IJMPR 2021, 5(3), 167-197

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 5.273

CHEMISTRY OF BENZIMIDAZOLE AND THEIR DERIVATIVES: MINI REVIEW

Rohit Verma[1]*, Chitra Gupta[2], Ali Mohd Ganie[2], Vaibhav Kumar[3], Sanjay Singh[1] and P.K. Singh[4]

[1]Department of Chemistry, T.R.S. P.G College, Rewa (M.P.) 486001, India.
[2]Department of Chemistry, Bundelkhand University, Jhansi (U.P.) 248124, India.
[3]Bundelkhand University, Jhansi (U.P.) 248124, India.
[4]Department of Chemistry, P.G College, Sidhi (M.P.) 486661, India.

Received on: 29/04/2021
Revised on: 19/05/2021
Accepted on: 09/06/2021

***Corresponding Author**
Rohit Verma
Department of Chemistry, T.R.S. P.G College, Rewa (M.P.) 486001, India.

ABSTRACT

Benzimidazole is a heterocyclic aromatic organic compound containing nitrogen. This bicyclic compound is formed by the fusion of benzene with imidazole ring. It is a vital Pharmacophore and privileged structure in medicinal chemistry which exhibits various therapeutic activities like antiulcer, antihypertensive, analgesic, antiviral, antifungal, anticancer and antihistaminic. The disease conditions targeted by these activities are discussed. The present article extensively covers various procedures of synthesis of 2-substituted benzimidazole and its analogs by utilizing different catalysts, solvent conditions, reactants and microwave irradiation with the aim to obtain an inexpensive, eco-friendly, less time-consuming procedure which ensures good yield and quick isolation of the pure product. Presence of benzimidazole nucleus in numerous categories of therapeutic agents such as antimicrobials, antivirals, antiparasites, anticancer, anti-inflammatory, antioxidants, proton pump inhibitors, antihypertensives, anticoagulants, immunomodulators, hormone modulators, CNS stimulants as well as depressants, lipid level modulators, antidiabetics, etc. has made it an indispensable anchor for development of new therapeutic agents. This review is summarized to know about the chemistry of benzimidazole and their derivatives of substituted benzimidazole along with their physical and chemical properties. We demonstrate the change in properties of benzimidazole with change in their structure, their isomers, uses and their pharmacological activity.

KEYWORDS: Benzimidazole derivatives, Synthesis, Physical and Chemical Properties and its Therapeutic Drugs.

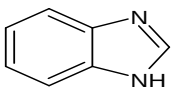
INTRODUCTION

The publication, many new strategies for the synthesis of benzimidazole derivatives are discovered and reportedabl.[1,2] A literature.[3-5] survey has uncovered that the various derivatives of benzimidazole have been synthesized for their pharmalogical activities and many of them supported the finding that benzimidazole derivatives are potent against various microorganism strains.

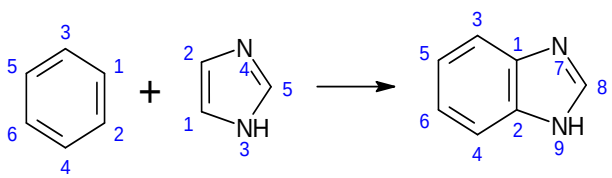
The aim of object of this paper is to review the discovery and the synthesis of benzimidazole containing nucleus derivatives by using different routes for obtaining good yield of them, mainly drugs for screening various therapeutic classes few of them are discussed below.

The Heterocyclic compound,[6] is a Carbocyclic compound in which at least one atom other than Carbon atom forms a part of the ring system. Besides the most common atoms like N,O and S the other Heteroatoms are known widely.[7] Furthermore there is rapid rise in number of Heterocyclic compound which may be aliphatic or aromatic in nature. Both these types of compound differ in their properties due to the presence of ring strain.

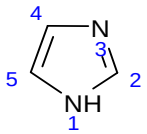
Among different Homoazoles Benzimidazole,[8] is bicyclic in nature which consists of the structure of Benzimidazole is as follows:

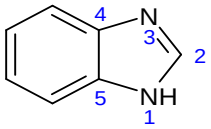


The Benzimidazole ring system can be theoretically derived,[9] by fusion of aromatic compound Benzene and Imidazole ring (containing two Nitrogen atoms at non adjacent positions) as indicated in the numbering system through its 1-2 bond to a benzene ring.[10]

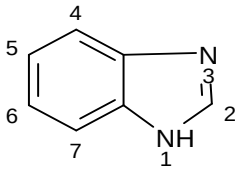


The numbering system for the Benzimidazole is as follows: Occasionally 2- positions is designated as the 5-position.



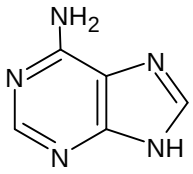


The numbering in the benzimidazole ring system is done as shown below.

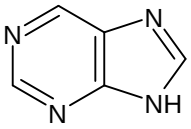


The Benzimidazole are also known as Benziminazolones or Benzoglyoxalines. They are also known as the derivative of o-phenylenediamines.

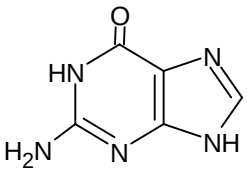
Some are the nucleobases (purines biomolecules derivatives) in the Nucleic acid of DNA and RNA. Also it is a 4,5 nitrogen containing compounds.



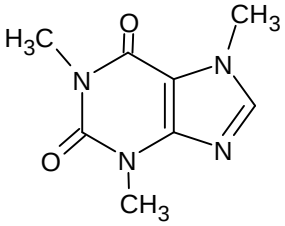
Adenine



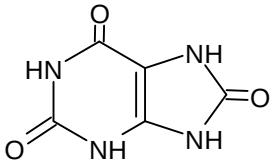
Purine



Guanine



Caffeine



Uric acid

Fig. Common biomolecules with a "6+5" heterocyclic structure.

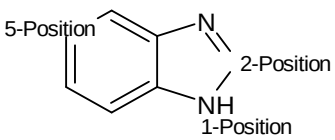
Isomerism Tautomerism

Tautomerism is a cyclic analogous to that found in Imidazoles and Amidines, the two Nitrogens present in the Imidazole ring are different from one another in their nature and this makes the properties of the ring system diverse in character. The Nitrogen bearing Hydrogen atom is sp^2 in character and is often referred as Pyrole Nitrogen and the other is sp^2 in character and is often referred as Pyridine Nitrogen.

Benzimidazole possesses each acidic also as basic nature. The NH cluster present in benzimidazole is relatively powerful acidic and frail basic extra characteristic of benzimidazole is that they need the capability to make salts. Benzimidazoles with unsubstituted NH teams show quick prototropic tautomerism that ends up in balance mixtures of asymmetrically substituted compounds. Benzimidazole that embrace an atom connected to the Nitrogen in the 1-position promptly tautomerize this could be delineating as follows.[9,11,12]

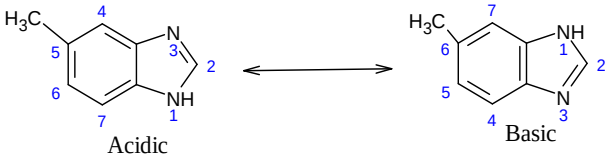
Benzimidazole structure with its tautomer.

Our target molecules were based on benzimidazole derivatives. It is possible to design a wide range of potential microbial inhibitors by replacing the hydrogen at various positions of the benzimidazole ring with different functional groups. However, the most accessible derivatives are those with substituents at the 1-, 2- and 5-positions. Retro synthesis analysis of a 2,5-disubstituted benzimidazole identified two fragments, which explain why these particular substitute benzimidazoles are easy to prepare.



Due to this tautomerism, certain Benzimidazole derivatives that appear as the first isomers in reality the tautomers 4- and 5- positions are equivalent to 6- and 7- positions because of this phenomenon. For example, 5-Methyl Benzimidazole is a tautomer of 6-Methyl Benzimidazole**.** Although two non-equivalent structures can be written, the two structures are tautomers and both structures represent the same compound known.

This may be illustrated with 5- or 6-methyl benzimidazole.



Benzimidazole structure with its tautomer.

To prevent any confusion between the two tautomers, both the designating structures are written with the second one in parenthesis, e.g., 5-or 6-Methyl Benzimidazole. When 5- group attached to the Nitrogen in the 1-position is other than Hydrogen, such tautomerism is prevented and only isomeric forms exist. Thus, 1,5-dimethylbenzimidazole and 1,6-dimethylbenzimidazole exist as distinct, isomeric compounds.

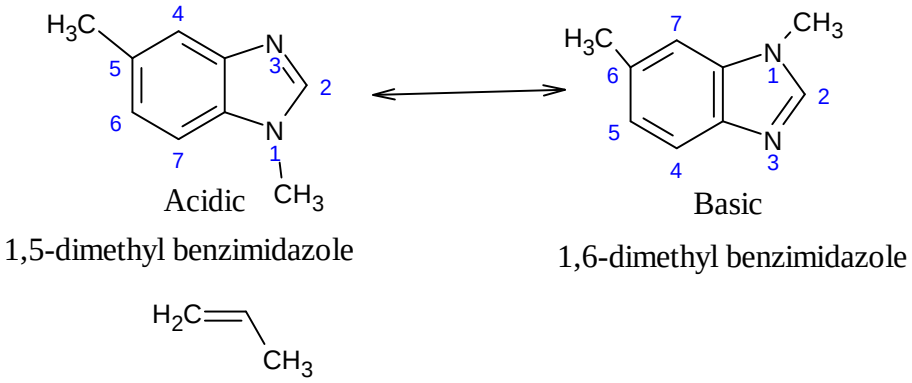
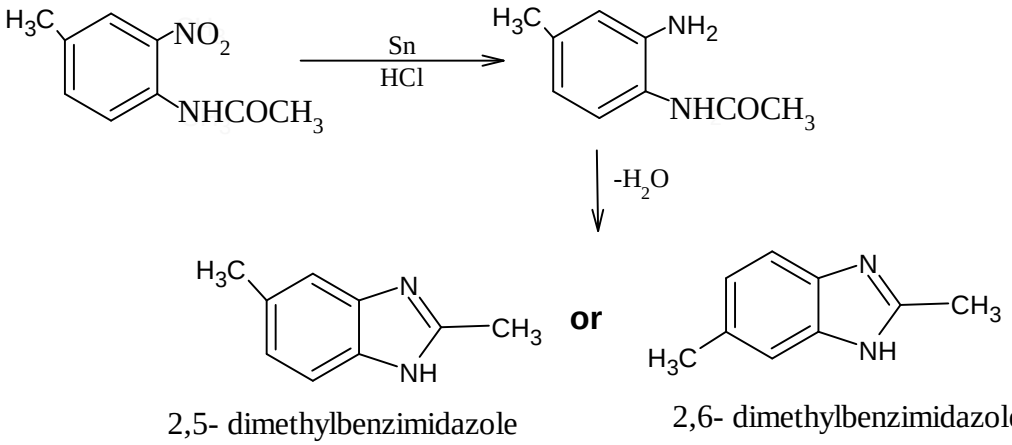


Fig. Isomeric structure of 1,5- and 1,6-dimethyl benzimidazole.

Due to clinical and pharmacological activities of benzimidazoles chemists tried to synthesize the benzimidazole in the laboratory.

Historically the first benzimidazole was prepared in 1872 by **Hoebrecker,**[13] who obtained 2,5- or 2,6-dimethyle benzimidazole by the reduction of 2-nitro-4-methylaacetanilide.



Synthesis of Benzimidazole[5,8,14-17]

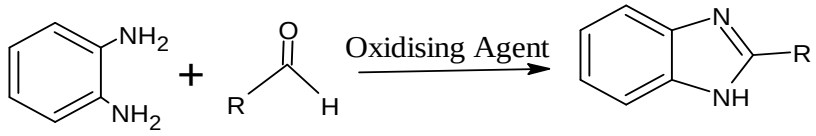
A) By reaction with Carbonyl compound[18]

1. Reaction with Aldehyde[19-20]

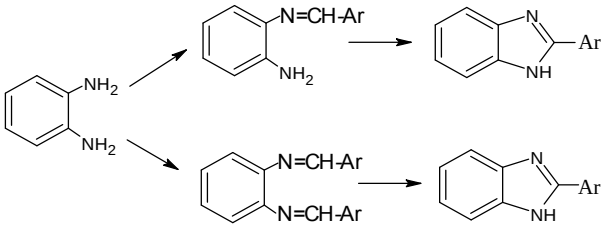
Since an oxidation is involved, the reaction is best carried out under oxidative conditions. This oxidation may be brought about by the air or more conveniently, by the use of other oxidizing agents such as Cupric acetate. This latter reagent was first introduced by **Weidenhagen. Weidenhagen's method,**[21] consists in reacting the diamine and aldehyde in water or alcoholic solution in the presence of Cupric acetate or a similar Cupric salt. The Cuprous salt of the benzimidazole separates and by means of Hydrogen sulfide it may be readily decomposed to the free benzimidazole and Cuprous sulfide. The sulfide may be removed readily by filtration. By means of **Weidenhagen's method,**[21]

excellent yields of 2-substituted benzimidazole may be obtained.

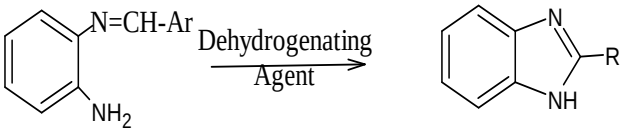
The reaction between o-phenylenediamine and aldehydes as a method to synthesize benzimidazoles has been reviewed independently by **Rao and Ratnam,**[22] and **Smith and Ho**.[23] Various 2-substituted benzimidazoles (R = alkyl or aryl) were synthesized by condensing o-phenylenediamine with aldehydes in the presence of oxidizing agents such as Cupric acetate **(Weidenhagen procedure)**[9,21] Mercuric oxide.[24] (for 2-NHCOOMe), Chloranil (for 2-furyl),[25] Lead tetraacetate,[26] Manganese dioxide,[27] Nickel peroxide,[28] and Nitrobenzene.[29] An improvement in the conventional method is the use of the sodium bisulfite addition product of the aldehyde,[30] which in boiling ethanol often results in good yields.



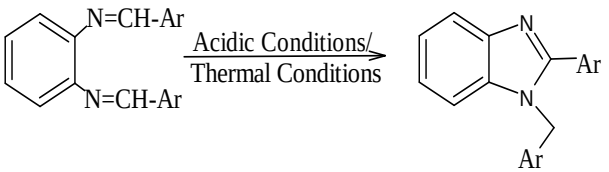
The reaction of o-arylenediamines with formaldehyde gives rise to 1-methyl Benzimidazoles.[31,32] and these types of processes have been studied in detail.[33] Its note worthy to mention here that the reaction of o-phenylenediamine with aromatic aldehydes in methanol medium gave monoanils (Schiff bases, commonly known as monoanils in benzimidazole chemistry) and in some cases the di-Schiff bases i.e., dianils,[22] depending on molar proportions of the aldehyde used in the reaction. The monoanils when treated with acetic acid at room temperature resulted in the dehydrogenatively cyclized products 2-arylbenzimidazoles (1:1 products) and the dianils resulted in the formation of 1-arylmethyl-2-arylbenzimidazoles (1:2 product) in varying proportions.



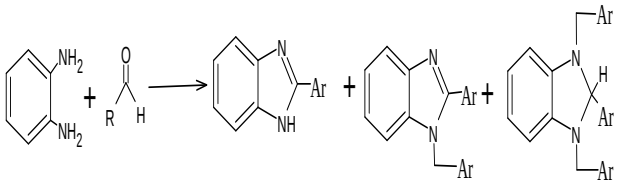
The monoanils prepared separately could be converted to 2-substiuted benzimidazoles with the help of dehydrogenating agents.[28,29,34-36]



Similarly, the dianils obtained from o-phenylenediamine with two moles of aldehyde were cyclised to 1,2-diarylsubstitutedbenzimidazoles both under acidic as well as thermal conditions.[33,35,37-39]

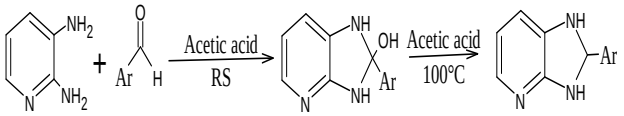


Rao and co-workers,[40] reported the isolation, although in poor yields of other products, 1,3-diarylmethyl-2-arylbenzimidazolines (1:3 product) in the condensation of o-phenylenediamine with o-chloro and m-nitrobenzaldehyde in acetic acid at room temperature.



Obviously, the above reaction proceeds through the disproportionation of the initially formed monoanils. The monoanils have been shown,[41] to exist in tautomeric equilibrium with the corresponding dihydrobenzimidazoles by NMR.

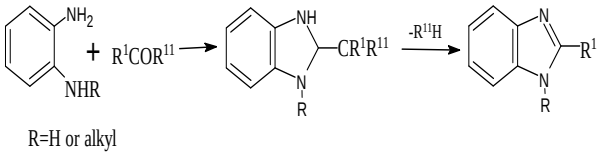
These dihydroderivatives could not be isolated in free state in the reaction of o-phenylenediamine with aromatic aldehydes. However, the intermediate dihydroderivative was isolated in pure form, during the preparation of imidazo[4,5-b]pyridine obtained from the reaction of 2,3-pyridinediamine with aromatic aldehydes[42].



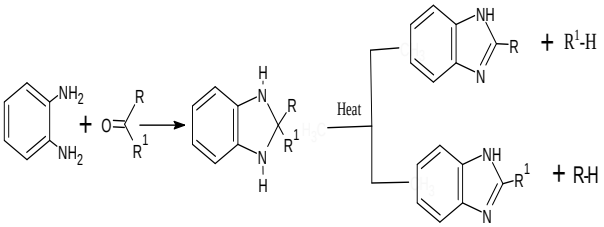
2. Reaction with ketones[18]

o-phenylenediamines has been investigated by **Elderfield** and **Kreysa,**[43-45] to condense with ketones to form 2,2- disubstititedbenzimidazole which decomposes under the influence of heat to give 2- substituted benzimidazole (R = R' = variously substituted) and a hydrocarbon. In several cases, the hydrocarbon was isolated and identified. In the decomposition of an

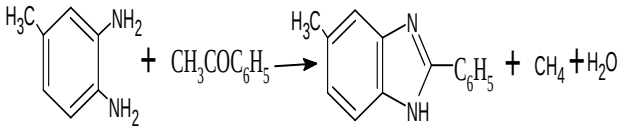
asymmetrically substituted benzimidazoline it has been observed,[44] that the C-C bond, which has greater degree of substitution, is generally broken. The reaction occurs as indicated in several cases the product represented by $R^{11}H$ was isolated and identified.



o-phenylenediamine reacts with ketones to form 2-disubstitued benzimidazolines, these decompose under the influence of heat with the formation of a 2-substituted benzimidazole and a hydrocarbon. The decomposition of unsymmetrically substituted benzimidazole may lead to formation of two different benzimidazole depending upon whether the substituent R or the substituent R^1 is eliminated preferentially.



