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Benzimidazole – A Potent Antimicrobial Agent

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ABSTRACT

The use of heterocyclic compounds in field of medicinal chemistry is increasing day by day due to various reasons like heterocyclic compounds are included in the structure of many biochemical materials, which are essential for life. Nucleic acid, many naturally occurring pigments like chlorophyll, vitamins and antibiotics contains heterocyclic nucleus. Modern society is also dependent on synthetic heterocycles for use as drugs, pesticides and dyes. The work embodied in this article relates to benzimidazole as it is a versatile heterocycle which exhibit broad range of biological activities. Benzimidazoles (known as *o*-phenylenediamine derivatives) are mostly synthesized from *o*-phenylenediamines. This ring system is present in numerous anti-protozoal, anti-helmintics, anti-HIV, anti-convulsant, anti-inflammatory, anti-neoplastic, and anti-ulcer agents. Several benzimidazoles such as albendazole, mebendazole, flubendazole, fenbendazole, omeprazole, lansoprazole, and clofazone are used in therapy. In this review, various antimicrobial benzimidazoles were summarized & reported. In addition this review highlights the antimicrobialpotency of benzimidazole to medicinal world.

Keywords: Benzimidazole, *o*-Phenylenediamine derivative, Antimicrobial, Antibacterial, Antifungal.

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INTRODUCTION

The diverse parasitic bacteria such as *Staphylococcus aureus*, *Staphylococcus pyogenes*, *Salmonella typhimurium* and *Escherichia coli* have significant impact on the mucosal health of humans. Infection with *Staphylococcus aureus*, *Staphylococcus pyogenes*, *Salmonella typhimurium* and *Escherichia coli* may have resulted in massive destruction of host tissue and life threatening diseases. These bacterial parasites cause food poisoning, rheumatic fever and diarrhea, which affect millions of individuals in developing countries. More than 50 million people worldwide are infected and up to 1,10,000 of these die every year. For these bacterial infections the most commonly used drugs are Amoxicillin, Norfloxacin and Ciprofloxacin but these drugs were associated with severe side effects. A continuous increase in the number of infections caused by bacteria resistant to one or multiple antibiotic classes poses a significant threat and may lead to treatment failures and complications. Therefore, significant efforts have been made by many research groups to find out new anti-microbial agents.

Heterocyclic compounds play an important role in the field of organic chemistry. They are acquiring more importance in recent years due to their extensive pharmacological properties and wide applications in the field of chemistry. It was found that benzimidazole **1** (Figure 1) and its analogs was one such important heterocyclic compound. A variety of chemical modifications were carried out so far around the benzimidazole backbone (core). Benzimidazoles have emerged as antimicrobial agents because of their broad spectrum of *in vitro* and *in vivo* chemotherapeutic activities. In this review, various benzimidazole antimicrobial agents were summarized and reported. This review highlights the importance of benzimidazole as potent antimicrobial agents in medicinal world[1].

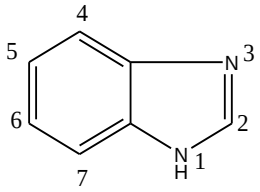

Figure 1: Structure of benzimidazole

ANTIMICROBIAL BENZIMDAZOLE

A series of novel benzimidazole derivatives containing chrysanthemum acid moieties **2** (Figure 2) was designed and synthesized by Weijie[2] *et al*. Preliminary investigation of biological activity indicated that all of the compounds exhibited lower activity than that of beta-cypermethrin against *Plutella xylostella* and *Lipaphis erysimi*; meanwhile, they showed good inhibitory activity against

Botrytis cinerea and *Sclerotinia sclerotiorum in vitro*. The fungicidal activity of one compound against *Botrytis cinerea* was approximately equal to that of thiabendazole and was twice as active against *Sclerotinia sclerotiorum* as was thiabendazole. In addition, another one compound displayed the most potent inhibitory activity against both fungi and was almost twice as potent as thiabendazole.

Govindaraj[3] *et al*. studied the biological activity of various benzimidazole derivatives [3] (Figure 2). In this study initially *o*-phenylenediamine reacted with anthranillic acid and yielded 2-(1*H*-benzo[*d*]imidazol-2-yl) aniline which further condensed with aromatic acid chlorides in the presences of pyridine to get compound *N*-(2-(1*H*-benzo[*d*]imidazol-2-yl)phenyl)benzamide. Further it treated with phosphorous pentachloride to get an intermediate compound then reacted with sodium azide to get compound 2-(2-(5-phenyl-1*H*-tetrazol-1-yl)phenyl)-1*H*-benzo[*d*]imidazole. The antimicrobial activity was studied against various bacteria and fungi. The result showed that all of the compounds possess good biological activity.

Archana[4] synthesized 2-(4-substitutedphenyl)-4-(4-sustitutedphenyl)-1,4-dihydropyrimido[2,3-*b*]benzimidazole derivatives[4] (Figure 2) and studied its antimicrobial activity. The target molecules were tested for antibacterial activity against *Escherichia coli, Pseudomonas aeruginosa and Salmonella tiphy* (gram-negative bacteria) and *Staphylococcus aureus, Bacillus subtilis and Staphyllococcus mutans* (gram positive bacteria) by the punch well and disc diffusion methods on the Muller Hinton agar medium using Gentamycin (100 µg/ml) as the standard drug. The screening results indicated that all compounds shown promising antifungal activity against *Candida albicans*. Fewer compounds exhibited activity against *Aspergillus niger*.

Fatmah[5] *et al*. synthesized substituted benzimidazole derivatives[5] (Figure 2). The synthesized compounds displayed antibacterial activity against two methicillin-resistant Staphylococcus aureus (MRSA) and antifungal activity. Priyanka[6] *et al*. worked on synthesis, screening, and antimicrobial activity of benzimidazole derivatives [6] (Figure 2) by disc diffusion technique. A series of benzopyrone substituted benzimidazole derivatives 7 (Figure 2) were synthesized by reacting benzopyrone-3-carboxylic acid with *o*-phenylene diamine by Sukhen[7]. The analogues were synthesized in a good yield and were subjected for antibacterial screening against *Staphylococcus aureus, Bacillus subtilis, Pseudomonus aeruginosa and Escherichia coli* by agar diffusion method. Among them two derivatives showed appreciable activity against all the strains. Mahalakshmi[8] *et al.* synthesized 2-chloromethyl-1H-benzimidazole derivatives [8] (Figure 2) by using the condensation of 2-chloromethyl-1*H*-benzimidazole with different heterocycles. The compounds

were screened for *in vitro* antimicrobial activity against panel of selected gram positive and gram negative bacterial strains using Ciprofloxacin as standard.

