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A SHORT REVIEW ON CHEMISTRY AND POTENTIAL ACTIVITIES OF BENZIMIDAZOLE MOLECULE

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Abstract:

Benzimidazole derivatives play important role in medical field with so many Pharmacological activities such as antimicrobial, antiviral, anti-psychotic, antidiabetic and anticancer activity. The potency of these clinically useful drugs in treatment of microbial infections and other activities encouraged the development of some more potent and significant compounds. Benzimidazoles are remarkably effective compounds, extensive biochemical and pharmacological studies have confirmed that these molecules are effective against various strains of microorganisms. This review is summarized to know about the chemistry of different derivatives of substituted benzimidazoles along with their pharmacological activities.

Keywords: Benzimidazole, antimicrobial, antiviral, anti-psychotic, antidiabetic and anticancer activity.

Introduction:

All the heterocyclic compounds have a great interest in pharmaceutical chemistry. Out of these heterocyclic compounds the benzfuzed heterocyclic compound i.e. benzimidazole and its derivatives have wide variety of biological activities, in addition to that benzimidazole have played a very important role in the development of theory in heterocyclic chemistry and also extensively in organic synthesis.[1]

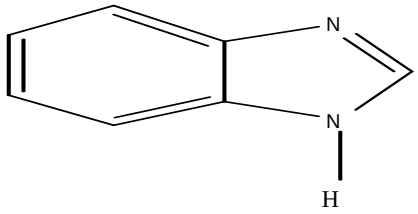


Figure 1: Benzimidazole

Benzimidazole is an important pharmacophore and a privileged structure in medicinal chemistry. Literature survey shows that among the benzimidazole derivatives, 2-substituted ones are found to be pharmacologically more potent and hence the design and synthesis of 2-substituted benzimidazoles are the potential area of research.[2]

Extensive biochemical and pharmacological studies have confirmed that its derivatives are effective against various strains of microorganism. The reason for a special interest of researchers towards benzimidazole derivatives has been 5,6 dimethyl benzimidazole which is a constituent of naturally occur ring vitamin B_{12}. Although vitamin B_{12} is capable of inducing the growth of bacteria, the benzimidazole component and some of its derivatives repress the bacterial growth. Due to the structural similarity to purine, antibacterial ability of benzimidazole is explained by their competition with purines resulting in inhibition of the synthesis of bacterial nucleic acids and proteins.[2]

Benzimidazoles drugs are widely used for prevention and treatment of parasitic infections. Thaibendazole (TBZ) was the first bezimidazole to be marketed over 40 years ago. It has been used widely for control of gastrointestinal nematodes, lung worms and as fungicidal agents. After its introduction, a number of alternative benzimidazole offering similar activity came to the market, such as paebendazole (PAR), cambendazole (CAM), mebendazole (MBZ), and oxibendazole (OXI). Benzimidazoles possessing sulphide and sulphoxide functional group were subsequently introduced, offering a wider spectrum of activities and improve efficacy. Albendazole (ABZ), fenbendazole (FBZ) and oxfendazole (OFZ) were the first such benzimidazole to be successfully used in the treatment of all growth stages of gastrointestinal nematodes. They may be used also in the treatment of lungworms, tapeworms and adult stages of liver fluke. The benzimidazole, triclabendazole (TCB) was later introduced as antihelmenthic agents for treatment of all stages of liver fluke, but it is ineffective against nematodes. Luxabendazole (LUX) is a benzimidazole-sulphide used in the treatment of food-producing animal but is not licensed for use in the EU. The low solubility of benzimidazole sulphides and sulphoxides leads to their low absorption from that gut, resulting in low bioavalability. Netobimin (NETO) and febantel (FEB), which are the pro-drugs of ABZ and FBZ, respectively, have greater water solubility resulting in improved absorption and increased bioavailability. Similar probenzimidazole have found widespread use as fungicidal agents, including benomyl (BEN) and thiophanate-methyl (TM), which are precursor of carbendazim (MBC).[2]

Chemistry of benzimidazole:

Benzimidazole is a fused aromatic imidazole ring system where a benzene ring is fused to the 4 and 5 positions of an imidazole ring. Benzimidazole is also known as 1, 3-benzodiazoles.[3]

