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A Review on Benzimidazole Heterocyclic Compounds: Synthesis and Their Medicinal Activity Applications

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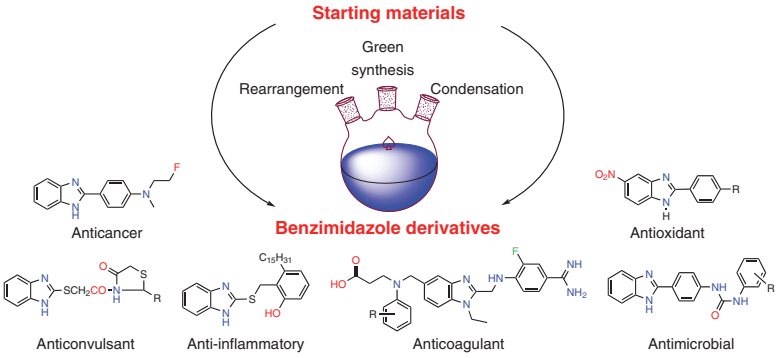

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Abstract Benzimidazole is a heterocyclic compound that contains two nitrogen atoms and is formed by fusing a benzene ring with an imidazole. Benzimidazole and its derivatives are prepared in a range of ways, including condensation of *o*-phenylenediamine with carbonyl compounds (aldehydes and ketones) or with carboxylic acids and their derivatives. Benzimidazoles can also be prepared by rearranging other heterocyclic compounds such as quinoxaline derivatives and triazole derivatives. In recent decades, benzimidazoles have been prepared using green methods such as microwaves and ultrasound, the use of environmentally friendly catalysts, and by using photochemical reactions. Benzimidazoles have attracted the interest of scientists and researchers due to the great medical efficacy exhibited by such derivatives against various diseases. The benzimidazole derivatives show many pharmacological activities such as anticancer, anti-inflammatory, antioxidant, anticoagulant, and antiviral action. This review focuses on benzimidazole and its derivatives, the most important methods used for its preparation, as well as the biological applications of the compound in our daily lives.

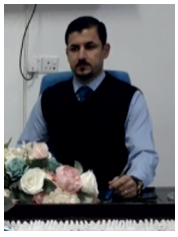
Keywords benzimidazole, *o*-phenylenediamine, green chemistry, biological activities

1 Introduction

Heterocyclic compounds are one of the basic organic materials that have a major role in the preparation of other organic compounds, including drugs. Heterocyclic compounds are very complex classes in chemistry because they contain hetero atoms and therefore possess a great diversity of properties. In addition to their importance in human life, where they play a major role, heterocyclic compounds are important in many applications such as medicine and agriculture and in the preparation of other organic compounds and polymers as well as their use in various industrial applications. Many heterocyclic compounds are also used as drugs, including hypnotics, anticonvulsants, antitumors, antihistamines, antiseptics and antivirals.[1–7] Every year, many new drugs featuring heterocyclic compounds are used in pharmacology to treat many human diseases. These new drugs, which consist of heterocyclic compounds, can be used to treat various diseases as many are active as antibacterial,[8–10] antifungal,[11] antiviral,[12] anti-inflammatory,[13] and antitumor[14,15] agents as well as being effective in other disease states. Recently, more successful paths have been developed for chemists to prepare heterocyclic compounds as useful drugs. The available methodologies for organic synthesis of heterocyclic compounds have been steadily improving with respect to not only the economic field, but also the environmental aspect, which is very important for future sustainability considerations.[16] Heterocyclic compounds are organic compounds consisting of a single ring or a polycycle and they contain at least one heterocyclic atom such as oxygen, nitrogen, sulfur and others.[17] In this review, we focus on benzimidazoles, and discuss their properties, methods of synthesis, as well as their important biological applications.

Biographical Sketches

Leqaa A. Mohammed obtained her doctoral degree in organic synthesis from Al-Mustansiriya University, Iraq. Following the completion of her Ph.D., she pursued a research stay at Diyala University, Iraq. Her academic pursuits encompass a broad range of research interests, ranging from the development of synthetic methodologies to exploring the applications of organic compounds in the field of nanomaterials.



Mohammed Alwan Farhan is an accomplished scholar who recently earned his Ph.D. from Al-Mustansiriya University, Iraq in 2021. His research primarily focuses on the synthesis of polymers and their applications in the removal of pollutants. With his expertise in the field, Mohammed has made significant contributions to the understanding and development of innovative materials for environmental remediation.

Safaa A. Dadoosh is a highly accomplished chemist specializing in organic compound synthesis and drug compounds. He obtained his Bachelor of Science degree from the University of Mustansiriyah in 2007, and pursued his Master's degree at Tikrit University, graduating in 2011. Building on his academic achievements, he continued his academic journey and completed his Ph.D. at the University of Mustansiriyah in 2020. Currently, he is affiliated with the Department of Chemistry at the College of Science, University of Diyala. In his role as a researcher and faculty member, he actively participates in cutting-edge research projects, mentoring students, and teaching undergraduate and graduate-level courses.

Dr. Mustafa A. Alheety completed his Bachelor's degree from Al-Anbar University in 2012, followed by a Master's degree in 2015 and a doctorate in 2018 from the University of Tikrit. He received support from Tokatgaziosmanpasha University in Turkey to fulfill the requirements for his Ph.D. During his academic journey, he worked at the Middle East University College and later joined Al-Hadi University College, both located in Iraq. Initially, Dr. Alheety's research interests focused on inorganic chemistry. However, he later expanded his scope to integrate inorganic chemistry with nanoscience. His work involved transforming inorganic materials into their nano counterparts, exploring the unique properties and applications of nanomaterials. Currently, Dr. Alheety is actively involved in research aimed at finding environmentally friendly methods for compound preparation. His primary areas of focus revolve around hydrogen storage applications and anticancer applications. In the field of hydrogen storage, he strives to develop sustainable approaches for efficiently storing hydrogen, which is crucial for the advancement of renewable energy sources. Additionally, he dedicates his efforts to investigating the potential of inorganic compounds and nanomaterials in the development of novel strategies for combating cancer.

Dr. Abdulwahhab H. Majeed is a lecturer in the Department of Chemistry at the University of Diyala. He holds a Ph.D. in chemistry from Tikrit University (2020) and specializes in nanomaterials and polymer nanocomposites. With a focus on synthesis, characterization, and applications, his research contributes to advancements in energy storage, environmental remediation, and biomedical engineering. Dr. Majeed's academic achievements and dedication to the field make him a valuable asset in the realm of nanomaterial research.

Ali Saadon Mahmood is a dedicated professional with a Master's degree in industrial chemistry. He is currently employed at the General Directorate of Education in Kirkuk, under the Ministry of Education Directorate in Iraq. Ali's primary research interest lies in the field of polymer applications and the synthesis of nanomaterials. His work focuses on exploring the practical applications of polymers and the synthesis of nanomaterials, contributing to advancements in materials science and related industries.

Dr. Zaid H. Mahmoud is an esteemed chemist affiliated with the Department of Chemistry at the College of Science, University of Diyala. His research interests span the fields of photochemistry and nanotechnology. Dr. Mahmoud actively engages in cutting-edge research and scholarly pursuits. His expertise in these areas contributes to advancements in understanding the interactions of light with matter and exploring the applications of nanotechnology in various scientific domains.

2 Imidazole and Benzimidazole

Imidazoles are very important heterocyclic compounds because they have medicinal properties that can be used in the preparation of many drugs. Imidazole is a planar heteropentacyclic compound, with the general formula $C_3H_4N_2$; it is easily soluble in water and polar solvents because it is a polar compound with a calculated dipole of 3.61. It is an amphoteric compound that can act as an acidic or basic compound. 1*H*-Imidazole and 3*H*-imidazole are the two equivalent tautomeric forms in which imidazole can exist because a hydrogen atom can be transformed from one nitrogen atom to the other.[18,19] Imidazoles are also considered to be aromatic compounds because of the presence of the sextet π-electron system, which include a pair of electrons from the protonated nitrogen atom and the remaining electrons from the other four atoms in the ring.[20]

Benzimidazole is a white solid, aromatic heterocyclic organic compound. It is formed by the fusion of the aromatic benzene ring with the heterocyclic imidazole aromatic ring (Figure 1). It is also called 1*H*-1,3-benzimidazole and 1*H*-benzo[*d*]imidazole and it has the general formula $C_7H_6N_2$.[21] The benzimidazole compound has aroused the interest of researchers over the past decades in research and application because of the distinctive properties of the organic compounds derived from it, and because of its well-known biological applications and many important medicinal properties. One of the most prominent forms of benzimidazole found in nature is N-ribosyl-dimethyl benzimidazole, which is the pivotal link coordinating to the cobalt element in vitamin B_{12}.[22]. Benzimidazole has many important biological activities such as antihistamine, antifungal, antimicrobial, antiviral, anti-inflammatory, antioxidant, antiulcerative, and anticancer action, as well as others; for this reason there is a great growth and wide development of the field by researchers wanting to prepare benzimidazole derivatives.[23,24]

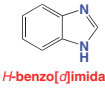


Figure 1 Structure of benzimidazole

Benzimidazole is a nitrogenous organic compound that has been known since ancient times. It was first synthesized by Hoebrecker and then by Ladenberg and Wundt between 1872 and 1878.[25] Although the discovery of benzimidazole was relatively simple, investigations into the effectiveness of this compound and its effective therapeutic potential against parasites was not noticed until 80 years after its discovery. In the early sixties, a compound formed from 2-phenylbenzimidazole and phenothiazine was prepared that turned out to be useful for anthelmintic treatment of sheep.[26] In 1961, 2-(thiazol-4-yl)benzimidazole was discovered in the laboratories of Merck Sharp and Dohme; the prepared compound was considered a broad-spectrum and very important anthelmintic.[27] The preparation of this organic compound and its use in the treatment of parasitic worms for humans and pets can be considered a very important sign and a qualitative transition to a new generation of design of these drugs. The ability of benzimidazole and its derivatives to undergo easy electrical reactions and field condensation led to the emergence of stable compounds within this class as well as to a diverse range of uses. Such compounds have been shown to be effective medicines for various diseases of humans and animals such as cattle, horses, poultry, sheep, goats, cats, dogs, and others.[28]

3 Methods of Synthesis of Benzimidazole Derivatives

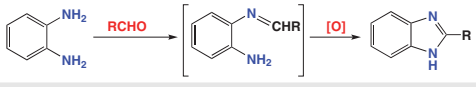
Many approaches have been developed and confirmed for the synthesis of benzimidazoles. One of these methods is the direct method for the preparation of benzimidazole through a direct condensation reaction between *o*-phenylenediamine and formic acid (Scheme 1).[29] There are also many ways to prepare benzimidazole derivatives. Some of these methods face some challenges, such as low yield, harsh reaction conditions, or long reaction times, and other methods are more suitable for preparation, as summarized in the following methods.

