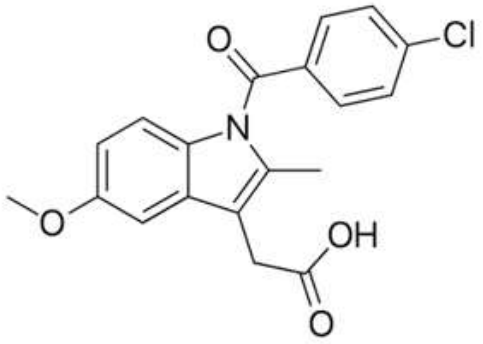


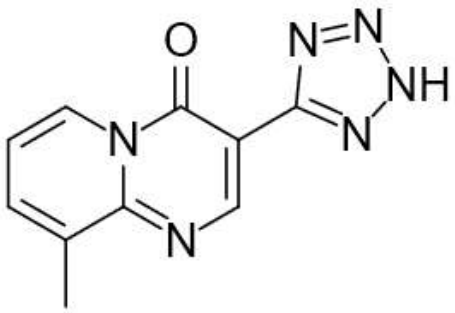
ALBENDAZOLE

4.8.Anti-inflammatory activity:

Significant anti-inflammatory activity has been demonstrated by benzimidazole derivatives, which is advantageous for medicinal applications. According to recent studies, several benzimidazole compounds can effectively reduce inflammatory responses by interacting with various inflammatory receptors and pathways. For instance, through the inhibition of cyclooxygenases (COXs) and the modification of transient receptor potential channels, drugs such as methyl benzimidazole N-hydrazone derivatives and methyl benzimidazole phenyl hydrazone derivatives have demonstrated intriguing results in reducing inflammation in animal experiments. Furthermore, research on the structure-activity relationship has demonstrated that certain substituents on the benzimidazole ring can boost the compound's anti-inflammatory properties. These findings suggest that benzimidazole derivatives may be used as novel anti-inflammatory medications to treat a range of inflammatory diseases.



INDOMETHACIN

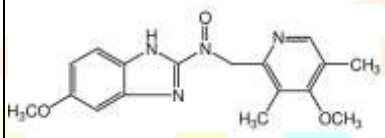
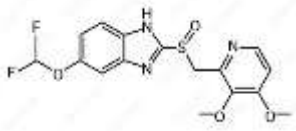
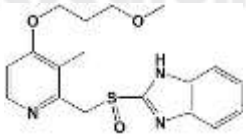
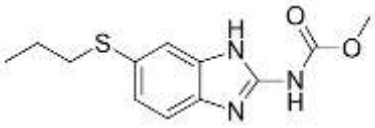


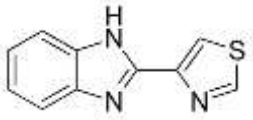
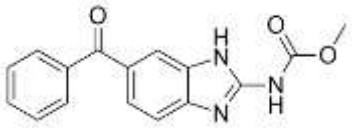
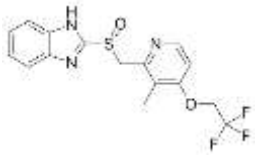
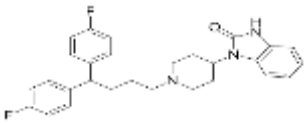
PEMIROLAST

5. **Present clinical applications:**

Because of their various pharmacological characteristics, benzimidazole derivatives are being used in a broad range of medicinal applications. They play a key role in the creation of anticancer drugs that target cancer pathways and have little toxicity to healthy cells, like bendamustine and binimetinib. Furthermore, benzimidazole compounds are potent antimicrobials; several of its derivatives have efficacy against bacterial and fungal infections. Additionally, they are used as anthelmintics (like albendazole) to treat parasite infections and as proton pump inhibitors (like omeprazole) to treat gastrointestinal diseases. Additionally, current studies are examining their potential in anti-inflammatory, antiviral, and antihypertensive treatments, emphasizing the structural adaptability of benzimidazole that enables the creation of new compounds that target a variety of biological pathways.

6. **Marketed Benzimidazole Drugs**

S.no	Drug name	Structure	IUPAC name	Drug Binding Receptor/Target
1	Omeprazole		5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]-1H-benzimidazole	H+/K+-ATPase (Proton Pump Inhibitor)
2	Pantoprazole		6-(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methylsulfinyl]-1H-benzimidazole	H+/K+-ATPase
3	Rabeprazole		2-[[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methyl]sulfinyl]-1H-benzimidazole	H+/K+-ATPase
4	Albendazole		methyl [5-(propylthio)-1H-benzimidazol-2-yl]carbamate	β-tubulin (Anthelmintic)

5	Thiabendazole		2-(1,3-thiazol-4-yl)-1H-benzimidazole	Fumarate reductase / β-tubulin
6	Mebendazole		methyl N-[6-(benzoyl)-1H-benzimidazol-2-yl]carbamate	β-tubulin (Anthelmintic)
7	Lansoprazole		2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulfinyl]-1H-benzimidazole	H+/K+-ATPase
8	Pimozide		1-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidyl]-3-benzimidazol-2-yl-2-propen-1-one	Dopamine D2, D3 receptor (Antipsychotic)

7. Conclusion:

To create more sustainable processes, synthetic organic procedures that employ more eco-friendly and effective techniques are essential. This procedure demonstrates more creative, economical, and ecological approaches that can use bio-renewable resources to fully address all green chemistry principles. By following the 12 principles of green chemistry, we can make science work smarter and safer using less energy, creating less waste, and choosing materials that are better for people and the planet. As more scientists and industries embrace these greener ways of working, we are taking meaningful steps toward a cleaner, healthier, and more sustainable future for everyone. The current study demonstrates the use of deep eutectic mixtures and microwave-assisted synthesis of benzimidazole and its derivatives, which is quick, inexpensive, clean, and ecologically friendly. The process offers a straightforward product recovery and does not require the use of a solvent. In terms of reactivity, economics, ecotoxicity, and eco-sustainability, the methodology was found to be comprehensive. Benzimidazoles are thought to be a potential class of bioactive heterocyclic molecules with a variety of biological actions, including antiviral, antimicrobial, anti-diabetic, and anti-cancer properties. In contemporary drug research, the benzimidazole ring is a crucial pharmacophore. The production of benzimidazole derivatives as a source of novel antibacterial agents has drawn more attention. The derivatives of benzimidazole are useful for medical research. We have seen numerous uses for benzimidazole, which will be highly beneficial to the next generation as well. The conventional method of benzimidazole production had numerous medicinal applications. Even additional uses were found with the green chemistry production of benzimidazole. The utilization of organic synthesis about green chemistry will therefore be beneficial

Declarations

Ethics approval and Consent to participate

Not applicable

Consent to Participate & Consent for publication

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The authors declare that they have no competing interests

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K. Gayatri and **K. Durga Mallesh** were the primary contributors to the conceptualization, experimental work, data analysis, and manuscript preparation. They led the execution of the study and coordinated the drafting of the article.

Y. Lokesh, **G. Sudhakar**, and **D. Bharathi** provided additional support by contributing to data collection, literature review, and assisting in the preparation of specific sections of the manuscript.

Ms. Neelam Vijaya Durga served as the research guide, offering key conceptual inputs, supervision, and continuous guidance throughout the research process. She also provided critical revisions and ensured the integrity of the overall study.

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