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BENZIMIDAZOLE DERIVATIVES AND THEIR ANTIMICROBIALACTIVITIES: A REVIEW

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ABSTRACT

Over the past decade, development of small heterocyclic molecules as potential therapeutics has been an area of major interest. A large number of benzimidazole derivatives are of considerable biological and chemical interest. Many substituted benzimidazoles have been reported to display a large panel of biochemical properties, like anti-microbial, anti-diabetic, anticancer activity, numerous anti-oxidant, anti-parasitic, anti-helmintics. Variation of substituents on the benzimidazole nuclei could potentially affect the interaction of the molecules with biological targets. The versatile synthetic applicability and biological activity of these heterocyclic compounds will help the medicinal chemists to plan, organize and implement new approaches towards discovery of novel drugs. The aim of this review is to focuson the research work reported in the recent two decades on the antimicrobial activity of various benzimidazole derivatives.

KEYWORDS: Benzimidazole, antimicrobial, antibacterial, derivatives, synthesis, compounds.

INTRODUCTION

Benzimidazole (Fig-1) is a heterocyclic aromatic compound which is bicyclic in nature in which benzene ring is fused to the imidazole ring at 4,5 positions. Imidazole indicates a five- membered heterocyclic ring system composed of imino group and a tertiary nitrogen. Imidazole skeleton is found in numerous natural compounds that found practical applications in wide variety of fields.[1]

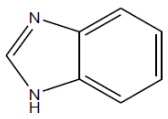


Fig. 1: Benzimidazole nucleus.

Benzimidazoles are also identified as derivatives of *o*-phenylenediamine or benziminazoles or benzoglyoxalines. In 1872, Hoebrecker developed first benzimidazole, 2,5(or 2,6)-dimethyl benzimidazole (Fig-2) which is part of the chemical structure of vitamin B12.[2] Thiabendazole was the first benzimidazole developed and licensed for human use which is used as anthelmintic along with other derivatives such as albendazole, mebendazole and flubendazole.Omeprazole, lansoprazole and pantoprazole has a value as proton pump inhibitors; astemizole as antihistaminic and enviradine as antiviral.[3]

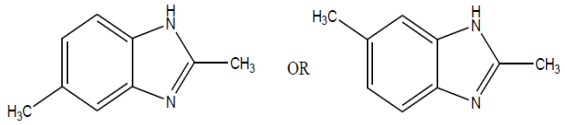


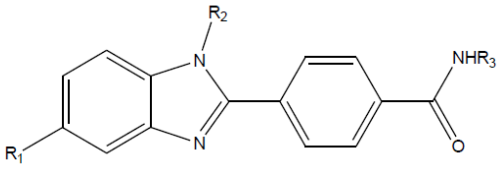
Fig. 2: Dimethyl benzimidazole.

Benzimidazole derivatives have occupied a prominent place in medicinal chemistry due to their significant properties and they are building blocks for many bioactive compounds used in clinical applications. As a result of the important heterocyclic pharmacophore contained in several benzimidazole derivatives with different substituents, they possess a broad spectrum of biological activities and therapeutic properties, such as antimicrobial, anthelmintic, anti- cancer, analgesic, anti-HIV, anti-viral, anti-bacterial, anti-fungal, anti-inflammatory, anti- Alzheimer's disease, antihistaminic, antioxidant, anti-malarial, anti-hypertensive and proton pump inhibitor. Benzimidazoles are also regarded as smooth muscle cell proliferation inhibitors, potential antitumor agents, a treatment for intestinal cystitis and in miscellaneous area of chemistry. Certain significant benzimidazole derivatives have been designated as gonadotropin releasing hormone receptor antagonists, non-nucleoside HIV-1 reverse transcriptase inhibitors, thyroid receptor agonist and fascinatingly alkynyl benzimidazoles as modulators of metabotropic glutamate receptors.[4-16] Their activity against bacteria, fungi and

helminths resulted from the blockage of microtubule in various nematode, trematode and cystode.[17] Numerous derivatives of benzimidazoles were soon synthesized to improve upon its activity. In this review, we will briefly summarize the antimicrobial activity of various benzimidazoles reported in the literature over the past two decades.

ANTIMICROBIAL ACTIVITY OF BENZIMIDAZOLES

Goker *et al*[18] reported the synthesis of 2-Phenyl-*N*-substituted Carboxamido-1*H*- benzimidazole derivatives (Fig.-3) and the antimicrobial activities of newly synthesized compounds were evaluated against *Staphylococcus aureus, Escherichia coli* and *Candida albicans*. The results of in vitro antimicrobial activity were determined by tube dilution method using fluconazole as reference standard. Among the synthesized compounds, best activity was shown with introduction of chlorine atom or trifluoromethyl group at C-5, and the *p*- chlorobenzyl group.



