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# A Review on Synthesis and Characterisation of Benzimidazole

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**Abstract:** *In the field of Medicinal Chemistry, the uses of heterocyclic compounds increased day by day, because in many biological materials, heterocyclic compound is a part of its structure. Benzimidazole is a heterocyclic compound which formed by fusion of benzene and imidazole. Benzimidazole contains two nitrogen's as heteroatom. Benzimidazole derivatives are more effective, medicinally useful compounds and extensive biochemicals. Derivatives of benzimidazole have found practical applications in various fields. Derivatives of Benzimidazole show many Pharmacological activities such as antihypertensive, anticancer, antiviral, antidiabetic, antimicrobial etc. Due to the applications of these drugs in treatment of microbial infections and other biological activities, motivates for the development of more potent and significant drugs. Pharmacological studies have been shown that these molecules are effective against various strains of microorganisms. The present review summarizes the various derivatives of benzimidazoles and their biological activities.*

**Keywords:** Heterocycle, Benzimidazole, antimicrobial activities

## I. INTRODUCTION

Heterocyclic compounds are essential for life and extensively distributed in nature. A significant role has been played by heterocyclic compounds in the metabolism of all living cells. The nitrogen based heterocyclic compound play important role for mankind. Particularly benzimidazole has an immense importance not only biologically but also industrially among the entire nitrogen based heterocyclic compound.

First benzimidazole derivative synthesized by Hobrecker in 1872 [1]. The first research paper on pharmacological properties of benzimidazole published by Goodman and Nancy Hart in 1943. Then Woolley reported the antibacterial activity of some benzimidazole derivatives in 1944. Afterward from the acid hydrolysis of Vitamin B-12, Norman GB and Karl Folker in 1949 reported 5, 6-dimethyl benzimidazole as a degradation product [2]. After long research, it concluded that benzimidazole is important heterocyclic system because it exhibits biological activity against a number of pathogens and physical disorders. Benzimidazole derivatives plays an active role in therapeutic agents like antiviral, anticancer, antihelmintics, anti-inflammatory agents, analgesics, antihistaminic, antiparasitics, anticonvulsants, antiulcer, antihypertensives, antifungals, proton pump inhibitors and anticoagulants etc.

The benzimidazole based compounds were synthesized by many researchers and studied their antibacterial activity against different bacterial strains. Nowadays bacterial resistance towards antibiotics increases and it is a serious issue. Many antibacterial drugs ineffective against bacteria due to bacterial resistance. World Health Organization also published priority list of antibiotic resistance bacteria [2]. In this review, emphasis is given on recently synthesized non-condensed benzimidazole derivatives along with their biological activity.

### 1.1 Chemistry of Benzimidazole

Benzimidazole is as aromatic heterocyclic organic compound.The synthesis of benzimidazole based polyheterocycles draw the attention of pharmacists from last few decades as it functions as an important pharmacophore in medicinal chemistry and pharmacology. Basically, benzimidazole is a bicyclic compound consisting of the fusion of benzene with imidazole which ultimately gives a privileged structure. This magical moiety possesses many pharmacological properties. Till now the most prominent benzimidazolemoiety is N-ribosyl-dimethylbenzimidazole present in nature and it serves as

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the axial ligand for cobalt in vitamin B12. Benzimidazolepossess many biological activities such as anti-microbial, anti-fungal, anti-histaminic, anti-inflammatory, anti-viral, anti-oxidant, anti-cancer, anti-ulcerative etc., that's why benzimidazole derivatives are considered as an important moiety for the development of molecules of pharmaceutical interest.

## II. MATERIALS AND METHODS

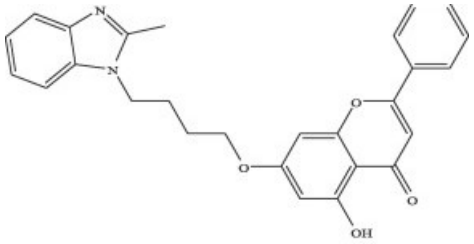
O-Phenylenediamine(5.4mg) , Formic acid(3.2mg), Sodium hydroxide(Q.S), Distilled Water(Q.S) .A mixture of O-Phenylenediamine (5.4 g), Formic acid (3.2 ml) and30 ml ofwater was taken in a 250 ml beaker.Heat the mixture on water bath at 100°C for 2 hour. Cool and added 10% sodium hydroxide slowly with constant shaking until the mixture just alkaline to litmus. Filtered off the crude benzimidazole at the pump, washed with ice-cold water drain well and washed again with 25ml of cold water. Dissolve the crude product in 400ml boiling water, added 2g of decolourising carbon and digest for 15 minutes. Filter rapidly at pump through a preheated Buchner funnel and flask. The compound was purified by recrystallization using boiling water.

