Review Article

Synthesis Characterization and Pharmacological Study of Some Novel Benzimidazole Derivatives

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ABSTRACT

A nitrogen-containing heterocyclic aromatic organic compound is benzimidazole. The benzene and imidazole rings fuse to generate this bicyclic molecule. O-phenylenediamine can be condensed with carbonyl compounds (aldehydes and ketones) or with carboxylic acids and their derivatives to create benzimidazole and its derivatives. Environmentally friendly catalysts, photochemical processes, and green techniques like microwaves and ultrasonography have all been used to manufacture benzimidazoles in recent decades. In medicinal chemistry, it is a crucial pharmacophore and a favoured structure with a variety of therapeutic properties, including antiulcer, antihypertensive, analgesic, antiviral, antifungal, anticancer, and antihistaminic properties. The main topics of this review are benzimidazole and its derivatives, the most crucial techniques for making them, and the biological uses of the compound.

Keywords: Heterocyclic compounds, Benzimidazole, Synthesis, Biological applications.

INTRODUCTION

One of the fundamental organic elements used in the synthesis of 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 variety of other fields, including medicine, agriculture, the synthesis of other organic chemicals and polymers, and a wide range of industrial uses. Numerous heterocyclic compounds, such as hypnotics, anticonvulsants, antitumors, antihistamines, antiseptics, and antivirals, are also utilised as medications. [1–4] In pharmacology, numerous novel medications containing heterocyclic compounds are used annually to treat a wide range of human illnesses. Since many of these novel medications, which are made up of heterocyclic compounds, are helpful in other disease states and have antibacterial, antifungal, antiviral, anti-inflammatory, and anticancer properties, [5-9] they can be utilised to treat a variety of illnesses.

More effective methods for scientists to create heterocyclic compounds as practical medications have recently been established. Both the economic and environmental aspects of the existing methods for the organic synthesis of heterocyclic compounds have been gradually improving, which is crucial for future sustainability considerations. [10-12] Organic compounds with a single ring or polycycle that contain at least one heterocyclic atom, such as oxygen, nitrogen, sulphur, and others, are known as heterocyclic compounds. [13] In this review, we focus on benzimidazoles, and discuss their properties, methods of synthesis, as well as their important biological applications.

1.1 Imidazoles: Since imidazoles have therapeutic qualities and can be utilised to make a variety of medications, they are very significant heterocyclic chemicals. With the generic formula C3H4N2, imidazole is a planar heterocyclic molecule that dissolves readily in water and polar liquids due to its predicted dipole of 3.61. It is an amphoteric substance that has the ability to function as either an acidic or basic substance. Since a hydrogen atom can change from one nitrogen atom to another, imidazole can exist in two equivalent tautomeric forms: 1H-imidazole and 3H-imidazole. [14] The sextet π-electron system, which consists of a pair of electrons from the protonated nitrogen atom and the remaining electrons from the other four atoms in the ring, is another reason imidazoles are regarded as aromatic compounds. [15]

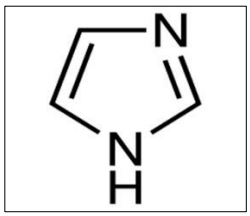


Figure 1: Imidazole

1.2 Benzimidazole: In medicinal chemistry, benzoimidazole, a heterocyclic aromatic organic molecule, is a popular and adaptable pharmacophore. One of the preferred scaffolds for the creation and synthesis of new compounds with medicinal potential is the benzimidazole ring[16]. Numerous biological actions, including antibacterial, anticancer, anthelmintic, anti-convulsant, antioxidant, anti-inflammatory, antifungal, antipsychotic, antihistaminic, and antiviral properties, are displayed by this nitrogen-containing heterocyclic moiety [17].

1.2.1 Chemistry: The benzene ring is fused to the imidazole ring's positions four and five to form the six-membered

bicyclic heteroaromatic molecule known as benzoimidazole. Two nitrogen atoms, positioned at positions 1 and 3, in the benzoimidazole ring are amphoteric, meaning they have both basic and acidic properties [18]. The hydrogen atom can be found on either of the two nitrogen atoms in either of the two equivalent tautomeric forms of the benzoimidazole ring[19].

