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BENZIMIDAZOLE : A Superfluity of Biological Load

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ABSTRACT :

All the heterocyclic compounds are of wide interest in pharmaceutical chemistry. The uses of heterocyclic compounds increased day by day in the field of medicinal chemistry. Benzimidazole is a formed by Fusion of benzene and imidazole. Benzimidazole consist of two nitrogen as heteroatom. Benzimidazole derivatives have wide variety of biological activity such as anti-microbial, anti-viral, anti-allergic property,anti-ulcer property,anti-inflammatory activity , anti- oxidant property, diuretic activity, anti-convulsant agent, anti-coagulant property. This article summarize the benzimidazole synthesis, physical properties and chemical properties for developement of newer synthetic method. This review is concerned with benzimidazole derivatives along with its biological importance.

KEYWORDS : Benzimidazole , Structural Activity Relationship (SAR) , Spectral properties, Pharmacological Activity , Chemistry

INTRODUCTION :

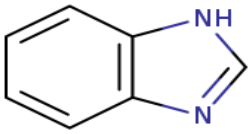
The Heterocyclic compounds are crucial for life and widely distributed in nature. A notable role has been played by heterocyclic compounds in the metabolism of all living Cells. Basically benzimidazole has an wide importance not only biologically but also industrially. Benzimidazole molecule plays an important role in medicinal chemistry as it is bioactive. Benzimidazole become a part of discovery and developement of new drug moiety with potential biological activity.

First benzimidazole derivative was synthesized by Habrecker in 1872. In 1944 ,Woolley reported the antibacterial activity of some benzimidazole derivatives. The degraded product 5,6-dimethyl benzimidazole from the acid hydrolysis of vitamin B-12 reported by Norman GB and Karl falker in 1949. The diverse therapeutic application of Substituted benzimidazole derivatives are anti-microbial, antibacterial effect, antiprotozoal activity, HIV inhibitors, anti-allergic activity, antiviral effect, anti-hypertensive agent, cardiotonic activity ,antiulcer activity, anti-inflammatory activity , analgesic activity, antioxidant activity, diuretic activity, anti-convulsant agent, DNA binding properties, anti-coagulant property.

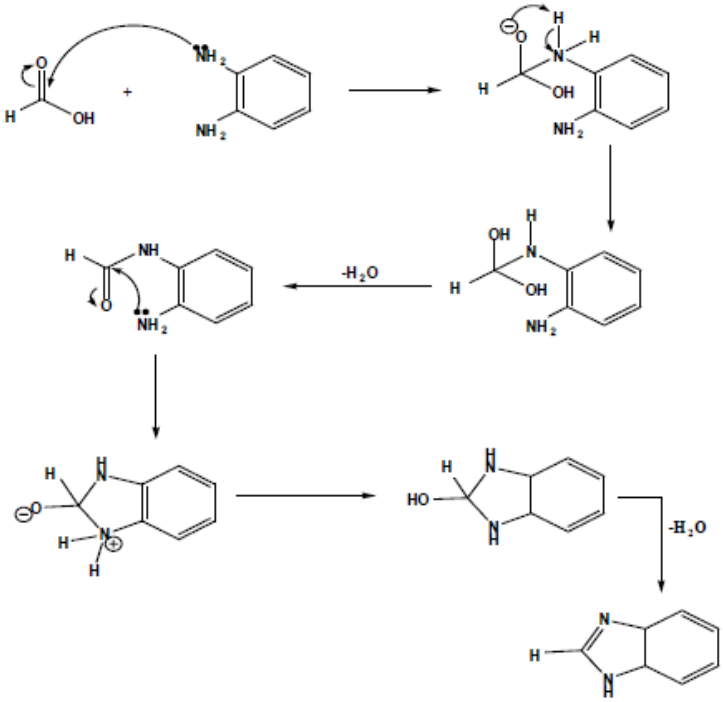
CHEMISTRY OF BENZIMIDAZOLE :

- Benzimidazole consist of fused aromatic imidazole ring system. where a benzene ring is fused to the 4 ,5 positions of an imidazole ring .
- Benzimidazole is called as azindole, 1-H-benzimidazole, O-benzimidazole benzoglyoxaline, 1,3-diazaindene.
- Benzimidazole possess both acidic & basic property.
- The NH group present in benzimidazole is strongly acidic and also weakly basic.
- Benzimidazole have capacity to form salts.