### 2.1 Biological Activity

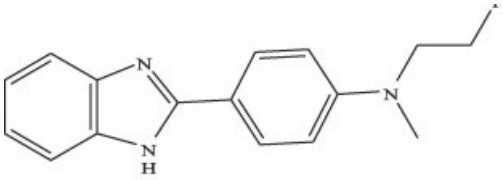
### A. Anticancer Activity

Worldwide cancer is the second prominent cause of death. To act as a anticancer drug, it should have toxic to the cancer affected cells and not to normal cells. The anticancer drugs has been used previously shows comparatively high toxicity to tumour cells, but to the normal cells also. Due to the side effects and toxicity of anticancer drugs, the rate termination of chemotherapy in cancer patients increased. It is noted that discovery of new anticancer drug with high efficiency and low side effects is urgent need and a critical challenge also.

**Zhe Wanga et al.** [3] were synthesized a series of chrysin benzimidazole derivatives and studied their anticancer activity. Among synthesized compounds, compound (1) showed the most potent anti-proliferative activity against MFC cells with IC50 values of 25.72 ± 3.95 μM. Results of flow cytometry displayed that compound (1) increases apoptosis of MFC cells in a dose-dependent manner. The anticancer activity was also studied in tumour bearing mice, and they observed that compound (1) suppress the tumour growth.




**Goreti Ribeiro Morais et al**. [4] were synthesized a series of benzimidazole derivatives containing fluorinated or hydroxylated alkyl substituents and tested their anticancer activity. Among the tested compounds, (2) displayed the most promising anticancer activity. Compound (2) having a non-substituted benzimidazole core and a 2-fluoroethyl chain at the aniline nitrogen, presented a reasonable cytotoxic activity against the U87 glioblastoma cell line (IC50 = 45.2 ± 13.0 μM) in comparison with DOX (IC50 = 16.6 ± 2.5 μM), which is used as standard antitumor drug




### B. Antihypertensive

Nowadays due to change in life style and increasing stress, hypertension is a serious issue in our society. In hypertension, the blood pressure of arteries increases (so it is also called as high blood pressure). Different heterocyclic compounds have been used as antihypertensive.

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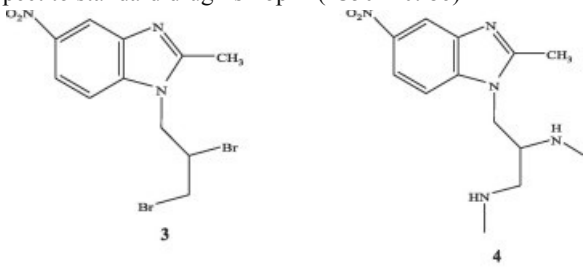
**Abdulaziz Hammad G. et al**[8] were designed series of benzimidazole derivatives and carried out their molecular docking study as ACE inhibitor. From molecular docking study and in silico toxicity study, they found compound 2-(2-(butylthio)-5-methoxy-1H-indol-1-yl)-1-(2-nitrophenyl) ethan-1-one (8) as an equipotent ACE inhibitor with respect to lisinopril as a standard drug. The in vitro ACE inhibitory assay of this compound (IC50 = 0.81) also revealed that it was almost equipotent with respect to standard drug lisinopril (IC50 = 0. 86)



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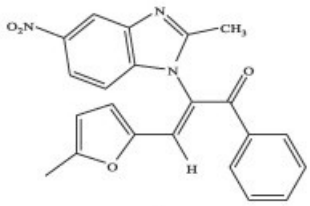
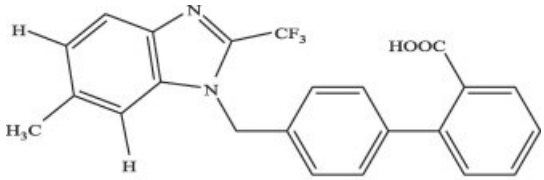


