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HETEROCYCLE-FUSED BENZIMIDAZOLE: A PRIVILEGED SCAFFOLD IN ANTIMICROBIAL DRUG DISCOVERY

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Keywords:

Heterocycle benzimidazole, Antimicrobial activities, Drug designing, Pharmacological activities

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ABSTRACT: Compounds with heterocyclic moiety are important for life and are abundant in nature. Heterocyclic compounds have a crucial part in the metabolism of all biological cells. Humanity relies heavily on nitrogen-based heterocyclic compounds. Benzimidazole, in particular, is a vital component of the entire nitrogen-based heterocyclic chemical family, not just physiologically but also industrially. Because once benzene, as well as imidazole, get merged around each other, a heterocyclic benzimidazole compound forms. Benzimidazole incorporates two nitrogens like a heteroatom. Benzimidazole analogues are often more powerful, medicinally significant chemicals with a wide range of biological activities. Benzimidazole analogues have been proven to be beneficial in several fields. The medicinal characteristics of benzimidazole analogue are diverse, including anticancer, antidiabetic, antihypertensive, and antimicrobial properties. Because of the medications' uses in the treatment of microbe-related infections and other biological activities, stronger and more significant pharmaceuticals are being developed. These compounds have been found to be efficient against various bacteria in pharmacological tests. The antimicrobial property of several benzimidazole compounds is summarised in this study.

INTRODUCTION: Because the heterocyclic molecule is a component of many biological components, the usage of heterocyclic compounds in medicinal chemistry is growing by the day. Benzimidazole [1, 2] is a heterocyclic molecule formed by combining benzene and imidazole. Benzimidazole is a nitrogen-containing heterocycle that has been around for a long time, synthesized first by Hoebrecker and then later by Ladenberg and Wundt between 1872 and 1878 [3].

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Glyoxaline [4], 1,3-diazole, iminazole, and imidazole [5] are all names for the heterocyclic part of the benzimidazole ring system. The most common name is imidazole (1), which refers to a five-membered heterocyclic moiety with imino and tertiary nitrogen. Various bioactive components include the imidazole ring, including histidine found in most histamine, proteins, biotin, and purine **Fig. 1.**

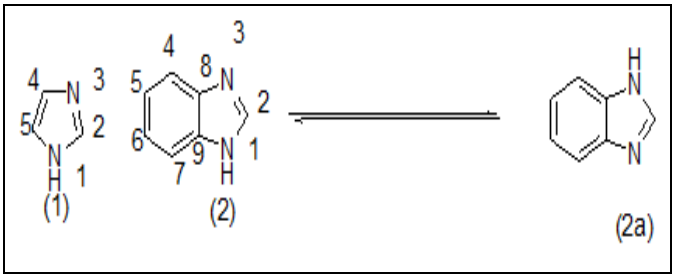


FIG. 1: NUMBERING SYSTEM INBENZIMIDAZOLE

In benzimidazole, the aromatic ring is linked to the imidazole ring's 4,5-positions, which is a completely planar ring structure (2). The structure illustrates the benzimidazole ring system's systematic numbering (2). Although the proton in benzimidazole is at N1 in (2), there is a quick tautomerismthe nitrogen atoms -NH and =N-, and the benzimidazole molecule can be represented as tautomers, (2) and (2a) **Fig. 2.**

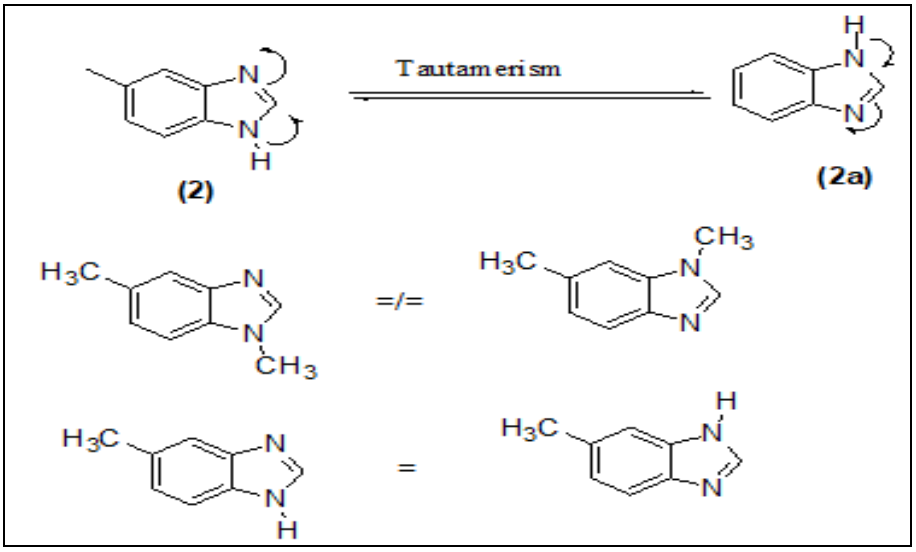


FIG. 2: TAUTAMERISM IN BENZIMIDAZOLE

In the field of medications and pharma, benzimidazole itself and analogues comprise an important group of bioactive components [6]. They can destroy human immunodeficiency virus [12], herpes virus [13] Ribonucleic acid [14], influenza [15,] and cytomegalovirus. To name a few benzimidazole derivatives, there's Omeprazole (3), Pimobendan (4), Triclabendazole (5), Oxfendazole (6), Mebendazole (7), Flubendazole (8), Fenbendazole (9), Cambendazole (10), Thiabendazole (11), Albendazole (12), Oxibendazole (13), Parbendazole (14), Luxabendazole (15) and all these are important for pharmacological activity **Fig. 3.**