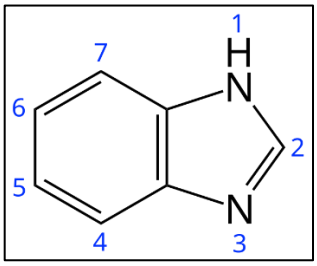


Figure 2: Benzimidazole

- Formula: $C_7H_6N_2$
- Molecular Weight: 118.053 g/mol
- Synonyms: 1H-Benzimidazole; 1,3-benzodiazole; benzoglyoxaline; N, N 'methylenyl-0-phenylenediamine; 3- azindole; 3-azaindole; O-benzimidazole; benzoimidazole; 1,3diazaindene.
- Molecular weight: 118.17
- Toxicity: Oral rat LD_{50}:2910mg/Kg[20]

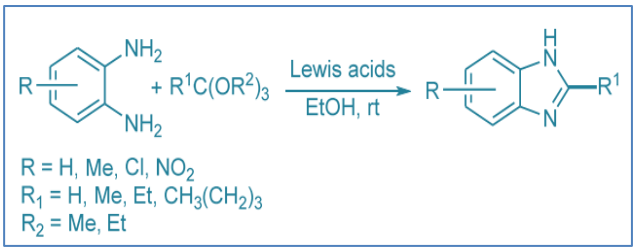
1.2.2 Physical and chemical properties:

- ✓ Physical state: Tabular crystals
- ✓ Colour: Whitish
- ✓ Odor: Characteristics
- ✓ Specific gravity: 1
- ✓ Boiling point: 360°C
- ✓ Melting point: 176°C
- ✓ Solubility: Freely soluble in alcohol, sparingly soluble in ether. Practically insoluble in benzene, petroleum ether. Soluble in aqueous solutions of acids and strong alkalis
- ✓ Auto ignition: 538°C
- ✓ Isomerism: Tautomerism
- ✓ Stability: Stable under normal temperature and condition. [21]

1.2.3 History: The nitrogenous chemical compound benzoimidazole has been known since antiquity. Between 1872 and 1878, Hoebrecker was the first to synthesise it, followed by Ladenberg and Wundt[22]. 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 chemical made from 2-phenylbenzimidazole and phenothiazine was prepared in the early 1960s and proved effective in treating sheep anthelmintic infections[23]. 2-(thiazol-4-yl)benzimidazole was found in Merck Sharp and Dohme's labs in 1961; the synthesised molecule was regarded as a broad-spectrum and highly significant anthelmintic. A significant indication and a qualitative shift to a new generation of medication design can be seen in the production of this organic molecule and its application in the treatment of parasitic worms in both humans and pets. The formation of stable compounds within this class and a wide variety of applications were made possible by the ease with which benzimidazole and its derivatives underwent electrical reactions and field condensation. It has been demonstrated that these substances work well as medications for a number of human and animal illnesses[24].

1.2.4 Synthetic Methodology: A lot of work has gone into creating libraries of benzimidazoles and their derivatives because of their synthetic significance and the range of bioactivities they exhibit.