Hamdan[9] *et al*. synthesized a series of benzimidazole derivatives [9] (Figure 2) by using a simple, inexpensive and rapid method using different ammonium salts. Some of these derivatives were exclusively isolated, characterized and tested for their antifungal activity. The biological activity of these compounds as fungicides was tested against three commercially known fungicides (*C. albicans*, *C. glabrata* and *C. krusei*). Most of the obtained compounds exhibited anti fungal activity and especially three compounds which showed significant activity when compared with that obtained from standard drug.

The QSAR studies were performed on a series of benzimidazole derivatives [10] (Figure 2) to find out the structural requirements of their antimicrobial activities by Mukesh[10]. The QSAR studies have been carried out using electronic, thermodynamic, spatial and structural descriptors along with a few structural parameters. The best QSAR (*S. aureus*) model having r_2= 0.7886 and q_2 = 0.7269 was developed by principle component regression. From the study they concluded that antibacterial activity of the compounds significantly depends on the electronic effect of hydroxyl and fluoro groups. QSAR model indicated that the antibacterial activity was increased with the presence of methoxy groups and fluorine atoms in benzimidazole nucleus will lead to improved activity. Variables in the equation revealed that thermodynamic, electronic, structural and molecular shape analysis descriptors contribute significantly to the antimicrobial activity.

Uthumporn[11] *et al*. used citronellal [which was extracted from Citrus hystrix (makrut lime) leaves that contains aldehyde functional group] as the starting material for the synthesis of novel benzimidazole derivatives [11] (Figure 2). The essential oil was reacted with 1,2-phenylenediamine *via* condensation reaction in ethanol to give benzimidazole derivative. In addition, these products was tested for antibacterial activity against Gram negative, *Escherichia coli* and Gram positive, *Staphylococcus aureus*, by disc diffusion methods at a concentration of 200 mg/ml, using ethanol as the control, and compared with antibacterial drug, Gentamicin. The results revealed that the derivative showed effective excellent antibacterial activity than antibacterial drug.

New chemical entities of benzimidazole [12] (Figure 2) condensed with benzothiazole were prepared and tested for their antibacterial property by Mayank[12] *et al*. A series comprising benzimidazole - benzthiazole carbohydrazide substituted by aromatic system were prepared. Investigation of antimicrobial activity of the compounds was studied against *S. aureus*, *E. coli*, and *P. aeruginosa*. Pavel[13] & co workers prepared and characterized 1-(1*H*-benzimidazol-2-yl)-*N*-(1*H*-benzimidazol-2-ylmethyl)methanamine and 2-(1*H*-benzimidazol-2-ylmethylsulfanylmethyl)-1*H*-benzimidazole

[13] (Figure 2). For the preparation of complexes these bis(benzimidazoles) have been further used in combination with trithiocyanuric acid. The crystal and molecular structures of two of them have been solved. The antimicrobial and antifungal activity of the prepared compounds have been evaluated on a wide spectrum of bacterial and yeast strains and clinical specimens isolated from patients with infectious wounds and the best antimicrobial properties were observed in strains after the use of title compounds, when at least 80% growth inhibition was achieved.

Some new pyrimido[1,2-*a*]benzimidazole derivatives [14] (Figure 2) were synthesized by reacting 2-amino benzimidazole and chalcones in *n*-butanol at reflux temperature by Nirav[14] *et al*. They used various heterocyclic chalcones derived from furfural and substituted acetophenones in this study. All synthesized compounds were screened for their antimicrobial activity against two gram +ve bacteria *Staphylococcus aureus and Staphylococcus epidermidis* and two gram –ve bacteria *Escherichia coli and Pseudomonas aeruginosa* and fungi strain *Aspergillus niger* by using the disc diffusion method. Standard drug Cephalexin and Greseofulvin were used for the comparison purpose. Rsults of antimicrobial data revealed that, two compounds shown good activity against bacterial pathogens while other three compounds were found good active against fungi pathogens as compare to the standard drugs.

Amit[15] *et al*. synthesized some derivatives of benzimidazole [15] (Figure 2) by nucleophilic substitution. In this work, 4- chloro-*o*-phenylene diamine is treated with formic acid / acetic acid to form 2-substituted-6-chloro-benzo[*d*]imidazole. This compound is further heated with ethylbromoacetate to synthesize 2-substitutedethyl 2-(6-chloro-benzo[*d*]imidazol-1-yl)acetate. The resulting intermediate on treatment with hydrazine hydrate yielded ethyl-2-(6-chloro-2-substituted-1*H*-benzo[*d*]imidazol-1-yl)hydrazide which on further reaction with one equivalent of different substituted aromatic carboxylic acids in the presence of phosphoryl chloride afforded the corresponding target compounds 6-chloro-2-substituted-1-[{(5-substituted aryl)-1,3,4-oxadiazol-2-yl} methyl]-1*H*-benzimidazole. All the synthesized compounds were screened for their antimicrobial activity against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Saccharomyces Cerevisiae*. The result revealed that most of newly synthesized compounds exhibited promising antibacterial and antifungal activities.

Zhang[16] *et al*. synthesized 2-arylbenzimidazole analogues [16] (Figure 2) by using phenylene diamine as starting material through cyclization, and acylation reactions. All these compounds were tested through novel yeast based screening method to evaluate their bioactivities. Based on the fact that benzimidazole containing compounds exhibit important biological activities Ahmadi[17] investigated synthesis, spectral studies and biological evaluation of nine novel benzimidazole derivatives 17

(Figure 2). The target new synthesized compounds were screened for antibacterial activity against various strains of *Escherichia coli* and *Staphylococcus aureus* and antifungal activity against *Candida albicans*. The preliminary screening results revealed that the newly synthesized compounds have not shown antifungal activity against *Candida albicans* but exhibited good antibacterial activity against various strains of bacteria as compared to standard ciprofloxacin.

Four new 2-substitutedbenzimidazole derivatives [18] (Figure 2) were synthesized from *o*-phenylenediamine by Yesu [18] *et al*. The newly synthesized compounds were characterized and screened for antimicrobial activity by broth dilutionmethod against *S. aureus*, *P. aeruginosa*, *S. pyogenus*, *E. coli*, *A. niger*, *A. clavatus*, and *C. albicans*. Few compounds have shown moderate to mild antimicrobial activity when compared to standard ampicilin. Divya[19] *et al*. synthesized a variety of 2-substituted benzthiazoles [19] (Figure 2) by a multi step synthesis. Initially they prepared benzo[*d*]thiazol-2-amine from aniline, followed by acetylation, bromination, and cyclization with urea / thiourea / acetamide / benzamide to form the various novel benzthiazole derivatives. They also reported the preparation of 2-substituted benzimidazoles by reacting *o*-phenylene diamine with lactic acid, and then with chromic acid followed by bromination and cyclization with urea / thiourea / acetamide / benzamide. The various novel benzimidazole and benzthiazole derivatives were evaluated for antimicrobial activity against a variety of bacterial and fungal strains. Some of these compounds have shown significant antibacterial and antifungal activities against the tested micro organism.

