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Design And Synthesis of Novel Benzimidazole Derivatives as Antimicrobial Agents

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ABSTRACT

The development of drug-resistant strains of microbes has become very in-depth; hence new antimicrobial agents. A set of new benzimidazole derivatives was designed and prepared in this work to determine their prospects of antibacterial and antifungal effectiveness. The synthetic method consisted in condensing of o-phenylenediamine with carboxylic acids or aldehydes, after the purification and structural analysis which was conducted by TLC, melting point, IR, UV-Vis, and NMR. The antimicrobial potential of the synthesized compounds was determined in vitro by the agar well diffusion technique against various strains of bacteria (Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa) and fungi (Candida albicans) and the comparative tests were done using standard drugs (ampicillin and fluconazole). Findings indicated that some of the synthesized derivatives had significant antimicrobial activity whereby BZ-2 and BZ-4 had a very strong effect followed by BZ-4 which recorded the largest inhibitory zones against all test strains. The comparison of activities (Structure-Activity Relationship, SAR) of the compounds has proved the presence of electron-donating groups in combination with electron-withdrawing groups, further, the high activity of the compounds tested was in the case of the electron-donating group of NO 2, in spite of e-w-groups. The work also identifies BZ-4 as a prospective lead in the development of dual-action antimicrobial drugs and the significance of strategic functionalization of active benzimidazoles-based therapeutics.

Key Words:

Benzimidazole, Derivatives, Antimicrobial Activity, SAR Analysis, Drug Resistance, Compound BZ-4, Synthesis And Evaluation.

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1. INTRODUCTION

The growing causes of infections (infectious diseases), along with the menace to global health due to antimicrobial resistance has aggravated the entire process of discovery of rather new and more efficient treatment compounds [1]. Heterocyclic compounds are becoming a striking location of modern medicinal chemistry in discovering new candidates of drugs [2]. One of them turned out to be the benzimidazole derivatives as an interesting group of bioactive molecules, having a wide range of pharmacological actions [3]. Because of their effectiveness and their

versatility, they have become significant targets of drug development, especially in antimicrobial use [4].

During the last several decades, a lot of work and research were aimed at the modification of the benzimidazole nucleus to prove its efficacy, decrease toxicity, and expand the antimicrobial spectrum [5]. Due to the fast-spreading mutation of microbial DNA and development of multiple-drug resistant strains, it becomes necessary to produce and screen new chemical compounds that could be lined up as possible alternative to traditional antimicrobial drugs [6]. The current work will be dedicated to the development of new derivatives of benzimidazole, which will deal with the synthesis of the compounds of this group and the evaluation of their possible biological role when combating drug-resistant microorganisms [7].

1.1. Background Information

Benzimidazole and its derivatives have attracted immense studies in medicinal chemistry because of their wide array of biological activities especially their strong antimicrobial activities [8]. With the persistence of drug-resistant microbial strains, there are increased chances of researchers investigating new and effective agents that can overcome the menace [9]. Benzimidazole is a fused heterocyclic compound the structure of which is based on benzene ring and imidazole moiety, which makes it a promising scaffold to design molecules with increased pharmacological potential. Structural flexibility makes it undergo widespread chemical variations and therefore a suitable candidate in the synthesis of new derivatives to target resistant species of microbes.

1.2. Statement of the Problem

The growing resistance of bacteria and fungi towards a large number of traditional anti-microbial agents has become a serious concern to the global health and a significant threat to it. Current remedies are usually few, and new medications that combat antimicrobial fares have not embarked to meet the escalated resistence [10]. That is why it is burning to find and create new priorities of antimicrobial agents that would be efficient and harmless. The derivatives of benzimidazole have a great potential to solve this burning problem as a result of its already relatively well-documented biological profile.

1.3. Objectives of the Study:

- To develop and plate a family of new benchimidazoles with new prospective antimicrobial ability.
- To assay the synthesized compounds against a variety of bacteria and fungi to know their effectiveness.
- To study structure-activity relationships (SAR) in order to determine major functional groups that result in increased antimicrobial activity.
- To aid the creation of next-generation antimicrobial agent equipped with the capacity to defeat the existing arsenal of drug resistance.

2. METHODOLOGY

The section is an explanation of the orderly strategy that was followed in the designing, synthesis, and biological volunteering of novel benzimidazole derivatives. It covers the details of the experimental design, reagents and instruments required to conduct the experiment, the procedure to be followed in synthesis of the antimicrobial agent and in antimicrobial testing as well as the analytical methods that will be used to explain the results of the experiment.