Ladenburg and Rugheimer,[46] have obtained 2-phenyl-5 (or 6)-methylbenzimidazole by heating 3,4-diaminotoluene with acetophenone at 180℃ for some time. Here again the methyl group is the one that is eliminated preferentially.



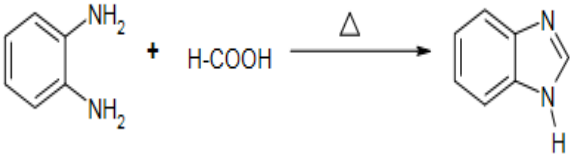
B) By Reaction with Carboxylic acids and their darivatives[47-50]

3. Reaction with carboxylic acids

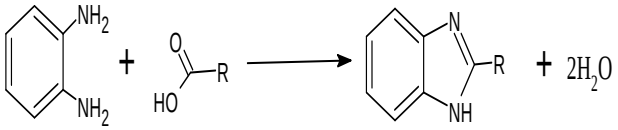
a) Monobasic acids

2-Substituted benzimidazoles may be synthesized in good yields while condensing o-phenylenediamine with carboxylic acid under a wide variety of conditions.

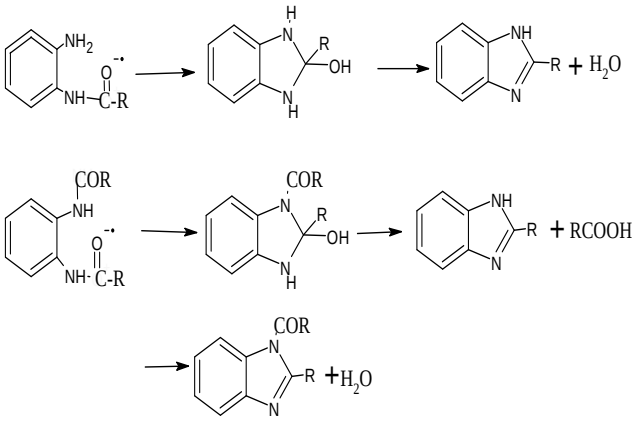
Ladenburg[51] first prepared 2, 5-(or 2,6)-dimethylbenzimidazole by refluxing 4-methyl-o-phenylenediamine in glacial acetic acid. The reaction is carried out usually by heating the reactants together on a steam bath, by heating together under reflux or at an elevated temperature or by heating in a sealed tube. Benzimidazole may be prepared in 83-85 % yield by using 90 % formic acid.[52] The parent benzimidazole was prepared in 1878.



Since then, a large number of benzimidazole have been synthesis from o-phenylenediamine and Formic acid or Aliphatic acid.[53]



Mono acyl derivative of o-phenylenediamine is readily converted into the corresponding benzimidazole by the action of heat alone. These conversions are generally carried out at a temperature somewhat above the melting point of the starting compounds. This is a convenient method for preparing benzimidazoles when monoacyl derivatives are easily obtainable. The procedure may be improved by heating the monoacyl derivative of diamine in an atmosphere of Nitrogen to prevent oxidation (**Kelly**, **1945**)[54] The diacyl derivatives of o-phenylenediamines are also converted into benzimidazoles but higher temperature are required (**Bistrzycki, 1980**).[55]



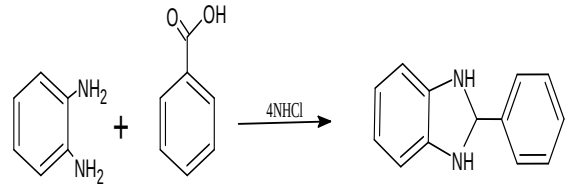
Benzimidazole is also synthesized from o-phenylenediamine and mono or di-basic acid. In this method, the diamine is simply heated with excess acid (**Fischer, 1905**)[56] This procedure has been recommended as a means of identifying fatty acid α-hydroxy acid as well as phenylacetic acid and diphenylacetic acid are converted into the corresponding benzimidazoles when heated with o-phenylenediamine.

Excellent results have been obtained by employing the **Phillip.**[57] modification of the addition of dilute mineral acid (usually about 4 N hydrochloric acid) to procedure consists in refluxing with the (**Phillip, 1928**)[57] o-phenylenediamine. The benzimidazole is then

precipitated by neutralizing the solution with ammonium hydroxide. Benzoic acid gives only traces of 2-phenylbenzimidazole. Apparently this method is not applicable to the aromatic monobasic acid.

The mechanistic pathway for the formation of benzimidazole by the reaction of o-phenylenediamine with organic acids has already been studied[58-61]. Further, the role hydrochloric acid in the reaction has also been investigated[62]. The catalytic action of hydrochloric acid is explained on the basis of activation of the carboxyl group by the protonation of oxygen. The intermediate in the reaction is the addition product formed by the attack of the unshared electron pair of one nitrogen onto the carbonyl group of the protonated acid. However, **Phillips**[57] concluded that the monoacyl derivative was the necessary key intermediate for formation of benzimidazole ring.

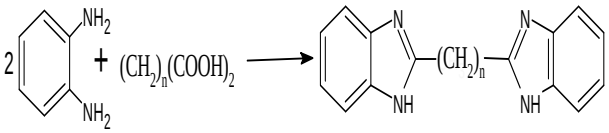
For aromatic carboxylic acid, however, **Phillips** procedure fails to give any respectable yields of 2-arylbenzimidazoles.[57] Aromatic carboxylic acids were reported[63-66] to give yields of 2-arylbenzimidazoles (R = Ar) when heated with 1 in a sealed tube at 180-190^{0}C. A better procedure for the preparation of 2-arylbenzimidazoles from o-phenylenediamine and aromatic carboxylic acid involves the use of polyphosphoric acid[67-69] (PPA) or polyphosphate ester[70] (PPE) as dehydrating agent. Alternatively, phosphorus pentoxide has also been reported as a dehydrating agent for the preparation of 2-arylbenzimidazole derivatives.[71]



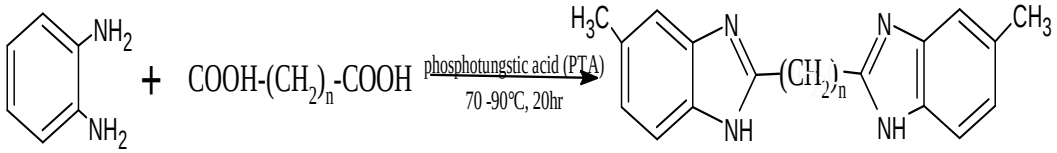
Recation……..add karna

b) Dibasic acids

When dibasic acids are caused to react with o-phenylenediamins the product formed depend on the mole ratio of the reactant and the experimental conditions. When two or more moles of o-phenylene diamines are heated with one mole of the dibasic acid, the products in most cases are bis –benzimidazole.[72]



A series of bis-benzimidazole derivatives were synthesized and found that compound has showed significant antidiabetic activity when compared to glibenclamide as standard drug.[73] Peroxisome Proliferator Activated Receptors.[74] (PPARs) act as regulators of lipids and glucose metabolism. This resulted in the development of synthetic drugs which represents a potential tool for therapeutic intervention in type 2 diabetes mellitus (T2DM).



Scheme 2: Benzimidazole as Peroxisome proliferator

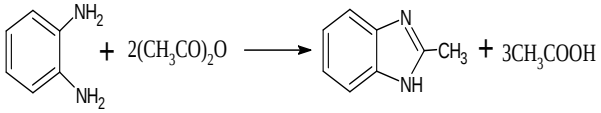
3. By reaction with acid anhydrides

a) Anhydrides of mono basic acids

Practically the acid anhydride that has been used in the preparation of Benzimidazole has been acetic anhydride. However mixed formic-acetic anhydride and benzoic anhydride have also been used successfully.[75] and the example is as under, o-Phenylene dSiamine when heated under reflux for several hours with acetic anhydride is completely converted to 2-Methyl Benzimidazole.[76]

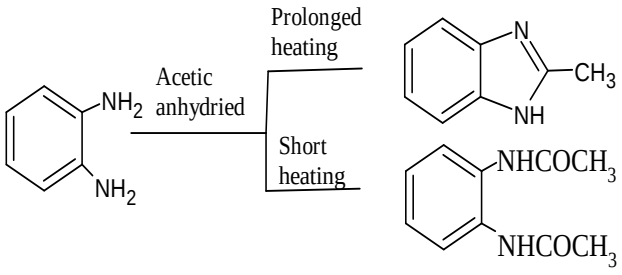
The reaction of o-phenylenediamine with acetic anhydride has been carried out with acetic anhydride alone or with acetic anhydride to which has been added sodium acetate, mineral acids, or acetic acid.

Excellent results have been obtained by employing the modification of **Phillps,**[60] involving the addition of dilute mineral acids (useally About 4N Hydrochloric acids) to the reaction mixture. Thus, 2-methylbenzidazole may be obtained in 93.3% yield from ortho-phenylene diamine and acetic anhydride on heating with 15% hydrochloric acid.



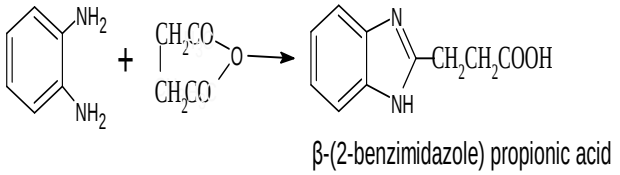
2-Methylbenzimidazole (3, R = CH3) was obtained by prolonged treatment of o-phenylene diamine with acetic anhydride, whereas treatment for a shorter period yielded only N, N'-diacetyl o-phenylenediamine,[77] **Wagner,**[78] reported improved yields of 2-methylbenzimidazole from o-phenylenediamine and acetic anhydride at the 90^{o}C temperature by using dilute hydrochloric acid. Similarly for the 2 to 3 h they found a 68% yield present, it was also observed that treatment of the free base of 5 i.e., 4-methyl-o-phenylenediamine with acetyl chloride in refluxing benzene yielded 2,5 (2,6)-dimethylbenzimidazole whereas the corresponding 4-methyl-N,N'-diacetyl-o-phenylenediamine was the sole

product when the reaction was carried out at room temperature.[79]



b) Anhydrides of di basic acids

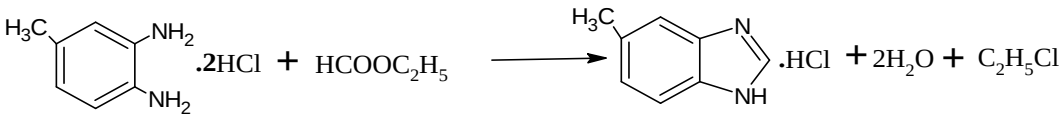
The anhydrides of dibasic acids reacts as monobasic acids for example succinic anhydride with o-phenylene diamine gives β-(2-benzimidazole) propionic acid and with phthalic anhydride gives β-(2-benzimidazole) benzoic acid.



β-(2-benzimidazole) propionic acid

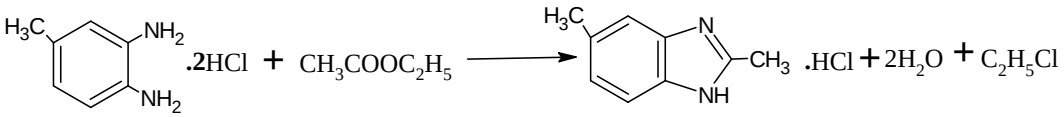
4. Reaction with esters[80]

Reaction of o-phenylene diamines with esters also yields Benzimidazoles. **Von Niementowski,[81]** first investigated the reaction of esters and o-phenylene diamines to give Benzimidazoles. Equimolecular amounts of 3, 4-diamino toluene dihydrochloride and ethyl formate when heated in a sealed tube for 3 hours at 225°C give 84% of 5- or 6-methyl benzimidazole hydrochloride.[76]



The product is not further alkylated by the ethyl chloride formed. Ethyl acetate under the same conditions gives only a poor yield of 2, 5- or 2, 6-dimethyl Benzimidazole and poor yields of Benzimidazoles would probably be obtained from esters of acids of higher molecular weight.

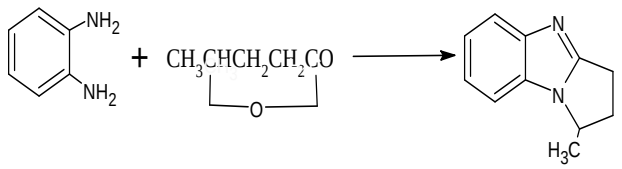
Here again the methyl group is the one that is eliminated preferentially. A good yield of 2-methylbenzimidazole may be obtained by allowing a mixture of o-phenylenediamine and ethyl acetate to stand.



The reaction of acid anhydrides and o-Phenylenediamines will lead to benzimidazole or to N N'-diacylphenylenediamines depending on the condition employed. It was formerly thought that o-Phenylenediamines yield Benzimidazole with acids and diacyl derivatives with acid anhydrides.

5. Reaction with lactones

The reaction of lactones with o-phenylene diamines was first studied by **Bistrzycki and Schmutz,[82]** who investigated several γ- lactones of alcohol acids and phenol acids. Velerolactone when refluxed with o-phenylene diamine gives only a small yield of 1, 2-(1'-methyl tri methylene) benzimidazole.



6. Reaction with acid chlorides[80]

The action of acid chlorides on o-phenylenediamines leads to Benzimidazoles or mono acylated or diacylated o-phenylenediamines, depending upon experimental conditions. Acetyl chloride with 3, 4-diaminotoluene in benzene solution yields 2,5- or 2,6-dimethylbenzimidazole if the reaction is carried out without cooling and diacetyl-o-phenylenediamine when the reaction is cooled.

Most reactions between o-phenylenediamines and acid chlorides to give Benzimidazoles have been carried out with aroyl chlorides. The reactions are carried out usually by heating the components together at about 200–220°C., by heating under reflux, or by heating on a steam bath in the presence of pyridine or a similar basic substance. Since benzimidazoles which possess no grouping in the l-position may undergo acylation with acid chlorides, most reactions have been carried out with N-substituted o-phenylenediamines. **Table 2** lists the compounds that have been prepared by the reaction of acid chlorides and N-substituted o-phenylene diamines.

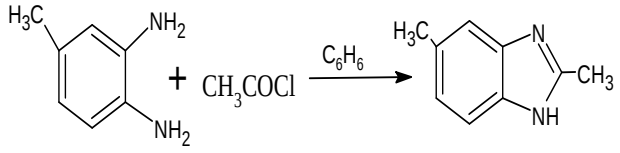
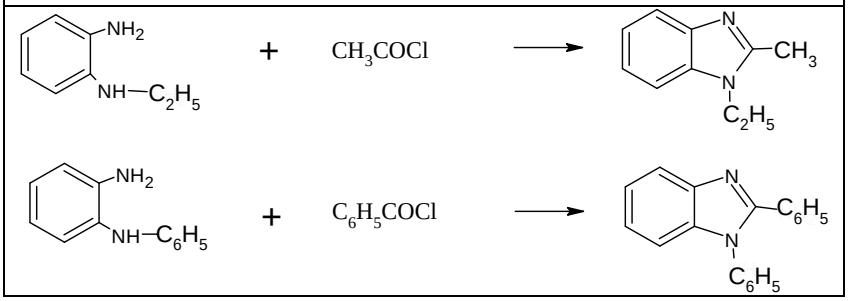


Table 2: Benzimidazoles form acid chlorides and N-substituted o-phenylenediamine.

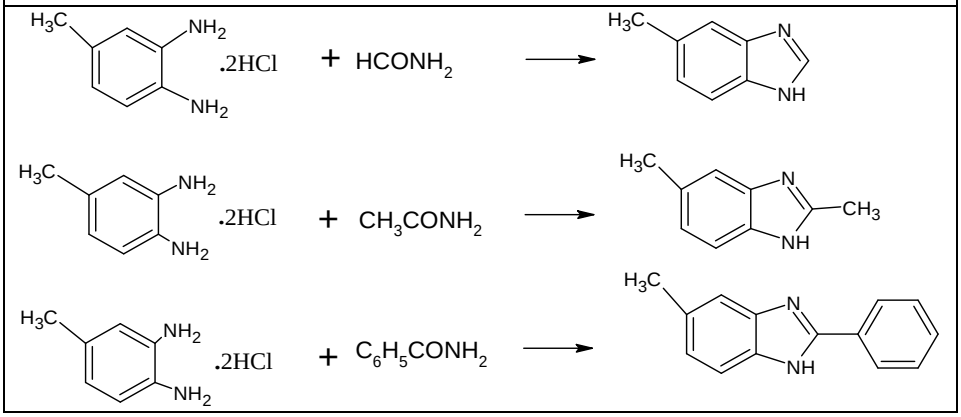
Diamine Acid chloride Product


7. Reaction with amides

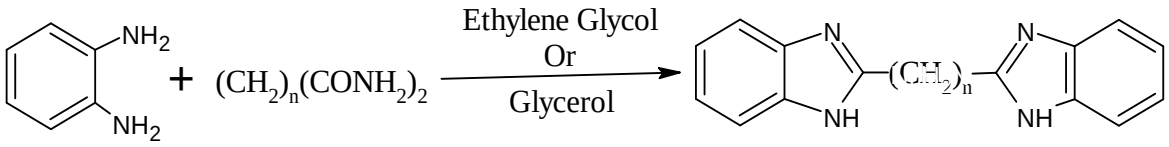
Relatively few amides have been used for the synthesis of benzimidazoles. However, good yields have been obtained **(Niementowski)**[83] in most cases.

The amides that have been used are listed in **Table 1**. Equimolecular amounts of 3,4-diamino toluene dihydrochloride and benzamide when heated to 240–250°C given an almost quantitative yield of 5-methyl benzimidazole, 2, 5-dimethyl benzimidazole and 2-phenyl 5-methyl benzimidazole.

Table 1: Benzimidazole from amide.

