MOHAMED ATEF IBRAHİM GAMALELDEN
EXPLORING THE SYNTHESIS AND ANTIBACTERIAL PROPERTIES OF BENZIMIDAZOLE DERIVATIVES
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M.Sc. THESIS

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Approval

We certify that we have read the thesis submitted by MOHAMED ATEF IBRAHİM GAMALELDEN titled **"Exploring the Synthesis and Antibacterial Properties of Benzimidazole Derivatives"** and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree Master of Pharmaceutical Chemistry.

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Declaration

I hereby declare that all information, documents, analysis and results in this thesis have been collected and presented according to the academic rules and ethical guidelines of Institute of Graduate Studies, Near East University. I also declare that as required by these rules and conduct, I have fully cited and referenced information and data that are not original to this study.

MOHAMED ATEF IBRAHİM GAMALELDEN

/FEB/2025

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MOHAMED ATEF IBRAHİM GAMALELDEN

Abstract

Exploring the Synthesis and Antibacterial Properties of Benzimidazole Derivatives

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The search for new compounds with strong antibacterial qualities has become necessary due to the rising incidence of antibiotic resistance. The heterocyclic molecule benzomimdazole has attracted a lot of interest due to its various biological activities, including antibacterial properties. The antibacterial potential of benzomimdazole derivatives is examined in this thesis, along with its effectiveness against a variety of pathogenic microorganisms, such as viruses, fungi, and bacteria. The study investigates the spectrum of activity, mode of action, and minimum inhibitory concentration (MIC) of benzomimdazole-based compounds using in vitro testing. According to the findings, benzomimdazole exhibits strong antibacterial action, especially against Gram-positive bacteria, and shows promise for further advancement as a substitute for traditional antibiotics.

Keywords: Benzimidazole; Mannich base; antimicrobial activity; Mannich reaction.

ÖZET

Benzimidazol Türevlerinin Sentezi ve Antibakteriyel Özelliklerinin Araştırılması

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Antibiyotik direncinin artan sıklığı nedeniyle güçlü antibakteriyel özelliklere sahip yeni bileşiklerin araştırılması gerekli hale gelmiştir. Heterosiklik molekül benzomidazol, antibakteriyel özellikler de dahil olmak üzere çeşitli biyolojik aktiviteleri nedeniyle çok ilgi çekmiştir. Bu tezde benzomidazol türevlerinin antibakteriyel potansiyeli, virüsler, mantarlar ve bakteriler gibi çeşitli patojenik mikroorganizmalara karşı etkinliği ile birlikte incelenmiştir. Çalışma, in vitro testler kullanılarak benzomidazol bazlı bileşiklerin aktivite spektrumunu, etki şeklini ve minimum inhibitör konsantrasyonunu (MİK) araştırmaktadır. Bulgulara göre benzomidazol, özellikle Gram pozitif bakterilere karşı güçlü antibakteriyel etki göstermektedir ve geleneksel antibiyotiklerin yerine daha fazla ilerleme için umut vaat etmektedir.

Anahtar kelimeler: Benzimidazol; Mannich bazı; antimikrobiyal aktivite; Mannich reaksiyonu.

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List of Abbreviations

NMR……. Nuclear Magnetic Resonance

FT-IR……Fourier Transform Spectroscopy

SAR……. Structural Activity Relationship

Rf……...Retention Factor

TLC……. Thin Layer Chromatography

ppm……..part per million

1. Introduction

Benzimidazole, also known as 1-H-benzimidazole, is a vital heterocyclic compound that plays a significant role in the development of various pharmacologically active chemical entities. This compound features a unique structure where nitrogen and carbon atoms contribute to its reactive properties (Figure 1.1), allowing for diverse chemical modifications. Numerous derivatives of benzimidazole have been synthesized, leading to crucial components in a broad range of therapeutic applications. (Lee et al., 2023)(Ebenezer et al.2022)

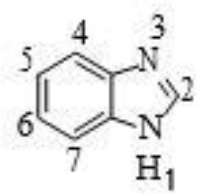


Figure 1.1 Benzimidazole

The antimicrobial effects of benzimidazole and its derivatives are particularly noteworthy. These compounds have demonstrated substantial antibacterial activity against a wide spectrum of bacteria, inhibiting the growth of both Gram-positive and Gram-negative organisms. Its mechanism of action often involves disrupting bacterial cell wall synthesis or inhibiting essential bacterial enzymes, leading to cell lysis or impaired cellular function. (Brishty et al.2021)

In addition to antibacterial properties, benzimidazole derivatives exhibit antifungal activity, effectively combating various fungal pathogens by interfering with their cellular processes. This action is particularly vital in treating infections caused by fungi that have developed resistance to conventional antifungal medications. Furthermore, benzimidazole structures have shown efficacy against specific viral infections, contributing to antiviral therapies that inhibit viral replication and spread. (Guzel et al.2023)

Moreover, the compound's anthelmintic qualities enable it to effectively target parasitic worms, disrupting their metabolic processes and leading to their elimination

from the host organism. The diverse mechanisms through which benzimidazole exerts its antimicrobial effects underline its significance in pharmacology and underscore the potential for further exploration in drug development aimed at tackling various infectious diseases. (Raj et al., 2020)Overall, the multifaceted antimicrobial properties of benzimidazole derivatives highlight their importance in contemporary medicine and their promise for future therapeutic advancements.. (Gondru et al., 2022)

The first synthesis of benzimidazole was reported by the German chemist Hermann von Fehling in 1872, representing a crucial milestone in the exploration of this distinctive compound. The synthesis methods for this bicyclic structure, which consists of a benzene ring fused to an imidazole ring, can be organized into three main pathways. The first method involves the condensation cyclization of o-phenylenediamine with various carbonyl compounds such as formaldehyde, methyl ketones, and other ketones.

The second method employs an extended treatment of aromatic compounds with anhydrides or, notably, with benzophenone. The third approach consists of heating substituted 1,2-phenylenediamine with carboxylic acids and their derivatives, typically using a mixture of MCl3 and NH4Cl while maintaining hydrogen chloride in the system. Substituted benzimidazoles and their cyclic analogs have been created through conventional chemical techniques, including reduction, oxidation, alkylation, and condensation, or by reacting ammonia with protective substituents.

In well-established literature, potassium cyanide and urea are identified as effective sources of cyanogen, while carbon disulfide is utilized in the preparation of benzimidazole derivatives. Emphasizing the importance of 1,3,4-benzotriazinn-2-ones and imidazolo[1,2-a]benzimidazole compounds, this investigation examines the synthesis and characterization of a Mannich base derived from benzimidazole, utilizing both traditional methods and microwave irradiation techniques.

2. LITERARATURE REVIEW

Benzimidazole derivatives contain an imidazoline heterocyclic ring system that possesses characteristics such as being a stable ion and an adsorbed part in molecular biological interactions. Therefore, these derivatives have a broad range of applications and effects. In evaluation, the antibacterial and antifungal activities of newly synthesized benzimidazole derivatives were found to be more effective on Gram-positive bacteria. (Brishty et al.2021)

The antimicrobial activity of benzimidazole compounds is not completely known. Herein, we prepared benzimidazole derivatives with different structures and determined their antimicrobial activities against various bacteria and fungi. This research contributes to medicinal chemistry and pharmaceutical science by synthesizing and evaluating the antimicrobial effects of these derivatives. Both the antibacterial and antifungal activities are presented for the first time. In this study, 2-(o-aminophenyl) benzimidazole derivatives and some of their substitutions were synthesized, and the antimicrobial effects of the derivatives were determined. (Dokla et al.2020)

In vitro antimicrobial activity includes the evaluation of the bactericidal effects of synthesized compounds, explaining the most desired therapeutic effects on highly sensitive bacterial families such as Gram-negative and Gram-positive bacteria.

