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# "Harnessing the power of Benzimidazole: Advances in synthesis

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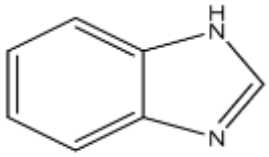
*Abstract :* Benzimidazole and its derivatives have attracted a lot of interest due to its ability to reduce inflammation. The research and use of drugs based on benzimidazoles that have anti-inflammatory properties have advanced recently, and this review covers such developments. It discusses their structural alterations, chemical production, and the methods by which they work. The article highlights the therapeutic potential of these compounds in treating inflammatory illnesses by combining current research findings. It also offers insights into prospects for optimizing the safety and efficacy of these compounds.

## I. INTRODUCTION

Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic in nature which consists of the fusion of benzene and imidazole. Nowadays is a moiety of choice which possesses many pharmacological properties. The most prominent benzimidazole compound in nature is N-ribosyl-dimethyl benzimidazole, which serves as an axial ligand for cobalt in vitamin B12.



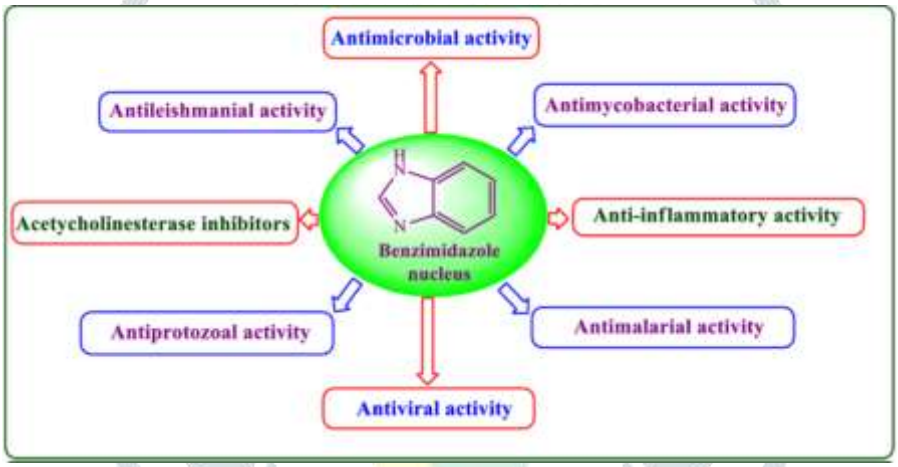

1*H*-benzo[*d*]imidazole

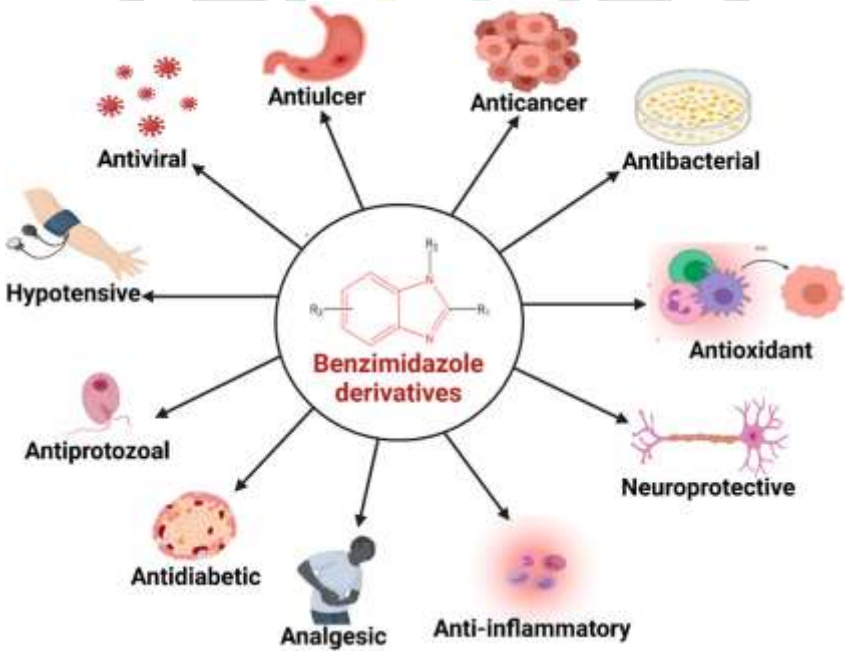
1H-benzimidazole

Study on Structural modifications and their pharmacological actions the use of Benzimidazole dates many years back2. In 1990 various benzimidazole derivatives were synthesized with substitution of fluorine, propylene, tetrahydroquinoline and cyclised compound which resulted in compounds with increased stability, bioavailability and significant biological activity3,4 It was also showed that substitution on pyridine by electron donating group increases activity. In 1991 benzimidazole derivatives were synthesized by derivatization at N-H of benzimidazole by electron donating group and substitution with long chain of propyl, acetamido, thio, thiazole-amino, tetramethyl piperidine on pyridine resulting in good antiulcer activity5,6.

Benzimidazole derivatives is used in different ways such as analgesic, anti-inflammatory, antibacterial antimicrobial, antifungal, antiviral, anti-helmenthic, anticonvulsant anticancer, antihypertensive, antiphrastic activity. Firstly, benzimidazole was synthesised by Hoebrecker in 1872, who obtained 2, 5(or 2, 6)-dimethylbenzimidazole by the using of 2-nitro-4- methylacetanilide 2.