● Benzimidazole with unsubstituted NH groups exhibit fast prototropic tautomerism which leads to equilibrium mixture of assymmetrically Substituted compounds.



Mechanical of benzimidazole ring formation :



Physical Properties Of Benzimidazole :

1) The melting point of benzimidazole is decreased due to insertion of substituent into 1position

2) The solubility of non-polar solvent can be increased by adding other non-polar substituents (H_2, N_2, Cl_2) at different position of benzimidazole .

3) Benzimidazole with imide generally soluble in polar solvent.

4) The introduction of polar group into molecule, increases the solubility in polar solvents.

5) Benzimidazole is soluble in dilute acids due to their weak basic nature.

6) Benzimidazale distilles over 300 °C.

Spectral Properties Of Benzimidazole :

1) **Mass Spectroscopy :**

The spectrum of benzimidazole indicates a Sequential loss of 2 molecules of hydrogen cyanide (HCN) from molecular ion, the first of which is nonspecific as Shown by deuterium labelling procedure.

Ex. 2-benzoyl benzimidazole are characterized by loss of carbon monoxide from molecular ion .

2) **Infra Red (IR) Spectroscopy :**

The absorption spectra of benzimidazole is near the 2850 A° indicates the presence of Aryl ring. The absorption near 3107 A° indicates the presence of C-N stretch the 1690 A°.

3) **Nudear Magnetic Resonance (NMR) Spectroscopy :**

The protonation parameter derived from simple, five and six membered heterocyclic compound can be used to detect chemical shift changes, resulting from nitrogen protonation & deprotonation in more complex molecules. The 7.9 Values shows multiplet indicates the of benzimidazole aryl ring.

4) **13 Carbon NMR:**

Benzimidazoles the range starts from 115 -144 .The overlapping is confirmed by triplet, doublet peaks obtained.

Different targets of benzimidazole :

1. Topoisomerase - | inhibitors
2. Topoisomerase - || inhibitors
3. Androgen Receptor Antagonist
4. PARP (Poly ADP Ribose Polymerase) inhibitor
5. Protein Tyrosine Kinase Inhibitor
6. Dihydro Folate Reductase (DHFR) inhibitor
7. Protein Tyrosine Phosphate inhibitor
8. Microtubule inhibitor
9. B - Glcoronidase inhibitor

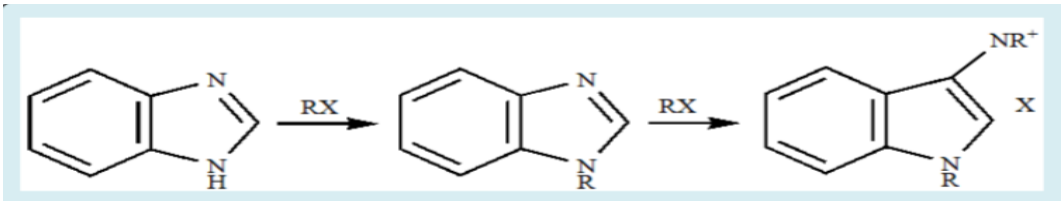
Chemical Properties Of Benzimidazole :

1) Benzimidazole Nucleus Reaction :

The benzimidazole ring has high degree of chemical stability. The concentrated sulfuric acid, alkalis as well as hot hydrochloric acid does not affect on the benzimidazole stability. During the oxidation reaction, benzene ring of benzimidazole is breaks. Due to reduction reaction, benzimidazole ring is resistant to reduction.

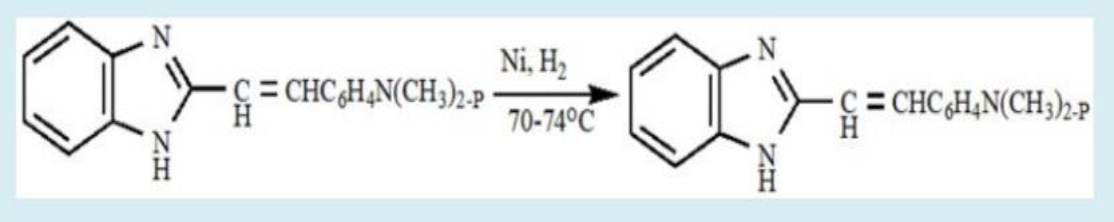
A) Alkylation Reaction :

The benzimidazole reacts with alkyl halides to form 1-alkyl benzimidazole. under more efficient condition, 1,3- dialkyl benzimidazolium halides.Benzimidazoles also react with Grignard reagent, acylating agent and metal.



