# A Review of Anti-Fungal Role of Benzimidazole Derivatives

Mohammed Fanokh Al-Owaidi, Sura L. Alkhfaji, Lamyaa S. Mahdi
College of Pharmacy/ University of Kerbala/ Kerbala 54001/ Iraq

**ABSTRACT**:

As a diverse group of microorganisms, fungi can cause anything from minor, superficial infections to serious, invasive infections that can be fatal. They are also naturally occurring in the environment and can be found in the normal flora of humans and animals. Systemic fungal infections are uncommon and can have a significant fatality rate; the majority of fungal infections are unintentional. The course of a systemic fungal infection is primarily determined by host variables as opposed to fungal virulence. Fungi have changed from being rare during the early 20th century, when bacterial diseases ravaged the world, to becoming a significant global health issue. A promising class of heterocyclic chemicals that are bioactive is benzomidazoles. In the fields of chemistry and medicine, benzimidazoles are widely used due to their notable and varied pharmacological action. For the best antibacterial action, one of the benzimidazole nucleus's 1st and 2nd positions should have a large electronic and hydrophobic group, while the other should have a small alkyl derivatives, according to a critical study of these widely modified derivatives. Additional activity is also incurred by a tiny lipophilic group that has a heteroatom at the 5/6-position. In conclusion, Benzimidazoles are remarkably effective compounds, extensive biochemical and pharmacological studies have confirmed that these molecules are effective against various strains of microorganisms.

## مقال مراجعة عن الدور المضاد للفطريات لمشتقات البنزيميدازول

محمد فنوخ العويدي, سرى لطيف الخفاجي, لمياء صالح مهدي
كلية الصيدلة/ جامعة كربلاء/ كربلاء 54001/ العراق

**الخلاصة**:

باعتبارها مجموعة متنوعة من الكائنات الحية الدقيقة، يمكن للفطريات أن تسبب أي شيء بدءًا من الالتهابات البسيطة والسطحية وحتى الالتهابات الخطيرة التي يمكن أن تكون قاتلة. كما أنها تحدث بشكل طبيعي في لإنسان والحيوان. الالتهابات الفطرية الجهازية غير شائعة ويمكن أن يكون لها معدل وفيات كبير وتحدث بصورة تلقائية. يتم تحديد مسار العدوى الفطرية الجهازية في المقام الأول من خلال متغيرات المضيف. لقد تغيرت الفطريات من كونها نادرة خلال أوائل القرن العشرين، عندما اجتاحت الأمراض البكتيرية العالم، إلى مشكلة صحية عالمية كبيرة. فئة واعدة من المواد الكيميائية الحلقية غير المتجانسة النشطة بيولوجيا هي البنزوميدازولات. يتم استخدام البنزيميدازول على نطاق واسع بسبب تأثيره الدوائي الملحوظ والمتنوع. للحصول على أفضل تأثير مضاد للجراثيم، يجب أن يحتوي أحد الموقعين الأول والثاني لنواة البنزيميدازول على مجموعة إلكترونية كبيرة وكارهة للماء، بينما يجب أن يحتوي الآخر على مشتقات ألكيل صغيرة. يتم أيضًا إحداث نشاط إضافي بواسطة مجموعة صغيرة محبة للدهون تحتوي على ذرة مغايرة في الموضع 6/5. البنزيميدازولات هي مركبات فعالة بشكل ملحوظ، وقد أكدت الدراسات البيوكيميائية والدوائية واسعة النطاق أن هذه الجزيئات فعالة ضد سلالات مختلفة من الكائنات الحية الدقيقة.

## 1. INTRODUCTION TO ANTIFUNGAL AGENTS:

Fungal infections have become increasingly common and more difficult to treat in recent years.[1] The use of more powerful and invasive medical treatments has led to the development of drug-resistant fungi that were once rare.[2] The risk of life-threatening infections caused by drug-resistant fungi is especially high in people with weakened immune systems, such as those with HIV, cancer, or who have undergone organ transplantation.[2, 3] People with HIV are more likely to develop candidiasis, a fungal infection, while cryptococcosis, a fungal infection caused by Cryptococcus neoformans, is a major cause of morbidity and mortality in people with AIDS.[3]

The number of antifungal agents available to treat fungal infections is limited, and many of these agents have drawbacks, such as drug-drug interactions, toxicity, and poor absorption into the bloodstream.[3] The World Health Organization has identified two crucial medications for the treatment of fungal infections: amphotericin B and fluconazole. The preferred medication for treating invasive fungal infections is amphotericin B, however there are serious adverse effects to be aware of, including low blood pressure, kidney damage, and elevated temperature. Despite being a significant advancement in antifungal therapy, fluconazole's limited spectrum of action limits its utilization.[2, 4, 5]

Another concern is that many of the antifungal agents currently in use are becoming less effective, and some fungi are becoming resistant to multiple drugs. As a result, the cure rates for invasive fungal infections are very low and the mortality rates are very high. The need to create novel antifungal medications that are less toxic and efficient against resistant fungal strains is developing due to the limits of the antifungal drugs that are currently on the market and the rising prevalence of fungal illnesses.[1]

New antimicrobial drugs are not being produced, according to the findings of the the European Society of Clinical Microbiology and Infectious Diseases.[3-5] Many large pharmaceutical corporations have stopped investing in antimicrobial research, or have just slightly increased it, despite the urgent need for new antimicrobial drugs. This is due to the lengthy, costly, and dangerous nature of the process involved in developing new antimicrobial drugs.