Diamine Amide Product


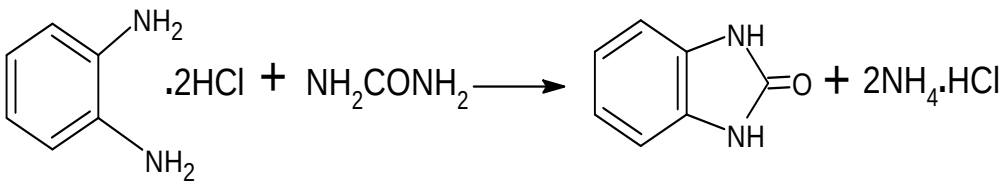
Bis-benzimidazoles were synthesized by heating o-phenylenediamine or its dihydrochloride salt with aliphatic dicarboxylic acid amides in high boiling solvents like ethylene glycol or glycerol.[84]



8. Reaction with urea

Rathod,[76] **et al.** have used o-phenylenediamine dihydrochloride and when it was heated with urea at 130°C under reflux in amyl alcohol solution gives 2(3H)-benzimidazolone.

This general method has been used also for the preparation of substituted benzimidazolones. By heating o-phenylenediamine and Urea under reflux in amyl alcoholic solution until the evolution of ammonia ceased, **Mistry and Guha,**[85] have obtained a 95% yield of 2(3H)-benzimidazolones.

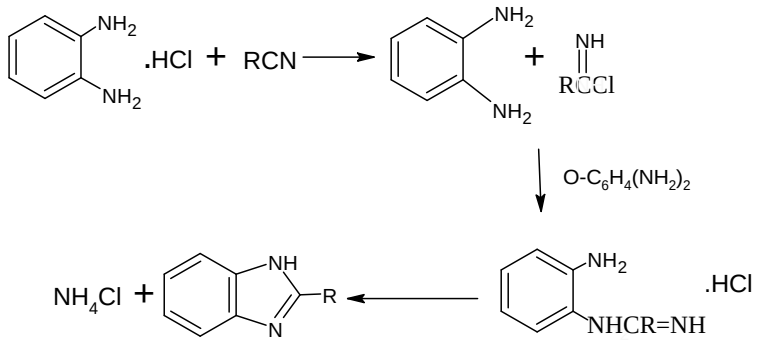


9. Reaction with nitriles[80,86,87]

Heating the mono hydrochloride of o- phenylenediamine with an Aliphatic or an Aromatic nitrile at 200°C results in the formation of a 2-substituted benzimidazoles. This reaction has been studied by **Holljes and Wagner,**[88] who find that the reaction proceeds under acid condition and probably involves hydrogen ion catalysis. The mechanism of the reaction is as under, The reaction is carried out usually at about 200℃ at this temperature ammonium chloride will undergo decomposition to regenerate additional Hydrogen chloride and cause the reaction to proceed further. The reaction proceeds further under anhydrous condition and is not due to the generation of acid or amide in situ. Formation of a mixture of an imino chloride and o-phenylenediamine may be the rate-determining step of the reaction. The combination of the two substances could lead to the formation of hydrochloride of an o-aminophenyl substituted amidine, which could lose the elements of ammonium chloride to give the 2-substituted benzimidazole.

This scheme is supported by the observation that N-phenylbenzimidazole chloride reacts with o-phenylenediamine to give 2-phenylbenzimidazole.

Nitriles when heated with o-phenylenediamine hydrochloride give 2-substituted benzimidazoles. The first step in the reaction appears to be the rate determining step.



At this recation temperature Ammonium chloride will undergo decomposition to generate additional Hydrogen chloride and cause the reaction to proceed further.

Nitriles that have been used in the synthesis of benzimidazole are listed in **Table 3.**

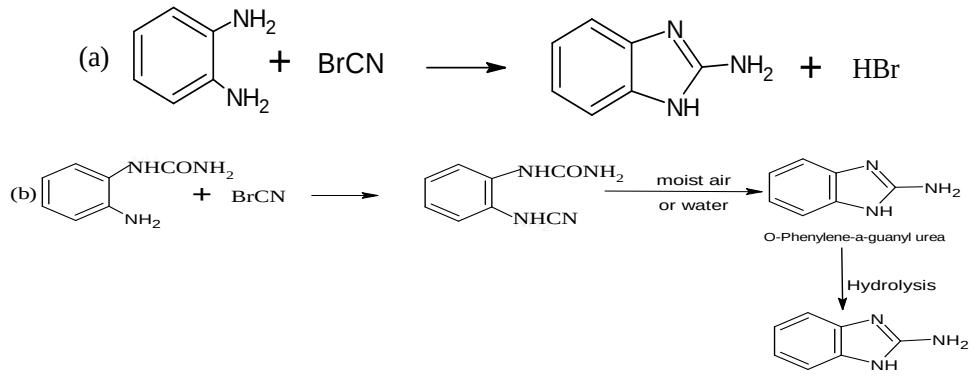
Table 3: Benzimidazole from nitriles.

Diamine	Nitrile	Product
o-phenylenediamine	HCN	Benzimidazole
o-phenylenediamine	CH_3CN	2-Methylbenzimidazole
o-phenylenediamine	C_2H_5CN	2-Ethylbenzimidazole
o-phenylenediamine	C_6H_5CN	2-Phenylbenzimidazole

10. Reaction with Cyanogen bromide

Cyanogen bromide will react with o-phenylenediamines to yield 2-amino benzimidazoles in good yields; for example, 2-amino benzimidazole may be prepared from cyanogen bromide and o-phenylenediamine.

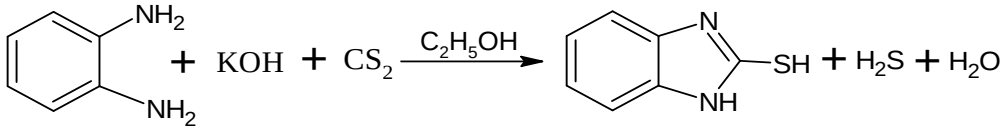
The reaction is carried out by mixing equimolecular amounts of the reactants in aqueous suspension. **Pellizzari,**[89] has obtained Benzimidazole derivatives by treatment of o-aminophenyl urea with cyanogen bromide. o-phenylene-a-guanyl urea is unstable and tends to hydrolyze to 2-amino benzimidazole.



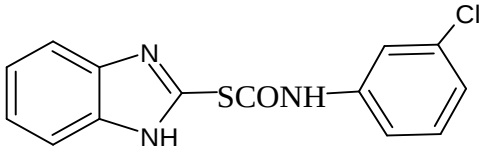
11. Synthesis of benzimidazoline 2- thione:[90] (derivative)

Preparation of 2-Mercapto benzimidazole

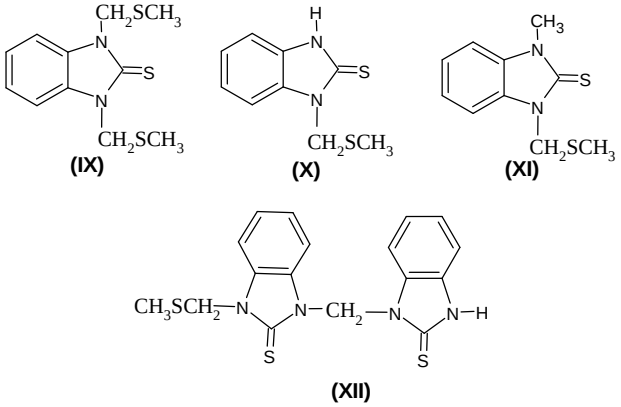
A mixture of o-phenylene diamine, Potassium Hydroxide and Carbon disulfide reacted in presence of 95% Ethanol and water in a round bottom flask heated under reflux for three hours. After 3 hrs Charcoal is added cautiously and the mixture is heated at the reflux for 10 minutes the Charcoal is removed by filtration. The filtrate is heated to 60-70^{0}C, warm water is added, and then acidified with acetic acid. The product separated as glistening white crystals, and the mixture is placed in a refrigerator for three hours to complete the crystallization. The product is recrystallised from Ethanol. M.P. is 300-305 ^{0}C.



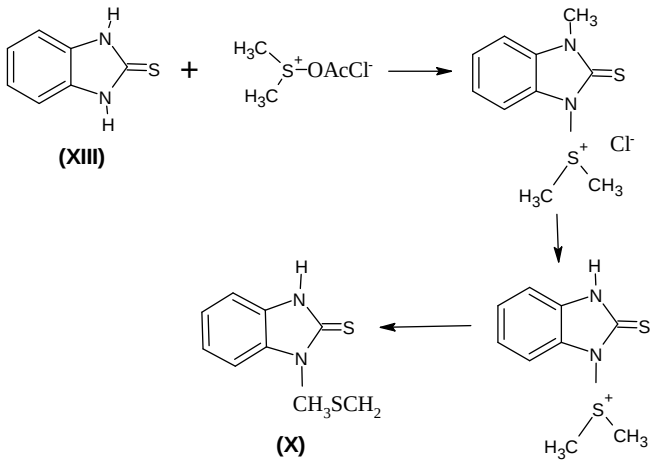
The majority of data on benzimidazoline 2-thione relates to S-alkylation and closely related processes are the synthesis of 2-thiocynatobenzimidazoles from the reaction of benzimidazoline 2-thione with cynogen chloride or bromide and 2-benzimidazolyl thiocarbomates (VIII) from addition of the 2-thione to aryl isocynates.



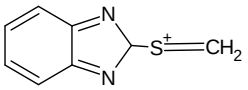
Other routine procedures are the oxidation of 2-thiones to bis benzimidazolyl disulfides and benzimidazole 2-sulfonic acids by hydrogen peroxide. The varieties of compounds are obtained and are as under **(IX, X, XI, XII).**



When benzimidazole 2-thione (X) is allowed to react with a mixture of dimethylsulfoxide and acetyl chloride at 50-60℃ the formation of these products can be satisfactorily rattionalised in terms of displacement reactions by the thione (VII) on an intermediate sulfonium acetate.



Interestingly if this reaction is carried out below 30℃ the reaction product includes the compound and also the novel 2-(methylene sulfonium) benzmidazolide in 20% yield (XIV).



(**XIV)**

Physical properties of Benzimidazoles.[91]

Physical state	**-**	**Tublar crystals**
Molecular formula	**-**	**$C_7H_6N_2$**
Molecular weight	**-**	**118.053**
Colour	**-**	**Whitish**
Odor	**-**	**Characteristics**
Boling point	**-**	**360^0C**
Melting point	**-**	**170^0C**

Benzimidazole have a high Melting Point. The indroduction of substitution at 1-position lower the melting point.

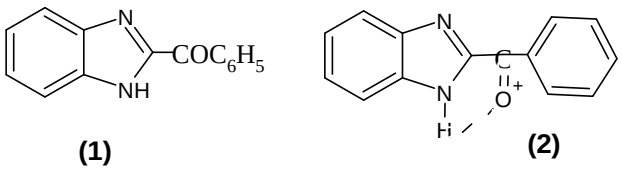
The melting point of a number of simple Benzimidazoles are.

Benzimidazole	**-**	**170℃**
1- methyl benzimidazole	**-**	**61℃**
2- methyl benzimidazole	**-**	**176℃**
2- phenyl benzimidazole	**-**	**294℃**
2(3H)- benzimidazole	**-**	**308℃**

From this melting point it will be noted that the introduction of a substituent into the 1-position in general lowers the melting point. This appears to be due to the fact that benzimidazole containing hydrogen in the 1-position.

Solubility – Benzimidazole with the imide Nitrogen (i.e. Hydrogen in the 1- position) is usually freely soluble in polar solvents, sparingly soluble in non-polar solvent (organic solvent) and less soluble in hot water but it is difficult to soluble in ether and insoluble in benzene. With the introduction of other non-polar substituent's in various positions of the benzimidazole ring, the solubility in non-polar solvents is increased. Conversely the introduction of polar groupings into the molecule increases solubility in polar solvent. i.e. 2-aminobenzimidazole is soluble in water. Benzimidazole distills unchanged above 300℃ i.e. 2-methylbenzimidazole is easily soluble in ether.

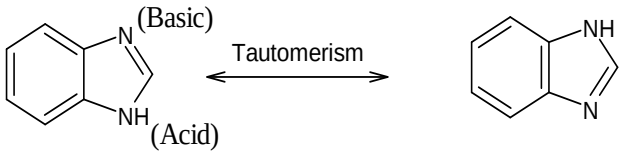
- Benzimidazole are weakly basic, being somewhat less basic then the imidazoles.
- Benzimidazole are also sufficiently acidic to be generally soluble in aqueous alkali and form N – metallic compounds.
- They are generally soluble in dilute acids.
- The more acidic benzimidazole may be soluble in less basic solutions, such as potassium carbonate solution.
- 2(3H)-benzimidazole is difficult to soluble in dilute sodium hydroxide solution. It is insoluble in dilute hydrochloric acid but is readily soluble in slightly warmed concentrated hydrochloric acid. 2-benzimidazolecarboxylic acids are easily soluble in dilute acids.
- The molecular weight of a number of benzimdazoles from freezing point data in naphthalene solution over a range of concentrations. Evidence was obtained indicating molecular association through N-H-N bonds in those compounds possessing an unsubsituted NH grouping. The strength of this bond is evidently enhanced by resonance of the benzimidazole nucleus. Those substances which are substituted in 1-position by an alkyl, aryl, acyl or amino group are not highly associated. Substances such as 2-benzoylbenzimidazole (1) occupy an intermediate position, being less highly associated then other benzimidazoles unsubstituted in the 1-position. It would appear that majority of the molecules possss the internal chelate structure(2). Such internal chelation is possible in a number of 2-substituted benzimidazole.



(1) **(2)**

- The dipole moment of benzimidazole have been determined, the value that have been obtained 3.93D (in dioxane) and 4.08D

- **Acidic/basic nature** – the acidic properties of benzimidazole like those of imidazole seem to be due to stabilization of the ion by resonance.



pk_a value-The pk_a value of benzimidazole =12.8 and 5.6 (for the conjugate acid)
pk_a = 5.30 for 2- methyl benzimidazole and
pk_a = 12.33 for 2- amino benzimidazole.

➢ **Chemical Properties of benzimidazoles[9,92-94]**

The benzimidazole ring possesses a high degree of stability. Benzimidazole is not effected by concentrated sulfuric acid, hot hydrochloric acids as well as Alkylation, Oxidation and Cleaves the benzene ring, Reaction involving substituent groups of benzimidazole only under vigorous condition. The benzimidazole ring is

also quite resistant to reduction except under certain consideration.

(A) Reaction of the benzimidazole ring

Reaction involving 1 and 3-positions

Benzimidazole from salt e.g. with acids readily forms monohydrochloride mono nitrate, monopicrate and monoacetate.

Benzimidazoles also react with acylating, Grignard reagents and metal. The benzimidazole also forms Mannich bases by reacting Formaldehyde and Piperidne.

Alkylations

Benzimidazoles, undergoes alkylation with alkyl halides, yielding 1-alkyl benzimidazoles and under more vigorous conditions 1,3-dialkyl benzimidazolium halides.

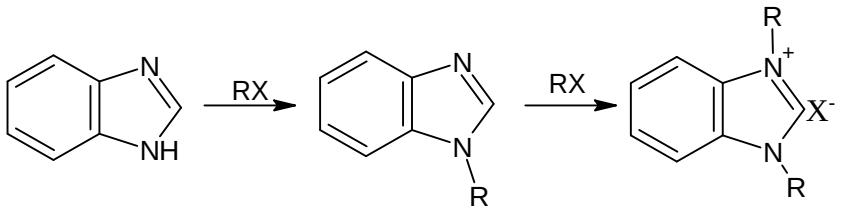
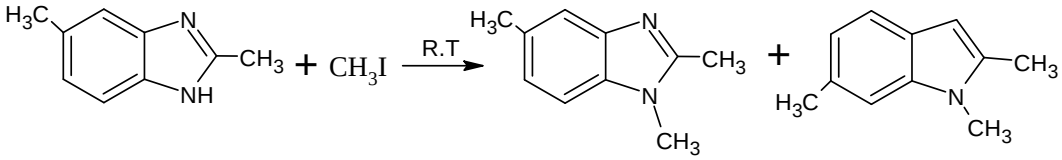


Fig: Alkaylation of benzimidazole.

The alkylation of benzimidazoles has been extensively studied especially by **O. Fisher,**[56] the alkylation is carried out by various alkyl and aryl groups, the reaction is carried out by heating the benzimidazole with an excess of alkyl halide in methanol under pressure at a temperature of about 110-150℃. Alkyl iodides are used usually and in some cases periodides are obtained as by product or as exclusive product.

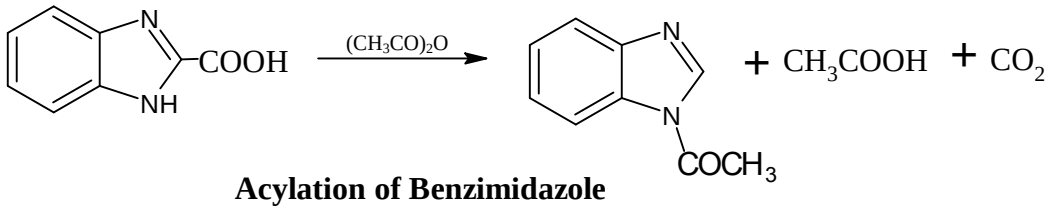
When alkylation reaction is carried out at lower temperature with one equivalent of alkyl halide, 1-alkyl benzimidazole may be the main product. Thus equimolar amounts of benzimidazole and methyl iodide in methanol at 90-100℃ give mostly 1-methyl benzimidazole. Example is given as under,



1. Acylation

N-acyl benzimidazole may be prepared by the action of acid chlorides or anhydrides on benzimidazoles. The reaction is usually carried out in the absence of water. In the presence of water and especially in the alkaline solution cleavage of imidazole ring may occur.

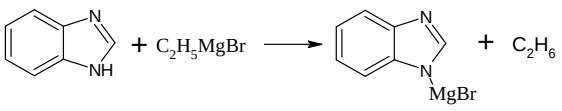
1-acetyl benzimidazole has been prepared by heating 2-benzimidazole carboxylic acid with acetic anhydride decarboxylation occurs and forms the product.



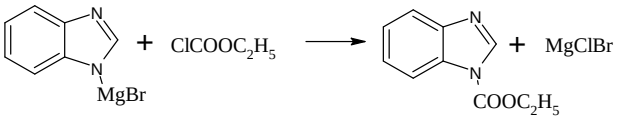
Acylation of Benzimidazole

2. The action of Grignard reagents on benzimidazole

Grignard reagent reacts with the active hydrogen in the 1-position of benzimidazole.