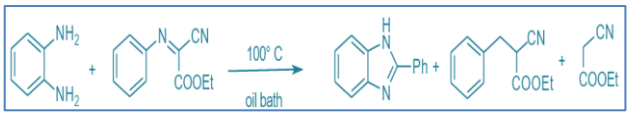
i) Use of Catalysis for the Synthesis of Benzimidazoles: The hunt for more appropriate and useful synthesis methods for benzimidazoles is still an active research area since the creation of novel synthetic procedures to obtain possible therapeutic compounds has grown to be a prominent research focus. Additionally, the application of catalysts has grown in significance. The production of benzimidazole derivatives was found to be more environmentally friendly when Lewis acids were used as effective catalysts in different transformations. The first example of the synthesis of benzimidazole derivatives is a simple process that uses o-phenylenediamines and orthoesters at ambient temperature. (**Scheme 1**)[25]. $ZrOCl_2.8H_2O$, $TiCl_4$, $SnCl_4$, $5H_2O$, and $HfCl_4$ have been proved to be highly effective catalysts. In contrast, other metal salts such as $Mg(ClO_4)_2$, $Bi(NO_3)_5$, $5H_2O$, $CuCl_2$, $2H_2O$, $CoCl_2$, $6H_2O$, $ZnCl_2$, $Zn(ClO_4)_2$, $NiCl_2.6H_2O$, LiCl, $LiBr.H_2O$, $CdCl_2.2.5H_2O$, $Ti(SO_4)_2$, $NH_4Ce(NO_3)_2$, $SiCl_4$, $BF_3.Et_2O$, BCl_3, and $Zr(SO_4)_2.4H_2O$ were either less active or inert as a catalyst. [26] The reaction produced no product in the absence of a catalyst. With good yields, the reaction ran smoothly at room temperature with $ZrCl_4$ (10 mol%) present and anhydrous EtOH.



Scheme 1

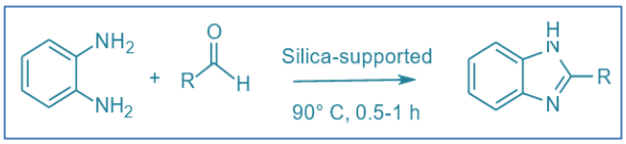
Catalysts such TFE/HFIP, 6 CuI/L-proline, TMS, amberlite IR-120, $SiO_2/ZnCl_2$, Dowex-50 W, SDS micelles, silica sulphuric acid, $FePO_4$, CAN, $Cu(NO_3)_2.3H_2O$, and $FeCl_3/Al_2O_3$ are used in the synthesis of disubstituted benzimidazole. [27, 28] The reaction frequently exhibits poor N-1 substitution selectivity, leading to the generation of a mixture of 2-substituted and 1,2-disubstituted benzimidazoles. Additionally, the use of costly reagents, lengthy reaction

times, and dangerous organic solvents are some of the main disadvantages of current methods. Regarding the latter, a transfer-hydrogenation procedure has been used to create substituted benzimidazoles from o-phenylenediamine and ethyl a-cyanocinnamate. A highly effective and metal-free transfer-hydrogenation method from in situ-generated benzimidazolines to activated olefins was proposed by Kappor et al. The reaction was conducted without the use of a catalyst or solvent. heating o-phenylenediamine and ethyl a-cyanocinnamate in equimolar amounts at 100 °C. It was discovered that when three new components appeared, the beginning material disappeared. Precipitation was used to separate the most polar component, and purification of the remaining compounds produced the matching benzimidazole (**Scheme 2**) [29, 30].



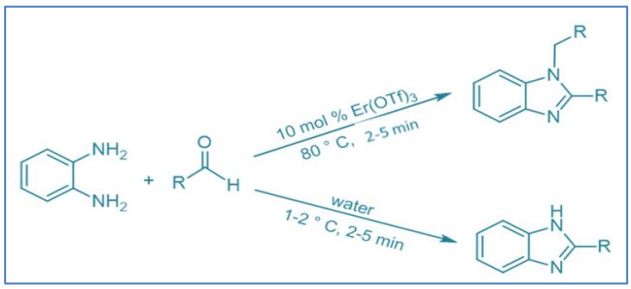
Scheme 2

Arylaldehydes or arylmethylene-malononitriles have been employed as starting materials in the synthesis of benzimidazole derivatives in conditions devoid of solvents and catalysts, with silica gel serving as an absorbent for the starting materials [31]. The reaction was conducted using either a microwave-assisted method or intermittent grinding (**Scheme 3**).



