Review Article

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Review on Benzimidazole Derivative

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ABSTRACT

Benzimidazole derivatives play very efficient role in the medical field with plenty of useful therapeutic activities like antiviral, anti-histaminic, anticancer, antiulcer, antihypertensive, antidiabetic, antifungal, and antimicrobial activity. The potency of these useful derivatives in treatment of microbial infections and including other activities especially anti-carcinogenic encouraged the development of some more potent and pharmacologically efficient compounds. Benzimidazole is outstandingly effective compounds and there are a number of reviews available for biochemical and pharmacological studies which confirmed that these molecules are useful against a wide variety of microorganisms. Benzimidazole and its derivatives have been showing hopeful activity in the treatment of several diseases, for these reasons, they achieved much attention as important pharmacophore and privileged structure in medicinal chemistry. This review summarizes to know about the different derivatives of Benzimidazole with their pharmacological activities.

Key words: Pharmacological activities, Substituted Benzimidazole, Benzimidazole derivatives.

1. INTRODUCTION

Benzimidazole is heterocyclic aromatic organic compounds formed by the fusion of benzene and imidazole rings. In medicinal chemistry it is an important pharmacophore structure. Benzimidazole possess many pharmacological activities out of many N-ribosyl-dimethyl benzimidazole is a most prominent benzimidazole derivatives, which serves as an axial ligand for cobalt in vitamin B_{12}. [1] The use of Benzimidazole dates many years back for Study of Structural modifications and their pharmacological actions. Various benzimidazole derivatives were synthesized with the substitution of fluorine, propylene, tetrahydroquinoline and cyclist compound which resulted in compounds with increased stability, bioavailability and significant biological activity in 1990. [2-3] Benzimidazole are divided as drugs1 depending on the possible substitutions at different positions on the benzimidazole nucleus. It is well known to play in many biological systems as a fundamental role. As interest in exploring benzimidazole derivatives and their metal complexes has continually increased, it has been recognised that these materials may serve as models that mimic both the structure and reactivity of metal ions in complex biological systems. [4-6]

1.1. Substitution on Benzimidazole nucleus and their pharmacological actions

The use of benzimidazole dates many years' back.[7] various benzimidazole derivatives were synthesized with substitution of fluorine, propylene, tetrahydroquinoline and cycles compound which resulted in compounds with increased stability, bioavailability and significant biological activity in1990.[8-9]The activity increases by substitution of electron donating group on pyridine .[10] Heterocyclic benzimidazole, their derivatives and metal complexes because of their well documented biological activities, have received considerable attention in coordination chemistry in last decades. The more effective antimicrobial activity obtained by using Zinc (II) complexes with 1-benzylbenzimidazole derivatives.[11] Benzimidazole derivatives was synthesized by 2-thioalkyl and thioaryl substitution resulting in good antiprotozoal and antibacterial activity in 2002.[12] A series of non peptide angiotensine (A-II) receptor antagonist i.e. 5- substituted (amino)-2- phenyl-1- (2'corboxyphenyl-4-yl) benzimidazole was synthesized in 2006 which produce a potent hypertensive effect upon oral administration.[13] Benzimidazole derivatives were synthesized with anticonvulsant, DNA cleavage and antidiabetic activities in 2010.[14] Some oxadiazole-1H-benzimidazole has been reported to have antimicrobial activities. This compound also showed moderate antifungal activity. [15] It was reported that by changing the amide group to the anilide on the 2-phenyl benzimidazole produces antimicrobial activity.[16] Benzimidazole structures are divided in number

of several classes of drugs, dependent on the different substitution positions on the benzimidazole nucleus. Introduction of a small substitution on 2nd and 5th position of benzimidazole shows anthelmintics activity where as bulky substitution on 2nd position showed proton pump inhibitory and antihistaminic activity. Thus benzimidazole skeleton was therapeutically important moiety. [17]