Benzimidazole-1-Magnesium bromide reacts with aliphatic acid chloride or anhydrides to 1-acyl benzimidazole with ethyl chloroformate, 1-carbethoxy benzimidazole is obtained.



(B) Reactions involving substituent groups

The various useful transformations can be successfully carried out various substituents in benzimidazoles. Some of the conversions are discussed below:

1. Nitration

The nitration of benzimidazole proceeds readily. In most cases nitration appears to take place preferentially at the 5- or 6- positions. However, the Nitro group may also enter the 4- or 7- position, especially if the 5- or 6- position is blocked.

Nitro benzimidazole that have been obtained by the nitration of benzimidazoles example is as under,

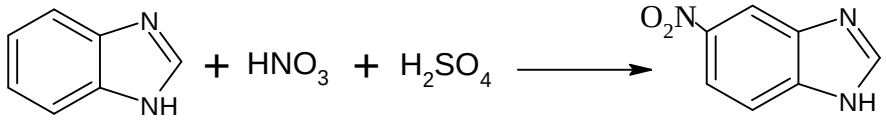


Fig. Reaction of nitration

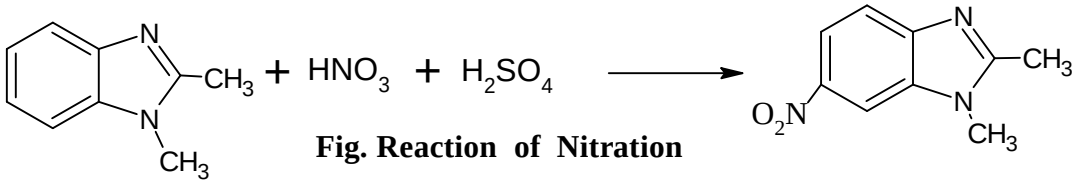
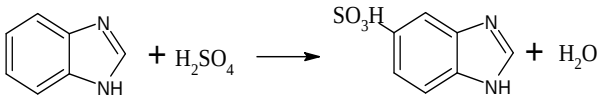


Fig. Reaction of Nitration

2. Salfonation reaction

Sulfonated benzimidazole are obtained by the sulfonation of benzimidazoles with either sulfuric acid or chloro sulfonic acid. Treatment of benzimidazole with concentrated sulfuric acid gives 5-benzimidazole sulfonic acid.



(C) Cleavage of the imidazole ring

The Imidazole ring of benzimidazoles may be cleaved by reacting with pseudo bases, acid anhydrides and halide.

Halogenation

When 2,5- or 2,6-dimethyl benzimidazole is an aqueous acid solution on treatment with saturated solution of bleaching powder at 0-5℃. 1-chloro-2,5- or 2,6-dimethyl benzimidazole is obtained.

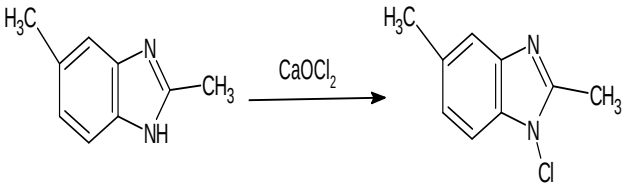
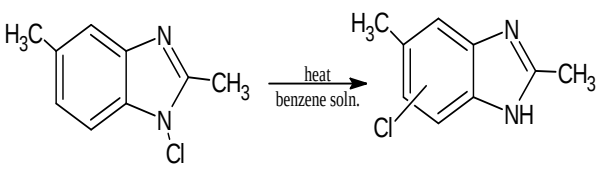
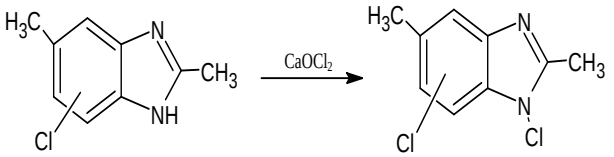


Fig. Halogination of benzimidazole

The N-chloro compound loses chlorine quite readily, even at relatively low temperature. When heated under reflux in benzene solution a rearrangement of the chlorine atom to the benzene ring takes place.



The N-Choloro derivative of this compound may then be prepared by treatment again with bleaching powder.



Treatment of the later compound by refluxing in benzene solution rearranges the N-chlorine atom again into the ring. This process may be repeated until the totally chlorinated compound (1,4,5,6-tetrachloro-2,5-dimethyl benzimidazole) is obtained.

(D) Reactions involving the 2-methyl or methylene group

The methyl group of 2-methyl benzimidazoles is comparable in its activity to the methyl group of α-picoline, quinaldine, or methyl ketones and shows most of the same reactions of these compounds. The benzimidazoles ring, like the pyridine and quinoline ring, because of its electron attracting nature imparts a positive character to the carbon atom of the 2-methyl group.

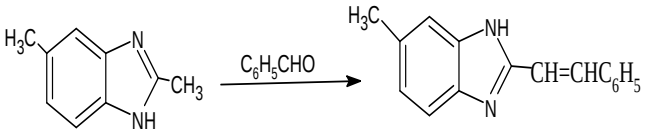
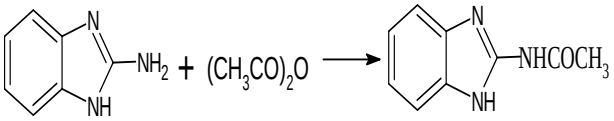


Fig. Reaction involving the 2-methyl or methylene group

1. Oxidation

Benzimidazoles are stable to oxidation. By vigorous conditions of oxidation (potassium permanganate in hot alkaline solution) it is partially possible to oxidize benzimidazoles to obtain a small amount of imidazoledicarboxylic acid.



Because of the stability of the benzimidazoles ring to oxidation it is possible to oxidize substituent group without affecting the ring. By the oxidation of the substituent groups a variety of benzimidazole carboxylic acids have been prepare.[9,95]

2. Hydrogenation and dehydrogenation reactions

Until very recently it was thought that benzimidazole ring was stable to reduction. Catalytic reduction of benzimidazole even under high pressure with Nickel as the catalyst is reported to give negative results. 2-Phenylbenzimidazole gives only 2-cyclohexylbenzimidazole. Hydrogenation of 2-(p-dimethylaminostyryl) benzimidazole with Nickel at atmospheric pressure saturates only the Olefinic linkage in the 2-positions.

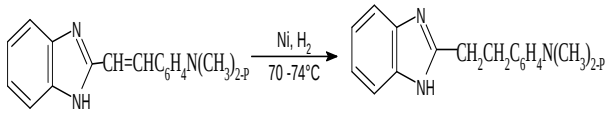


Fig. Hydrogenation of benzimidazole.

A number of hydrogenated benzimidazoles have been prepared also by chemical methods. Hexahydro 2(3H)-benzimidazolone may be obtained by the reaction between hexahydro o-phenylenediamine and phosgene in sodium hydroxide solution. Attempted dehydrogenation of tetrahydrobenzimidazoles with Palladium sponge does not give the corresponding benzimidazole but instead a compound of high molecular weight.

3. Reactions of 2-benzimidazole Carboxylic acids

Benzimidazoles containing a Carboxyl group in the 2-positions readily undergo decarboxylation on heating. 2-benzimidazole carboxylic acid on heating above its melting point, for example, yields benzimidazoles.

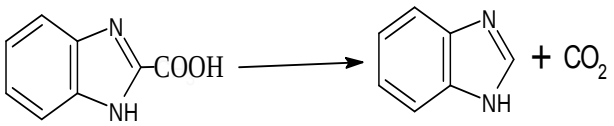


Fig. Reaction of 2-benzimidazole carboxalic acid

4. Reactions of 2-(α-halo alkyl)benzimidazoles

2-(α-Chloroisopropyl) benzimidazole when refluxed in dry alcoholic solution in the presence of pyridine gives a good yield of 2-(α-ethoxyisopropyl)benzimidazoles and hence reacts in a manner analogous to tritylchloride (triphenylmethyl chloride).

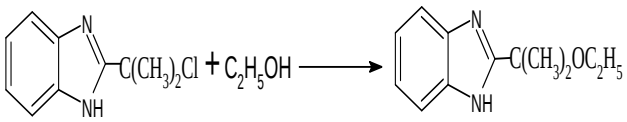


Fig. Reaction of 2-(α-halo alkyl) benzimidazole

5. Reactions of 2-(3H)-Benzimidazolones

2-(3H)-Benzimidazolones (or 2-hydroxy benzimidazoles) are extremely stable treatment of substances. 2-(3H)-benzimidazolone is not split by treatment with benzoyl chloride in alkaline solution. 2-(3H)-benzimidazolones show many of the reactions of 2-hydroxy pyridines and 2-hydroxyquinolines; for example, 2-(3H)-benzimidazolone with phosphorous oxychloride or phosphorous pentachloride yields the 2-chloro derivative.

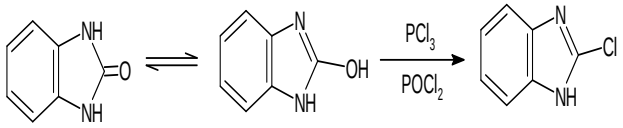


Fig: Reaction of 2-(3H)-benzimidazole

6. 2-(3H)-Benzimidazolethiones

2-(3H)-Benzimidazolethiones or 2-mercaptobenzimidazoles) are generally stable substances and are soluble in dilute alkali. Alkylation occurs readily with replacement of the mercapto hydrogen to yield S-alkylated derivatives, and a number of these derivatives have been prepared.

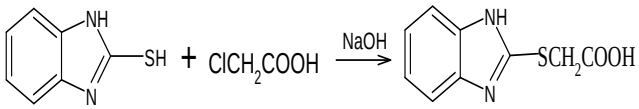


Fig: Reaction of 2-(3H)-benzimidazolethiione

7. 2-Aminobenzimidazoles

2-Aminobenzimidazole with acetic anhydride gives 2-acetyl aminobenzimidazole.

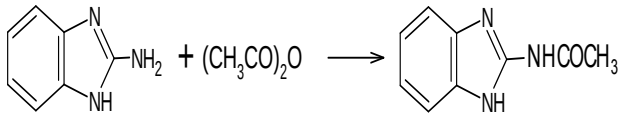


Fig: Reaction of 2-Aminobenzimidazoles

- **Mechanism of Action[96]**

The primary action of the benzimidazole is associated with the ability of these drugs to bind to the protein tubulin and thus prevent tubulin polymerization to microtubules.

- **Metabolism:[97]**

The Benzimidazole have been limited water solubility and as results are poorly absorbed from the GI tract (a fatty meal will increase absorption). Poor absorption may

be beneficial since the drugs are used primarily to treat intestinal helminthes.

- **Uses of Benzimidazole**

A large number of patents describe benzimidazole derivatives of use in the textile industry as wetting, emulsifying, foaming agents or as dispersants for use in dying. In the main, these compounds are sulfonated benzimidazoles. Another use is in the treatment of fibers to improve whiteness of the undyed material or as optical bleach. A number of 2-aminobenzimidazoles have been used in the preparation of fluorescent dyes for use in such preparation as inks for making clothes to the dry cleaner.

5-Methyl benzimidazole has been used as a camphor substitute. 2-methyl benzimidazole is said to be a value as a polymerization inhibitor and initiator in isoprene. 1-piperdinomethyl benzimidazole has been used as a booster compound with antioxidants in rubber. A number of salts of benzimidazole sulfonic acid are said to be value in the preparations for the care of the mouth and teeth.

Benzimidazole fluorescent compounds containing hydroxymethyl and carboxyl substituents were produced by replacing salicylaldehyde and substituted ortho-phenylenediamine. The fluorescent properties of these compounds was studied along with the influence of substituent on the properties by measuring the spectral properties. Studies have also been carried out in investigating the effect of such fluorescent compounds as fluorescent latent agents for sweat fingerprinting. The obtained latent fingerprint of hydroxymethyl and carboxyl substituted benzimidazole have shown better adsorption performance along with stability and fluorescence effect.[98] Hence bezimidazole derivatives have shown to be good in criminal detection technology.

The fluorescence of benzidimidazole derivatives was studied by Cu^{2+} determination method.[99] Hence the ion sensing properties of the compound is given proper attention. The ligand has better fluorescent property. The production of the compound is economical a well as it possess more advantages over other methods. The method.[99] was also used for samples from tap water.

In recent Years, benzimidazloe compounds have emerged as a hot research topic due to their varied biological activities. Indeed, benzimidazole is a privileged scaffold in medicinal chemistry and Agrochemistry. Several commercial fungicides containing the benzimidazole scaffold have been launched or announced. On the other hand, because of their high efficiency, low toxicity and low residue. To mitigate crop damage caused by pests and diseases, we must utilize various crop agrochemicals, such as insecticides, herbicides and fungicides, to control harmful insects, weed species and plant diseases that afflict crops. However, the heavy usage of crop-protection chemicals has resulted in a number of negative impacts, such as pest resistance to pesticides, pest resurgence and environmental pollution. Benzimidazole (especially Carbendazim) have been and are still widely used to control varieties of fungal diseases but their resistance problems may result in failure to control disease. Studies have also proved that not only carbendazim but also thiabendazole shows serious resistance to some diseases. Therefore, it is necessary to discover and develop novel agro-chemicals that could overcome or minimize the side effects of agrochemicals that are currently used.**[100]**

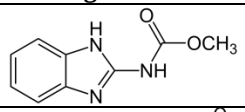
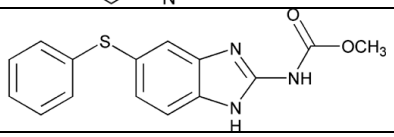
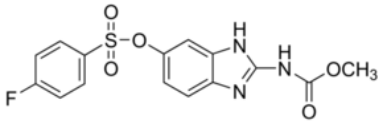
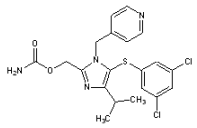
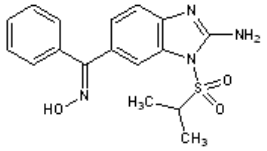
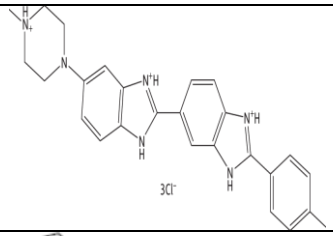
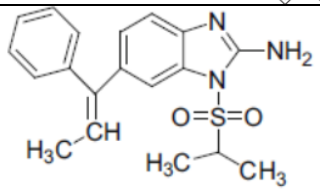
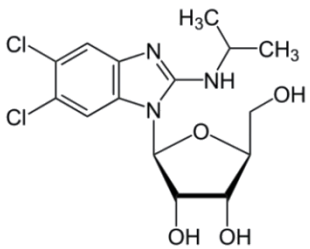
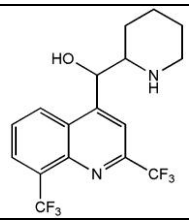
Tuberculosis is one of the deadly diseases which posses both drug resistance and multi-drug resistance. The surveys have shown that almost 700,000 cases were reported,**[101]** in the year 2017 TB was also seen to be associated with AIDS/HIV and lead to the death of many patients, were TB was the major reason.

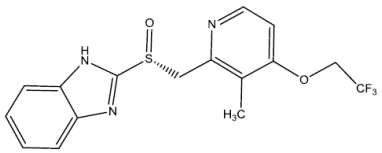
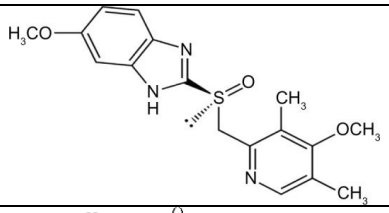
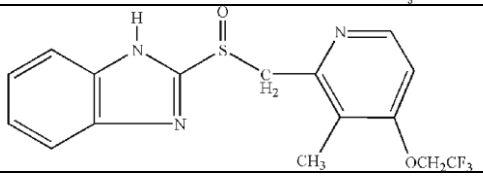
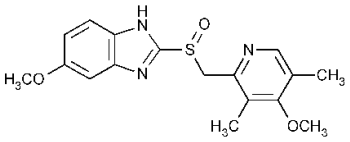
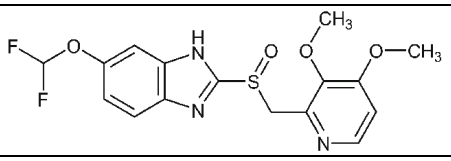
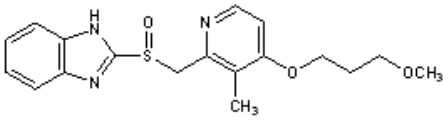
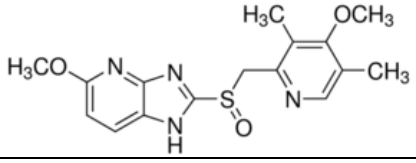
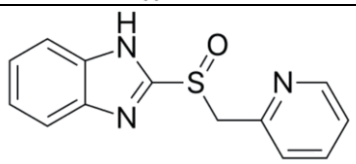
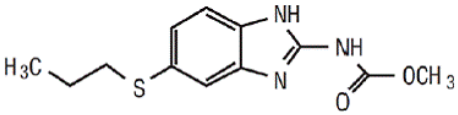
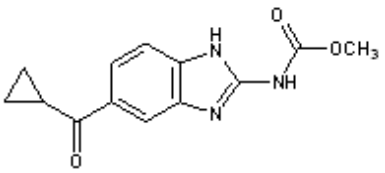
The major drugs that have shown effect for TB is the nitrogen heterocyclic compounds mainly the five and six member ring derivatives. The main among the group includes pyridine and imidazole/ benzimidazole.**[102]**

