REVIEW ON SYNTHESIS OF BENZIMIDAZOLE AND ITS DERIVATIVES WITH THEIR BIOLOGICAL ACTIVITIES

Mr.Soham Wagh[1], Mr.Rahul Lokhande[2], Ms.Pranali Kale[3]

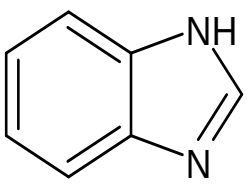
[1] *Student of Samarth Institute of Pharmacy,Belhe,Maharashtra,India*
[2] *Department of Pharmaceutical Chemistry,Samarth Institute of Pharmacy,Belhe,Maharashtra,India*
[3] *Student of Samarth Institute of Pharmacy,Belhe,Maharashtra,India*

ABSTRACT

Benzimidazole constructing holds imidazole ring melded accompanying phenyl ring at 4- and 5-position. The methods for the synthesis of benzimidazoles have become a focus of synthetic organic chemists, as they are useful building blocks for the development of important therapeutic compounds in medicine. Benzimidazole nucleus plays a very important role as a therapeutic agent e.g. antiulcer and anthelmintic drugs. Other benzimidazole derivatives exhibit pharmacological activities such as antimicrobial, antiviral, anticancer, anti-inflammatory and analgesic.Benzimidazole merchandise are strangely lively compounds to many illnesses and might also have the possible predicted the first lively Therapy towards Ebola bacterium. Benzimidazole are revered as major heterocyclic standards that showcase a expansive vary of Pharmaceutical requests containing anticancers, antihypertensives, antivirals, antifungals, and Anti-HIVs.

Keyword: - *Benzimidazole, Anticancer, Ebola bacterium, Heterocyclic, Amoebas.*

INTRODUCTION:-



1*H*-1,3-benzimidazole

The benzimidazole nucleus is found in a variety of naturally occurring compounds and is of significant importance in medicinal chemistry. Owing to its conspicuous pharmacological properties, benzimidazoles have become an

important pharmacophore and sub-structure in drug design and have been screened for a wide range of biological activities.[1]

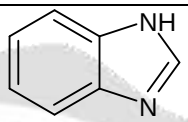
Organic molecules bearing different heterocyclic ring systems have attracted a great deal of attention in now a day, both in chemical and medicinal research that could be attributed to their different pharmacological applications. Benzimidazoles represent a class of nitrogen heterocyclic which possesses biological and pharmacological activities. Synthetically produced heterocycles designed by organic chemists are used as pharmaceuticals, dyestuff, agrochemicals and are of increasing importance in many other areas including adhesives, molecular engineering, polymers etc. In biological processes naturally occurring heterocyclic moieties played a vital role. They are broadly found in naturally in plant alkaloids, nucleic acids, and anthocyanins and flavones as well as in chlorophyll. additionally several proteins, hormones, vitamin's contain aromatic heterocyclic ring system.[2,3] Heterocycles act as drugs because they have specific chemical reactivity and they provide convenient building blocks to which pharmacologically active substituent can be attached. Thus, we needed the development of innovative methodology for bioactive heterocyclic in synthetic organic and medicinal chemistry with some advantages including its simplicity of operation, greener approach, easy workup procedure, selectivity, higher yields, and high-atom economic.[4] Nitrogen heterocyclic compounds are among the most privileged and significant structural components of pharmaceuticals.[5,6] A recent analysis of the nitrogen heterocyclic composition of U.S. FDA approved drugs has revealed the relative frequency by which various nitrogen heterocyclic compounds have been incorporated into approved drugs architecture.[7] Benzimidazole is an aromatic N-heterocyclic formed by the fusion of benzene and imidazole ring.