The antimicrobial properties of synthesized compounds at different concentrations were compared to reference antibacterial drugs. In evaluation, the antibacterial and antifungal activities of newly synthesized benzimidazole derivatives were found to be more effective on Gram-positive bacterial families than in the reference material. (Pathare & Bansode, 2021)

The antimicrobial activity of synthesized benzimidazole compounds at various concentrations was a powerful source of active compounds. They have been artificially synthesized and offer significant results in developing an alternative antibiotic against various infectious diseases. The results of antimicrobial activities show that benzimidazole derivatives have promising antimicrobial potential against pathogenic microorganisms. With further studies, in vitro and in vivo antimicrobial activities can be increased. (Marinescu et al.2020)

2.1 Chemistry of Benzimidazoles

Benzimidazole is an important class of bicyclic heterocycles with widespread biological activities. Benzimidazoles are part of many clinically active pharmaceuticals such as reproductive inhibitors, antiparasitic, anti-inflammatories, antiglycative, antitumor, antivirals, and anti-neuropeptidics. The structure and activities of benzimidazoles are revised. The diverse compounds with a broad range of biological activities have attracted medicinal chemists to develop novel benzimidazole derivatives with desirable drug–target interactions. (Nishanth et al.2021)

Benzimidazole rings are structural analogues of purines and pyrimidines that are components of nucleic acids DNA and RNA molecules. Benzimidazole and its derivatives are biologically active compounds for many pharmaceutical activities, including antiviral, antibacterial, antiparasitic, anti-inflammatory, antifungal, antimicrobial, antiplatelet, ant ulcerative, intervascular, antiprotozoal, anthelmintic, antihypertensive, antitumor, and photoluminescent. (Lee et al., 2023) Benzimidazole derivatives have a potential role in the medicinal field with the potential to start new products and have shown a wide range of biological activity. Benzimidazoles are a nice playground for synthetic chemists due to their broad spectrum of biological properties. Benzimidazole is a benzene ring fused to an imidazole ring.

Benzimidazoles belong to the heterocyclic compounds and are also six-membered rings. These are majorly studied for their biological activities, having the ability to invade complex systems. Benzimidazoles are very small in size with aromaticity. While substituting the benzimidazole nucleus, it possesses diversity by modifying the positions of the two nitrogen atoms. It has a variety of pharmacological actions, such as antiviral and anticancer properties. (Brishty et al.2021)

2.2 Tautomerism in benzimidazoles

Tautomerism is the ability of protons to migrate within a molecule in rapid equilibrium with each other. It is considered that tautomerism is the property of several cyclic compounds such as pyridine, pyrrole, and imidazole. In benzimidazole, tautomerism mostly takes place on nitrogen atoms unlike the other heterocyclic compounds, and the azole ring becomes a unique site of tautomerism.

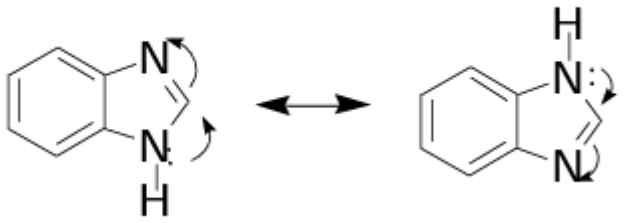


Figure 2.1 Tautomerism in benzimidazole

The benzimidazole molecule is able to adopt three common tautomeric forms where the central amino group may adopt three possible positions, i.e., the 1-CH-N-3-CH, 2-CH-CH-1-CH, and 3-CH-CH-2-CH tautomers, which rapidly interconvert through hydride migration. These different tautomers can interconvert at room temperature or even faster. The chemical and physicochemical properties of benzimidazole depend on the tautomerism (Faheem et al.2020) (Carvalho et al.2021).

It is evident that the various forms of benzimidazole interconvert rapidly between each other, and therefore, all forms are present. However, it is easy to isolate the 2-methylbenzimidazolium tosylate and the deprotonated 1-methylbenzimidazole and 2-methylbenzimidazole, as well as three derivatives. As hydrogen bond donor and acceptor abilities are crucial in biological systems, protein binding, receptor recognition, and enzyme action, the availability of these cations or anions affects the bioactivity of the molecule. Since tautomers can change their relative proportions based on the intermolecular or intramolecular interaction forces, in the condition with larger hydrogen bonding capacities in different tautomers, if the electronic distribution becomes more optimal, the stability, packing, and bioactivity could be highly influenced. (Mucha et al.2021)

2.3 Solubility of Benzimidazoles

Because benzimidazoles are weak bases in nature, slightly less basic than imidazoles they are soluble in dilute acids. Benzimidazoles are also sufficiently NH-acidic to form N-metallic compounds in aqueous alkali. The acidic properties of benzimidazoles, like those of imidazoles appear to be the result of ion stabilization via resonance. Above 300°C, benzimidazoles can be distilled unchanged.

Benzimidazoles with hydrogen at position 1 position (i.e., imide nitrogen) are typically soluble in polar solvents but less so in organic solvents. Thus, while benzimidazole is easily soluble in hot water, it is very poorly soluble in ether and insoluble in benzene and ligroin. However, incorporation of nonpolar substituents at various sites on the benzimidazole nucleus increases solubility in nonpolar solvents, as seen with 2- methylbenzimidazole, which is easily soluble in ether. In contrast, adding polar substituents to the benzimidazole nucleus increases its solubility in polar solvents; for example, 2-aminobenzimidazole is soluble in water. Overall, the solubility of various benzimidazole derivatives in alkaline solutions is dependent on the compound. There is also enough evidence to suggest molecular association via N-H-N bonds in benzimidazoles with an unsubstituted NH grouping (Singh & Silakari, 2018a).

The solubility of benzomidazole is crucial for its pharmaceutical applications, as solubility directly influences bioavailability and therapeutic efficacy. Recent research has highlighted the significance of solvent selection in enhancing the solubility of compounds such as benzomidazole. (Cysewski et al., 2023) provided valuable insights into this area by investigating the solubility profiles of benzenesulfonamide, a compound structurally related to benzomidazole, in various solvents. Their study underscores the effectiveness of aprotic polar solvents like dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) in solubilizing sulfonamides due to their ability to form hydrogen bonds with the solute, indicating that solvation effects may be more significant than the thermodynamic properties of the solid itself.

The authors employed advanced analytical techniques, such as differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy with attenuated total

reflectance (FTIR-ATR), to analyze the interactions between the solute and solvents. Their findings suggest that solvent choice is not only a matter of solubility but also impacts the physical properties of the solute, as evidenced by the observed deviations in melting points of residues from solubility experiments. This emphasizes the importance of considering solvent purity and its effects on experimental outcomes.

In conclusion, the research conducted by (Cysewski et al., 2023) lays a foundation for future studies on the solubility of benzomidazole and similar compounds. The findings advocate for a paradigm shift in solubility research, where the interactions between solute and solvent are prioritized to optimize solubility profiles. This approach is essential for advancing drug formulation strategies within the pharmaceutical industry, ultimately improving the therapeutic effectiveness of challenging compounds like benzomidazole.