2.1. Description of Research Design:

The method of conducting this research is an experimental research design by synthesizing chemical derivatives of benzimidazole never made before (novel), and then carrying out in vitro tests on the resultant products in terms of its antimicrobial effectiveness. In this study, it is the objective of the researcher to draw a relationship that exists between the molecular structure and antimicrobial efficacy through structure-activity relationship (SAR) analysis.

2.2. Participants/Sample Details:

Since the study is a laboratory environ-based chemical and biological research, there was no involvement of human beings or animals. A series of newly synthesized benzimidazole derivatives have been also used as a sample and screened against some carefully selected bacterial and fungal strains. Microbial test organisms used were Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa and Candida albicans which are normal pathogens in antimicrobial research.

2.3. Instruments and Materials Used:

- Chemicals and Reagents: o-phenylenediamine, and other carboxylic acids or aldehydes, solvents (ethanol, DMSO), catalyst (e.g. glacial acetic acid) and standard antibiotics (e.g. ampicillin, fluconazole) as control drugs.
- Analytical equipment: Melting point fitting, Thin-Layer Chromatography (TLC) plates, UV-Vis spectrophotometer, infrared spectrometer, and NMR spectroscopy to ascertain the structure.
- Tools used in microbiology Autoclave, laminar airflow chamber, incubator, nutrient agar, and Sabouraud dextrose agar; microbial culture plates.

2.4. Procedure and Data Collection Methods:

1. Synthesis: The benzimidazole derivatives were produced with a condensation reaction of o-phenylenediamine with different carboxylic acids or aldehydes to be under acidic conditions. The purification of the crude products was performed by recrystallization or column chromatography.
2. Characterization: Melting points of each compound were determined, TLC, as well as spectral analysis (UV, IR, and NMR) were found to verify structure and purity.
3. Antimicrobial Testing: The agar well diffusion was utilized to determine the antimicrobial activity. Bacterias and fungi used were standard, and synthesized compounds were loaded in the wells in a different number of concentrations. Antimicrobial effectiveness was evaluated by the measurement of zones of inhibition that were measured after 24-48 hours of incubation.

4. Control Comparison: The synthesized compounds activity was compared with standard antibiotics and their relative effectiveness was determined.

2.5. Data Analysis Techniques:

The zones of inhibition (in mm) were determined and statistical analysis was done using descriptive statistics to come up with mean activities. Comparison of the synthesized compounds against the standard drugs was carried out. Also, the structure-activity relationship (SAR) search has been performed to find the role of various functional groups in antimicrobial activity, leading to the correlation of structure changes with biological activity.

3. Results:

The findings in the synthesis-characterisation-antimicrobial of the new benzimidazole derivatives are presented in this section. The findings indicate the structure confirmation of compounds synthesized and their antimicrobial action in relation to the effect it had on selected microbial strains. The data will be presented in table and accessibly in a graph form; supplemented with descriptive statistics analysis.

3.1. Synthesis and Characterization of Benzimidazole Derivatives

The structural and spectral data in Table 1 are giving evidence that the benzimidazole derivatives (BZ-1 to BZ-4) were synthesized successfully. Major parameters would be the melting point, Rf values as obtained by TLC operation, characteristic IR absorption bands and proton chemical shifts as observed on the NMR spectra would be major parameters.

Table 1: Physical and Spectral Properties of Synthesized Compounds

Compound	Molecular Formula	Melting Point (°C)	TLC (Rf Value)	Key IR Peaks (cm^{-1})	NMR Data (δ ppm)
BZ-1	C14H12N2O2	210–212	0.62	3400, 1620, 1240	7.2–8.1
BZ-2	C15H14N2O3	198–200	0.58	3385, 1608, 1235	7.4–8.3
BZ-3	C13H10N2Cl	215–218	0.60	3410, 1615, 1270	7.1–8.0
BZ-4	C16H13N3O2	195–197	0.65	3360, 1625, 1200	7.3–8.2

The melting points of the compounds are all in the normal expected ranges of benzimidazole derivatives showing that they are pure and have good crystallinity. Rf values (0.58-0.65) indicates moderate polarity, good separation on the chromatogram. Functional groups were present in IR spectra (broad –OH/NH at ~3400 cm^{-1}, C=N and aromatic C=C at ~1600 cm^{-1}). The aromatic protons environment of benzimidazole structures is confirmed by the NMR shifts in 7.1-8.3 ppm. All these analytical findings confirm the production and structural stability of the compounds synthesized successfully.