Figure -1: Structure of Benzimidazole

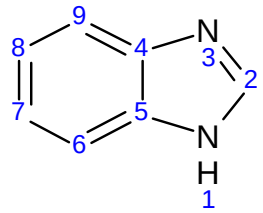
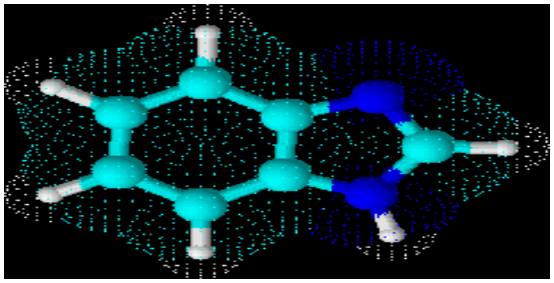
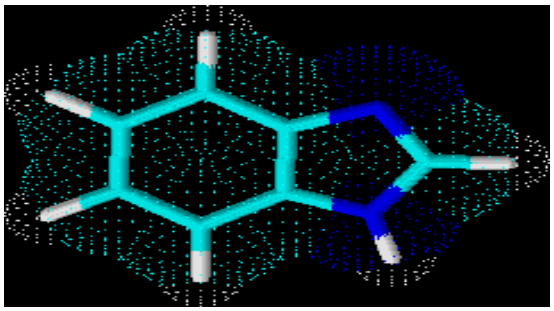


Figure-2: 2D and 3D Structure of Benzimidazole ($C_7H_6N_2$)





Benzimidazole is made by fusion of benzene to imidazole ring or possess (aromatic imidazole ring system) where a benzene ring is fused to 4 and 5 positions of an imidazole ring. It is also known as 1, 3-benzodiazoles. Benzimidazole possesses both acidic as well as basic characteristics. The NH group present in benzimidazole is relatively strongly acidic and also weakly basic. Another important characteristic of benzimidazole is that they have salt forming capacity. Benzimidazole with unsubstituted NH groups, exhibit fast prototropic tautomerism which leads to equilibrium mixtures of asymmetrically substituted compounds. The useful structural modification for the development of molecules of pharmaceutical or biological interest is a benzimidazole scaffold. Appropriately substituted benzimidazole derivatives have found diverse therapeutic applications such as in antiulcer, antihypertensive, antiviral, antifungal, anticancer, and antihistaminic. [18]

1.1. Synthesis of Benzimidazole

Benzimidazoles are commercially available and its synthesis involves condensation of o-phenylenediamine with formic acid or the equivalent trimethyl ortho formate.

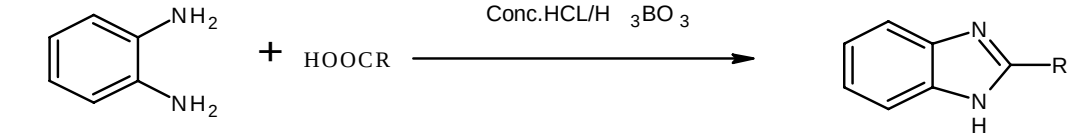
$C_6H_4(NH_2)_2 + HC(OCH_3)_3 \rightarrow C_6H_4N(NH)CH + 3\,CH_3OH$

The 2-substituted benzimidazole obtained by changing the carboxylic acid used in this method. Benzimidazole acts by stopping hyphal growth and by binding to the fungal microtubules. So it has fungicidal properties. It blocks nuclear division by binding to the spindle microtubules. [19] Benzimidazoles have most commonly been prepared from the reaction of 1, 2-diaminobenzenes with carbonyl-containing compounds (Carboxylic acids, Aldehyde, etc.) under harsh dehydrating reaction conditions, utilizing strong acids such as polyphosphoric acid, hydrochloric acid, boric acid, or p-toluenesulfonic acid. The use of milder reagents, particularly Lewis acids, inorganic clays6, or mineral acids, has improved both the yield and purity of this reaction. [20]

1.3. Reported Activities of Benzimidazole [21]

1. Anticancer
2. Anthelmintics
3. Antihypertensive
4. Antimicrobial
5. Antiulcer
6. Antidiabetic
7. Anti-inflammatory
8. Antiallergic
9. Antidepressant
10. Analgesic