Novel benzimidazole derivatives [20] (Figure 2) was synthesized and evaluated for their antibacterial activity by Rekha[20] *et al*. The newly synthesized compound were subjected to antibacterial activity at 1000 µg/ml concentration against bacterial strains such as gram-positive (*S. aureus* and *B. subtilis*) and gram-negative (*E. coli & P. vulgaris*). Ciprofloxacin and amoxicillin were used as standard drugs for antibacterial screening at 10 µg/ml concentration. In general, from the study it was found that most of the compounds showed significant antibacterial activity but some compounds are more specific to particular strains of bacteria. In the present research Sridevi[21] *et al*. synthesized new benzimidazole derivatives [21] (Figure 2) by condensing *o*-phenylene diamine with carboxylic acid by using Phillip's condensation. The free N-H group in benzimidazole was allowed for acetylation. The acetylated product was made to react with different aromatic aldehydes in the presence of alkali to give different chalcones by aldol condensation. The compounds were synthesized in good yield and their structures were confirmed by spectral studies. All the synthesized compounds were screened for their antibacterial activity by employing the cup

plate method against *Bacillus subtilis*, *Staphylococcus aureus, Escherichia coli*, and *Pseudomonas aeruginosa*.

A series of 2-(2´-pyridyl)benzimidazole derivatives [22] (Figure 2) have been synthesized and investigated for their antibacterial and antifungal properties by Arfa[22] *et al.* The synthetic analogs were tested against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aureginosa, Salmonella typhii, Shigella flexenari, Aspergillus flavis, Candida albican, Microsporum canis, Fusarium solani, and Candida glabrata* by agar well diffusion method. From the study it was found that, out of the eleven derivatives of 2-(2´-pyridyl) benzimidazole four compounds showed activity against the tested antibacterial strains and seven compounds showed antifungal activities. Gupta[23] *et al.* synthesized 2-substituted phenyl-1-(substituted piperazin-1-yl)methyl)-1*H*-benzo[*d*]imidazoles [23] (Figure 2) by using the reaction of *o*-phenylenediamine with the derivatives of benzoic acid in presence of 4*N* HCl followed by the reaction with piperazine and formaldehyde to undergo Mannich reaction. The synthesized compounds were evaluated for their anthelmintic activity by the identification of paralyzing and death time by using Mebendazole as standard.

Kranthi[24] *et al.* synthesized phenyl 1-benzyl-1*H*-benzo[*d*]imidazol-2-ylcarbamates [24] (Figure 2) by the reaction between 1*H*-benzo[*d*] imidazol-2-amine, bezylhalides, and phenylchloroformate. They screened synthesized compounds for their antibacterial activity. Misbah[25] *et al*. synthesized Mannich base derivatives [25] (Figure 2). The synthesized compounds were evaluated antibacterial, antihelmintic, antifungal, anti-inflammatory, anti-viral and analgesic activity. Gurvinder[26] *et al*. synthesized substituted benzimidazole derivatives [26] (Figure 3). The synthesized compounds was evaluated for their antimicrobial, anti-viral, anti-diabetic, anti-oxidant, anti-cancer, analgesic, anti-protozoal, anti-ulcer, anti-hypertensive, anti-neoplastic, anti-inflammatory, antifungal and anti-convulsant activity. Shastri[27] *et al*. synthesized some novel 2-(2-benzisoxazol-3yl)ethyl)-1*H*-benzimidazoles [27] (Figure 3) by the condensation of 1,2-benzisoxazole-3-propionic acid with *o*-phenylene diamine hydrochloride in aqueous alcohol. The synthesized compounds were evaluated for their antibacterial and antifungal activity.

Namrata[28] *et al*. synthesized substituted benzimidazole derivatives [28] (Figure 3). Some of important benzimidazole derivatives reported as thyroid receptor agonist gonadotropin releasing hormone receptor antagonist, non-nucleoside HIV-1 receptors. The synthesized compounds were evaluated anti-malarial, antifungal, antibacterial, anti-ulcer and anti-viral activity. Murugesan[29] *et al*. synthesized novel *N*-Mannich bases of benzimidazole derivatives [29] (Figure 3) by the reaction of *N*-1 hydrogen of 2-substituted benzimidzole with primary or secondary amines in ethanol. The

synthesized compounds were evaluated by antimicrobial activity by disc diffusion method. Margan[30] *et al*. synthesized a new tetradentate bis-benzimidazole [30] (Figure 3) based on diamide ligand, *N*-butyl-*N*,*N*'-bis-(2-methyl-benzimidazolyl)-benzene-1,3-dicorboxamide [B-GBBA]. The complexes had been screened for their antimicrobial activities against *E. coli* and *S. aureus*.