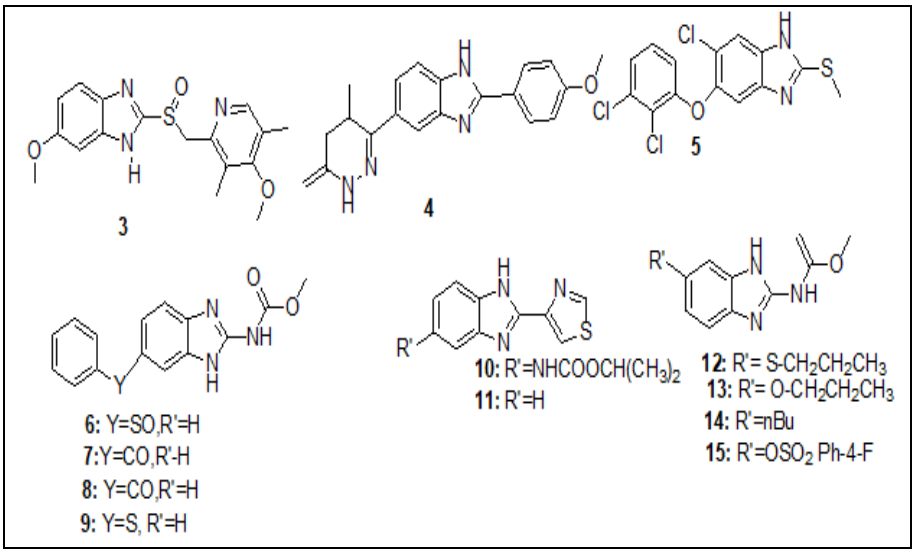


FIG. 3: BENXIMIDAZOLE, A MULTIFUNCTIONAL NUCLEUS

Many scientists developed benzimidazole-based compounds and tested their antimicrobial potential against number of bacterium types. Antibiotic resistance is on the rise these days, and it's a major problem. Due to bacterial resistance, many antibacterial medications are useless against germs. A priority list of antibiotic-resistant micro-organisms was also released by the World Health

Organization [17, 18, 19]. Our research group has recently developed and synthesized several heterocycle-fused benzimidazoles with outstanding antibacterial activity. Altering fusion sites, adjusting substitution patterns and stereochemical features, making them complex with transition metals, and exploring their antibacterial capabilities at the molecular level are among the most important applications of this chemical class for microbial treatment.

Despite the abundance of literature demonstrating the amazing importance of the benzimidazole moiety in antimicrobial drug development, to the best of our knowledge, none of the prior artwork explored the role of heterocycle-fused benzimidazole in antimicrobial drug discovery. As a result, this paper is dedicated to evaluating the previously published scientific research on this structural motif and diverting scientific focus to hitherto untapped insights into heterocycle-fused benzimidazole for the future identification of novel antimicrobial leads. This study focuses on newly synthesized benzimidazole derivatives and their antibacterial properties.

Benzimidazole Derivatives' Antimicrobial Activity: An antimicrobial is a substance that inhibits or kills germs. Antimicrobial drugs are classified based on how they affect microorganisms. Antifungals are used to treat fungus, whereas antibiotics are used to treat bacteria. There are two varieties of them, depending on the purpose. Agents that kill microorganisms are referred to as microbicidal, whereas those that prevent microbe development are biostatic. Because benzimidazole has a structural resemblance to purine, it inhibits protein synthesis in bacteria. In general, 2-substituted benzimidazole derivatives are more powerful in pharmacological action. The quest for antibacterial chemicals has been more important in recent years, as global worry about the rise in antibiotic-resistant infectious germs has grown. As a result, in this review, substances with antimicrobial properties are grouped as specified in the title of antimicrobials.

Al-Tel and colleagues synthesized benzimidazole pyridine/pyrimidine derivatives and analyzed them for antibacterial potential against a variety of microorganism. Several motifs demonstrated significant antibacterial action when compared to amoxicillin and cefixime. The antibacterial activity of the chemical molecule 16(a,b) with Br at the aromatic ring residing at the imidazopyridine moiety and a 17th group elementscontains compound at the benzimidazole moiety was excellent [20].