Figure- 3: Scheme for the synthesis of Benzimidazole from o-arylenediamine

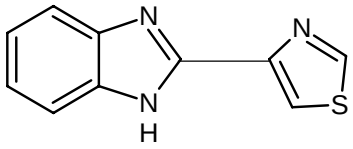
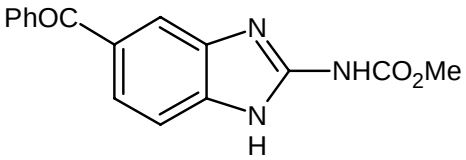
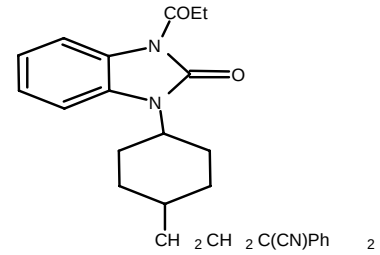
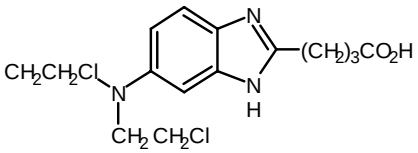
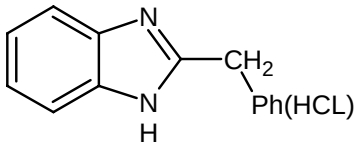
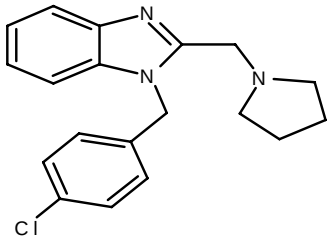


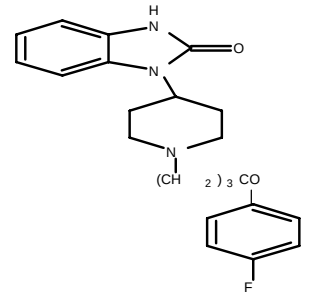
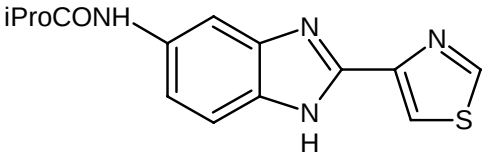
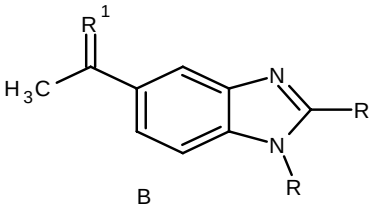
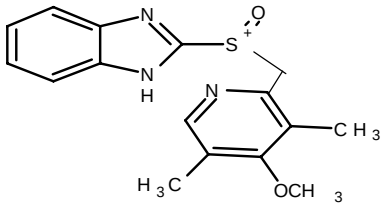
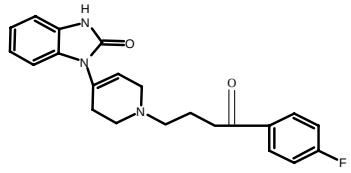
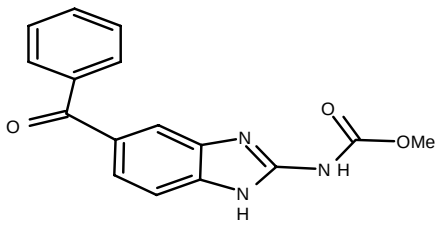
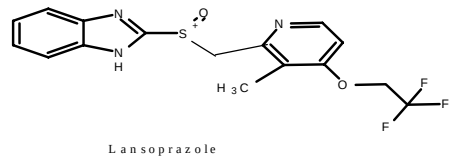
ortho-phenylene diamine

Carboxylic acid

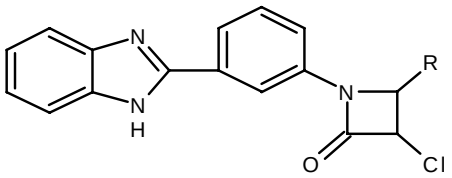
Benimidazole

Table1:-Benzimidazole Derivative [18, 22-40]