Scheme 1 Synthesis of benzimidazole

3.1 Condensation of 2-Aminoaniline (*o*-Phenylenediamine)

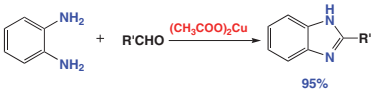
3.1.1 With Aldehyde

In this method, the benzimidazole derivatives are prepared from the condensation reaction between various aldehydes and 2-aminoaniline (*o*-phenylenediamine) (Scheme 2). This reaction occurs in an oxidation process with either air or several other oxidizing agents.[30]



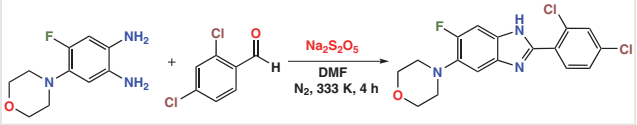
Scheme 2 General condensation of *o*-phenylenediamines with aldehyde to synthesize benzimidazoles

It was also reported that *o*-phenylenediamine can be used with alkyl, aryl, and heterocyclic aldehydes in the presence of palladium or copper catalysts. Good product and purity were obtained under these conditions (Scheme 3).[31,32]



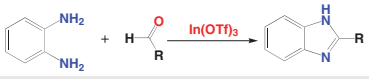
Scheme 3 Synthesis of benzimidazole using copper acetate as catalyst

The benzaldehyde derivative shown in Scheme 4 was prepared by the reaction of 2,4-dichlorobenzaldehyde with *o*-phenylenediamine in the presence of sodium pyrosulfite $Na_2S_2O_5$ (sodium metabisulfite).[33]



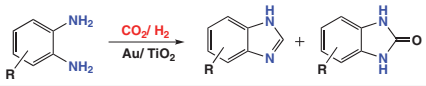
Scheme 4 Synthesis of benzimidazole using sodium metabisulfite catalyst

Furthermore, 2-substituted benzimidazoles were prepared by Rushi et al. as shown in Scheme 5, by condensing aldehydes with *o*-phenylenediamine under solvent-free conditions using [In(OTf)$_3$] as catalyst at room temperature. This method gave good and dependable yield.[34]



Scheme 5 Use of solvent-free conditions for the synthesis of benzimidazoles

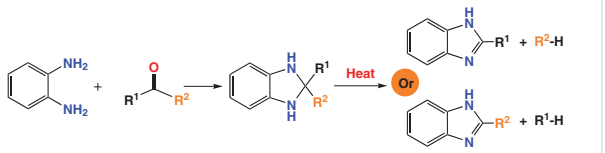
Benzimidazoles have also been prepared in the presence of gold nanocomposites in different form such as Au/ZnO, Au/TiO_2, Au/Al_2O_3, which is a very effective method. This procedure was reported by L. Hao et al. (Scheme 6).[35]



Scheme 6 Synthesis of benzimidazole catalyzed by Au/TiO_2 nanoparticles

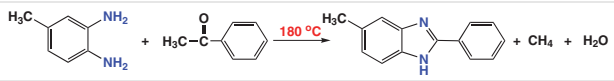
3.1.2 With Ketones

Another method that is used to prepare benzimidazole derivatives is through the condensation reaction between ketones with *o*-phenylenediamine; however, this procedure includes some limitations that make this reaction not as widely used to prepare benzimidazole derivatives, which will be discussed later. The general method includes a condensation reaction between diamine and ketones at temperatures that differ from one reaction to another according to the reaction conditions (Scheme 7).[30]



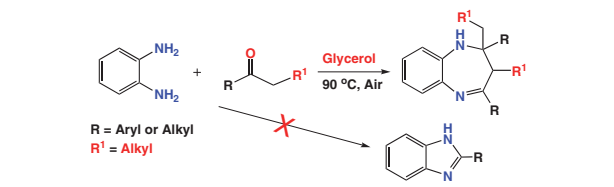
Scheme 7 Synthesis of benzimidazoles using condensation reaction between ketones and *o*-phenylenediamines

Alaqeel reported in 2017 that it is possible to prepare benzimidazole derivatives in this way and that the stability of the prepared products depend on the alkyl group substituent on the ketones. In the same way, Ladenbrug and Rugheimer documented the possibility of synthesizing 2-phenyl-5(or 6)-methylbenzimidazole compounds by conducting a condensation reaction between acetophenone and 3,4- diaminotoluene by heating at 180 °C (Scheme 8).[36]



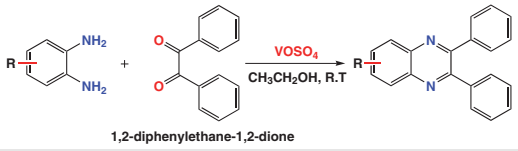
Scheme 8 Using the reaction of *o*-phenylenediamine with acetophenone to synthesize benzimidazole derivatives

The reaction suffered from some difficulties such as the formation of undesirable products, long reaction time, as well as some challenging working conditions, which led to the development of better conditions for this type of reaction, such as the possibility of completing the reaction under solvent-free conditions or using other catalysts. Despite these improvements in the method, this method could not be used to produce benzimidazoles, with other heterocyclic compounds being produced instead. For example, as presented by Radatz et al., when the reaction of acetophenone or other ketones with *o*-phenylenediamine was conducted at moderate temperatures using glycerin as a recyclable, economical, and environmentally friendly solvent, the resulting product was a low yield of benzodiazepine instead of benzimidazole. A similar product was formed when the temperature was increased, but with higher yields (Scheme 9).[37]



Scheme 9 Schematic reaction between the ketones and o-phenylenediamine.

Digwal et al. confirmed that quinoxaline derivatives)2,3-diphenyl quinoxaline derivatives) are formed instead of benzimidazoles when dibenzyl ketones react with *o*-phenylenediamines using $VOSO_4$ as a catalyst (Scheme 10).[38]

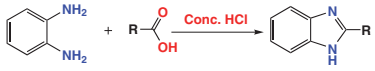


Scheme 10 Reaction of 1,2-diphenylethane-1,2-dione with *o*-phenylenediamine using $VOSO_4$ as catalyst

In summary, the reaction of *o*-phenylenediamine or its derivatives with ketones did not give the expected benzimidazoles; on the contrary, other heterocyclic organic compounds were sometimes obtained as discussed above.

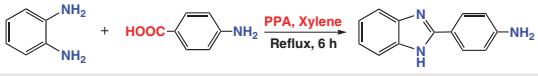
3.1.3 With Carboxylic Acids

Many studies and research centers have presented research over a period of years indicating that it is possible to prepare benzimidazole and its derivatives through a condensation reaction between carboxylic acids and *o*-phenylenediamine or its derivatives in the presence of hydrochloric acid as a catalyst (Scheme 11).[36]



Scheme 11 General condensation of *o*-phenylenediamines with carboxylic acids to synthesize benzimidazole derivatives

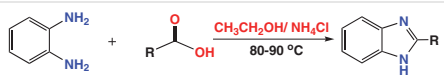
Alam et al. documented the preparation of new benzimidazoles under reflux in xylene and polyphosphoric acid with equimolar amounts of *o*-phenylenediamine with *p*-aminobenzoic acid. The reaction took place within 6 hours and the yield was good and reliable (Scheme 12).[39]



Scheme 12 Condensation of *o*-phenylenediamines with aromatic carboxylic acids to synthesize benzimidazole derivatives

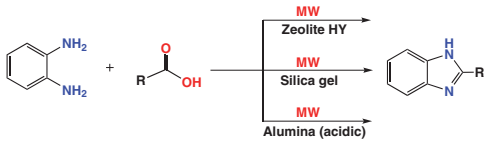
Rithe et al. reported the possibility of preparing new benzimidazole derivatives in good yield by using a one-step condensation reaction with equimolar amounts of aromatic acid and *o*-phenylenediamine at 80–90 °C, with ammonium chloride as catalyst. This method gives good yield and high purity as well as being an economical and environmentally friendly approach (Scheme 13).[40]

In 2015, A. Saberi documented the possibility of preparing new benzimidazole derivatives using alumina, silica gel,



Scheme 13 Synthesis of benzimidazole derivatives using ammonium chloride as catalyst

or zeolite as catalyst under solvent-free conditions under microwave irradiation. The reaction was performed by mixing equal moles of aromatic, aliphatic, and heterocyclic carboxylic acid with *o*-phenylenediamine with 50 g of catalyst, grinding the mixture well in a mortar, and then irradiating the ground mixture in a microwave for 5–9 minutes (Scheme 14).[41]



Scheme 14 Synthesis of benzimidazole derivatives using Al_2O_3, SiO_2, or zeolite as catalyst

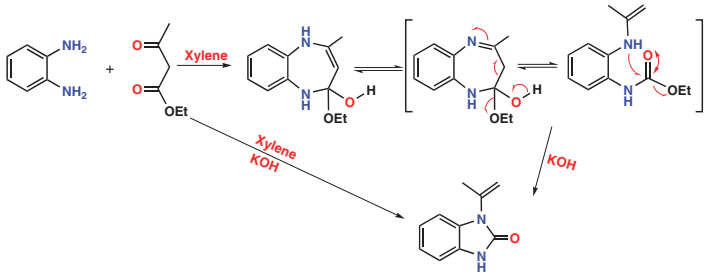
Huynh et al., recently used the same microwave irradiation method to prepare new benzimidazole derivatives through condensation of monocarboxylic acids with *o*-phenylenediamine under catalyst-free conditions (Scheme 15).[42] This method is considered very important and is one of the most economical and environmentally friendly methods. It gave a good yields for the benzimidazole derivatives targeted in the preparation.

