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Review Article

BENZIMIDAZOLE DERIVATIVES – AN OVERVIEW

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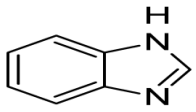
ABSTRACT

Benzimidazole derivatives play important role in medical field with so many Pharmacological activities such as antimicrobial, antiviral, antidiabetic and anticancer activity. The potency of these clinically useful drugs in treatment of microbial infections and other activities encouraged the development of some more potent and significant compounds. Benzimidazoles are remarkably effective compounds, extensive biochemical and pharmacological studies have confirmed that these molecules are effective against various strains of microorganisms. This review is summarized to know about the chemistry of different derivatives of substituted benzimidazoles along with their pharmacological activities.

Keywords: Substituted Benzimidazoles, Chemistry, Pharmacological activities.

INTRODUCTION

Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic in nature which consists of the fusion of benzene and imidazole. Nowadays is a moiety of choice which possesses many pharmacological properties. The most prominent benzimidazole compound in nature is *N*-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B_{12}.[1] [1]



1*H*-benzimidazole [1]

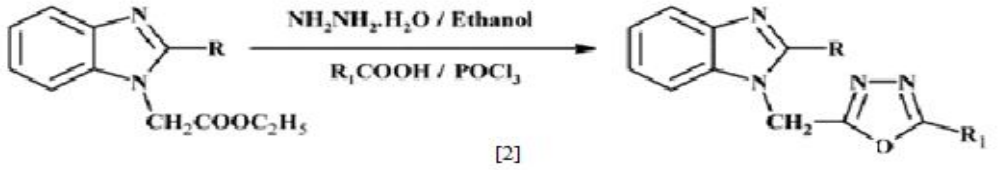
Study on Structural modifications and their pharmacological actions

The use of Benzimidazole dates many years back[2]. In 1990 various benzimidazole derivatives were synthesized with substitution of fluorine, propylene, tetrahydroquinoline and cyclised compound which resulted in compounds with increased stability, bioavailability and significant biological activity[3,4] It was also showed that substitution on pyridine by electron donating group increases activity. In 1991 benzimidazole derivatives were synthesized by derivatization at N-H of benzimidazole by electron donating group and substitution with long chain of propyl, acetamido, thio, thiazole-amino, tetramethyl piperidine on pyridine resulting in good antiulcer activity[5,6].

Nowadays Infectious microbial diseases are causing problems world-wide, because of resistance to number of antimicrobial agents (β-lactam antibiotics, macrolides, quinolones, and vancomycin). A variety of clinically significant species of microorganisms has become an important health problem globally[7]. One way to fight with this challenge is the appropriate usage of the available marketed antibiotics the other is the development of novel anti-microbial agents[8]. Hence, there will always be a vital need to discover new chemotherapeutic agents to

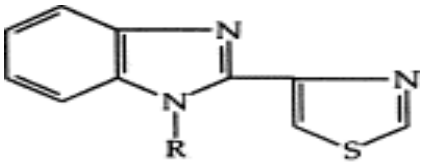
overcome the emergence of resistance and ideally shorten the duration of therapy. Due to the structural similarity to purine, antibacterial ability of benzimidazoles are explained by their competition with purines resulting in inhibition of the synthesis of bacterial nucleic acids and proteins.[9, 10]

Antimicrobial & antibacterial effects: - Literature survey shows that among the benzimidazole derivatives, 2-substituted ones are found to be pharmacologically more potent and hence the design and synthesis of 2-substituted benzimidazoles are the potential area of research.[11-13][2]

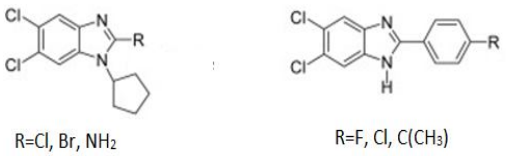


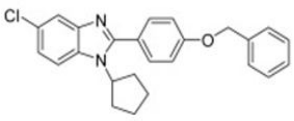
[2]

Some oxadiazol-1H-benzimidazole has been reported to possess antimicrobial activities. The compounds also showed moderate activity against tested fungi.[13] Extensive biochemical and pharmacological studies have confirmed that its derivatives are effective against various strains of microorganisms.[14-24][3]. In a study it was reported that by modifying the amide group to the anilide on the 2-phenyl benzimidazole produces antimicrobial activity.[17] Hydrazone is another considerable pharmacophore group for antimicrobial activity.



