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A REVIEW ON THE RECENT DEVELOPMENT OF BENZIMIDAZOLE DERIVATIVES AND ITS BIOLOGICAL SIGNIFICANCE

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ABSTRACT

Nitrogenous heterocyclic compounds have recently attracted the interest of medicinal chemists. Benzimidazole scaffolds are surprisingly common in these potential heterocyclic molecules. It has numerous pharmacological properties and so plays a key role in medicinal chemistry and drug discovery. Substitution of the benzimidazole nucleus is an important synthetic method in the drug development process. The importance of benzimidazole derivatives as chemotherapeutic medicines in many clinical circumstances may be linked to their isostructural pharmacophore of naturally occurring active biomolecules. Researchers have generated a large number of benzimidazole derivatives over the last few decades, and a major fraction of these compounds have exhibited tremendous biological efficacy against a variety of diseases, as well as excellent bioavailability, safety and stability features. In this comprehensive study, we have summarized the biological activity of the benzimidazole derivatives reported in recent literature, as well as known structure-activity connections. The broad-spectrum pharmacological activity of compounds with benzimidazole nucleus include common antibacterial properties as well as the capacity to treat the most serious illnesses. A variety of promising therapeutic prospects are undergoing human trials, with some of them being approved for usage in clinical settings. Significant difficulties, such as drug resistance, costly and time-consuming synthetic techniques, a lack of sophisticated software, limited structural knowledge of receptors, and others, can yet be solved to allow for more research.

Keywords: Benzimidazole, isostructural pharmacophore, drug resistance, biological activity, anti-bacterial effect

INTRODUCTION

Benzimidazole, a crucial heterocyclic pharmacophore, is made up of a benzene ring fused with a five-membered imidazole ring and is also known as 1*H*-benzimidazole and 1,3-benzodiazole. Because of its ties to several biological processes, benzimidazole is classified as a "privileged structure" in heterocyclic chemistry **[1, 2]**. Nowadays is a moiety of choice which possesses many pharmacological properties. The most prominent benzimidazole compound in nature is N-ribosyl-dimethyl benzimidazole, which serves as an axial ligand for cobalt in vitamin B12 **[3]**. Due to its presence in a variety of biologically active compounds, including anti-parasitics, antimicrobials, antivirals, antifungals, anticonvulsants, anti-hypertensives, anti-histaminics, analgesics, anti-inflammatory agents, anti-cancer, anti-coagulants, and proton pump inhibitors, benzimidazole has emerged as a significant heterocyclic system over the course of many years of research **[4, 5]**.

Numerous medications from a wide range of therapeutic lines have been developed as a result of changing the substituents around the core structure, including Albendazole, Mebendazole, and Thiabendazole as Antihelmintics; Maribavir as an Antiviral; Carbendazim as a fungicidal; Omeprazole, Lansoprazole, and Pantoprazole as proton pump inhibitors; Candesartan cilexitil and Telmisartan as antihypertensives, and Lerisetron as Antihistaminic **[6, 7] (Figure 1)**. The medicinal chemists have synthesized a number of innovative chemotherapeutic medicines that contain the benzimidazole moiety due to the great therapeutic potential of benzimidazole-related medications **[8]**.

First benzimidazole derivative was synthesized by Hobrecker in 1872 **[9]**. In 1943 the first research paper on pharmacological properties of benzimidazole published by Goodman and Nancy Hart. In 1944 Woolley reported the antibacterial activity of some benzimidazole derivatives **[10]**. Benzimidazole **(Figure 2)** have a molecular formula $C_7H_6N_2$, its molecular weight is 118.139 g/mol, melting point of 170-172℃.

Benzimidazole ring exists in two equivalent tautomeric forms **(Figure 3)**, in which the hydrogen atom can be located on either of the two nitrogen atoms **[11]**.

Several synthetic methodologies are available for the synthesis of benzimidazoles. Generally, the condensation of o-phenylene diamine with carboxylic acids **(Figure 4)** and their nitrile, imidates and ortho ester derivatives have been widely used for benzimidazole synthesis **[12, 13]**.