Scheme 15 Synthesis of benzimidazole derivatives using microwave under catalyst-free conditions

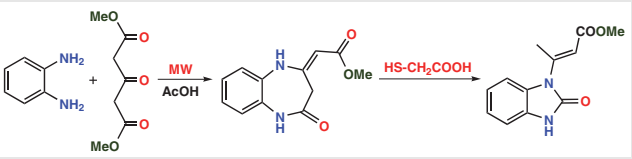
Benzimidazole derivatives can also be prepared by using a condensation reaction between *o*-phenylenediamines with different classes of organic compounds such as carboxylic acid derivatives (anhydrides, esters, amides, acid chlorides), nitriles, as well as urea. These methods can give benzimidazole derivatives with different yield ratios and purity, depending on the presence of by-products.[36]

3.2 Via Rearrangement

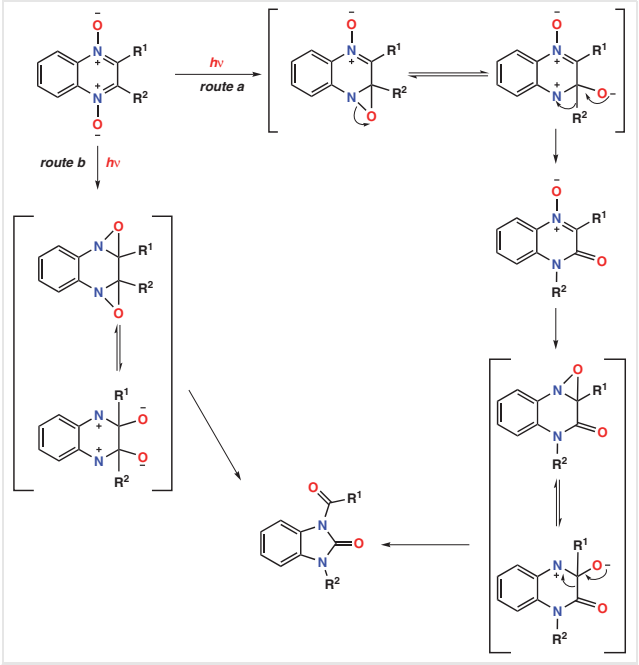
Benzimidazole derivatives are synthesized by condensation reactions as discussed above. In addition, some of the most effective methods that are used to prepare benzimidazole derivatives have been based on rearranging heterocyclic compounds.



Scheme 16 General method for the synthesis of benzimidazolone from benzodiazepinones via a rearrangement process



Scheme 17 Synthesis of benzimidazolone from benzodiazepinones via rearrangement



Scheme 18 Suggested mechanism for the preparation of benzimidazolone from quinoxaline-1,4-dioxides

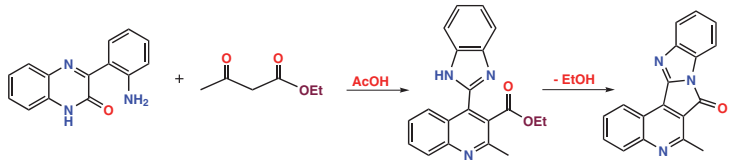
Heating of a mixture of ethyl acetoacetate with *o*-phenylenediamine in xylene solvent to reflux gives a derivative of benzodiazepinone (4,7-dihydro-5-methyl-1*H*-2,3-benzo-1,4-diazepin-7-one). But when this reaction is carried out under the same conditions and then potassium hydroxide is added to this mixture, benzimidazole derivatives are formed (Scheme 16).[43]

It was also mentioned that dicarbonyl compounds can be used in this reaction, making it readily applicable.[30] Eleftheriadis et al. showed that the reaction of dimethylacetone dicarboxylate compounds with *o*-phenylenediamine could give a benzimidazolone through the formation of a diazepine derivative, with subsequent action of mercaptoacetic acid to afford the benzimidazolone (Scheme 17).[44]

Moreover, in 2017, the rearrangement of quinoxaline-1,4-dioxides was documented by which different benzimidazole derivatives were prepared. These studies revealed that the rearrangement process depends on the composition of the compound quinoxaline-2-one as an intermediate material. This study is distinguished because it depends on the preparation of benzimidazole derivatives that contain a wider range of functional groups (Scheme 18).[43]

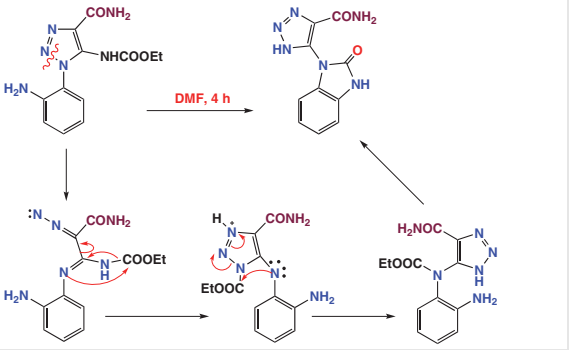
This method was also used to prepare a series of benzimidazole derivatives that are difficult to prepare by other methods. For example, the polynuclear benzimidazole derivatives shown in Scheme 19 were prepared through a reaction between ethyl acetoacetate and 3-(2-aminophenyl)-quinoxalin-2(1*H*)-one, with acetic acid as a solvent.[45]

On the other hand, 1,2,3-triazole derivatives were used as basic rearranged materials to prepare benzimidazolone derivatives. In 2017, the use of 5-amino-4-carbamoyl-1-(2-nitrophenyl)-1*H*-1,2,3-triazol was reported as a base compound for the preparation of benzimidazole derivatives.



Scheme 19 Using rearrangement for the synthesis of polynuclear benzimidazole derivatives from quinoxalinone derivatives

When the 1,2,3-triazole derivative was heated to reflux for 4 hours, the corresponding benzimidazole derivative was generated, as shown in Scheme 20.[30]

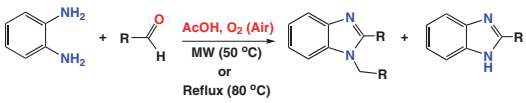


Scheme 20 Rearrangement of triazole derivative to synthesize a benzimidazole derivative

3.3 Green Synthesis of Benzimidazole

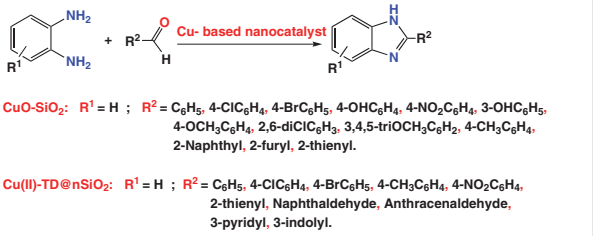
Green chemistry is the invention, design, and application of products and processes that reduce the use and synthesis of substances that are hazardous to the environment. Green chemistry begins with the process of researching the type of product or type of process that reduces the use of hazardous substances. The principle of green chemistry has been focused on since the beginning of the 1990s, as the world began to pay attention to this principle as the only way to ameliorate the danger of chemicals and life-threatening processes. The preparation of organic compounds is one of the processes that leads to environmental pollution due to the gases and vapors emitted during the production process, as well as the waste that is generated as by-products. Therefore, it is necessary to devise or use alternative means to prepare organic materials that preserves the natural balance of the environment.[46–48] Currently, there are many technologies that are used to prepare organic compounds that are considered green technologies because they improve the quality of the prepared organic compounds, reduce waste emitted and save energy. Such technologies include microwave-mediated processes, photochemical reactions, reactions that occur in the presence of water as a solvent, organic synthesis using ultrasound methods, reactions that occur in the presence of catalysts (catalytic reactions), and other new technologies that are used to produce chemicals.[48]

Benzimidazole and its derivatives are organic compounds that have been prepared using green techniques instead of the traditional industrial or chemical methods. Microwave technology (MW) was used to prepare some benzimidazole derivatives by condensing aldehydes with *o*-phenylenediamine in the presence of specific amounts of acetic acid (Scheme 21). Advantages of this method are that the reaction times are short, they use non-toxic solvents, and give high yields of the products.[49]



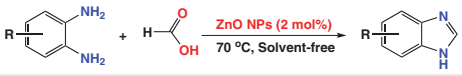
Scheme 21 Synthesis of benzimidazole using a microwave-assisted method

Some benzimidazole derivatives have been prepared with various transition-metal nanocatalysts by condensing aldehydes with *o*-phenylenediamine (Scheme 22). The approach gave good yields of 76–93% when new benzimidazole derivatives were prepared by Inamdar et al. in the presence of nanomaterials (CuOnp-SiO_2 10%) as a catalyst. The yield reached 88–97% when the new benzimidazole derivatives were prepared in the presence of the nanocatalyst ((Cu(II)-TD@nSiO_2)) when it was reported by Nasr-Esfahani et al.[50]



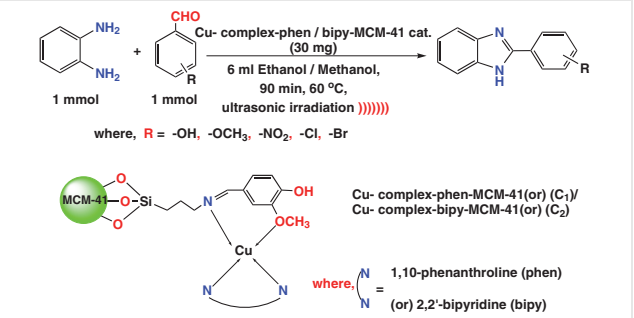
Scheme 22 Use of a copper-based nanocatalyst for the synthesis of benzimidazole derivatives

Benzimidazole derivatives were also prepared from the reaction between formic acid and substituted *o*-phenylenediamine with zinc oxide nanoparticles as a catalyst at 70 °C (Scheme 23). The advantages of this method are the use of solvent-free conditions, excellent yields, the use of an inexpensive catalyst, as well as the moderate conditions under which the reaction takes place.[51]