2.4 Some Benzimidazole Reactions

Benzimidazole is a heterocyclic compound with each nitrogen and carbon atoms in its structure, which imparts wonderful chemical reactivity. The traits of benzimidazole in chemical reactions rely on its useful businesses and the presence of nitrogen atoms, that can take part in diverse reactions. Below are the important thing traits of benzimidazole in chemical reactions:

2.4.1. Alkylation

In small quantity of alkyl halides, benzimidazole supply the primary product and beneathneath lively conditions, the second one product is obtained.

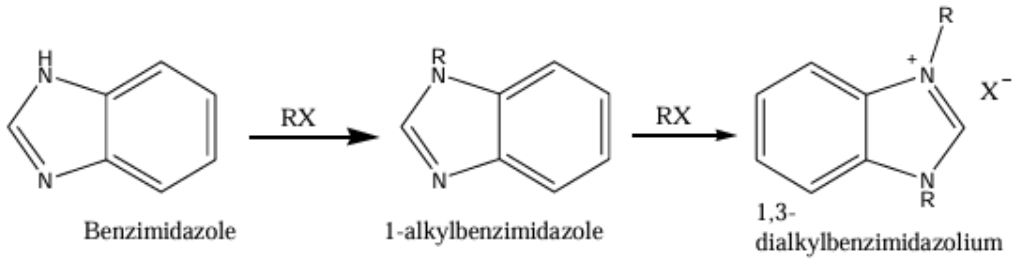


Figure 2.2 Reaction of benzimidazole with alkyl halides

2.4.2. Acylation

Acetylation is a reaction of a compound with a resulting introduction of the acetyl group by acetic anhydride, acetate chloride, or prefabricated acetic acid. Acetylation is the most frequently applied way to get acetyl or acetachloride derivatives of many natural or synthetic compounds, including the derivatives of nitrogen and aromatic heterocycles such as benzimidazole. The target molecules with this ring system were not new in the field of chemistry, but many of them have strong antimicrobial or cytostatic activities, which suggests that they should be immersed in pharmaceutical studies. Benzimidazole ring compounds are mainly derived from alkyl-benzimidazoles. The parent compounds of benzimidazole are 1-benzimidazole, 2-benzimidazole, and 4-benzimidazole. (Raducka et al.2022)

To prepare N-acyl benzimidazole, anhydrides or acid chlorides may be used with the corresponding benzimidazoles. The response has to be executed withinside the absence of water due to the fact withinside the presence of water and particularly alkaline solution, cleavage of the imidazole ring can arise as proven through Schotten-Baumann procedure.

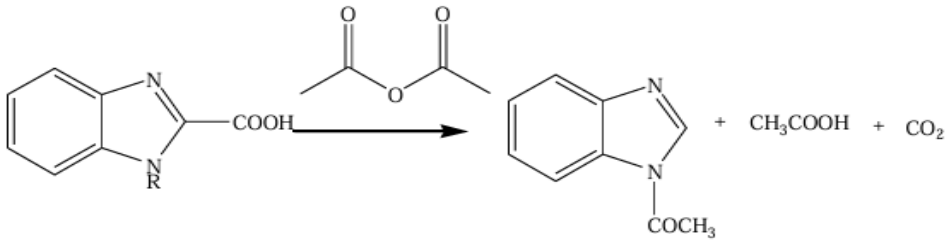


Figure 2.3 Acylation of 2-benzimidazole carboxylic acid with acetic anhydride to give 1-acetylbenzimidazole

2.4.3 Action of Grignard reagents on benzimidazoles

Benzimidazoles are known to react with Grignard reagents to produce anthelmintics. Sometimes, the C-2 proton is deuterated in the first place. Grignard reagents attack the A site of benzimidazoles, and due to this attack, the C-2 proton is exchanged through the collection of the reagent by the A site. The addition of Grignard reagents to benzimidazole results in the formation of 2-methylbenzimidazole through the creation of aromatic intermediates. This process provides benzimidazole, which is presented to anthelmintic and anticancer research. In addition, these reactions work under high dilution conditions at low temperatures to prevent dimerization of benzimidazoles. (Bhavsar et al.2020)

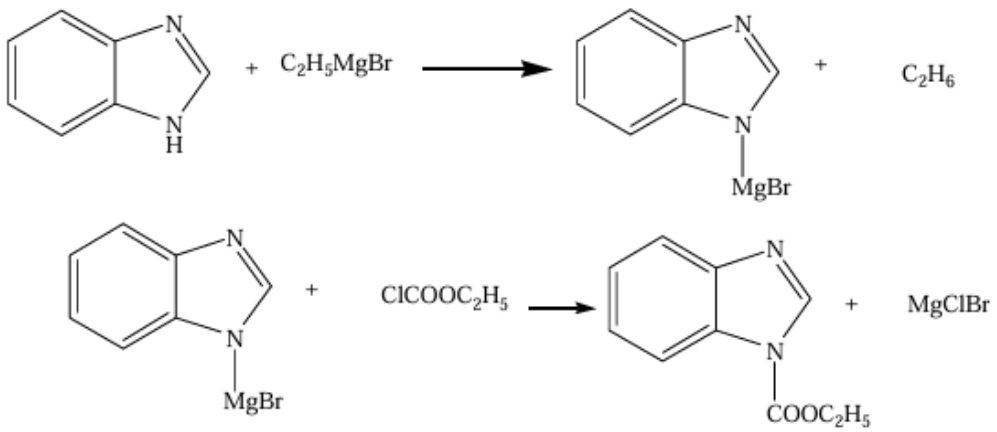


Figure 2.4: Action of Grignard reagent on benzimidazole

Grignard reagents showing the compatibility of various phenyl magnesium halides are usually used. These reactions typically result in a 60% yield of the benzerase 2 complex and an 80–90% yield of the aldehyde. After reacting with a strong base, at low temperature, the Grignard reagents add smoothly to the benzimidazoles. The storage of Grignard reagents in this research is usually performed as a solution in ether. (Banerjee et al.2022) The rate of reaction of these Grignard reagents with the benzimidazole was found to be within the range of 85–100% depending on the subsequent reaction time. (Jordan et al., 2022) These reactions often provide a highly effective and reliable method for the synthesis of 2-methylbenzimidazole.

2.5 Benzimidazoles and Mannich bases

Benzimidazole binary is an important type of pharmaceutically powerful substance and is widely used in the therapy of many diseases. The benzimidazole derivative still has antimicrobial effects used nowadays. The Mannich reaction involving benzimidazoles, as demonstrated by Bachman and Heisey, is a significant synthetic method that leads to the efficient production of 1-(piperidinomethyl)benzimidazole. By using equal moles of benzimidazole, formaldehyde, and piperidine, this reaction yields an impressive 97% of the desired product. The resulting benzimidazole derivatives hold substantial pharmaceutical potential, particularly in the development of new antimicrobial agents. Given the rising threat of drug-resistant pathogens, the synthesis of such compounds is crucial. Additionally, benzimidazoles have shown

promise in various therapeutic areas, establishing their relevance in combating contemporary health challenges. (Marinescu, 2021)

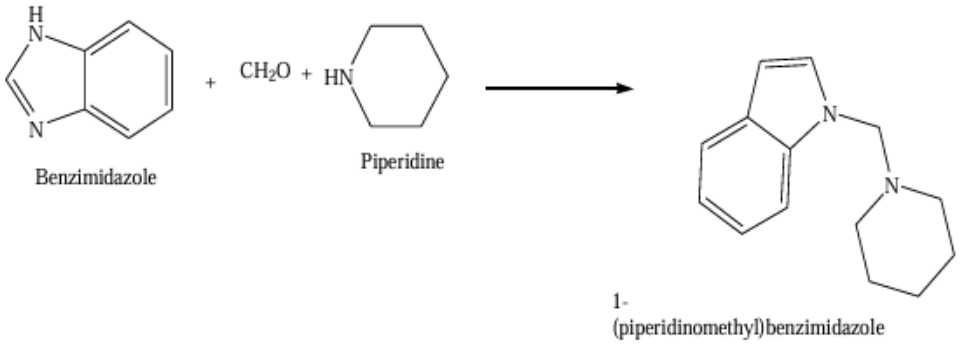


Figure 2.5: Synthesis of 1-(piperidinomethyl)benzimidazole

It is important to note that using primary amines or replacing formaldehyde with higher aldehydes will make this reaction impossible.