***N*-alkyl and *N*-acyl derivatives of 2-(4-thiazolyl)-1*H*-benzimidazole [3]**

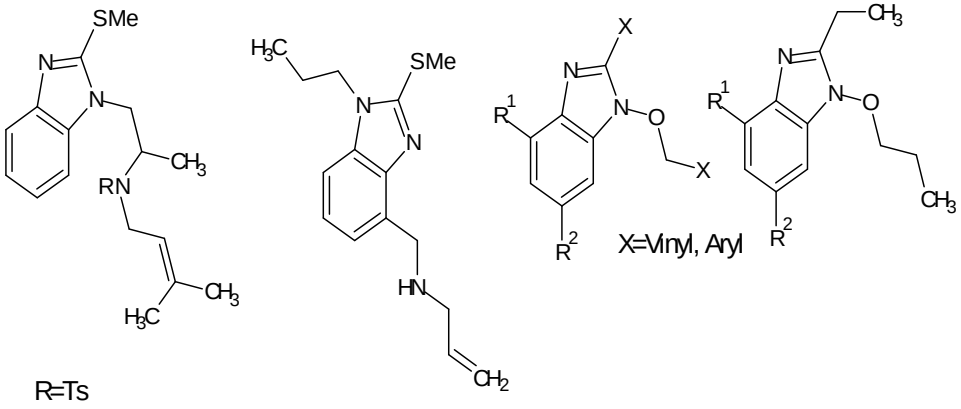




[3]

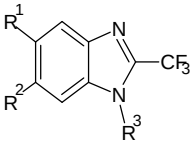
Some widely used antibacterial drugs such as furacilin, furazolidone and ftivazide are known to contain this group[25]. In past decades, hydrazones have received much attention and many studies [26-31] have been reported due to their chemotherapeutic value in the development of novel anti- microbial agents. A series of 1, 2-disubstituted-1*H*-benzimidazole-*N* alkylated- 5-carboxamidine derivatives are very potent antibacterial activities against *S. aureus* and methicillin resistant *S. aureus*.[32] The study revealed the best activity, with MIC values of 0.78 - 0.39 μg/mL against these species. Various Chloro and dichloro substituted benzimidazole also possess antibacterial activities.[23]

HIV Inhibtors:- Tetrahydro-imidazo[4,5,l-jk][1,4]-benzodiazepin-2 (1H)one (TIBO) is a noncompetitive non nucleotide antiretroviral drug with a specific allosteric binding site of HIV-1 RT**.** TIBO derivatives have proved to be potent, highly selective and specific inhibitors of HIV-1 replication in vitro. The reverse transcriptase (RT) of HIV-1, but not HIV-2, is inhibited by the TIBO compounds. Several compounds other than TIBO have recently been reported to specifically inhibit HIV-1 replication. In a research it was investigated that some novel benzimidazole derivatives, bearing analogy to TIBO, have been synthesized, and were evaluated for inhibition of HIV-1 infectivity. The most active and selective compounds are a series of N-alkoxy-2-alkyl-benzimidazoles, several having EC_{50} < 10Mm (one sub-micromolar at 600nM), and selectivity ratios of 10–167. The selective benzimidazoles, show modest RT inhibition.[33] [4]



[4]

Antiparasitic effect:- 2-(Trifluoromethyl)-1*H*-benzimidazole derivatives showed the most desirable *in vitro* antiparasitic profile against *Giardia intestinalis*, *Entamoeba histolytica*, *Trichomonas vaginalis* and *Trichinella spiralis*.[34] [5]



1b : R^1=2,3-$Cl_2C_6H_3O$, R^2=H, R^3=CH_3

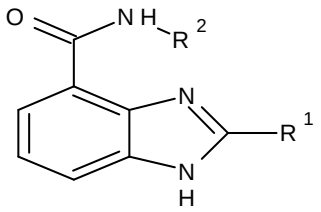
1c: R^1=H, R^2=2,3-$Cl_2C_6H_3O$, R^3=CH_3

1e: R^1=$C_{10}H_7O$, R^2=Cl , R^3=H

[5]

The anthelmintic drugs derived from benzimidazole 2-carbamates, such as albendazole (**ABZ**) and mebendazole (**MBZ**), are used mainly to treat endoparasitic diseases in domestic animals and humans. These types of compounds are characterized by a high therapeutic index and low toxicity; however, they find little use in tissue-dwelling parasites mainly due to poor solubility and absorption problems.[35]