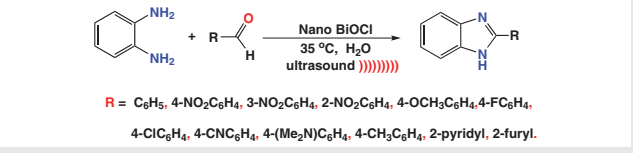
Scheme 23 Synthesis of benzimidazole from *o*-phenylenediamine derivatives and formic acid using ZnO NPs as catalyst

Recently, Bharathi et al. reported that new benzimidazole derivatives were prepared with Cu-phen-MCM-41 and Cu-complex-bipy-MCM-41 as catalysts under ultrasonic irradiation for 90 minutes at 60 °C. The process was carried out in the presence of small amounts of a mixture of ethanol/methanol as solvent (Scheme 24). After completing the preparation of purified benzimidazole derivatives, the catalyst was re-used three times without any significant loss in its catalytic activity. Advantages of this method include the use of environmentally friendly techniques, the catalyst can be reused, and high yields of up to 95% can be achieved.[52]



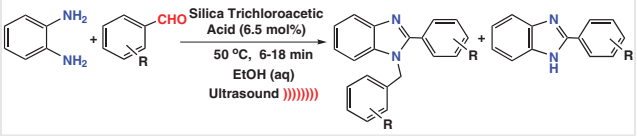
Scheme 24 Synthesis of benzimidazole derivatives using Cu-complex-(phen or bipy)-MCM-41 as catalysts with ultrasonic irradiation

Sapkal et al. developed a highly efficient green protocol for the preparation of substituted 1*H*-benzimidazole derivatives. The reaction between phenylenediamine with aldehydes was carried out using water as solvent under the influence of ultrasound, and nano-BiOCl was used as a catalyst. It was found that this nanocatalyst could be used seven more times in the activation process without significant loss in activity. The important advantages of this approach, which depends on the use of ultrasound, are the low temperature required to complete the reaction (35 °C), the reduced time required to complete the process, the possibility of reusing the catalyst, and the use of water as a solvent, which is a natural friend of the environment. The productivity reached 94% in some cases (Scheme 25).[53]



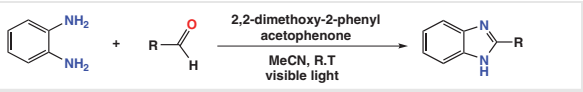
Scheme 25 Synthesis of 2-substituted benzimidazole using BiOCl NPs as catalysts with ultrasound

In 2014, Kumar et al. were able to synthesize 2-aryl-1-arylmethyl-1*H*-benzimidazole derivatives from aromatic aldehydes with *o*-phenylenediamine by sonication in the presence of silica-gel-supported trichloroacetic acid. The process was carried out at 50 °C and gave high yields. This reaction is considered to have been achieved by green technologies, because it represents an excellent modified method that proceeds in a short time, does not cause pollution to the environment, and uses an inexpensive catalyst (Scheme 26).[54]



Scheme 26 Synthesis of 1,2-disubstituted benzimidazole derivatives from aromatic aldehydes with *o*-phenylenediamine under sonication

Skolia et al. in 2021 reported a new approach to the synthesis of benzimidazole derivatives using a photochemical protocol. In this process, CFL lamps were used as a light source with 2,2-dimethoxy-2-phenylacetophenone as a photoinitiator. The method relied on mixing substituted *o*-phenylenediamine with aldehydes at room temperature, which led to the cyclization of diamine with aldehydes and the synthesis of benzimidazole derivatives in good to high yields. This method is considered a green approach because it does not produce compounds that pollute the environment, is performed at room temperature in a short time in the presence of visible light, and is economical (Scheme 27).[55]



Scheme 27 Synthesis of benzimidazole derivatives from *o*-phenylenediamine and aldehydes under visible light

Finally, we note the focus of researchers over the past years on the use of different methods to synthesize substituted benzimidazole derivatives with different groups as presented above. This reflects the importance of these compounds and their significant role in various aspects of life, especially in biological applications, as will be discussed in the next section.

4 Biological Activity of Benzimidazole Derivatives

Benzimidazole derivatives have been associated since their first synthesis to this day with biological applications, due to the high efficacy of this class of heterocyclic compounds in medicine, which has been effectively proven over the past years. Benzimidazole derivatives have been used in many applications, including as antitumors, antimicrobials, anti-inflammatories, and anticonvulsants.[56–63] The following are the most important biological applications that use benzimidazole derivatives as basic compounds.

4.1 Anticancer Activity

The second leading cause of death worldwide is cancer. Therefore, researchers have recently been directed towards preparing compounds that have high efficacy as anticancer drugs. Effective anticancer drugs must have a high selectivity, so that they are toxic to cancer cells and do not affect normal cells. Previously prepared anticancer drugs showed a high toxic activity against cancer cells, but they also had a significant effect on normal cells. Because of these side effects and the toxicity of anticancer drugs, there is a strong tendency to halt chemotherapy for cancer patients. Among all this, heterocyclic compounds have been repeatedly dis-

covered as anticancer drugs that have high selectivity and low side effects. These advantages in anticancer drugs have presented a critical challenge for researchers and an urgent need for humanity. The benzimidazole derivatives have been shown to be highly effective in this regard.[64]

Wanga et al.[65] studied the preparation of chrysin benzimidazole derivatives and their anticancer activity. The strongest antiproliferative activity of MFC tumor cells appeared in compound **1**, which gave IC50 values of 25.72 ± 3.95 μM (Figure 2). The results showed that it is the dosing regimen that increases the death of MFC cells. These compounds have also been studied for their anticancer activities in mice, for which compound **1** also inhibited tumor growth.

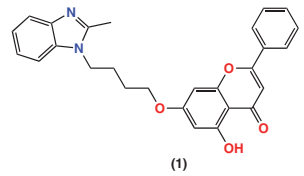


Figure 2 Antiproliferative agent **1**

Morais et al.[66] also prepared a series of compounds and studied their anticancer activity. The prepared compounds consisted of benzimidazole derivatives containing hydroxylated or fluorinated alkyl substituents. Compound **2** showed a distinct anticancer activity (Figure 3).

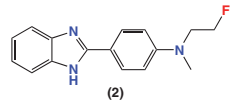


Figure 3 Anticancer agent **2**

Onnis et al.[67] studied the synthesis of a series of benzimidazole derivatives and then tested their antiproliferative activity. The growth of all tested cell lines was were inhibited by hydrazone derivatives **3a** and **3b** (Figure 4). Table 1 shows the IC50 values and the cell lines used. The researchers also noted that a new type of derivative showed a clear antiproliferative activity when the pharmaceutical drug hydrazone was combined with benzimidazole derivatives.

Cevik et al.[68] tested the anticancer activity of the prepared benzimidazole derivatives. The results showed that toxic activity against diseased cells was shown by com-

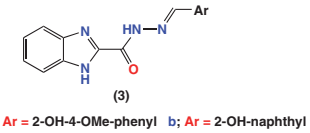


Figure 4 Antiproliferative derivatives **3a** and **3b**

Table 1 Growth Inhibition by **3a** and **3b** Against Tested Cell Line

Cell line used	IC50 (μM)	
	3a	**3b**
Murine leukemia (L1210)	1.6±0.9	2.9±1.3
Human T-lymphoblastic leukemia (GEM)	0.98±0.02	1.0±0.01
Human cervix carcinoma (Hela)	4.0±0.4	2.5±1.4
Human pancreas carcinoma (Mia paca-2)	6.3±3.2	7.9±0.3

pounds **4a** and **4b** (Figure 5). The standard anticancer drug cisplatin was also compared with the derivative **4c**, which showed significant efficacy compared to the standard compound. Table 2 summarizes the IC50 values with the cell line used.

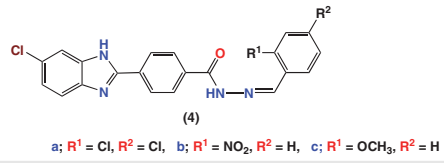
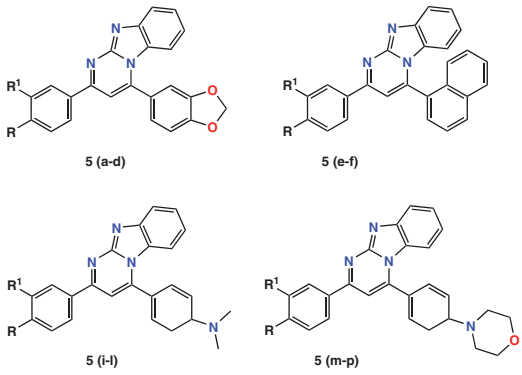


Figure 5 Cytotoxic compounds **4a–c**

Shaldam et al.[69] developed new compounds **5a–p**, derived from pyrimido[1,2-*a*]benzimidazole, with potential anti-AML properties (Figure 6). The compounds were tested for their ability to inhibit tumor growth in vitro, and compound **5h** showed effective activity against various human cancer cell lines, particularly in leukemia. Another set of compounds (**5e–l**) was tested specifically on human acute leukemia cell lines, and **5e–h** demonstrated promising activity. The compounds were initially screened against leu-



Comp. No.	R	R^1
a, e, i, m	Cl	H
b, f, j, n	Me	H
c, g, k, o	OMe	H
d, h, l, p	OMe	OMe

Figure 6 Potential anti-AML compounds **5a–p**

Table 2 Cytotoxic Activity of Compounds **4a–c** Against Tested Cell Line

Cell line used	IC50 (μM)			Cisplatin
	4a	**4b**	**4b**	
Human lung adenocarcinoma (A549)	0.0316	0.0316	0.06	0.045
Human breast adenocarcinoma (MCF-7)	0.0316	0.0316	0.03	0.052

kemia-associated mutant FLT3-ITD, ABL, CDK2, and GSK3 kinases, but they showed no significant activity. Subsequently, a broader kinase profiling revealed that compounds **5e** and **5h** effectively inhibited BMX kinase. The researchers also investigated the impact of the compounds on cell cycle, and caspase 3/7 activity in HL60 and MV4-11 cells.