Fang *et al.* synthesized bis-azole molecules incorporating benzimidazoles and tested an antimicrobic activity in case of bacterial and fungal infection. Molecule (17) has remarkable antibacterial activity in the case of *P. aeruginosa* infection, with a Minimum inhibitory concentration of 4µg/ml that was 16-times higher than the reference medication Chloramphenicol. In comparison to monohalobenzyl groups, dihaloaryl groups are very useful for improving antibacterial and antifungal effectiveness, according to SAR [21]. Jubie and colleagues used microwave irradiation as a microbiological agent to synthesize Ciprofloxacin & norfloxacin Mannich bases comprising various benzimidazoles.

At 50 and 100 µg/mL, all benzimidazole substituted norfloxacin and ciprofloxacin substituents 18(a-c), and 19(a-c) demonstrated substantial activity relative to the reference norfloxacin and ciprofloxacin [22]. The antimicrobial activity of benzimidazole-containing thiadiazolo-thiazolidinediones (20) was investigated. The halogen-containing compound on the phenyl ring was shown to have extremely active antimicrobial action in a SAR investigation [23]. Mundra *et al.* revealed how to make benzimidazolequinoline hybrids for testing antibacterial activity in vitro. Compound (21) was shown to be as effective as regular ampicillin against Gram-positive bacteria *B. subtilis* [24]. Synthetic benzimidazole-thiazolidinone conjugates were created and tested for antifungal activity.

Antifungal activity of the compound (22) against *P. nicotianae* and *B. elliptica* is similar to that of regular carbendazim [25]. Reddy and colleagues developed benzimidazole – thiazol – 2 - amine compounds and tested them for antibacterial activity. When compared to the control (Streptomycin), compounds (23) and (24a) had approximately equal inhibitory efficacy against B.

subtilus. The most active compounds were 24(a,b), which had better efficacy against *F. oxysporum* than Fluconazole [26].

Rohini and colleagues identified aryl-benzimidazole-quinazoline as an antibacterial agent. The appearance of heterocyclic isoquinoline, pyridyl, and nitro substituted benzyl groups at the C6 position of the benzimidazo[1,2-c]quinazoline molecule in (25c), (25i), and (25j) demonstrates the most effective antagonistic effect in case of organisms upon which test is carried out, possibly because of heterocyclic isoquinoline, pyridyl and nitro substituted benzyl groups at the C6 position [27].

In-vitro antibacterial efficacy of nitro substituted benzimidazole derivatives produced and tested. The antibacterial activity of most microorganisms is enhanced as a nitro group is found in the benzyl ring. The bactericidal property of 26(a-d) particularly promised [28].

The antibacterial and antitubercular activities of sulfonyl-benzimidazole substituents (27(a-j) / 28(a-j) were investigated *in-vitro*. Chemical molecules (27b), (27d), (27e), and (27h) were shown to be effective in the fight against microorganisms' strains that were examined. Furthermore, the chemical molecule (27b), (27e), and (27h) showed substantial efficacy against the MTB H37Rv strain of mycobacterium tuberculosis. The halogen-substituted aromatic molecules' lipophilic quality will improve, while the methyl, methoxy-containing aromatic molecules will operate as an electron donor [29].

Synthesized 2-arylbenzimidazole derivatives were tested for antibacterial and antioxidant properties. *In-vitro* compounds containing a hydroxyl at the 5-position can be easily oxidized and behave as potent reducing agents and is a very good radical scavenger at OH and Diphenyl picrylhydrazyl radicals, with compound (30b) exhibiting particularly efficient antioxidative activity in a cellular system. At noncytotoxic doses, several of the compounds had outstanding antibacterial action against *S. aureus*, with molecules (29) and (30a) being same potential as the reference antibiotic such as ciprofloxacin [30]. Zhang and colleagues created a variety of fluconazole analogues of the benzimidazole type and their analysis was done for antibacterial property *in-vitro*. Among all the compounds examined, molecule (31) had the most powerful antibacterial efficacy; MIC values range from 2 to 16 g/ml.

The halobenzyl benzimidazole derivatives outperformed the alkyl ones in terms of bioactivity, with the bis (trifluoromethyl) aryl molecule (32) inhibiting *S. aureus* and *M. luteus* strains excellently (Minimum inhibitory concentration =8 µg/ml) [31]. Antimicrobial activity has been found for styryl benzimidazole derivatives. Molecules 33 (a,b) have stronger action against S. *aureus, E. coli*, as well as *Candida albicans*, inhibiting them by 72-93 % [32]. The antimicrobial potential of trifluoromethyl benzimidazole analogues was investigated. The antibacterial and antifungal properties of molecules (34) and (35) were promising [33]. Ravinder Nath and colleagues recently published a paper describing benzoimidazole-chromeno [2,3-d]pyrimidones as antibacterial and antioxidant.

Molecule (36a) with a methoxy family as a substituent at phenyl moiety had higher efficacy against fungus than (36b) with Bromo-containing compound on the benzene ring. Bromo and dibromo-containing compounds at the aromatic ring exhibited greater efficacy against DPPH free radicals in compound 36 (b,c) [34].