2.6 Reaction of Benzimidazole with Metals

Zinc, mercury, cadmium, cobalt, nickel, copper, and silver are among the metals that combine with benzimidazoles to produce salt. It was initially demonstrated by Lorenzen and Bamberger that metals may substitute the acidic hydrogen at position 1 to create benzimidazole salts. Additionally, it was demonstrated that 2-methoxymethylbenzimidazole, 2-phenoxymethylbenzimidazole, and 2-ethoxymethylbenzimidazole generated silver and mercury salts. However, due to the absence of hydrogen at the first position, 1-benzylbenzimidazole, 1,6-dimethylbenzimidazole, and 1-benzylbenzimidazole do not form salts with silver, zinc, cobalt, cadmium, and copper. However, mercurous chloride was found in 1-1-phenylbenzimidazole and 1-tolylbenzimidazole salts.

For instance, 2-aminomethylbenzimidazole's coordination results in the combination below:

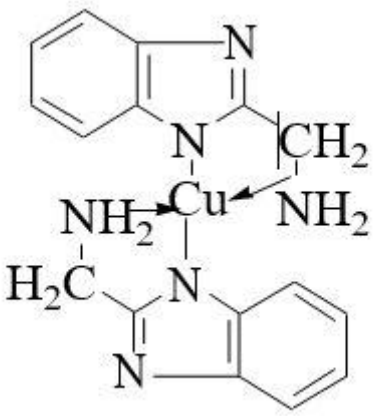


Figure 2.6 2-aminomethylbenzimidazole's coordination results

2.7 Acid base reactions

The title compound was obtained by the Verali-mer–Elmhirst method. 2-Aminomethylbenzimidazole HCl and 2-aminothiophenol were refluxed in ethanolic solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. The removal of the DDQ molecules after partition of the quinazoline nucleus is achieved in a reductive atmosphere under the use of ethanol.

Benzimidazole exhibits a basic, alkaline reaction on the nitrogen of the thymidine ring as well as other benzimidazole derivatives. These alkaline-halide reactions also yield bromides and iodide salts. The alkaline-halide methods used for its preparation are either of the commercially available 1,2-methylene chloride in methanol or two equivalents of hydrochloric acid in ethanol with potassium benzimidazole. (Henary et al.2020)

As demonstrated below, examples of such reactions include the reaction of benzimidazoles with bases like formaldehyde and primary or secondary amines.

a)

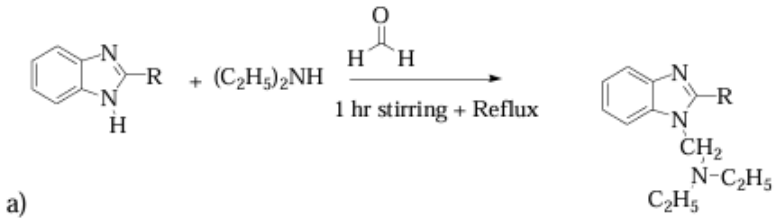


Figure 2.7: Reaction of 2-substituted benzimidazole with secondary amine andformaldehyde

b)

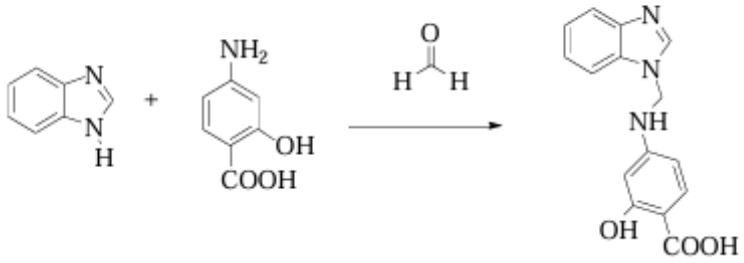


Figure 2.8: Reaction of 4-amino salicylic acid with benzimidazole andformaldehyde

c)

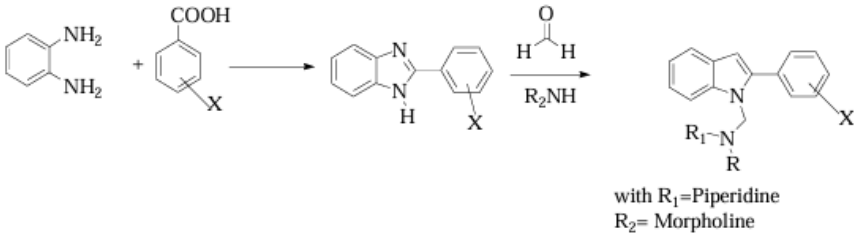


Figure 2.9: Reaction of 2-phenylbenzimidazole with formaldehyde and secondary amine

d)

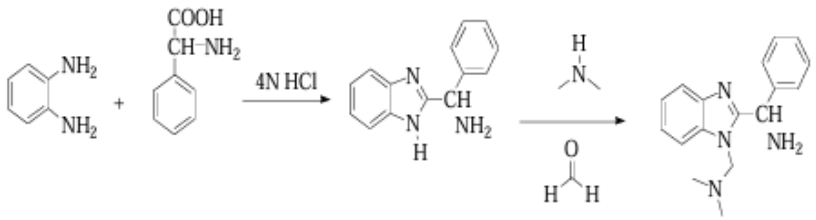


Figure 2.10: Synthesis of 1,2-Disubstituted Mannich base

In addition to this reaction, cleavage of the benzimidazoles may occur.

2.8 Cleavage of the Benzimidazoles

Benzimidazolyl polymers find numerous applications such as therapeutic agents for a broad spectrum of diseases, dyes, plasticizers, additives, glass poisons, mordants, and pH indicators. In addition, some benzimidazoles possess the interesting property of being cleaved by enzymes under physiological conditions. This property has led to their use as prodrug model systems and as carriers of drugs in several targeting strategies. Most of these examples describe the benefit of the incorporation of the benzimidazole in the active principal design and functionalities. However, this unit can also be used for the benzenoid leaving group attached to the inactive molecule. (Mahurkar et al.2023) The system can be obtained by cyclization of the deshydroxydipeptides and amides using a reagent. The addition of benzimidazoles in S2, under the same conditions, was not successful at all. In the current conditions, there is no joint release of the two oxazolidenol moieties since the stabilization of the neighboring anion system itself, through its intramolecular hydrogen bond, occurs to one inclusion per cycle. However, its release in alcoholic solution occurs quite well using the localization of the 3-hydroxy-1H-indole moiety and its removal from the vicinity of the phenolic group, from one inclusion to another. The cleavages of the benzimidazolyl unit followed well the absorption of UV light at 293 nm and depended on the system itself and the solvent propertie (Hernández-López et al.2022).

