International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319-6718, ISSN (Print): 2319- 670X
www.ijpsi.org Volume 10 Issue 9 ǁ September 2021 ǁ PP. 19-27

A Review on Biologiv|Cal Activity of "Benzimidazole as a Imidazole Derivatives"

KOMAL SABALE; ROHIT JAYSING BHOR*[1]; MAYUR BHOSALE
[1]*Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy Pravaranagar, Tal-Rahata, District-Ahmednagar, Maharashtra, India*
[*2]*Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy Pravaranagar, Tal-Rahata, District-Ahmednagar, Maharashtra, India*
[2]*Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy Pravaranagar, Tal-Rahata, District-Ahmednagar, Maharashtra, India*
Corresponding Authors Name: Rohit Jaysing Bhor[1]*
Mailing Address of Author: B-10, Lane 2, Musale vasti, Hasanapur road, Loni (B.K.), Tal: Rahata, District: Ahmednagar, Maharashtra.

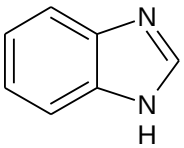
ABSTRACT:
Benzimidazole is an example of heterocyclic organic compound. It is a bicyclic compound or derivatives of imidazole. It contains the fusion of benzene with imidazole heterocylic ring which ultimately gives a privileged structure. Benzimidazole and its derivatives play an important role in the medicinal chemistry and drug discovery with many pharmacological activities. Substitution of various chemicals on benzimidazole nucleus gives important synthetic product and strategy in the drug discovery process. Benzimidazole nucleus plays a very important role as a therapeutic agent. Benzimidazole and its derivatives gives a pharmacological activities such as antimicrobial, antiviral, anticancer, antiinflammatory, analgesic activity, anti-ulcer, anti-diabetic activity etc. Benzimidazole nucleus always gives active sites for the reaction like 2 and 5 position which gives potent therapeutic agents. The present review covers the chemistry and pharmacological activities of substituted benzimidazole. In the present review, benzimidazole derivatives with different synthetic derivatives and their pharmacological activities are given. The main aim of review is to help medicinal chemists for the development of SAR on benzimidazole and its derivatives for each activity during 10 years.

KEY WORDS: *OPD; antimicrobial; antiviral;, antiinflammatory; analgesic activity; anti-ulcer; anti-diabetic activity*

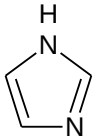
Date of Submission: 08-12-2021 Date of acceptance: 23-12-2021

I. INTRODUCTION:

Imidazole and Benzimidazole is an example of aromatic heterocyclic organic compound. The new method of preparation for benzimidazole based on poly heterocycles draw the attention of pharmacists from last few decades[1]. Imidazole and Benzimidazole have important pharmocophore in medicinal chemistry and pharmacology. Benzimidazole and its derivatives are an example of bicyclic compound consisting of the fusion of benzene with imidazole [2]. The structure of benzimidazole and imidazole are given below;



1*H*-benzimidazole



1*H*-imidazole

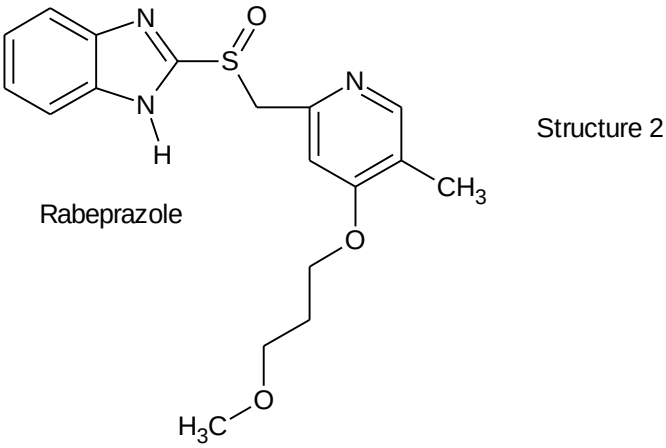
Structure 1

It gives magical properties with many pharmacological properties. Imidazole and Benzimidazole possess many biological activities such as anti- microbial, anti-fungal, anti-histaminic, anti-inflammatory, anti-viral, anti-oxidant, anti-cancer, anti-ulcerative[3-6] etc so that Imidazole and Benzimidazole having important moiety for the development of molecules of pharmaceutical interest. Many benzimidazole derivatives having heterocyclic building blocks are due to the structural similarity to purine nucleobase. It selectively inhibits the