Scheme 3

As Lewis acid catalysts, lanthanide triflates have shown great effectiveness in the catalytic production of benzimidazoles. Novel benzimidazole-linked triazole compounds have been synthesised using $Zn(OTf)_2$.[32] Triazoles, like benzimidazoles, are used extensively as agrochemicals and medicines and also show a variety of biological functions. Given the biological significance of 1,2,3-triazoles and benzimidazole, it was thought to be beneficial to create some new chemical products that integrated the pharmacophores of 1,2,3-triazoles and benzimidazole in a single molecule in order to understand the combined effect of the two moieties. The reaction was carried out by treating 2-(4-azidophenyl)-1H-benzo[d] imidazole (6) with various terminal alkynes in t-BuOH/H_2O, $Zn(OTf)_2$, and sodium ascorbate. The production of 1,2-disubstituted benzimidazoles was aided by the use of $Er(OTf)_3$, a readily recyclable and commercially accessible catalyst [33, 34]. Additionally, with water as a solvent at 1-2 ◦C or at 80 ◦C (for electron-deficient aldehydes), 2-substituted benzimidazoles were selectively produced in high yield and short reaction durations (**Scheme 4**).

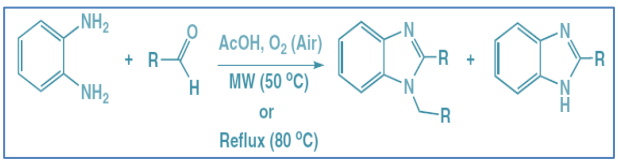


Scheme 4

ii) Green Synthesis of Benzimidazole: Researching the kind of product or method that uses less dangerous materials is the first step in green chemistry. The concept of "green chemistry" has been the centre of attention since the early 1990s, when many saw that it was the only option to reduce the risk of chemicals and potentially fatal processes. Because of the waste that is produced as byproducts and the gases and vapours released during the production process, the preparation of organic compounds is one of the processes that pollutes the environment.

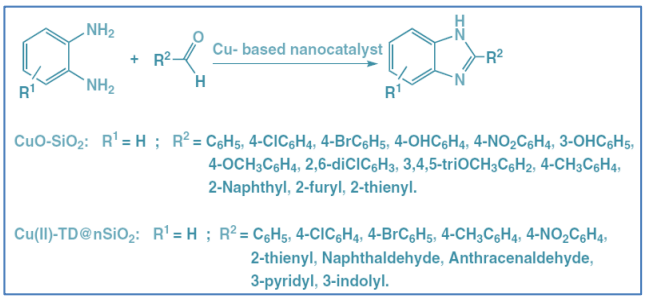
As a result, alternate methods of preparing organic materials that maintain the environment's natural equilibrium must be developed or employed. [35–37] Many of the technologies used today to prepare organic compounds are regarded as green technologies since they save energy, lower waste emissions, and increase the quality of the organic compounds that are produced. These technologies include organic synthesis through ultrasound techniques, photochemical reactions, microwave-mediated processes, reactions with catalysts (catalytic reactions), reactions that take place in the presence of water as a solvent, and other novel chemical production technologies.

Green approaches have been used to create benzoimidazole and its derivatives, which are organic compounds, rather than the conventional industrial or chemical procedures. Some benzimidazole derivatives were prepared using microwave technology (MW) by condensing aldehydes with ophenylenediamine when acetic acid was present in certain proportions **(Scheme 5)**. This method's benefits include rapid reaction times, the use of non-toxic solvents, and excellent product yields. [38]



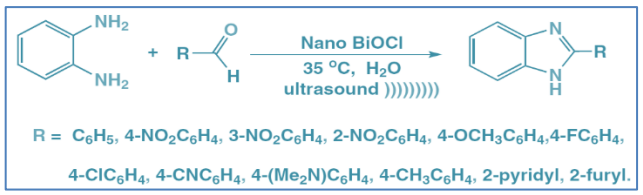
Scheme 5

Aldehydes have been condensed with o-phenylenediamine to produce a number of benzimidazole derivatives using different transition-metal nanocatalysts **(Scheme 6)**. When novel benzimidazole derivatives were created by Inamdar et al. using nanomaterials (CuOnp-SiO2 10%) as a catalyst, the method produced good yields of 76–93%. Nasr-Esfahani et al. discovered that when the novel benzimidazole derivatives were synthesised with the nanocatalyst ((Cu(II)-TD@nSiO_2)), the yield increased to 88–97%. [38]