Now a days is a moiety of choice which possesses many pharmacological properties. The most prominent benzimidazole compound in nature is N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B12. In 1990 various benzimidazole derivatives were synthesized with substitution of fluorine, propylene, tetrahydroquinoline and cyclised compound which resulted in compounds with increased stability, bioavailability and significant biological activity. In 1991 benzimidazole derivatives were synthesized by derivatization at N-H of benzimidazole by electron donating group and substitution with long chain of propyl, acetamido, thio, thiazole-amino, tetramethyl piperidine on pyridine resulting in good analgesic activity. Nowadays Infectious microbial diseases are causing problems world-wide, because of resistance to number of antimicrobial agents (β-lactam antibiotics, macrolides, quinolones, and vancomycin). A variety of clinically significant species of




microorganisms has become an important health problem globally. One way to fight with this challenge is the appropriate usage of the available marketed antibiotics the other is the development of novel anti- microbial agents. Hence, there will always be a vital need to discover new benzimidazole derivatives as a chemotherapeutic agent.

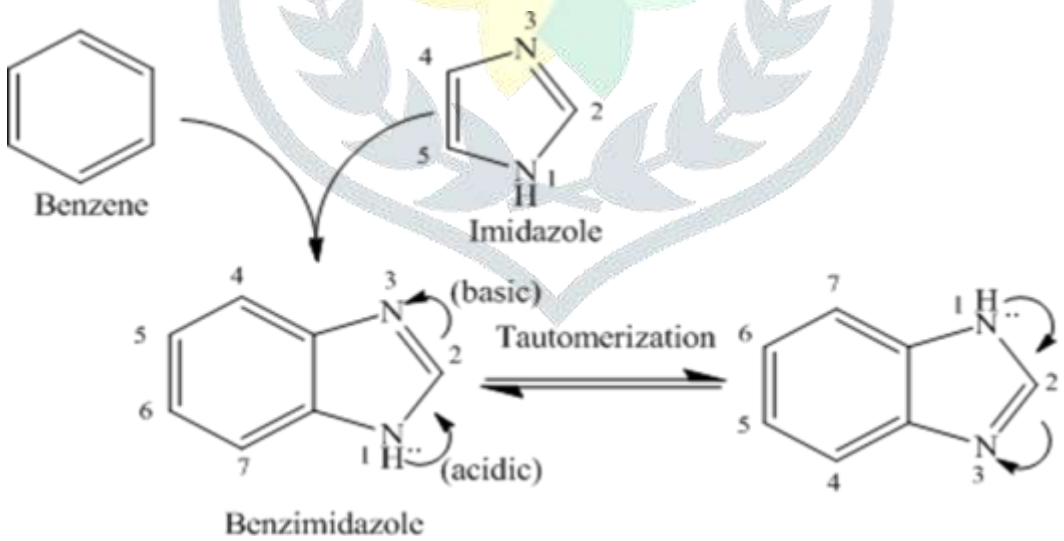
**CHEMISTRY OF BENZIMIDAZOLE**

The benzene nucleus and imidazole ring interact to produce the benzimidazole nucleus. A heterocyclic scaffold called benzoimidazole is formed when the imidazole molecules and benzene rings, respectively, merge at the fourth as well as the fifth positions. displays the numbering in the nuclei of imidazole and benzimidazole. Hobrecker (Wright) first published a reduction of 2-nitro-4-methylacetanilide in 1872 for the synthesis of benzimidazole. Ladenburg subsequently reported the same synthesis in 1875 utilising 3,4-diamino toluene in acetic acid. Dehydration is occurs all through the entire procedure, and this is when the term

"anhydrobase" evolved to be. Benzoglyoxaline and benzimidazole constituted the common nomenclature for these o-phenylenediamine (OPDA) analogues.

explains the tautomerism in benzimidazole; the isomerization is caused by the tautomerization of the H-atom linked in the scaffold's N1 atom. Methenyl-o-phenylenediamine and ethenyl-ophenylenediamine were the words applied for referring to benzimidazole and 2-methylbenzimidazole, respectfully. Aside from this, benzimidazole was formerly referred to as a derivative of groups that had an imidazole scaffold component. It initially appeared as benzimidazole, or o-phenylene formamidine. Historically, the compounds 2(3H)-benzimidazolone (4a) and 2 (3H)-benzimidazolethione had been identified as o-phenylenethiourea and ophenylurea, respectively. The first investigation paper on benzimidazole was published in 1943 by Goodman and Nancy Hart, who intended to inquire into the potential uses of the medication in drugs. In 1944, Woolley showed the antimicrobial agents effort 5,6-dimethylbenzimidazole was identified as a vitamin B12 breakdown product by Brink et al. in 1949. The additional compounds were found to possess the same properties as the form of vitamin B12 that Emerson et al. have investigated. After that time, a variety of synthetic techniques have been developed found to manufacture benzimidazole derivatives. As an example, Karl Folker and Norman G.B. generated 5,6-dimethyl benzimidazole, a degradation product.Benzimidazole shows an amphoteric characteristics due to the existence of the -NH molecule in the a molecule. Its ability to produce salt results in to both basic and acidic behaviour.