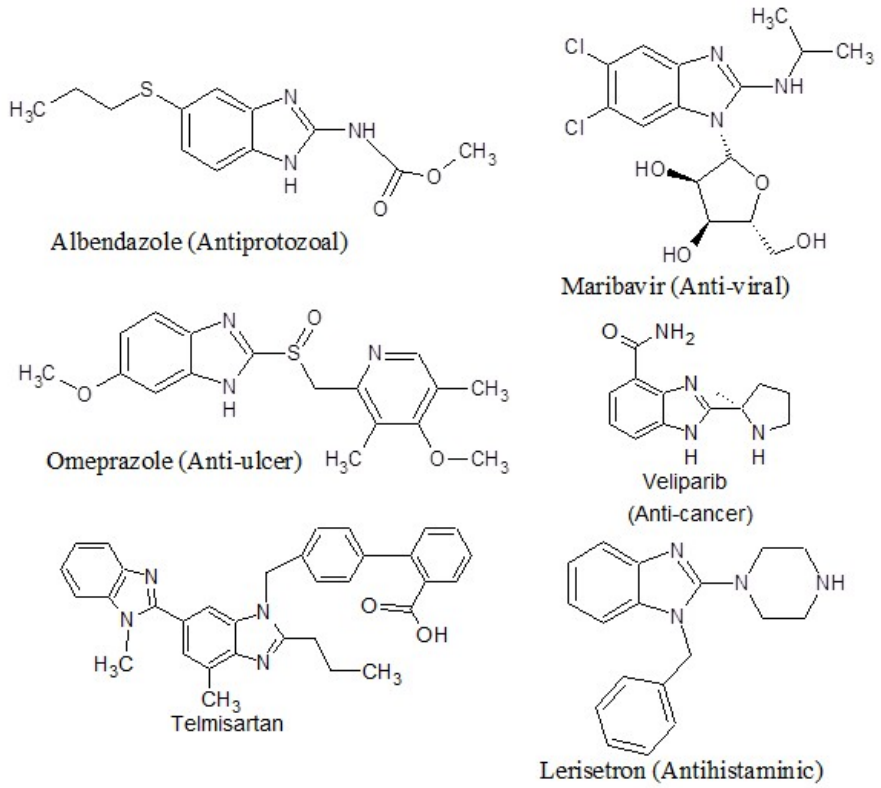


Figure 1: Benzimidazole containing drugs

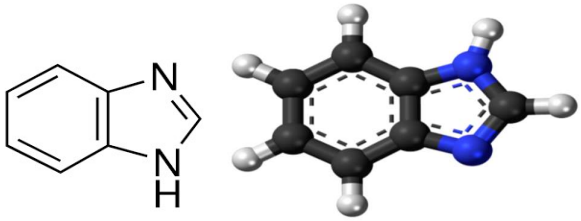


Figure 2: Structure of Benzimidazole

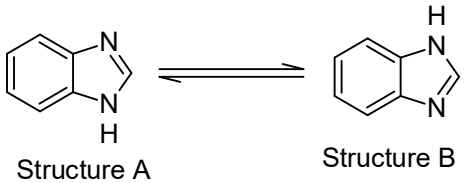


Figure 3: Tautomeric forms of Benzimidazole

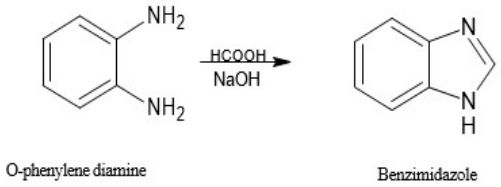


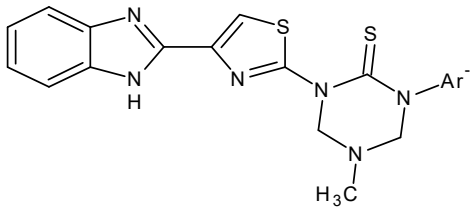
Figure 4: Synthesis of Benzimidazole from o-phenylene diamine and Formic acid

PHARMACOLOGICAL ACTIVITIES:

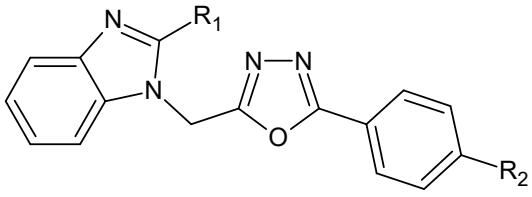
The following sections address the wide range of benzimidazole derivatives synthesized in recent years as well as their various biological uses.

