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A review on the Production, Utilization, and Biological Activity of Benzimidazole Derivatives

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ABSTRACT

Benzimidazole is an aromatic heterocyclic chemical molecule that is white and solid. It is created when the heterocyclic imidazole aromatic ring and the aromatic benzene ring fuse. Its usual formula is $C_7H_6N_2$, and it is also known as 1H-1, 3-benzimidazole and 1H-benzo[d]imidazole. The unique characteristics of the chemical molecules formed from the benzimidazole substance, along with its several significant therapeutic capabilities and well-known biological uses, have piqued researchers' interest in its study and use during the past few decades. Since benzimidazole resistance is common in many fungal populations, effective resistance management strategies must be put into place as soon as possible to postpone or stop additional changes in the target infections' sensitivity. For benzimidazoles, there are no particular guidelines. Alternations and mixes are both effective ways to reduce the likelihood that resistance may emerge. When using tank mixes, the benzimidazole fungicide must be sprayed at the recommended dosage in conjunction with the proper dosage of a partner fungicide that is both effective and non-cross-resistant.

KEYWORDS: - Benzimidazole, Synthesis, Reaction, Biological Activity.

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1. INTRODUCTION

One of the fundamental organic components used to make other organic molecules, such as medications, is heterocyclic compounds. Because they include heteroatoms and thus have a wide range of characteristics, heterocyclic compounds are extremely complex classes in chemistry. Apart from their significant significance in human life, heterocyclic compounds are also critical in a wide range of fields, including medicine, agriculture, the synthesis of other organic chemicals and polymers, and several industrial uses. Numerous heterocyclic compounds, such as hypnotics, anticonvulsants, antitumors, antihistamines, antiseptics, and antivirals, are also utilized as medications [1-7].Pharmacology uses a large number of novel medications with heterocyclic compounds each year to treat a wide range of human illnesses. These novel medications, which are made up of heterocyclic substances, which can be applied to a number of illnesses because many of them have antiviral, antifungal, and antibacterial [8–10, 11, 12], anti-inflammatory [13], and anticancer [14-15] properties in addition to being useful in other disease states. More effective methods for scientists to create heterocyclic molecules as practical medications have recently been established. The methods for the organic synthesis of heterocyclic compounds that are currently available have been continuously improving in both the economic and environmental domains, which is crucial for sustainability considerations in the future [16]. Organic molecules with a polycycle or single ring that have a minimum of one heterocyclic atom like oxygen, nitrogen, sulfur, and others—are known as heterocyclic compounds[17]. In this review, concentrate on benzimidazoles and go over their characteristics, production techniques, and significant biological uses.

2. Benzimidazole

Benzimidazole is an aromatic heterocyclic chemical molecule that is white and solid. It is created when the heterocyclic imidazole aromatic ring and the aromatic benzene ring fuse (Figure 1). Its general formula is $C_7H_6N_2$, and it is also known as 1H-1, 3-benzimidazole and 1H-benzo[d]imidazole[18]. The unique characteristics of the chemical molecules formed from the benzimidazole substance, along with its several significant therapeutic capabilities and well-known biological uses, have piqued researchers' interest in its study and use during the past few decades. Dimethyl benzimidazole N-ribosyl, the crucial component coordinating with the

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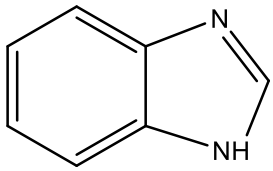
vitamin B12 cobalt element [19], is one of the most common types of benzimidazole discovered in nature. Due to benzimidazole's numerous biologically significant properties, including its antiviral, antimicrobial, antifungal, antihistamine, and anti-inflammatory, antioxidant, antiulcerative, and anticancer effects, among others, the field is expanding rapidly as researchers seek to create benzimidazole derivatives [20, 21].



1*H*-benzo[*d*]imidazole

Figure 1. The Benzimidazole structure

The chemical that is nitrogenous compound benzoimidazole has been recognized since antiquity. Between 1872 and 1878[22], Hoebrecker was the first to synthesize it, followed by Ladenberg and Wundt.25 Even though benzimidazole was discovered in a reasonably straightforward manner, it wasn't until 80 years later that research into the compound's efficacy and potential as a treatment for parasites became apparent. A mixture of 2-phenylbenzimidazole and phenothiazine was created in the early 1960s. Produced that proved beneficial for treating sheep with anthelmintics.26 2-(thiazol-4-yl)benzimidazole was first used in1961[23] and found in Merck Sharp and Dohme's labs; the produced substance was regarded as a crucial and broad-spectrum anthelmintic[24] .The process of making this organic substance and using it to how parasitic worms are treated for dogs and people can be regarded as a significant indicator as well as a qualitative shift to a new generation of medication creation. Stable compounds within this class and a wide variety of applications were made possible by the facile electrical reactions and field condensation that benzimidazole and its derivatives could undergo.