S. No.	Compounds	Substituent's	Reported Activity
1	 Thiabendazole		Anthelmintics
2	 Mebendazole		Anthelmintic
3	 Bezitramide		Analgesic
4	 Imet 3393		Anticancer
5	 Diabazole		Vasodilators
6	 Clemizole		Antihistamine

7	 Benperidol	Psychopharmacological agent
8	 Cambendazole	Anthelmintic
9	 2-Arylbenzimidazoles	Antiviral and Antiproliferative Agents
10	 Omeprazole	Anti-ulcer drugs
11	 Droperidol	Anti-psychotic agents
12	 Mebendazole	Anthelmintic
13	 Lansoprazole	Anti-ulcer drugs

14)

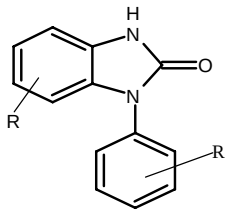


(1H-Benzo[d]imidazol-2-yl)phenyl)-3-chloro-4-(4- substituted phenyl)azetidin-2-one

R
-C6H5NO2
-C6H5CH3
-C6H5OCH3

Antimicrobial

15)

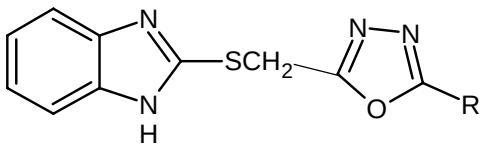


Substituted benzimidazole derivatives

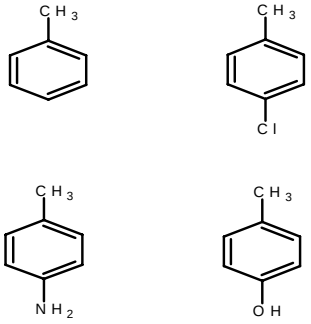
R
H
P-CH3
m-CH3
m-NO2
o- Br
p-Cl
m-Cl

Antibacterial, Antifungal Activities

16)

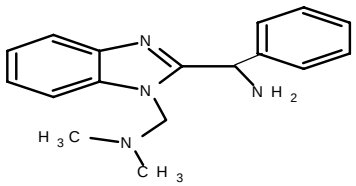


2-(5-phenyl-[1,3,4]-oxadiazole-2-ylmethylsulfanyl)-1H-benzimidazole derivative



Antidiabetic Activity

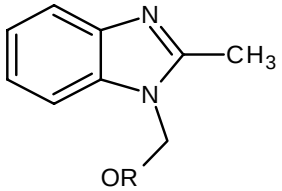
17



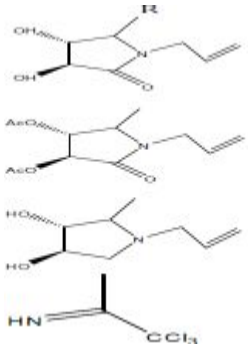
Mannich Bases of benzimidazole derivatives

Ant-inflammatory Activity

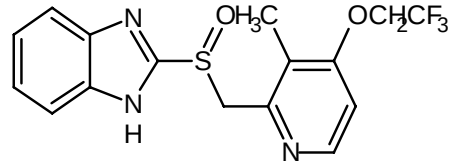
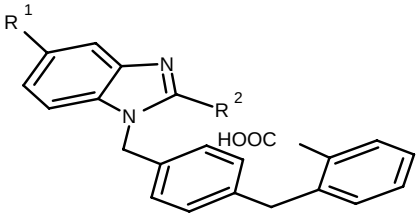
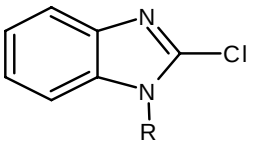
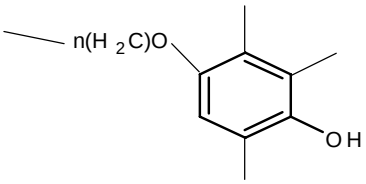
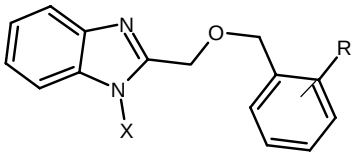
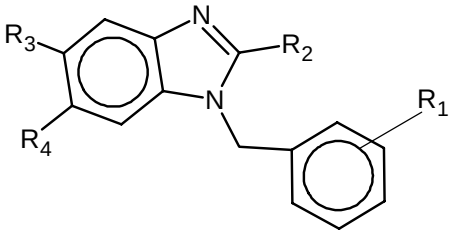
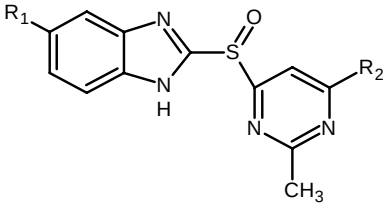
18