Anti-Microbial Activity:

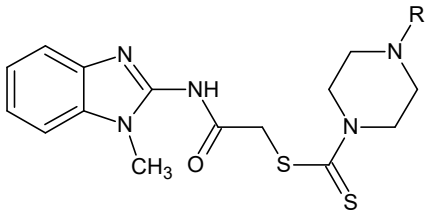
Kumaraswamy Gullapelli *et.al,* (2017) synthesised New analogs of benzimidazole fused heterocyclic compounds such as triazinane and oxadiazinanes by classical amino methylation with different aryl-N, N' unsymmetrical thioureas. he antibacterial activity of triazinane and oxadiazinane compounds have been assessed with zone of inhibition by well diffusion method using a panel of selected gram positive and gram negative bacterial strains and which have showed good activity. The synthesised molecules were subjected to molecular docking studies with two proteins, namely *topoisomerase II* (*PDB ID*: 1JIJ) and *DNA gyrase subunit b* (*PDB ID*: 1KZN). The molecular docking studies are supporting the antibacterial activity exhibiting high inhibition constant and binding energy **[14]**.



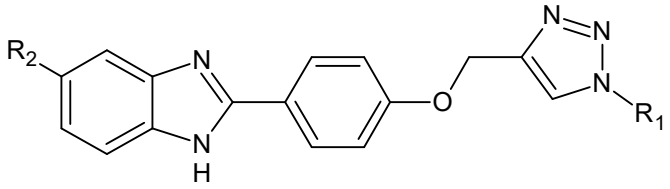
Gowda *et al.,* (2010) reported synthesis of 2-substituted-1-[(5- substituted-phenyl-1, 3, 4-oxadiazole-2-yl) methyl-1*H*-benzimidazoles and has screened for their antibacterial activity with 50 and 250 µg/ml MBC (Minimum bactericidal concentration) against Gram negative bacteria E.coli and gram positive bacteria *S. aureus and Pseudomonas aeruginosa* compared with the standard Ampicillin which showed 50 and 100 µg/ml MBC **[15]**.



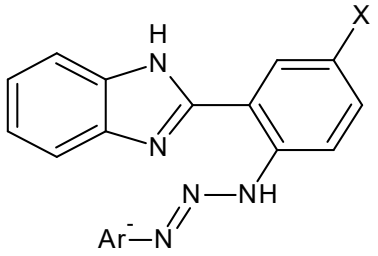
Altintop *et al.,* (2015) reported synthesis of 1, 2-disubstituted benzimidazole derivatives and studied their antimicrobial activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escherichia coli*, and for antifungal activity against *Aspergillus flavus, Aspergillus Niger* and *Fusarium Solani.* These showed good activity as compared with the standard ketoconazole as an antifungal and streptomycin as an antibacterial **[16]**.



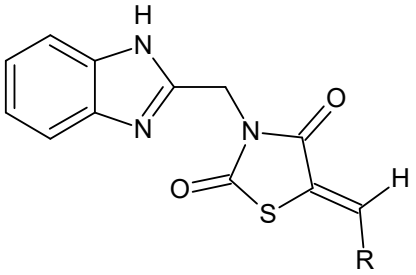
Andrea Bistrovic *et al.*, (2018) reported the designing and synthesis of new biologically active triazole ring linked benzimidazoles and studied their anti-bacterial activity against gram positive and gram negative bacteria. They also reported the structure activity relationship **[17]**.



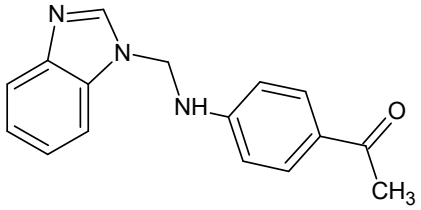
Sujit Kumar Mohanty *et al.*, (2018) reported synthesis of novel azo derivatives of benzimidazole by coupling diazonium derivative of benzimidazole with various appropriate aromatic compounds. The synthesized compounds were evaluated for in vitro antimicrobial and anti-tubercular activities against *Bacillus subtilis, Escherichia coli* and *Mycobacterium tuberculosis* **[18]**.



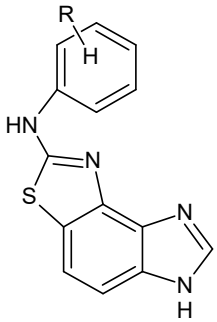
Araujo D.M.L *et al.*, (2018) reported synthesis of 3-((1H -benzimidazol-2-yl) methyl)-substituted thiazolidine 2, 4-dione and studied for their mycobacterium inhibitory activity against Mycobacterium tuberculosis H37Rv strain. Further molecular docking study were carried out in order to rationalize the biological activity **[19]**.