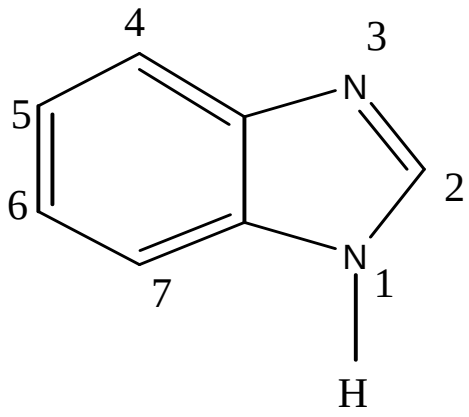
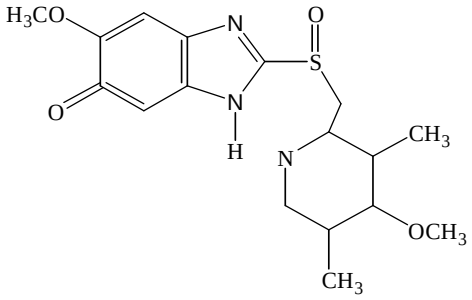


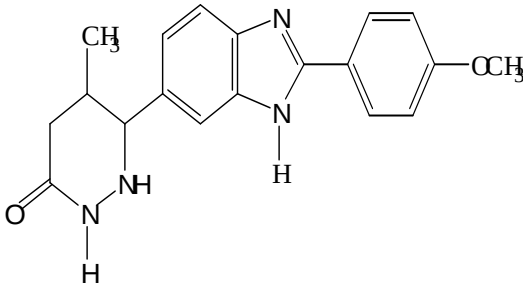
Figure 2: Benzimidazole

They possess both acidic and basic characteristics. The NH group present in benzimidazole is relatively strongly acidic and also weakly basic. Another characteristic of benzimidazole is that they have the capacity to form salts. Benzimidazole with unsubstituted NH groups, exhibit fast prototropic tautomerism which leads to equilibrium mixtures of asymmetrically substituted compounds. The benzimidazole scaffold is a useful structural modification for the development of molecules of pharmaceutical or biological interest. Appropriately substituted benzimidazole derivatives have found diverse therapeutic applications such as in antiulcer, antihypertensive, antiviral, antifungal, anticancer, and antihistaminics[3]. The optimization of benzimidazole-based structures has resulted in various drugs that are currently on the market, such as omeprazole (Proton pump inhibitor), pimobendan (Ionodilator), and mebendazole (Anthelmintic) figure2.

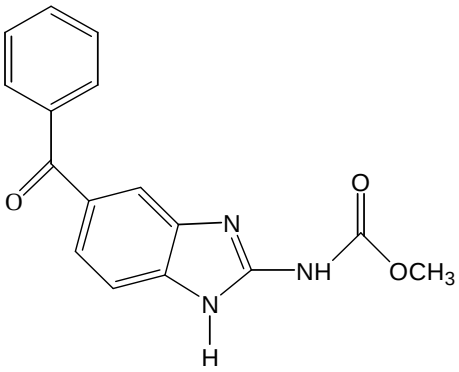
The spectrum of pharmacological activity exhibited by benzimidazoles has been reviewed by several authors[3-6]. Since the publications of these reviews, a number of new methods for the synthesis of benzimidazoles have been discovered and reported; such work continues due to their wide range of pharmacological activities and their industrial and synthetic applications. The present review focuses on the synthetic methodologies and biological activities of the benzimidazoles reported from 2000 to early 2007.



Omeprazole



Pimobendan



Mebendazole

Figure 3: Pharmacologically Active Benzimidazole Drugs.[7]

Synonyms:

1H-Benzimidazole; 1,3-benzodiazole; benzoglyoxaline; azindole; N,N^{I}-methylenyl-o-phenylenediamine; 3-azaindole; o-benzimidazole; benzoimidazole; BZI; 1,3-diazaindene.