Once these characteristics of benzimidazole were investigated, it became clear that this heterocyclic scaffold had bioactivities and served as an antiviral, anticancer, and anti-inflammatory agent. In accordance Wang et al., benzimidazole may bind to receptors that are and enzymes in biology to generate the bonds of hydrogen, and it may also function as a ligand for ions of meta




**PHYSICAL PROPERTIES:**

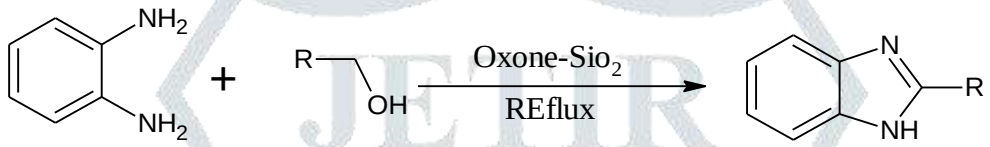
| Sr. No | Content | Properties |
|---|---|---|
| 1. | Amphoteric | Benzimidazole is amphoteric in nature |
| 2. | Molecular formula | $C_7H_6N_2$ |
| 3. | Molecular weight | 118.14 g/mol |
| 4. | Melting point | 170-172$^0$ C |

| | | |
|---|---|---|
| 5. | Activity (PKa) | 12.8(for benzimidazole) & 5.6 (for the conjugate acid) |

**CHEMICAL PROPERTIES:**

**i) Addition Reaction:**

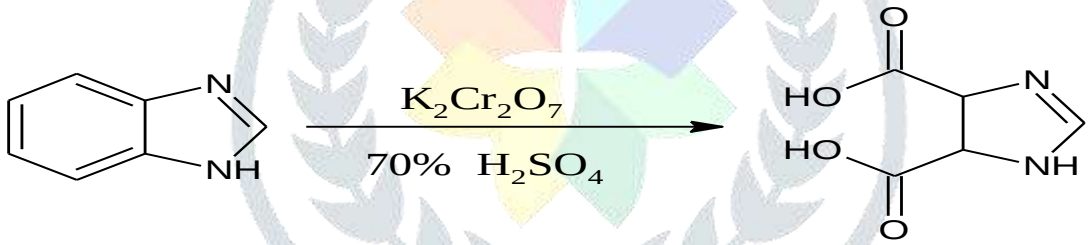
O-Phenylenediamine addition in the presence of ethanol and silicon oxidation to form a 2-methyl-1H-benzimidazole.




O-Phenylenediamine 2-methyl-1H-benzimidazole

**ii) Oxidation Reaction:**

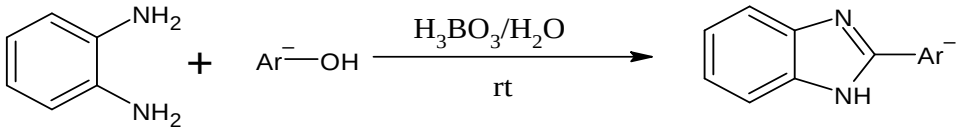
Benzimidazole oxidation in the presence of Potassium dichromate and 70% $H_2SO_4$ to form a 4, 5-dihydro-1H-imidazole -4, 5-dicarboxylic acid.




Benzimidazole 4, 5-dihydro-1H-imidazole – 4, 5-dicarboxylic acid.

**iii) Reduction Reaction:**

O-Phenylenediamine reduction in the presence of methanol and boric acid to form a 2-methyl-1H-benzimidazole.

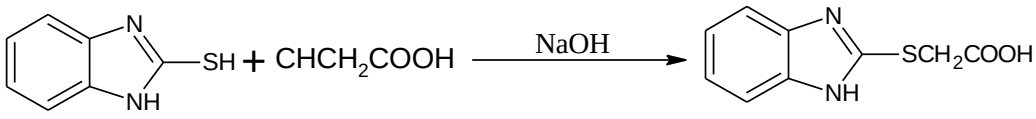



O-Phenylenediamine

2-methyl-1H-benzimidazole

**iv) Substitution Reaction:**

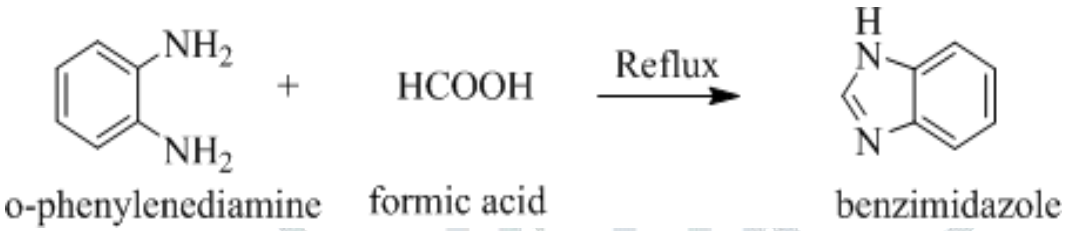
1H-benzimidazole-2-thiol substitution in the presence of carboxylic acid and NaOH to form a [(1H-benzimidazole-2-yl) sulfonyl] acetic acid.