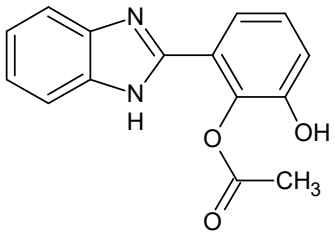
Chandrasekar *et al.*, (2019) reported synthesis of 1-(4-((1H–benzimidazol-1-yl) methylamino) phenyl) ethanone and studied their anti-bacterial activity. The derivatives were screened for their antibiotic susceptibility test (AST) and minimum inhibitory concentration (MIC) against gram negative and gram positive clinical isolates and compared the results with the standard drug Norfloxacin **[20]**.



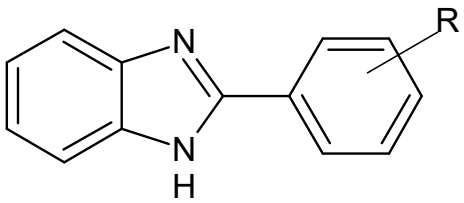
Vasu N *et al.*, (2013) reported synthesis of novel phenyl – (6H-thiazolo [4, 5] benzoimidazole-2-yl)-amines and screened for their antibacterial and anti-fungal activity **[21]**.



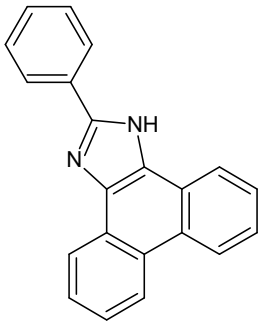
Chavan B B *et al.*, (2012) reported synthesis and of novel benzimidazole derivative (2, 3- dihydro-2-[(2-acetyloxy) phenyl]-1H-benzimidazole) from aspirin and studied their anti-microbial and anti-fungal agents. The MIC of benzimidazole derivative was found to be in the range of 20-200 mg/ml on all the tested microorganisms **[22]**.



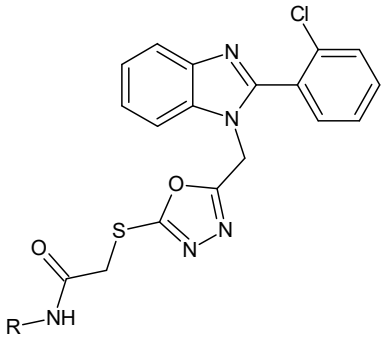
Rohit verma *et al.*, (2021) reported the synthesis of 2- substituted benzimidazole derivatives using on both microwave irradiation and conventional heating method. The syvthesized compounds were screened for their anti-bacterial activity **[23]**.



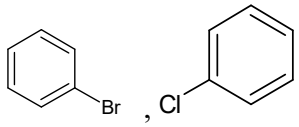
Jerad Suresh *et al.*, (2016) reported a series of benzimidazole derivatives were designed and docked against crucial mtb enzyme target Cyclopropane mycolic acid synthase 2. The molecules with good docking score were chosen for the synthesis using microwave irradiation technique and then screened for anti-tubercular activity using Microplate Alamar Blue Assay method (MABA) **[24]**.



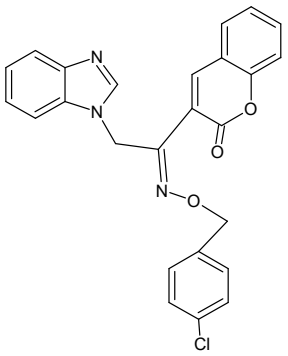
Hessah Abdullah Alzahrani *et.al,* (2023) reported synthesized 1, 3, 4-oxadiazole derivatives bearing benzimidazole scaffold and screened for their antimicrobial activity against s.aureus and S. epidermidis. The compounds were also screened for their cytotoxicity activity against MCF-7 Breast carcinoma and the results were compared with standard drug Doxorubicin **[25]**.



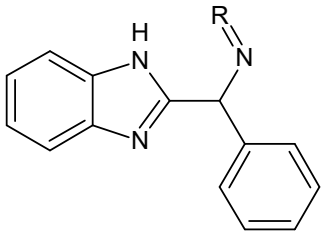
R-



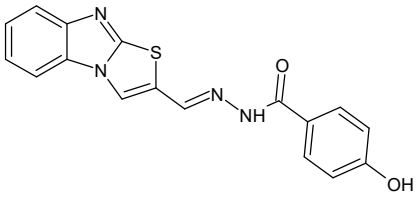
Ravithej Singh *et al.*, (2017) synthesized coumarin–benzimidazole derivatives by simple and efficient method and studied for their antibacterial activity. One of the compound showed remarkable activity at MIC 1.56 and 3.12 µg/ml against *S. aureus* and *E. coli* bacterial strains respectively **[26]**.