General Description and Application:

Benzimidazole is a white to slightly beige solid; melting at 172 C, boils at 360 C, slightly soluble in water, soluble in ethanol. It is a dicyclic compound having imidazole ring (containing two nitrogen atoms at nonadjacent positions) fused to benzene. Benzimidazole and its derivatives are used in organic synthesis and vermicides or fungicides as they inhibit the action of certain microorganisms. Examples of benzimidazole class fungicides include benomyl, carbendazim, chlorfenazole, cypendazole, debacarb, fuberidazole, furophanate, mecarbinzid, rabenzazole, thiabendazole, thiophanate. Benzimidazole structure is the nucleus in some drugs such as proton pump inhibitors and anthelmintic agents.

Physical and Chemical Properties:

Physical property - slightly beige powder

Melting point - 172 C

Boiling point - 360 C

Specific gravity - 1

Solubility in water - Slightly

Autoignition - 538 C

Flammability - 1

Stability - Stable under normal temperatures and conditions.[8]

Data supplided by datasourcesm and users:

- Experimental physchem properties :
  1. Melting point :

     169-171¡æ J&K Scientific

     169-174 deg C SynQuest

     173 °C Tokyo Chemical Industry Ltd

     170-174 deg C Alfa Aesar

     173 Tokyo Chemical Industries Ltd

     170-174 deg C Alfa Aesar

     170 - 172 C Oxford University Chemical Safety Data
  2. Boiling point :

     360¡æ J&K Scientific

     360 deg C Alfa Aesar

     360g C / mmHg Alfa Aesar

Miscellaneous:

1. Stability: Stable, Combustible, Incompatible with strong oxidizing agents. Oxford University Chemical Safety Data.
2. Toxicity: ORL-RAT LD50 500 mg kg-1, ORL-MUS LD50 2910 mg kg-1, IPR-MUS LD50 445 mg kg-1, IVN-MUS LD50 280 mg kg-1, IPR-RAT LD50 385 mg kg-1 Oxford University Chemical Safety Data

3. Safety: May irritate eyes, skin, and respiratory tract Alfa Aesar Harmful and irritating. Possible irreversible damage risk Alfa Aesar Safety glasses, adequate ventilation. Oxford University Chemical Safety Data.[9]

Air And Water Reactions: Insoluble in water.

Reactivity Profile

An amine neutralizes acids to form salts plus water. These acid-base reactions are exothermic. May be incompatible with isocyanates, halogenated organics, peroxids, phenols (acidic), epoxids, anhydrides, and acid halides. Flammable gaseous hydrogen is ganerated in combination with strong redusing agents, such as hydrides.May is shock sensitive.

Health Hazard

Acute / Cronic Hazards:

When heated to decomposition Benzimidazole emits highly toxic fumes.

Fire Hazards

Flash point data for benzimidazole are not availeble. Benzimidazole is probably combustible.[10]

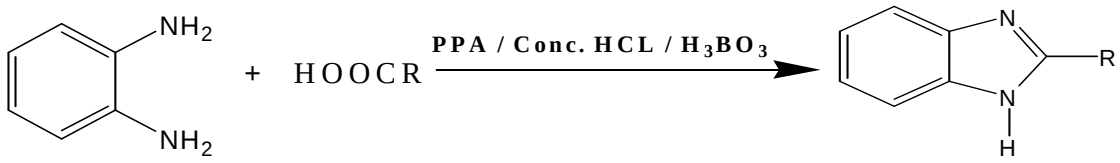
Sales specifications:

APPEARANCE	-	slightly beige powder
ASSAY	-	98.0% min
VOLATILE MATTER	-	0.2% max
CHLORIDE	-	20ppm max
SODIUM	-	500ppm max.[8]

Synthesis of Benzimidazole

Method–1:

Benzimidazoles have most commonly been prepared from the reaction of 1, 2-diaminobenzenes with carbonyl-containing compounds (Carboxylic acids, Aldehyde, etc.) under harsh dehydrating reaction conditions, utilizing strong acids such as polyphosphoric acid, hydrochloric acid, boric acid, or p-toluenesulfonic acid. The use of milder reagents, particularly Lewis acids, inorganic clays[11], or mineral acids, has improved both the yield and purity of this reaction[12].