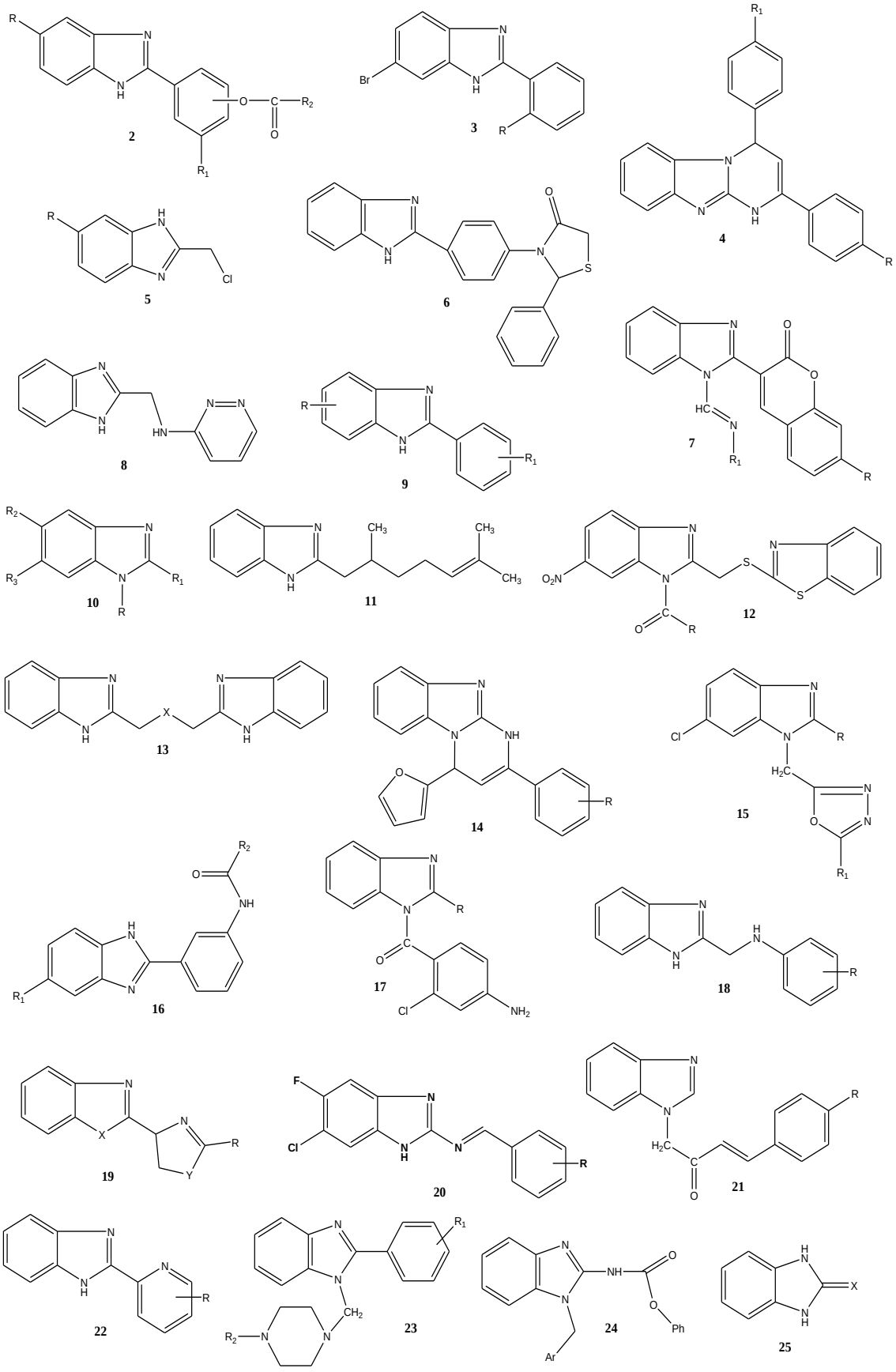

Figure 2: Structure of anti-micribial benzimidazole(2-25)

Khabnadideh[31] *et al*. synthesized some new benzimidazole, benzotriazole and aminothiazole derivatives [31] (Figure 3) and evaluated their activity against some species of *Candida*, *Aspergillus*, and *dermatophytes*. They synthesized the desired compounds by the reaction of benzimidazole and benzotriazole with bromoalkanes and also by the reaction of an amide derivative of aminothiazole with 2-piperazino-1-ethanol in an efficient solvent in the presence of tetraethyl ammounim bromide or triethylamine) as catalyst. Antifungal activities of the new compounds were evaluated by broth micro dilution method. Among the tested compounds, 1-nonyl-1*H*benzo[*d*]imidazole and 1-decyl-1*H*-benzo[*d*]imidazole exhibited the best antifungal activities. Of the examined synthetic compounds in different categories, benzimidazole derivatives established better antifungal activities than benzotriazole derivatives, and the piperazine analogue had no significant antifungal effect. By condensation of 2-nitroaniline with different carboxylic acids some new 2-substituted benzimidazole derivatives [32] (Figure 3) were synthesized using microwave irradiation method by Kuldeep[32] *et al*. The compounds synthesized were characterized by spectroscopic techniques and were screened for their *in vitro* antimicrobial activities against *Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Bacillus pumilus, Candida albicans,* and *Aspergillus niger*. The antimicrobial potency of title compounds was determined by agar well diffusion method. Amongst the series compound 2-pyridin-3-yl-1*H*-benzimidazole was found to be the most active antimicrobial compound. Compounds 2-(2-chloro-4-nitro-phenyl)-1H-benzimidazole and 2-(1*H*-benzimidazol-2-yl)-6-nitro-benzoic acid also showed good antimicrobial activity.

Nour[33] *et al*. reported structural studies of (1*H*-benzimidazol-2-ylmethyl)-*N*-(4-chloro-phenyl)-amine and (1*H*-benzimidazol-2-ylmethyl)-*N*-(4-iodo-phenyl)-amine [33] (Figure 3) by a variety of physico-chemical techniques. Optimized geometrical structures, harmonic vibrational frequencies, natural bonding orbital analysis, and Frontier molecular orbitals were obtained by DFT/B3LYP method. TD-DFT calculations help to assign the electronic transitions. The polarizable continuum model (PCM) fails to describe the experimental chemical shift associated with the NH pro-tons as calculated by applying Gauge-invariant atomic orbital method, but a very good correlation between the theoretical and experimental values was achieved by taking into account the specific solute-solvent interactions. DFT calculations showed a good agreement between the theoretical and observed results. These compounds exhibited a high biological activity through the inhibition of the metabolic growth of the investigated bacteria. A new series of 2,5-disubstituted benzimidazole derivatives [34] (Figure 3) have been synthesized by Sugumaran[34] *et al*. The synthesized compounds were evaluated for their antibacterial activity against *Proteus vulgaris*, *Klesibella pneumonia*, *Bacillus cereus,* and *Enterococcus faecium* and antifungal activity against

Aspergillus niger and *Aspergillus fumigatus* by disc diffusion method. All of the synthesized compounds showed good antibacterial and antifungal activity. However against the tested organisms at tested dose level, the antibacterial and antifungal activity of the synthesized compounds was found to be less than that of respective standard drug.

Some novel benzimidazole derivative [35] (Figure 3) was synthesized with aspirin and evaluated for their antimicrobial & antifungal activities by Chavan[35] *et al*. The newly synthesized compound was subjected to antibacterial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, & antifungal activity against *Candida albicans*. The antibacterial & antifungal activities were compared with the respective standard drugs (Amikacin & Ampicillin trihydrate for antibacterial & fluconazole for antifungal, respectively). The MIC of Benzimidazole derivative was found to be in the range 20-200 mg/ml on all the tested microorganisms. Rajanarandar[36] *et al.* synthesized a new series of 5-(1*H*-benzo[*d*]imidazol-2-yl-methyl)-3-(5-methyl-3-isoxazolyl)-2-aryl-1,3-thiazolan-4-ones [36] (Figure 3) by the cyclocondensation of 3-benzalamino-5-methylisoxazole with mercapto succinic acid, followed by cyclization with 1,2 phenylene diamines and were screened for antimicrobial activity.