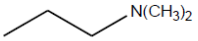
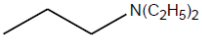
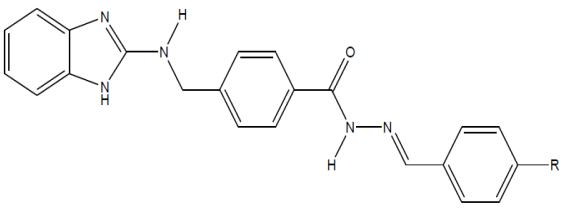
R_1 = CF3, Cl, R_2 = butyl, p- chlorobenzyl, R_3 =  , 

Fig. 3.

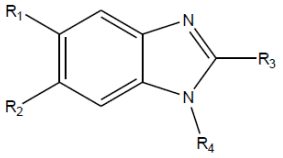
Y. Ozkay *et al*[19] synthesized series of benzimidazole derivatives (Fig.- 4) and evaluated for their antibacterial activity. Final products were evaluated for their in vitro growth inhibitory activity against gram-positive bacteria; *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Bacillus subtilis* and *Listeria monocytogenes*, gram-negative bacteria; *Klebsiella pneumoniae* ATCC 13883, *Escherichia coli* ATCC 35218, *E. coli* ATCC 25922, *Salmonella thyphimurium* NRRL B-4420 and *Proteus vulgaris* NRLL B-123 and yeast as *Candida albicans*, *Candida tropicalis* and *Candida globrata* ATCC 36583. Antimicrobial activity was performed by micro-dilution method using chloramphenicol and ketoconazole as control drugs. Majority of the synthesized compounds exhibited good to moderate activity against a number of gram-positive and gram-negative bacteria and fungal strains. Among them, nitro substituted and cyano substituted compounds showed two-fold better potency (MIC = 25 µg/mL) than reference drug ketoconazole (MIC = 50 µg/mL).



R = H, NO2, CF3, CN, COOH

Fig. 4.

M. Tuncbilek *et al*[20] prepared some novel substituted benzimidazole derivatives (Fig.- 5) and tested for their antimicrobial activity. The in vitro antibacterial activity of newly synthesized compounds was assessed via tube dilution method against gram-positive bacteria; *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA, standard and clinical isolate), *Bacillus subtilis*, Gram-negative bacteria; *Escherichia coli* and antifungal activity against *Candida albicans*. Ciprofloxacin, ampicillin and sultamicillin were used as reference standard. The results showed that, 2,5,6-Trihalogenobenzimidazole analogues, 5,6-dichloro-2-amino derivative, 5,6-dichloro-2-(4-fluoro/chlorophenyl)-1-nonsubstituted and 5-chloro-2-(4-benzyloxyphenyl) benzimidazole exhibited excellent activity. Compounds having free NH group of the benzimidazole moiety were slightly more effective against MRSA standard and MRSA clinical isolate than other compounds.

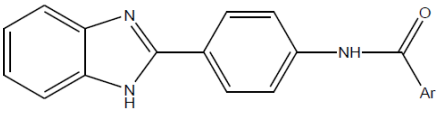


R1 = Cl, R2 = Cl, H,
R3 = Cl, Br, NH2, 4-fluorophenyl, 4-chlorophenyl, 4-tert-Butylphenyl, 4-benzyloxyphenylR4 = cyclopentyl, H

Fig.- 5

G. Ayhan-Kilcigil *et al*[21] worked on the synthesis of benzimidazolylbenzamides (Fig.- 6) and evaluated for in vitro antibacterial and antifungal activity by tube dilution technique. *Staphylococcus aureus* ATCC 25923, *Streptococcus faecalis* ATCC 19433 and *Bacillussubtilis* ATCC 6633 as gram-positive, *Escherichia coli* ATCC 23556 and *Pseudomonas aeruginosa* ATCC 10145 as

gram-negative bacteria and *Candida albicans* ATCC 10231 as fungus were used for estimation of in vitro antimicrobial activity using ampicillin trihydrate, miconazole and fluconazole as standard drugs. Some of the tested compounds exhibited goodactivity with a MIC value of 25 µg/mL against *P. aeruginosa*. From results it was revealed that, substitution of amine function to anilide at the 2-phenyl moiety of benzimidazole ring decreases the activity against *S. aureus* and *C. albicans*. It was also reported that sulfur bearing compound showed moderate activity against the tested microorganism.