Ortho-phenylene Diamine | Carboxylic acid | Benzimidazole

FIGURE 4: SCHEME FOR THE SYNTHESIS OF BENZIMIDAZOLE FROM O-ARYLENEDIAMINES

Method–2: From O-nitro aryl amines and O-Dinitroarenes

The synthesis of benzimidazole from O-nitro aryl amines and O-dinitroarenes is an acid catalyzed cyclization reaction. In this N-(O-nitroanilino) - substituted amines are cyclized to N-aminobenimidazoles under reflux in aqueous hydrochloric acid.

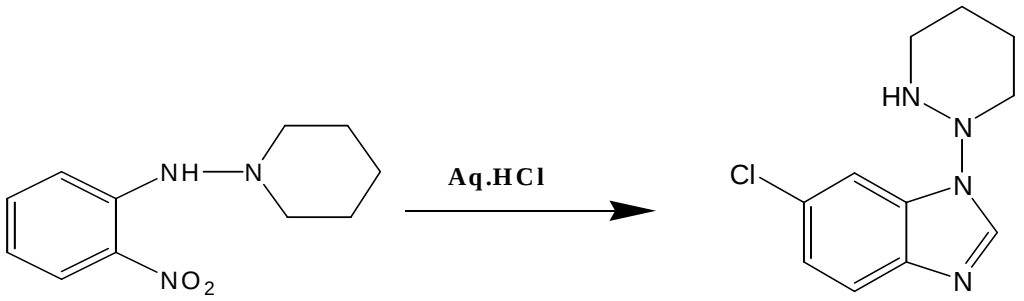


Figure 5: Scheme for The Synthesis Of Benzimidazole From O-Nitro Anilines

Method–3: From Amidines and Related Compounds.

The formation of benzimidazoles from N-aryl amidines is obtained by reacting it with benzenesulfonyl chloride in triethylamine under anhydrous condition.

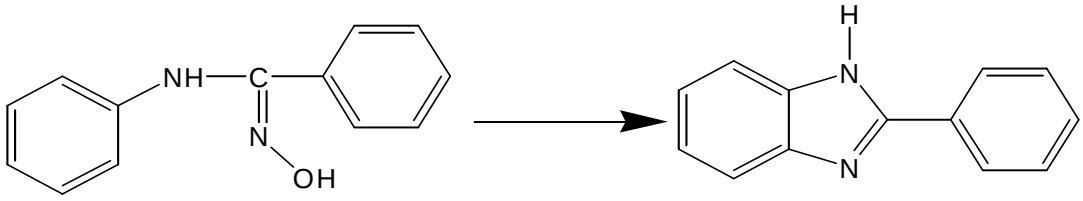


Figure 6: scheme for the synthesis of benzimidazole from amidines.

Method-4: From Five-Membered Ring Heterocycles.

Benzimidazole is formed in good yield by photolysis of indazoles.

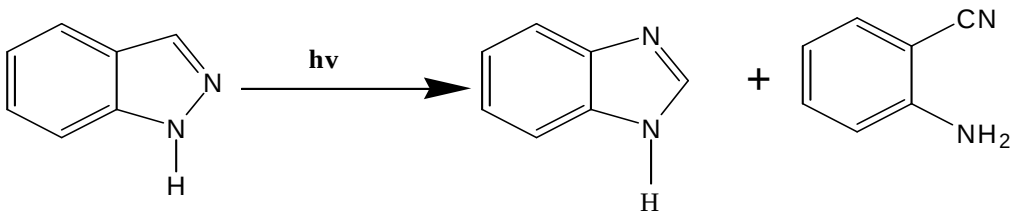


Figure 4: Scheme for the synthesis of benzimidazole from five- membered ring Heterocycles.

Method-5: From Six-Membered Ring Heterocycles

Benzimidazole and its 1-methyl derivative are obtained in 100 and 50% yields, respectively. By allowing O-phenylene diamine or N-methyl-O-phenylene diamine to react with S-triazine at temperature just over the melting point of diamine.