3. Techniques for Benzimidazole Derivative Synthesis

Regarding the production of benzimidazoles, numerous methods have been established and validated. One of these is the direct approach, which involves o-phenylenediamine and formic acid undergoing a direct condensation reaction to produce benzimidazole (Scheme 1). [25] Benzimidazole derivatives can also be prepared in a variety of ways. As outlined in the following

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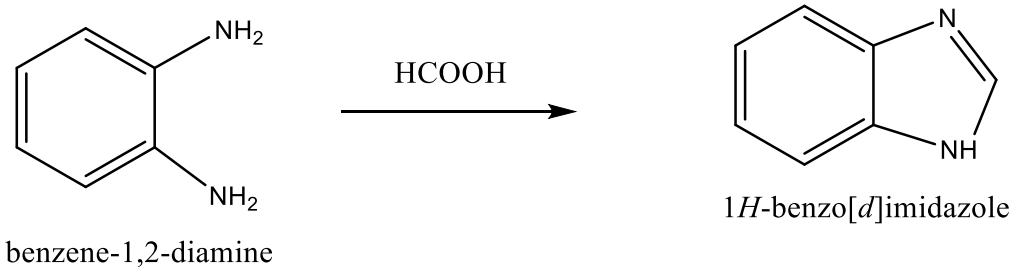
procedures, some of these approaches have drawbacks, such as low yield, severe circumstances of reaction, or lengthy reaction durations. Other approaches are better suited for preparation.



benzene-1,2-diamine

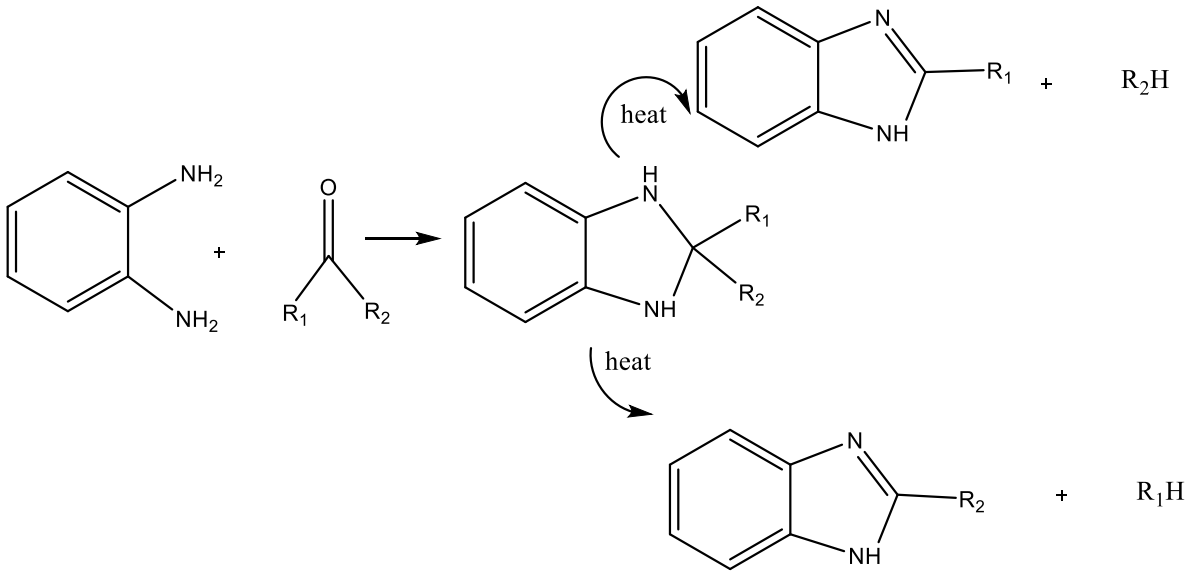
1*H*-benzo[*d*]imidazole

Scheme 1. The production of benzimidazole.