Anti Viral effect:- Benzimidazoles have reported to have anti viral properties against Picornavirus[36], Poliovirus[37], Enterovirus, so a research indicate that N-substituted and 2-substituted Benzimidazoles have activity against Tobacco Mosaic virus[38]. Another approach reported was preparing Benzimidazole hetercycles bearing amidino substituent at C-5 position.[39] In a reported research[40] series of novel benzimidazole derivatives were designed, synthesized, and evaluated for their activities against four Kinds of enteroviruses, i.e., Coxsackie virus A16, B3, B6 and Enteroviruses 71 in VERO cells. The most Promising compound was (L)-2-(pyridin-2-yl)-*N*-(2-(4-nitrophenyl) pentan-3-yl)-1*H*-benzimidazole-4-carboxamide, with a high antiviral potency (IC_{50} = 1.76 μg/mL) and a remarkable selectivity index (328). [6]

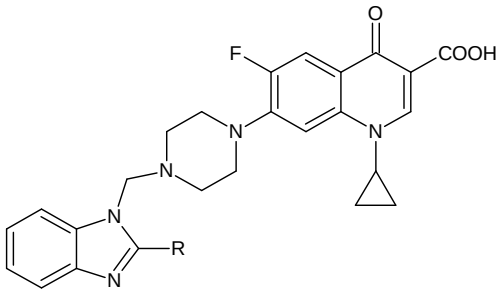


[6]

Anti hypertensive Agents: The biphenyl benzimidazoles have potent antihypertensive action as compared to the previous related drugs due to better availability upon the oral administration, 2- position of biphenyl is essential for the activity[41].5 substituted aryl or alkyl caboxamido derivatives have reported to possess Angiotensin-II AT_1 receptor antagonistic activity so are good antihypertensives agents.[42]

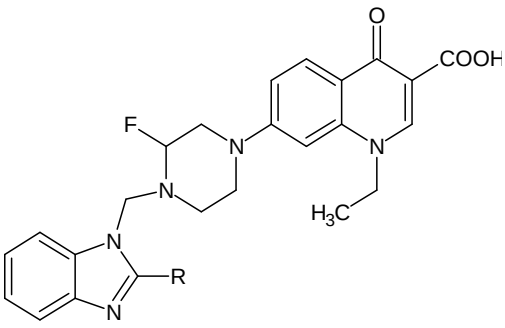
Anti Ulcer Activity: - Substituted benzimidazoles are potent inhibitors of Parietal cell proton pump, the H^+/K^+ ATPase, the substituted benzimidazoles are capable of blocking gastric acid secretion in response to some stimuli. For the activity sulfoxide group, methylene group with hetercycles is important for activity.[43]

Antimicrobial and anti fungal activity :- Isoxazolyl substituted compounds were screened for activity against Gram Negative species like E.coli and Proteus vulgaris,Gram positive like Bacillus mycoides and staphylococcus aureus[44]. Some Benzimidazole compounds possessing hydrazone moiety were studied in order to investigate their possible antibacterial and antifungal activity. Most of the test compounds found to be significantly effective against Proteus vulgaris, Staphylococcus typhimurium, Klebsiella pneumoniae and Pseudomonas aeruginosa gram-negative bacterial strains[6]. Some fluroquinolones substituted Benzimidazole derivatives have been reported by microwave assisted method. The synthesized compounds are reported to be the derivatives of Ciprofloxacin [7] & Norfloxacin [8][45]