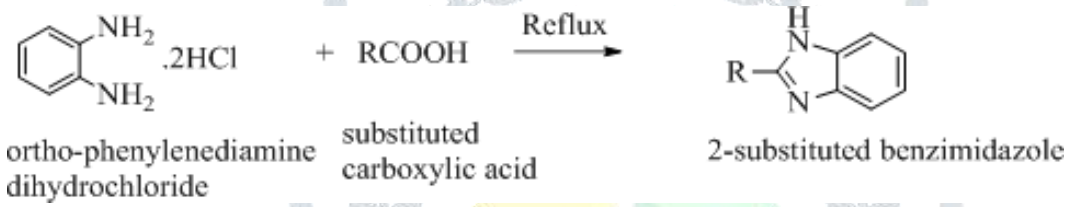

1H-benzimidazole-2-thiol [(1H-benzimidazole-2-yl) sulfonyl]

**v) Reaction with carboxylic acids:**

Expected preparation of benzimidazole analogues involves condensation of Ortho-phenylene diamine with formic acid under suitable heating conditions (100°C) endow 2-substituted benzimidazole derivatives in appropriate yield.

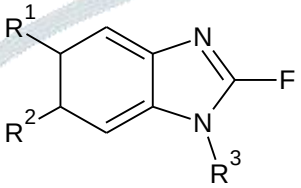



Reaction of O-phenylenediamines in the midst of affixed carboxylic acids (other than formic acid) only by adding hydrochloric or phosphoric acid yield 2-substituted benzimidazole.

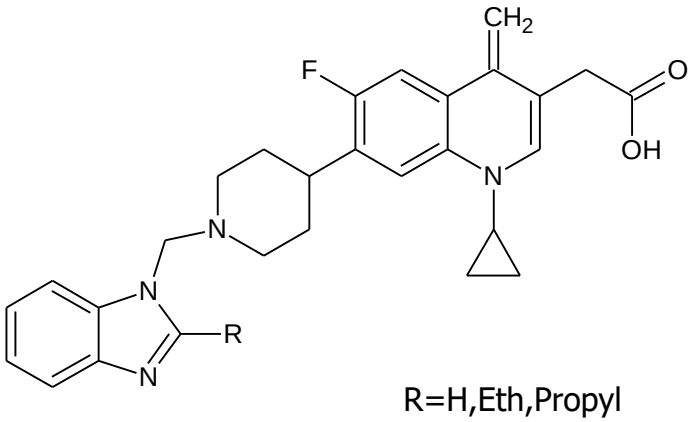



**SYNTHESIS AND BIOLOGICAL ACTIVITY OF BENZIMIDAZOLE:**

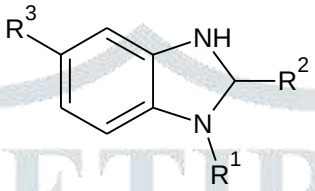
**Walia R,*et.al*** have reported Benzimidazole compounds that are N-substituted are created. A newly created compound's antibacterial activity was assessed. Employing two deception techniques, against Staphylococcus aureus, Bacillus subtilis, E-coil, pseudonymous as anginose (Gram Negative), Candida albicans, and Aspergillus Niger. It was discovered that the chemical 2-(Trifluoromethyl)-1Hbenzimidazole derivatives exhibited greater antibacterial activity than another compound.



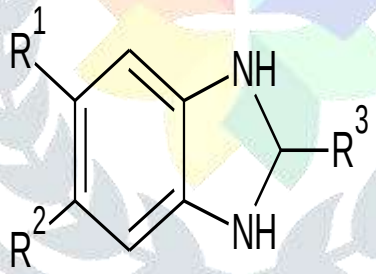

**HS. Lamba *et al*** have reported Benzimidazole compounds that are N-substituted are created. A newly created compound's antibacterial and antifungal properties were assessed. Compounds substituted with isoxazolyl were tested for their ability to inhibit the growth of bacteria, including Staphylococcus aureus and Escherichia coli, as well as Gram-positive organisms like Bacillus mycoides. A few benzoimidazole compounds with hydrazone moiety were examined to look into any potential antifungal and antibacterial properties. Microwave assisted methods have been used to report the majority of test compounds that were found to be significantly effective against gram-negative bacteria strains of Pseudomonas aeruginosa, Staphylococcus typhimurium, Klebsiella pneumonia, and Proteus vulgaris. These compounds were also substituted with fluroquinolones. It is stated that the chemicals that were produced are Ciprofloxacin derivatives.



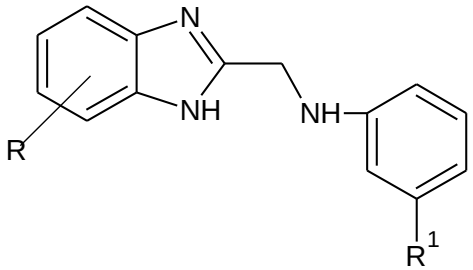
**Khalid Iqbal *et al*** have reported the creation of derivatives of benzoimidazoles that are N-substituted. A recently created compound's anticonvulsant potential was assessed.using two deception methods against Aspergillus Niger, Candida albicans, Bacillus subtilis, E-coil, pseudonomous as aenginosa (Gram Negative), and Staphylococcus aureus. It was discovered that the 1, 2, 5-trisubstituted benzimidazole derivative chemical had more anticonvulsant activity compared to the other compound. Benzimidazole derivatives: A number of 1, 2, 5-trisubstituted benzimidazole derivatives have been described, and some possible anticonvulsant drugs have been produced.