3.1 2-Aminoaniline (o-Phenylenediamine) condensation

3.1.1 with Ketones

The process of condensation between ketones and o-phenylenediamine is the method used to create benzimidazole derivatives; however, this process has many drawbacks that prevent it from being employed as frequently as it may be. These will be covered in more detail later. According to Scheme 2, the overall technique involves a condensation reaction involving diamines and Temperature-dependent ketones that vary depending on the reaction conditions [26].



Scheme 2. Condensation reaction between ketones and o-phenylenediamines produces benzimidazoles.

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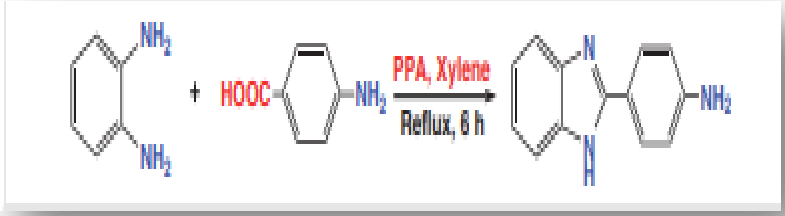
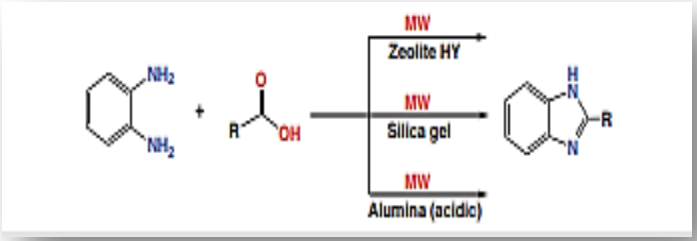
3.1.2 with Carboxylic Acids

Alam et al.[27] reported creating novel benzimidazoles using equimolar quantities of o-phenylenediamine and paminobenzoic acid under reflux in xylene and polyphosphoric acid. Within six hours, the reaction occurred, and the yield was dependable and good (Scheme 3). [27].



Scheme 3. Create benzimidazole derivatives, o-phenylenediamines are condensed with aromatic carboxylic acids.

A. Saberi reported in 2015 that novel benzimidazole derivatives might be made without the need of solvents by employing zeolite, silica gel, or alumina as a catalyst under microwave radiation. Equal moles of o-phenylenediamine and aromatic, aliphatic, and heterocyclic carboxylic acid molecules were combined with 50 g of catalyst to accomplish the reaction. The mixture was then thoroughly ground in a mortar and exposed to microwave radiation for 5 to 9 minutes (Scheme 4) [28].



Scheme 4. Benzimidazole derivative synthesis employing zeolite, SiO_2, or Al_2O_3 as a catalyst.

An o-phenylenediamine condensation reaction and many kinds of chemical compounds, including nitriles, urea, and derivatives of carboxylic acids (anhydrides, esters, amides, and acid chlorides), can also be used to create benzoimidazole derivatives. Depending on whether by-

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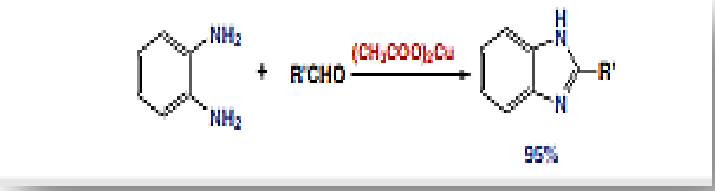
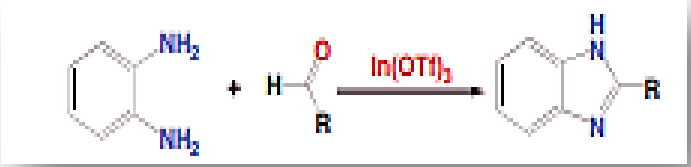
products are present, these techniques can produce benzimidazole compounds that have varying yield ratios and purity [29].

3.1.3 with Aldehyde

When palladium or copper catalysts are present, the o-phenylenediamine is capable of utilized with alkyl, aryl, and heterocyclic aldehydes. Under these circumstances, a high-quality and pure product was produced (Scheme 5) [30, 31].Additionally, Rushi et al. created 2-substituted benzimidazoles, as illustrated in (Scheme 6) by employing [$In(OTf)_3$] as a catalyst to condense aldehydes with o-phenylenediamine at ambient temperature without the use of a solvent. The yield from this procedure was reliable and good [32].