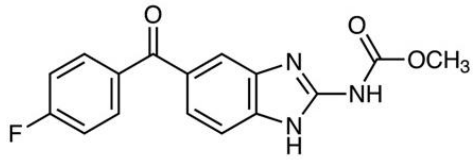
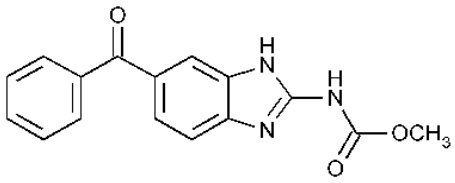
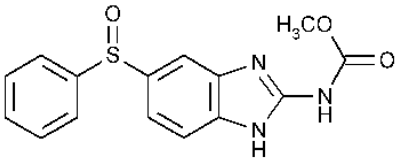
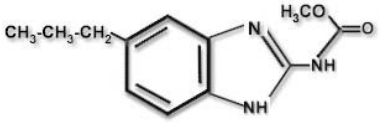
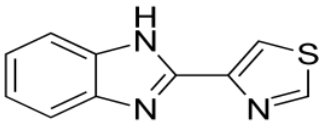
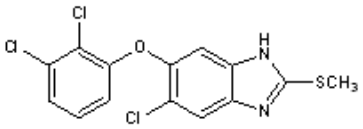
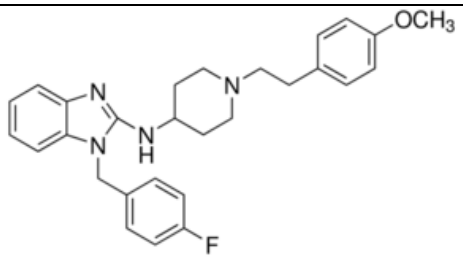
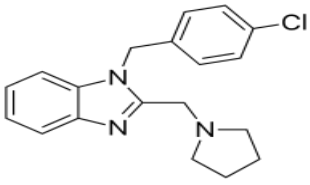
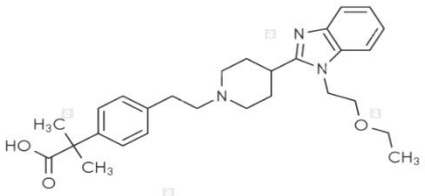
The benzimidazole nucleus which is a useful structure for rese arch and development of new pharmaceutical molecule has received much attention in the last decade. Due to their clinical and biological application,[103-109] numerous attempts have been made to develop new structural prototypes to search for more biological and clinical activities. They are remarkably effective compounds both with respect to their inhibitory activity and their favorable selective ratio. Benzimidazoles are regarded as the range of biological activities as well as synthetic approach of medicinal chemistry specially, this nucleus is the constituent of Vitamin-B_{12}[110,111] this ring system is present innumerous Antioxidant,[112-117] Anti-Tuburculosis,[118-125] Anti –Hepatitis,[126-129] B & C Virus, Antiparasitic.[130-134] Antiviral,[135-139] including Anti-HIV,[140-144] Antiulcer,[145-152] Anthelminthic,[153-159] Antihistaminic,[160-166] Anticonvulsant,[167-170] Anti –Inflammatory,[171-176] Anticancer,[177-194] Antineoplastic,[195-197] Antitumor,[198-205] Antiproliferative,[206-209] Antihypertensive,[210-215] Anti-diabetic,[216-218] Analgesic,[219-222] Anti-Trichinellosis,[223,224] Cardiac drug,[180,225-227] (Carditonic drug, Ion dilator), Psychopharmacological drugs (Antipsychotic agent)[103,107,228] Urine infection,[107,229,230] Antileishmania,[231,232] Antiprotozoal,[233,234] Pesticide,[235,236] Antimicrobial,[237-245] and Antifungal[246-251] activities is also well documented that benzimidazole is associated with a variety of pharmacological activities viz Antimicrobial and Antifungal. Benzimidazole structure is the nucleus in some drugs such as proton pump inhibitors and anthelminic agents.Different classes of heterocyclic compounds have been identified through molecular biology,empirical screening and rational drug development in search of potent and effective new molecules . Especially Nitrogen containing heterocyclic

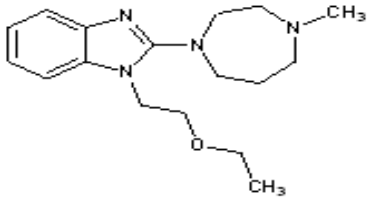
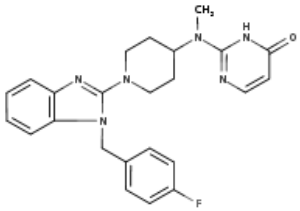
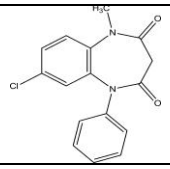
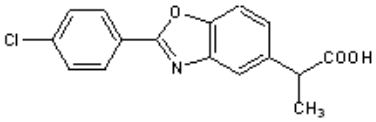
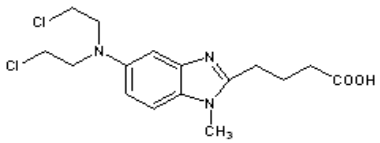
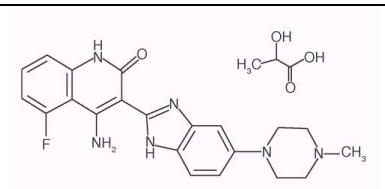
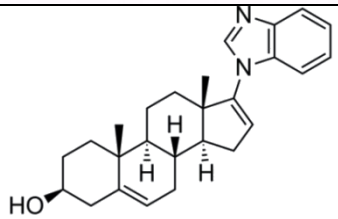
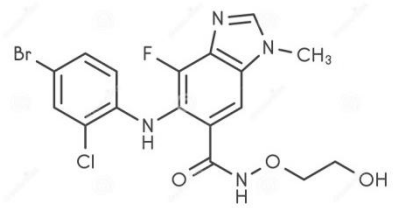
system like Azoles nucleus playing a vital role in discovering of novel drugs with potential activity. The moleculer structures of some benzimidazole containing nucleus compounds, which are commonly used for various therapeutic application, are present in Table.

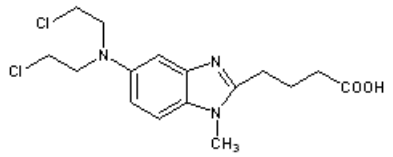
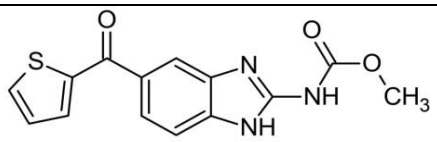
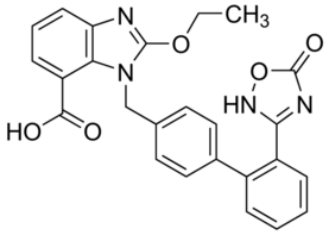
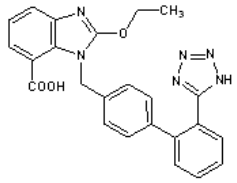
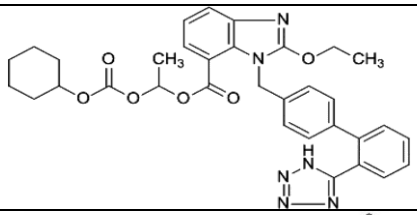
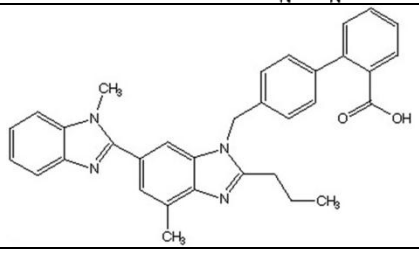
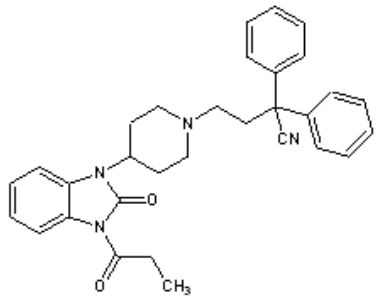
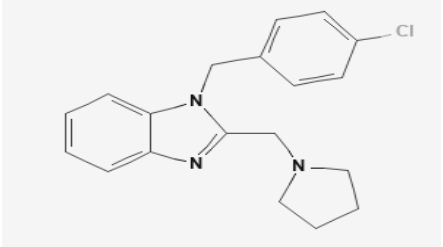
Table 1: Antioxidant drugs act against the effect of reactive oxygen species (ROS). Apart from therapeutic areas, benzimidazole-based drugs have also been used in various other fields. This includes anticonvulsants, immunosuppressant and analgesics.

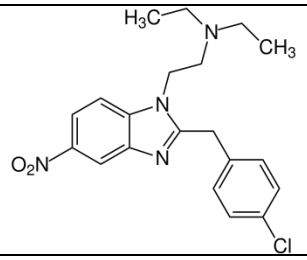
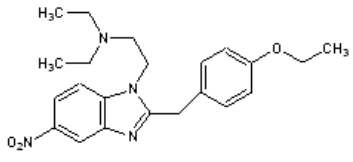
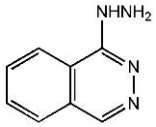
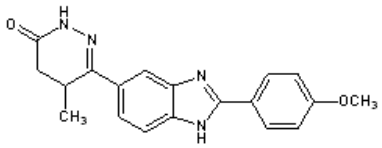
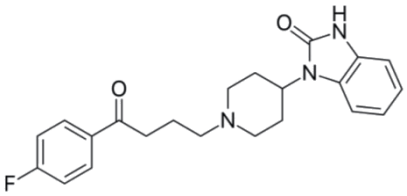
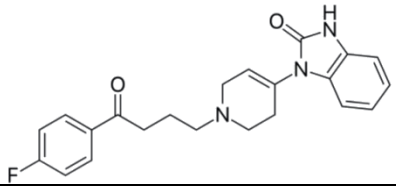
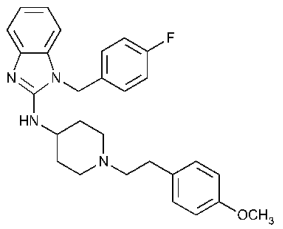
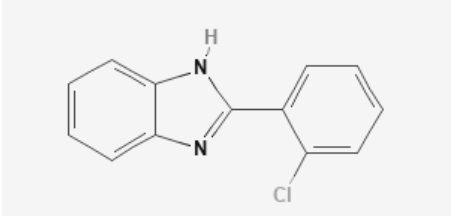
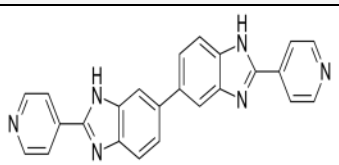
S.No.	Drug structure	Name	Medicinal uses
1		Carbendazim	Antiparasitic / Antifungal
2		Fenbendazole	Antiparasitic drug, Antithelminitic
3		Luxabendazole	Antiparasitic
4		Capravirine	Treatment of HIV
5		Enviroxime	Antiviral/ Anticancer
6		Hoechst 33342	Antiviral
7		Enviradine	Antiviral
8		Maribavir	Antiviral
9		Mefloquine	Treatment of Malaria.

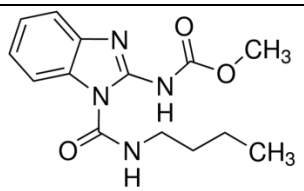
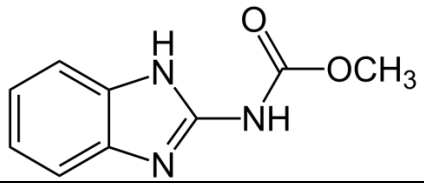
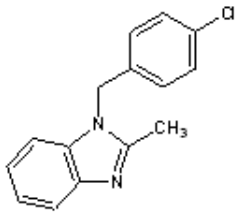
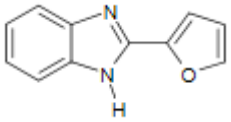
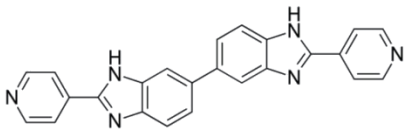
10		Dexlansoprazole	Treatment in Gastroesophageal reflux diseases.
11		Esomeprazole	Treatment of heartburn , acid reflux and gastro-oesophageal reflux disease (GORD), Antiulcer, Proton-pump-inhibitor
12		Lansoprazole	Antisecretary agent, Proton-pump-inhibitor
13		Omeprazole	Stomach ulcers, Antiulcerative (Proton-pump-inhibitor)
14		Pantoprazole	Used in acid reflux, Antiulcer (Proton-pump inhibititor)
15		Rabeprazole	Treatment of heartburn and peptic ulcer disease, Proton-pump-inhibitor
16		Tenatoprazole	Antiulcerative
17		Timoprazole	Cytoprotective agent used for gastric acid secretion.
18		Albendazole	Treatment of variety of parasitic worm infestations. (Anthelmintic/ Antiprotozol/ Antimicrobial)
19		Cyclobendazole	Antihelmentic

20		Flubendazole	Anthelmintic
21		Mebendazole	Worm infection such as Pinworm, roundworm, and hookworm (Anthelmintics)
22		Oxfendazole	Roundworm, strongyles and pinworms, Antihelmintics
23		Oxibendazole	Treatment of helmintic diseases
24		Thiabendazole	First line therapy of interobiasis (pinworm), (Anthelmintic/ Antiparasitic/ Anti-fungicuide)
25		Triclabendazole	Treatment of fascioliasis and paragonimiasis, Antithelminitic
26		Astemizole	Antihistaminic drug
27		Clemizole	Antihistaminic
28		Bilastine	Antihistaminic

29		Emedastine	Antihistaminic drug
30		Mizolastine	Antihistaminic drug
31		Clobazam	Anticonvulsant
32		Benuxaprofen Analog	Anti inflammatory
33		Bendamustine	Chronic lymphocytic leukemia, lymphomas and advanced ovarian and breast cancernomas (Anticancer) Hodgkins's disease
34		Dovotinib	Anticancer
35		Galeterone	Anticancer
36		Selumetinib	Tumor

37		Imet 3393	Antineoplastic
38		Nocodazole	Antineoplastic/ Antitumor
39		Azilsartan	Treatment of hypertension / Antihistaminic
40		Candesartan	Antihypertensive/ Antihistaminic
41		Cilexitil	Antihypertensives
42		Telmisartan	Treatment of high blood pressure Antihypertensives / Antihistaminic
43		Benzitramide	Analgesic drug
44		Clemizole	Analgesic drug/Antitumor

45		Clonitazene	Narcotic analgesic agent
46		Etonitazene	Analgesic drug
47		Vasodilator	Analgesic
48		Pimobendam	Carditonic drug, Ion dilator/Anti-diabetic agent
49		Benperidol	Antipsychotic Agents/ psychopharmacological agent
50		Droperidol	Sedative, Tranquilizer, anti-nausea, psychopharmacological agent
51		Astemizole	Uricosuric, Urine infection (Receptor Artagonist agent)
52		Chlorfenazole	Pesticide/Fungicide
53		Ridinalazole	Nobel Antimicrobial

54		Benomyl	Antifungal
55		Carbendazim	Antifungal
56		Chlormidazole	Antifungal
57		Fuberidazole	Fungicide
58		Ridinalazole	Treatment of Clostridioides difficile infection/ Anti-microbial

CONCLUSION

Form the present study it becomes evident that benzimidazole and its derivatives being an important moiety for various biological activities. Various synthetic methods were reported from time to time. Among these methods some of them gives good yields and Chemist must try new routes for the synthesis of these biologically active compounds which are afforadable and are green. The present review provides a brief overlook of the works done by the different scientists on this topic which helps chemists to develop the strategy for the design and the synthesis of benzimidazole derivatives by using new routes and methods which results good yield and have good biological activities.

REFERENCE

1. Verma Rohit, Gupta Chitra, Ganie Ali Mohd, Singh Sanjay and Singh P.K. Synthesis, characterization and potent antimicrobial and antifungal activity of 2- substituted benzimidazole derivatives. *Indian Journal of Chemistry*, 2021; 60B(1): 148-151.
2. Ganie Ali Mohd, Dar Ayaz Mahmood, Khan Fairooz Ahmad and Dar Bashir Ahmad Benzimidazole Derivatives as Potential Antimicrobial and Antiulcer Agents A Mini Review. *Mini Reviews in Medicinal Chemistry*, 2019; 19: 1-6.
3. Preston P. N. Synthesis, reactions and spectroscopic properties of benzimidazloe, *Chemical Reviews*, 1974; 74(3): 279-314.
4. Divya S., Ramesh K. and Poornima N. Synthesis, Characterization of Novel Benzimidazole derivatives. *IJPBS*, 2012; 2(2): 143-149. *(a)* Shahayar M., Majumdar A., Salahuddin, Garg P. and Pandey R.D. Synthesis,Characterization and Pharmmmacological Screening of Novel Benzimidazole Derivatives, *Arabian Journal of Chemistry*, 2011; 1-6. (b) Shatha Ibrahim Alaqueel Synthetic approaches to benzimidazole from o-phenylenediamine: A Literature Review, *Journal of Saudi Chemical Society*, 2017; 21(2): 229-237. (c)Singh Vineet Kumar and Prle Amrita The Intriguing Benzimidazole: A Review, *IJPSR*, 2019; 10(4): 1540-1552.
5. Eicher T., Hauptmann S. and Speicher A. The Chemistry of Heterocycles: Structures, Reactions, Syntheses and Applications. *John Wiley-VCH GmbH and Co. KGaA, Germany*, 2004.
6. Bansal R. K. Heterocyclic Chemistry.*4th Ed. Tunbridge Wells: Anshan Ltd*.1-2.; Publisher,New Delhi,New Age International, 2007; 401.
7. Burger A., Hansch C., Sammes, P.G. and Taylor J.B. Isosterism and Bioisosterism in drug design, Eds. Comprehensive Medicinal Chemistry, *Pergamon press*, 1990; 37: 287-371.
8. Wright John B. (29 January) The Chemistry of the Benzimidazoles. Research Laboratories,The