**Juan Valdez *et al*** have reported the creation of derivatives of benzimidazoles that are N-substituted. A recently created compound's antiparasitic properties were assessed.using two deception methods against Aspergillus Niger, Candida albicans, Bacillus subtilis, E-coil, pseudonomous as aenginosa (Gram Negative), and Staphylococcus aureus. It was discovered that the benzimidazoles derivative (2-methoxycarbonylamino derivatives) exhibited greater antiparasitic activity compared to other compounds. Creation and Antiparasitic Properties of 1H-Benzimidazole Compounds. These are Synthesized compounds 1 through 14 were evaluated in vitro against the helminth Trichinella spiralis, Entamoeba histolytica, and protozoa Giardia lamblia.




**Achar KC *et al*** have reported Benzimidazole compounds that are N-substituted are created. A newly manufactured compound's analgesic and anti-inflammatory properties were assessed. Using two deception methods against Aspergillus Niger, Candida albicans, Bacillus subtilis, E-coil, pseudonymous as anginose (Gram Negative), and Staphylococcus aureus. It was discovered that the chemical 2-methylaminobenzimidazole derivative exhibited greater analgesic and anti-inflammatory activity in comparison to other compounds. Newly synthesized benzimidazole derivatives' in vivo analgesic and anti-inflammatory properties.




**Anti-bacterial activity**

Using the well diffusion method, the antibacterial activity of the synthesized compounds was assessed against six different bacteria. Gentamycin was used as a reference medication to compare the outcomes.

Microbiology department, Kakatiya University Warangal, provided strains of Bacillus subtilis MTCC 441, Bacillus cereus ATCC 9372, the strain Staphylococcus aureus ATCC 96, E. coli ATCC 8739, Gram-negative bacteria MTCC 109, and Salmonella typhi ATCC 4420. Selective nutrition broth was used for growing the bacterial cultures at 37 C, and they were then preserved at 4 C for later use. There was nutrient broth used.

**Antiproliferative activity: -**

A new Schiff base derived from substituted aromatic aldehydes and 2-aminobenzimidazole has been described. NaBH4 reduced the compounds to generate 2-benzylaminobenzimidazoles, which cinnamoyl chloride then acylated to form 2-(obromobenzylamino)-1-cinnamoylbenzimidazole. The antiproliferative activity of the substances was assessed in vitro.

**Antibacterial and antifungal properties:**

In order to determine their effectiveness against Gram Positive and Gram-Negative species such as Bacillus mycoides and Staphylococcus aureus, isoxazolyl substituted compounds were evaluated against E. Coli and Proteus vulgaris. The potential antibacterial and antifungal activity of several benzo imidazole compounds with hydrazone moiety was investigated. Against gram-negative bacterial strains of Proteus vulgaris, Staphylococcus typhimurium, Klebsiella pneumoniae, and Pseudomonas aeruginosa, the majority of test

chemicals were found to be significantly effective. Benzimidazole compounds substituted with fluroquinolones have been reported using a microwave-assisted technique.

**Antitumor activity:**
It has been observed that a number of novel nitro benzimidazoles exhibit cytotoxic action against breast cancer. It was also discovered in the published research that compounds with similar properties to imidazole's, tetrazole, thiadiazol, and triazines also have an effect.

**Antioxidant activity:**
It has also been found that certain compounds with dihydrochlorides have antioxidant properties. These salts also exhibit minor antiaggregant properties against platelets and erythrocytes. By inhibiting 5-lipoxygenase, it was shown that combining a trimethyl group with benzimidazole also adds antioxidative properties.

**Antagonists of Androgen Receptors:**
There are also 5, 6 dichloride benzimidazole compounds that have been identified in a study. Non-steroidal antiandrogen Bicalutamide is a well-known antiandrogen used to treat androgen-dependent prostate cancer.

**Anticancer activity:**

1, 3-diarylpyrazinobenzimidazole derivatives have been synthesized and their anticancer properties have been studied. For this, 2-(2-aryl-2-oxoethyl)-2-aryloylbenzimidazoles were produced by reacting 2-aryloylbenzimidazole derivatives with 2-bromoacetophenones in acetone. The chemical was obtained by reacting the resultant substance with ammonium acetate in acetic acid. It was said that the microwave irradiation method was used to carry out the procedure mentioned earlier. The synthesis and assessment of 1-(4-methoxyphenethyl)-1H-benzimidazole-5- carboxylic acid derivatives is another strategy that has been investigated documented.1-(4-methoxyphenethyl)-2-(4-fluoro-3-nitrophenyl) is the substance that Maximum cell death was elicited in leukemic cells by -1H-benzimidazole-5-carboxylate, with an IC (50) value of 3 micro

.