Scheme 5. Benzimidazole synthesis making use of copper acetate as a catalyst.



Scheme 6. Benzimidazole synthesis using solvent-free conditions.

A highly efficient technique has also been used to manufacture benzoimidazoles in the presence of different types of gold nanocomposites, including Au/ZnO, Au/TiO_2, and Au/Al_2O_3. L. Hao et al. reported this process (Scheme 7) [28]

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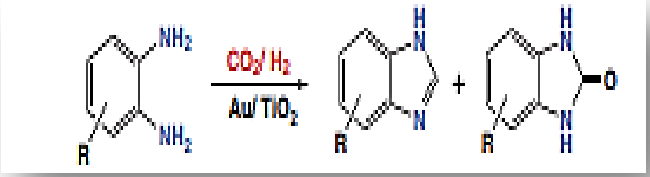
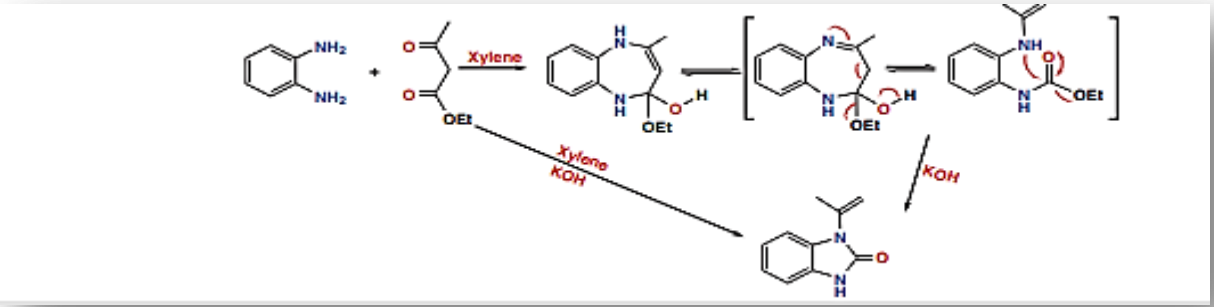


Scheme 7. The Au/TiO_2 nanoparticle-catalyzed benzimidazole synthesis.

3.1 Via Rearrangement

An ethyl acetoacetate and ophenylenediamine mixture heated to reflux in xylene solvent yields a benzodiazepinone derivative (4-diazepin-7-one, 3-benzo-1, and 7-dihydro-5-methyl-1H-2). However, benzimidazole derivatives are produced when this reaction is conducted under the identical circumstances and potassium hydroxide is subsequently added to this combination (Scheme 8). [33]



Scheme 8. The general procedure for creating benzimidazolone by rearrangement from benzodiazepinones.

Furthermore, it was shown in 2017 that quinoxaline 1, 4-dioxides might be rearranged to produce several benzimidazole derivatives. These investigations showed the substance quinoxaline-2-one's composition as an intermediary substance affects the rearrangement process. The production of benzimidazole derivatives with a greater variety of functional groups is what makes this study unique (Scheme 9) [33].