The market for new antimicrobial agents is also relatively small, as these drugs are only needed to treat a small number of patients. The lack of new antifungal agents is a serious problem. Antifungal agents represent only about 1% of novel compounds in development. This is not enough to meet the needs of patients who are at risk of developing fungal infections. The advancement of new antifungal agents are critical public health priority. It is important to take action to address this issue before it is too late. (**Fig. 1**). [4, 5]

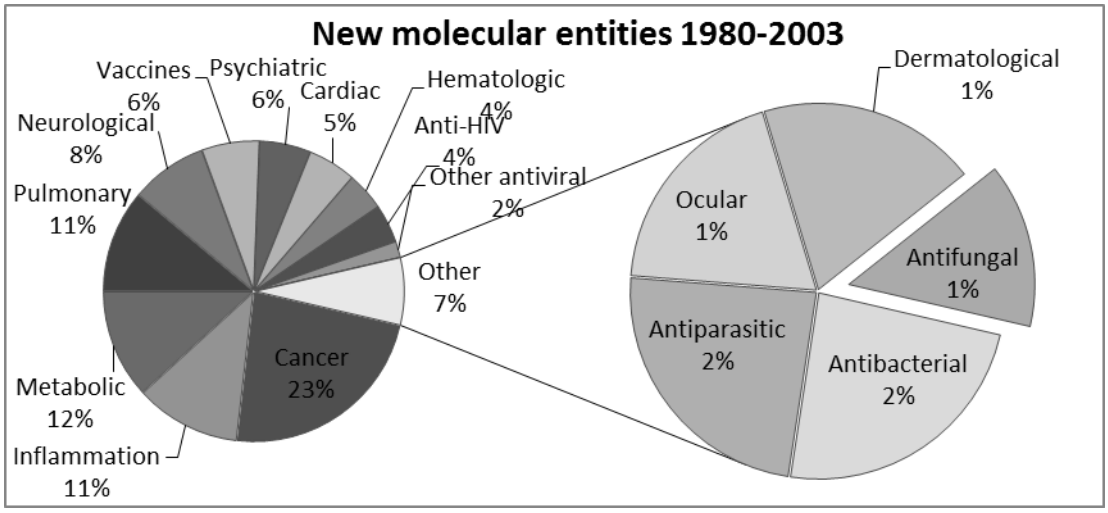



Figure 1: The development timeline of new antifungal agents over the next decade

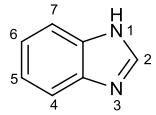
## 1.1 RESISTANCE OF ANTIFUNGAL:

The management of invasive fungal infections still faces significant challenges due to medication resistance, despite advancements in antifungal therapy. This is because fungi can develop resistance to antifungal drugs just as bacteria can develop resistance to antibiotics. This can make it difficult to treat fungal infections, especially in patients with low immunity.[3, 6, 7] Antifungal medication resistance might be innate, acquired, or clinical. Fungi that are inherently resistant to antifungal medications are known as innately resistant. Acquired resistance is when a fungus develops resistance to an antifungal drug after being exposed to it. Clinical resistance is when a fungus is resistant to an antifungal drug that is typically used to treat infections caused by that fungus. Resistance to antifungal drugs is often associated with high minimum inhibitory concentrations (MICs). This means that the fungus requires a higher concentration of the antifungal drug to inhibit its growth. High MICs are often associated with poor clinical outcomes, as they can make it difficult to treat the infection.[7, 8]

There are a number of mechanisms that can lead to acquired resistance to antifungal drugs. These include the decreased drug penetration: This can happen when the fungus develops a way to prevent the antifungal drug from entering its cells. Furthermore, Mutations in the gene coding for the target site: This can happen when the fungus mutates the gene that codes for the protein that is the target of the antifungal drug. This can make the protein less susceptible to the drug. And finally,Development of pathways that decrease in antifungal affinity: This can happen when the fungus develops a way to break down the antifungal drug or to pump it out of its cells.For example, resistant mutants of the fungus A. nidulans have three loci, benA, benB, and bene, which are involved in resistance to the antifungal drug carbendazim. The binding affinity of carbendazim to tubulin has been established using wild-type strain and allelectin (benA) mutants containing the mutations benA15 and benA16. Tubulin is a protein that is essential for the growth and division of cells. Carbendazim works by binding to tubulin and preventing it from functioning properly. The benA15 and benA16 mutations make it more difficult for carbendazim to bind to tubulin, which is why these mutants are resistant to the drug. [6-9] Apart from the previously discussed processes, fungal cells have the ability to form biofilms, which are extracellular matrices rich in polysaccharides. Biofilms are structured communities of microorganisms that are embedded in a matrix of extracellular polymeric substances. They are often resistant to antibiotics and antifungal drugs. The ability to create biofilms is a rare trait among pathogenic fungus, but those that do have a higher resistance to antifungal medications. This is because the biofilm provides a physical barrier that protects the fungi from the drug. Additionally, the fungi in the biofilm can communicate with each other and share genes that confer resistance to the drug. [8]

## 1.2 THE CHARACTERISTICS OF BENZIMIDAZOLE DERIVATIVES

Heterocyclic compounds known as benzimidazoles (1) contain a fused ring structure made up of an imidazole ring fused to the 4, 5-position of a benzene ring (Fig. 3). They possess both basic and acidic qualities. With a pKa of 16, the N-H group is classified as weakly basic and strongly acidic.




(1)

**Figure 1:** Structure of the benzimidazole molecule

Prototropic tautomerization (Fig. 4) is a sort of chemical reaction that includes the passage of a proton (hydrogen atom) from one atom to another, and it can easily occur with the unsubstituted hydrogen atom of the N-H group. This tautomerization is responsible for the isomerization of benzimidazole-derived compounds, which is the process of changing from one structural isomer to another. Tautomerization produces equilibrium mixes of molecules with asymmetric substitutions.[10]


**Figure 2:** Tautomerism in benzimidazole

The finding that the most prevalent benzimidazole in nature, N-ribosyl-dimethylbenzimidazole, is an essential component in the structure of vitamin B12 sparked interest in benzimidazoles. Since then, benzimidazoles have been the subject of in-depth research, leading to the discovery of a variety of pharmacological actions. They have been employed in the creation of compounds with biological and pharmacological applications.[11]

Due to their remarkable biological activity, many substituted derivatives have been used in a variety of therapeutic purposes. For instance, 2-[(4-diarylmethoxy)phenyl]-benzimidazole has been found to be a possible hepatitis C treatment. Furthermore, a number of pharmaceuticals that are already on the market were produced by optimizing benzimidazole-based structures, including the anthelmintic mebendazole (2), the ionodilator pimobendan (3), and the proton pump inhibitor omeprazole (4). Benzimidazoles are acknowledged as a potent fungicide component. It is well known that derivatives of 2-substituted benzimidazoles exhibit strong biological activity. Both 5-fluoro benzimidazole carboxamide derivatives (5) and benzimidazole isoxazolines (6) have shown antifungal activity. (Fig. 5).[11]