Desai *et al*. synthesised and evaluated benzoimidazole-thiazolidin – 4 - one analogues for antimicrobial activity against various strains. Molecules 37(b-d) have strong antibacterial action against *E. coli*, but compound (37a) has greater antibacterial activity against *P. aeruginosa* [35].

Antimicrobial properties of benzimidazole-thiazolidine and benzimidazole-oxadiazole hybrids have been observed. Molecules 38(a-d) and 39(a-d) showed potential antimicrobial properties against various bacteria. The electron-withdrawing groups -NO_2, -Cl and -OH on the aromatic ring were shown to significantly impact antimicrobial activity in a SAR investigation [36]. **Fig. 4** shows the structures of benzimidazole-containing compounds as antibacterials. **Table 1** lists some of the additional antibacterial compounds found in benzimidazoles.

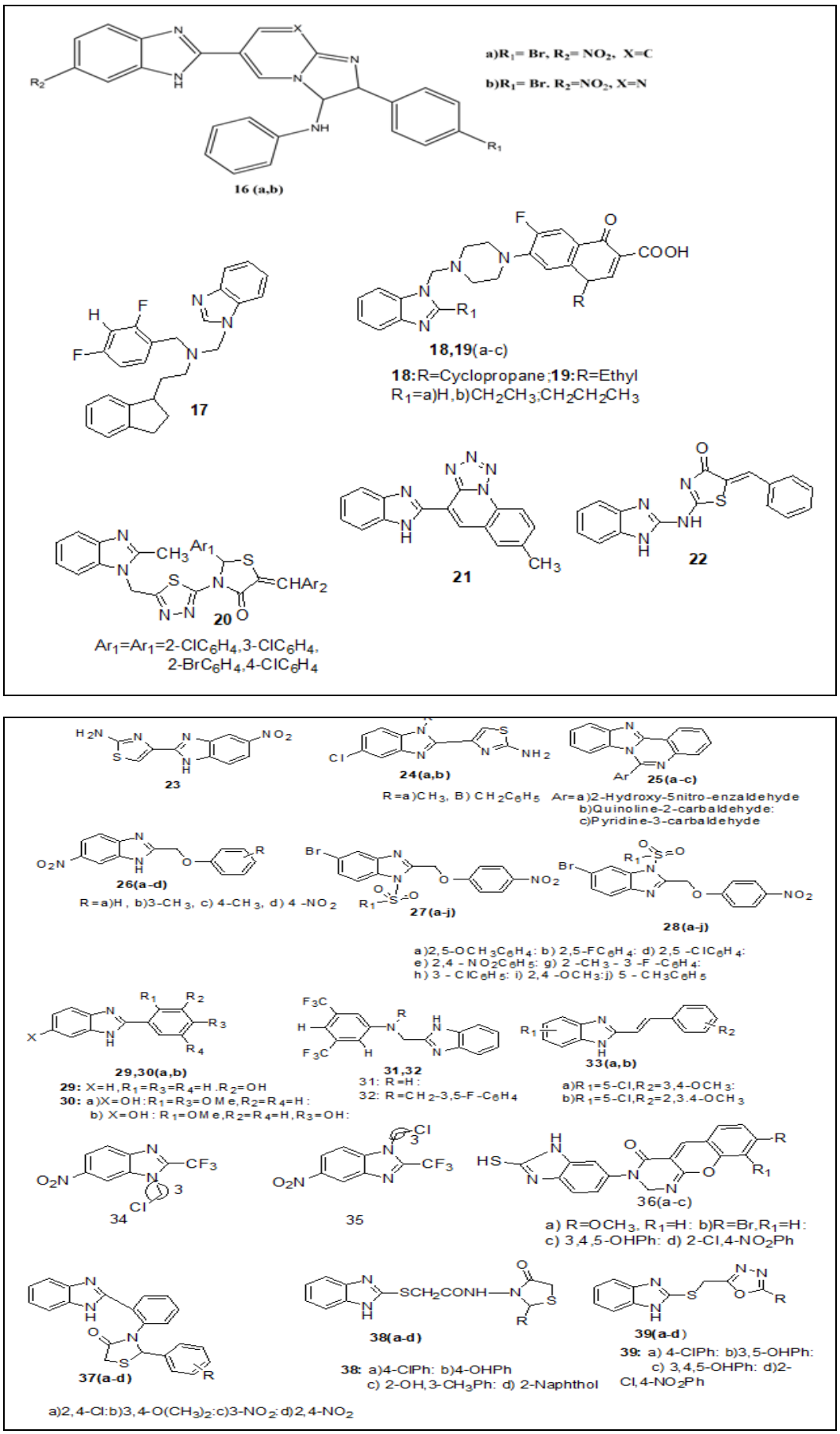
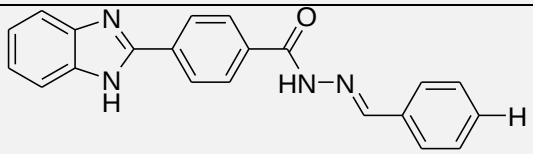
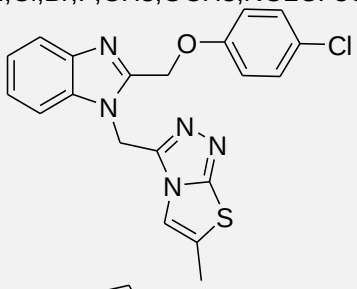
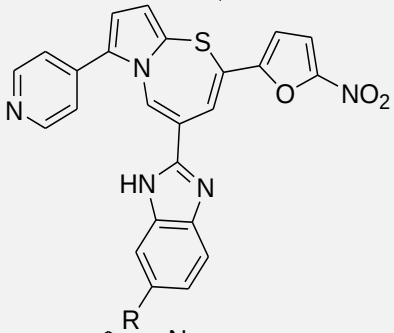
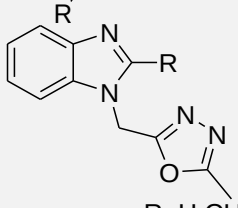
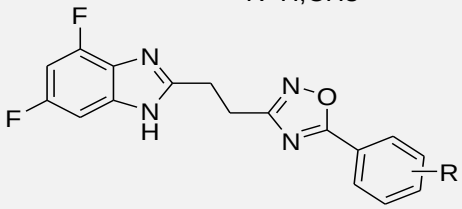
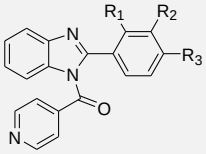
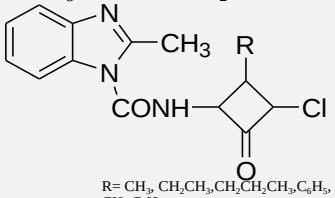
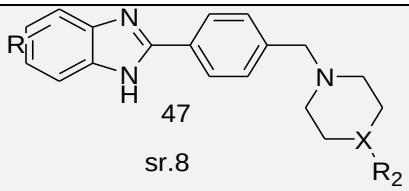
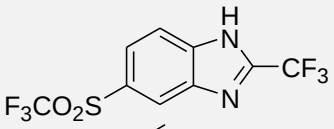
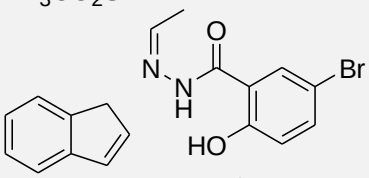
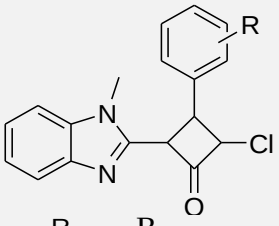
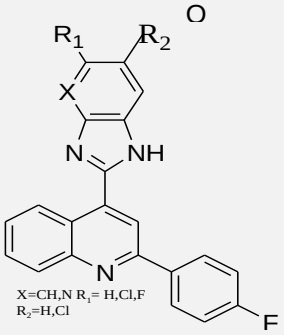
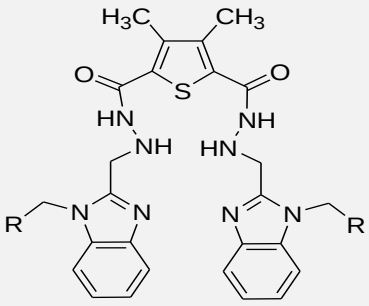
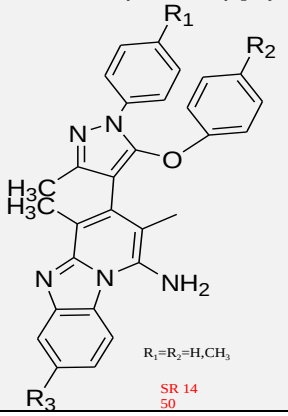