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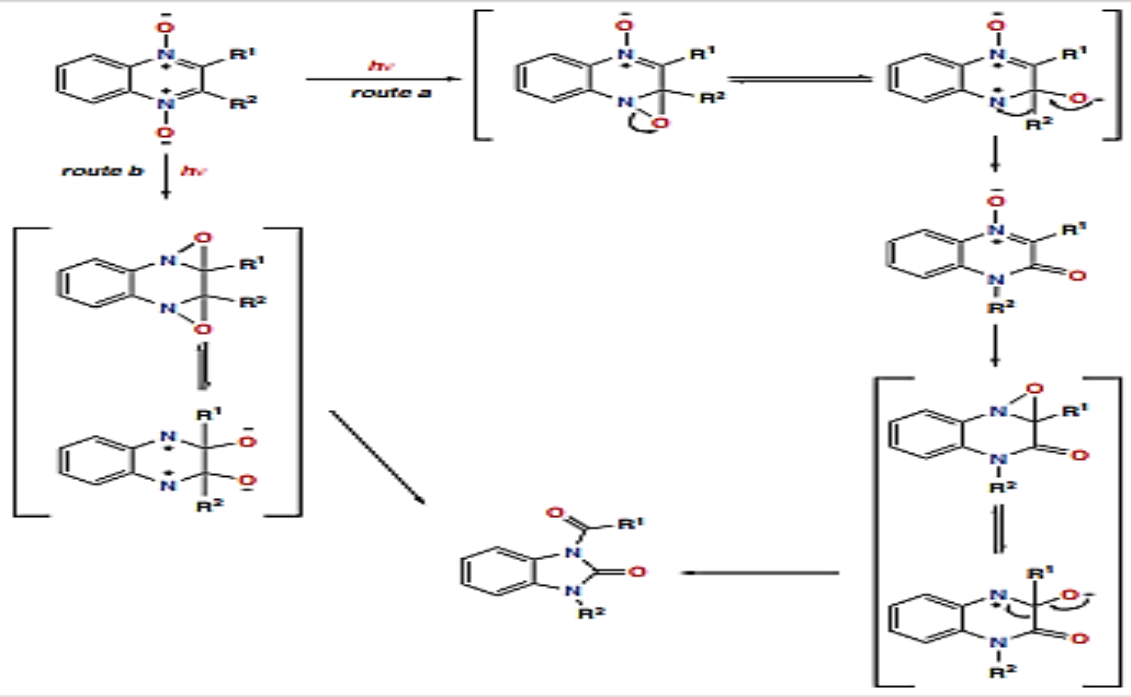
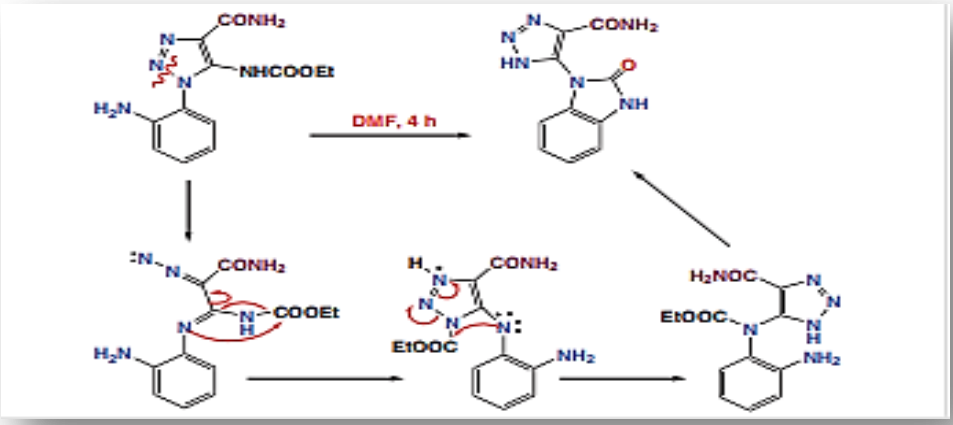


Scheme 9. The proposed mechanism for the synthesis of quinoxaline to benzimidazolone -1, 4-dioxides.

As soon as the 1, 2, 3-triazole compound was heated to reflux for 4 hours, the corresponding benzimidazole derivative was produced., as shown in Scheme (10) [26]



Scheme 10. Triazole derivative rearrangement to synthesize a benzimidazole derivative.

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4. The Biological Activity of Derivatives of Benzimidazoles

Since their initial synthesis, benzoimidazole derivatives have been linked to biological uses because of the great medical efficacy of this family of heterocyclic compounds, which has been successfully demonstrated in recent years. Derivatives of benzoimidazole have been employed as anticonvulsants, antitumors, antimicrobials, and anti-inflammatories, among other uses [34–41]. The most significant biological uses for benzimidazole derivatives as basic chemicals are listed below.

4.1 Anti-inflammatory Activity

Substances with characteristics that lessen the impact of different inflammations in the body are referred to be anti-inflammatories. Numerous analgesic medications have several benefits, particularly anti-inflammatory medications, which lessen inflammation and so relieve pain. In medicinal chemistry, benzoimidazole derivatives—organic compounds with a heterogeneous aromatic ring joined containing a benzene ring —have a unique structure that has made them the go-to pharmaceutical material for creating reducing pain and inflammation drugs that target various clinically recognized pain and inflammation targets[42]. Sharma et al. [43] used a sample of rat paw edema caused by carrageenan to evaluate a number of produced compounds. Anti-inflammatory properties of the compounds produced from 5-methanesulphonamido benzimidazole were investigated. As conventional medications for testing, rofecoxib and indomethacin were also utilized. At the tested doses, derivatives a, b, and c displayed the highest edema activity (92.73, 95.64, and 97.62%, respectively) (Figure 2). This suggests that benzimidazole derivatives are actively involved in this field.