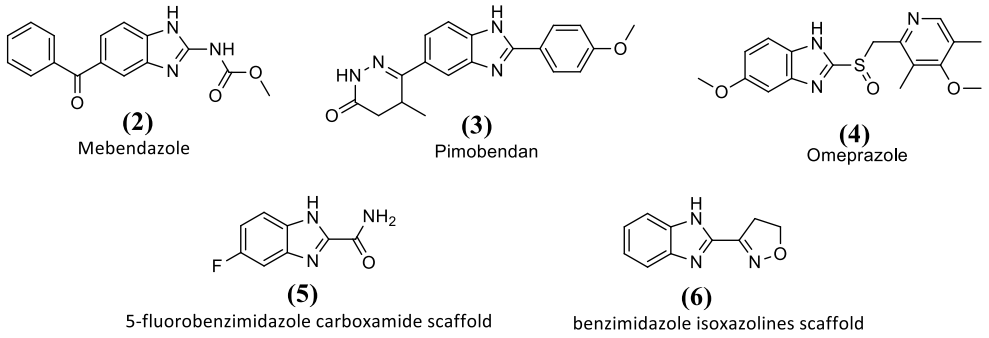



**Figure 3:** Benzimidazole derivatives

## 1.3 THE ANTI-FUNGAL ACTIVITY MECHANISMS OF BENZIMIDAZOLE:

Microtubules, which are composed of the tubulin protein, are found in fungi.[9] These cylindrical structures make up majority of spindle fibers, that aid in the movement of chromosomes, nuclei, and cell wall precursors through mitosis and meiosis (Fig. 6). Anti-microtubule drugs attach to proteins elaborate in tubulin construction, stopping mitosis at the metaphase stage of the cell cycle. Cell wall formation may be inhibited when cytoplasmic microtubules vanish because they obstruct the movement of materials to the cell's perimeter. The pathogenic fungus becomes more susceptible to several environmental conditions when its cell wall is lost. [12]

Benzomidazoles show a biological action as particular inhibitors of microtubule assembly. They achieve this by vying for the β-tubulin binding site, which is responsible for inactivating the spindle. As a result of this inactive spindle, aberrant microtubule assembly occursSince microtubules are dynamic structures that are constantly built and dismantled, this interference eventually results in the microtubules' elimination. [9, 12]

Research has indicated that the inhibition of microtubule assembly is the reason behind the cytotoxic effects of benzimidazoles on fungus. One of the main elements of the eukaryotic cytoskeleton and a distinctive characteristic of eukaryotic cells are microtubules. For this reason, when they finally vanish, the cytoskeleton's structural integrity is compromised. A

malfunctioning cytoskeleton has significant effects on the development and proliferation of cells. As a result, blocking the creation of microtubules interferes with various biological processes, such as cell division, mitosis, meiosis, intercellular transport, and, ultimately, DNA and RNA synthesis.[9]

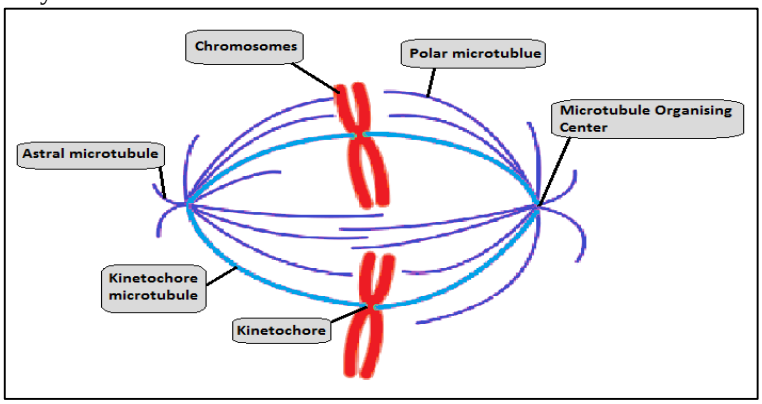



**Figure 4:** A spindle found in fungal cells.

### 1.4 THE SELECTIVE TOXICITY OF BENZIMIDAZOLES:

Certain chemicals have the ability to kill a virus without endangering its host, a feature known as selective toxicity. The diversity of fungal species, the pharmacological target's orientation toward humans, and the cytological distinctions between fungal and human cell lines can all be utilized to assess selective toxicity. Because of the cellular makeup of the organisms, the progress of antifungal agents has generally trailed overdue that of antibacterial medications. Although bacterial cells are prokaryotic and have distinct structural and metabolic goals from human cells, the cells of fungi are eukaryotic, much similar human cells. As a result, a lot of substances that are harmful to fungus are also harmful to the host.[9, 11, 12]

All eukaryotic cells have microtubules, however benzimidazoles exhibit strong selectivity. This is demonstrated by the fact that benzimidazoles can treat both people and animals. With little to no impact on the host, benzimidazoles function as antifungal drugs, inhibiting or eliminating the contaminating pathogen. Because of this, medications in this class are referred to as fungicidal and fungistatic. The varied affinity that benzimidazoles exhibit for the tubulins of various organisms has been proposed as one of the reasons influencing benzimidazole selectivity. Furthermore, the role of different metabolisms in human and animal cells compared to fungal cells could account for selectivity.[11]

## 1.5 STRUCTURE ACTIVITY RELATIONSHIP (SAR) OF BENZIMIDAZOLES

When designing and synthesizing possible medication candidates with the highest potency and the fewest side effects, structural activity connection is crucial. Benzimidazole libraries with particular objectives have been developed by researchers through studies employing different substitution patterns. The presence of electron-withdrawing groups (EWG) has been shown to enhance or maintain antifungal action. Furthermore, bulky groups at position two enhance activity in addition to helping to increase lipophilicity.[13]