Othman et al.[70] developed two new series of benzimidazole-triazole hybrids **6a–h** and **7a–g** as multi-target inhibitors of EGFR, VEGFR-2, and Topo II (Figure 7). The compounds were tested for their anticancer activity and compounds **5a** and **6g** showed the highest potency against four cancer cell lines: HepG-2, HCT-116, MCF-7, and HeLa. These compounds were further evaluated for their inhibitory effects on EGFR, VEGFR-2, and Topo II. Compound **5a** was a particularly good inhibitor of EGFR, a moderate inhibitor for VEGFR-2, and a stronger inhibitor for Topo II compared to reference drugs. Compound **6g** exhibited moderate inhibition of EGFR and VEGFR-2, and weaker inhibition of Topo II.

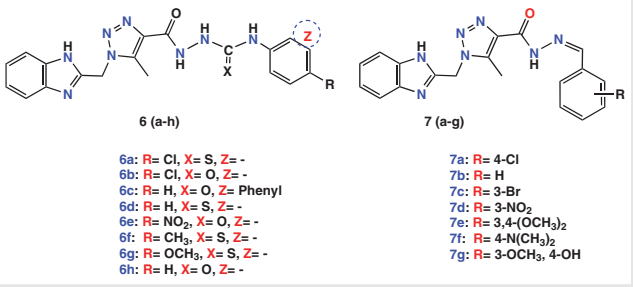


Figure 7 Benzimidazole-triazole hybrids **6a–h** and **7a–g** as multi-target inhibitors of EGFR, VEGFR-2, and Topo II

Gali et al.[71] developed a series of new compounds called 3-(1*H*-benzo[*d*]imidazol-2-yl)-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazines. The compounds were synthesized using a two-step process and their structures were confirmed with a range of analytical techniques (Figure 8). The anticancer activity of compounds **8a–k** was evaluated against two breast cancer cell lines (MCF 7 and MDA-MB-231), compared to the standard drug Doxorubicin. Compound **4e** showed the highest activity against both cell lines, with IC50 values of 8.60±0.75 μM and 6.30±0.54 μM, respectively. Compound **8i** also displayed good activity with an IC50 value of 9.85±0.69 μM against MCF-7 cells. Compound **8g** exhibited the best activity with an IC50 value of 8.52±0.62 μM against the MDA-MB-231 cell line. Docking studies against the target EGFR revealed that all compounds exhibited strong binding affinities. The compounds demonstrated favorable drug-like properties, indicating their potential as therapeutic agents.

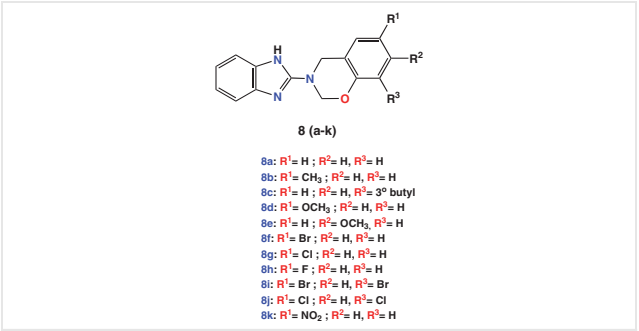


Figure 8 Potential anticancer compounds **8a–k**

4.2 Anti-inflammatory Activity

Anti-inflammatories are a term used for substances that have properties that reduce the effect of various inflammations in the body. Many analgesic drugs have multiple properties, especially anti-inflammatory drugs; these analgesic drugs reduce inflammation and thus stop the pain. Benzimidazole derivatives are organic compounds possessing a heterogeneous aromatic ring combined with a benzene ring, and this gives them a distinct structure in medicinal chemistry that has recently emerged as the preferred pharmaceutical material from which to design analgesic and anti-inflammatory agents that act on different clinically approved targets for pain and inflammation.[72]

Gaba et al. investigated the ability of some substituted benzimidazole derivatives such as **9** to inhibit the selective COX-2 enzyme in the kidneys and stomach using celecoxib as a standard drug (Figure 9). Most of the prepared derivatives showed a characteristic activity equivalent to that of the standard drug.[73]

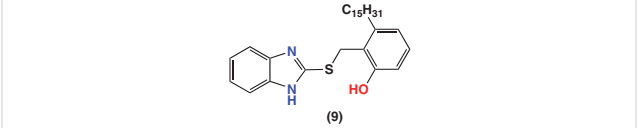


Figure 9 Anti-inflammatory compound **9**

Sharma et al.[74] tested a series of prepared compounds in a sample of carrageenan-induced rat paw edema. The substances derived from 5-methanesulphonamido benzimidazole were tested as anti-inflammatory compounds. Rofecoxib and Indomethacin were also used as standard drugs for testing. Derivatives **10a**, **10b**, and **10c** showed the maximum activities (92.73, 95.64, and 97.62%, respectively) in edema at the tested doses (Figure 10). This indicates the active role played by benzimidazole derivatives in this field.

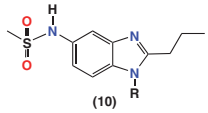


Figure 10 Potential anti-inflammatory compounds **10a–c**

Saha et al.[75] tested a number of substituted benzimidazole derivatives as anti-inflammatory agents by inhibiting carrageenan-induced rat claw edema (Figure 11). Benzimidazole derivatives **11b**, **11c**, and **11d** showed prominent anti-inflammatory activity at a dose of 100 mg/kg body weight (% inhibition of claw edema 81.75, 79.09, and 86.69%, respectively), which is comparable to standard aceclofenac (87.83%).

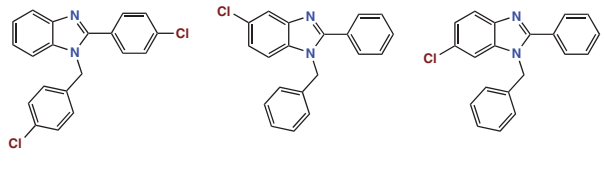


Figure 11 anti-inflammatory agents **11b–d**

Kankala et al.[76] prepared a series of substituted benzimidazole derivatives and tested their efficacy as analgesic and anti-inflammatory. The notable prepared compound **12** consisted of isoxazole-mercapto-benzimidazole derivatives (Figure 12). The researchers found that substituted derivatives with electron-donating groups had higher activity than those with electron-donating groups, and it was found that these derivatives substituted with electron-withdrawing groups were more effective than diclofenac for anti-inflammatory activity and pentazocine for analgesic, which were used as standard drugs.

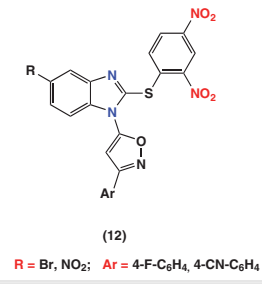


Figure 12 Compound **12** as an anti-inflammatory and analgesic compound

Moharana et al.[77] developed new benzimidazole compounds with anti-inflammatory properties. The compounds **13**, **14**, and **15** were synthesized, purified, and characterized (Figure 13). The compounds were found to be non-toxic both in vitro (at a concentration of 100 µM for 24 hours on 3000 Vero cells/well) and in vivo (at a dose of 100 mg/kg in female Wistar rats, with a 48 h observation period for mortality). Compounds **13** and **14** exhibited significant anti-inflammatory properties. In silico analysis indicated that both compounds are drug-like and have good oral bioavailability. These findings suggest that further research should be conducted to explore the potential of these benzimidazoles as anti-inflammatory agents for various diseases.

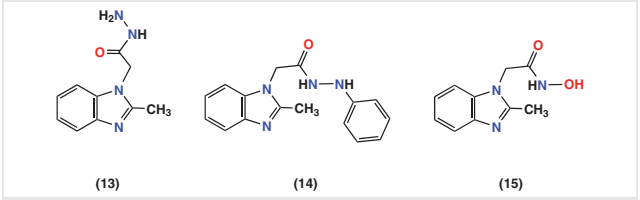
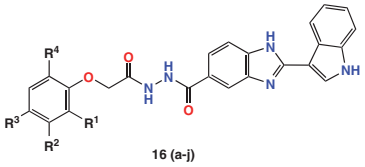


Figure 13 Anti-inflammatory compounds **13–15**

Nagesh et al.[78] focused on developing safer non-steroidal anti-inflammatory drugs (NSAIDs) for inflammation therapy. They aimed to achieve dual inhibition of COX/5-LOX, which improves efficacy and reduces side effects. To this end, they designed, synthesized, and characterized a series of compounds **16a–j** for their anti-inflammatory, analgesic, and ulcerogenic properties (Figure 14). The investigation revealed that these compounds exhibited significant anti-inflammatory activity. The compounds showing potential analgesic activity were further evaluated for their analgesic, anti-inflammatory, and ulcerogenic effects. In vitro analyses were conducted for COX-1, COX-2, and 5-LOX. Compound **16c**, which had a *para*-fluoro substitution on the benzoyl ring and two *ortho*-chloro groups on the phenyl ring of benzophenone, demonstrated good inhibitory potency. Additionally, in silico docking studies were performed using AutoDock tools docking software.

There are also many studies showing the use of benzimidazole derivatives as anti-inflammatories, and most of them were shown to have great efficacy equal to or exceeding the effectiveness of the drugs used as standard substances.[79–85]



16 (a-j)

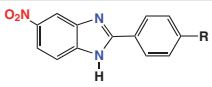
Compounds	R^1	R^2	R^3	R^4
16 a	$-CH_3$	-H		-H
16 b	$-CH_3$	-H		-H
16 c	$-CH_3$	-H		$-CH_3$
16 d	$-CH_3$	-H		-H
16 e	$-CH_3$	-H		$-CH_3$
16 f	$-CH_3$	-H		$-CH_3$
16 g	-H	-H	$-CH_3$	
16 h	$-CH_3$	-H	-Cl	
16 i	-F	-H		-Cl
16 j	-H	$-OCH_3$	-H	

Figure 14 Potential non-steroidal anti-inflammatory drugs **16a–f**

4.3 Antioxidant Activity

An antioxidant is a molecule capable of slowing down or preventing the oxidation of free radicals that cause a destructive danger to the cells of an organism's body. The formation of free radicals in air-breathing organisms is inevitable, because of the dependence on the aerobic oxidation process, which is necessary for life. These emerging free radicals are highly toxic and are likely to cause cell malfunction, malignant transformation, or death. Oxidative stress can cause damage to proteins, lipids, and DNA, and the latter may lead to a change in the arrangement of chromosomes or the occurrence of genetic mutations that lead to cancer tumors, diabetes, neurodegeneration, and cardiovascular diseases.[86] Therefore, it has become necessary to remove these free radicals from the body before exposing the body to diseases, and this is done by taking antioxidants. Antioxidants may be present in fruit in the form of vitamins, such as vitamins A, C, and E, or antioxidants may be synthesized from some organic compounds.[87] The benzimidazole derivatives have a notable record in this field because they consist of two aromatic rings (benzene and imidazole), so the free radical enters the state of resonance with the electrons of the aromatic rings, and its effect decreases or ends.[88,89]

Archie et al.[90] evaluated the antioxidant activity of some prepared benzimidazole derivatives **17** (Figure 15). All the derivatives showed good antioxidant activity, with IC50 values in the region 3.17 to 7.59 µg/mL, while 18.42 µg/mL was found for butylated hydroxytoluene (BHT). It was also found that the best compound used as an antioxidant in this study was compound **17c** (IC50 = 3.17 µg/mL).