DRUG PROFILE:-

Name of Drug:- Benzimidazole

Fig -1:- Benzimidazole Product

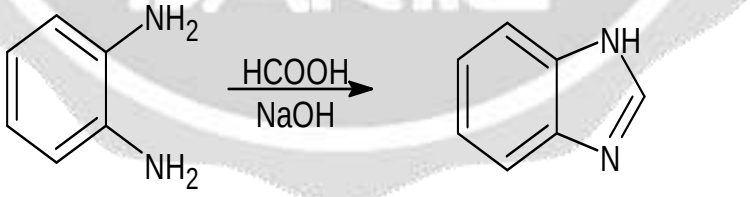
Table -1:- Properties of Benzimidazole

Synonym	1H-Benzimidazole, 1H-Benzo[d]imidazole, 1,3-Benzodiazole
Structure	
Molecular Formula	$C_7H_6N_2$
Molecular Weight	118.14g/mol
Colour	White Solid
Melting point	170°C
Boiling point	250°C

Uses:-

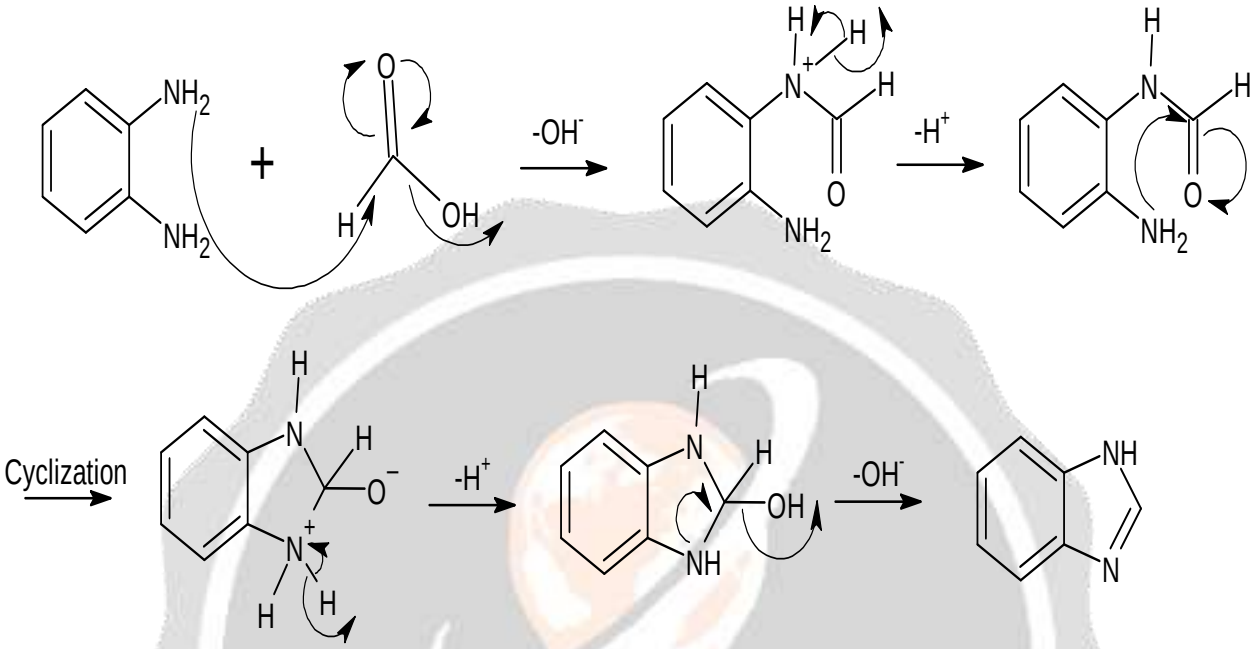
1. The benzimidazoles are a large chemical family used to treat nematode and trematode infections in domestic animals.
2. They also have limited activity against cestodes.

Reaction of Benzimidazole:- [8,9]



benzene-1,2-diamine 1*H*-1,3-benzimidazole

Mechanism of Benzimidazole:- [8,9]

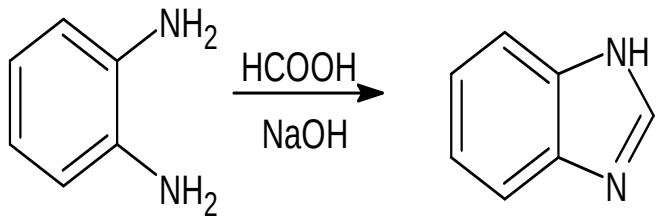


METHODS FOR SYNTHESIS OF BENZIMIDAZOLE :-

Conventional method:- [8,9]

1. Add 27g of o-phenylenediamine in a round bottomed flask.
2. Add 17.5 g of 90% formic acid.
3. Heat the mixture on a water bath at 100 °C for 2 h.
4. Cool and add 10% sodium hydroxide solution slowly, until the mixture is just alkaline to litmus.
5. Filter off the synthesized crude benzimidazole.
6. Wash with ice cold water, drain well wash again with 25 ml of cold water.