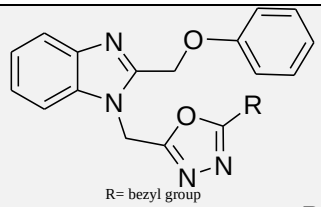
FIG. 4: STRUCTURES OF ANTIBACTERIAL BENZIMIDAZOLE DERIVATIVES

TABLE 1: SOME OF THE OTHER ANTIMICROBIAL AGENTS OF BENZIMIDAZOLES

S. no.	STRUCTURE	Ref.
1	 R= H, OH,Cl,Br,F,CH3,OCH3,NO2CF3COOH,CN	37
2		38
3		39
4	 R=H,CH3	40
5	 R= 4-NO2,3-Br,H,3-Cl,3-Pyridyl,3-Furan,Naphthalene, 4-OMe,3-F,3-OMe	41
6	 R_1=H, Cl, NO_2,OCH_3,COOH R_2= H,Cl,NO_2 R_3 = H, OH, Cl,NO_2	42
7	 R= CH_3, CH_2CH_3,$CH_2CH_2CH_3$,C_6H_5, 3-$CH_3C_6H_4$	43

8	 47 sr.8 X=CH_2,N,R_2=Methyl,P-Flourophenyl,m-methoxyphenyl,R=H,5-Methyl,6-Methyl 5-Nitro,5,6-dichloro	44
9		45
10		46
11		47
12	 X=CH,N R_1= H,Cl,F R_2=H,Cl	48
13	 R=alkyl and halobenzyl group	49
14	 R_1=R_2=H,CH_3 SR 14 50	50

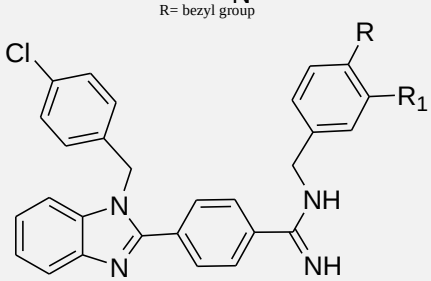
15



R= bezyl group

51

16



a:R=Cl; R_1=H
b:R=Cl;R_1=Cl

52

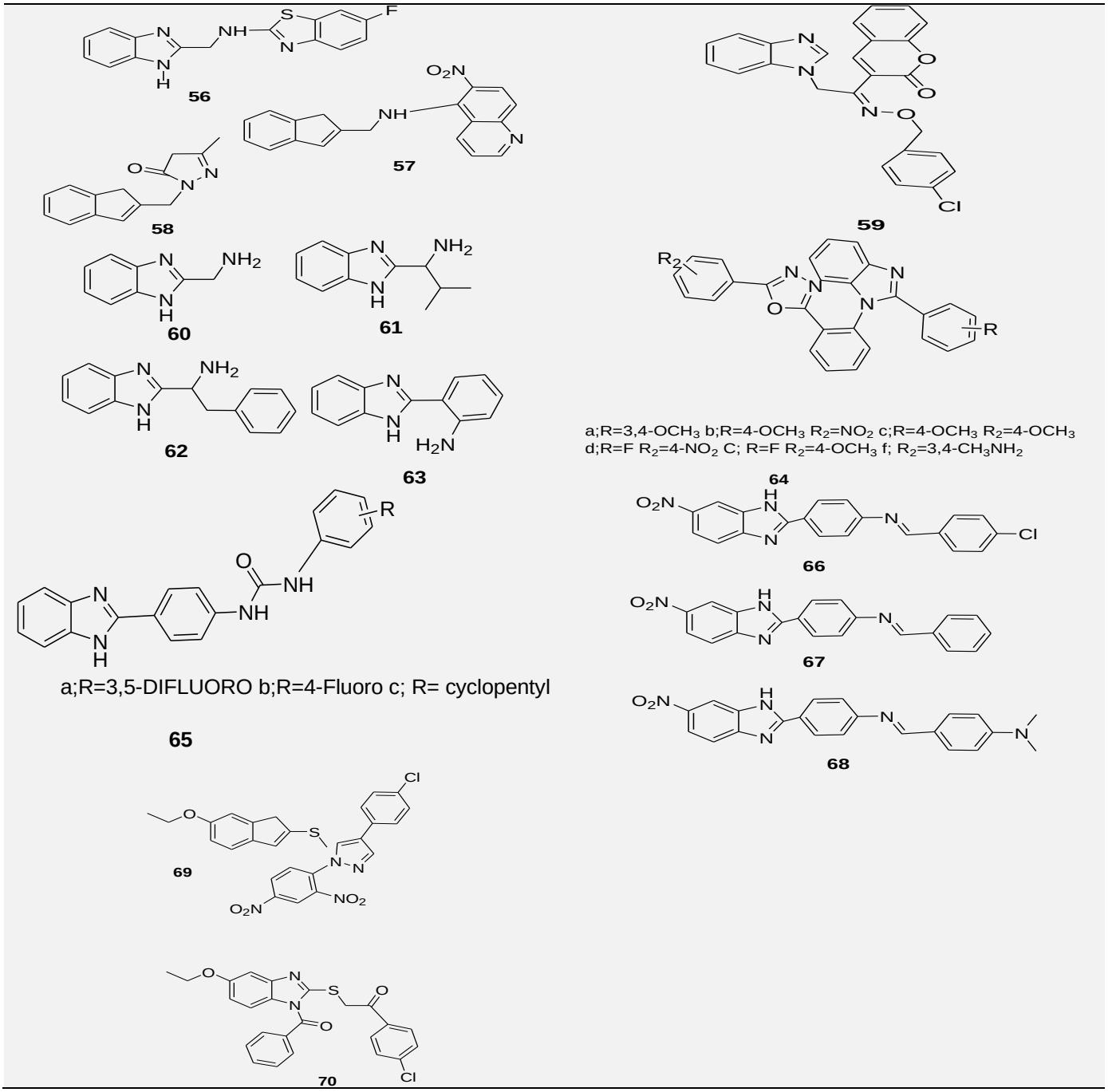
N.S. El-Gohary *et al.* [53] developed and evaluated a number of benzimidazole derivatives for antibacterial activity. Compounds (56) and (58) with MIC values of 0.524 µg/ml and 0.684 µg/ml, respectively, showed excellent action against *S. aureus*, whilst compound (57) with MIC value of 0.489 µg/ml showed outstanding activity against B. cereus. With a MIC of 0.262µg/ml, the chemical molecule (56) was shown to be a very effective antifungal analogue against *C. albicans*. Furthermore, compound (58) showed promise against *A. fumigatus* 293 with a minimum concentration of 1.37µg/ml. (Standard medicines included ampicillin and fluconazole.) L Ravithej Singh *et al* [54] used a simple and efficient technique to create novel coumarin–benzimidazole compounds. The antimicrobial activity of the produced chemical molecules was analysed.