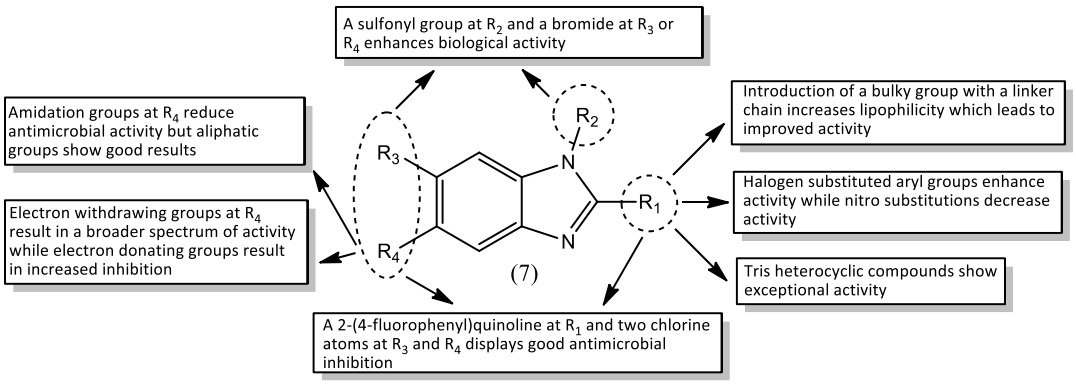



**Figure 5:** The SAR of benzimidazole scaffold

## 2 SYNTHESIS OF BENZIMIDAZOLES

Hobrecker initially described the synthesis of 2,5- and 2,6-dimethylbenzimidazole in 1872. This was achieved by reducing 4-methyl-2nitroacetanilide with tin and hydrochloric acid. Later on, Ladenburg produced the same compound by

refluxing 3,4-diaminotoluene with acetic acid. Since then, a number of techniques for producing benzimidazoles have been developed. [10, 14]

***2.1 Synthesis from carboxylic acids:*** Using equimolar ratios of an o-phenylenediamine (8) and a carboxylic acid (9) in diluted hydrochloric acid is a technique often known as the Phillips method. The application of aliphatic acids readily generates high yields. However, for aromatic acids, the reaction must be carried out in a pressure tube at 180–190°C. Figure 8. [10, 14]

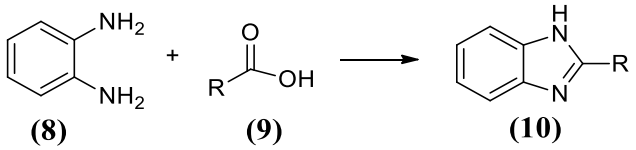



**Figure 6:** Formation of benzimidazoles (10) from carboxylic acids

***2.2 Synthesis from aldehydes:*** Under oxidative circumstances, aldehydes (12) can react with o-phenylenediamine (11). For instance, the Beaulieu approach is ozone mediated, whereas Weidenhagen's method is carried out in the presence of a cupric salt. More recently, benzimidazoles were created by reacting an aryl halide with hydrogen peroxide, hydrochloric acid, and acetonitrile in a one-pot synthesis. Concurrent formation of 1- and 2-substituted benzimidazoles (13) and (14) is possible in the absence of an oxidizing agent. (**Fig. 9**) [10, 14]

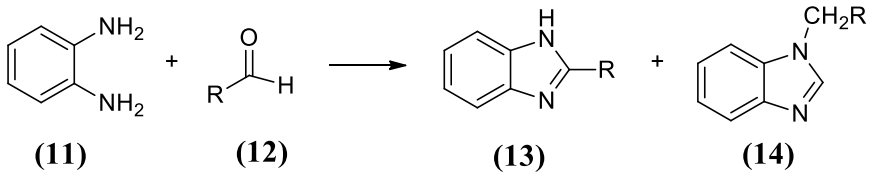



**Figure 7:** Benzimidazole formation from aldehydes

***2.3 Synthesis from acid anhydrides:*** When o-phenylenediamine (15) is heated under reflux with an acid anhydride (16) of monobasic acids for several hours, benzomidazoles (17) are generated in good yield. Acid anhydrides of monobasic and dibasic acids react in a similar way **(Fig 10)**. [10]

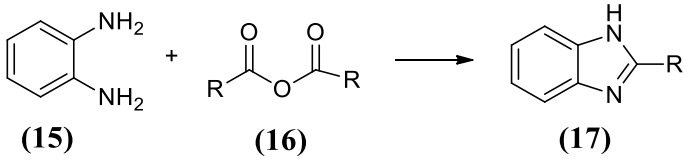



**Figure 8:** Benzimidazoles formation from acid anhydrides

***2.4 Synthesis from esters:*** Benzomidazoles (20) can be generated in good yields by reacting equimolar amounts of o-phenylenediamine (18) with esters (19) under hot reflux for many hours. Several benzimidazole compounds have been made using triethyl orthoformate, such as reactions with o-phenylenediamine and 4-nitro-2-amino-diphenylamine. (**Fig. 11**) [10]

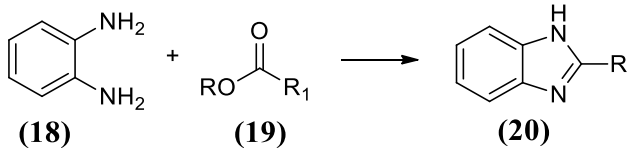


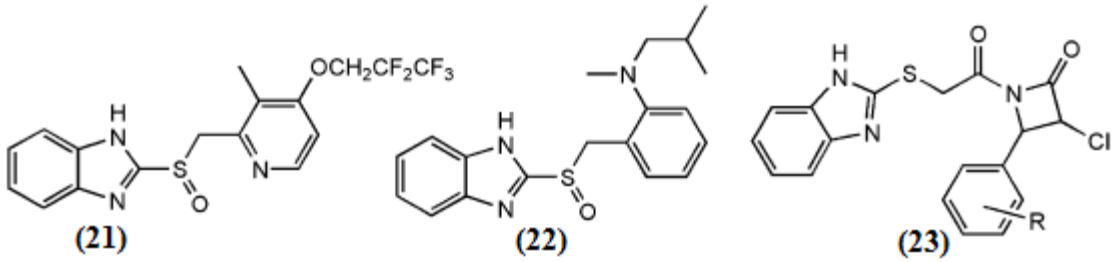

**Figure 9:** Formation of benzimidazoles from esters

***2.5 Further synthetic approaches:*** 2-substituted benzimidazoles can be produced by equimolar reactions between o-phenylenediamine hydrochloride salts and nitriles in an acidic environment at 200°C. Benzimidazoles are the main result of reactions between ketones and o-phenylenediamines or 8-aminoquinolines. Additional techniques involve the use of alkylamines and carbonitriles as reactants and o-nitroanilines and 2-haloanilines as starting materials.[10, 14]