Ravinder[37] *et al.* synthesized novel 2-[(E)-2-aryl-1-ethenyl]-3-[2-sulfanyl-1*H*-benzo[*d*]imidazole-5-yl]-3,4-dihydro-quinazolinones [37] (Figure 3) analogs by the reaction of 2-methylbenzoxamine-4-one with 5-amino-1*H*-benzo[*d*]imidazole-2-thiol. The antibacterial activity was determined for the test compounds. Jadhav[38] *et al*. synthesized new series of substituted benzimidazole derivatives [38] (Figure 3) and the structures of these compounds were evaluated for antimicrobial activity. Saritha[39] *et al*. synthesized benzimidazolyl dithiocarbamates [39] (Figure 3) by reacting with 2-chloromethyl benzimidazole with carbon disulfide and various alkyl and aralkyl and heterocyclic amines in dimethylformamide. The synthesized compounds were evaluated for their antibacterial and antifungal activity. Ozkay[40] *et al*. synthesized 4-(5,6-dichloro-1*H*-benzimidazole-2yl)phenoxy acetic acid-4-substituted benzylidene hydrazide derivatives [40] (Figure 3). The synthesized compounds were evaluated in Brine-Shrimp lethality assay.

Sharma[41] *et al*. synthesized 2-{2'-[4"-substituted phenyl]-2'-methylthiazolidine-4-one-3-ylamino}-1*H*-benzo[*d*]imidazoles [41] (Figure 3) by the reaction of 2-hydrazinobenzimidazole with substituted acetophenones yielded Schiff's bases which on further reaction with thioglycollic acid in the presence of anhydrous zinc chloride. The antimicrobial activity of the newly synthesized compounds had been evaluated. Hamdan[42] & co workers prepared a set of six novel benzimidazoles derivatives [42] (Figure 3) such as 5-nitro-2-phenyl-1-ethylbenzimidazol, 2-(*p*-bromophenyl)-5-nitro-1-ethylbenzimidazol, 2- (*p*-bromophenyl-5-nitro-1–

cyclopentylbenzimidazol, 2-(*p*-bromophenyl)-5-nitro-1-cyclopentyl benzimidazol, 5-amino-2-(*p*-bromophenyl)-1-ethylbenzimidazol, and 5-amino-(2-(*p*- bromo phenyl)-1-cyclopentylbenzimidazol. The biological activity of these compounds as fungicides was tested against three commercially known fungicides (*C. albicans*, patient isolate *C. glabrata* and *C. krusei*). The biological activity of two compounds [2-(*p*-bromophenyl)-5-nitro-1-ethylbenzimidazol & 5-amino-2-(*p*-bromophenyl)-1-ethylbenzimidazol] was found to be comparable to that of the commercially available fungicides.

Shefali[43] prepared and screened some benzimidazole derivatives [43] (Figure 3) for their antimicrobial activities with various strains. They prepared various benzimidazole derivative from *o*-phenylenediamine, 4,5-dimethyl-1,2-phenylenediamine, 4-chloro-1,2-phenylenediamine, 3,4-diaminobenzophenone by reacting with 4-isothiocyanato-4-methylpentan-2-one. All synthesized derivatives have been screened against various bacterial and fungal strains such as *Escherichia coli, Bacillus pumilus, Micrococcus luteus, Bacillus cereus, Klebsiella pneumonaie, Aspergillus niger, Aspergillus flavus, Trichosporum flavurusclem and Microsporum gypseum*. From the study it was found that the S-methylated 3,4-diamino benzophenone derivative showed more inhibition zone than the standard drug Amoxycillin against bacterial strain *Klebsiella pneumonaie*. Jeyanthi[44] *et al*. prepared 2-*p*-substitutedphenyl-2-benzimidazoloacetonitriles [44] (Figure 3) by the reaction of benzimidazole with *p*-substitutedbenzaldehydes and trimethylsillylcyanide in acetonitrile in the presence of bismuthtrichloride. A series of 2-(α-p-substitutedphenyl-α-benzimidazolo)methylbenzimidazoles were synthesized by the reaction of 2-*p*-substituted phenyl-2-benzimidazolo acetonitrile with *o*-phenylenediamine in presence of hydrochloric acid. These compounds were found to exhibit both antibacterial and antifungal activities.

Panneer[45] *et al*. synthesized and characterized a novel series of 2-substituted benzimidazole derivatives [45] (Figure 3). The compounds were screened for antibacterial (*Staphylococcus aureus, Staphylococcus epidermidis, klebsiella pneumoniae* and *Esherichia coli*) and antifungal (C*andida albicans* and *Aspergillus niger*) activities by agar streak dilution method. 1-(4-(1*H*-benzo[*d*]imidazol-2-yl)phenyl)-3-chloro-4-(4-nitrophenyl)azetidin-2-one was found to exhibit the most potent *in vitro* antimicrobial activity with MIC of 15, 17, 19, 9, 11 and 15 µg/ml against *E. coli, K. pneumoniae, S. aureus, S. epidermidis, C. albicans* and *A. niger*, respectively. All the other compounds exhibited moderate activity against the bacterial and fungal organism tested. A number of *N*'-(arylmethylidene)-2-(2-methyl-1*H*-benzimidazol--1-yl)acetohydrazide and 4-aryl-5-[(2-methyl-1*H*-benzimidazol-1-yl)methyl]--4*H*-1,2,4-triazole-3-thiol derivatives [46] (Figure 3) were synthesized by incorporating various aromatic and heterocyclic substituent on 2-methyl-1*H*-

benzimidazole by Ansari[46] *et al*. The *in vitro* activities of these compounds against bacteria and fungi were evaluated by the disc diffusion and the MIC of test compounds were determined against the tested micro organism. Some of the synthesized derivatives were found to be as active as kanamycin which was used as standard drug for comparision.

Manish[47] *et al*. synthesized N-(1*H*-benzimidazol-2-yl)-6-substituted-1,3-benzothiazol-2-amines and 6-substituted-N-(4,5-dihydro-1*H*-imidazol-2-yl)-1,3-benzothiazol-2-amines [47] (Figure 3) by the reaction of substituted 2-aminobenzothiazoles with carbondisulphide and methyl iodide followed by the reaction with *o*-phenylene diamine/ethylene diamine. The potent antibacterial and entomological (antifeedant, acaricidal, contact toxicity and stomach toxicity) activities of the synthesized compounds were investigated. The antibacterial activities of the tested compounds are much less than those of standard antibacterial agents used. Antifeedant activity, contact toxicity and stomach toxicity against *Spodoptera litura* and acaricidal activity against *Tetranychus urticae* were moderate for test compounds.