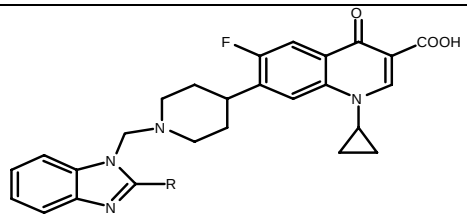
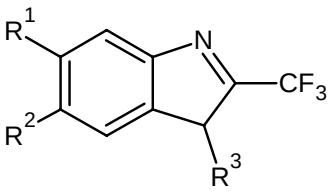
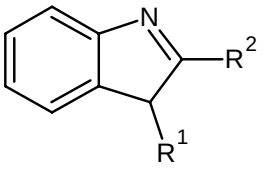
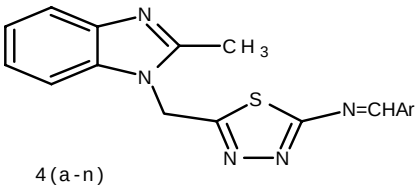
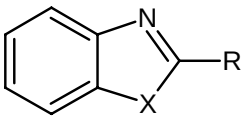
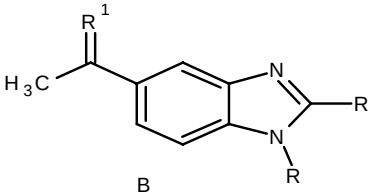


2-methyl-N-substituted benzimidazole Derivatives



Antidepressant, Anti-inflammatory Activities

19	 2-[(3-methyl,4 trifluroethoxy) 2pyridyl) methyl,sulfinyl] Benzimidazole			Antiulcer Activity
20	 5-nitro2-phenyl-[(2'carboxyphenyl-4-yl)methyl] Benzimidazole	R1 NO2, NH2,	R2 phenyl ethyl	Antihypertensive activity
21	 2-chloro-1-[2-(4-hydroxy-2,3,5-trimethylphenoxy)ethyl]-1Hbenzimidazol	R  n=2,3,4,6,7		Antiallergic activity
22	 1-Alkyl-2-substituted-phenoxymethyl			Antibacterial, Antifungal, Antitubercular activities
23				Antibacterial
24	 2-(Pyrimidinyl sulfinyl)Benzimidazole Derivatives	R1 H H H NO2 NO2 NO2	R2 methyl ethyl propyl methyl ethyl propyl	Antiulcer, Antisecretory Activity

25	 Ciprofloxacin derivatives	**R = H** Ethyl Propyl	Antimicrobial and Anti fungal activity
26		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	Antiparasitic effect
27	 1,2,5-trisubstituted Benzimidazole derivatives	Where R^1= Picoline R^2= Varying alkyl chain	Anti convulsant Agents
28	 4(a-n)		Antifungal
29			Antibacterial and Antifungal Activity
30	 B 2-Arylbenzimidazoles		Antiviral and Antiproliferative Agents

1.3. Current Inventions on Benzimidazole derivatives

The newly synthesized Benzimidazole compounds were recommended to be inhibitors of Plasmodium falciparum plasmepsin II and human cathepsin D with virtual screening of an inside library of synthetic compounds. This is detected by enzyme inhibition studies that yields IC50 values in the low micromolar range (2–48 μM).The binding of Benzimidazole compounds at the center of the extended substrate-binding cleft was predicted by Ligand docking studies with plasmepsin. According to the possible mode of binding, the pyridine ring of Benzimidazole compounds interacted with S1′ subsite residues, while the acetophenone moiety was in contact with S1–S3 subsites of plasmepsin II active center. The Benzimidazole derivatives are evaluated for capacity to inhibit the growth of intraerythrocytic P. falciparum in culture. The most active compound 10, 1-(4-phenylphenyl)-2[2-(pyridinyl-2-yl)-1, 3-benzdiazol-1-yl] ethanone showed an