2.9 Halogenation of Benzimidazole

The introduction of halogen atoms into benzimidazole derivatives increases lipophilicity and general biological activity in line with its cellular accumulation. However, the replacement of hydrogen in benzimidazole compounds is relatively difficult due to the high reactivity of aromatic hydrogen. Halogenation occurs primarily at the benzimidazole C1 or N1, and N2 is often decreased. The C1 halogenation of the 2-alkyl benzimidazole compound at the C1 consists of multiple components in the solution, and the pure product can only be obtained by fractional crystallization. The first halogenation position was the C2 position of the benzimidazole, and multiple halogenation products were obtained. Later, the

halogenation of benzimidazole for the preparation of specific 2-halogen benzimidazole was also presented. (Faydalı & Arpacı, 2024)

The quantitative yield of 2-iodobenzimidazole is obtained by treating benzimidazole in aqueous solution with the theoretical amount of iodine (N/10) in the presence of sodium hydroxide. (Satija et al.2022)

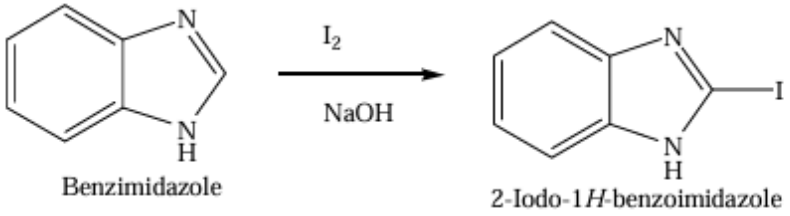


Figure 2.11: Halogenation reaction of benzimidazole

2.10 Nitration

The various nitration methods that are traditionally applied for nitration preparations lead to the introduction of highly reactive nitro groups to the aromatic or heterocyclic compound where substitution reactions or the generation of side products may occur in the preparation of 5-Nitro-1H-benzimidazole, traditional nitration methods often introduce highly reactive nitro groups into the aromatic or heterocyclic compounds, which can result in substitution reactions and the formation of side products. Typically, these reactions require multiple derivatization steps and extensive work-up processes to isolate a pure final product. However, the method described here is notably efficient, eliminating the need for purification of the intermediate alkylated benzimidazole derivative. (Zlotin et al.2020)

This reaction with benzimidazoles is a simple procedure. In most situations, nitration is seen at the 5- or 6-position. On the other hand, if it is inhibited, the nitro group can show up at benzimidazole positions 4- or 7-.

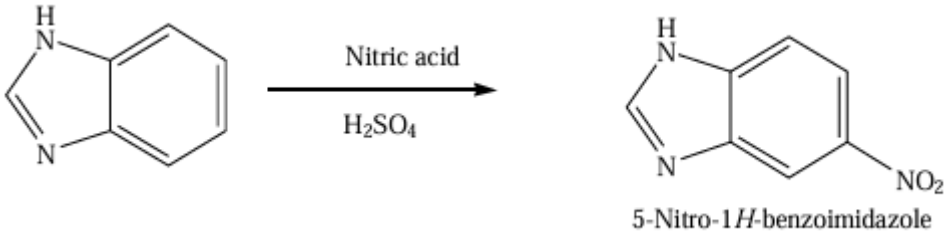


Figure 2.12: Nitration of benzimidazole

2.11. Mannich Reaction

The Mannich reaction is an organic reaction that consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group. The reaction is also a condensation. The precise reactants are usually a compound containing protons connected to a carbonyl (such as a ketone, aldehyde, or carboxylic acid) and ammonia, along with one or more aldehydes or ketones. The reaction of aldehydes with secondary amines, such as dimethylaniline, in the presence of acetic anhydride typically affords the N-substituted Schiff base. This product forms from nucleophilic addition of the amine to the carbonyl group, followed by a proton transfer. The aldimine condenses with a secondary amine and formaldehyde in a Mannich reaction. (Tokuhiro et al.2022)

The reaction forms the β-amino-carbonyl compound with two commonly used reactants, which are formaldehyde and dimethylaniline. The base-catalyzed reaction mechanism is related only to the catalysis. The first step involves the addition of dimethylaniline to formaldehyde, forming an imine. In the presence of base, the imine is doubly deprotonated, and the carbanion reacts with formaldehyde to form the enolate. This species then performs a nucleophilic addition to the carbon in the imine, forming a second anion. Protonation by the presence of base to displace the amine allows water to leave, thereby creating the Mannich product. (Faisca et al.2020)

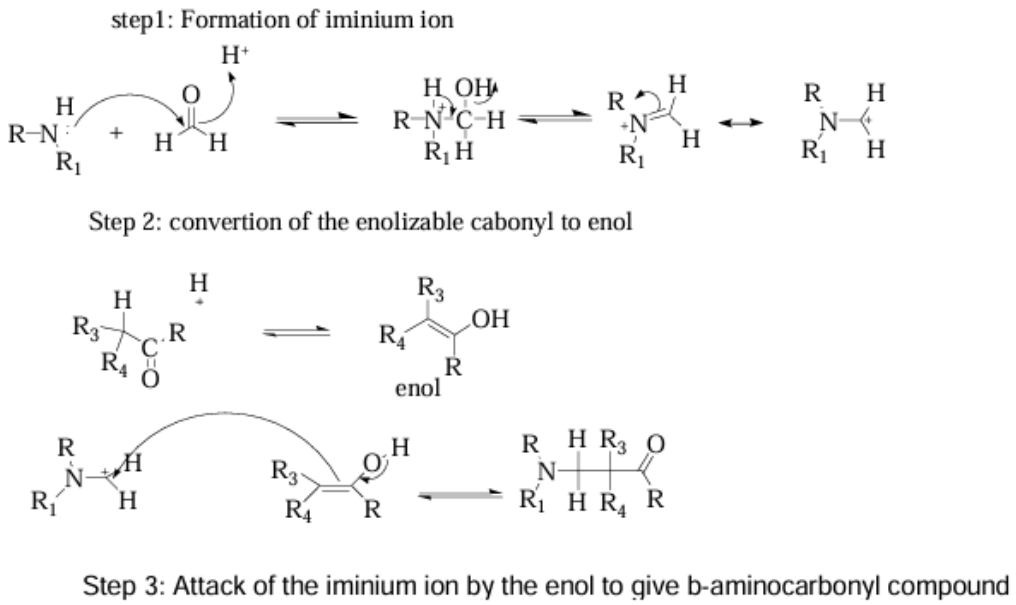


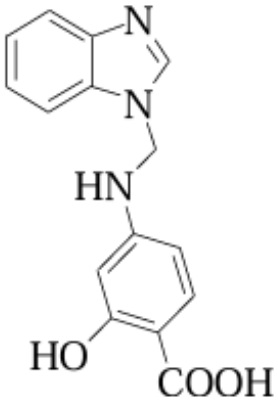
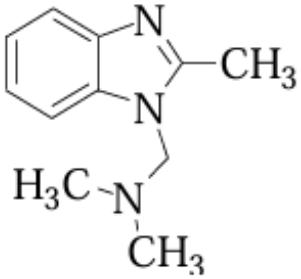
Figure 2.13: Mannich reaction mechanism

2.11.1 Some examples of Mannich bases

A series of substituted Mannich bases of benzimidazole were synthesized. These compounds were evaluated for their antimicrobial effects. The evaluation results were compared to a benzimidazole derivative. The results indicated that the newly synthesized compounds were effective against bacteria and yeast. Some compounds were more effective against some kinds of bacteria or both yeast when compared to the derivative. Newly synthesized compounds showed reduced antimicrobial effects on fungi when compared to the derivative. (Nashaan & Al-Rawi, 2023)

A specific benzimidazole derivative has been found to be effective against bacteria and some kinds of yeasts. In light of these data, it was planned to produce a benzimidazole precursor and to synthesize diverse substituted Mannich bases. Each synthesized compound structure was confirmed by various analytical techniques. This study is of the antimicrobial effects of Mannich bases; the results obtained in parallel with other data are reported. (Antolak et al., 2021)

Examples of Mannich bases that have been synthesized and shown to have biological action are displayed in the following table (Vinoth et al., 2013).