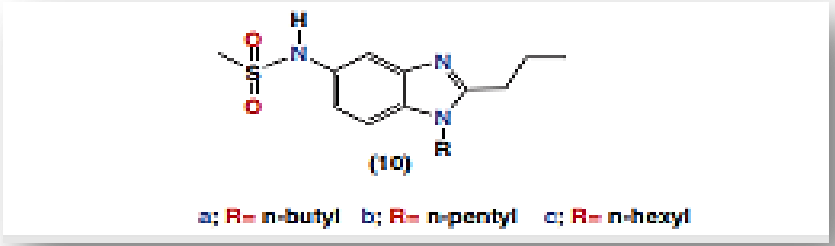

Figure 2. Possible anti-inflammatory substances 10a–c.

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Kankala et al. [44] synthesized many compounds of substituted benzimidazoles and evaluated their anti-inflammatory and analgesic properties. Derivatives of isoxazole-mercapto-benzimidazole made up the noteworthy chemical that was synthesized (Figure 3).

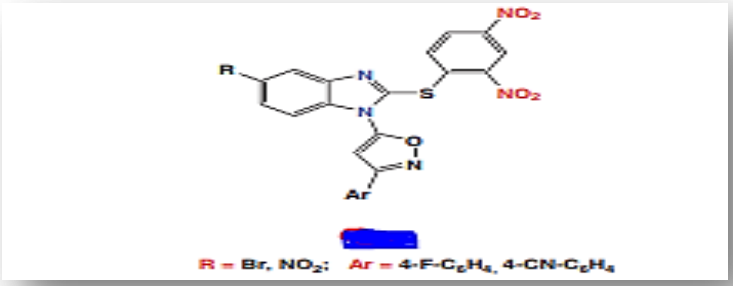

Figure 3. The anti-inflammatory and analgesic compounds.

4.2 Antioxidant Activity

An antioxidant is a substance that has the ability to reduce or halting the free radicals' oxidation, which pose a deadly threat to an organism's cells. Because air-breathing organisms rely on the aerobic oxidation process, which is essential to existence, free radicals will inevitably arise. These newly liberated. Radicals are extremely harmful and can lead to cell death, malignant change, or malfunction. Proteins, lipids, and DNA can all be harmed by oxidative stress. DNA damage can result in chromosome rearrangements or genetic abnormalities that cause cancerous tumors, diabetes, dementia, and cardiovascular disorders [45]. Archie et al. [46] assessed the antioxidant capacity of a few made benzimidazole derivatives (Figure 4). Every derivative demonstrated good antioxidant activity, with IC50 values in the area 3.17 to 7.59 g/mL, while 18.42 g/mL was discovered for hydroxytoluene butylated (BHT).

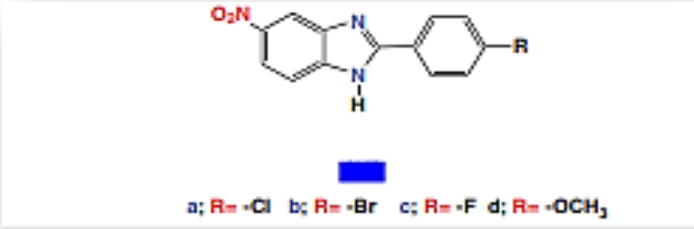

Figure 4. The Benzimidazole compounds with Anitoxidant properties.

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4.3 Anticoagulant Activity

Strong substances called anticoagulants, sometimes referred as blood thinners., are intended to lessen or stop clots of blood within the body [47] Certain blood-feeding animals, including leeches and mosquitoes, naturally have anticoagulants that aid in preventing blood clots from forming in the bite site for a while so that blood can be absorbed [48]. Many conditions, such as stroke, heart attack, fibrillation in the atrium, deep vein thrombosis, pulmonary embolism, are treated with anticoagulants. A few anticoagulants are also found in medical devices such sampling tubes, heart-lung machines, dialysis machines, and blood transfusion bags. [49] The effectiveness of benzoimidazole derivatives as anticoagulants has been developed and evaluated. Benzimidazole derivatives made from derivatives of substituted fluorinated 1-ethyl-1H-benzimidazole were prepared and physiologically assessed by Wang and Ren [50] to determine their antithrombin activity. In comparison to argatroban, the conventional medication employed in this investigation, the researchers found that all of the examined compounds exhibited superior anticoagulant activity against thrombin (Figure 5). Additionally, compound 28f was more potent than the usual medication as an inhibitor of thrombin (IC50 = 3.21±0.57 nM) compared to 9.88±2.26 nM.