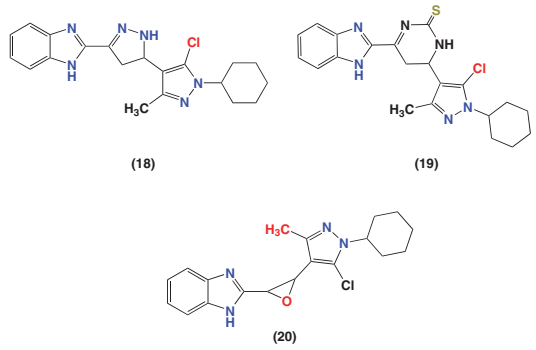


(17)

a; R= -Cl b; R= -Br c; R= -F d; R= $-OCH_3$

Figure 15 Anitoxidant compounds **17a–c**

Abd et al.[91] synthesized substituted benzimidazoles by including chalcone, oxirane, pyrimidines, oxazoline, and pyrazolines derivatives. The DPPH method was used to evaluate the antioxidant activity of these prepared compounds. The researchers from this study found that compounds **18** and **19** showed antioxidant properties comparable to that of ascorbic acid when using the DPPH method at a concentration of 100 µM (Figure 16). Moreover, the results of the study showed that the pyrazoline ring system, as in compound **18**, is not responsible for this inhibitory activity; rather, the presence of the pyrimidine thione in compound **19** and the epoxide ring in compound **20** are responsible for this activity.

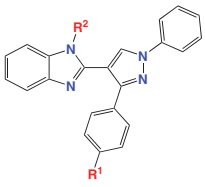


(18) (19) (20)

Figure 16 Antioxidant compounds **18–20**

Bellam et al.[92] reported the preparation of some N-substituted pyrazole-containing benzimidazole derivatives (Figure 17). The research team studied the effectiveness of all these prepared compounds as antioxidants to evaluate their ability to scavenge free radicals versus against DPPH and H_2O_2. Compounds **21a**, **21b**, and **21c**, which all contained a benzyl group as a substitute for the benzimidazole nitrogen, exhibited distinct activity in both methods.

Patagar et al.[93] synthesized a series of benzimidazole-coumarin-3-carboxamide analogues **22a–j** and evaluated their antioxidant potential using DPPH and ABTS assays

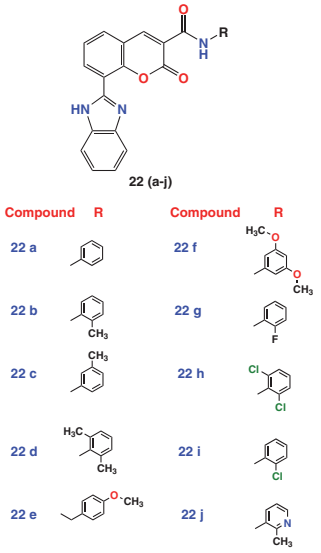


(21)

a; R^1= H, R^2 = Bn, b; R^1 = NO_2, R^2 = Bn, c; R^1 = Cl, R^2 = Bn

Figure 17 Antioxidant compounds **21a**, **21b**, and **21c**

(Figure 18). The authors also assessed the α-amylase inhibition activity of the compounds using the DNSA method. Compound **22j**, with a picoline substitution on the carboxamide linker, demonstrated the highest potency for DPPH radical scavenging, with an IC50 value of 89.57 µM, compared to the standard ascorbic acid (IC50 value of 92.67 µM). Compound **22f**, with a 3,5-dimethoxyphenyl substituted carboxamide linker, exhibited the strongest scavenging activity against ABTS radical, with an IC50 value of 93.45 µM, surpassing the standard drug Trolox (IC50 value of 96.24 µM). However, all compounds in the series exhibited moderate α-amylase inhibition, and compound **22f** emerged as the most effective antidiabetic analogue, with an IC50 value of 67.52 µM, compared to the standard metformin (IC50 value of 54.13 µM). Molecular docking studies with the α-amylase receptor protein (PDB ID 4x9y) using Autodock Vina software provided further insights into the obtained results.

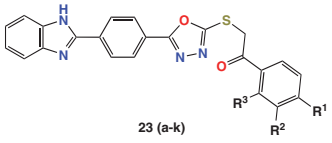


22 (a-j)

Compound	R	Compound	R
22 a		22 f	
22 b		22 g	
22 c		22 h	
22 d		22 i	
22 e		22 j	

Figure 18 Antioxidants **22a–j**

Küçükoğlu et al.[94] synthesized 11 new benzimidazole-1,3,4-oxadiazole derivatives **23a–k** and evaluated their inhibitory activities against human carbonic anhydrase isoforms (hCA I, hCA II) and antioxidant activity (Figure 19). The compounds were characterized using ^{1}H NMR, ^{13}C NMR, and HRMS. Compound **23a** showed the highest potency against hCA I, with an IC50 value of 1.322 µM, whereas compound **23d** exhibited an IC50 value of 1.989 µM. Among all the compounds, **23a**, **23d**, and **23g** were the most active against hCA II. Compound **23a**, containing a 4-bromophenyl structure, demonstrated efficacy against both hCA I and hCA II, indicating its potential as a promising candidate for CA inhibition. Antioxidant activity was evaluated using the TAS assay, and cytotoxic activity was assessed using the MTT assay on the L929 cell line. Finally, molecular docking studies were conducted to compare the biological activities of the most active compounds against hCA I and hCA II enzymes.



23 (a-k)

Compound	R^1	R^2	R^3
23a	-Br	-H	-H
23b	$-CH_3$	-H	-H
23c	-CN	-H	-H
23d	-Cl	-Cl	-H
23e	-Cl	-H	-H
23f	-H	-H	-H
23g	-F	-H	-H
23h	$-OCH_3$	-H	-H
23i	$-NO_2$	-H	-H
23j	-Phenyl	-H	-H
23k	-Cl	-H	-Cl

Figure 19 Antioxidants **23a–k**

There are also a large number of studies regarding the use of benzimidazole derivatives as antioxidants because of their great role in capturing free radicals formed in the body. This is because they contain electrons of the π-bonds present in the aromatic rings, which are always in a state of delocalization, and the entry of free radicals in this delocalization state reduces or halts the harmfull effects of the radicals.[82,94–100]

4.4 Anticonvulsant Activity

Anticonvulsants are a diverse group of drugs that are currently used to treat patients with recurrent epileptic seizures. Many anticonvulsants are also used for the treatment of neuropathic pain and as mood stabilizers. Anticonvulsants also prevent the spread of the seizure within the brain.[101–103] Benzimidazole derivatives have been examined in a number of studies as anticonvulsant substances, and these studies have established their success in use.

Shingalapur et al.[104] investigated the anticonvulsant activity of some benzimidazole derivatives that consist of 2-mercapto benzimidazole containing 4-thiazolidinones **24a–j** (Figure 20). The prepared derivatives were studied with respect to their efficacy as in vivo anticonvulsants using the

Maximal Electroshock (MES) model. Compounds **24c**, **24d**, **24g**, and **24i** showed strong anticonvulsant results. Pharmacophores derived from active molecules suggested that the presence of an OH group was a common feature in all active compounds.

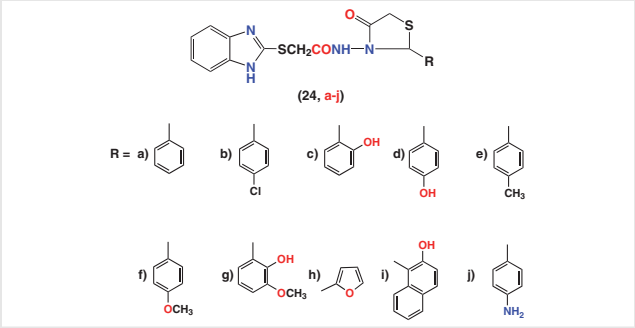


Figure 20 Anticonvulsants **24a–j**

Shaharyar et al.[105] examined the anticonvulsant activities of the benzimidazole derivatives prepared in their study. In this study, the researchers synthesized a number of compounds consisting of 2-[2-(phenoxymethyl)-1*H*-benzimidazol-1-yl]acetohydrazide derivatives (Figure 21). The results obtained from the study of anticonvulsants were compared with the standard drugs phenytoin and ethosuximide. The study proved that compounds **25g** and **25j** gave more effective anticonvulsant activity than the other prepared compounds as well as the standard drugs used. The protection index of these compounds was also studied, and it was found that the two compounds **25g** and **25j** possess indices of 40.5 and 24.7, respectively, which is much higher than this of the standard drugs. The neurotoxicity values TD50 for compounds **25g** and **25j**, which are very high, indicate that these compounds have much lower neurotoxicity than standard drugs. From this study it was found that the effect of substitution plays a key role in the biological activity of the compound. Compounds substituted with electron-withdrawing groups (such as nitro and fluorine) had higher biological activity than others. Compounds with strong electron-withdrawing groups were more effective

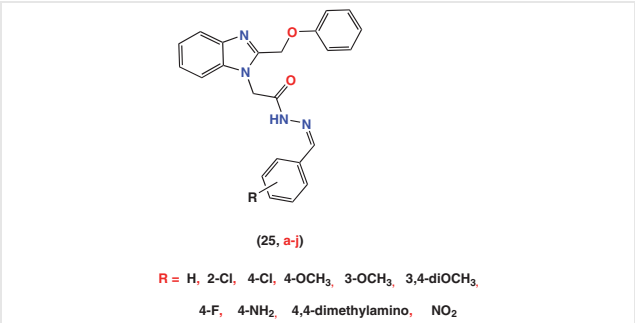


Figure 21 Anticonvulsants **25a–j**

than those with weak electron-withdrawing groups. On the other hand, it was found that the substitution of electron-donating groups on the basic structure has no effect on the biological activities studied.