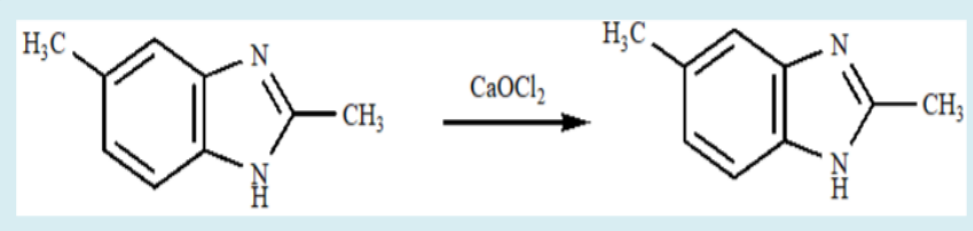
B) Hydrogenation Reaction :

In the presence of nickel catalyst , 2-(P- dimethyl aminostyryl benzimidazole) undergoes hydrogenation reaction to form 2- phenyl benzimidazole at atmospheric pressure .



C) Halogenation Reaction :

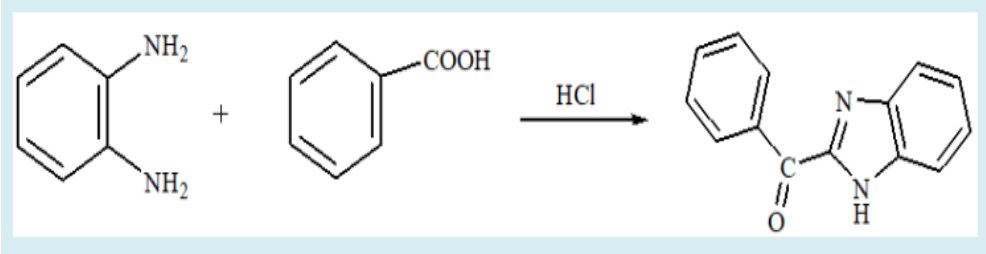
The 2.6 dimethyl benzimidazole treated with Saturation Solution of bleaching powder at 0-5 °C to form 1-chloro 2,6-dimethylbenzimidazole.



2) Synthesis process of benzimidazole :

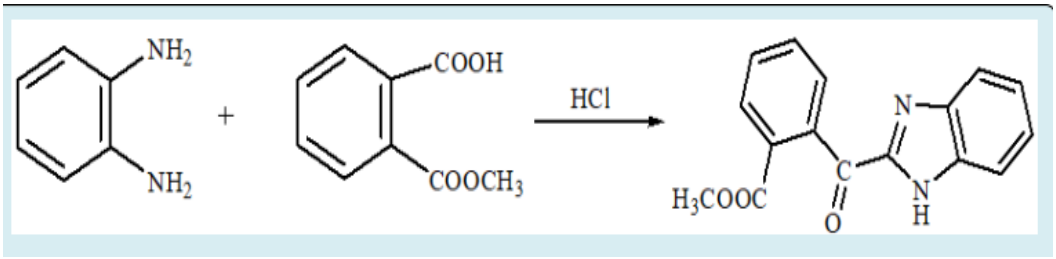
A) Reaction of OPDA with Benzoic acid :

The benzimidazole was prepared by O-phenylene diamine and benzoic acid in the presence of hydrochloric acid (4N). The percentage yield of was found to be 83%.



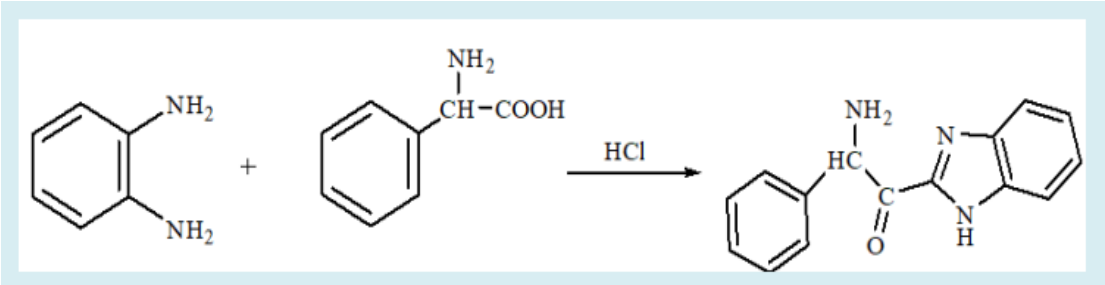
B) Reaction of OPDA with Acetyl salicylic acid :

The benzimidazole was prepared by o-phenylenediamine and Acetyl Salicylic Acid in the presence of hydrochloric acid (4N). The percentage gield was found to be 81.4 % .