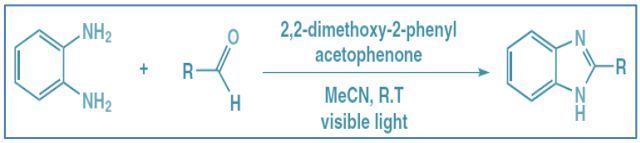
Scheme 6

A very effective green procedure for the synthesis of substituted 1H-benzimidazole derivatives was created by Sapkal et al. Under the effect of ultrasound, the reaction between phenylenediamine and aldehydes was conducted with water as the solvent and nano-BiOCl as a catalyst. It was discovered that there would be no discernible decrease in activity if this nanocatalyst was utilised seven more times during the activation process. The key benefits of this ultrasonic-based method include the low temperature (35 °C) needed to finish the reaction, the shorter processing time, the potential for catalyst reuse, and the use of water as a solvent—a naturally environmentally friendly solvent. In several instances, the productivity reached 94% (**Scheme 7**).[39]



Scheme 7

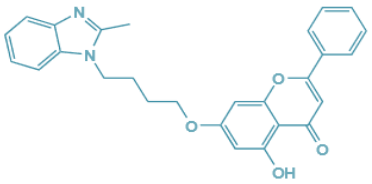
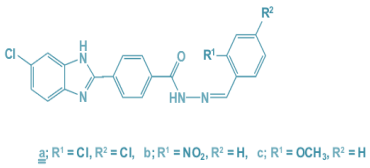
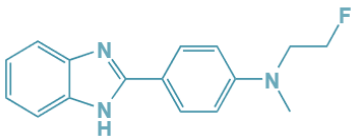
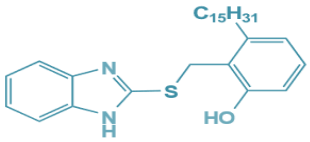
In 2021, Skolia et al. described a novel method for creating benzimidazole derivatives by a photochemical process. 2,2-dimethoxy-2-phenylacetophenone was employed as a photoinitiator in this procedure, while CFL bulbs served as the light source. The process involved cyclizing diamine with aldehydes and synthesising benzimidazole derivatives in good to high yields by combining modified ophenylenediamine with aldehydes at room temperature. Because it is inexpensive, operates quickly at room temperature under visible light, and doesn't produce any environmentally harmful substances, this technology is regarded as green **(Scheme 8)**. [40]

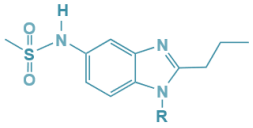
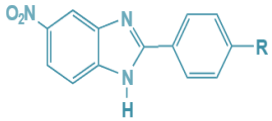
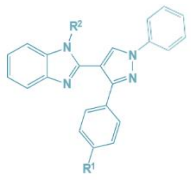
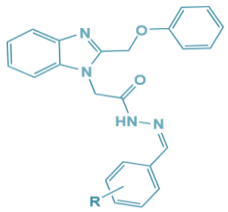
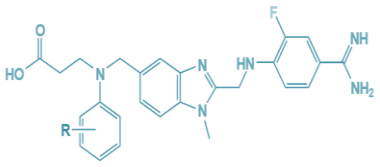
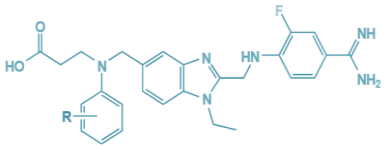
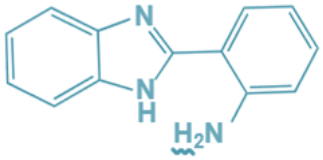
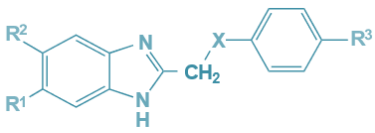