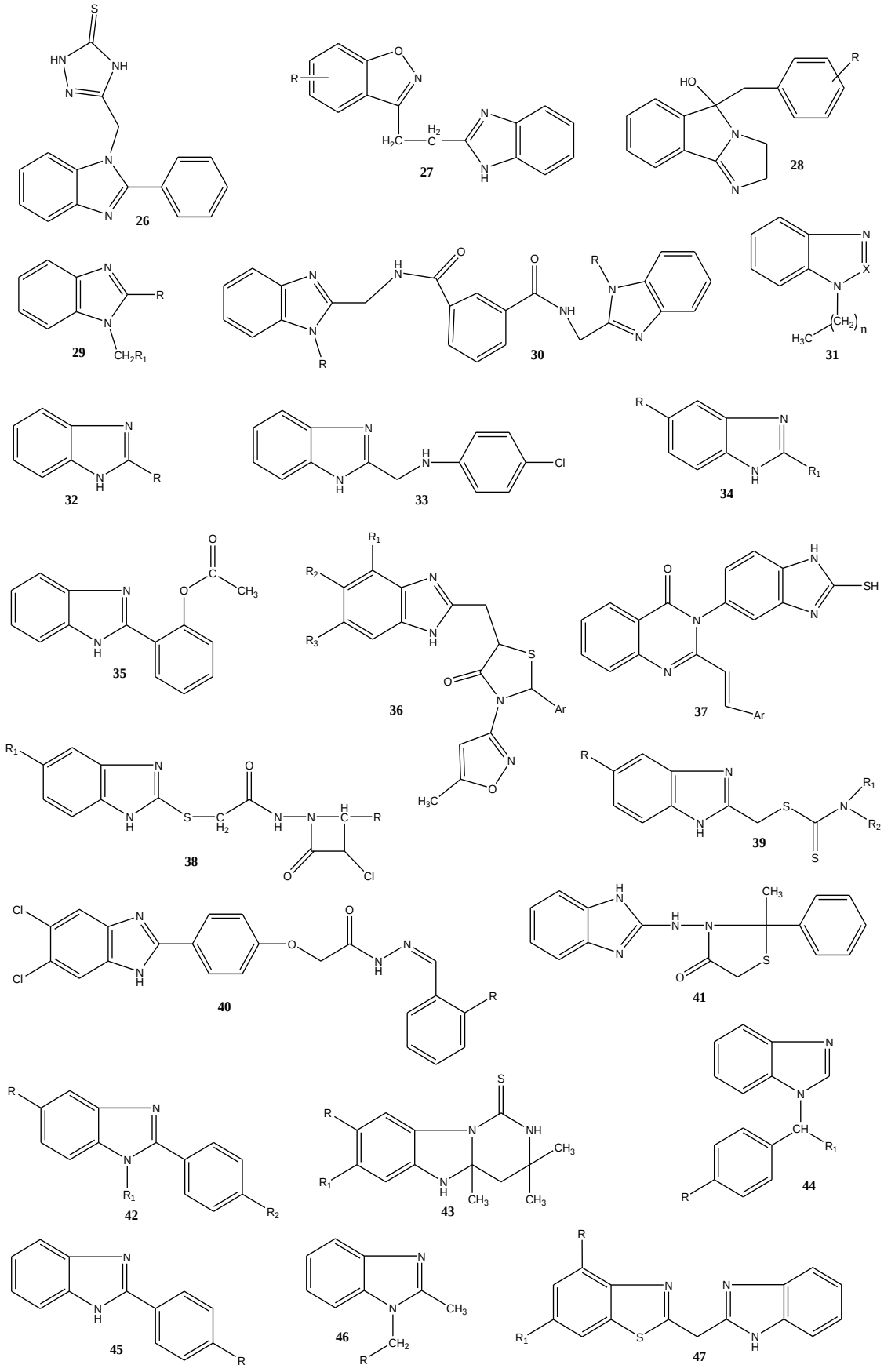

Figure 3: Structure of anti-microbial benzimidazoles (26 - 47)

Ranjith[48] *et al*. described a convenient method using TMSCl (20 mol %) and microwave induced technique for the synthesis of various benzimidazole derivatives [48] (Figure 4). When compared to conventional heating this has reduced the reaction time drastically as well as improved the yield. The synthesized compounds were evaluated for their *in vitro* antibacterial and antifungal activities against four strains each. Preliminary results indicated that, some of the compounds demonstrated very good antimicrobial activity, comparable to the first line standard drugs. The most effective compounds have exhibited activity at MIC of 6.25 µg/ml.

Umarani[49] *et al.* synthesized a new series of 2-mercaptobenzimidazoles [49] (Figure 4) bearing 1,2,4-triazole, 1,3,4-thiadiazole, and 1,3,4-oxadiazole. The synthesized compounds were investigated *in vitro* antimicrobial activities against gram positive bacterium *Staphylococcus aureus*, gram negative bacterium *Escherichia coli* and fungus *Aspergillus niger* by cup plate method. Janardhana[50] *et al.* synthesized a new series of 2-(1*H*-benzimidazol-2-yl)-6-substitutedthieno quinolines [50] (Figure 4) by using process in which 2-(chloromethyl)-1*H*-benzimidazole / 2-(mercaptomethyl)-1*H*-benzimidazoles undergo nucleophilic substitution and cyclisation with 2-mercaptoquinoline-3-carbaldehyde. The synthesized compounds were screened for antimicrobial activity. Sharma[51] *et al.* synthesized 2-{2'-[substituted phenyl]-2'-methylthiazolidine-4-one-3-ylamino}-1*H*-benzo[*d*]imidazoles [51] (Figure 4) by the reactions of 2-hydrazinobenzimidazole with acetophenones which on further reaction with thioglycollic acid in the presence of anhydrous zinc chloride. The antibacterial activity was tested.