They discovered that when compared to the standard antibioticampicillin (Minimum Inhibitory Concentration = 25 µg/mL), tetracycline and kanamycin (MIC = 450 µg/mL), the compound (59) had higher antibacterial action against *P. aeruginosa* (MIC 3.12 µg/ml). Furthermore, compound (59) demonstrated exceptional efficacy against *S. aureus* and *E. coli* bacterial strains with MICs of 1.56 and 3.12 µg/mL, respectively. According to molecular studies, molecules with a halogen atom demonstrated high antibacterial action. They discovered that the quantity, as well as location of halogen atoms in a molecule, had an impact on antibacterial activity. According to the researchers, coumarin–benzimidazole compounds containing a chlorine atom in the para position had the best antibacterial action. They concluded that compounds containing chlorine atoms in the meta or ortho orientations lacked antibacterial action. Using a zone of inhibition approach, Olayinka O. Ajani *et al* [55] synthesised 2-substituted benzimidazole derivatives and tested their antibacterial effectiveness against gram-positive bacteria (*Staphylococcus aureus, Proteus vulgaris*, and *Enterococcus faecalis*) and gram-negative bacteria (*Klebsiella pneumoniae, Pseudomonas aeruginosa* and *E. coli*). Compared to the gentamicin standard, the compounds (60 to 63) demonstrated bigger inhibition zones against all six species. Compound (63) had the biggest zone of inhibition against Klebsiella pneumonia, measuring 42 ± 0.10 mm. Different 2-substituted benzimidazole derivatives were produced by Archana Kapoor *et al.* [56].

Among the produced compounds, (64b) had the highest activity against *E. coli* (MIC = 1.30 µmol/ml). Other compounds (64a to 24f) showed excellent action against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *A. niger* (MIC = 1.58 to1.88 µmol/ml). Ciprofloxacin (MIC = 2.33 µmol/ml) and fluconazole (MIC = 1.99 µmol/ml) are standard medicines utilised. Based on the findings, it was determined that replacing electron-donating groups for the benzylidene benzene ring contributes more to antibacterial property. Sandeep V. Shinde *et al.* [57] synthesised novel benzimidazole compounds and tested their antifungal and antibacterial activities at 10 µM. Compounds (65a and 65b) have strong inhibitory efficacy against TNF- α (82 % and 80 %,

respectively) and IL-6 (96% and 91%, respectively). When compared to dexamethasone, compound (65c) showed moderate action (64–78 % inhibition). Saritha Garrepalli *et al.* [58] created novel benzimidazole compounds and tested their antimicrobial efficacy against S. aureus and *E. coli* at various doses. When compared to norfloxacin as the standard treatment, the results show that (68) had least activity, It's Zone of inhibition is 11 mm and (66 and 67) had the most activity, It's Zone of inhibition is 16 mm and 15 mm, respectively). As a result of this discovery, it is obvious that aromatic ring replacement boosts antibacterial action. Raad H. Turkey [59] synthesized novel 5-ethoxy-2-mercapto benzimidazole derivatives. These were tested for antibacterial activity against *S. aureus*, *S. agalactiae*, *P. mirabilis*, and *P. aeruoginosa* using the zone inhibition technique at 50 and 100 µg/mL concentrations. The antibacterial property of (69) and (70) was greatest among the investigated compounds (Zone of inhibition = 21 to 37mm). Cefotaxime and Imipenem were employed as reference medicines. **Table 2** lists some of the most current benzimidazole antibacterial drugs.

TABLE 2: BENZIMIDAZOLE DERIVATIVESAS ANTITUBERCULAR AGENTS



Agents Antitubercular: Tuberculosis (TB) is a serious public health problem, through one of the country's populations contaminated with Mycobacteria, eight million people living with the disease and two million deaths each year [60]. Tuberculosis (TB) is one of the leading causes of death in humans, with 8.7 million unique visitors and 1.4 million deaths each year, outranking anywhere else single infectious disease. TB is among India's most dangerous human diseases, accounting for almost a third of all worldwide health difficulties [61, 62]. Novel medications that may reduce this protracted treatment duration and target multidrug-resistant TB strains are urgently needed [63]. The TB actions of benzimidazole and its derivatives are addressed as follows [64].