Ar = phenyl, 3-nitrophenyl, p-toluene, 2-chlorophenyl

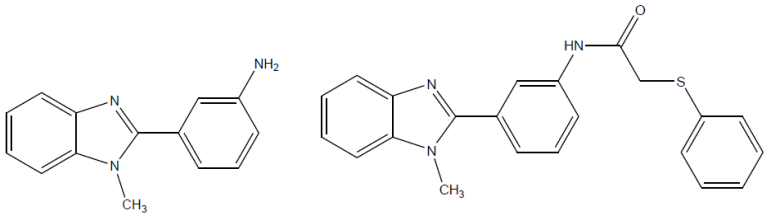
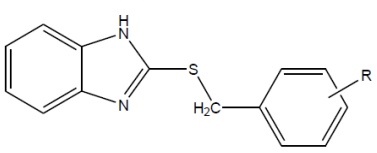


Fig.- 6.

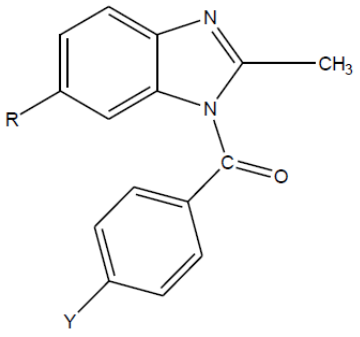
V. Klimesova *et al*[22] synthesized and evaluated series of 2-alkylsulphanylbenzimidazoles (Fig.- 7). *Mycobacterium tuberculosis* CNCTC My 331/88, *Mycobacterium kansasii* CNCTC My 235/80, *Mycobacterium kansasii* 6509/96 and *Mycobacterium avium* CNCTC My 330/88 were used for the estimation of in vitro antimycobacterial activity via the micromethod for the determination of the minimum inhibitory concentration using isoniazid as reference standard. In vitro antifungal activity of the compounds was evaluated against a panel of one ATCC; *Candida albicans* ATCC 44859 and seven clinical isolates of yeasts; *Candida tropicalis* 156, *Candida krusei* E28, *Candida glabrata* 20/I and filamentous fungi; *Trichosporon beigelii* 1188, *Trichophyton mentagrophytes* 445, *Aspergillus fumigatus* 231, *Absidia corymbifera* 272 by the microdilution method and the ketoconazole was used as reference standard. Modification of the benzyl moiety by electron withdrawing groups showed improved activity. A significant activity was observed for the compounds containing 3,5-dinitro and 2,4-dinitro groups in the benzyl moiety. The thioamide derivative also showed promising effect with MIC value 8-62 µmol L^{-1}. Results indicates that the activity is linked to the substitution at position 2 of the benzimidazole ring, as the substitution of the hydrogen atom of the -SH group at this position with an alkyl/ arylalkyl chain improves the activity.



R = 3,5-$(NO_2)_2$, 2,4-$(NO_2)_2$, 4-$CSNH_2$

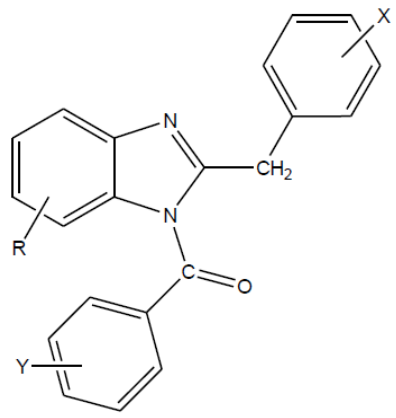
Fig. 7.

P. S. Rathee *et al*[23] did synthesis of two series of novel benzimidazole derivatives, the first one contains of 2-methyl (Fig.- 8), the second one contains of 2-phenyl (Fig.- 9) substitution on benzimidazole moiety. The newly synthesized compounds were screened for their in vitro antimicrobial activities against *Candida albicans* and *Aspergillus fumigatus* by using tube dilution method. Amphotericin B was used as a standard drug. Some of the synthesized compounds exhibited considerable antifungal activity. From results of antimicrobial activity, it was concluded that hydroxyl group at position 5 of benzimidazole may be essential for activity, the electron withdrawing groups at para position of benzoyl group may shows the positive effect on the antifungal activity and the p-substitutions at 2-phenyl benzimidazoles may have no effect on the activity.