Reaction:- [8,9]

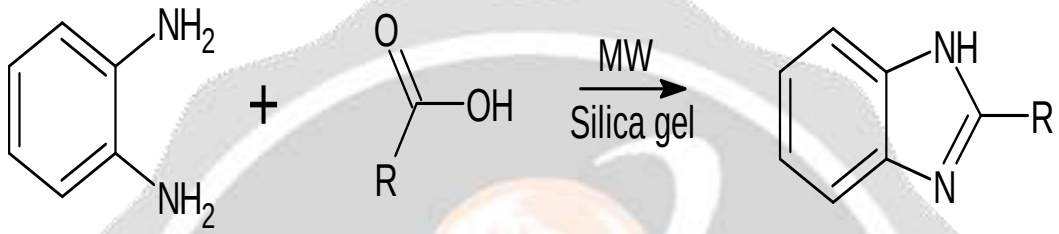


benzene-1,2-diamine 1*H*-1,3-benzimidazole

Microwave Method:-

synthesis of benzimidazoles under microwave irradiation and solvent-free conditions which is catalyzed by alumina, silica gel and zeolite HY , o-phenylenediamine (2 mmol) with aromatic, aliphatic and heterocyclic carboxylic (2 mmol) and 50 mg of Alumina or Silica gel or Zeolite were mixed thoroughly in a mortar.
The reaction mixture was then irradiated in a domestic microwave oven for 5–9 min at 160–560. [10]

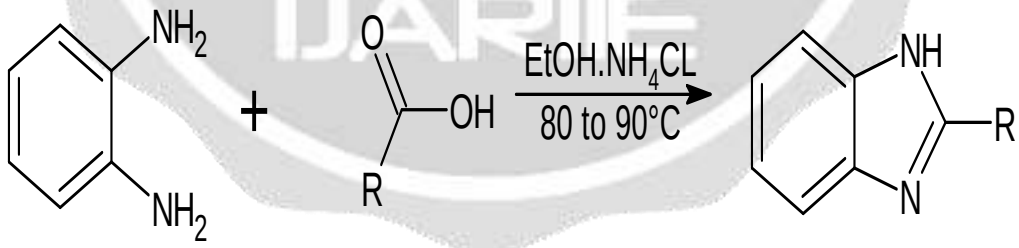
Reaction:-



Preparation of Benzimidaole:-

1. Benzimidazole in moderate to good yield have been prepared in one-spot reaction by condensation of o-phenylenediamine (0.01 mol) and different aromatic acid (0.01 mol) in the presence of ammonium chloride as catalyst at 80–90°C.
   The reaction is green and economically viable. [11]

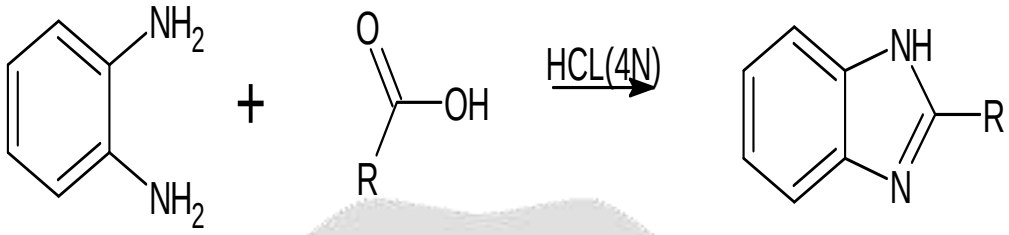
Reaction:-



Reaction-1

2. The most commonly used involves the condensation of o-diaminobenzenes with carboxylic acids or its derivatives, including heating the reagents together in the presence of concentrated hydrochloric acid, this is the most common synthetic method for preparation of a wide range of benzimidazoles. [12]