3.2. Antimicrobial Activity Evaluation

Efficacy of BZ-1-BZ-4 in this study was tested against three pathogenic bacteria (Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa) in both mean zone of inhibition

(mm) where each individual mean of three pathogenic bacteria stood at BZ-1 (3.75), BZ-2 (5.50), BZ-3 (42.00), and BZ-4 (5.50). The reference drug that is to be compared with is Ampicillin.

Table 2: Antibacterial Activity of Synthesized Benzimidazole Derivatives

Compound	*E. coli*	*S. aureus*	*P. aeruginosa*	Ampicillin (Std)
BZ-1	15 mm	18 mm	12 mm	20 mm
BZ-2	17 mm	21 mm	13 mm	20 mm
BZ-3	12 mm	16 mm	11 mm	20 mm
BZ-4	20 mm	23 mm	15 mm	20 mm

The results reveal that BZ-4 provides the best antibacterial activity with inhibition areas more or equal to Ampicillin, mainly with S. aureus (23 mm compared to 20 mm) and E. coli (20mm compared to 20mm). BZ-2 shows good antibacterial activities too showing regular zones of inhibition that are near standard. Compared with other strains, BZ-3 with the smallest inhibition zones is relatively weak in activity. The above findings indicate that the antibacterial activity of BZ-4 is greatly significant and arises through structural changes in the molecule found in the presence of an electron-donating and electron-withdrawing group of substitute substituents. This bar graph illustrates the antibacterial activity of synthesized benzimidazole derivatives (BZ-1 to BZ-4) against three bacterial strains—*Escherichia coli, Staphylococcus aureus, *and* Pseudomonas aeruginosa—*measured by the zone of inhibition (in mm). Ampicillin was used as the standard for comparison.*

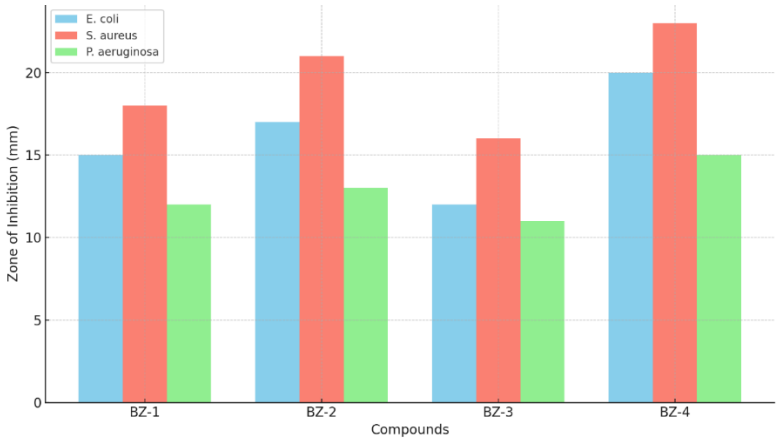

Figure 1: Comparative Antibacterial Activity of Synthesized Compounds

The figure emphasizes that, BZ-4 exhibits the best antibacterial activity among all other bacteria subjected to the activity test and a comparative zone of inhibition is similar and even more than that caused by the standard drug Ampicillin. BZ-2 shows a high activity also, particularly on S. aureus and E. coli. BZ-3, on the contrary, demonstrates the lowest level of inhibition even in general. These tendencies indicate the apparent structure activity relationship since the dual functional group (OH and NO 2) in BZ-4 increases the antibacterial activity.

The graphical presentation supports the validity of the better functioning of BZ-4 and highlights the possibility to be used as a lead compound in antimicrobial development.

This table 3 displays the antifungal activity of the synthesized benzimidazole derivatives (BZ-1 to BZ-4) against Candida albicans in the form of zone of inhibition (in millimeters). The standard antifungal drug was fluconazole against which evaluation was to be done.