R = H, OH, Y = NO_2, H

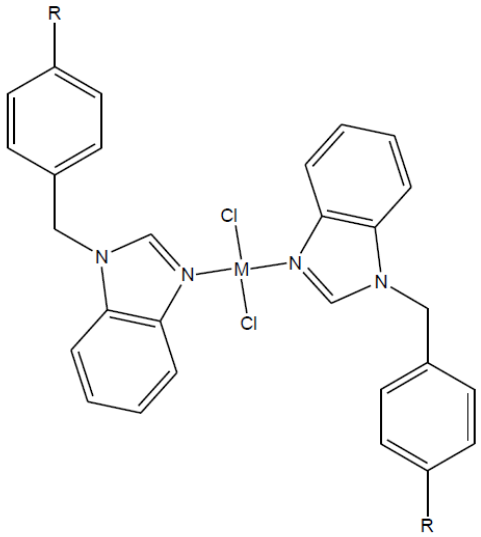
Fig.- 8



R = H, OH, X = NO_2, H, Y = NO_2, H

Fig. 9.

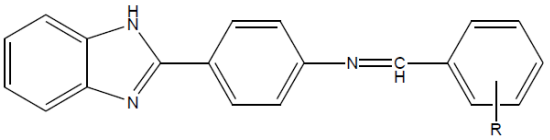
E. Apohan *et al*[24] reported synthesis of novel cobalt and zinc complexes of benzimidazoles (Fig.-10) from the 1-(4-substitutedbenzyl)-1*H*-benzimidazoles and $CoCl_2.6H_2O$ or $ZnCl_2$. *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecium* NJ-1 and *Candida albicans* were used for testing the antibacterial and antifungal activity respectively. Antibacterial and antifungal activity of the newly synthesized compounds were evaluated via minimum inhibitory concentration method. The position and type of the substituent on the benzimidazole moiety gives variety of biological activity to the compounds. Among the compounds, high antimicrobial activity shown with the 4-bromobenzyl, 4-chlorobenzyl and 4-methylbenzyl substituent at the position 1 of the benzimidazole ring and also showed low cytotoxicity againsthealthy human lung bronchial epithelium cells (BEAS-2B). These compounds are also more cytotoxic on A549 cells than cisplatin.



R = Cl, Br, CH_3, M = Zn, Co

Fig. 10.

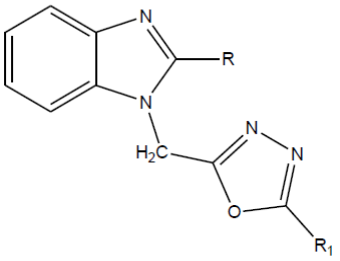
Pradeep Kumar *et al*[25] synthesized some new 2-phenyl benzimidazole derivatives (Fig.- 11) by cyclocondensation with appropriate reagents. All the newly synthesized compounds were screened for their in vitro antimicrobial activities against the *Staphylococcus aureus* ATCC - 25923, ATCC - 441 and *Bacillus subtilis* ATCC- 6633 as gram positive bacteria and *Escherichia coli* ATCC - 11775 and *Pseudomonas aeruginosa* ATCC 10145 as gram negativebacteria. Some of the compounds inhibited the growth of the gram-positive and gram-negative bacteria. The basic N=C group believed to improve antimicrobial activity. Substitution of amine function to anilide at the 2-phenyl moiety of benzimidazole moiety enhances the activity against *B. subtilis*. It was also reported that the presence of N=CH-group (azomethine) increase the potencies of the synthesized compounds.



R = 3-NO_2, H

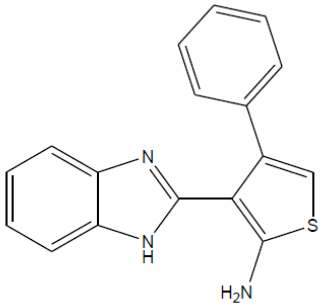
Fig. 11.