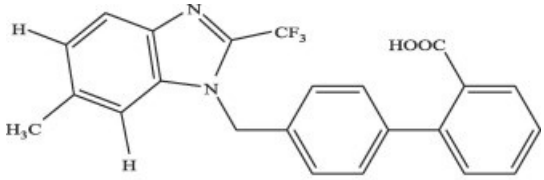
**Rani S. Kankate et al**. [9] were synthesized series of benzimidazole deriveatives, deliberately to establish the moieties which are responsible for Angiotensin-II inhibition. All synthesized compounds were tested for antihypertensive activity. Out of all the tested compounds, 4′-((6-methyl-2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)methyl)-[1,1′-biphenyl]-2-carboxylic acid (9) was found effective antihypertensive agent. Dexamethasone used for induction of hypertension and Losartatan is used as standard.



**C. Anti-Inflammatory**

Anti-inflammatory term used for the property of a substance which reduces swelling or inflammation. Many analgesics have anti-inflammatory property. Anti-inflammatory drugs reduces pain by reducing inflammation

**Ratika Sharma et al**. [10] synthesized series of 5-methanesulphonamido benzimidazole derivatives. The anti-inflammatory activity of synthesized compounds were tested in carrageenan induced rat paw edema model. Among tested compounds, (10a, 10b and 10c) showed maximum (92.73%, 95.64 % and 97.62% respectively) reduction in edema and were also non-ulcer genic at the tested doses. Indomethacin and Rofecoxib were used as standard drugs



**Purva Sethi et al.** [11] synthesized new benzimidazole derivatives from medicinally important moieties, coumarin and benzimidazole nuclei. Among the synthesized compounds (11b and 11f) exhibited maximum anti-inflammatory activity (45% inhibition), which is equivalent to the activity of indomethacin (48% inhibition) after 3 h (peak inflammatory

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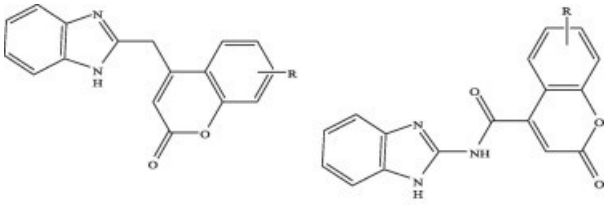
response time). Compounds of second series (12a–12f) shows anthelmintic activity. Amongst these, compound (12e) is found to be the most potent antioxidant with remarkable EC50 value (0.08 µM/mL). Compound (12f) has mortality activity marginally higher than albendazole (10–11s)



a;R= 7-OH b; R=7-$CH_3$ c;R=6-$CH_3$ d;R=8-$CH_3$ e;R=8- $NO_2$ f;R=H

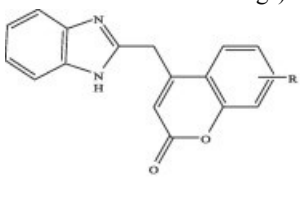


a;R= 7-OH b; R=7-$CH_3$ c;R=6-$CH_3$ d;R=8-$CH_3$ e;R=8- $NO_2$ f;R=H

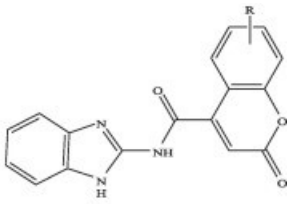
**D. Antimicrobial**

An antimicrobial is used to prevent growth of microorganisms or to kill them. Antimicrobial medicines are categories according to their action on microorganism type. It means antifungals are used against fungi and antibiotics are used against bacteria. On the basis of function they have two type i.e. agents that kill microbes are called microbicidal, while those inhibit growth of microbes are called biostatic. Benzimidazole inhibits protein synthesis in microbes because benzimidazole has structural similarity with purine. Generally 2-substituted derivatives of benzimidazole are more potent in showing pharmacological activity.