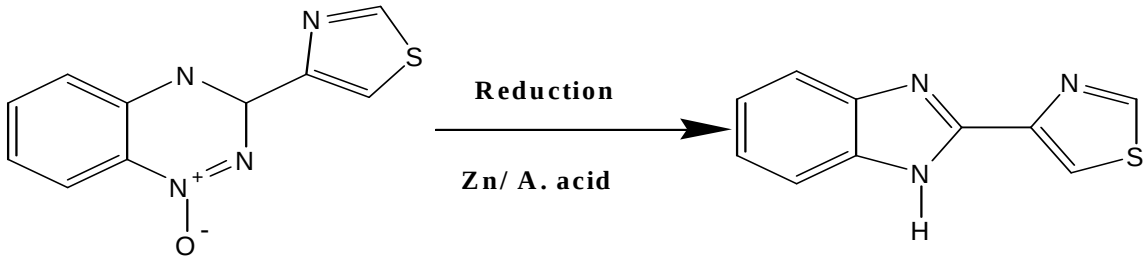


Figure-7: scheme for the synthesis of benzimidazole from six- membered heterocycles.

Reaction of Benzimidazole

Nucleophilic substitution in the imidazole ring:

The chichibabin reaction is used for the synthesis of a number of 2-aminobenzimidazole derivatives. For unsubstituted 2-halobenzimidazole a competition exist between proton abstraction by the nucleophile at the 1 position with concomitant retardation of 2-substitution. Accordingly chloride ion is not displaced from 2-Chlorobenzimidazole by powerful nucleophiles. Whereas, 2-Chloro-1-mehtyl benzimidazole reacts readily with sodium methoxide or ethoxide.

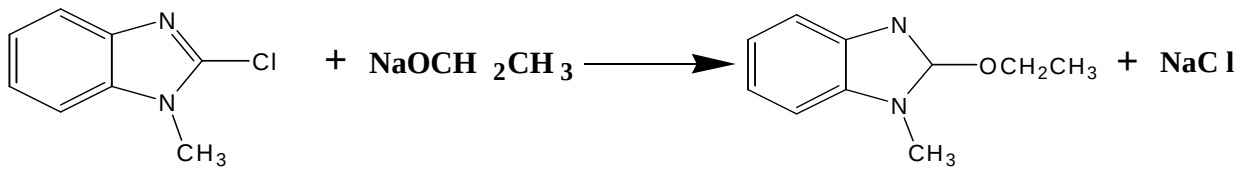


Figure-8: Scheme For The Nucleophilic Substitution In The Imidazole Ring.

Reaction involving Aryens and Free radicals:

Benzimidazole reacts as a nucleophile with benzyne to give 2-phenyl benzimidazole.

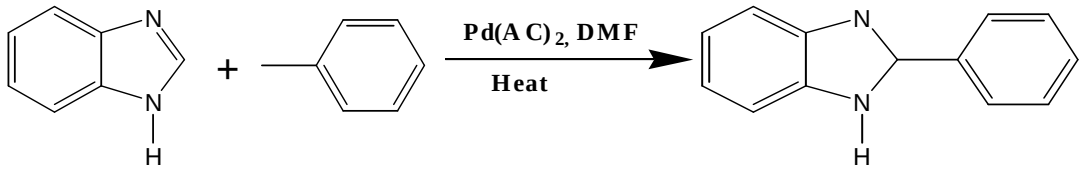


Figure 9: Scheme for Reaction with Aryne

Benzimidazole reacts with free radicals by thermal or photochemical methods.

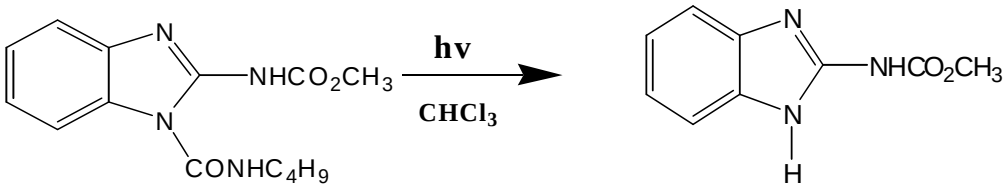


Figure 10: Scheme for Reaction with Free Radical

Reduction:

The standard method for reduction of benzimidazole involves hydrogenation in the presence of a platinum catalyst in acetic acid, palladium used.