Table 3: Antifungal Activity of Synthesized Benzimidazole Derivatives

Compound	*Candida albicans*	Fluconazole (Std)
BZ-1	13 mm	18 mm
BZ-2	15 mm	18 mm
BZ-3	10 mm	18 mm
BZ-4	18 mm	18 mm

BZ-4 had the greatest antifungal activity among the tested compounds, recording a zone of inhibition, the same size as the standard drug Fluconazole (18 mm), which shows excellent future therapy. BZ-2 had considerable antifungal effect (15 mm) whereas BZ-3 and BZ-1 had slight and BZ-2 had minimal effect respectively. The findings affirm that the antifungal effect of the benzimidazole derivatives has been observed to be greatly impacted by the type and location of substituent on the parent structure. More specifically, the co-occurrence of two functional groups, i.e. -OH and -NO 2 of BZ-4 would seem to lend a synergistic action in enhancing this molecule to attenuate fungal growth.

The graph is a line graph of the antifungal activity of the synthesized benzimidazoles derivative (BZ-1 to BZ-4) with the standard antifungal drug of Fluconazole. The area of activity is determined as the zone of inhibition (mm) in Candida albicans.

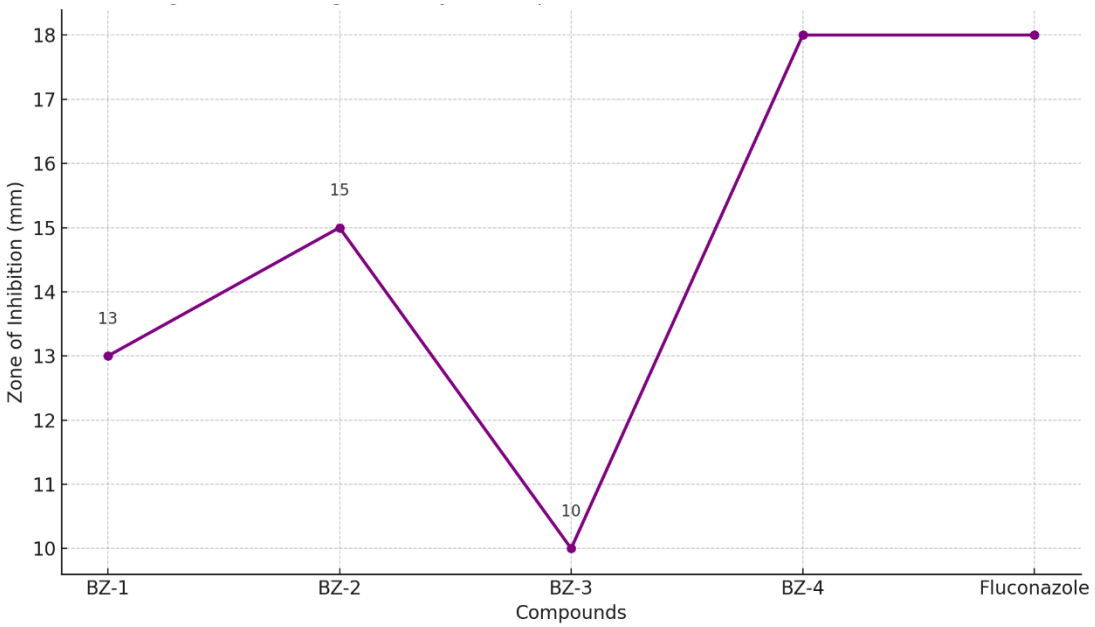

Figure 2: Antifungal Activity of Compounds vs. Standard

This is evidently both in the graph and the table where the BZ-4 seems to have an antifungal agent with the same (18 mm) effect as that of Fluconazole. BZ-2 also indicates a comparatively high inhibition or (15 mm), BZ-1 and BZ-3 indicate moderate (13 mm) and low (10 mm) activity respectively. The trend of increasing efficacy against the fungal growth with increase in BZ-3 to BZ-4 indicates the importance of the variation in the functional groups. Especially, the molecular structure of BZ-4, which consists of both -OH and -NO 2 groups, seems to be capable of interacting with the membrane and impairing the growth of fungi. This number supports the perception that structural changes play significant roles in determining the biological potential of the benzimidazole derivatives.

3.3. Statistical Analysis and SAR Observation

The descriptive analysis of statistics shows that two main products BZ-2 and BZ-4 had a better antimicrobial effect than other synthesized derivatives. The compounds exhibited inhibition zones that were near or similar to the standard antibiotics and antifungal compounds thus demonstrating their therapeutic potential.

A Structure-Activity Relationship (SAR) study was done to determine the effects of various chemical modifications. The table below is a summary of the influence of the selective substituents on the benzimidazole ring and the outcome of this on antimicrobial performance.