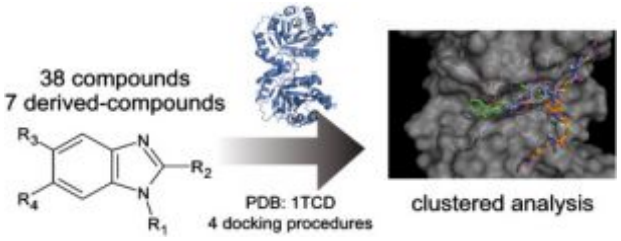
IC50 of 160 nM. When Para position of the acetophenone was substituted by a phenyl group and chlorine atom, then acetophenone moiety shows essential antiplasmodial activity.

The present invention relates to novel Benzimidazole derivatives and their use as potent calcium channel blockers in the treatment or prevention of chronic stable angina, hypertension, ischemia (renal and cardiac), cardiac arrhythmias including atrial fibrillation, cardiac hypertrophy, or congestive heart failure, containing pharmaceutical compositions and their derivatives and to processes for their preparation. The benzimidazole derivatives of the current invention may also be used, alone or with other pharmaceutical compositions, for the treatment of renal diseases, diabetes and its complications, hyperaldosteronism, epilepsy, neuropathic pain, or cancer in humans and other mammals. Benzimidazoles characterize the only class of truly broad-spectrum Anthelmintics; still they also show activity against fungi and mammalian cells. [41]

1.4. Future Research on Benzimidazole Derivatives

To produce efficient inhibitory activity against the triosephosphate isomerase of Trypanosoma cruzi (TcTIM) there is need to construct a new set of compounds; a group of Benzimidazole derivatives was studied using four different docking procedures. These docking procedures differ in the number and type of mobile residues considered in the analysis. As a result of this methodology, a clustered analysis of plausible candidate structures was produced. A different set of previously synthesized compounds was used to validate this analysis. The validation showed that the best results correspond to the docking procedure in which the residues near the hydrophobic pocket of the protein's interface were considered mobile. A binding site for the best candidates was identified. Residues Tyr103, Glu105 and Lys113, among others, are important for the binding of this kind of compound. Residue Tyr103 is different in the human TIM, thus establishing a key feature for the future design of selective inhibitors. [41]

Figure- 2: Benzimidazole Derivatives Docking Studies on Peptide Deformylase and Heptosyltransferase.



1.5. Benzimidazole Derivatives Docking Studies on Peptide Deformylase and Heptosyltransferase WaaC as Antibacterial Agent

A series of benzimidazole containing isoxazoline-5-one and pyrazoline-5-one compounds were computationally designed and optimized with the Auto Dock 4.0.1 to investigate the interactions between. The target compounds and the amino acid residues of the Escherichia coli PDF enzyme and Escherichia coli heptosyltransferase WaaC. In this study, the docking studies were done using auto dock between computationally designed benzimidazole derivatives and peptide deformylase (PDF) and also with heptosyl transferase WaaC. The free energies of binding (Δ G) and inhibition constants (Ki) of the docked.Ligands were calculated by the Lamarckian Genetic Algorithm (LGA). These values suggested that the designed benzimidazole derivatives are excellent inhibitor of both Escherichia coli PDF enzyme and heptosyl transferase WAAC. [42]

2. CONCLUSION

From the above literature surveys it is concluded that, among all Benzimidazole derivatives 2-substituted Benzimidazole shows more potent and efficient pharmacological activities, hence their design and synthesis become potential area of research. Also a small change in Benzimidazole moiety can cause an extensive change in biological activities, and these modifications used as potent therapeutic agents in future. So researchers move towards designing more potent, efficient with minimum side effects Benzimidazole derivatives.

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