Structures	IUPAC Name	Use
	4-[(Benzimidazol-1-ylmethyl)-amino]-2-hydroxy-benzoic acid	Antimicrobial
	N, N-Dimethyl-1-(2-methyl-1H-benzimidzol-1-yl) methanamine	Antimicrobial

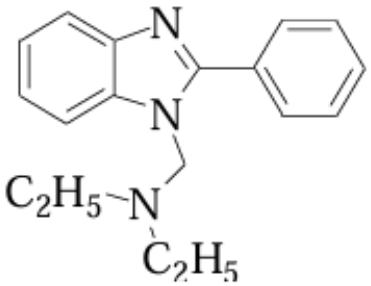
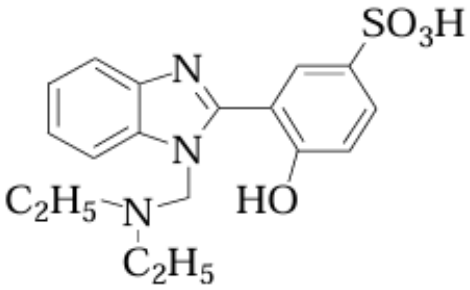
	N-Ethyl-N-[(2-phenyl-1H-benzimidazol-1-yl) methyl] ethanamine	Antimicrobial
	3-{1-[(Diethylamino) methyl] -1H-benzimidazol-2-yl}-4-hydroxy benzene sulfonic acid	Antifungal

Table 2.1: Mannich bases

2.12 Laboratory synthesis of benzimidazole

Benzimidazoles and their derivatives have attracted research interest due to their strong antiviral, antifungal, antivirus, and anthelminthic effects as important members of the azole family. Therefore, benzimidazoles possess excellent research value and are often utilized as the leading compound for the subsequent design and synthesis of azole derivative libraries in various pharmaceutical research fields. At present, benzimidazole derivatives are being used widely in antiviral, anticancer, and antibiotic research as they have a broad range of biological activities. The synthesis of average benzimidazoles has a number of disadvantages such as low selectivity, long reaction periods, low yield, high price, and poor conversion rates. (Das et al., 2021)

The synthetic pathways to benzimidazoles include traditional preparation, which consists of nitrating, nitrosation, and chlorination due to their strong dehydrogenation amidating activity. The following is the benzimidazole synthesis equation, according to Wagner and Miller (1939):

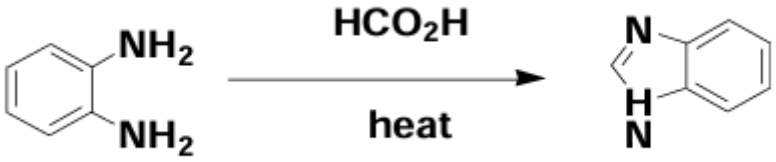


Figure 2.14: Synthesis of benzimidazole

2.13. Pharmacological Activities of Benzimidazoles

A benzimidazole is a heterocyclic aromatic organic compound. It is similar to benzene, except that two nonadjacent carbon atoms are replaced by nitrogen atoms. The chemical formula is C7H6N2. The carbon-nitrogen-carbon angles are approximately 120°. The simplest member of the benzimidazole family is benzimidazole itself. Benzimidazoles have recently attracted considerable attention due to their diverse and promising pharmacological activities. (Mohapatra & Ganguly, 2024)

Benzimidazoles and their derivatives are significant building blocks in the pharmaceutical industry due to their strong biological activity (Daw et al., 2017). Table 2 below illustrates the range of bioactivities that have resulted from the ability to arrange substituents on different positions of the benzimidazole nucleus. The benzimidazole moiety's structural resemblance to naturally existing nucleotides is another significant characteristic that makes it preferred. This enables it to detect biopolymers found in the human body, including proteins, enzymes, and receptors (PRESTON, 1974). The biological activities of benzimidazole derivatives have also been the subject of extensive research by numerous medicinal chemists. The pharmacophore has been extensively studied in medicinal chemistry and shown to have uses in a variety of therapeutic and clinical domains (Rashid, 2011). Additionally, a significant pharmacophore in contemporary drug research is the benzimidazole skeleton.

Its byproducts are significant bioactive compounds. Currently, medications like thiabendazole and mebendazole are used as antifungal and anthelmintic treatments (Li et al., 2019).

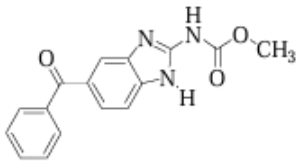
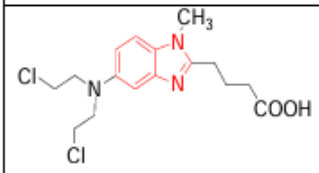
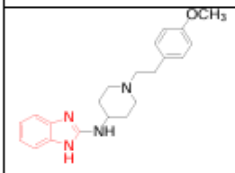
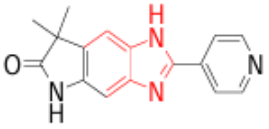
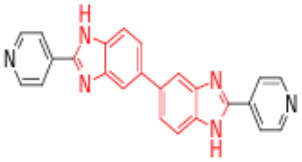
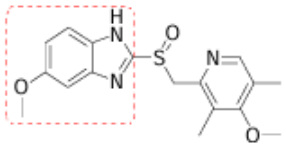
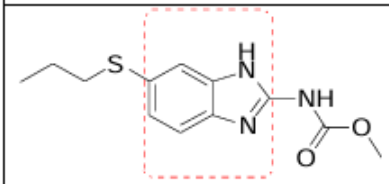
Drug structure	Name	Use
	**Mebendazole**	Worm infections
	**Bendamustine**	For the treatment of cancer
	**Astemizole**	For the treatment of allergic rhinitis
	**Adibendan**	For the treatment of patients with severe congestive heart failure (Voelker et al., n.d.)
	**Ridinazole**	For the treatment of bacterial infections
	**Omeprazole**	Gastric ulcer
	**Albendazole**	Anthelmintic

Table 2.2: Clinical used drugs with benzimidazole moiety Source : (Salahuddin et al., 2017)

Proton pump inhibitors, anthelmintics, anticancer (Hameed et al., 2019), anti-inflammatory, and antihypertensive medications are some of their therapeutic actions. Derivatives of benzomidazole have sparked a lot of interest in the medical field. It has been demonstrated that 2-substituted benzimidazoles and N-Mannich bases of different heterocyclic compounds had both anti-inflammatory and analgesic qualities among the many compounds created as anti-inflammatory and analgesic medicines (Jesudason et al., 2009). Numerous benzimidazole compounds have also been used as therapeutic medications or as prospects for the treatment of different kinds of illnesses. These include antiviral (Samatasvir), anticancer (Pracinostat, Bendamustine), antihistamine (Astemizole) (Richards, 1984), anthelmintic (Albendazole, Mebendazole), antibacterial (Ridinazole), antihypertensive (Candesartan), proton pump inhibitors (Pantoprazole, Omeprazole), antiviral (Samatasvir), and phosphodiesterase inhibitors (Adibendan).