Mahesh[52] *et al*. synthesized benzimidazolyl β-ketosulfones and β-hydroxysulfones [52] (Figure 4) by the condensation of 2-mercaptobenzimidazoles with α-bromoacetylbenzene gives benzimidazolyl β-ketosulfides, which on oxidation with hydrogen peroxide giving β-ketosulfones and subsequent reduction with sodium borohydride gave β-hydroxysulfones. The synthesized compounds were evaluated for their antifungal activity. Janardhana[53] *et al*. synthesized 2-substituted-1-[(5-substituted phenyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazole [53] (Figure 4). The synthesized compounds were evaluated for their antifungal and antibacterial activity. Davoodnia[54] *et al*. synthesized pyrimido[4',5':4,5]thiazolo[3,2-*a*]benzimidazol-4(3*H*)-ones [54] (Figure 4) by the reaction between 3-aminothiazolo[3,2-*a*]benzimidazol-2-carboxamide with aromatic aldehydes in presence of boiling glacial acetic acid. The synthesized compounds were evaluated for their antibacterial and antifungal activity.

Dubey[55] *et al*. synthesized benzimidazole β-keto sulfones and β-hydroxy sulfones [55] (Figure 4) and their regiospecific derivatives by alkylation of benzimidazole moiety. The synthesized compounds were evaluated antifungal activity. Devmurari[56] *et al*. synthesized a series of methyl 2-substituted

benzimidazole-1-carbodithioats 56 (Figure 4) by using condensation of *o*-phenylenediamine with substituted carboxylic acid and by condensation of substituted benzaldehydes, sodium metabisulphate and *o*-phenylenediamine. The synthesized compounds were analyzed against three gram-positive bacterial species and gram negative species using agar well diffusion method (cup plate method). Venkataramana[57] *et al*. reported the synthesis and the biological activity of various phenyl hydrazine substituted benzimidazole derivatives [57] (Figure 4). In this study they condensed *o*-phenylenediamine with chloro acetic acid to produce 2-chloromethylbenzimdazole, which undergoes halide replacement with phenylhydrazines and produced corresponding *N*,*N*'-disubstituted hydrazines. The synthesized compounds were subjected to microbiological screening against various bacteria and fungi. All compounds have shown antibacterial activity against Gram positive bacteria (*Staphylococcus aureus*, and *Enterococci*) as well as Gram negative bacteria (*Escherichia coli*, and *Shigella*). The 6-nitro derivative of benzimidazole shows good activity against *Aspergillus niger* and *Aspergillus flavus.*

Hassan[58] *et al.* synthesized novel benzimidazole and fused benzimidazole derivatives [58] (Figure 4) such as triazinobenzimidazoes, oxadiazolylthiomethyl-1*H*-benzimidazole, triazolyl thiomethyl-1*H*-benzimidazole, thiazolidinyl-methyl-1*H*-benzimidazoles, and pyrimidinopyrrolo benzimidazoles. The synthesized compounds were evaluated for antimicrobial activity.

Hasan[59] *et al.* synthesized new derivatives of benzimidazole [59] (Figure 4) by the reaction of benzimidazole with alkylhalides. The synthesized compounds were screened for their *in vitro* antimicrobial activities against the standard strains *i.e*., *Enterococcus faecalis*, *Staphylococcus aureus*, *E. coli*, *Psedomonas aeruginosa* and the yeasts *Candida albicans* and *Candida tropicalis*.

Shet[60] *et al*. synthesized a new series of 2-substituted alkyl thioarylbenzimidazole derivatives [60] (Figure 4) by condensing *o*-phenylenediamine with aryl and naphthyl thioglycolic acid. The synthesized compounds were characterized by spectroscopic data and screened for *in vitro* antibacterial activity against *K. pneumoniae, E. coli, S. aureus and E. fecalis*. Ciprofloxacin was used as standard drug for comparision and the compounds shown varying degree of antimicrobial activity. 2-(2-(5-phenyl-1*H*-tetrazol-1-yl)phenyl)-1*H*-benzo[*d*]imidazole [61] (Figure 4) was synthesized from *o*-phenylenediamine and anthranillic acid by a multi step synthesis by Ahamed[61] *et al*. Antimicrobial activity of these compounds were tested against various strains of bacteria and fungi by disc diffusion method.

Valarmathy[62] *et al*. synthesized 2-pyridin-3-yl-1,3-benzoxazole and 2-pyridin-3-yl-1,3-benimidazole [62] (Figure 4) by using microwave irradiation. The synthesized compounds were evaluated for their antimicrobial activity and exhibit a variable degree of activity. Srivastava[63] *et*

al. synthesized few Mannich bases of 2-(benzimidazolyl aminomethyl)thiazolidin-4-one [63] (Figure 4) by using amination at position 5 using formaldehyde and various secondary amines. The synthesized compounds posses' antibacterial activity. Ganesh[64] *et al*. synthesized substituted 4-{[4,6-difluro-1-substituted-1*H*-bezo[*d*]-imidazol-2-yl]methoxy} benzonitriles [64] (Figure 4) by alkylation of 4-{[4,6-difluoro-1*H*-benzo[*d*]imidazol-2-yl] methoxy}benzonitriles with alkyl and substituted aryl halides. The synthesized compounds were evaluated for *in vitro* antibacterial activity against *Pseudomonas aeruginosa*, and *E. coli*.

Shet[65] *et al*. synthesized a new series of chiral derivatives of 3-(2,2-dihalovinyl)-2,2-dimethyl-*N*-(2-oxo-2,3-dihydro-1*H*-benzimidazole-5-yl) carboxamide [65] (Figure 4). The synthesized compounds were screened for *in vitro* antibacterial activity against a variety of bacterial strains using Ciprofloxacin as a standard. Shet[66] *et al.* synthesized a new series of 2-substituted alkyl thioarylbenzimidazole derivatives [66] (Figure 4) by using condensation of *o*-phenylenediamine with aryl and naphthyl thioglycolic acid. The synthesized compounds were screened for *in vitro* antibacterial activity against a variety of bacterial strains using Ciprofloxacin as standard. Jadhav[67] *et al*. synthesized *N*-substituted benzimidazoles [67] (Figure 4). The synthesized compounds were evaluated for their antibacterial and antifungal activity.

Goudagaon[68] *et al.* synthesized 2-(2-benzylthiopyrimidin-4-yl)substituted benzimidazoles [68] (Figure 4) by using 5-sustituted-2-benzylthiouracil and 5,6-disustituted-2-benzylthiouracil on chlorination with $POCl_3$ to form 5-sustituted-4-chloro-2-benzylthiopyrimidines and 5,6-disustituted-4-chloro-2-benzylthiopyrimidine. These two compounds were reacts with 2-mercaptobenzimidazole in methanol in presence of anhydrous potassium carbonate. Rajanarendar[69] *et al*. synthesized a series of novel 2/3(1*H*-benzimidazol-2-yl)-*N*-(5-methyl-3-isoxazolyl)-benzamides, acrylamides and propionamides [69] (Figure 4). The synthesized compounds were evaluated against two Gram-positive and two Gram-negative bacteria and two plant pathogenic fungi. Shelar[70] *et al*. synthesized a series of alkyl thioaryl substituted benzimidazoles [70] (Figure 4). The synthesized compounds were showed good antifungal and antibacterial activity.