Ansari *et al*[26] worked-on synthesis of some new derivatives of benzimidazole by nucleophilic substitution of 2-substituted-1*H*-benzimidazole. The resulting 2-substituted-1- [{(5-substituted alkyl/aryl)-1,3,4-oxadiazole-2-yl} methyl]-1*H*-benzimidazole derivatives (Fig.- 12) were screened for their antimicrobial activities. Gram positive bacteria including *Staphylococcus aureus* (ATCC 29213), *Bacillus subtilis* (MTCC 121) and *Streptococcus mutans* (MTCC 890) and gram-negative bacteria including *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (MTCC 741) and *Salmonella typhi* (MTCC 733) were used to evaluate in vitro antibacterial activity. Antifungal activity was performed against yeast including *Candida albicans* (MTCC 1637) and fungi including *Aspergillus flavus* (AIIMS) and *Aspergillus niger* (AIIMS). All the synthesized compounds showed good activity against gram- positive bacteria and negligible activity against gram-negative bacteria and some of thecompounds showed moderate activity against tested fungi. Benzene ring of 2-substituted-1- (1,3,4-oxadiazole-2-ylmethyl)-1*H*-benzimidazole substituted at *ortho* position generates sterichindrance, therefore it was found to be less active than corresponding *para*-substituted compounds. From results, it was inferred that as the number of carbon atom increases in side chain at 2-position of oxadiazole heterocyclic ring causes an increase in the intensity of the activity against *S. aureus*, *B. Subtilis* and *C. albicans*.



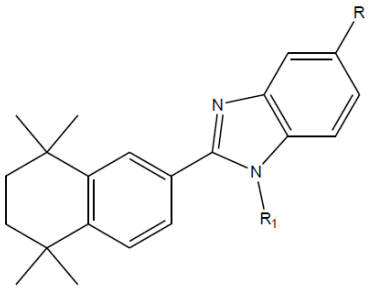
R = CH_3
R1 = CH_3, C_2H_5, CH_2CH_2Cl, C_6H_5, 4-ClC_6H_4, 4-OHC_6H_4, 2-$OCH_3C_6H_4$, 4-$OCH_3C_6H_4$
Fig. 12.

S. M. Rida *et al*[27] reported synthesis of novel benzofuran and related benzimidazole derivatives and evaluated for their antimicrobial activities. All the synthesized compounds were assessed by the agar cup diffusion technique using a 2 mg/mL solution in DMF. The test organisms used were *Staphylococcus aureus* (ATCC 6538) and *Bacillus subtilis* (DB 100), Gram-positive bacteria, *Pseudomonas aeruginosa* (ATTC 27853) and *Escherichia coli* (DH5a), Gram-negative bacteria, and *Candida albicans* (0443P), a representative fungus and ampicillin and clotrimazole in DMF were used as reference drugs. Among the synthesized compounds 2- [2-amino-4-phenyl thien-3-yl]-I H-benzimidazole (Fig.- 13) showed mild activity towards *S. aureus* and *C. albicans*.



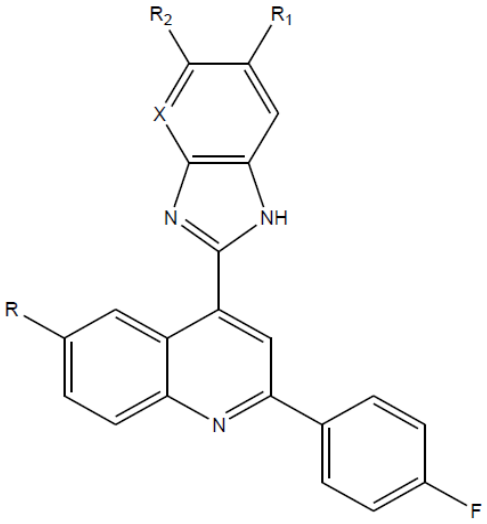
H_2N
Fig. 13.

Zeynep Ates-Alagoz *et al*[28] worked-on synthesis of novel retinoid derivatives containing a benzimidazole moiety (Fig.- 14). All the synthesized compounds were investigated for antimicrobial activity by the diffusion method against the Gram-negative bacteria *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853), the Gram-positive bacteria *Staphylococcus aureus* (ATCC 25923), MRSA (clinical isolate), *Enterococcus faecalis* (ATCC 29212) and antifungal activity against *Candida krusei* (ATTC 6258) and *Candida albicans* (ATCC 10231). From results, it was concluded that the compound bearing nitro group at 5th position showed the highest antimicrobial activity.



R= NO_2, R_1= H
Fig. 14.