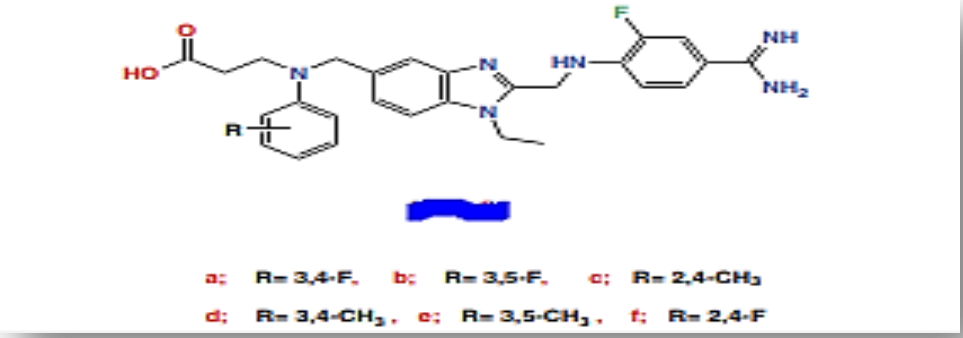

Figure 5. The Benzimidazole compounds with anticoagulant activity.

4.4 Antimicrobial Activity

Materials classified as antimicrobials are compounds that are employed to eradicate or inhibit the growth of germs, including dangerous bacteria and fungus. Antimicrobial medications can be categorized based on the bacteria they are effective against. Antibiotics, for instance, are used to

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combat germs and fungi are combated using antifungals. Another way to partition the class is by function. Microbicides are substances that destroy microorganisms, whereas biostatics are substances that prevent the growth of microorganisms [51]. The antibacterial activity of several 2-substituted benzimidazoles was reported by Ajani et al. [52] (Figure 6). Using the zone of inhibition technique, the biological certain chemicals' activity was assessed using gram-positive bacteria (S. aureus, P. vulgaris, and S. faecalis) and gram-negative (Pseudomonas aeruginosa, E. coli, and K. pneumoniae) bacterial strains. Comparing the investigated compounds to the conventional medication gentamicin, showed larger zones of inhibition for all of the aforementioned pathogens.

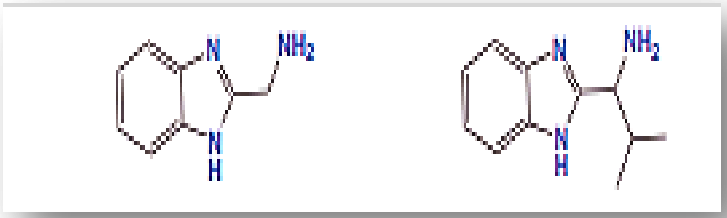

Figure 6. The Benzimidazole compounds with Antimicrobial activity.

Numerous investigations are currently being conducted on derivatives of substituted benzimidazoles, which exhibit a unique ability to eradicate or inhibit the growth of microorganisms. Numerous manufactured compounds are as effective as or more effective than the conventional medications used for the same purpose [53–55].

Conclusion

Because of their crucial biological significance in the production of numerous medications and antibiotics, benzimidazoles rank among the most significant classes of synthetic organic chemicals. As a result, the production of derivatives of benzimidazoles became a primary focus for the creation of numerous additional chemical compounds that, upon testing, demonstrated unique medical value. This review aims to assist researchers in identifying the many chemical characteristics of benzimidazoles and their derivatives. Additionally, it offers a concise synopsis of the key green chemistry and chemical methods for creating various benzimidazole derivatives, along with the advantages and disadvantages of each technique. It has also been demonstrated that benzimidazole derivatives have a variety of biological actions, including anticoagulant, anticancer, anti-inflammatory, and anticonvulsant properties. It is evident from the foregoing that

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benzimidazole derivatives have played a significant role in the advancement of medicine in recent years.

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