Siddiqui et al.[106] biologically evaluated the anticonvulsant activity of new benzimidazole derivatives **26a–p**, consisting of 2-[(1-(2-substituted-benzyl)-1*H*-benzo[*d*]imidazole-2-yl)methyl]-*N*-substituted-phenylhydrazinecarbothioamides derivatives (Figure 22). For albino rats, the two most well-known models are maximal electroshock seizure (MES)- and subcutaneous pentylenetetrazole (scPTZ)-induced seizures. Compound **26p** is the most biologically active and promising anticonvulsant in MES and scPTZ screens.

Moreover, many other studies during the past years have focused on studying the medicinal activity of benzimidazole derivatives as anticonvulsants, which gave distinctive results that, in some of these compounds, were superior to standard drugs. This indicates the great efficacy of benzimidazole derivatives, which could for the basis of future drugs in the field of anticonvulsants.[107–113]

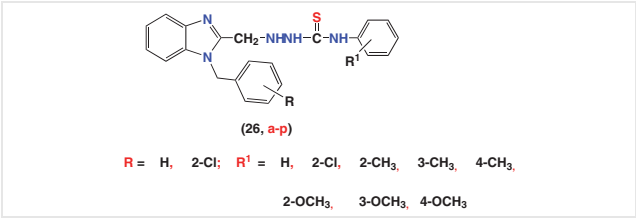


Figure 22 Anticonvulsants **26a–p**

4.5 Anticoagulant Activity

Anticoagulants, also known as blood thinners, are potent chemicals designed to reduce or prevent blood clots in the body.[114] Anticoagulants are naturally present in some animals that feed on blood, such as mosquitoes and leeches, which help prevent the formation of blood clots in the bite area for a period of time in order to absorb blood.[115,116] Anticoagulants are used in many cases, including stroke, heart attack, atrial fibrillation, deep venous thrombosis, pulmonary embolism, and others. Some anticoagulants are also used in medical equipment, such as blood transfusion bags, heart-lung machines, dialysis machines, and sample tubes.[117–119] Benzimidazole derivatives have been prepared and tested for their efficacy as anticoagulants.

Yang et al.[120] synthesized a series of substituted benzimidazole derivatives and evaluated their potential as anticoagulants (Figure 23). In this study, the researchers investigated the synthesis of new 1,2,5-trisubstituted benzimidazole fluorinated derivatives, and these compounds were used initially to verify their inhibitory activity against thrombin. Compounds **27a**, **27b**, and **27c**, with IC50 values of 2.26, 1.54 and 3.35 nmol/L, respectively, showed higher anticoagulant activity than standard argatroban used as a

reference, for which the IC50 value was 9.88 nmol/L. It was also observed from this study that a methyl group substituent at the *ortho*-position of the benzene ring on the main structure give useful results as anticoagulants.

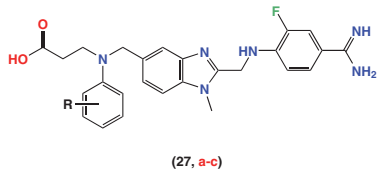


Figure 23 Anticoagulants **27a**, **27b**, and **27c**

Wang and Ren[121] documented the preparation of benzimidazole derivatives consisting of fluorinated derivatives of substituted 1-ethyl-1*H*-benzimidazole, then biologically evaluated these compounds to study their antithrombin activity. The researchers in this study discovered that all the tested compounds **28a–f** had better anticoagulant activity against thrombin than argatroban, which was used as a standard drug (Figure 24). Moreover, compound **28f** had a higher potency as a thrombin inhibitor IC50 = 3.21±0.57 nM than the standard drug IC50 = 9.88±2.26 nM.

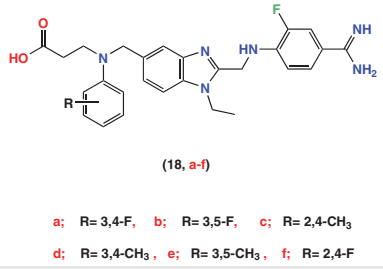


Figure 24 Antithrombin compounds **28a–f**

Several other studies during the past years have documented the synthesis of a large number of new substituted benzimidazole derivatives and their biological evaluation for their use as anticoagulants. The results obtained from these studies were very positive and could be applied for the development of thrombin inhibitors in the future.[122–127]

4.6 Antimicrobial Activity

Antimicrobial materials are a class of substances that are used to kill microorganisms (fungi and harmful bacteria) or stop their growth. Antimicrobial drugs can be divided according to the microorganisms that they can work against. For example, antibiotics are used against bacteria, and antifungals are used against fungi. The class can also be subdivided according to function. Compounds that kill microbes are called microbicides, while compounds that stop microbes from growing are called biostatic.[128,129] Benzimidazoles inhibit protein synthesis in microbes because the structure of benzimidazole mimics the structure of purine. Commonly, 2-substituted benzimidazoles show stronger pharmacological activity.[72,130]

El-Gohary et al.[131] tested the antimicrobial activity for new synthesized benzimidazole derivatives (Figure 25). These new derivatives were assessed for antimicrobial efficacy toward *Staphylococcus aureus* (*S. aureus*), *Bacillus cereus* (*B. cereus*), *Escherichia coli* (*E. coli*), *Candida albicans* (*C. albicans*), and *Aspergillus fumigatus* 293 (*A. fumigatus* 293). Among the studded compounds, **29** and **30** displayed good activity against *S. aureus*, with a minimum inhibitory concentration (MIC) value 0.524 μg/mL and 0.684 μg/mL, respectively, whereas compound **31** showed good activity toward *B. cereus*, with an MIC value of 0.489 μμg/mL. In addition, compound **30** exhibited the good results toward *A. fumigatus* 293, with an MIC value of 1.37 μg/mL.

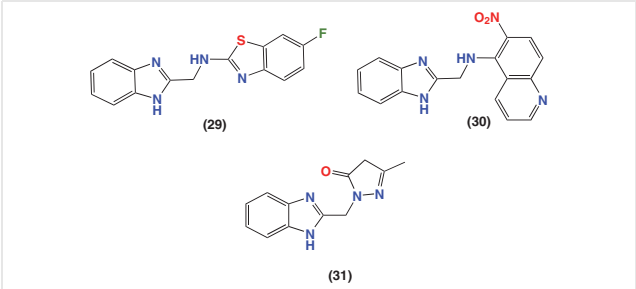


Figure 25 Antimicrobial compounds **29–31**

Ajani et al.[132] reported the antimicrobial activity for some 2-substituted benzimidazoles (Figure 26). The activity of these compounds was biologically evaluated with gram-positive bacteria (*P. vulgaris*, *S. faecalis*, and *S. aureus*) and gram-negative bacterial strains (*Pseudomonas aeruginosa*, *E. coli* and *K. pneumoniae*) by using the zone of inhibition system. Of the studied compounds, **32–35** presented higher zones of inhibition toward all the above organisms as compared with the gentamicin as a standard drug. Specifically, compound **35** provided the highest inhibition area against *Klebsiella pneumonia*, which was 42±0.10 mm.

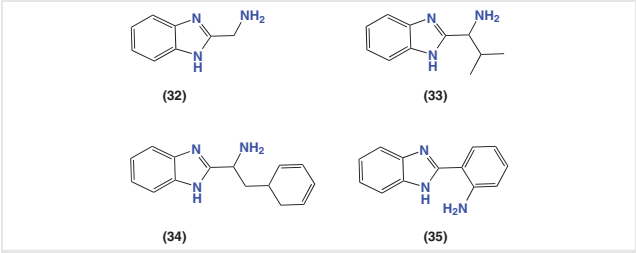
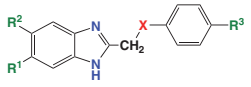


Figure 26 Antimicrobial compounds **32–35**

Ersan et al.[133] synthesized new 2-phenyl substituted benzimidazole derivatives and evaluated their biological activity as anticancer and antimicrobial agents (Figure 27). In the antimicrobial study, all compounds were tested to confirm

their antimicrobial properties against gram-positive bacteria, gram-negative bacteria and fungi. All compounds presented moderate activity against all tested bacteria and fungi. However, some phenoxy methyl derivatives 5-chloro-2-((4-chlorophenoxy) methyl)-1*H*-benzo[*d*]imidazole (**36**) and 5,6-dichloro-2-((4-chlorophenoxy) methyl)-1*H*-benzo[*d*]imidazole (**37**) showed the highest activity against *Candida*, which gave the same MIC value (<3.90 µM) as the reference compound uconazole possess against *Candida albicans* and *Candida parapsilosis*. In general, the benzimidazole derivatives that showed the highest biological effect on bacteria and fungi were those containing Cl-substitutes.

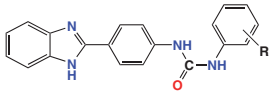


(36) X= -O- , R^1=Cl, R^2=H, R^3=Cl

(37) X= -O- , R^1 = R^2 = R^3 = Cl

Figure 27 Antimicrobial compounds **36** and **37**

Shinde et al.[134] reported new 2-(3-arylureido)benzimidazole derivatives via sequential oxidative cyclization of 4-nitrobenzaldehyde and 2-amino aniline (*o*-phenelynediamine), then evaluated their antifungal and antibacterial activity at 10 µM concentration (Figure 28). The compounds **38b**, **38f**, and **38g** showed effective antifungal and antibacterial biological activity. The compounds **38f** and **38g** provided effective activity against most of the microbes used in the test, 1.5–2.5 times higher than the control drugs Micanazole and Fluconazole.