Upjohn Company,Kalamazoo,Michigan, *Chemical Reviews,* 1951; 48(3): 397-541.
9. Delepine M. Joseph Pelletier and Joseph Caventou. *Journal of Chemical Education*, 1951; 454.
10. Roger R. and Neilson D.G. The Chemistry of Imidates. *Chemical Reviews*, 1961; 61: 179-211.
11. Camille G. and Wermuth Eds. Efficient one-step synthesis of 3-amino-6-arylpyridazines, The Practice of Medicinal Chemistry, *Elsevier*, 2001; 42(11): 2115-2117.
12. Hoebrecker F. *Ber.,* 1872; *5*: 920–926. (a) Hofmann K. (1953) In the Chemistry of Heterocyclic Compounds: "Imidazole and its derivatives", *part-1, Wiley Interscience,New York*. (b) Schipper S. and Day A. R. (1957) "Heterocyclic Compounds", Vol. V. (c) Elderfield R. C. (1957) (Ed), *Wiley Interscience, New York*, 267. (d) Pozharskii A. D. and Garnovskii Simonov A. M. *Russ. Chem. Rev.,* 1966; 35: 122.
13. Wilfred C.D. and Taylor R.J.K. Preparation of 2-Substituted Benzimidazoles and Related Heterocycles Directly from Activated Alcohols Using TOP Methodology, *Synlett,*, 2004; 9: 1628-1630.
14. Heravi M.M., Sadjadi S., OsKooie H.A, Shoar R.H. and Bamoharram F.F. "Heteropolyacids as heterogeneous and recyclable catalysts for the synthesis of benzimidazoles," *Catalysis Communications*, 2008; 9(4): 504-507.
15. Grimmett M.R. *In Comprehensive Heterocyclic Chemistry*; Katritzky A.R. and Rees C.W. (1984) *Eds.:Pergamon New York*, 5:457 ; Grimmett M.R. (1984) In Comprehensive Heterocyclic Chemistry 2 ; Katritzky A.R., Rees C.W. and Scriven E.F.V. *Eds. : Pergamon Oxfored UK*, 1996; 3: 77.
16. Zelenin K.M.,Ukraintsev I.V. and Alekseev V.V. In termediates in the reaction of o-phenylene-diamine with Carbonyl Compounds and their subsequent conversions. *Chemistry of Heterocyclic Compounds*, 1998; 34(3): 329-333.
17. Venkateswarlu Y., Kumar S.R. and Leelavathi P. (2013) *Organic and Medicinal Chemistry Letters*, 3(7):2-8. Beaulieu P.L., Hache B. and Von Moon E. (2003) A Practical Oxone -Mediated, High-Through, Solution-Phase Synthesis of Bezimidazoles form 1,2- phenylenediamines and Aldehydes and its Application to preparative scale Synthesis. *Synthesis*, 2003(11): 1683-1692.; (b) Jeshma K., Nagaraju B., Ahmed K. and Ajay K. An efficient synthesis of 2-substituted benzimidazole via photocatalytic condensation of o-phenylene diamines and aldehydes. *ACS Combinational Science*, 2016; 18(10): 644-50.
18. Weidenhagen R. *Chemische Berichte*, 1936; 69: 2263-2272.
19. Rao N. V. S., Ratnam C. V and Veeranagaiah Studies in the formation of Heterocyclic ring containing nitrogen. *Proceedings of the Indian Academy of Science*, Section A, 1974; (79): 230-235.
20. Smith J.G. and Ho I. *Tet. Lett.*, 1971; 3541.
21. Rombi M. and Dick P. R. (1972) FR2178385 *Chem.Abstr*, 1974; 80: 108526s.
22. Harnish H. (1975) DE2346316; *Chem. Abstr*, 1975; 83: 79240y.
23. Stephens F. F. and Bower J. D. *J. Chem. Soc*., 1949; 2971.
24. Bhatnagar K. S. and George M. V. *Tetrahedron*, 1968; 24: 1293.
25. Balachandran K. S. and George M. V. *Indian J. Chem*., 1973; 11: 1267.
26. Jerchel V. D., Fischer H. and Kracht M. Justus Liebigs *Ann. Chem*., 1952; 575: 162.
27. Ridley H. F., Spickett R. G. W. and Timmis G. M. *J. Heterocyclic Chem*., 1965; 2: 453.
28. Fischer O. and Wreszinski H. *Chem. Ber.,* 1892; 25: 2711.
29. Morgan T. and Challenor W. A. P. *J. Chem. Soc.*, 1921; 119: 1537.
30. Eilis P. and Jones R. T. *J. Chem. Soc. Perkin -I*, 1974; 903.
31. Hinsberg O. and Funke Fr. *Ber.,* 1894; 27: 2187.
32. Hinsberg O. and Koller P. *Ber.,* 1896; 29: 1497-1504.
33. Crippa G. B. and Maffei S. *Gazz. Chim. Ital.*, 1941; 71: 194.
34. Rao N. V. S. and Ratnam C. V. *Current Science.*, 1955; 24: 299.
35. Rao N. V. S. and Ratnam C. V. *Proc. Indian Acad. Sci.*, 1956; 43: 173; (1957) 45: 253; (1958) 48: 256; (1959) 49: 193.
36. Fischer O. and Limmer H. *J. Prakt. Chem.,* 1906; 74: 58.
37. Rao N. V. S., Veernagaiah V. and Ratnam C. V. *Indian. J. Chem*., 1970; 8: 790.
38. Reddy P. S. N., Veernagaiah V. and Ratnam C. V. *Proc. Indian. Acad. Sci.*, 1975; 81A: 124.
39. Dubey Pramod K. and Ratnam C. V. Formation of heterocyclic rings containing Nitrogen: Part XXVI-Condensation of pyridine 2,3-diamine with aromatic aldehydes, *Proc. Indian. Acad. Sci.*, 1977; 85 A(4): 204-209.
40. Elderfield R. C. and Kresya F. J. The reaction of o-phenyldiamine and of 8-Amino-1,2,3,4-tetrahydroquinoline derivatives with carbonyl compound , *J. Am. Chem. Soc*., 1948; 70(1): 44-48.
41. Elderfield Robert C. and McCarthy John R. The reaction of o-phenylldiamines with carbonyl compounds .II. Aliphatic Ketones, *J. Am. Chem. Soc*., 1951; 73(3): 975-985.
42. Elderfield R. C. and Meyer B.Victor The reaction of o-phenyldiamines with carbonyl compounds.III Benzophenons and diabenzyl Ketones, *J. Am. Chem. Soc*., 1954; 76(7): 1883-1887.
43. Ladenburg A. and Rugheimer L. (1880) Synthesis der Tropasaure. *Diese Berichte XIII,* 1978; 373: 2041-2043. 11: 1656.
44. (a)Copeland R.A.B. and Day A.R. The preparation and reactions of 2-benzimidazole carboxylic acid and 2-benzimidazole acetic acid. *Journal of the*

American Chemical Society, 1943; 65(6): 1072-1075. (b) Day A.R. Electronic mechanism of organic synthesis. *American Book Company*, 1950; 242-243.

45. Preston P. N. The Chemistry of Heterocyclic Compounds,6-60. ; Weissberger A. and Taylor E.C. (1981) Benzimidazole and Cogeneric Tricyclic Compounds,Part 2, John Wiley Interscience New York. Chapter 10, pp 1-285,s531. The Chemistry of Heterocyclic Compounds. *Eds., John Wiley and Sons : New York, USA*, 1980; 40: 1-285.
46. Grimmet M.R., Katritzky A.R. and Rees C.W. *Heterocyclic Chemistry Oxford UK*, 1984; 5: 457.
47. Wermuth C.G., Ganellin C.R., Lindberg P. and Mitscher L.A. *Eds Annual Reports in medicinal chemistry, Academic press,* 1998; 33: 385-395.
48. Ladenburg A. *Ber*, 1875; 8: 677.
49. Wundt E. (1878) The reaction of o-phenylenediamine with Formic acid.*Chem.Ber.*,11: 826. (a) Wagner E.C. and Millett W.H. (1946) The Chemistry of Formic acid and its Simple derivatives. *Org. Synthesis,Coll.Vol.II,John Wiley and Sons.Inc.,New York*, 2:65.; (b) Seka and Muller. (1931) *Monatsch*, 57, 97.; (c) Brown E. L. and Campbell N. *J. Chem. Soc*., 1937; 1699.
50. Kelly Day Preparation of 2-phenylnapth [1,2] imidazole and 2- methylnapth [1,2] imidazole *J.Am. Chem. Soc.*, 1945; 67: 1074.
51. Bistrzycki Ulffers and Schmutzi Ueber Diacyl-o-Diamine *Ber.*, 1980; 38: 1876.
52. Fischer O' Veiel The Chemistry of Benzimidazole. *Ber*., 1905; 38: 320.
53. Phillip M.A. CCCXVII-The formation of 2-substituted benzimidazole, *J. Chem. Soc.* (Resumed) 172: 2393.; (1929) Phillips-Ladenburg benzimidazole synthesis. *J.Chem.Soc.*, 1971; 2810: 1143–1145.
54. Green H. and Day A. R. *J. Am. Chem. Soc*., 1942; 64: 1167.
55. Mecoy G. and Day A. R. *J. Am. Chem. Soc.*, 1943; 65: 2159.
56. Phillips M. A. *J. Chem. Soc.*, 1930; 1409.
57. Roeder H. and Day A. R Benzimidazole and Imidazole Synthesis. *J. Org. Chem*., 1941; 6: 25.
58. Porai-Koshits B. A., Ginzburg O. F. and Efros L. S. *J. Gen. Chem.*, 17: 1768; (1948) *Chem. Abstr.*, 1947; 42: 5903.
59. Porai-Koshits B. A., Efros L. S., Ginzburg O. F. and Zh. Obshch. Khim.(1949) *J. Gen. Chem*., 19: 1545 ;(1950) *Chem. Abstr*. 44: 1100. (a) Dubey P. K., Kumar R., Grossert J.S. and Hooper D.L. (1999) A Facile and Convenient method for the Preparation of 2-styrylbenzimidazoles.*Indian Journal of Chemistry B*, 38 (10) : 1211-1213. (b) Dudd L.M., Venardou E., Garcia-Verdugo E., Licence P., Blake A.J., Wilson C. and Paliakoff M. Synthesis of Benzimidazoles in high-temperature water. *Green Chem*, 2003; 5(2): 187-192.
60. Rithe S.R., Jagtap R.S. and Ubarhande S.S. One pot synthesis of substituted benzimidazole derivatives and their characteristics, *RASAYAN J. Chem*, 2015; 8(2): 213–217.
61. Wagner E.C. and Millett W.H. Synthesis of Benzimidazole. *Organic Synt. Coll. John Wiley & Sons. Inc. New York*, 1943; 2: 65.
62. Hein D.W., Alheim R.J. and Leavitt J.J. The Use of Polyphosphoric Acid in the Synthesis of 2-Aryl- and 2-Alkyl-substituted Benzimidazoles, Benzoxazoles and Benzothiazoles. *J.Am. Chem. Soc.*, 1957; 79(2): 427-429.
63. Winferriet S. *J. Prakt. Chem.*, 1964; 24: 164.
64. Wen X., Bakali J.E., Deprez-Poulain R. and Deprez B. Efficient Propylpoyphosphonic mediated synthesis of Benzothiazoles, Benoxazoles and Benzimidazoles, *Tetrahedron Lett.*, 2012; 53: 2440.
65. Kanaoka Y., Yonemitsu O., Tanizawa K. and Ban. Y. *Chem. Pharm. Bull.(Tokyo)*, 1964; 12: 773. (1964) *Chem. Abstr.*, 61: 9487.
66. Sluka J., Novak J. and Budesinsky Z., (1976). *Collect. Czech. Chem. Commun.,*. 41: 3628. (a) Shriner R.L. and Robert W. Upson (1941) Synthesis of bis-benzimidazoles from diabasic acids. *J.Am. Chem. Soc.*, 63(8):2277. (b) Wang Lillian Li-Yen and Joullie Madeleine M. (1957) Synthesis of Bis-Benzimidazoles. *J. Am. Chem. Soc.*79(21):5706-5708. (c) Abboud Y., Abourriche A., Saffaj T., Maoufoud S., Mouhou H., Berrada M., Charrouf M. and Bennamara A. (2004) Synthesis and Bioactivities of some Benzimidazoles Derivatives.*Conference Paper,7th Italian Conference on Supercritical Fluids and Their Applications 9th Meeting on Supercritical Fluids.At 13-16 June, Trieste(Italy), 2004.*
67. Lemberger T., Desvergne B. and Wahli W. Peroxisome proliferator-activated receptors a nuclear receptor signaling pathway in lipid physiology. *.Annu. Rev. Cell Dev. Biol*, 1996; 12: 335-363.
68. Evans R.M., Barish G.D. and Wang Y.X. PPARs and the complex journey to obesity. *Nat Med.*, 2004; 10: 355-361.
69. Walther R Von and Kessler A. *J.Prakt Chem.*, 1906; 74: 245.
70. Rathod C.P., Rajurkar R.M. and Thonte S.S. *Indo Am. J. Pharm. Res.*, 2013; 3(2): 2323–2329.
71. Auwers V.K. and Frese E. *Ber.*, 1926; 59B: 539.
72. Wagner E.C. *J. Org. Chem.*, 1940; 5: 136.
73. Bistrzycki A. and Cybulski G. *Ber.*, 1891; 30: 631.
74. (a)Tidwell R.R., Geratz J.D., Dann O., Volz G., Zeh D. and Loewe H. (1978) Diarylamidinc derivatives with one or both of the aryl moieties consisting of an indole or indole-like ring. Inhibitors of arginine-specific esteroproteases. *J. Med. Chem.*; 21(7): 613-23.(b) Fairley T.A., Tidwell R.R., Donkor I., Naiman N. A., Ohemeng K.A., Lombardy R.J., Bentley J.A. and Cory B.M. Structure, DNA minor groove binding and base pair specificity of alkyl- and aryl-linked bis (amidinobenzimidazoles) and bis

(amidinoindoles).*Med.Chem.*, 1993; 36(12): 1746-1753.
75. Von Niementowski S. Benzimidazole Synthesis. *Ber*, 1897; 30: 3062.
76. Bistrzycki A. and Schmutz Walther Einwirkung von ortho-und peri-Diaminen sowie von Athylendiamin auf Y-Lactone. *Justus Liebigs Annalen Der Chemie*, 1918; 415(1): 1-28.
77. Niementowski V.S. *Ber*., 1897; 30: 3064.
78. Lans S. *J.Chem.Soc.*, 1953; 2238.
79. Mistry S.M. and Guha Praphulla Chandra An improved method of preparation of substituted amides and hydrazides.*J.Indian Chem.Soc.*, 1930; 7: 793-797.
80. Czarny A, Wilson WD, Boykin DW Synthesis of mono cationic and dicationic analogs of Hoechst 33258. *J Heterocycle Chem*, 1996; 33-1393.
81. Wu Z, Rea P, Wickam G. Tetrahedron Lett. (2000) 41: 9871-4, and the reference cited therein*; Mazurov A. Bioorg Med Chem Lett*., 2000; 10: 67-70.
82. Edward Holljes L. and Wagner E.C. Some reactions of Nitriles as acid anammonides. *J.Org.Chem.*, 1944; 9(1): 31-49.
83. Pellizzari G. *Gazz. Chim. Ital. Chemical Society*, 1911; 41: 20.
84. Van Allan J.A. and Deacon B.D. Synthesis of 2-mercapto benzimidazole. *Organic Synthesis*, 1950; 30: 56.
85. Shahnaz M., Kaur Parminder, Prakash J. and Parsad D.N. Synthesis, Characterization of 2-substituted benzimidazole derivatives and evaluation of Antimicrobial activity, *Jour. Of Drug Delivery and Theraputics*, 2018; 8(5): 460-464.
86. Srestha Nomi, Banerjee Janmajoy and Srivastava Sujiti A Review on chemistry and biological significance of benzimidazole nucleus *IOSR journal of pharmacy*, 2014; 4(12): 28-41.
87. Eswara Rao G., Srinivasa Babu P., Sai Koushik O., Sharmila R., Vijayabharathi M., Maruthikumar S., Prathyusha R. and Pavankumar P. A review on Chemistry of Benzimidazole Nucleus and its biological significance. *International Journal of Pharmaceutical, Chemical and Biological Sciences*, 2016; 6(2): 227-232.
88. Srivastava Rahul, Ali Meraj and Nishad Urmila Synthesis and Biological Activity of Different Aromatic Compounds of Benzimidazole Derivatives. *Jour. Sci. and Res.*, 2020; 12(4): 507-515.
89. Kalidhar Uday and Kaur Amandeep (October-December) An Overview on Some Benzimidazole and Sulfonamide Derivates with Anti-Microbial Activity, *RJPBCS*, 2011; 2(4): 1116.
90. Lacey E. Mode of action of Benzimidazole. *Parasitology Today*, 1990; 6(4): 112-115.
91. Gottschall D.W., Thedorides V.J. and Wang R. Metabolism of Benzimidazole Anthelmintics. *Parasitology Today*, 1990; 6(4): 115-124.
92. Shuai Liang, Shengfeng Cui, Gang Wang and Yiyang Zhou Synthesis of Benzimidazole Sweat Fingerprinr Fluorescent Developer and Florescent Effect. *The Italian Association of Chemical Engineering Transactions*, 2018; 66: 157-162.
93. Zafer Ocak. A Fluorimetric Method Based on an Imidazole Compound for Cu^{2+} Determination in Tap Water. *Hindawi Journal of Chemistry*. February, 2020; 1-7.
94. Weijie Si, Tao Zhang, Yaofa Li, Dongmei She, Wenliang Pan, Zhanlin Gao, Jun Ning and Xiangdong Mei Synthesis and biological activity of novel benzimidazole derivatives as potential antifungal agents. *J. Pestic Sci.*, 2016; 41(1): 15-19.
95. WHO, Global tuberculosis report www.who.int/tb/publicatons/global_reports/en/, 2017.
96. Vasilichia Antoci, Dumitrela Cucu, Gheorghita Zbancioc, Costel Moldoveanu, Violeta Mangalagiu, Dorina Amariucai-Mantu, Aculina Aricu and Lonel I Mangalagiu. Bis-(imidazole/benzimidazole)-pyridine derivatives: synthesis, structure and antimycobacterial activity. *Future Medical Chemistry*, 2020; 12(3): 207-222.
97. Bansal Yogita and Silakari Om The therapeutic journey of benzimidazole a review,*Bioorganic and Medicinal Chemistry*, 2012; 20(21): 6208-6236.
98. Singh Gurvinder, Kaur Maninderjit and Chander Mohan Benzimidazole: The latest information on biological activities, *IRJP*, 2013; 4(1): 82-87. oISSN: 2230-8407.
99. Anand Keshav and Wakode Sharad Development of drugs based on Benzimidazole Heterocycle: Recent advancement and insights. *International journal of chemical studies*, 2017; 5(2): 350-362.
100. Salahuddin Shaharyar M. and Mazumder Avijit Benzimidazole: A biologically active Compounds. *Arabian Journal of Chemistry*, 2017; 10(1): S157-S173.
101. Hodole C.D., Rajput J.D. and Bendre R.S. Concise on Some Biologically Important 2-Substituted Benzimidazole Derivatives. *Organic Chemistry : Current Research*, 2018; 7(3): 1-9.
102. Tahlan S., Kumar S. and Narasimhan B. Pharmacological significance of heterocyclic 1H-benzo[d]imidazole scaffold : A Review. *BMC Chemistry*, 2019; 13(101): 1-21.
103. Mahesh S. Vasava, Bhoi Manoj N., Rathwa Sanjay K., Jethava Divya J., Acharya Prachi T., Patel Dhaval B. and Patel Hitesh D. Benzimidazole :A Milestone in the field of Medicinal Chemistry. *Mini-Reviews in Medicinal Chemistry Bentham Science*, 2020; 20(7): 532-565.
104. (a) Scott D.M., Rogers M.L. and Rose C. Benzimidazole as Specific Inhibitors of Vitamin B_{12} or Thymine in Bacterial Mutants 1,2. *Journal of the American Chemical Society*, 80: 2165-2169. (b) Barker H.A., Smyth A.D., Weissbach H., Toohey J.I., Ladd J.N. and Volcani B.E. (1960) Isolation and properties of crystalline cobamide

Coenzymes Containing benzimidazole or 5,6-dimethylbenzimi-dazole. *J. Biol. Chem.* ,235:480-488. (c) Bonnett R. (1963) *Chem.Rev.*, 1958; 63(6): 573-605.