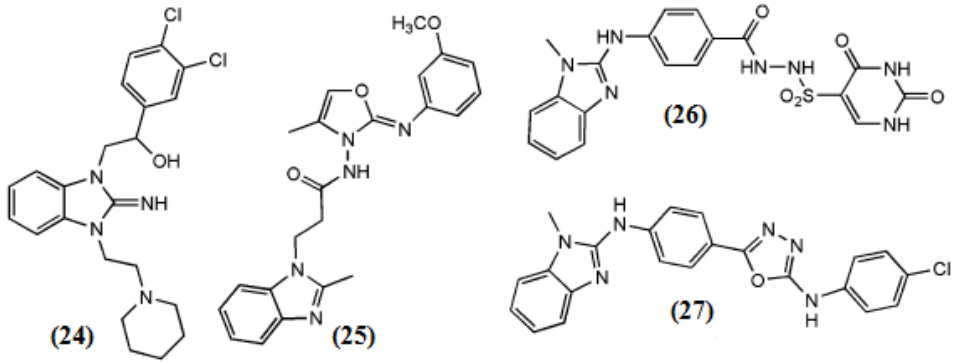
## 3 ANTIMICROBIAL ACTIVITY OF BENZIMIDAZOLE DERIVATIVES:

A broad class of chemical substances known as antimicrobial agents works against a variety of microorganisms, such as viruses, bacteria, helminths (worms), fungus, and protozoa. Numerous research teams have simultaneously assessed the antibacterial, antiprotozoal, anthelmintic, and/or antifungal properties of compounds, but the assessment of antiviral compounds has been conducted separately. Thus, under the heading of "antimicrobials," substances having antibacterial, antiprotozoal, anthelmintic, and antifungal qualities are investigated in combination in this work.

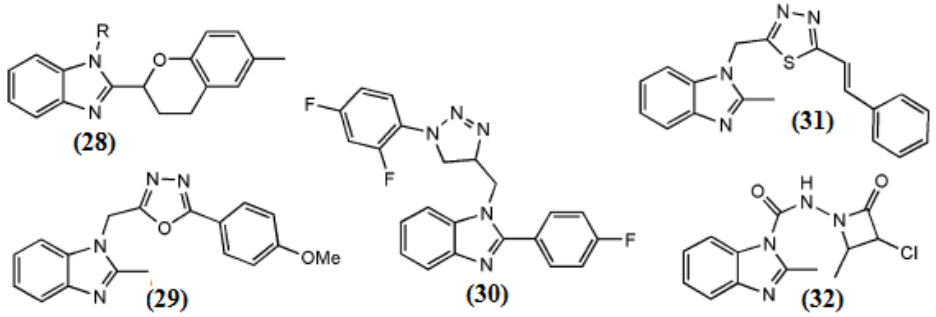
Since the year 2000, the majority of research efforts have been focused on the creation of antimicrobials utilizing the benzimidazole nucleus. 2-(Substituted pyridyl methylsulfinyl) benzimidazole (21) has been shown to be antibacterial against Campylobacter pylori by Iwahi and Satoh. Modifications to (21) provide a chemical (22) that is similar to omeprazole in that it has antibacterial qualities against C. pylori. [15] Compound (23) is the result of coupling 2-alkylthiobenzimidazole with a b-lactam ring; its antibacterial and antifungal properties are dependent on the type of R group.[16]



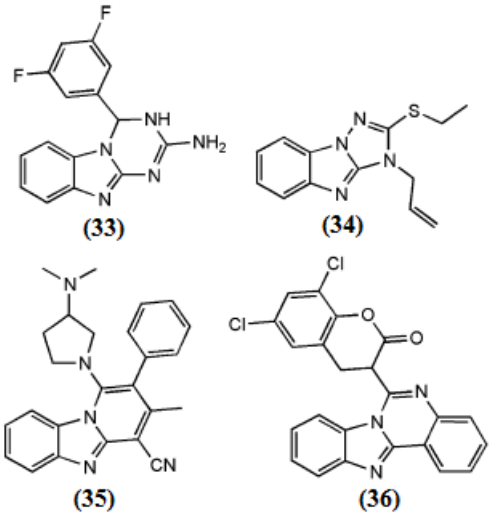

2-Iminobenzimidazoles (24) have been identified by Holloway et al. as having antibacterial properties that work by inhibiting the bacterial enzyme trypanothione reductase.[17] It has been discovered that 1-substituted benzimidazole compounds have weak antibacterial capabilities.[18] On the other hand, strong antimicrobials have been created by substituting benzimidazole at both its 1 and 2 locations. It has been reported that the subsitiution at 1-position as shown in semicarbazide, thiosemicarbazide and carbamate substituent along with a methyl group at 2-position has been yielded compounds (25–27) as potent bactericidal. [19]



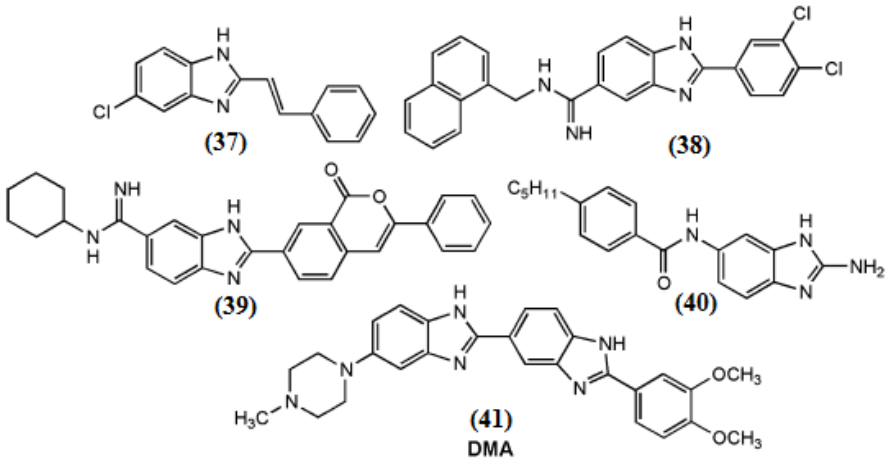

The benzimidazole nucleus might be joined to other heterocyclic compounds, such as chromane, b-lactam, thiadiazole, and oxadiazole, to form hybrid compounds (28–32) with potent antibacterial and/or antifungal properties.[20-22]