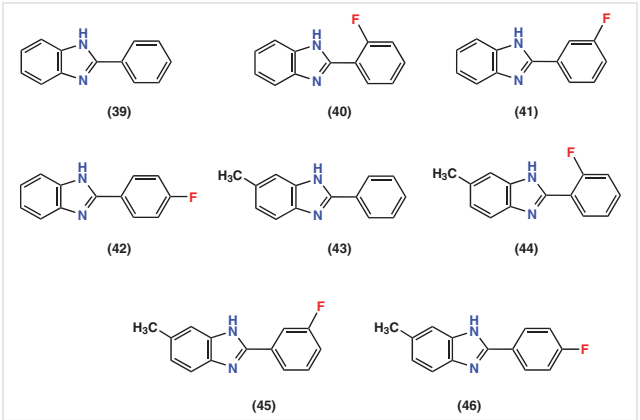


(38, a-i)

R = 38a 3,4-dimethoxy
38b 3-methoxy
38c 3,5-difluoro
38d 2,4-difluoro
38e 2-fluoro
38f 2,4-dichloro
38g cyclopentyl
38h 4-methoxy
38i 3-methyl

Figure 28 Antimicrobial compounds **38a–i**

Jasim et al.[135] conducted a study on a series of benzimidazole compounds **39–46** containing a fluoro-benzene moiety (Figure 29). The compounds were tested for their antimicrobial activity against gram-positive bacteria, gram-negative bacteria, and fungal strains. The results indicated that the fluoro-substituted compounds **40–42** and **44–46** exhibited better antibacterial and antifungal properties compared to the unsubstituted parent compounds **39** and **43**. Compound **45**, which contained a fluorine atom in the *meta*-position of the phenyl ring side chain, showed high activity against gram-negative bacteria, with a MIC value of 31.25 µg/mL. Additionally, derivatives **41** and **45**, with a 2-(*m*-fluorophenyl)benzimidazole structure, demonstrated good activity against *B. subtilis*, with a MIC value of 7.81 µg/mL. Structure-activity relationship (SAR) analysis suggested that the presence of a methyl substitution group at the 5-position of benzimidazole is beneficial for significant antifungal activity against *C. parapsilosis*. The strong potency of compound **45** suggests its potential as a starting point for the development of novel antimicrobial agents.



(39) (40) (41) (42) (43) (44) (45) (46)

Figure 29 Antimicrobial compounds **39–46**

Rajagopal et al.[136] synthesized bis-benzimidazole derivatives **47a–h** using simple and environmentally friendly reaction conditions and crystallization procedures (Figure 30). The structures of the compounds were determined using ^{1}H NMR, ^{13}C NMR, and mass spectrometry. Compound **47c** was crystalline and its structure was confirmed through single-crystal X-ray analysis. The synthesized bis-benzimidazole compounds were tested for antimicrobial activity against gram-positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*), gram-negative bacteria (*Escherichia coli*, *Serratia* sp.), and the fungal pathogen *Candida albicans*. Compound **47e** exhibited the strongest activity, with a minimum inhibitory concentration of 16 µg/mL against *C. albicans*. The purified compound showed no hemolysis except at a concentration of 100 µg/mL. Molecular docking of compound **47g** was performed with fungal protein from *C. albicans* (dihydrofolate reductase PDB ID: 1IA4), and pose 1 exhibited the best binding energy of –6.23 kJ mol^{-1}.

Myeloperoxidase (MPO) is an enzyme involved in the human antimicrobial system, but its release outside phagocytes can cause tissue damage. It has been implicated in various inflammatory diseases. Saylam et al. designed isomeric derivatives of 1,3-dihydro-2*H*-benzo[*d*]imidazole-2-thione with amide compound **48C$_{1–17}$**, hydrazide compound **48C$_{19}$**, and hydroxamic acid groups compound **48C$_{20}$** on nitrogen or sulfur atoms (Figure 31). The inhibitory activity of these derivatives on the chlorination and peroxidation cycles of MPO was assessed. Compound **48C$_{19}$**, specifically 2-

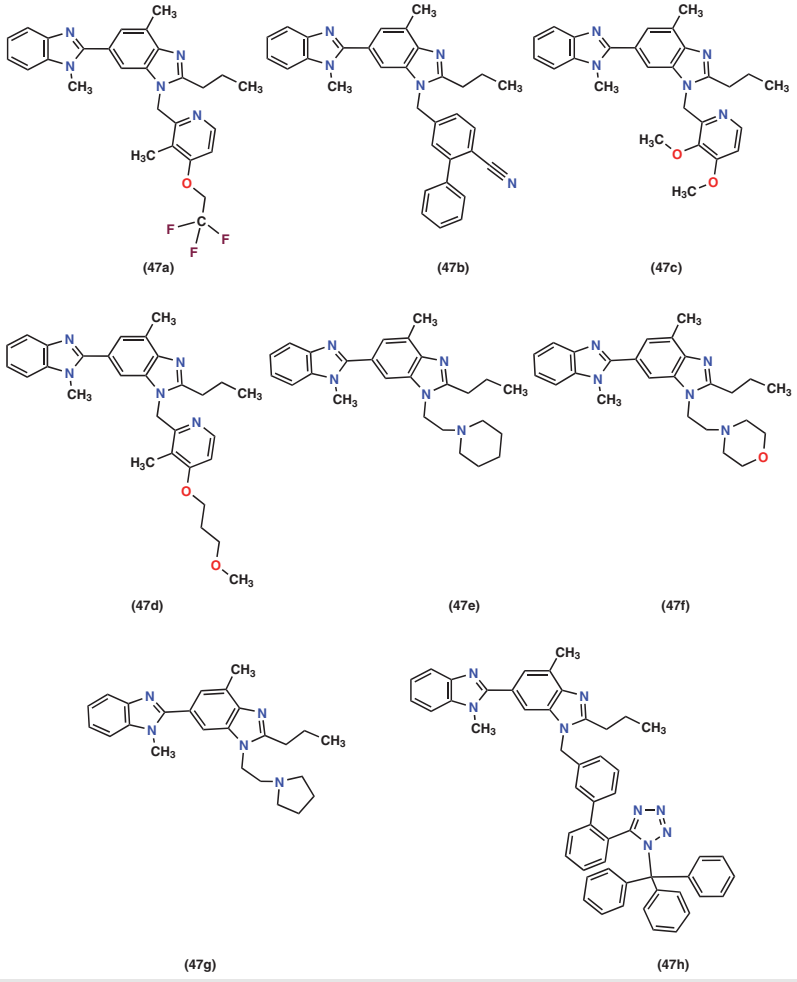


Figure 30 Antimicrobial compounds **47a–h**

(2-thioxo- 2,3-dihydro-1*H*-benzo[*d*]imidazole-1-yl)acetohydrazide, showed the highest inhibitory activity on both cycles.[137]

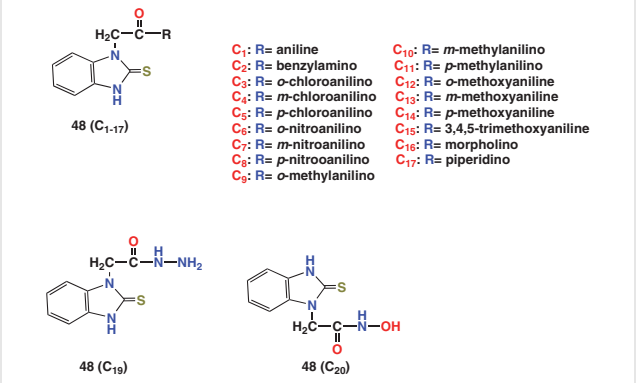


Figure 31 Inhibitors of the chlorination and peroxidation cycles of MPO

At the present time, there are very many studies on substituted benzimidazole derivatives, which show a distinctive activity to kill microbes or stop their growth. Many of the prepared derivatives have efficacy comparable or superior to the standard drugs used for the same purpose.[138–153]

4.7 Other Biological Applications

In addition to the above medical applications, benzimidazole derivatives have been widely used as an essential part of biological applications including: antihypertensive activity,[154–158] antiprotozoal activity,[159–163] antiviral activity,[164–167] anthelmintic activity,[168–172] antidiabetic agents,[173–177] analgesic activity,[78,178–181] antispasmodic activity,[182,183] antidepressant activity,[184–189] sphingosine kinase 1 inhibitor,[190,191] anti-Alzheimer's agents,[192–194] angiotensin II-AT1 receptor antagonists,[195–200] antiulcer activity,[201–204] anti-tubercular activity,[205–211] anti-HIV agents,[212–218] and anti-secretory activity.[219–221]

In the end, we can conclude that benzimidazole derivatives are considered one of the most important classes of synthetic heterocyclic compounds, which have shown great biological activity over the past years. The pharmacological efficacy of these compounds may be comparable to those of the standard drugs at the present time, as was shown above when their efficacy was compared with the drugs used for most studies. This is clear evidence of the high efficacy of benzimidazoles in these applications. The large number of studies directed previously and currently towards the development of benzimidazole derivatives as antibiotics for various diseases also indicates the importance of this class of organic compounds. This is the main reason for writing this review on the synthetic and biological chemistry of benzimidazoles to serve researchers working in this field.

5 Conclusion

The benzimidazoles are one of the most important classes of synthetic organic compounds, due to the significant biological role they play in the preparation of various drugs and antibiotics. Therefore, the methods of synthesis of benzimidazole derivatives became a major focus for the preparation of many other organic compounds that showed distinctive medicinal efficacy when tested. We hope that this review will help researchers to discern the different chemical properties of benzimidazoles and its derivatives. It also provides a brief overview of the most important chemical and green chemistry methods used for preparing different benzimidazole derivatives, including the beneficial and negative aspects of each preparation method. A summary of the biological activities of benzimidazole derivatives has also been shown, including various applications such as anticancer, anti-inflammatory, anticonvulsant, anticoagulant, and others. From the above, the great importance of benzimidazole derivatives in the development of medicine over the past years is clear.

Conflict of Interest

The authors declare no conflict of interest.

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