endothelial cell growth and then suppresses the process of angiogenesis in vitro as well as in vivo biological activity [7]. Benzimidazole is also called as 1*H*-benzimidazole or 1,3-benzodiazole. Imidazole and Benzimidazole with nitrogen-containing heterocyclic ring was present in the structures of various biologically active synthetic compounds. The magical properties of the benzimidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel derivatives with chemotherapeutic agents. Imidazole and Benzimidazole are commonly used for the prevention and treatment of parasitic infections [8]. Some examples of benzimidazole containing drug are given below;

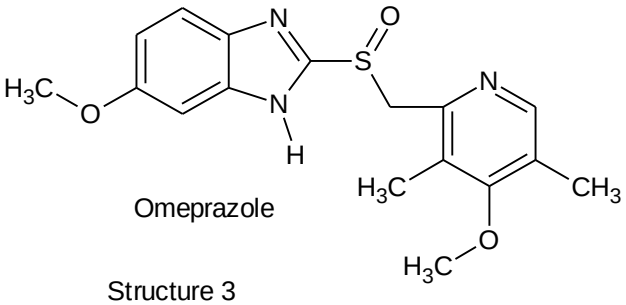
- Omeprazole
- Rabeprazole
- Lansoprazole
- Pantoprazole
- Esomeprazole

They are well known discovered benzimidazole drugs. There are some other drugs with different hetero atoms like Thiabendazole (TBZ); Parbendazole (PAR) Cambendazole (CAM) Mebendazole (MBZ) Oxibendazole. Thiabendazole (TBZ) was the first benzimidazole to be marked over 40 year's ago[9].



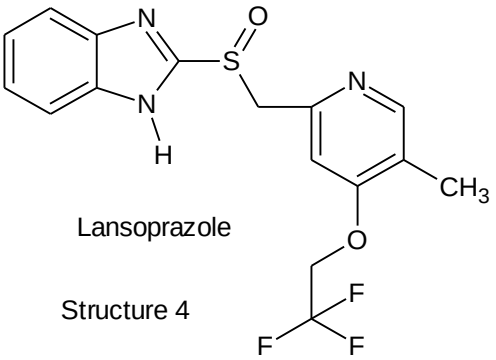
Rabeprazole

Structure 2



Omeprazole

Structure 3



Lansoprazole

Structure 4

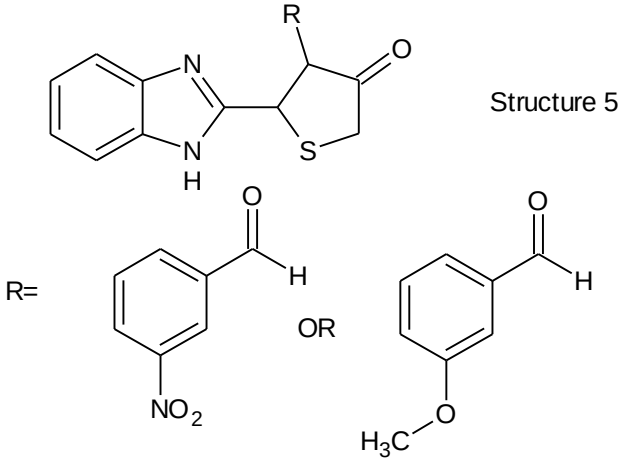
Benzimidazoles having the well known heterocyclic compounds which have common and characteristic features of a variety of medicinal agents. Benzimidazole is soluble in water and other polar solvents. Benzimidazoles exist in two equivalent tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atoms. It having calculated dipole of 3.61D, and it was soluble in water [10].