**E. N.S. El-Gohary et al**. [13] synthesized series of benzimidazole derivatives and tested their antimicrobial activity. Among the tested compounds, (14) and (16) showed good activity toward S. aureus with MIC value 0.524 µg/ml and 0.684 µg/ml respectively, whereas compound (15) with MIC value 0.489 µg/ml exhibited remarkable activity toward B. cereus. Compound (14) was found the most active antifungal analog toward C. albicans with MIC value 0.262 µg/ml. Moreover, compound (16) displayed the promising activity against A. fumigatus 293 with MIC value 1.37 µg/ml. (Ampicillin and Fluconazole were used as standard drugs)

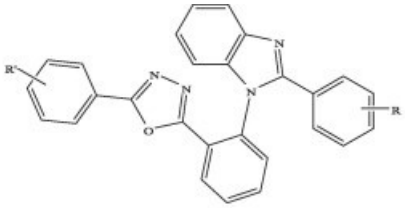


a;R= 7-OH b; R=7-$CH_3$ c;R=6-$CH_3$ d;R=8-$CH_3$ e;R=8- $NO_2$ f;R=H



a;R= 7-OH b; R=7-$CH_3$ c;R=6-$CH_3$ d;R=8-$CH_3$ e;R=8- $NO_2$ f;R=H

**Archana Kapoor et al.** [16] synthesized different 2-substituted benzimidazole derivatives. Among the synthesized compounds, (22b) shows prominent activity (MIC = 1.30 µmol/ml) against E. coli. Other compounds (22a to 22f) exhibited good activity (MIC = 1.58 to1.88 µmol/ml) against E. coli, P. aeruginosa, S. epidermidis and A. niger. Standard drugs used are ciprofloxacin (MIC = 2.33 µmol/ml) and fluconazole (MIC = 1.99 µmol/ml). From the results obtained, it concluded that substituting benzylidene benzene ring with electron donating groups is contributing more towards antimicrobial activity.



a;R=3,4-$OCH_3$ R'=4-$OCH_3$ b; R=4-$OCH_3$ R'= $NO_2$ c; R=4-$OCH_3$ R'=4-$OCH_3$ d; R=F R'=4- $NO_2$ e; R=F R'=4-$OCH_3$ f; R=F R'=3,4-$CH_3NH_2$

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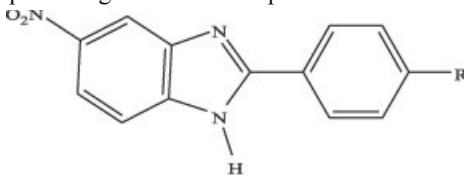
**E. Antioxidant Activity**

The ability of bioactive compounds to delay or prevent oxidation of various substrates in living organisms and in food products called antioxidant activity.

**Sabrina Rahman Archie et al.** [20] were synthesized series of benzimidazole derivatives and evaluated 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. The activity of compound (29c) (IC50 = 3.17 µg/ml) was found more promising than other compounds.

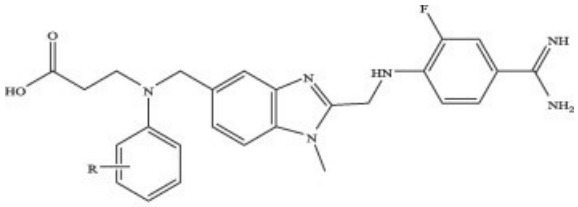


a;R=Cl b;R=Br c;R=F d;R=OMe

**F. Anticoagulants**

Anticoagulants are used to prevent the formation of blood clots. Conditions and diseases like heart attack, stroke, atrial fibrillation, pulmonary embolism and deep venous thrombosis requires anticoagulant treatment to reduce the risk of blood clots.

**Yang Haoran et al**. [23] were synthesized 1,2,5-trisubstituted benzimidazole fluorinated derivatives and tested for anticoagulant activity. Compounds (34a, 34b and 34c) with IC50 values of (2.26 ± 0.38), (1.54 ± 0.09) and (3.35 ± 0.87) nmol/L, respectively exhibited better anticoagulant activity than argatroban, of which the IC50 values was (9.88 ± 2.26) nmol/L. It is observed that methyl substituent at the ortho position of the benzene ring is beneficial for anticoagulant activity.

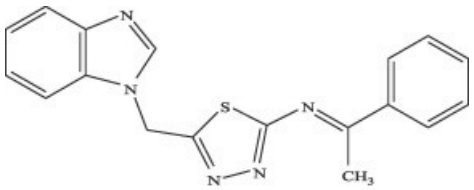


a;R=3-$CH_3$ b;R=2,3-$CH_3$ c;R=2,5-$CH_3$

**G. Antidiabetic agents**

Diabetes is a condition in which body does not produces insulin or uses insulin efficiency. Diabetes is also considered as a leading cause of death and affects large population of the world. To treat diabetes many natural and synthetic drugs have been developed

**Sandhya MJ Nair** [25] synthesized novel N-[(2-amino-5-methylene)-1,3,4-thiadiazole]-2-methyl benzimidazole analogues. Among the synthesized compound, based on the Libdock score, (36) was selected for in vitro antidiabetic and found that it shows 49.25% inhibition at 100 µg conc. Reference Acarbose showed 68.61% inhibition at 100 µg concentration.