105. Neil O',Smith M.J. and Heckelman M. *The Merck Index,13th Ed. Merck & Co. Inc.*, 2001; 1785,10074.
106. Brand-Williams W., Cuvelier M. and Berset C. Use of a free radical method to evaluate Antioxidant activity, *Lwt.-Food Sci.Technol*., 1995; 28,25,30.
107. Can-Eke B., Puskullu M.O., Buyukbingol E. and Iscan M. A study on the Antioxidant capacities of some benzimidazole in Ret Tissues. *Chem. Biol.Interact*, 1998; 113: 65-77.
108. Sarika S., Dhimim N., Aman M., Gaurav K. Synthesis and Antioxidant activity of the 2-methyl benzimidazlole. *Jour. of Drug Delivery Therapeutics.*, 2016; 6(3): 100-102.
109. Anand Keshav and Wakode Sharad Synthesis Characterization and biological evaluation of benzimidazole derivatives. *International Journal of Pharmaceutical Sciences and Research,* 2018; 9(2): 617-624.
110. Odame F., Krause J., Hosten E.C., Betz R., Lobb K., Tshentu Z.R. and Frost C.L. Synthesis, Characterization and DPPH scavenging activity of some benzimidazole derivatives. *Bull. Chem. Soc. Ethiop.*, 2018; 32: 271-284.
111. Singh Vineet Kumar and Parle Amrita Synthesis, Characterization and Antioxidant Activity of 2-Aryl Benzimidazole Derivatives. *Asian Journal of Pharmaceutical Research and Development,* 2020; 8(2): 35-44.
112. Telvekar V.N., Bairwa V.K., Satardekar K. and Bellubi A. Novel 2-(-2(4-aryloxybenzylidene) hydrazinyl) benzothiazole derivatives as Anti-tubercular agents. *Bioorganic and Medicinal Chemistry Letters*, 2012; 22(1): 649-652.
113. Kale Sachin C., Kale M.K. and Biyani K.R. Synthesis of some new benzimidazole acetic acid derivatives and evaluation for their Antimicrobial and Anti-tubercular activities, *International Journal of Biomedical and Advance Research*, 2014; 04: 321-327.
114. Desai N.C.et al. Synthesis, Antibacterial and Anti-tubercular activities of benzimidazole bearing substituted 2- pyridone motifs. *European Journal of Medicinal Chemistry*, 2014; 82: 480-489.
115. Benzimidazoles and their use in the treatment of Tuberculosis: World Intellectual Property Organization. WIPO/PCT/WO2015/0577276 A1, 2015.
116. Keng Yoon Yeong , Chee Wei Ang. And Soo Choon Tan Antituberculosis agents bearing the 1,2-disubstituted benzimidazole scaffold. *Medicinal Chemistry research*, 2017; 26(1): 770-778.
117. Fan Y.L.,Jin X.H. and Huang Z.P. et al Recent advances of imidazole-containing derivatives as Anti-tubercular agents. *Eur. J. Med.Chem*., 2018; 150: 347-365.
118. Kale Sachin C. and Kale M.K, Synthesis and biological evaluation of benzimidazole derivatives as an Anti-tubercular and Antimicrobial agents, *International Journal of Biomedical and Advance Research*, 2018; 9(1): 37-44.
119. Mohanty Sujit kumar, Khuntia Anuradha, Yellasubbaiah N. Ayyanna C., Naga Sudha B. and Sai Harika M. Design, synthesis of novel azo derivatives of benzimidazole as potent antibacterial and Anti tubercular agents. *Beni-Suef University Journal of Basic and Applied Sciences*, 2018; 7: 646-651.
120. Li Y.F. ,Wang G.F., He P.L., Huang W.G. , Zhu F.H., Gao H.Y., Tang W., Luo Y., Feng C.L., Shi L.P., Ren Y.D., Lu W. and Zuo J.P. Synthesis and Anti-Hepatitis B Virus Activity of Novel Benzimidazole Derivatives *J. Med.Chem.*, 2006; 49(15): 4790-4794.
121. Luo Y., Yao J.P., Yang L., Feng C.L., Tang W. and Wang G.F. et al. Design and synthesis of novel benzimidazole derivatives as inhibitors of Hepatitis B Virus. *Bioorganic and Medicinal Chemistry*, 2010; 10: 5048-5055.
122. Vausselin T., Srron K., Lavie M., Mesalam A.A. and Lemasson M. et al. Identification of a new benzimidazole derivative as an Antiviral against Hepatitis C Virus. *Jour. of Virology*, 2016; 90: 8422-8434.
123. Fat –Moon Suk, Chao- Lien Liu ,Ming- Hua Hsu, Yu-Ting Chuang, Jack P. Wang and Yi-Jen Liao Treatment with a new Benzimidazole derivative bearing a pyrrolidine side chain overcomes sorafenib resistance in Hepatocellular Carcinoma.*Scientific Reports*, 2019; 9: 17259.
124. Brown H.D., Matzuk A.R., Ilves I.R., Peterson L.H., Harris S.A., Sarett L.H et al. Antiparasitic drugs. IV. 2-(4'- Thiazolyl)-benzimidazole, a new anthelmintic. *J Am Chem Soc.*, 1961; 83: 1764-1765.
125. DoCampo R. Sensitivity of parasites to free radical damage by Antiparasitic drugs. *Chem Biol Interact*, 1990; 73: 1-27.
126. Navarrete-Vazquez G., Yepez L., Hernandez-Campos A., Tapia A., Hernandez-Luis F. and Cedillo R. et.al. Synthesis and Antiparastic activity of Albendazole and Mebenazole analogues. *Bioogranic & Medicinal chemistry*, 2003; 11(21): 4615-22.
127. Farahat A.A., Ismail M.A., Kumar A., Wenzler T., Brun R. and Paul A. Indole and benzimidazole bichalcophenes: Synthesis, DNA binding and Antiparasitic activity. *European Journal of Medicinal Chemistry*, 2018; 143: 1590-1596.
128. Meta Leshabane, Godwin Akpeko Dziwornu, Dina Coertzen, Janette Reader, Phananko Moyo, Kelly Chibale and Lyn-Marie Birkholtz Benzimidazole derivatives are potent against Multiple Life Cycle Stages of *Plasmodium Falciparum Malaria Parasites.ACS Infectious Diseases*,

https://dx.doi.org/10.1021/acsinfecdis.0c00910, 2021.
129. Heinz B.A. and Vance L.M. The Antiviral compound Enviroxime targets the 3A coding region of rhinovirus and poliovirus. *J.Virol*, 1995; 69: 74189-74197.
130. Fonseca T., Gigaante B., Marques M.M., Gilchrist T.L., and Clercq E.D., Synthesis and Antiviral evaluation of benzimidazole *Bioorg Med Chem*, 2004; 12: 103-112.
131. Tewari A.K. and Mishra A. Synthesis and Antiviral activities of N-substituted -2 benzimidazole derivatives .*Ind. J. Chem.*, 2006; 5(B): 489-493.
132. Tonelli M., Simone M., Tasso B., Novelli F., Boido V. and Sparatore F. et al Antiviral activity of benzimidazole derivatives 2 antiviral activity of 2-phenylbenzimdazole derivatives. *Bioorganic and Medicinal Chemistry*, 2010; 18: 2937-2953.
133. Shaker Y.M., Omar M.A. and Mahmoud K.et al. Synthesis *in vitro* and *in vivo antitumor* and *antiviral* activity of noval 1-substituted benzimidazole derivatives. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 2015; 30(5): 826-845.
134. Gardiner J.M., Loyns C.R., Burke A., Khan A. and Mahmood N. Synthesis and HIV-1 Inhibition of novel Benzimidazole derivatives. *Bioorg. And Med. Chem. Lett.*, 1995; 5(12): 1251-1254.
135. Miller J.F., Turner E.M., Gudmundsson K.S., Jenkinson A.S., Thomsan M. and Wheelan P. Novel N-substituted benzimidazole $CXCR_4$ antagonists as potential Anti-HIV agents. *Bioorganic & Medicinal Chemistry Latter*, 2010; 20: 2125-2128.
136. Monforte A.M., Ferro S., Luca L.D., Surdo G.L., Morreale F. and Pannecouque C. et al. Design and synthesis of N1-aryl-benzimidazole 2-substitued as novel HIV-1 non nucleoside reverse transcriptase inhibitors. *Bioorganic and Medicinal Chemistry*, 2014; 22(4): 1459-1467.
137. Pan T., He X., Chen H., Geng G., Luo H., Zhang H. and Bai C. Development of Benzimidazole Derivatives to Inhibit HIV-1 replication Through Protecting APOBEC3G Protein.*Europeen Journal of Medocinal Chemistry*, 2015; 95: 500-513.
138. Yadav G., Ganguly S., Murugesan S. and Dev A. Synthesis, Anti-HIV, Antimicrobial Evaluation and Structure Activity Relationship Studies of some Novel Benzimidazole Derivatives. *Anti-Infective Agents*, 2015; 13(1): 65-77.
139. Sachs G., Collier R.H., Schoemaker R.L. and Hirschowitz B.I. The energy source of Gastric acid secretion. *Biochim Biophys Acta*, 1968; 162: 210–219.
140. Fellenius E., Berglindh T., Sachs G., Olbe L., Elander B. and Sjostrand S. Substituted benzimidazoles inhibit gastric acid secretion by blocking (H+/K+) ATPase. *Nature*, 1981; 290: 159-161.
141. Sachs G. and Wallmark B. The gastric H+, K+ - ATPase: The site of action of Omeprazole. *Scand J Gastroenterol*, 1989; 24 (sup166): 3-11.
142. Kromer W. Similarities and differences in the properties of substituted benzimidazoles: a comparison between Pantoprazole and related compounds. *Digestion*, 1995; 56: 443-454.
143. Olbe L., Carlsson E. and Lindberg P. A Proton - Pump Inhibitor Expedition The Case Histories of Omeprazole and Esomeprazole. *Nature Rev. Drug Discovery*, 2003; 2(2): 132–139.
144. Lindberg P., Carlsson E. Analogue-based drug discovery. In: Fischer J, Ganellin CR (eds) Esomeprazole in the framework of Proton-pump inhibitor development. *Wiley-VCH Verlag, Weinheim*, 2006; 81-113.
145. Senn-Bilfinger J. and Sturm E. Analogue-based drug discovery. In: Fischer J, Ganellin CR (eds) The development of a new Proton-pump inhibitor: The case history of Pantoprazole. *Wiley-VCH Verlag, Weinheim*, 2006; 115–136.
146. Patil Avinash, Ganguly Swastika and Surana Sanjay A Systemic review of benzimidazole derivayives as an Antiulcer agent .*Rasayan jour.of Chemistry*, 2010; 1(3): 447-460.
147. Mc Kellar Q.A. and Scott E.W. The benzimidazole Anthelminitic agents-A review . *Journal of Veterinary Pharmacology and Therapeutics*, 1990; (13): 223-247.
148. Townsendand L.B., Wise D.S. The synthesis and chemistry of certain Anthelmintic benzimidazoles. *Parasitol Today*, 1990; 6: 107–112.
149. Sreena K.et al. Synthesis and Anthelmintic Activity of Benzimidazole Derivatives.*HYGEIA*, 2009; 1(1): 9.
150. Longo M., Zanoncelli S., Colombo P.L., Harhay M.O., Scandale I., Mackenzie C., Geary T., Madrill N. and Mazue G. Effects of the benzimidazole , Anthelmintic Drug Flubendazole on Rat embryos in *Vitro*, *Reproductive Toxicology*, 2013; 36: 78-87.
151. Yadav Geeta and Ganguly Swastika Structure activity relationship (SAR) study of benzimidazole scaffold for different biological activities: a mini-review. *Eur J Med Chem*, 2015; 97: 419–443.
152. Rao Ch. M. M. Prasada, Lakshmi A. Jala, Grace Mani Y., Santhi Sudha B., Bhanu Rekha P., Satyaprakash Kumar and Dhachinamoorthi D. In vitro Anthelmintic activity of novel benzimidazole derivatives from o-phenylenediamine. *World Journal of Pharmaceutical and Medical Research*, 2018; 4(4): 245-248.
153. Sethi P., Bansal Y. and Bansal G. synthesis and PASS-assisted evaluation of coumarin-benzimidazole derivatives as potential Anti-inflammatory and Anthelmintic agents. *Medicinal Chemistry Research*, 2018; 27(1): 61-71.
154. Deshpande S.M. and Nam K. The Synthesis of Benzimidazole Derivatives as Potential Antihistaminic Compound. *Bulletin of the Chemical society of japan*, 1967; 40: 988-989.

155. Brimblecombe R.W., Duncan W.A., Durant G.J., Emmett J.C., Ganellin C.R. and Leslie G.B. Characterization and development of cimetidine as a Histamine H2-receptor antago- nist. *Gastroenterology*, 1978; 74: 339-347.
156. Prakash A., Lamb H.M. Mizolastine: a review of its use in Allergic rhinitis and chronic idiopathic urticaria. *BioDrugs*, 1998; 10: 41–63.
157. Nikano H. and Inoue T. Synthesis of Benzimidazole derivatives as Antiallergic (Histamines) agents with 5- lipoxygenase inhibiting action. *Chem. Pharm. Bull.*, 1999; 47(11): 1573.
158. Zhou Z., Vorperian V.R., Gong Q., Zhang S., January C.T. Block of HERG potassium channels by the Antihistamine Astemizole and its metabolites desmethyl Astemizole and nor Astemizole. *J Cardiovasc Electrophysiol*, 1999; 10: 836–843.
159. Bielory L., Lien K.W. and Bigelsen S. Efficacy and tolerability of newer Antihistamines in the treatment of allergic conjunctivitis. *Drugs*, 2005; 65: 215-228.
160. Wang X.J., Xi M.Y., Fu J.H., Zhang F.U., Cheny G.F., Yin D.L., and You Q.D. Synthesis, Biological evaluation and SAR studies of Benzimidazole derivatives as H,-Antihistamine agents, *Chin-chem.Lett.*, 2012; 23: 707-710.
161. Cakir B., Yildirim E., Ercanli T.,Erol K. and Sahin M.F. Synthesis and Anticonvulsant activity of some (2:4-substituted) benzaldehyde (2-oxobenzothiazolin-3-yl) acetohydrazone. *Farmaco*, 1999; 54: 842-845.
162. Jain P., Sharma P.K., Rajak H., Pawar R.S., Patil U.K. and Singour P.K. Design synthesis and biological evaluation of some novel benzimidazole derivatives for their potential Anticonvulasant activity, *Archives of Pharmacal Research*, 2010; 33(7): 971-980.
163. Salahuddin Shaharyar Mohammad , Mazumder A., Garg R. and Pandey Rishabh D. Synthesis, Characterization and pharmacological screening of novel benzimidazole derivatives, *Arabian Journal of Chemistry*, 2016; 9(1): S342-S347.
164. Vasil'ev P.M., Kalitin K.Y. and Spasov A. et al. Prediction and study of Anticonvulsant properties of benzimidazole derivatives. *Pharmaceutical Chemistry Journal*, 2017; 50(12): 775-780.
165. Winter C.A, Risely E.A. and Nuss G.W. Carrageenin-induced oedema in hind paw of rats as an assay for *Anti-Inflammetry* drugs. *Proceedings of the Society for Experimental Biolog. Med.*, 1962; 3(111): 544-547.
166. Evans D., Hicks T.A., Williamson W.R.N., Meacock S.C.R. and Kitchen E.A. Synthesis of a group of 1H-benzimidazoles and their screening for *Anti-Inflammatory* activity, *Eur. Jour.Med.Chem.*, 1996; 31: 635.
167. Thakurdesai Prasad A., Wadodkar S.G. and Chopade C.T. Synthesis and *Anti-Inflammatory* Activity of Some Benzimidazole -2-Carboxylic Acids, *Pharmacology Online*, 2007; 1: 314-329.
168. Tupe A.P.,et al. Synthesis Analgesic and *Anti-Inflammatory* activity of some 2- substituted 3-acetic acid benzimidazole derivatives, *RJPBCS*, 2013; April-June 4(2): 928.
169. Gaba M., Singh S. and Mohan C. Benzimidazole: an emerging scaffold for Analgesic and Anti-Inflammatory agents. *Eur J Med Chem*, 2014; 76: 494-505.
170. Gaba M., Gaba P., Uppal D., Dhingra N., Bahia M.S., Silakari O. and Mohan C. Benzimidazole derivatives: search for GI- friendly Anti-Inflammatory analgesic agents. *Acta Pharm Sinica B*, 2015; 5(4): 337-342.
171. Kohler P. and Bachmann R. International tubulin as possible target for the Chemotherapeutic action of Mebendazole in parasitic nematodes. *Mol. Biochem.Parasitol*, 1984; 325-336.
172. Fisher M.H. Chemistry of antinematodal agents. In: Campbell WC, Rew RS (eds) Chemotherapy of Parasitic diseases. *Plenum Press, New York.*, 1986; 239-266.
173. Thimmegowda N.R. Synthesis and biological evaluation of novel 1-(4-methoxyphenethyl)-1Hbenzimidazole-5-carboxylic acid derivatives and their precursors as Antileukemic agents. *Bioorg. Med. Chem*, 2009; 19: 4594-600.
174. Boiani M and Gonzalez M. Imidazole and benzimidazole derivatives as Chemotherapeutic agents. *Mini Reviews in Medicinal Chemistry*, 2005; (5): 409-424.
175. Refaat H.M. and Omar M.A. Synthesis and Anticancer activity of some novel 2-substituted Benzimidazole derivatives. *Eur. J. Med. Chem.*, 2010; 14(17): 6106-6119.; 45(7):2949-2956.
176. Tageja N. and Nagi J. Bendamustine: something old, something new. *Cancer Chemother Pharmacol*, 2010; 66: 413– 423.
177. Fei Fan and Zhou Z. New substituted benzimidazole derivatives: a patent review (2010–2012*). Expert Opin Ther Pat*, 2013; 23: 1157-1179.
178. Katarzyna B.S., Paulina O. and Elzbieta M.O. Biological approach of Anticancer activity of new Benzimidazole derivatives, *Pharmacol Rep.*, 2014; 66: 100-106.
179. Farmanzadeh D. and Najafi M. Benzimidazole derivatives as Anticancer drugs : A theoretical investigation. *J.Theor.Comput Chem.*, 2015; 14: 1550018.
180. Wang Miao, Han Xiaofeng and Zhou Zhiming New Substituted Benzimidazole Derivatives: A Patent Review (2013-2014). *Expert Opinion on Therapeutic Patents*, 2015; 5: 595-612.
181. Hasanpourghadi M., Karthikeyan C., Pandurangan A.K., Looi C.Y., Trivedi P., Kobayashi K., Tanaka K., Wong W.F. and Mustafa M.R. Targeting of tubulin polymerization and induction of mitotic blockage by Methyl 2-(5-Fluoro-2-hydroxyphenyl)-1H-benzo[d] imidazole-5-carboxylate(MBIC) in human cervical Cancer

HeLa cell. *Jour. of Exp. Clin. Cancer Res.,* 2016; 35: 58.