Scheme 8

1.2.5 Pharmacological Property: Since their initial synthesis, benzoimidazole derivatives have been linked to biological uses because of the great effectiveness of this family of heterocyclic chemicals in medicine, which has been successfully demonstrated in recent years. Derivatives of benzoimidazole have been employed as anticonvulsants, antitumors, antimicrobials, and anti-inflammatories, among other uses. [41–42] The most significant biological uses for benzimidazole derivatives as basic chemicals are listed below.

Table 1: Pharmacological Activity of Benzimidazole Derivatives

S. no	Derivative	Structure	Pharmacological Activity
1	Chrysin benzimidazole derivatives		Wanga et al., [43] reported anticancer activity
2	benzimidazole derivatives	 a; R1 = Cl, R2 = Cl, b; R1 = NO2, R2 = H, c; R1 = OCH3, R2 = H	Cevik et al., [44] reported anticancer activity
3	benzimidazole derivatives (hydroxylated or fluorinated alkyl substituents)		Morais et al., [45] reported anticancer activity
4	Benzimidazole derivatives		Gaba et al., [46] reported anti-inflammatory activities

5	5-methane-sulphonamido benzimidazole	 a; R= n-butyl b; R= n-pentyl c; R= n-hexyl	Sharma et al., [47] reported anti-inflammatory activities
6	Benzimidazole derivatives	 a; R= -Cl b; R= -Br c; R= -F d; R= $-OCH_3$	Archie et al., [48] evaluated the antioxidant activity
7	N-substituted pyrazole-containing benzimidazole derivatives	 a; R^1= H, R^2 = Bn, b; R^1 = NO_2, R^2 = Bn, c; R^1 = Cl, R^2 = Bn	Bellam et al., [49] reported antioxidant activity
8	Benzimidazole derivatives	 R = H, 2-Cl, 4-Cl, 4-OCH_3, 3-OCH_3, 3,4-diOCH_3, 4-F, 4-NH_2, 4,4-dimethylamino, NO_2	Shaharyar et al., [50] examined the anticonvulsant activities
9	Substituted benzimidazole derivatives	 a; R= 3-CH_3, b; R= 2,3-CH_3, c; R= 2,5-CH_3	Yang et al., [51] evaluated for anticoagulants
10	Fluorinated derivatives of substituted 1-ethyl-1H-benzimidazole	 a; R= 3,4-F, b; R= 3,5-F, c; R= 2,4-CH_3 d; R= 3,4-CH_3, e; R= 3,5-CH_3, f; R= 2,4-F	Wang and Ren., [52] reported as antithrombin activity
11	2-substituted benzimidazoles		Ajani et al., [53] reported the antimicrobial activity
12	2-phenyl substituted benzimidazole derivatives	 X= -O- , R^1=Cl, R^2=H, R^3=Cl X= -O- , R^1 = R^2 = R^3 = Cl	Ersan et al., [54] evaluated their biological activity as anticancer and antimicrobial agents

CONCLUSION

Because of their vital biological significance in the production of numerous medications and antibiotics, benzimidazoles are one of the most significant groups of synthetic organic chemicals. As a result, the synthesis of benzimidazole derivatives became a primary focus for the production of numerous additional chemical compounds that, when examined, demonstrated unique medical value. This review aims to assist researchers in identifying the many chemical characteristics of benzimidazoles and their derivatives. The most significant chemical and green chemistry techniques for creating various benzimidazole derivatives are also briefly reviewed, along with the advantages and disadvantages of each preparation technique. Numerous pharmacological effects, including antibacterial, antifungal, antioxidant, antiviral, anticancer, and anti-inflammatory properties, are exhibited by benzomidazole. As a result, we may conclude that benzimidazole is a moiety that has demonstrated pharmacological activity diversity and has the ability to investigate more undiscovered pharmacological actions.

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Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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