2.13.1. Antimicrobial Structural Activity Relationship of benzimidazoles

Sahoo et al. (2019) define the structural activity relationship (SAR) as the connection between a drug molecule's chemical or three-dimensional structure and its biological activity. It is predicated on changing the structure of the medicine to change its action or boost its potency. When a medication can stop the growth of bacteria, protozoa, helminthes, fungi, and viruses, it is said to have antimicrobial activity. Researchers began creating antibacterial medications from the benzimidazole nucleus after the year 2000. in order to create powerful antibacterial and antifungal medications. For example, they joined the β-lactam ring to 2-alkylthiobenzimidazole.

Benzimidazoles have been shown to be inhibitory for Helicobacter pylori; other benzimidazole derivatives have been shown to have antibacterial activity against a number of gram-positive and gram-negative bacteria, and some of these derivatives have shown similar or better activity than those of metronidazole and ciprofloxacin. The presence of a quinone type of ring in the side chain of the compound could provide an effective structure capable of expressing maximum antibacterial properties. (Marinescu, 2021)

An agent that is cost-effective and able to cure infections caused by some pathogenic organisms is currently an urgent requirement. In recent years, it has been found that bacterial pathogens are evolving and becoming resistant. At present, the development of new benzimidazole moieties is research that could be a potent multi-target scaffold-based approach to direct inhibitors. Benzimidazole moieties, when subjected to antimicrobial, antifungal, anticancer, antiviral, and anthelmintic positive organic molecules, have been demonstrated to have different pharmacological activities. (Veerasamy et al., 2021)

Additionally, they discovered that the compounds with substitution on both the 1 and 2-positions were the most effective among those derived from the benzimidazole.

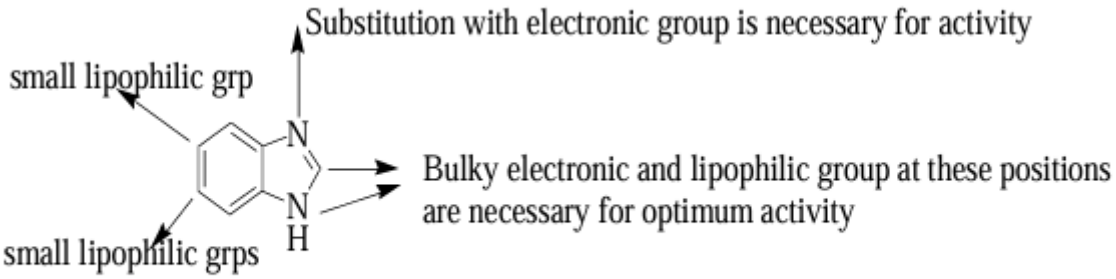


Figure 2.15 Antimicrobial SAR of benzimidazole

Some small electronic groups include halogens, nitro, amino, methyl and arylalkyl groups. (Singh & Silakari, 2018b)

3. MATERIALS AND METHODS

The design of this study was underpinned by contributions from several individuals who undertook the synthesis and characterization of benzimidazole derivatives.

3.1. Materials

Sigma Aldrich Chemical Co. provided the ingredients utilized in organic synthesis, and the Mettler Toledo FP 900 Thermo System instrument was used in the lab to monitor the melting temperatures of the molecules.
A Perkin Elmer Spectrum 100 spectrophotometer was used to analyze the produced molecule's attenuated reflection from infrared spectroscopy, which is displayed in wave numbers (cm^{-1}). Using tetramethylsilane as a reference solution, the proton nuclear magnetic resonance spectra of each molecule was analyzed using a Mercury Varian 400 MHz NMR apparatus. Dimethylsulfoxide ($CDCl_3$) and deuterated chloroform were appropriate solvents for the analysis. The chemical shifts (δ) of the various proton types on the structure were measured in parts per million (ppm). The thin layer chromatography technique was applied to silica gel GF 254 to purify the chemicals. (DC: Germany's Alufplien-Kieselgel)

3.2. Synthesis of (2,6-Dichloro phenyl piperazine) benzimidazole

Twelve milliliters of ethanol were used to dissolve 500 mg (0.004 mol) of 1H-benzimidazole and 690 mg (0.004 mol) of 1-(2,6-dichlorobenzyl) piperazine. Before being added to the benzimidazole solution, 0.3 mL of a 35% (w/v) formalin solution was dissolved in 3 ml of ethanol. After that, the mixture was refluxed for three hours in a water bath. When the mixture was finished, it was poured upon crushed ice, causing a precipitate to develop. The vacuum filtration method was used to filter the resultant solid. The product was observed by TLC, and acetonitrile recrystallization was used to purify the white precipitate that resulted.

3.3 Spectroscopy

Every spectrometric analysis was carried out at Ankara University's Central Laboratory in Turkey. Each manufactured molecule's attenuated reflection was analyzed via infrared spectroscopy using a Perkin Elmer Spectrum 100 spectrophotometer, which displays wave numbers (cm^{-1}). Each molecule's proton and

carbon nuclear magnetic resonance spectra were analyzed using a Mercury Varian 400 MHz NMR instrument with deuterated chloroform ($CDCl_3$) as the solvent.

3.4. Microbiology

3.4.1. Antibacterial Activity Testing:

The antibacterial activity of the synthesized benzimidazole derivative was evaluated against Enterococcus faecalis (ATCC strain). The compound was dissolved in dimethyl sulfoxide (DMSO) to prepare a stock solution and subsequently diluted to a final concentration of 100 µM for testing.

3.4.2. Agar Well Diffusion Assay:

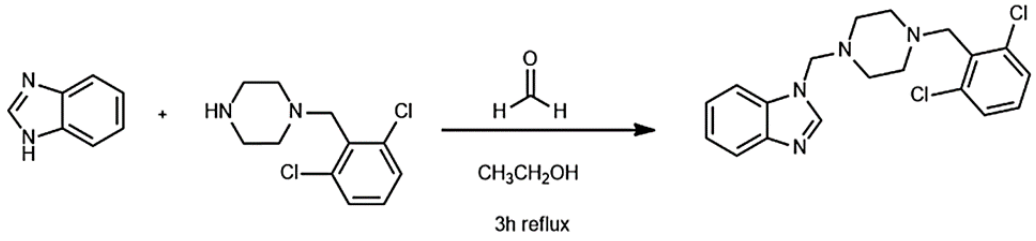
Agar plates were inoculated with E. faecalis suspension (0.5 McFarland standard). Wells were created on the agar, and 100 µL of the 100 µM compound solution was added to each well. Plates were incubated at 37°C, and inhibition zones were measured at 24, 48, and 72 hours. All experiments were performed in triplicate, and the results were statistically analyzed ($p < 0.005$).