Sugandha Singhal *et.al,* (2019) reported the novel Schiff bases by condensation of 2-(1-Amino benzyl) benzimidazole with heterocyclic and aromatic carbonyl compound. The global reactivity descriptors were calculated using DFT approach. The molecular docking result of SBs with ct-DNA suggested interaction via groove binding mode. The antibacterial activity was tested against *S. aureus* and *E. coli*, indicated significant inhibition than reference drug **[27]**.

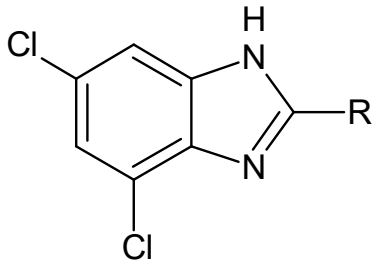


Vinuta Kamat *et.al,* (2021) reported the synthesis of benzimidazole-containing tricyclic systems and studied their antimicrobial activity against some Gram-positive, Gram-negative strains, and their anti-inflammatory activity as well as a hemolytic assay in terms of percentage **[28]**.

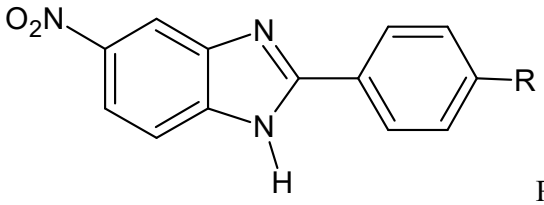


Anti-Oxidant Activity:

Muhammad Taha *et.al,* (2018) synthesis of benzimidazole derivatives by treating of 3, 5-dichlorobenzene-1, 2-diamine with aryl aldehyde and studied their anti-glycation and anti-oxidant potentials. Among the series some analogs showed antiglycating potential ranging in between 182.30 ± 1.20 and 473.51 ± 2.17 when compared with standard rutin (IC50 value 295.09 ± 1.04 mM) and for antioxidant potential ranging between 22.42 ± 0.26 and 82.30 ± 1.33 when compare with standard Propyl gallate (IC50 value 29.20 ± 1.25) **[29]**.

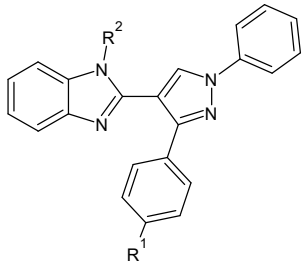


Sabrina Rahman Archie *et al.* (2017) reported synthesis of benzimidazole derivatives and studied their antioxidant activity. All the tested compounds exhibited good antioxidant activity with IC50 values in the range of 3.17 to 7.59 µg/ml while that of standard butylated hydroxytoluene (BHT) was 18.42 µg/ml **[30]**.



R- Cl, Br, F, OMe

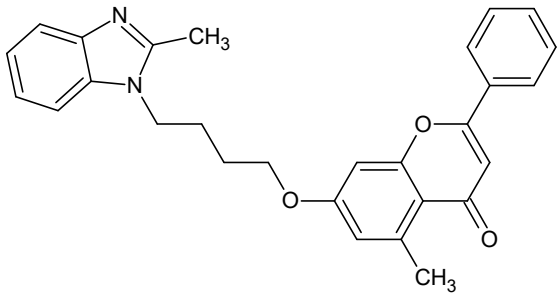
Mahesh Bellam *et al.* (2017) reported synthesis of N-substituted pyrazole-containing benzimidazoles and studied their antioxidant properties by evaluating their radical scavenging activity against DPPH and H_2O_2 **[31]**.



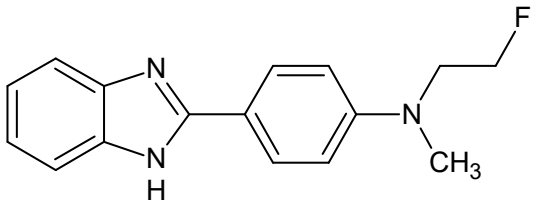
R1-H, NO2, Cl R2- C_6H_6

Anti-cancer Activity:

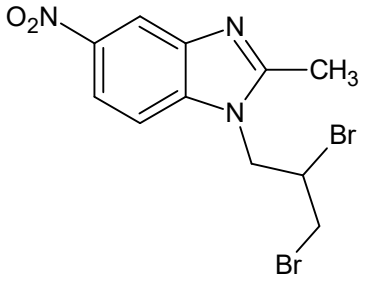
Zhe Wanga *et al.* (2018) were reported the synthesis of chrysin benzimidazole derivatives and studied their anticancer activity. Synthesized compound showed the most potent anti-proliferative activity against MFC cells with IC50 values of 25.72 ± 3.95 Mm **[32]**.