2-benzimidazole analogue were produced and tested for antitubercular, antifungal and antibacterial property against MTB H37Rv. Antitubercular activity of substances 71(a-e) was greater and compounds 71(b,c) were shown to be effective with antimicrobial agents. In comparison to nitro compounds, the inclusion of the Br group on the phenyl ring has greatly boosted the activity of the compounds [65]. Synthetic triazole-benzoimidazole derivatives were made. These were tested for antimycobacterial property. Compounds 72 (a-c) showed potential antimycobacterial action. Compounds with fluorine replacements at the aromatic ring boost antimycobacterial action, according to a SAR analysis [66].

The antibacterial and antitubercular efficacy of flouro substituted triazole-benzoimidazole derivatives against MTB H37Rv strain was investigated *in-vitro*. Electronegative elements like chlorines and fluorine 73(a-c) showed excellent action (up to 96 % inhibition at 6.25 µg concentration) [67]. Pandey *et al.* reported the synthesis of alkyl-substituted benzimidazoles. These was tested for antitubercular activity against the toxic strains MTB H37Ra and MTB H37Rv at various dosages. When comparing the activity of imidazole and benzimidazole derivatives 74(a,b), the imidazole containing compounds showed better results [68]. Antimycobacterial activity of substituted 2-polyfluoroalkyl and 2-nitrobenzylsulphanyl benzimidazoles against MTB, *M. kansasii*, *M. kansasii* and *M. avium* was investigated. Every substance examined, especially 5,6-dichloro-2-nonafluorobutylbenzimidazole (75), 5-halogen 76(a-c) and 4,6-(76d) and 2-(3,5-dinitrobenzyl-sulphanyl) benzimidazoles, exhibited significant antimycobacterial activity (76e). 3,5-dinitrobenzylsulfanyl benzimidazoles halogenated at position 5 with iodine, bromine, or chlorine, 76(a-c) demonstrated greater activity against all mycobacterial strains, according to a SAR investigation [69]. Antimycobacterial activity of alkylsulfanyl-benzimidazole derivatives against MTB and nontuberculous mycobacteria was investigated. In tests against *M. kansasii* and M. *avium*, the 3,5-dinitro derivative (77) outperformed the conventional isoniazid [70].

The conjugated benzimidazole-oxadiazole compounds were produced and tested for antituberculosis efficacy against MTB H37Rv *in-vitro*. Compound (78), which is comparable to normal pyrazinamide and has a methoxy (-OCH_3) group attached to the N-aryl acetamide moiety, had the maximum inhibition (99 %) against MTB H37Rv at a constant concentration level (6.25 µg/mL). According to Kumar and colleagues, trisubstituted benzimidazoles demonstrated excellent antituberculosis action against MTB. The antimicrobial activity of compounds 79(a-d) against clinical MTB strains is strong, with MIC values ranging from 0.5 to 6.1 g/mL [72].

Substituted benzimidazoles derivatives were tested for antimycobacterial activity against MTB H37Rv. Compound (80), the most active with an IC_{50} of 11.52 µM [73], exhibited excellent activity with an IC50 of less than 15 µM. The anti-TB activity of pyrido-benzimidazole-4-carbonitrile derivatives against MTB H37Rv was excellent. *In-vitro* compound (81) had the same activity as the susceptible control strain. The anti-TB activity of 5-nitrofuran or 5-nitrothiophene-benzoimidazole-5-carbohydrazide derivative was tested against sensitive MTB. When compared to INH (0.063 µg/ml) and RIF (32 µg/ml), compounds (82) had modest antimycobacterial action, with MIC values of 12.5 µg/ml against MTB strain and 6.25 µg/ml against MDR clinical isolates [74]. Table 2 depicts the structure of benzimidazole derivatives having antitubercular properties.

CONCLUSION: According to the findings of the aforementioned study, benzimidazole pharma-

cophorehas a vital function in pharmaceutical chemistry and the associated study has been particularly vast. For more than a century, benzimidazole and its derivatives have been reported. In current drug research, the benzimidazole ring is a notable pharmacophore. Numerous notable breakthroughs have indicated that benzimidazole-based compounds have a number of medicinal applications as antimicrobials and diagnostic agents. The functional group present on the molecule has a crucial impact on the physicochemical qualities shown by the molecule, according to the literature study.

The researcher should understand the proportional contributions of each functional group to develop a better therapeutic drug. Because it is a bioactive and structurally simple heterocyclic compound, the benzimidazole molecule has played a significant role in medicinal chemistry.

It has the potential to help in the development and discovery of new antimicrobial drugs. Efforts to synthesis medicinally relevant benzimidazole derivatives have been made in the recent decade, and researchers have found several benzimidazole derivatives with potential antibacterial action. The goal of this study is to describe synthesizing a new benzimidazole derivative and also its antibacterial property. As multiple various molecular targets, this interesting moiety has a lot of potentials, and further research of this scaffold might provide some more positive discoveries in the area of medicine. This knowledge is expected to lead to the creation of new synthetic techniques and the production of better molecules with improved biological characteristics and selectivity. This review is intended to help aspiring researchers in benzimidazole-based medication creation.

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