Reaction:-



Reaction-2

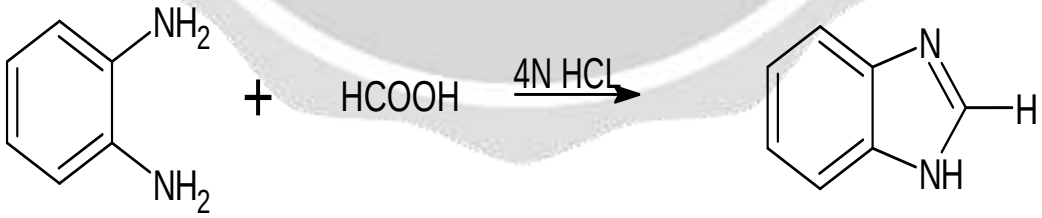
3. O-phenylenediamines react readily with most carboxylic acids to give 2-substituted benzimidazoles, usually in very good yields. The reaction is carried out usually by heating the reactants together on a steam bath, by heating together under reflux or at an elevated temperature, or by heating in a sealed tube. [13]

Reaction:-

Reaction-3

4. Refluxed o-phenylenediamine with formic acid under the acidic conditions (4N HCl) at 120 ºC for 2 to 4 h to give 75% yield of benzimidazole (C). This is a prevalent laboratory method for synthesis of benzimidazole. [14]

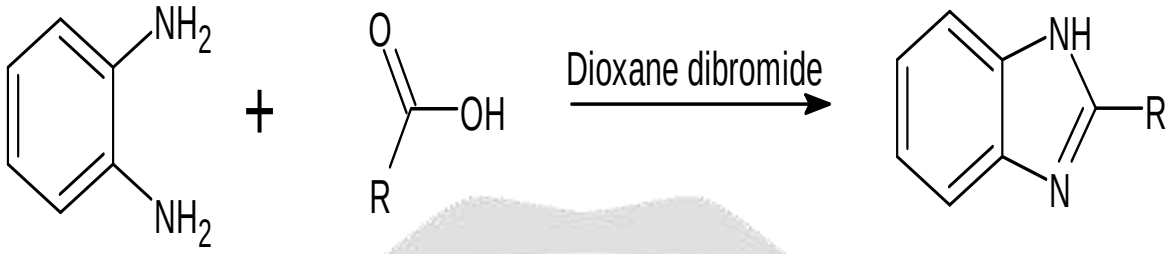
Reaction:-



Reaction-4

5. Synthesized a mild and efficient approach for the synthesis of benzimidazole ring through oxidative cyclization of o-phenylenediamine and different aldehydes using dioxane dibromide, as a user-friendly reagent. This is a new, convenient and facile methodology for the synthesis of 2-substituted-1H-benzo[d]imidazoles.[15]

Reaction:-



Reaction-5

ACTIVITIES OF BENZIMIDAZOLE:-

Antiviral activity:-

Chronic infection with the hepatitis C virus (HCV) is a major risk factor for developing cirrhosis and hepatocellular carcinoma. Approximately 3% of the worldwide population is chronically infected with HCV (Alter and Seeff, 2000; Bialek and Terrault, 2006). A preventive vaccine has not been developed and limits of current therapeutics include serious side effects and therapy usually lasting 48 weeks with only a 50% sustained virological response rate. [16]

Antibacterial activity:-

The increase in bacterial resistance has attracted considerable interest in the discovery and development of new classes of anti-bacterial agents. The new agents should preferably consist of chemical characteristics that clearly differ from those of existing agents. Actinonin was first isolated from a Malayan strain of Actinomyces and found to show a weak inhibitory activity against Gram-positive and Gram-negative bacteria. However, recently actinonin has been proven to have anti-proliferative effects on human tumor cells. The action mechanism of actinonin is believed to be the inhibition of the peptide deformylase that is a new class of metal-loenzyme which is essential for bacterial survival. The hydroxamate group of actinonin, which can complex with the metal ion in the active pocket of the peptide deformylase, is necessary for its activity. Nevertheless, actinonin lacks in vivo efficacy, due to the poor bioavailability. [17]