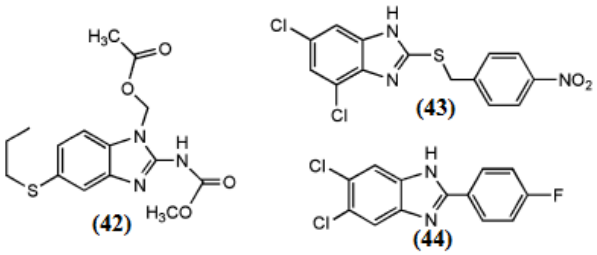

Tricyclic derivatives of benzimidazole, such as triazino[1,2-a] benzimidazole, are created when a 5- or 6-membered heterocycle fuses at the N1–C bond of the benzimidazole nucleus attaching fluorophenyl group-containing benzimidazole (33) is somewhat antimicrobial, Pyridobenzimidazole derivatives (35) have antifungal properties, while 1,2,4-triazolo[2,3-a]benzimidazole with short alkyl and alkenyl groups (34) has strong antimycobacterial properties.[23, 24] Benzimidazo[1,2-c]quinazolin-5-yl chromene derivative (36) has been described as an antibacterial agent recently by Kuarm *et al*. The compound became antifungal when the bromo groups were substituted for the chloro ones. The antibacterial properties of several 2,5- and 2,6-disubstituted benzimidazole derivatives have also been investigated. [25]



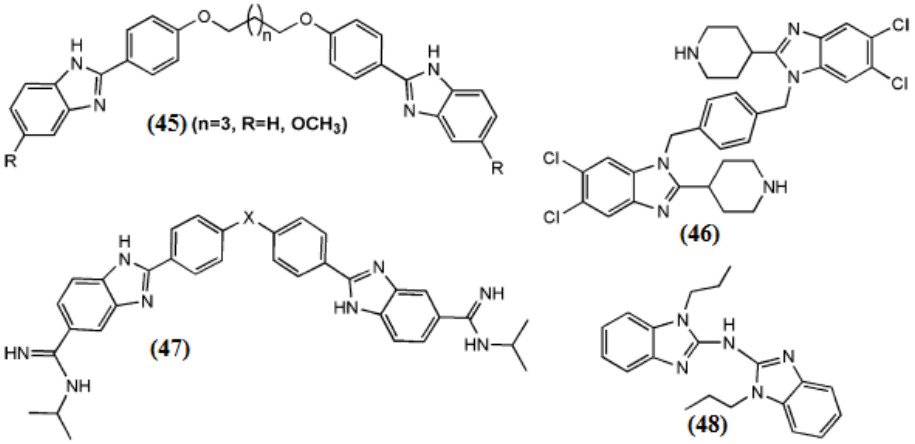

The compounds, (37) and (38) are 2,5-substituted derivatives that shown moderate to good antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and gram (+)ve and gram (-)ve bacteria.[26, 27] Another similar derivative, DMA (41) has been discovered by Bansal *et al*. to constrain topoisomerase I of bacterial.[28] Two of the 2,6-substituted derivatives, (39) and (40), exhibit superior efficacy against *Candida albicans*, methicillin-resistant *Staphylococcus epidermidis* (MRSE), and MRSA..[29, 30]




Numerous trisubstituted benzimidazoles have investigated for their potential antifungal and antibacterial properties. Compounds (42) and (43) have emerged as promising antimicrobials to inhibit MRSA and MRSE [31, 32] While compounds (43) and (44) are discovered to act as neomatocidal and antimycobacterial activity, respectively.[33, 34] A 2,5,6-trihalogeno analog, compound (44) has strong antibacterial action against MRSA.[35]

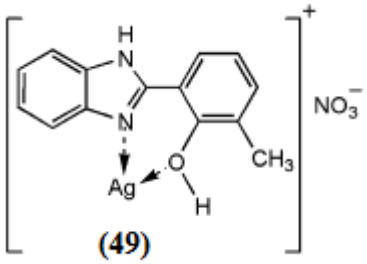



Derivatives of bis-benzimidazoles have shown great promise as antiviral and antibacterial drugs. Compound 45 is a chemical that has strong antiprotozoal properties. Any alteration in the linker methylene chain's length reduces the activity [15], but adding a methoxy group to the benzimidazole nucleus greatly boosts the activity.[36] A powerful broad spectrum antibacterial chemical (46), polysubstituted bis-benzimidazole, has formed then investigated as a paromomycin-equivalent.[37] After creating a variety of compounds (47), Hu *et al.* discovered that the ethereal linker (–O–) has superior antibacterial activity to Penicillin-G.[38] A new bis-benzimidazole (48) with more antifungal activity than albendazole was created by connecting two benzimidazole nuclei at their 2nd positions with an amino group.[39]




It has been observed that complexing benzimidazole compounds with different metal ions such as Fe3+, Cu2+, Zn2+, Ag+, and Co2+ increases the compounds' antibacterial properties. When 2-(2-hydroxyphenyl)benzimidazole analogs were complexed with several transition metals, Tavman et al. discovered that an Ag+ complex (49) acted as a strong antibacterial

agent.[40] Strong antibacterial properties of several bis-benzimidazole Zn2+ and Pd2+ complexes have also been observed.[41] Cobalt complexes of 2-aminobenzimidazole and 1-(1H-benzimidazol benzimidazol-2-yl)ethanone thiosemicarbazone are two more benzimidazole derivative complexes that show antibacterial activity,[42] gold complexes of 1,3-di-isoproylbenzimidazolinium bromide,[42] cadmium complexes of 1,10-(1,3-propanediyl)bis-1H-benzimidazole,[43, 44] transition metal complexes of bis(benzimidazole-20-yl methyl)amine, [44] zinc complexes of 2-(5-substituted benzimidazol-2-yl)-phenols [45] and silver complexes of 1-(2,4,6-trimethylbenzyl)-3- methoxyethyl)benzimidazolidine.[46]