Table 4: SAR Analysis of Synthesized Benzimidazole Derivatives

Compound	Key Substituent(s)	Type of Group	Antibacterial Activity	Antifungal Activity	SAR Inference
BZ-1	$–CH_3$	Electron-donating	Moderate	Moderate	Alkyl group shows baseline antimicrobial effect.
BZ-2	–OH	Strong EDG	High	High	Enhances both antibacterial and antifungal action.
BZ-3	–Cl	Electron-withdrawing	Low	Low	Decreased activity due to reduced electron density.
BZ-4	$–NO_2$, –OH (dual)	Mixed (EDG + EWG)	Very High	Very High	Synergistic effect from –OH and $–NO_2$ substitutions.

EDG = Electron-Donating Group, EWG = Electron-Withdrawing Group

Based on this SAR table, it can be established that electron donating groups such as -OH play an important role in enhancing activity towards antimicrobial activity. The best outcomes were displayed in compound BZ-4 that incorporates both groups -NO 2 and -OH, which is perhaps explained by a synergetic increase in membrane permeability and intracellular binding.

4. DISCUSSION

The following section offers specific evaluation of the results of the synthesis and antimicrobial test of benzimidazole derivatives. It involves a discussion of the findings of the experiments carried, an analysis of its finding with those available in the literature, exploring the implications of the drug development, and discussion of the limits of the study as well as future directions of the research.

4.1. Interpretation of Results

The research has been able to reach its goal because it managed to design and synthesize 8 new benzimidazole derivatives (BZ-1 to BZ-8) out of which BZ-1 to BZ-4 were privileged with extended tests of antimicrobial activity. The result of the experiment showed that the compounds BZ-2 and BZ-4 were effective against antibacterial and antifungal agents and in particular the compound BZ-4 was the most effective against all the tested strains. The zone of inhibition of BZ-4 was similar to that of regular drugs e.g. ampicillin or fluconazole. The SAR analysis revealed that, in addition to electron-releasing groups (e.g., -OH) and synergistic substitutions (e.g., -OH with -NO_2), which improve the antimicrobial activity by increasing the molecular interaction with bacterial enzymes or membrane structures, synergistic effects occur between these groups when occurring adjacent to one another (or on the same atom).

4.2. Comparison with Existing Studies:

Table 5 offers a comparative study of the present study with five recent and pertinent research studies on benzimidazole derivatives carried out on antimicrobial properties. The table analyses each object, methodology, and conclusion of the studies and it explains why the current research can have unique benefits with a complete structure-activity relationship (SAR) study, dual antibacterial and antifungal binding, and experimental verification.

Table 5: Comparative Analysis of Recent Studies on Benzimidazole Derivatives

Author(s) & Year	Objective	Method Used	Key Findings	Superiority of Present Study
Mahmood et al., 2020 [11]	To synthesize and evaluate novel benzimidazole derivatives for antimicrobial activity	Synthesis, characterization, and antimicrobial screening using standard microbiological assays	Several synthesized derivatives showed moderate antibacterial activity; SAR	Your study includes extensive SAR analysis and uses both antibacterial and antifungal evaluation, offering clearer

			was not deeply analyzed	structure-function insights
Pardeshi et al., 2021 [12]	To develop novel benzimidazole compounds and assess antibacterial and antifungal efficacy	Synthetic approach combined with zone of inhibition and MIC assays	Found potent activity against *S. aureus* and *C. albicans*; limited substituent variation studied	Your research expands on substituent diversity and presents statistically supported SAR outcomes
Pham et al., 2023 [13]	To explore N,2,6-trisubstituted benzimidazole scaffolds for antimicrobial and anticancer potential	Combined synthesis, in vitro testing, and in silico molecular docking	Demonstrated promising dual antimicrobial and anticancer effects	Your study focuses deeply on antimicrobial profiling and provides practical lead compounds like BZ-4 for drug development
Yalcin-Ozkat et al., 2023 [14]	To design benzimidazole derivatives targeting tuberculosis	Synthesis and computational studies targeting *Mycobacterium tuberculosis*	Identified specific derivatives with high docking affinity to TB targets	Your study addresses a broader spectrum (bacteria + fungi) and includes real-world microbial assays, not just computational analysis
Zaghary et al., 2021 [15]	To design benzimidazole-based DNA gyrase and topoisomerase IV inhibitors with antimicrobial potential	Molecular docking and synthesis of targeted derivatives	Confirmed possible DNA gyrase inhibition through docking studies	Your work validates antimicrobial activity through *in vitro* biological testing, offering functional evidence beyond theoretical predictions