C) Reaction of OPDA with phenyl glycine :

The Benzimidazole was prepared by o-phenylene diamine react with phenyl glycine in the presence of 4 N was Hcl.The percentage yield of the compound to be 82%.



SAR Of Benzimidazole :

1. The introduction of coumarin and aryl nitro group at 2 position, 5 position and 6 position shows anti-viral activity.

2. The introduction of methyl group at 2 position, Nitro, amino, halo group at 5,6 position shows anti-microbial property.

3. The introduction of mercapto, alkyl group at 2 position, Halo group at 5,6 position and oxadiazole group at 3 position shows anti-convulsant activity.

4. introduction of Carbamate, ethyl acetate group 2 position, Alkyl group at 3 position & at chloro, methoxy group at 5,6 position shows anti-parasitic activity.

5. The introduction of pyridine group at 2 position, methyl group at 3 or 5,6 position shows Anti-diabetic activity.

6. The introduction of alkyl, aryl group at 2 position, methoxy, amino, chloro group at 5,6 position shows anti-hypertensive activity.

7. The introduction of methyl amino, alkyl, aryl, mercapto group group at 2 position, sulphonyl group at 3 position and Halo, Nitro, amino group 5,6 position shows anti-inflammatory activity.

Pharmacological Activities Of Benzimidazole :

Drugs from different class that they are intended to inhibit the growth or kill the infected microorganism. The systemic infections can be treated with specific drugs

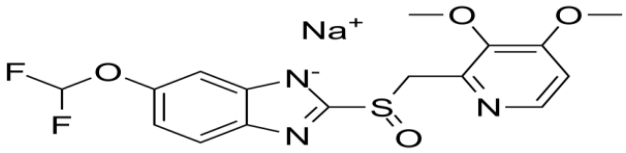
which Selectively suppress the infecting microorganism. without affecting the host.

- **Anti - Ulcer Agent :**

The sore that developes on the lining of the stomach, oesophagus or small intestine.The causative agent of ulcer is the Helicobacter pylori bacteria. Ulcer occurs when the gastric acid damages the lining of digestive tract.

Anti- ulcer agent acts by inhibition or suppression of gastric acid production, protection of gastrointestinal mucosa from acid injury or neutralization of Acid.

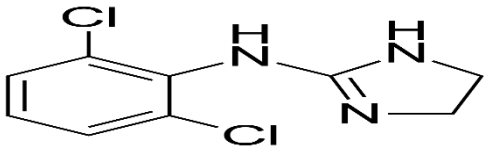
ex. Pantoprazole.



2. Anti - hypertensive agent :

The condition in which the force of blood against the artery wall is increased. The rise in blood pressure usually above 140/90 mm of Hg. Now a days, due to change in life style, tension and stress. hypertension become more common in our society. The class of drugs that are used for prevention or treatment of hypertension is called anti- hypertensive agent.

ex . Clonidine



3. Anti - fungal agent :

Fungal infection is caused by fungus that can invade the epithelial tissue. Fungi are heterotrophic in nature, they obtain mutrients from the environment. Anti- fungal agent are the drugs which inhibit the Spreading of fungus either by killing fungal cells or by preventing fungal growth. The agent which kill fungi are called fungicidal. The agent which only inhibit growth of fungi are called fungistatic.

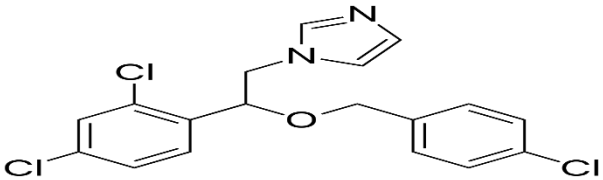
Antifungal agent acts by following mechanism:

i) Inhibition of cell wall synthesis

ii) cell membrane Disruption.

iii) inhibition of cell division.