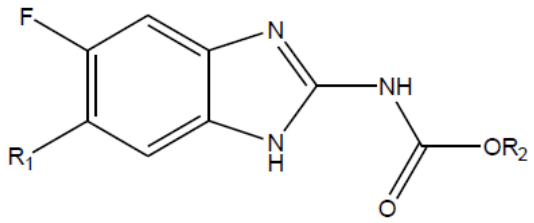
B. Garudachari *et al*[29] prepared two new series of quinoline incorporated benzimidazole derivatives (Fig.- 15) from substituted aniline and statin through multi-step reaction. All the newly created compounds were screened for their *in-vitro* antibacterial activity via well plate method (Zone of inhibition) using ciprofloxacin as standard. *Staphylococcus aureus*, *Escherichia coli*, *Xanthomonas sp.* and *Salmonella sp.* were used for determination of antibacterial activity and *Aspergillus niger*, *Aspergillus flavus*, *Aspergillus terreus* and *Penicillin sp.* were used to investigate antifungal activity. Some of the quinoline incorporated benzimidazole derivatives showed significant activity. Presence of fused pyridine ring in benzimidazole moiety as well as 4-Flurophenyl group on second position of quinoline ring is the reason for enhanced antibacterial activity. It is also concluded that the enhanced activity ofcompounds is due to presence of two chlorine atoms on benzimidazole ring.



R= Cl, H, R_1= H, Cl, R_2= H, Cl, X= N, CH
Fig. 15.

Synthesis of 5-fluoro-1,2,6-trisubstituted benzimidazole carboxamide and acetamide derivatives (Fig.- 16) was done by Canan Kus *et al*.[30] Direct condensation of the corresponding 4,5disubstituted-*o* -phenylenediamines with 1,3-dicarbalkoxy-*S* -methyl- isothiourea resulted in the synthesis of benzimidazole carbamate derivatives.

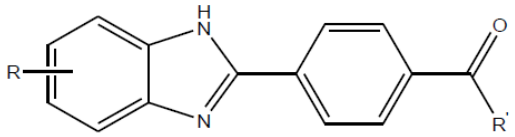
All the newly synthesized compounds were evaluated for their in vitro antimicrobial and antifungal activity against *B. subtilis*, *S. aureus*, *E. coli*, and *C. albicans* by the agar diffusion method using fluconazole, ketoconazole and ampicillin as reference standard. Among them, methyl 5-fluoro-6-(4-methylpiperidin-1-yl)-1 *H* -benzimidazole-2-carbamate exhibited best activity.



R_1= 4 methylpiperidine, R_2= Methyl

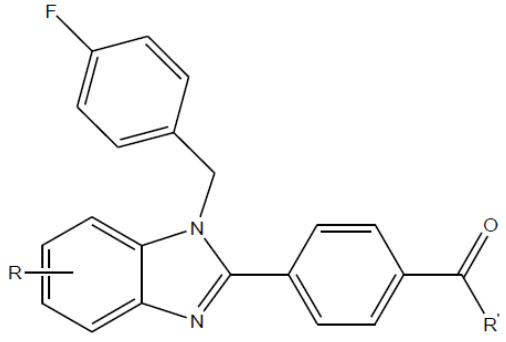
Fig. 16.

C. Kus *et al*[31] did synthesis of several new 4-(1*H*-benzimidazol-2-yl) benzamides (Fig.- 17)and 5-chloro-1-(*p*-fluorobenzyl)-2-{4-[(4-methylpiperazin-1-yl) carbonyl] phenyl}-1*H*- benzimidazole (Fig.-18). The antibacterial activity of newly synthesized compounds was evaluated by tube dilution method against *Staphylococcus aureus* ATCC 25923, MRSA clinical isolate, and antifungal activity against *Candida albicans* ATCC 10231, *Candida krusei* ATCC 6258, *Candida glabrata* clinical isolate. Ampicillin and fluconazole were used as reference standard. The result showed that, the nitro- or dichloro-groups at the 5- and / or 6- position of the benzimidazole moiety and *p*-fluorophenylpiperazine or *N*-methylpiperazine at the 4-position of phenyl improves activity.



R= 5(6) Cl, 5(6) NO_2, 5,6-dichloro
R'= *N*-Methylpiperazine, *p*-Fluorophenylpiperazine

Fig. 17.



R= 5-Cl, R'= *N*-Methylpiperazine

Fig. 18.

CONCLUSION

Benzimidazoles are important class of heterocyclic compounds that possesses a variety of biological actions. In this review, we have summarized antimicrobial activity of various benzimidazole derivatives along with recent advancement in this field during past two decades. Variety of benzimidazoles have been reported in literature having good antimicrobial activities. We can conclude that this review will help researchers further to design and synthesis new benzimidazole derivatives with promising antimicrobial activities.

CONSENT FOR PUBLICATION

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None.

CONFLICT OF INTEREST

None.

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