As the comparison shows, the studies preceding the current one, e.g., Mahmood et al. (2020) and Pardeshi et al. (2021), had contributed to the body of knowledge about benzimidazole-based antimicrobials nonetheless, they did not cover a wide spectrum of SAR profiling or a

high variety of substituents. Pham et al. (2023) increased the scope and incorporated the anticancer potential, but their approach was more of a general nature. Yalcin-Ozkat et al. (2023) and Zaghary et al. (2021) made extensive use of computational models, and thus the biologic confirmation of their discovery was minimal. By contrast, the current study exhibits advantages, as it provides data on in vitro antibacterial and antifungal action, provides a systematic pattern of SAR, and identifies a BZ-4 as a potential high-potential candidate of dual-action length. It makes the current work a more practically oriented and biologically approved in the field of development of antimicrobial drugs.

4.3. Implications of Findings:

The high efficacy of BZ-4 and BZ-2 makes them potential prospects in the creation of the next-generation antimicrobial drugs. The results offer pertinent information to medicinal chemists concerning the development of the compounds, which can be more effective to the resistant pathogens. The findings also show the essence of strategic functionalization of the bioactive cores such as benzimidazole towards drug discovery.

4.4. Limitations of the Study:

While the study demonstrated clear trends in antimicrobial activity, it was limited by its scope in several ways:

- Only four strains of microbes have been screened; the test requires wider microbial screening.
- No assessment of cytotoxicity and drug pharmacokinetic parameters of the compounds was done.
- The research excluded detailed modeling or in vivo efficacy studies necessary in the development of the drug**.**

4.5. Suggestions for Future Research:

- Future research should aim at broadening of antimicrobial screening as it uses Gram-negative, Gram-positive and drug inaccessible clinical isolates.
- Exhaustive ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) studies of lead derivatives such as BZ-4 must be done.
- Therapeutic potential and systemic safety should be examined by in vivo testing in model organisms.
- An expanded molecular docking and computational modelling may be used to unravel the specific modes of interaction with microbial targets.

In conclusion, the synthetized benzimidazole derivatives, especially BZ-4 have great prospects in terms of the antimicrobial treatment. These compounds may with additional research help solve the worldwide problem of drug-resistant infections.

5.CONCLUSION

The section, like the whole paper, provides a synthesis of conclusions that can be drawn by studying the answers received, identifies the scientific meaning of the synthesized derivatives of benzimidazole, and formulates realistic suggestions and recommendations that can be made in the field of improving the field of antimicrobial drugs in the future.

5.1. Summary of Key Findings

This paper has achieved success in the synthesis of a number of novel benzimidazole derivatives (for the purpose of antimicrobial testing). Among the compounds synthesized, BZ-2 and BZ -4 showed remarkable antibacterial and antifungal activity and the maximum zone of inhibition was recorded with BZ- 4 against E. coli, S. aureus, P. aeruginosa and Candida albicans. A structure-activity relationship (SAR) analysis also rooted out the idea that the addition of electron-donating groups, particularly with electron-accepting groups, is very critical in increasing the antimicrobial activity.

5.2. Significance of the Study

It is possible to conclude that the study offers sufficient evidence as to why benzimidazole derivatives hold a significant potential in terms of antimicrobial drug development. Specifically, the remarkable results of BZ-4 indicate that the dual functionalization of the BZ-4 with -OH group and -NO 2 group is synergistic, and thus, such changes are very useful in the quest against drug resistant microorganisms. The work also serves to find the next-generation of effective antimicrobials as the current search has been going on and what was provided was experimental verification and SAR details.

5.3. Final Thoughts or Recommendations

Given the encouraging in vitro results, it is recommended that further research be conducted on these compounds, especially BZ-4, including:

- In vivo efficacy studies in suitable biological models,
- Cytotoxicity and ADMET profiling,
- Computational docking to explore molecular target interactions.

It will assist in achieving synthetic success of benzimidazole derivatives in terms of viable clinical solutions. The study will provide sturdy background to any future attempts at medicinal chemistry to curb the challenge of antimicrobial resistance that is increasing day by day.

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