Ciprofloxacin derivatives

[7] R=H, Eth, Propyl



Norfloxacin derivatives

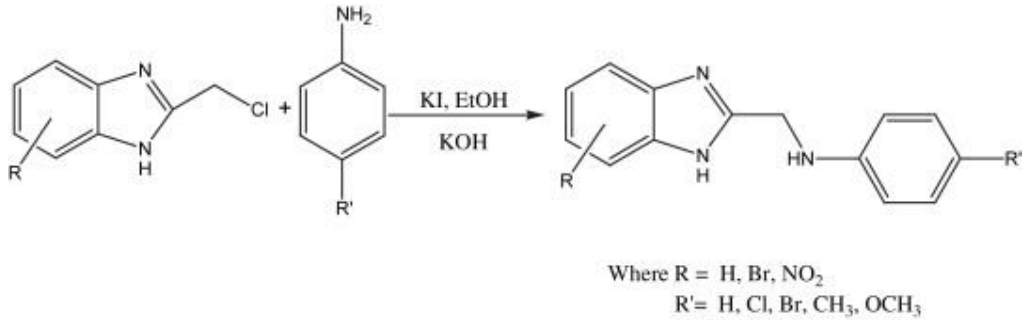
[8] R=H, Eth, Propyl

Compounds which have no substitution of N-1 position displayed better antibacterial activities, the trihalogen benzimidazole analogues exhibited the most potent antibacterial activity with MIC 3.12 $\mu g/ml$ against *S. aureus*.[23] In a study it was reported that by modifying the amide group to the anilide on the 2-phenyl benzimidazole produces antimicrobial activity.[46]A series of 2-alkylsulphanylbenzimidazoles was synthesised and the compounds were evaluated for their in vitro antimycobacterial activity. The structures of the compounds were confirmed by instrumental methods. Antimycobacterial activities against *Mycobacterium tuberculosis* and non-tuberculous mycobacteria as well as antifungal activities against *Candida albicans*, *Candida tropicalis*, *Candida krusei*, *Candida glabrata*, *Trichosporon beigelii*, *Trichophyton mentagrophytes* and *Aspergillus fumigatus* were expressed as the corresponding MIC values. The substances exhibited appreciable antimycobacterial activity, in particular, against non-tuberculosis mycobacteria. The activity of the most active compound in the set, 3, 5-dinitro derivative has also been reported. Another approach to synthesize antimicrobial agents is by synthesis of N-alkyl-2 Phenyl-1H Benzimidazole-5-carboximidines. These compounds have been reported to be active against S. aureus and methicillin resistant S.aureus. The reported MIC is 0.78-0.39 µg/mL.[47] Some new compounds have been synthesised bearing azetidin-2-one and 1, 3, 4 thiadiazole moieties.[48]

Antiproliferative activity:-A novel Schiff bases, the derivatives of 2-aminobenzimidazole and substituted aromatic aldehydes, has been reported. The Compounds were reduced by $NaBH_4$ formed 2-benzylaminobenzimidazoles which were acylated by cinnamoyl chloride gave 2-(*o*-bromobenzylamino)-1-cinnamoylbenzimidazole. The compounds were evaluated for their antiproliferative activity in vitro.[49]

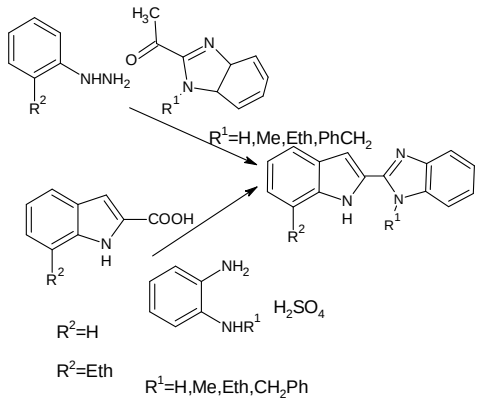
Antitumor activity: - Several new nitrobenzimidazoles have been reported to possess cytotoxic activity against breast cancer. In the reported research it was also found out that the compounds like thiadiazole, tetrazole, triazines and imidazoles also possess the activity .[50]

Anti-inflammatory activity:- A series of 2-methylaminobenzimidazole derivatives were synthesized and reported [51][9] by the reaction of 2-(chloromethyl)-1H-benzimidazole derivatives with primary aromatic amines.



[9]

The new synthesized compounds were screened for analgesic and anti-inflammatory activities by the author on acetic acid induced writhing in mice and carrageenan induced paw oedema in rats. Some Compounds showed a potent analgesic (89% at 100 mg/kg b.w) and anti-inflammatory (100% at 100 mg/kg b.w) activities compared with standard drug Nimesulide (100% at 50 mg/kg b.w) respectively. Another research was carried out indicating that benzimidazole on combination with iodole Skelton give potent anti inflammatory action similar to indomethacin.[52] [10] A series of benzamides has been synthesized with N – acridin -9-yl substituent.[53]



[10]