(49)

## 4 CONCLUSIONS AND FUTURE DIRECTIONS

In the clinic, a wide range of substances synthesized from the benzimidaozle nucleus are utilized to treat various illnesses. The key elements of the SAR of benzimidazole as an antifungal motif have been supplied with this review. Additionally, it covers significant references that should give drug designers and medicinal chemists a brief overview of the compounds formed from benzimidazoles as well as comprehensive and goal-aimed information for the production of therapeutically worthwhile molecules.

## 5 CONFLICT OF INTEREST:

The authors declare no conflict of interest.

## REFERENCES:

1. Fang B, Zhou C-H, Rao X-C. Synthesis and biological activities of novel amine-derived bis-azoles as potential antibacterial and antifungal agents. European journal of medicinal chemistry. 2010;45(9):4388-98.
2. Shao P-L, Huang L-M, Hsueh P-R. Recent advances and challenges in the treatment of invasive fungal infections. International journal of antimicrobial agents. 2007;30(6):487-95.
3. Talbot GH, Bradley J, Edwards Jr JE, Gilbert D, Scheld M, Bartlett JG. Bad bugs need drugs: an update on the development pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America. Clinical infectious diseases. 2006;42(5):657-68.
4. Norrby SR, Nord CE, Finch R. Lack of development of new antimicrobial drugs: a potential serious threat to public health. The Lancet infectious diseases. 2005;5(2):115-9.
5. Spellberg B, Powers JH, Brass EP, Miller LG, Edwards Jr JE. Trends in antimicrobial drug development: implications for the future. Clinical infectious diseases. 2004;38(9):1279-86.
6. Pemán J, Cantón E, Espinel-Ingroff A. Antifungal drug resistance mechanisms. Expert review of anti-infective therapy. 2009;7(4):453-60.
7. Vandeputte P, Ferrari S, Coste AT. Antifungal resistance and new strategies to control fungal infections. International journal of microbiology. 2012;2012.
8. Pfaller MA. Antifungal drug resistance: mechanisms, epidemiology, and consequences for treatment. The American journal of medicine. 2012;125(1):S3-S13.
9. Davidse LC. Benzimidazole fungicides: mechanism of action and biological impact. Annual review of phytopathology. 1986;24(1):43-65.
10. Wright JB. The chemistry of the benzimidazoles. Chemical reviews. 1951;48(3):397-541.
11. Gaba M, Singh S, Mohan C. Benzimidazole: an emerging scaffold for analgesic and anti-inflammatory agents. European journal of medicinal chemistry. 2014;76:494-505.
12. Levinson W, Jawetz E. Medical microbiology and immunology: examination and board review: Appleton & Lange; 1996.
13. Yadav G, Ganguly S. Structure activity relationship (SAR) study of benzimidazole scaffold for different biological activities: A mini-review. European journal of medicinal chemistry. 2015;97:419-43.