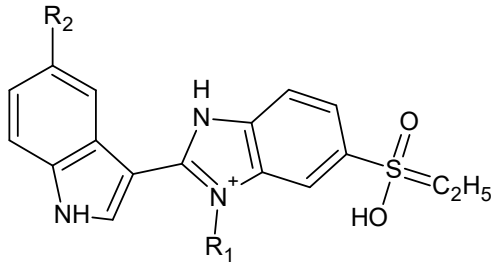
Goreti Ribeiro Morais *et al.* (2017) were synthesized benzimidazole derivatives containing fluorinated or hydroxylated alkyl substituents and studied their anticancer activity **[33]**.



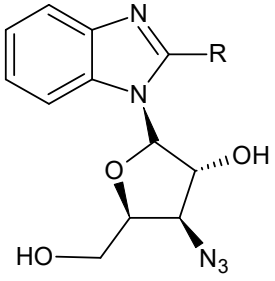
Yasser M. Shaker *et al.* (2015) were synthesized 1-substituted benzimidazole derivatives and studied their cytotoxicity **[34]**.



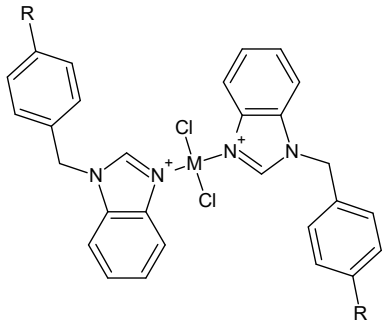
Fikriye Zengin Karadayi *et al.*, (2020) reported synthesis of indole benzimidazoles with p-fluorobenzyl or small alkyl groups at the R1-position and electron withdrawing groups at the R 2-position have highly effective anticancer activities **[35]**.



V. Shinde *et al.*, (2020) reported synthesise of sugar-modified benzimidazole nucleosides with different substituents at the 2- position and shows the anti-cancer activity **[36]**.

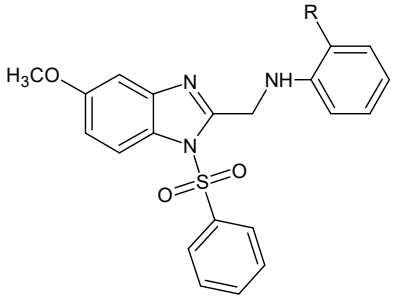


Elif Apohan *et. al.,* (2016) reported novel cobalt or zinc complexes of benzimidazoles were synthesized from the 1-(4-substitutedbenzyl)-1H-benzimidazoles. Cytotoxic activities of novel complexes were investigated against lung cancer cells (A549) and BEAS-2B **[37]**.



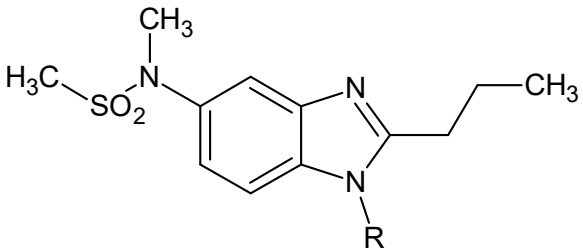
Anti-inflammatory activity:

Monika Gaba *et. al.* (2015) were synthesized 1, 2 and 5- substituted benzimidazole derivatives and studied their anti-inflammatory activity by carrageenan-induced rat paw edema model **[38]**.



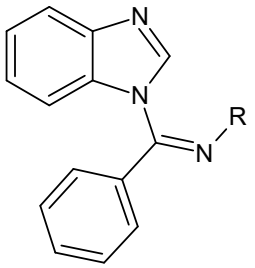
R-H, CH3, NO2

Ratika Sharma *et al.* (2017) synthesized 5-methanesulphonamido benzimidazole derivatives and studied their anti-inflammatory activity by carrageenan-induced rat paw edema model **[39]**.