Antifungal activity:-

Infectious diseases have been serious and growing threatens to human health during the past few decades. The decrease of sensibility to anti-microbial agents in current use has also been increasing for a great variety of pathogens and the resistance to multiple drugs is more and more prevalent for several microorganisms, especially for Grampositive bacteria and some intractable fungi. Their inhibitory properties as regard representative fungi have been extensively exploited. Especially, it is worthy to note that Fluconazole, the first -line triazole-anti-fungal drug Recommended by World Health Organization (WHO) has established an exceptional therapeutic record for Candida infec-tions, and become the first choice in the treatment of infections by Candida albicans and Cryptococcus neoformans due to its potent activity, excellent safety profile, and favorable pharmacokinetic characteristics. However, Fluconazole is not effective against invasive aspergillosis and is not fungicidal. In addition, extensive clinical use of Fluconazole has resulted in the increasing Fluconazole- resistant C albicans isolates. [18]

Antimalarial activity:-

Malaria caused 350-500 million clinical episodes annually and result in over one million deaths, most of which affect children under 5 years old in sub Saharan Africa. Malaria is the fifth cause of death from infectious diseases worldwide (after respiratory infections, HIV/AIDS, diarrhoeal diseases and tuberculosis). Recent estimates so that as many as 3.3 billion people live in areas at risk of malaria in 109 countries. In addition to its health toll, malaria puts a heavy economic burden on endemic countries and contributes to the cycle of poverty people face in many countries. Malaria mortality and morbidity began to increase in the 1980s due to a combination of factors such as increase in parasite and vector resistance to the current anti-malarial drugs and insecticides, the weakening of traditional malaria control programs, rapid decentralization and integration into deteriorating primary health service, and the development of humanitarian crisis situations in many malaria-endemic areas. This dramatic increase led to a compelling and urgent necessity for new malarial, with mechanisms of action different from the existing ones, and to identify new drug targets. Cloroquine has recently been shown to inhibit hemozoin formation within the parasite food vacuole. This process is also thought to be the molecular target of other quinoline anti-malarial. Hemozoin was originally considered to be formed by the polymerization of heme, but has now been demonstrated to be a crystalline cyclic dimmer of ferriprotoporphyrin IX. Thus, hemozoin synthesis, a process unique to the malaria parasite, offers a logical and valuable potential target for new anti-malarial drug development. New drugs that attack the same vital target of chloroquine but that are not subject to the same resistance mechanism would be highly desirable. [19]

Anticancer activity:-

Cancer is one of the most common causes of death through out the world. It occurs when a tumor or liquid cancer results from a loss of control over cell growth. Recent studies have introduced a new generation of anticancer drugs that target hypoxic cancer cells and offer a potential treatment for the early stages of neoplastic diseases. Nitro compounds and those containing bioreducible N-oxide groups are the most effective. Based on these facts,synthesized a series of 5-nitro-1H-benzo[d]imidazole derivatives and predicted that they would possess anticancer properties and have a selective affinity for cells under hypoxic conditions. They evaluated their cytotoxic properties by testing them against human malignant melanoma cells. [20]

Antiparasitic activity:-

Malaria is the fifth most common cause of death due to infectious disease worldwide. Four Plasmodium species are responsible for human malaria: Plasmodium vivax, P. ovale, P. malariae, and P. falciparum. Only P. falciparum has developed resistance to nearly all the available antimalarial drugs.Saify et al.identified a series of benzimidazole compounds plasmepsin II and human cathepsin D, which were expected to be inhibitors of P. falciparum, after virtual screening of an internal library of synthetic compounds. This was confirmed by enzyme inhibition studies that provided IC50 values in the low micromolar range (2 - 48 µM). [21]

CONCLUSION:-

Synthesis of benzimidazole derivatives has long been an area of intense development due to the great synthetic and medicinal importance of this heterocyclic core and still constitutes an active domain from academic and industrial points of view. This review has attempted to summarize the various synthetic routes for the synthesis of benzimidazoles. Benzimidazole has a wide range of pharmacological activities like- antimicrobial, antifungal,

antioxidant, antiviral activity, anticancer activity, anti-inflammatory activity, etc. Thus, we can say that benzimidazole is a moiety which has exhibited versatility in pharmacological action and has further potential for exploring its unexplored pharmacological activities.