Benzimidazole and its derivatives are classified as aromatic due to the presence of a sextet of π-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring. When it having acidic p*k*a is 14.5, then it gives less acidic than carboxylic acids, phenols, and imides, but slightly more acidic than alcohols. When it having basic p*k*a is approximately 7 then it gives benzimidazole approximately sixty times more basic than pyridine [11].

II. PHARMACOLOGICAL ACTIVITIES

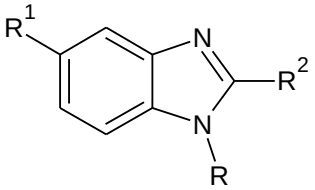
Anti-inflammatory activity

Suresh *et al.,* (2011) was synthesized derivatives having cyclopentane nuclei bind with benzimidazole moiety or nucleolus (Structure 5). Newly synthesized compounds were then screened for anti-inflammatory activity and these derivatives showed significant effect when compared with standard Diclofenac sodium.[12]



Structure 5

Thakurdesai *et al.,* (2007) was synthesized benzimidazole-2-carboxylic acid derivatives (Structure 6). These derivatives show acute anti-inflammatory activity and found to be potent anti-inflammatory agent.[13]



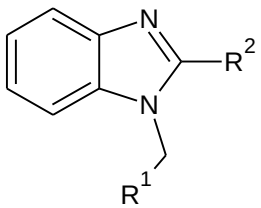
Structure 6

R= H

R^2= - COOH; CH_2COOH

R^3=H; NO_2; Cl; OC_2H_5; OCH_3

Jesudason *et al.,* (2009) was synthesized a novel series of *N*- Mannich bases of benzimidazole derivatives (Structure 7). These compounds were tested or screened for analgesic, anti-inflammatory and *in-vitro* anti bacterial biological activity. These compounds having good or potent activity.[14]

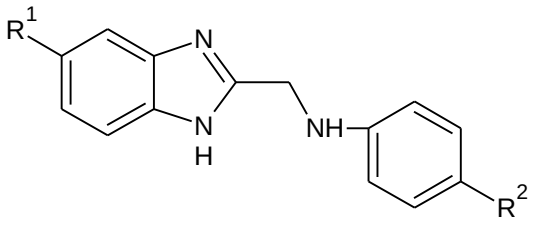


Structure 7

R^1= - NC_5H_5; NC_2H_5

R^2= - CH=CHC_6H_5

Achar *et al.,* (2010) was synthesized a series of 2- methyl amino benzimidazole derivatives (Structure 8). The newly synthesized compounds were screened and tested for analgesic and anti-inflammatory activities. Structure 8 showed a potent analgesic activity (89% at 100 mg/kg.) and anti-inflammatory (100% at 100 mg/kg.) activities.[15]

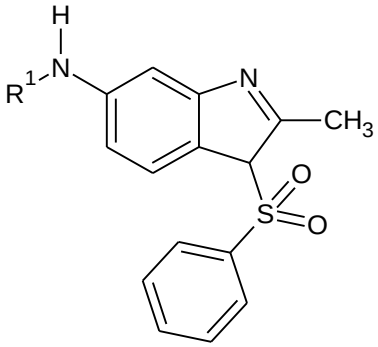


Structure 8

R^1= - H; Br

R^2= - Cl

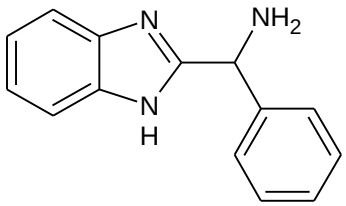
Gaba *et al.,* (2010) was synthesized a series of novel derivatives like 5-substituted-1- (phenylsulfonyl)-2-methylbenzimidazole derivatives (Structure 9). These compounds were screened for anti-inflammatory and analgesic activity[16].