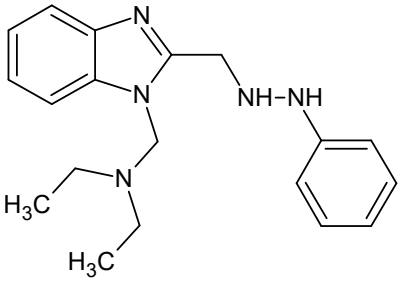


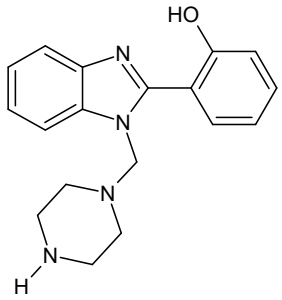
Analgesic Activity:

Asma Eswayah *et al.,* (2017) were reported synthesis of N-substituted benzimidazole derivatives and studied for their analgesic activity **[40]**.



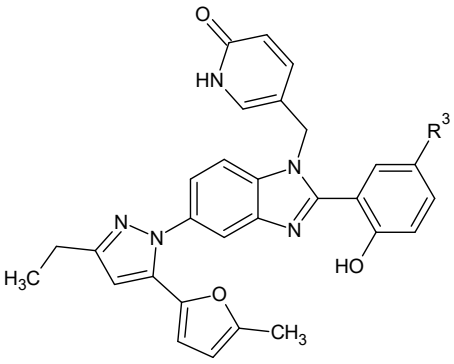
Shobhit Srivastava *et al.* (2013) were synthesized 2-(2-hydroxyphenyl) and 2-phenylhydrazinomethyl-benzimidazole derivatives and studied their analgesic activity **[41]**.

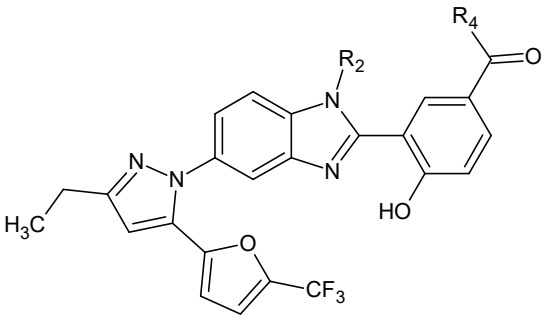




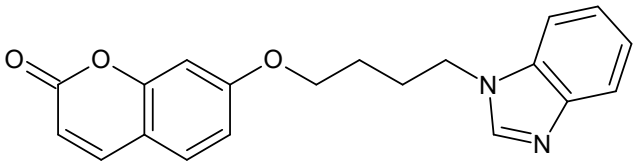
Anti-Viral Activity:

Martin Tremblay *et al.*, (2012) were synthesized 5-(5-furan-2- yl-pyrazol-1-yl)-1H-benzimidazole derivatives as HIV capsid assembly inhibitors **[42]**.



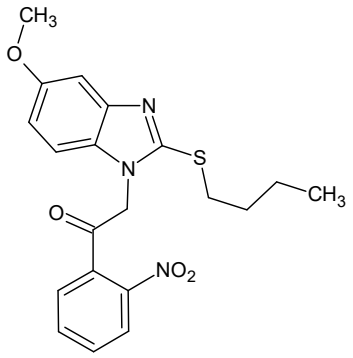


Lei Liu *et al.*, (2014) were synthesis of 7-(4-benzimidazole-butoxy) - coumarin and studied their antiviral activity **[43]**.

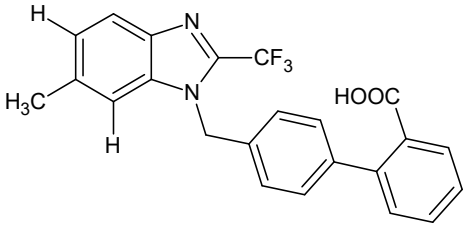


Anti-hypertnesive Activity:

Abdulaziz Hammed G. *et al.*, (2017) were synthesis of benzimidazole derivatives and carried out their molecular docking study as ACE inhibitor **[44]**.

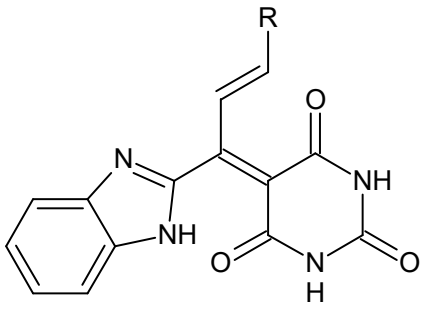


Rani S. Kankate *et al.* (2016) were synthesis of 4′ - ((6- methyl-2-(trifluoromethyls)-1H-benzimidazol-1-yl) methyl)-[1, 1′ - biphenyl]-2-carboxylic acid benzimidazole derivatives was found effective antihypertensive agent **[45]**.