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## III. CONCLUSION

With an aim of developement potent antimicrobial agent, benzimidazole were synthesized from o-Phenylenediamine by the condensation and substitution typereaction. The synthesized benzimidazole were characterized by the Biological properties. Anticancer activity, anti-inflammamatory, anti-Hypertensive activity, antimicrobial activity.

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## REFERENCES

**[1].** G.R. Morais, E. Palma, F. Marques, L. Gano, M.C. Oliveira, A. Abrunhosa, H.V. Miranda, T.F. Outeiro, I. Santos, A. Paulo Synthesis and biological evaluation of novel 2-aryl benzimidazoles as chemotherapeutic agents J. Heterocyclic Chem., 54 (1) (2017), pp. 255-267

**[2].** A.H. Alanazi, Md.T. Alam, M. Imran Design, molecular docking studies, in silico drug likeliness prediction and synthesis of some benzimidazole derivatives as antihypertensive agents Md. Imranl. Indo American J. of Pharmaceutical Sci., 4 (04) (2017), pp. 926-936

**[3].** R. Sharma, A. Bali, B. Chandhari Synthesis of methanesulphonamido-benzimidazole derivatives as gastro-sparing antiinflammatory agents with antioxidant effect Bioorg. Med. Chem. Lett., 27 (2017), pp. 3007-3013

**[4].** H. Yang, Y. Ren, X. Gao, Y. Gao Synthesis and anticoagulant bioactivity evaluation of 1,2,5-trisubstituted benzimidazole fluorinated derivatives Chem. Res. Chin.Univ., 32 (6) (2016), pp. 973-978

**[5].** A. Kapoor, N. Dhiman Synthesis and evaluation of 2-aryl substituted benzimidazole derivatives bearing 1,3,4-oxadiazole nucleus for antimicrobial activity Der. PharmaciaLett., 8 (12) (2016), pp. 97-104

**[6].** Z. Wang, X. Deng, S. Xiong, R. Xiong, J. Liu, L. Zou, X. Lei, X. Cao, Z. Xie, Y. Chen, Y. Liu, X. Zheng, G. Tang Design, synthesis and biological evaluation of chrysin benzimidazole derivatives as potential anticancer agents Nat. Prod. Res., 32 (24) (2018), pp. 2900-2909

**[7].** S.R. Archie, B. Das, M.S. Hossain, U. Kumar, A.S.S. Rauf Synthesis and antioxidant activity of 2-substituted-5-nitro benzimidazole derivatives Int. J. Pharm.Pharm. Sci., 9 (1) (2017), pp. 3083

**[8].** 10)S. Nair, J. Beevi, N. Merlin, B. Emmanuel, S. Dharan, C. Remya Insilico design, synthesis and in vitro antidiabetic and anti-inflammatory activities of 1,3,4-thiadiazole substituted 2-methylbenzimidazole derivatives J. Pharm. Res. Clin. Pract., 6 (1) (2016), pp. 27-36

**[9].** R. Kankate, A. Pangare, R. Kakad, P. Gide, V. Nathe Synthesis and biological evaluation of benzimidazolyl biphenyl derivatives as antihypertensive agents Int. J. Chem. Concepts, 2 (2) (2016), pp. 111-119

**[10].** N. Gohary, M. Shaaban Synthesis and biological evaluation of a new series of benzimidazole derivatives as antimicrobial, antiquorum-sensing and antitumor agents Eur. J. Med.Chem., 131 (2017), pp. 255-262

**[11].** Advanced Medicinal Chemistry, A Laboratory Guide, Dr. M. Raghu Prasad, Dr. A. Raghuram Ray, Page no. 134-136

**[12].** Mark G. Cantwell, Julia C. Sullivan and Robert M. Burgess, Benzotriazole : History, Environmental Distribution, and Potential Ecological Effects.

**[13].** Avhad Datta, Asnani Alpana, Mohurle Shrikant, Kumar Pratyush, Bais Abhibnav and Tale Ruchita, Review on Synthetic Study of Benzotriazole.