Structure 9

R^1= o -$NH_2C_6H_4$; p -$NH_2C_6H_4$

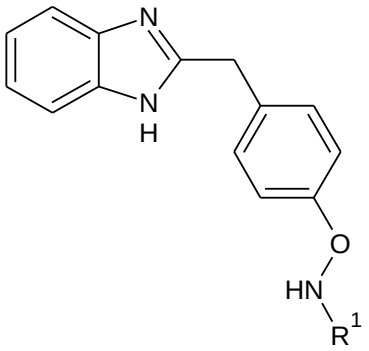
Reddy (2010) was synthesized 1, 2-disubstituted benzimidazole derivatives (Structure 10). These derivatives were screened and tested for anti-inflammatory activity. These derivatives or compound showed potent activity[17].



Structure 10

Analgesic activity:

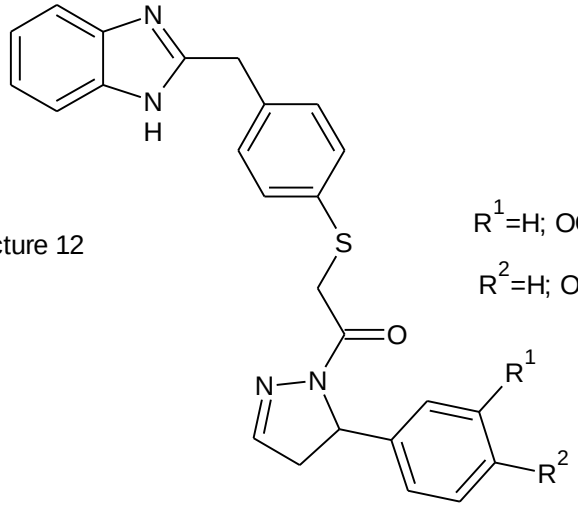
Shukla A. (2012) was synthesized benzimidazoles derivative involves synthesis of 4-(2-chloro-ethoxy)- benzaldehyde, 4-methyl benzaldehyde followed by benzimidazoles derivative (Structure 11). These synthesized benzimidazole compounds were screened for analgesic and anticonvulsant activity and some derivatives or compounds showed significant analgesic activities.[18]



R^1= N methyl Piperazine

Structure 11

Kaplancikli *et al.,*(2008) was synthesized the new product like 1-[(Benzoxazole /benzimidazole-2-yl) thio acetyl] pyrazoline derivatives (Structure 12) which then screened for analgesic activity and the synthesized compounds were found to be potent.[19]



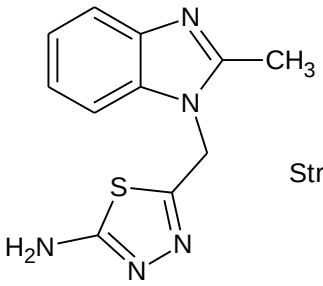
Structure 12

R^1=H; OCH_3; CH_3

R^2=H; OCH_3;CH_3

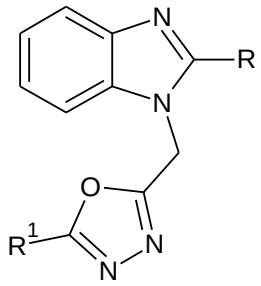
Antibacterial Activity and Anti Fungal Activity:

Novel azetidine-2-one (Structure 13) was synthesized by Ansari and Lal, 2009 and evaluated for their antibacterial activity against *Bacillus subtilis, Escherichia coli, Candida albicans, Aspergillus niger* and *Aspergillus flavus.* These compounds or derivatives are more effective against gram positive bacteria[20].