**Anticonvulsant Substances:**

In addition to a number of 1, 2, 5-trisubstituted benzimidazoles derivatives, other possible anticonvulsant compounds have also been produced. The anti-convulsant activity of the synthesized compounds is attributed to the optimal chain length at position two (the value of R2), rather than the linker at position one (R1), according to the findings of the QSAR inquiry and the analysis of several physical-chemical parameters. Additionally, the results demonstrated that, in line with QSAR investigations, synthetic compounds with electron-withdrawing groups, like nitro at position five (R3), have been reported to exhibit superior anti-convulsant efficacy.

## MATERIAL AND METHOD

All reagent and solvent were purchased AR grade from Bansal sales corporation and Morden science apparatus Nasik. Solvents were dried by standard procedures. The purity of compound was checked by TLC using precoated Silica Gel G plates. Melting point were determined in capillary tubes on Remi apparatus and were presented uncorrected. Infrared (IR) Spectra were recorded using FTIR Spectrophotometer Model: IR affinity1-S.

Nuclear magnetic resonance spectra were recorded on Bruker Ultra Shield Model DPX 500MHz spectrometer in $CDCl_3$ Solvent and TMS as internal standard. In silico modelling of the molecule was performed using Chem Draw were used for drawing, 2D molecule and calculating various physiochemical properties of the proposed molecules. The Molecular docking was carried out using by Vlife MDS 4.6 Software.

**Synthesis of 2-(2-amino phenyl) -1H-Benzimidazole**

Synthesis of Ortho phenylene diamine Dihydrochloride Salt

Ortho Phenylene Diamine(0.024mol) was dissolved in conc HCl to it stannous Chloride (0.024 mol) was added the reaction mixture was warmed & filtered allowed to cool in ice bath. Crystals of Dihydrochloride were collected and dried. M.P 130º C % Yield 56%.

**Synthesis of 2-(2-Chloro phenyl) -1H-Benzimidazole**

O-Phenylene diamine dihydrochloride (0.024mol), 3-Chloropropionic acid (0.024mol) and5N HCl Hydrochloric acid were placed in an RBF and refluxed Fig.1. The reaction was monitored by TLC. After Completion of the reaction the reaction mixture was poured in ice cold water. It was then basified. The solid precipitated was obtained which was filtered and dried. M.P 98º C %Yield 57.22%.

**Synthesis of N-(2-(1H-benzimidazole-2-yl)phenyl)-2-chloroaniline (UB1)**

2-(2-chloro phenyl)-1H-Benzimidazole (0.005mol) o-Chloro aniline (0.005mol) were Separately dissolved in dioxone and placed in RBF, trimethylamine (0.005mol) was added to it and the reaction mixture was refluxed. The reaction was monitored by TLC. After completion of the reaction reaction mixture was dumped in ice cold water. Obtained oily liquid then converted to HCl salt. Other derivatives were prepared using substituted anilines with same procedure.[5]

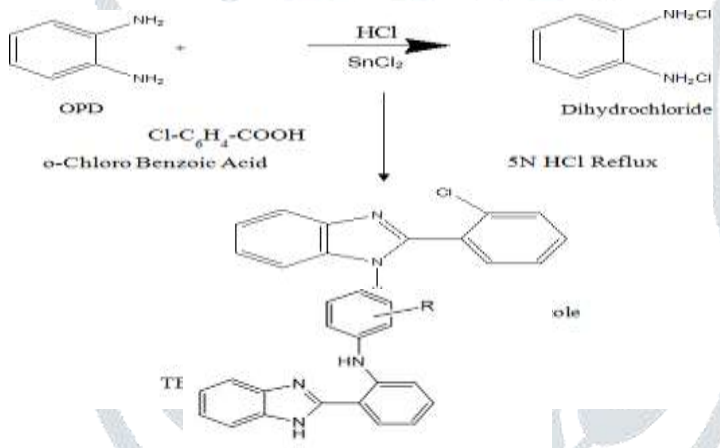


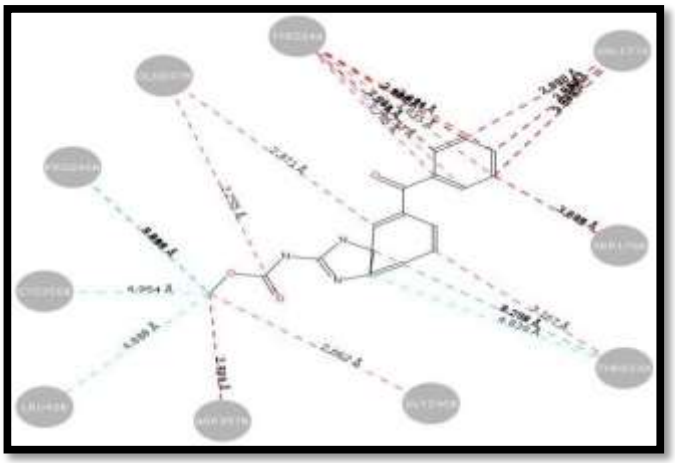

**Figure: Scheme for the synthesis route**

R= o,m,p-Cl/H/$CH_3$/OH (UB1-UB7)