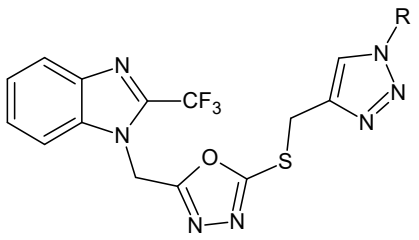


Anti-Depressant Activity:

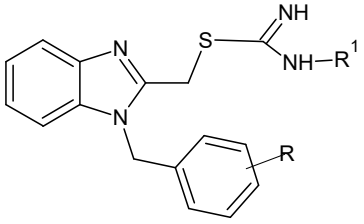
B. Mathew *et al.*, (2016) reported synthesis of s novel (1-H) benzimidazole bearing pyrimidine-trione based MAO-A inhibitors were achieved by the reaction between 2E)-1-(1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-ones and barbituric acid and studied their anti -depressant activity **[46]**.



Mushtaq A Tantray *et al.* (2016) were synthesized benzimidazole-based 1, 2, 3-triazole and 1, 3, 4-oxadiazole conjugates and evaluated for GSK-3β inhibitory **[47]**.

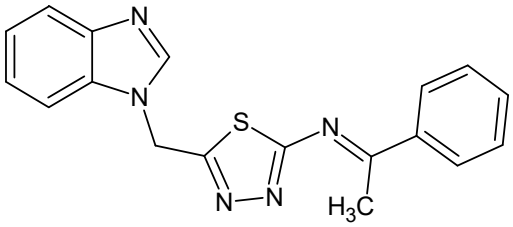


Nadeem Siddiqui *et.al.* (2016) were synthesised benzimidazole derivatives and studied their anti-depressant activity **[48]**.

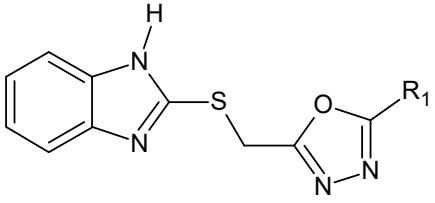


Anti-Diabetic Activity:

Sandhya MJ Nair *et.al,* (2016) synthesized novel N-[(2-amino-5-methylene) - 1, 3, 4-thiadiazole]-2-methyl benzimidazole analogues and studied their anti-diabetic activity **[49]**.

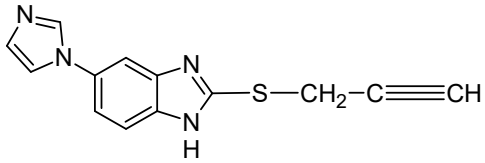


Ramya V. Shingalapur *et al.* (2010) reported synthesized 1, 3, 4-oxadiazoles derivatives containing 2-mercapto benzimidazole moiety and studied their antidiabetic activity **[50]**.

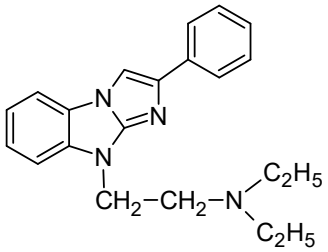


Anti-ulcer activity:

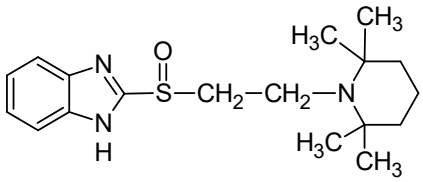
Brumagniez *et al.,* (1990) reported the synthesis of 2-(thiopropyne)- 5- (imidazole -1-yl.) benzimidazole which exhibited moderate antiulcer activity against ulcer induced by anti inflammatory agents in rats orally **[51]**.



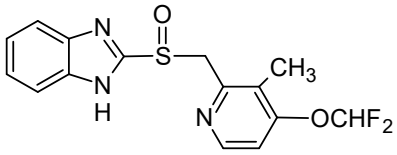
Kovalev *et al.*, (1990) reported the synthesis of 9-(diethyl amino ethylene) 2 – phenyl imidazo [1,2-a] benzimidazole which was found to be more potent than omeprazole **[52]**.



Katano *et al*., (1991) reported the synthesis of 2 - [(2, 2, 6, 6 tetramethyl piperidine) ethyl thio] 5- methoxy benzimidazole which showed moderate activity **[53]**.



Braendstroem *et al.*, (1991) reported the synthesis of 2- [(3, 4 dimethoxy, 2 –pyridyl) methyl, sulfinyl] 5- acetyl, 6-methyl benzimidazole which inhibited gastric acid secretion in dogs **[54]**.



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