REFERENCE:-

1) Fei F, Zhou ZM. New substituted benzimidazole derivatives: a patent review (2010-2012). Expert Opin Ther Pat 2014;23:1157-79
2) Divyani G, Priyanka K, Shikha A.Synthetic aspects and Biological Studies of some Heterocycles.Chemistry & Biology Interface. 2017; 7:79-101.
3) Nasir H , Saba K, Maqbool A , Joshi A , Mohammod A, Prabhunath Y.Synthesis and Antiviral Evaluation against cytomegalovirus (CMV) and Varicella-zoster virus (VZV) in human embryonic lung (HEL) cells of thiadiazoland thioazolidinone derivatives,Chemistry& Biology Interface.2015;5:365-377.
4) VioletaI , Perez N . Editorial (Thematic Issue: Towards the Integration of Quantitative and Systems Pharmacology into Drug Discovery: a Systems Level Understanding of Therapeutic and Toxic Effects of Drugs).Current Pharmaceutical Design.2016;22:6881-6884
5) Gaba M, Singh S, Mohan C. Benzimidazole: an emerging scaffold for analgesic and anti-inflammatory agents.Eur. J. Med. Chem.2014;76:494-505.
6) Yadav G, Ganguly, S. Structure activity relationship (SAR) study of benzimidazole scaffold for different biological activities: A mini-review.Eur. J. Med. Chem.2015;97:419-443.
7) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. J. Med. Chem.2014;57:10257-10274.
8) Vogel's Textbook of Practical Organic Chemistry by Brian S. Furniss, Antony J. Hannaford, Peter W. G. Smith & Austin R. Tatchell; Fifth Edition; Page No.- 1162
9) Practical in organic chemistry, by Hitesh G. Raval, Sunil L. Baldania and Dimal A. Shah, Nirav Prakashan, Page No.- 301.
10) A. Saberi, Iran. J. Sci. Technol. 39A1 (2015) 7–10
11) S.R. Rithe, R.S. Jagtap, S.S. Ubarhande, RASA-YAN J. Chem.8 (2) (2015) 213–217
12) M. Phillip, J. Chem. Soc. C. (1971) 1143–1145.
13) C.P. Rathod, R.M. Rajurkar, S.S. Thonte, Indo Am. J. Pharm.Res. 3 (2) (2013) 2323–2329.
14) Raut CN: Microwave-assisted sonogashira coupling of novel 2-[6-(arylethynyl) pyridin-3-yl]-1H-benzimidazole derivatives. Arkivoc 2009; 11: 105.
15) S.S. Birajdar, G.D. Hatnapure1, A.P. Keche1, V.M. Kamble1, Res. J. Pharm. Biol. Chem. Sci. 5 (1) (2014) 487–493.
16) Bowen and Walker, 2005; De Francesco and Migliaccio, 2005; Fried. 2002; Houghton and Abrignani, 2005.
17) Zhang, D., Wang, Z., Xu, W., Sun, F., Tang, L., Wang, J. (2009). Design, synthesis and anti-bacterial activity of novel actinonin derivatives containing benzimidazole heterocycles. Eur. J. Med.Chem. 44:2202-2210
18) Fang, B., Zhou, C.H., Rao, X.C. (2010). Synthesis and biological activities of novel amine-derived bis-azoles as potential anti-bacterial and anti-fungal agents. Eur. J. Med. Chem. 45: 4388-4398
19) Camacho J., Barazarte A., Gamboa N., Rodrigues J., Rojas R., Vaisberg A., Gilman R., Charris J. (2011). Synthesis and biological evaluation of benzimidazole-5-Carbohydrazide derivatives as anti-malarial, cytotoxic and anti-tubercular agents. Bioorg. & Med. Chem.19: 2023–2029
20) Błaszczak-S´wia¸tkiewicz K, Mirowski M,Kaplin´ska K. New benzimidazole derivatives with potential cytotoxic activity study of their stability by RP-HPLC. Acta Biochim Pol 2012;59:279-88
21) Saify ZS, Kamran Azim M, Ahmad W. New benzimidazole derivatives as antiplasmodial agents and plasmepsin inhibitors: synthesis and analysis of structure--activity relationships.Bioorg Med Chem Lett 2012;22:1282-6