14. Hofmann K. Imidazole and Its Derivatives, Volume 6, Part 1: John Wiley & Sons; 2009.
15. Bansal Y, Silakari O. The therapeutic journey of benzimidazoles: A review. Bioorganic & medicinal chemistry. 2012;20(21):6208-36.
16. Desai KG, Desai KR. Green route for the heterocyclization of 2-mercaptobenzimidazole into β-lactum segment derivatives containing–CONH–bridge with benzimidazole: Screening in vitro antimicrobial activity with various microorganisms. Bioorganic & medicinal chemistry. 2006;14(24):8271-9.
17. Holloway GA, Baell JB, Fairlamb AH, Novello PM, Parisot JP, Richardson J, et al. Discovery of 2-iminobenzimidazoles as a new class of trypanothione reductase inhibitor by high-throughput screening. Bioorganic & medicinal chemistry letters. 2007;17(5):1422-7.
18. Güven ÖÖ, Erdoğan T, Göker H, Yıldız S. Synthesis and antimicrobial activity of some novel phenyl and benzimidazole substituted benzyl ethers. Bioorganic & Medicinal Chemistry Letters. 2007;17(8):2233-6.
19. Nofal Z, Fahmy H, Mohamed H. Synthesis and antimicrobial activity of new substituted anilinobenzimidazoles. Archives of pharmacal research. 2002;25:250-7.
20. Wadhawa GC, Shivankar VS, Charansingh YAG, Gill H, Gavali LV. Review on antibacterial activity of benzimidazole containing compounds. World Journal of Pharmaceutical Research. 2018;7(7):483-95.
21. Ansari K, Lal C. Synthesis, physicochemical properties and antimicrobial activity of some new benzimidazole derivatives. European journal of medicinal chemistry. 2009;44(10):4028-33.
22. Ansari K, Lal C. Synthesis and biological activity of some heterocyclic compounds containing benzimidazole and beta-lactam moiety. Journal of Chemical Sciences. 2009;121:1017-25.
23. Kitamura A, Someya K, Hata M, Nakajima R, Takemura M. Discovery of a small-molecule inhibitor of β-1, 6-glucan synthesis. Antimicrobial agents and chemotherapy. 2009;53(2):670-7.
24. Takeshita H, Watanabe J, Kimura Y, Kawakami K, Takahashi H, Takemura M, et al. Novel pyridobenzimidazole derivatives exhibiting antifungal activity by the inhibition of β-1, 6-glucan synthesis. Bioorganic & medicinal chemistry letters. 2010;20(13):3893-6.
25. Kuarm BS, Reddy YT, Madhav JV, Crooks PA, Rajitha B. 3-[Benzimidazo-and 3-[benzothiadiazoleimidazo-(1, 2-c) quinazolin-5-yl]-2H-chromene-2-ones as potent antimicrobial agents. Bioorganic & medicinal chemistry letters. 2011;21(1):524-7.
26. Ören İ, Temiz Ö, Yalçın I, Şener E, Altanlar N. Synthesis and antimicrobial activity of some novel 2, 5-and/or 6-substituted benzoxazole and benzimidazole derivatives. European journal of pharmaceutical sciences. 1999;7(2):153-60.
27. Göker H, Özden S, Yıldız S, Boykin DW. Synthesis and potent antibacterial activity against MRSA of some novel 1, 2-disubstituted-1H-benzimidazole-N-alkylated-5-carboxamidines. European journal of medicinal chemistry. 2005;40(10):1062-9.
28. Bansal S, Tawar U, Singh M, Nikravesh A, Good L, Tandon V. Old class but new dimethoxy analogue of benzimidazole: a bacterial topoisomerase I inhibitor. International journal of antimicrobial agents. 2010;35(2):186-90.
29. Göker H, Boykin D, Yıldız S. Facile ionic liquid-mediated, microwave assisted green synthesis, and antioxidant studies of novel indolin-2-one annulated spirochromanone conjugates. Bioorg Med Chem. 2005;13:1707-18.
30. Huigens III RW, Reyes S, Reed CS, Bunders C, Rogers SA, Steinhauer AT, et al. The chemical synthesis and antibiotic activity of a diverse library of 2-aminobenzimidazole small molecules against MRSA and multidrug-resistant A. baumannii. Bioorganic & medicinal chemistry. 2010;18(2):663-74.
31. Özden S, Atabey D, Yıldız S, Göker H. Synthesis and potent antimicrobial activity of some novel methyl or ethyl 1H-benzimidazole-5-carboxylates derivatives carrying amide or amidine groups. Bioorganic & medicinal chemistry. 2005;13(5):1587-97.
32. Sharma P, Kumar A, Sharma M. Synthesis and QSAR studies on 5-[2-(2-methylprop1-enyl)-1H benzimidazol-1yl]-4, 6-diphenyl-pyrimidin-2-(5H)-thione derivatives as antibacterial agents. European journal of medicinal chemistry. 2006;41(7):833-40.
33. Márquez-Navarro A, Nogueda-Torres B, Hernández-Campos A, Soria-Arteche O, Castillo R, Rodríguez-Morales S, et al. Anthelmintic activity of benzimidazole derivatives against Toxocara canis second-stage larvae and Hymenolepis nana adults. Acta Tropica. 2009;109(3):232-5.
34. Kazimierczuk Z, Andrzejewska M, Kaustova J, Klimešova V. Synthesis and antimycobacterial activity of 2-substituted halogenobenzimidazoles. European journal of medicinal chemistry. 2005;40(2):203-8.
35. Tuncbilek M, Kiper T, Altanlar N. Synthesis and in vitro antimicrobial activity of some novel substituted benzimidazole derivatives having potent activity against MRSA. European Journal of Medicinal Chemistry. 2009;44(3):1024-33.
36. Torres-Gómez H, Hernández-Núñez E, León-Rivera I, Guerrero-Alvarez J, Cedillo-Rivera R, Moo-Puc R, et al. Design, synthesis and in vitro antiprotozoal activity of benzimidazole-pentamidine hybrids. Bioorganic & medicinal chemistry letters. 2008;18(11):3147-51.
37. He Y, Yang J, Wu B, Risen L, Swayze EE. Synthesis and biological evaluations of novel benzimidazoles as potential antibacterial agents. Bioorganic & medicinal chemistry letters. 2004;14(5):1217-20.
38. Hu L, Kully ML, Boykin DW, Abood N. Synthesis and in vitro activity of dicationic bis-benzimidazoles as a new class of anti-MRSA and anti-VRE agents. Bioorganic & Medicinal Chemistry Letters. 2009;19(5):1292-5.
39. Mavrova AT, Denkova P, Tsenov YA, Anichina KK, Vutchev DI. Synthesis and antitrichinellosis activity of some bis (benzimidazol-2-yl) amines. Bioorganic & medicinal chemistry. 2007;15(18):6291-7.

40. Tavman A, Ikiz S, Bagcigil AF, Özgür NY, Ak S. Spectral characterizations and antibacterial effect of 2-(5-R-1H-benzimidazol-2-yl)-4-methyl/bromo-phenols and some metal complexes. Bulletin of the Chemical Society of Ethiopia. 2010;24(3).
41. Köse A, Bal M. SYNTHESIS, STRUCTURE AND PHOTOLUMINESCENCE PROPERTIES OF A Cd2+ COMPLEX OF A PYRIDINE-BIS-BENZIMIDAZOLE LIGAND. Journal of Structural Chemistry. 2022;63(12):1981-7.
42. Poyraz M, Sari M, Demirci F, Kosar M, Demirayak S, Büyükgüngör O. Synthesis, crystal structure and biological activity of 1-(1H-benzoimidazol-2-yl)-ethanone thiosemicarbazone and its cobalt complex. Polyhedron. 2008;27(9-10):2091-6.
43. Yang H, Meng X, Liu Y, Hou H, Fan Y, Shen X. Syntheses, crystal structures and properties of two 1-D cadmium (II) coordination polymers based on 1, 1′-(1, 3-propanediyl) bis-1H-benzimidazole. Journal of Solid State Chemistry. 2008;181(9):2178-84.
44. Siddiqi ZA, Shahid M, Khalid M, Noor S, Kumar S. Spectroscopic and antimicrobial studies of La3+, Pr3+, Nd3+ and Gd3+ complexes of a dipodal [N, N, N] chelating ligand. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2009;74(2):391-7.
45. Tavman A, Boz I, Birteksöz AS. Spectral characterization and antimicrobial activity of 2-(5-chloro/nitro-1H-benzimidazol-2-yl)-4-bromo/nitro-phenols and their zinc (II) complexes. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2010;77(1):199-206.
46. Özdemir İ, Demir S, Günal S, Özdemir İ, Arıcı C, Ülkü D. Synthesis, characterization and antimicrobial activity of new silver complexes with N-heterocyclic carbene ligands. Inorganica chimica acta. 2010;363(14):3803-8.