Structure 13

Ansari and Lal, 2009 was synthesized some benzimidazole derivatives by nucleophilic substitution and their product be like substituted benzimidazole 2- substituted-1-[{(5-substituted-alkyl/aryl)-1,3,4-oxadziazolyl-2- yl}] (Structure 14) and they were evaluated for antimicrobial activities toward Gram positive and Gram negative bacteria. Some of the synthesized compounds showed moderate activity against tested fungi.[21]

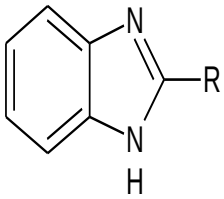


R= H; CH_3

R^1= CH_3; C_2H_5; OCH_3; ClC_6H_4; OHC_6H_4

Structure 14

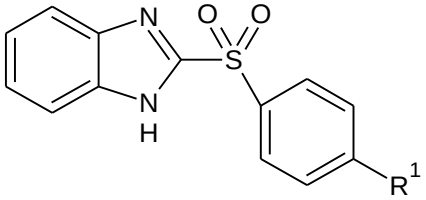
Gupta and Rani (1977) was synthesized 2-thiohalogenonitro- phenyl benzimidazole by the condensation of halogeno nitrobenzene and sodium salt of 2-mercapto benzimidazole (Structure 15) and tested for their antifungal activity against some spices like *Helmithosporium sativum, A. niger and Fusarium oxysporum* by spore germination method. The percentage inhibition of the spores at 10 ppm has been recorded[22].



Structure 15

R= ,4-DNP, 2,6-DNP, 2,4,6-TNP, 2-chloro 4,6-DNP, 2-methyl- 4,6-DNP, 2-chloro-4-bromo-3,5-DNP(DNP= dinitrophenyl, TNP= trinitrophenyl

Ghoneim et al. (1998) synthesized 2-[(4-aminophenyl)sulphonyl] derivative (Structure 16) of benzimidazole and tested the antimicrobial activity of compounds against *E. coli* using agar diffusion method[23].

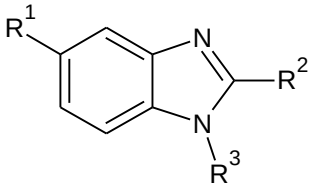


Structure 16

R^1= 4 NH_2; 2,4 NH_2

Anti-convulsant activity

Singh *et al.,* (2010) synthesized a series of 1, 2, 5-trisubstituted benzimidazoles derivatives (Structure 17-19). The compounds with optimum chain length at position two (R_2) and electron withdrawing group at position five (R_3) showed better anticonvulsant activity.[24]

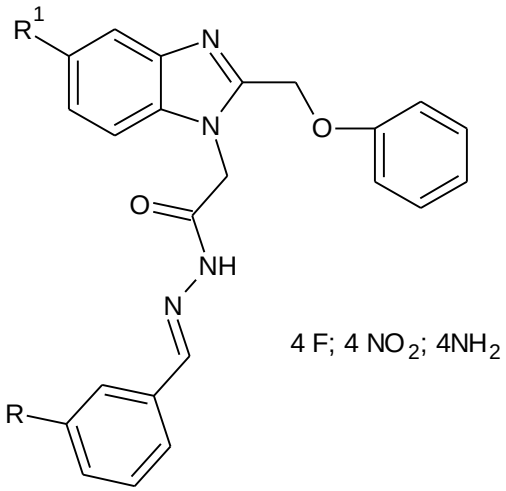


R^1= H, CH_3, C_2H_5; C_3H_7 Structure 17

R^2= H; CH_3; C_2H_5; C_3H_7 Structure 18

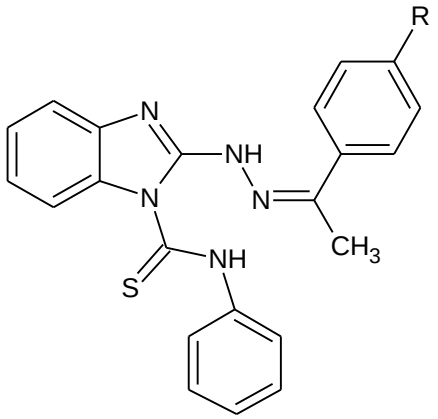
R^3=H; C_6H_5; CH_3; C_2H_5 Structure 19