Shelar[71] *et al.* synthesized a series of 2-substituted chiral benzimidazole derivatives [71] (Figure 4). They tested for their antimicrobial and antibacterial activities. Oztekin[72] *et al.* synthesized 1,5(6)-*H*/or-methyl-2-sustituted benzimidazole derivatives [72] (Figure 4). Goel[73] *et al.* synthesized 1*H*-benzimidazole derivatives [73] (Figure 4) with anti-protozoal activity against *Entamoeba hystolytica* was subjected to the three dimensional quantitative structure activity relationship studies using various combinations of thermodynamic, electronic, and spatial descriptors. Nyati[74] *et al.* synthesized 3-benzimidazolyl-5-aryl-2-isoxazolines [74] (Figure 4) using microwave irradiation from

corresponding chalcones and hydroxylamine hydrochloride in presence of pyridine. The synthesized compounds were evaluated for their antibacterial and antifungal activity.

The *in vitro* antibacterial and antifungal activities of six benzimidazole and benzoxazole derivatives [75] (Figure 4) were tested against standard strains and 59 clinical isolates by Elamin[75] *et al*. Of the six compounds, only two benzoxazoles derivatives were active, whereas the rest were devoid of any activity. The most susceptible were the *S. aureus* isolates. The two compounds were of comparable activity against all of the isolates, with one compound showing a slightly higher activity than another compound. Their respective minimal inhibitory concentrations for 90 % inhibition of *S. aureus* were 25 and 50 µg/ml. The gram-negative bacteria were resistant to the two compounds and required minimal inhibitory concentrations of 200 µg/ml for a similar degree of inhibition.

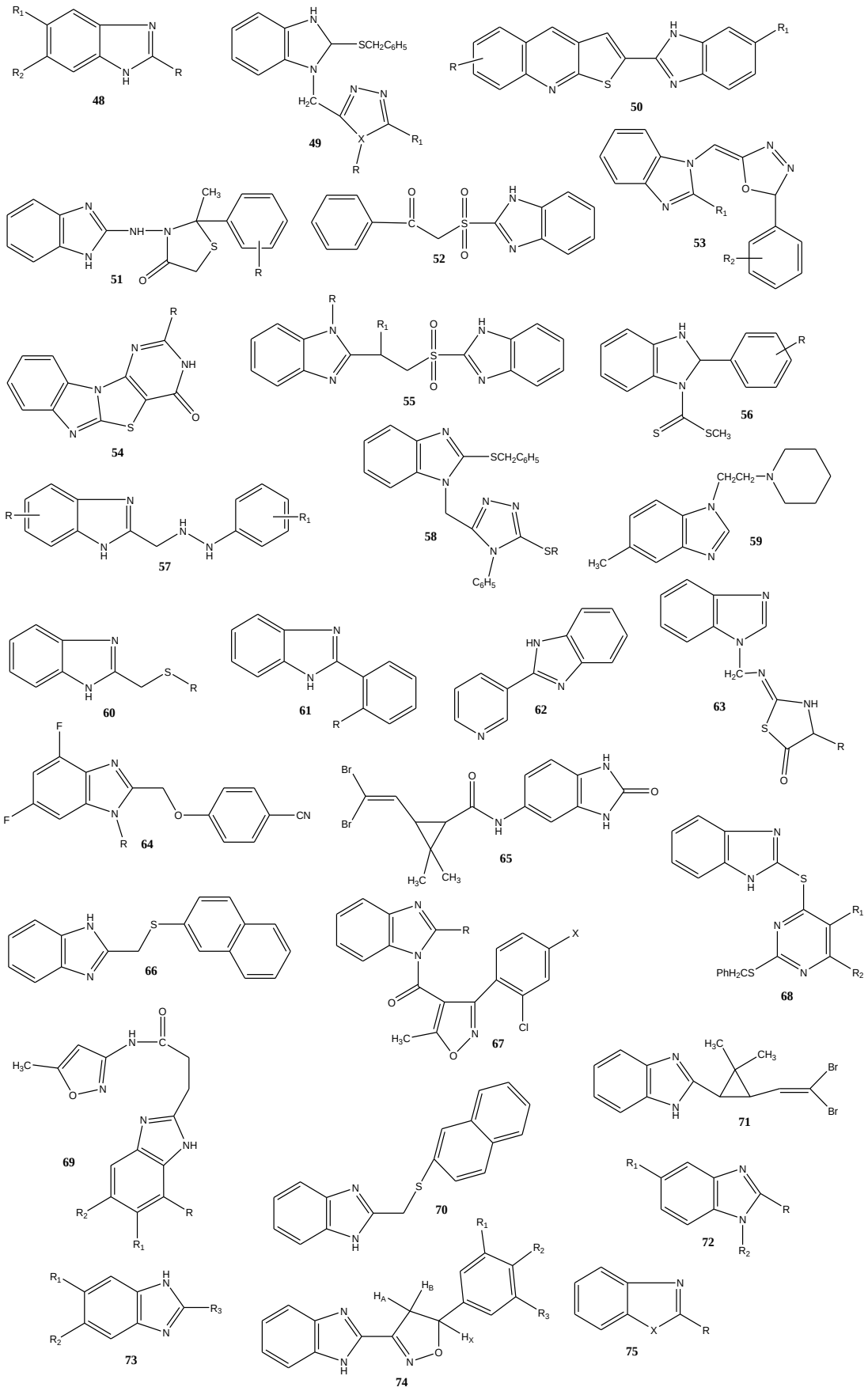

Figure 4: Structure of anti-microbial benzimidazoles (48 - 75)

CONCLUSION

Large numbers of antimicrobial agents were available to treat various diseases, but they are associated with some drawbacks like resistance, toxicities and other adverse effects. To combat with these problems there is need to discover and synthesize newer chemical entities with better efficacy and novel mechanism of action. The benzimidazole ring is an important pharmacophore in modern drug discovery. The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research. There is still scope for more research work to be done in this field to find a novel agent. The versatility of new generation benzimidazole would represent a fruitful pharmacophore for further development of better medicinal agents. Therefore this substrate has a tremendous scope for the discovery of new, better, safe and more potent antimicrobial agents.

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