182. Karthikeyan C., Solomon Viswas Raja, Lee H. and Trivedi Piyush Synthesis and biological evaluation of 2-(phenyl)-3H-benzo[d] imidazole-5-carboxylic acids and its methyl esters as potent Anti-breast Cancer agents. *Arabian Journal of Chemistry*, 2017; 10: S1788-S1794.
183. Bistrovic A., Krstulovic L., Harej A., Grbcic P., Sedic M. and Kostrun S. et al. Design, synthesis and biological evaluation of novel benzimidazole amidines as potent multi-target inhibitors for the treatment of non-small Cell Lung Cancer. *European Journal of Medicinal Chemistry*, 2018; 143: 1616-1634.
184. Yadav Snehlata, Narasimhan B., Lim S.M., Ramasamy K., Vasudevan M., Shah S.A. and Mathur Abhishek Synthesis and evaluation of Antimicrobial, Antitubercular and Anticancer activities of benzimidazole derivatives. *Egyptian Journal of Basic and Applied science*, 2018; 5: 100-109.
185. Mostafa A.S., Gomaa R.M. and Elmorsy M.A. Design and synthesis of 2- Phenyl benzimidazole derivatives as VEGFR-2 inhibitors with Anti-breast Cancer activity. *Chemical Biology and Drug Design*, 2019; 93: 454-463.
186. Puranik Purushottamachen, Senthilmurugam Ramalingam and Vincent C.O. Njar Development of Benzimidazole Compounds for Cancer therapy. *Intech open access peer-reviewed chapter june*, 2019.
187. Nerella Sridhar Goud, Pardeep Kumar and Rose Dawn Bharath Recent developments of Target-Based Benzimidazole Derivatives as potential Anticancer Agents. *Intech open Chapter* January, 2020; 90758: 2-18.
188. Rashid Mohammad Design synthesis and ADMET prediction of bis-benzimidazole as Anticancer agent. *Bioorganic Chemistry ELSEVIER*, 2020; 96: 103576.
189. Ibrahim El-Sebaii, Omar A-Mohsen M.E., Khalil M.A. Novel Potential Anticancer (Antineoplastic) agents derived from Benzimidazole. *Journal of Pharmaceutical Sciences*, 1980; 69(11): 1348-1350.
190. Yadav Snehlata, Narasimhan Balasubramanian and Kaur Harmeet Prespectives of Benzimidazole Derivatives as Anticancer (Antineoplastic) Agents in the New Era. *Bentham Science*, 2016; 16(11): 1403-1425.
191. Goud Nerella Sridhar, Kumar Pardeep and Bharath Rose Dawn Recent Developments of Target-Based Banzimidazole Derivatives as Potential Anticancer (Antineoplastic) Agents *IntechOpen*, 2020; 1-19.
192. Wouters. W., Van Dun J., Dillen A., Coene M.C., Cools W. and De Coster R. Effects of Liarozole, a new Antitumoral compound, on retinoic acid-induced inhibition of cell growth and on retinoic acid metabolism in MCF-7 human breast cancer cell. *Cancer res.,* 1992; 52(10): 2841-2846.
193. Gravatt G.L., Baguley B.C., Wilson W.R. and Denny W.A. DNA-directed alkylating agents 6. Synthesis and Antitumor activity of DNA minor groove-targeted aniline mustard analogs of Pibenzimol Hoechst 33258 *Journal of Medicinal Chemistry*, 1994; 37(25): 4338-45.
194. Ramla M.M., Omar M.A., El-khamry A.M.M. and El-Diwani H. Synthesis and Antitumor activity of 1- substituted -2- methyl-5-nitrobenzimidazoles. *Bioorg. Med. Chem*, 2006; 14: 7324-7332.
195. Starcevic K., Kralj M., Ester K., Sabol I. and Grce M. et.al. Synthesis and Antitumor activity of 2-substituted -5- amidino-benzimidazoles. *Bioorg. Med. Chem*, 2007; 15: 4419-4426.
196. Omar M.A., Shaker Y.M., Galak S.A., Ali M.M., Kerwin S.M. and Li J. et al. Synthesis and docking studies of novel Antitumor benzimidazole. *Bioorganic and Medicinal Chemistry*, 2012; 20: 6989-6901.
197. Soni B., Ranawat M.S., Bhandari A. and Sharma R. Synthesis and in vitro Antitumor activity of benzimidazloe derivatives. *International Journal of drug Research and Technology*, 2012; 2(7): 479-485.
198. Wang X.J., Yang M.L., Zhang L.P., Yaot; ChenC., Mao L.G., Wang Y., and Wu J. Design of novel bis-benzimidazole derivatives as DNA, minor groove binding agents, *Chin.Chem.Lett*., 2014; 25(4): 589-592.
199. El-Gohary N.S. and Shaaban M.L. Synthesis and biological evaluation of a new series of benzimidazole derivatives as antimicrobial, antiquorum-sensing and Antitumor agents. *Eur. J.Med. Chem.*, 2017; 131: 255-262.
200. Blaszczak-Swiatkiewicz K., Olszewska P. and Mikiciuk-Olasik E. Antiproliferative of new Benzimidazole derivatives. *Acta Biochem.Pol.*, 2013; 60: 427-433.
201. Katarzyna Blaszczak-Swiatkiewicz,Paulina Olszewska and Elzbieta Mikiciuk-Olasik Antiproliferative Activity of New Benzimidazole Derivatives..*Acta biochimica Polonica*, 2013; 60(3): 427-433.
202. Mohamed A. Abdelgawad and Hany A. Omar Design, Synthesis and Biological Evaluation of some novel Benzothiazole/ Benzoxazole and /or Benzimidazole derivatives incorporating a Pyrazole Scaffold as Antiproliferative Agents.*Bioorganic Chemistry*, 2017; 74: 82-90.
203. Tahlan Sumit, Kumar Sanjiv, Kakkar Saloni and Narasimhan Balasubramanian Benzimidazole Scaffolds as Promising Antiproliferative agents: A Review.*BMC Chemistry*, 2019; 13(1): 66.
204. Serafin B., Borkowska G., Glowczyk J., Kowalska l. and Rump S. Potential Antihypertensive Benzimidazole Derivatives. *Pol. J. Pharmacol. Pharm.*, 1989; 41(1): 89-96.
205. Jat Rakesh K., Jat Jawahar Lal and Pathak D.P. Synthesis of Benzimidazole Derivatives : As Anti-

hypertensive Agents. *E-Jour. of Chem.*, 2006; 3(4): 278-285.
206. Reddy B.A. Synthesis and Characterization of Some Benzimidazole Derivative using as Antihypertensive Agents. *JPRNS*, 2010; 2(1): 103-113.
207. Sharma M.C. Synthesis and Antihypertensive activity of some new benzimidazole derivatives of 4'-(6-methoxy-2-substituted-benzimidazole-1-ylmethyl)-bipheny-l,2-carboxylic acid in the presence of $BF_3.OEt_2$, *Pelagia Res Library*, 2010; 1: 104-15.
208. Minra S., Okabe A., Matsuo Y., Karnik S.S. and Saku K. Unique binding behavior of the recently approved angiotensin receptor blocker Azilsartan compared with that of condensation. *Hypertens Res.*, 2013; 36: 134-139.
209. Danao Kishor R. and Mahapatra Debarshi Kar Recent Advances of Benzimidazole Derivatives as Anti-Hypertensive Agents. *Biochemistry, Biophysics and Molecular Chemistry*, 2020; 175-181.
210. Shingalapur R.V., Hosamani K.M., Keri R.S. and Hugar M.H. Derivatives of Benzimidazole Pharmacophore: Synthesis, Anticonvulsant, Antidiabetic and DNA Cleavage Studies. *Eur. J. Med. Chem*., 2010; 45(5): 1753-1759.
211. Hassan Y Aboul-Enein and Ahmed A EI Rashedy Benzimidazole Derivatives as Antidiabetic agents, *Medicinal Chemistry*, 2015; 5: 318-325.
212. World Health Organization. Global priority list of Antibiotic – resistant bacteria to guide research, discovery and development of new antibiotics. Geneva World Health Organization, 2017.
213. Srivastava S., Pandeya S.N., Yadav M.K. and Singh B.K. Synthesis and Analgesic activity of novel derivatives of 1,2-substituted benzimidazole, *Hindawi Publication Journal of Chemistry*, 2013; 1-6.
214. Tupe A. P., Pawar P. Y., Mane B.Y. and Magar S.D. Synthesis and Analgesic and Anti-Inflammatory Activity of Some 2- Substituted 3-Acetic Acid Benzimidazole Derivatives. *RJPBCS*, 2013; 4(2): 928.
215. Mariappan Gurusamy, Hazarika Rajib, Alam Furk, Karki Rashmi, Patangia U. and Nath Shyamalendu Synthesis and biological evaluation of 2-substituted Benzimidazole derivatives. *Arabian Journal of Chemistry*, 2015; 8(5): 715-719.
216. Eswayah A., Khalieln S. and Saad S. et al. Synthesis and Analgesic Activity Evaluation of Some New Benzimidazole Derivatives. *American Journal of Chemistry and Application*, 2017; 4(5): 30-35.
217. Mavrova Anelia Ts and Vutchev Dimitar I. Synthesis and Antitrichinellosis activity of some Bis-(Benzimidazole-2-yl)amines.*Bioorganic and Medicinal Chemistry*, 2007; 15(18): 6291-6297.
218. Anichina K., Mavrova A., Vuchev D., Kondeva-Burdina M. and Tzankova V. Synthesis and Anti-Trichinella Spiralis Activity in Vitro of some new 1H-Benzimidazoles.*World Science*, 2016; 2(6): 11-13.
219. Lubsen J., Just H., Hjalmarsson A., La Framboise D., Remme W., Heinrich-Nols J., Dumont J. and Seed P. Effect of Pimobendan on exercise capacity in patients with heart failure: main result from the Pimobendan in Congestive Heart Failure (PICO) trial. *Heart*, 1996; 76(3): 223-231.
220. Summerfield N. J., Boswood A., O'Grady M. R., Gordon S. G., Dukes-McEwan J., Oyama M.A., Smith S., Patteson M., French A. T. and Culshaw G.J. Effect of Pimobendan in the prevention of congestive heart failure or sudden death in Doberman Pinschers with Preclinical dilated Cardiomyopathy (The PROJECT Study). *J.Vet. Intern. Med.*, 2012; 26(6): 1337-1349.
221. Saberi Ali Short Review: Effects of Benzimidazole Derivatives on Digestive system and Cardiovascular system.*Journal of Pharmaceutical and Health Sciences*, 2012; 1(4): 99-107.
222. Al-Wasidi Asma S., Refat Moamen S., Naglah Ahmed M. and Elhenawy Ahmed A. Different Potential Biological Activities of Benzimidazole Derivatives. *Egypt, J. Chem.*, 2021; 64(5): 2631-2646.
223. Sinha Meetali In silico identification of a novel Compound against Urinary tract infections, 2016.
224. Roberta Ibba, Carta Antonia,Silvia Madeddu,Paola Caria,Gabriele Serreli, Sandra Piras,simona sestito, Roberta Loddo and Giuseppina Sanna Inhibition of Enterovirus A71 by a Novel 2-Phenyl-Benzimidazole Derivative. *Viruses*, 2021; 13(58): 1-19.
225. Juan Carlos Sanchez-Salgado, Pablo Bilbao-Ramos, Maria Auxiliadora Dea-Avuela, Francisco-Hernandez-Luis, Francisco Bolas-Fernandez, Jose L. Medina-Franco, Yareli Rojas-Aguirre systematic search for Benzimidazole compounds and derivatives with Antilesishmanial effects. *Molecular Diversity Cross Mark*,1-13.https: //www.researchgate.net/publication/325068235, 2018.
226. Tonelli M., Gabriele E., Piazza F., Basilico N. and Parapini S. Benzimidazole derivatives endowed with potent Antileishmanial activity. *J Enzyme Inhib Med Chem*, 2018; 33(1): 210-226.
227. Katiyar S. K., Gordon V.R., McLaughlin G. L. and Edlind T.D. Antiprotozoal Activities of Benzimidazoles and Correlations with β-Tubulin Sequence. *Antimicrob. Age and Chemotherap*, 1994; 38(9): 2086-2090.
228. Vezquez G.N., Vilchis M.D., Mulia L.Y., Melendez V. and Gerena L. Synthesis and Antiprotozoal activity of some 2-trifluoromethyl-1H benzimidazole bioisosteres. *European Journal of Medicinal Chemistry*, 2006; 41(1): 135-141.
229. Watkins D.A. Benzimidazole Pesticides. Analysis and Transformations, *Pesticide Science*, 1976; 7: 184-192.

230. Si W., Zhang T., Li Y., She D., Pan W., Gao Z., Ning J. and Mei X. Synthesis and biological activity of novel benzimidazole derivatives as potential antifungal agents. *J.Pestic Sci.*, 2016; 41(1): 15-19.
231. Bauer A.W., Kirby M.D.K., Sherries J.C. and Tuck M. Antibiotic susceptibility testing by standard single disc diffusion method, *J. Am. Clin. Pathol.*, 1966; 45: 493-496.
232. Barry A.L. "The antimicrobial susceptibility test: principle & practices", edited by Illus Leu and Febiger, Philadelphia, Pa. USA *Biol. Abstr*, 1976; 64: 25783. (1999) 4 th edition, ELBS :London,180.
233. Prescott L.M., Harley J.P. and Klein D.A. *Microbiology 6 th Ed. McGraw-Hill, Boston*, 2005; 992.
234. Ansari K.F. and Lal C. (2009a) Synthesis, physiocochemical properties and antimicrobial activity of some new benzimidazole derivatives, *European Journal of Medicinal Chemistry*, 44(10): 4028-4033 ; (2009b) Synthesis and evaluation of some new benzimidazole derivatives as potential antimicrobial agents. *Eur. J. Med. Chem.*,44(5): 2294-2299; Synthesis and Biological Activity of Some Heterocyclic Compounds Containing Benzimidazole and beta -lactam Moiety. *J.Chem. Sci.*, 2009c; 121(6): 1017-1025.
235. Ozkay Y., Tunai Y., Karaca H. and Isikday I. (2010) Antimicrobial activity and a SAR study of some novel benzimidazole derivatives bearing hydrazone moiety *Eur.J.Med. Chem.* 45: 3293-3298.; *Arch Pharm Res.*, 2011; 34(9): 1427-35.
236. Paneer Selvam T.P.P., Radhica, Janagraj S. and Siva Kumar A. Synthesis of noval 2-substituted benzimidazole derivatives as potential antimicrobial agents. *Research in Biotechnology*, 2011; 2(3): 50-57.
237. Rathee P.S., Dhankar R., Bhardwaj S., Gupta M. and Kumar R. Synthesis and antimicrobial studies of substituted 2-phenylbenzimidazole derivatives. *Journal of Applied Pharmaceutical Science*, 2011; 1(10): 14.
238. Kumari Pooja and Sharma Umakant Gyanendra Synthesis and Antibacterial activity of some newer Benzimidazole derivatives. *Research J. Pharm. and Tech.*, 2020; 13(6): 2597-2600.
239. Ahmed A. El-Sayed, Sherifa M. Abu- Bakr, Samira A. Swelam, Nahid Y. Khaireldin, Kamel R. Shoueir and Ahmed M. Khalil Applying Nanotechnology in the Synthesis of Benzimidazole Derivatives: A Pharmacological Approach. *BRIAC*, 2021; 12(1)L 2022:992-1005.
240. Stringer A., Wright M.A. The toxicity of Benomyl and some related 2-substituted benzimidazoles to the earthworm Lumbricus terrestris. *Pest Sci.*, 1976; 7: 459–464.
241. Wooley D. Some biological effects produced by Benzimidazole and their reversal by Purines. *Jour. Bio.Chem.*, 1944; 152-255.
242. Maxwell B. Antifungal activity of selected benzimidazole compounds. *Appl. Micro biolol*., 1971; 21: 944-945.
243. Patel Ojash and Arora Pankaj Newer Heterocyclic Molecules Act As Antifungal. *IJSRR*, 2019; 8(2): 3342-3347.
244. Saxena A., Hegde V., Mutalikdesai S. and Maste M. Versatility of Benzimidazole and its derivatives; An Insight. *International Journal of Pharmaceutical Sciences and Research*, 2020: 11(9): 4152-73.
245. Thuraya Al-Harthy, Abdullah M.Al-Sadi, Wajdi Zoghaib, Ebrahim Saeedian Moghadam, Raphael Stoll and Raid Abdel-Jalil Design, Synthesis and Bioactivity of Benzimidazole -2-Carbamates as Soil-Borne Anti-Fungal Agents. *MDPI Jour. Chemistry Proceedings*, 2020; 3(64): 1-7.