**MOLECULAR DOCKING**

Receptor βTubulin is anticancer and anthelmintic drug target, investigation of β tubulin inhibitors may lead to the development of anthelmintic drug, Inhibitors bind selectively of β Tubulin of nematodes, cestodes and fluke, a protein unit of microtubule and thereby disrupting microtubule structure and function. The receptor β Tubulin (TUBULIN- COLCHICINE: STATHMIN-LIKE DOMAIN COMPLEX) (pdb code 1Sa0) was

downloaded from RCBS pdb site and water molecules were removed from the protein. Receptor was loaded for docking in Biopredicta module of the software, virtual library of compound was prepared the Structure were drawn in **2D** in Vlife Engine Module of Software and converted to **3D.** Then binding of compounds with the receptor was studied as shown in Fig 2 to 9 & score was noted and Compounds with lowest Score were studied for 2D & 3D interaction (hydrogen bonding, hydrophobic bonding & Vander wall forces, pi Stacking).



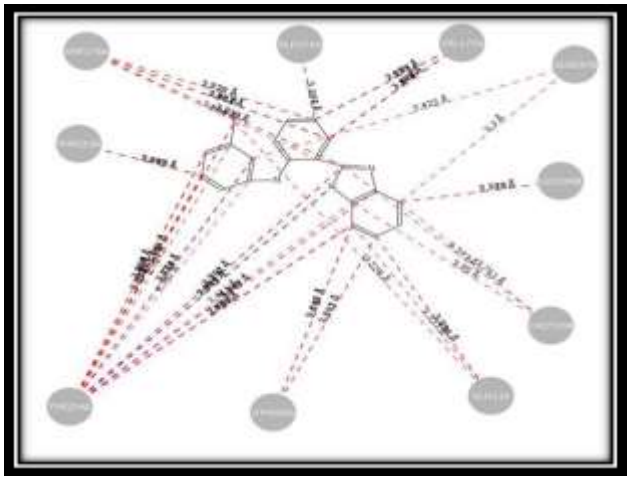


FIG. NO. 2 2D INTERACTION OF MEBENDAZOLE WITH RECEPTOR.

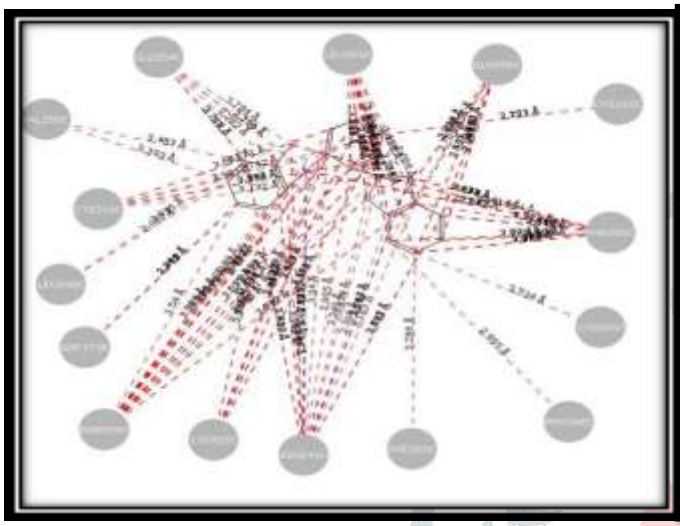


FIG. NO: 3 2D INTERACTION OF UB1 WITH RECEPTOR.

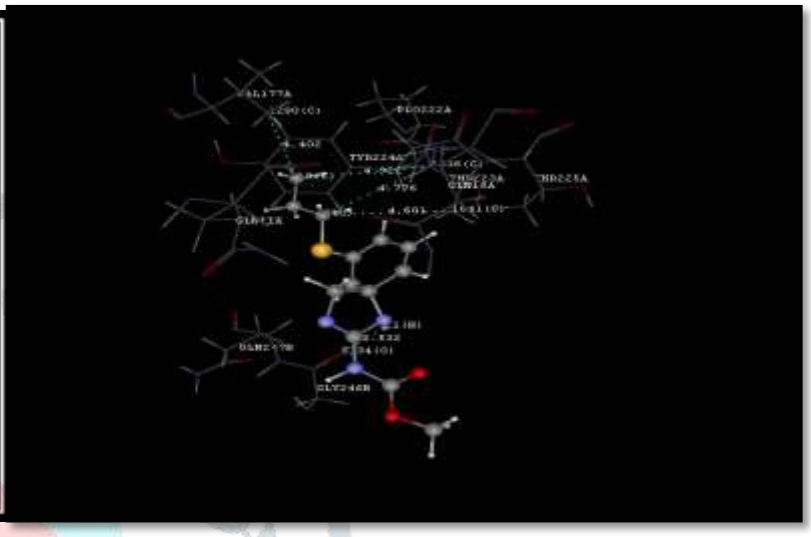


FIG. NO. 4: 2D INTERACTION OF UB2 WITH RECEPTOR.