Shaharyar *et al.,* (2011) synthesized various derivative of 2-[2-(phenoxymethyl)-1*H*-benzimidazole-1-yl]-*N'*-[(*Z*)-phenyl methylidene] aceto hydrazide and some compounds containing oxadiazole bearing benzimidazole (Structure 20). Compound was found to have better protective index than standard drugs used.[25]



Structure 20

Bhrigu *et al.,* (2012) synthesized a series of new 2-[(1- substituted phenyl ethylidine) hydrazine]-*N*-phenyl-1*H*-benzo[*d*]imidazole-1-carbothioamides (Structure 21) which were then screened for anticonvulsant activity. Some of the compounds exhibited anticonvulsant activity.[26]

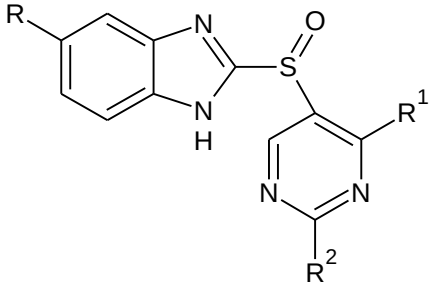


R= 4 Br; 4 F; 4 Cl; 4 NO_2

Structure 21

Anti-ulcer activity:

Nadeem and **Khan** (2011) studied to investigate the effect of 2-(pyrimidinylsulfinyl) benzimidazole derivative (Structure 22) and thecompound was found to have good antiulcer activity.[27]



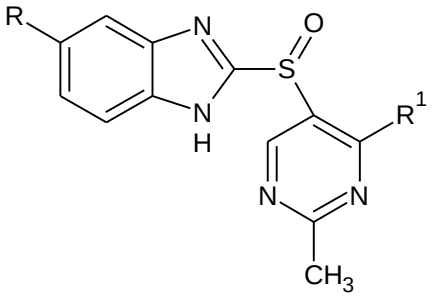
R= 4 Br; 4 F; 4 Cl; 4 NO_2

R_3=H; C_6H_5; CH_3; C_2H_5

R^2=H; CH_3

Structure 22

Thakare and **Asnani** (2011) synthesized a series of all new substituted 2-(pyrimidinylsulfinyl) benzimidazole (Structure 23). All compounds were tested for antiulcer and anti-secretary activity and found to be potent.[28]

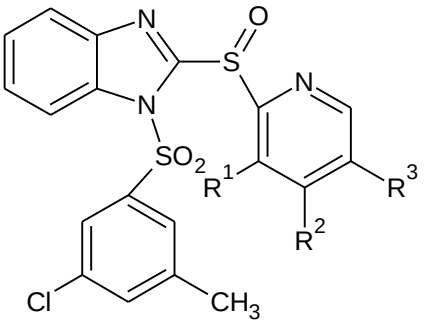


R= Br; F; Cl; NO_2

R^1=H; C_6H_5; CH_3; C_2H_5

Structure 23

Shin *et al.,* (2009) synthesized new aryl sulfonyl proton pumpinhibitor (PPI) (Structure 24) prodrug forms. These prodrugs provided longer residence time of an effective PPI plasma concentration, resulting in better gastric acid inhibition.[29]



Structure 24

R^1=H; OCH_3; CF_2

R^2= CH_3; OCH_3

R^3= OCH_3

III. CONCLUSION:

The review has concluded with the key synthetic approaches and pharmacological activities of the Benzimidazole. It gives one of the most useful biological activities. Benzimidazoles and its derivatives are utilized in much therapeutic or biological activity such as anti-inflammatory, anti anxiety and antimicrobial activity. The efficient and economical methods of synthesizing benzimidazole and its derivatives by condensation reaction between OPD i.e. orthophenylenediamine and various compounds in the presence of various conditions presented in this review. This review helps to other chemist chemists to get the first hand information for the synthesis of benzimidazole and become very useful for chemists and workers in this field. This can be developed from year to year to produce new economical and environmental clean protocols for the large scale production of important heterocyclic compounds.

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