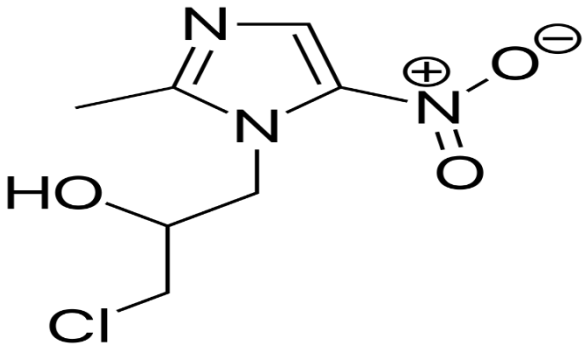
ex. Econazole



4. Anti - protozoal agent :

Protozoa are the microorganism which belongs to kingdom protozoa which include organisms like E. histolytica, plasmodium. Anti-protozoal agents are the drugs which are used in the treatment of protozoan infection Such as Malaria, Amoebiasis, Giardiasis. The amoebiasis is caused by Entamoeba histolytica.

ex . Ornidazole

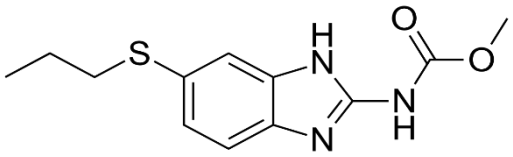


5. Anti - helminthic agent :

Helminths are worm like parasite which live on living host to get nourishment and protection. Helminths Causes wide spectrum of disease. Infection can Cause physical, Cognitive and nutritional disability in young and children.

Anti-helminthics are a group of anti-parasitic drugs that kills the parasite without causing damage to the host.They are also Called Vermicides or vermifuges.

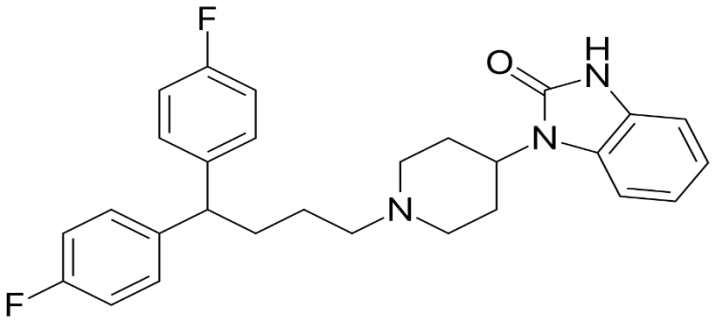
ex . Albendazole



6. Anti - psychotic agent :

A psychotropic drugs that inhibits or alters mood, behavioural and emotional response. It can be divided into psychoses and neuroses. The anti-psychotic agent are also called as neuroleptics. Antipsychotic agent that have ability to dignify the aggressive behaviour, emotional and impulsive behaviour.

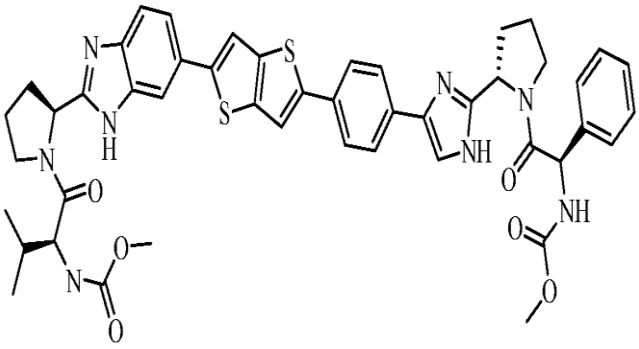
ex . Pimozide



7. Anti - viral agent :

viruses are the obligate parasite which have ability to multiplication only inside are specific cells. Virus Contains either RNA or DNA as a genetic material. To produce infection virus enter a cell and replicate its nucleic acid and attached to cell surface. Anti-viral drugs are used to treat and prevent viral infection. Anti-viral drugs do not destroy target pathogen rather than they inhibit their developement.

ex. Samatasvir



Conclusion :

The majority of procedure and evaluation for pharmacological activity have been noted in Various literatures of benzimidazole and it's derivatives. Based above literature Survey, it is satisfied that substituted benzimidazole is a important pharmacophore for pharmacological activity in modern drug discovery. Benzimidazole is a heterocyclic compound made up of imidazole and phenyl ring. It is observed that functional group present plays important role. In this review, we summarize synthesis of different derivative of benzimidazole and along with their biological

activity. The therapeutic drugs which Consist of benzimidazale nucleus are used in building drugs that assist to be an active area of research. This article become a source for all researchers concerned in benzimidazole - based heterocyclic medicinal chemistry .

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