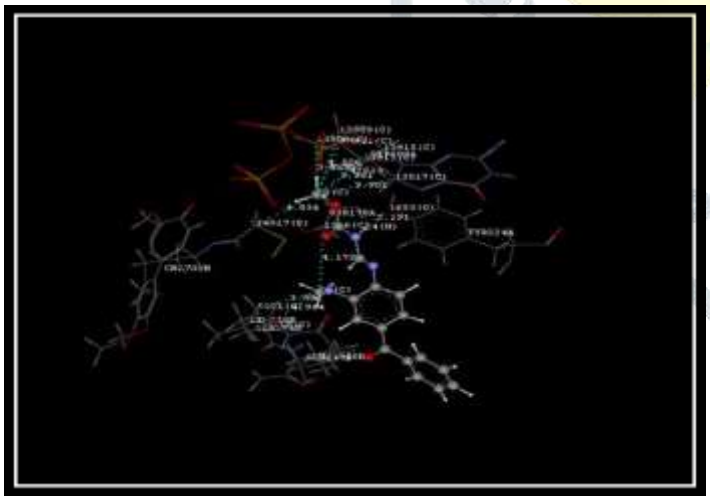


FIG. NO:6 3D INTERACTION OF MEBENDAZOLE WITH RECEPTOR.

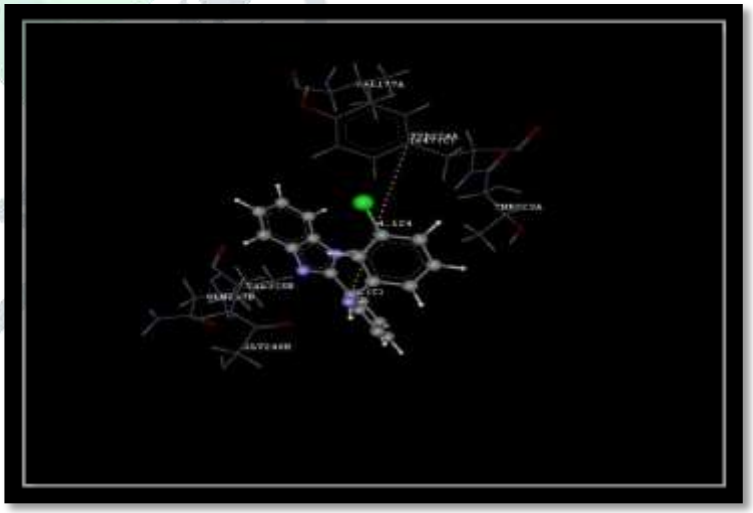


**Figure No. 7: 3D Interaction of UB1 with receptor**

Figure No. 8: 3D Interaction of UB2 with receptor.

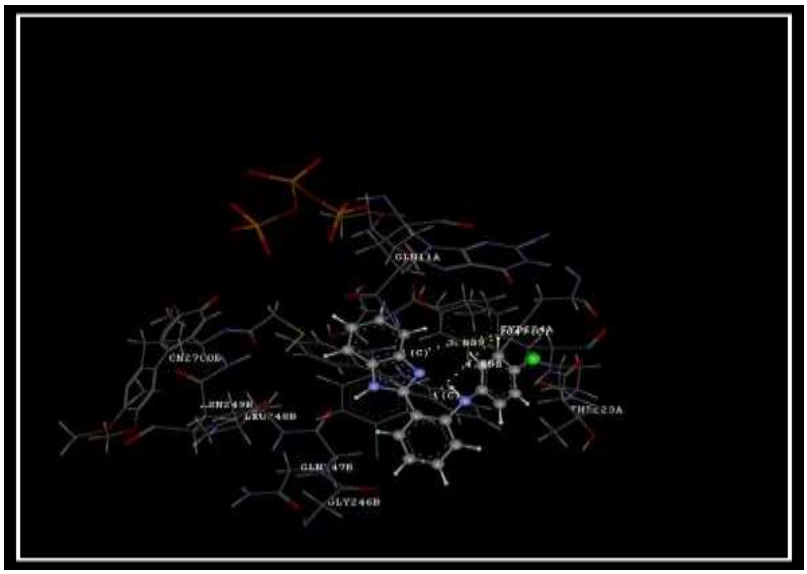


**Figure No: 9 3D Interaction of UB3 with receptor**

## APPLICATIONS

Benzimidazole was found to be an intriguing hetero scaffold having biological activity since these properties were examined. It provides a number of objectives as an antiviral in nature, anticancer, antibacterial, anti-inflammatory, antiparasitic, analgesic, antifungal, anticoagulant, and antiulcer drug. gives a modelled representation of the numerous applications for benzimidazole. The initial legally available benzimidazole-based attitudes are a fungicide and antiparasitic drug. In the past few decades, many molecules constructed from benzimidazoles have been identified. The biological purposes of a few of them are explained. In view of the above, the main objective of investigation for investigators as well as those that synthesized organic materials is the manufacture of medicinal products as such

## CONCLUSION

The benzimidazole ring is an important pharmacophore in modern drug discovery. Attention has been increasingly given to the synthesis of benzimidazole derivatives as a source of new antimicrobial agents. The Benzimidazole derivatives are a resource for medicinal research. The knowledge gained by various researches has suggested that substituted benzimidazoles and heterocycles, which are the structural isosteres of nucleotides allow them to interact easily with the biopolymers, possess pharmacological activity with lower toxicities. Since now, researchers have been attracted toward designing more potent Benzimidazole derivatives having wide diverse of biological activity.

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