Antioxidant activity: - Some compounds possessing dihydrochlorides have also been reported possessing antioxidant activity, these salts also possess mild platelet and erythrocyte antiaggregant activity.[54] In another approach it was found out that using trimethyl group with benzimidazole also adds antioxidative property by 5-lipoxygenase inhibitory action.[55]

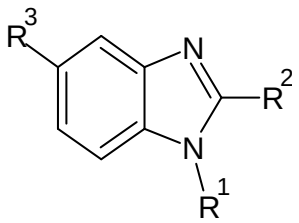
Antiprotozoal activity: - Another benzimidazole derivatives reported are 5, 6 dinitro and thioalkyl or thioaryl substituted compounds .These active compounds reported to possess activity against Stenotrophomonas malthophilia. These compounds have activity related to metronidazole against gram positive and gram negative bacteria. Substituted 2-trifluorobenzimidazoles have been reported.[56, 57] Earlier it have reported anti-giardial activity.[58, 59] One of another research involves the synthesis of series of 2-(trifluoromethyl)-1*H*- Benzimidazole derivatives by using Phillips cyclocondensation of a substituted 1, 2-phenylenediamine and trifluoroacetic acid. The compounds were evaluated *in vitro* against various protozoan parasitesnaming *Giardia intestinalis*, *Entamoeba histolytica*, *Trichomonas vaginalis* and *Leishmania mexicana*, and they showed nanomolar activities against some of the above mentioned protozoa. The compounds were also tested *in vitro* and *in vivo* against the nematode *Trichinella spiralis*. [60]

Androgen Receptor antagonist:-Another benzimidazole derivatives reported[61] in a research are 5, 6 dichloride benzimidazole derivatives .It was found out that trifluoromethyl group greatly enhances

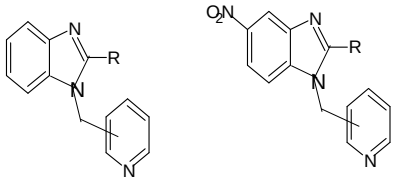
prostrate antagonistic activity. Bicalutamide is a non steroidal antiandrogen which is prominent antiandrogen for the treatment of androgen dependant prostrate cancer.[62]

Anti cancer activity: - The syntheses of 1, 3-diarylpyrazinobenzimidazole derivatives have been reported and the investigated for their anticancer activities. For this, 2-aryloylbenzimidazole derivatives were reacted with 2-bromoacetophenones in acetone to give 1-(2-aryl-2-oxoethyl)-2-aryloylbenzimidazoles. The resulting material was reacted with ammonium acetate in acetic acid to obtain the compound. The above process was reported to be carried out by microwave irradiation method.[63] Another approach reported is the synthesis and evaluation of 1-(4-methoxyphenethyl)-1H-benzimidazole-5-carboxylic acid derivatives .The compound methyl 1-(4-methoxyphenethyl)-2-(4-fluoro-3-nitrophenyl)-1H-benzimidazole-5-carboxylate induced maximum cell death in leukemic cells with an IC(50) value of 3 microM. [64]

Anti convulsant Agents: - Some potential anticonvulsant compounds have been synthesized, a series of 1, 2, 5-trisubstituted benzimidazoles [11] [12] [13] derivatives has been reported.[65] The results of QSAR investigation and the study of various physicochemical properties indicates that the change in linker at position one (R_1) does not change the activity of the synthesized compounds and optimum chain length at position two (R_2) is responsible for the anti-convulsant activity. The results also showed that the synthesized compounds with electron withdrawing group such as nitro at position five (R_3) have been reported to possess better anti-convulsant activity as predicted by QSAR studies.



1, 2, 5-trisubstituted benzimidazole [11] where R_1= picoline, R_2= varying alkyl chain R_3=NO_2



R=H, CH_3, C_2H_5, C_3H_7, C_4H_9

R=H, CH_3, C_2H_5, C_3H_7, C_4H_9

[12] **[13]**

CONCLUSION

The benzimidazole ring is an important pharmacophore in modern drug discovery. Attention has been increasingly given to the synthesis of benzimidazole derivatives as a source of new antimicrobial agents. The Benzimidazole derivatives are a resource for medicinal research. The knowledge gained by various researches has suggested that substituted benzimidazoles and heterocycles, which are the structural isosteres of nucleotides allow them to interact easily with the biopolymers, possess pharmacological activity with lower toxicities. Since now, researchers have been attracted toward designing more potent Benzimidazole derivatives having wide diverse of biological activity.

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