3.4.3. Determination of Minimum Inhibitory Concentration (MIC):

The MIC value of the compound was determined using the broth microdilution method. Serial dilutions of the compound were prepared in Mueller-Hinton broth (concentration range: 100 to 0.39 µg/mL). E. faecalis cultures were inoculated into each well and incubated at 37°C for 24 hours. The MIC was defined as the lowest concentration of the compound that inhibited visible bacterial growth. The experiment was repeated in triplicate to ensure reproducibility.

4. RESULTS and DISCUSSION

4.1. Synthesis scheme



4.2. Chemical information of the synthesized compound

Yield (%): 85%

For TLC (Thin Layer Chromatography) Stationary phase:

Silica gel GF 254

Mobile Phase:

1.Hexane (3): Methanol (1) with Rf1=0.56

2.Hexane (3): Ethylacetate (5) with Rf2= 0.3

Physical Appearance: white crystalline powder Solubility:
Completely soluble in chloroform and DMSO.

4.3. Nuclear Magnetic Resonance Results

1-H NMR: δ 2.50-2.67 (8H, 2.58 (ddd, J = 15.6, 6.7, 2.5 Hz), 2.59 (ddd, J = 16.1, 6.7, 2.5 Hz)), 3.89 (2H, s), 5.02 (2H, s), 6.90-7.09 (2H, 6.96 (td, J = 7.7, 1.2 Hz), 7.02 (ddd, J = 7.9, 7.6, 1.3 Hz)), 7.26 (2H, dd, J = 8.3, 1.5 Hz), 7.39 (1H, t, J = 8.3 Hz), 7.62-7.79 (2H, 7.68 (ddt, J = 7.9, 1.2, 0.5 Hz), 7.73 (ddt, J = 7.7, 1.3, 0.5 Hz)), 7.90 (1H, t, J = 0.5 Hz).

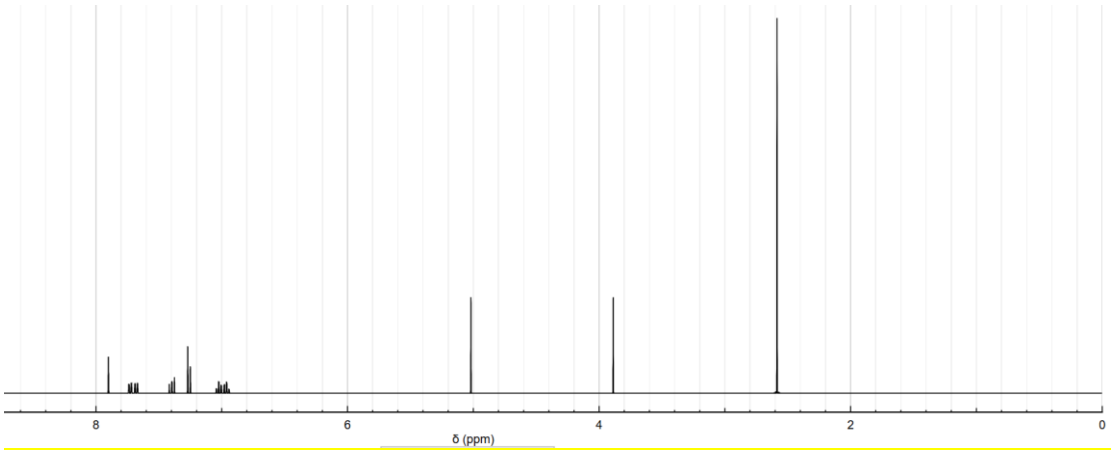


Figure 4.1: ^{1}H-NMR spectra of synthesized benzimidazole derivative.

The reaction involves the synthesis of a compound through the condensation of benzimidazole with a substituted chlorophenyl-piperazine derivative in the presence of formaldehyde under reflux conditions in ethanol for 3 hours. The mechanism likely follows a Mannich-like condensation process, where the benzimidazole nitrogen reacts with formaldehyde to form an iminium intermediate. This intermediate is subsequently attacked by the nucleophilic piperazine derivative, leading to the formation of a C-N bond and the final product.

The structure of the product features a benzimidazole moiety linked via a methylene (-CH_2-) bridge to the piperazine derivative, which is substituted with chlorophenyl groups. The NMR data provided earlier supports the successful synthesis of this compound. Key signals in the aromatic and aliphatic regions of the spectrum are consistent with the expected structure, confirming the integrity of the product.

The reaction conditions are carefully optimized, with ethanol serving as the solvent to facilitate mixing and ensure smooth progress of the condensation reaction. Refluxing the mixture for 3 hours at an elevated and constant temperature enhances the reaction rate and ensures the complete formation of the product.

This synthesis has potential applications in the development of biologically active compounds, as it incorporates pharmacophores like benzimidazole and chlorophenyl groups. These moieties are often found in antimicrobial, anticancer, and CNS-active agents, suggesting that the compound may possess significant pharmacological potential. Further characterization using techniques such as IR and MS could provide additional confirmation of the product's structure and its potential activity.

4.4. Antimicrobial Activity Results

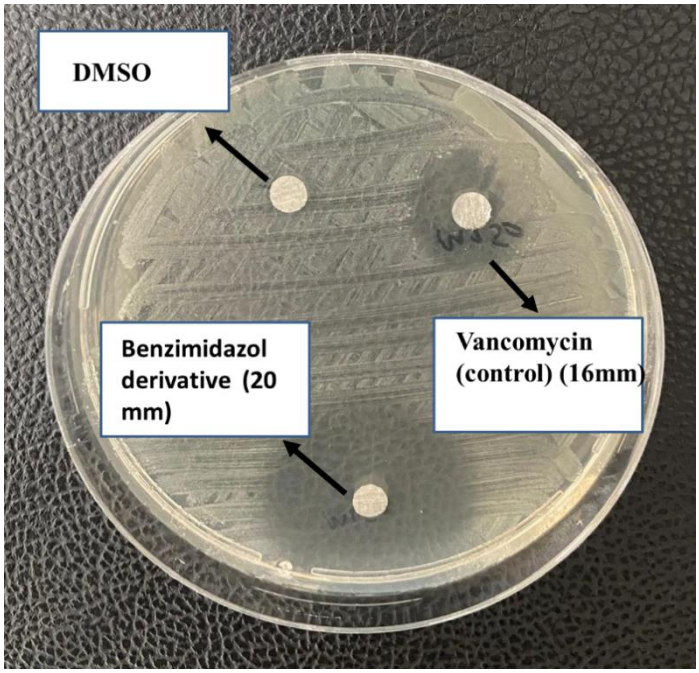


Figure 4.2: *The zone of inhibition results of synthesized benzimidazole derivative. 100 µM benzimidazole derivative produced a 19 mm inhibition zone on E. faecalis at 24 hours; at 48 and 72 hours, it was observed to be 20 mm ($p < 0.005$). Additionally, the compound demonstrated a significant MIC value of 6.25 µg/mL, indicating strong antibacterial activity.*

5. CONCLUSION

The synthesized benzimidazole derivative demonstrated promising antibacterial activity against Enterococcus faecalis. The compound produced a notable inhibition zone of 19 mm at 24 hours, which increased to 20 mm at 48 and 72 hours, indicating sustained antibacterial effects. Furthermore, the compound exhibited a significant MIC value of 6.25 µg/mL, highlighting its potency as an antimicrobial agent. These results suggest that the benzimidazole derivative could serve as a potential candidate for further development as an antibacterial drug. Future studies should focus on exploring its mechanism of action, evaluating its activity against a broader range of bacterial strains, and assessing its pharmacokinetic and safety profiles to establish its therapeutic potential.

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