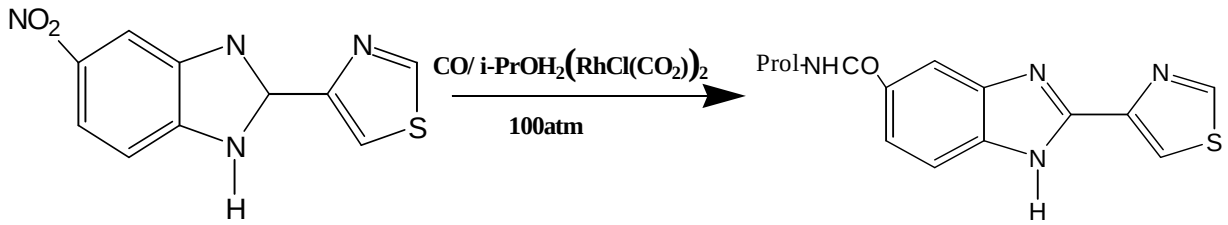


Figure 11: Scheme for Reduction of Benzimidazole

Oxidation: Oxidation is carried out in hydrogen peroxide, lead oxide, lead tetra acetate and chromic acid.

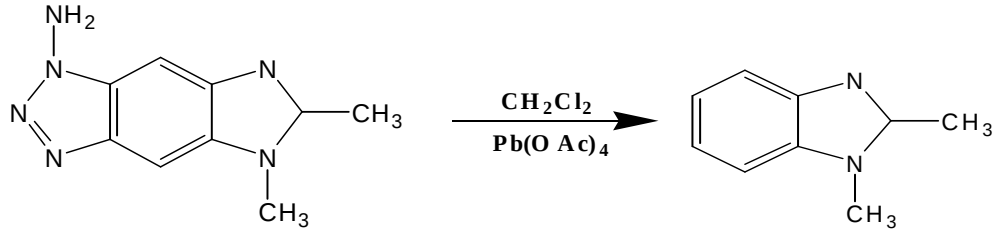


Figure-12: Scheme for the Oxidation of Substituted Benzimidazole.[11]

Benzimidazole Resistance:

Benzimidazole resistance has emerged as the most serious problem confronting the successful control of G.I. nematodes in ruminants, especially in small ruminants, in several parts of the world (Nari, 2005). The first report of anthelmintic resistance in Haemonchus contortus, in India was by Varshney and Singh (1976), against phenothiazene and thiabendazole at State Sheep and Wool Research Station, Pashulok, Rishikesh, U.P. (now in Uttaranchal). However, there was no report of anthelmintic resistance from 1976 to 1990. Since 1990 onwards, there has been a renewed interest in India on this aspect and a considerable number of reports of anthelmintic resistance observed in G.I. nematodes are pouring-in from various parts of the country (Yadav and Gupta, 2005). To circumvent the problem of drug resistance, the only realistic strategy would be to develop novel non-chemical approaches that decrease the need or treatment and to use the anthelmintics that remain effective in a more intelligent manner (Sanyal, 2005).[13]

Therapeutic Journey:

Drugs in this class differ from all other in that they are designed to inhibit/kill the infecting microorganism and to have no/minimal effect on the recipient. This type of therapy generally called as chemotherapy which has come to mean treatment of systemic infections with specific drugs that selectively suppress the infecting micro-organism without significantly affecting the host. From this they are referred as bacteriostatic and bactericidal respectively.[11]

Anti-ulcer drugs:

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[32-35]. 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 activity[36-39].

These are the drugs which inhibits both basal and stimulated gastric acid secretion. Some drugs containing benzimidazole nucleus are Pantoprazole, Rabeprazole, Lansoprazole, Omeprazole etc.[11]

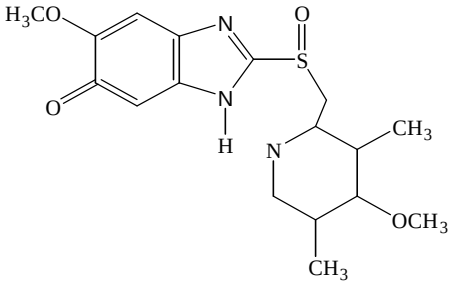


Figure 13: Omeprazole

Anti-psychotic agents:

In psychosis thinking of patient becomes illogical, bizarre and loosely organized. Patient has difficulty in understanding reality and their own conditions. Some drugs containing benzimidazole nucleus are droperidol, pimozide, and benperidol.[11]

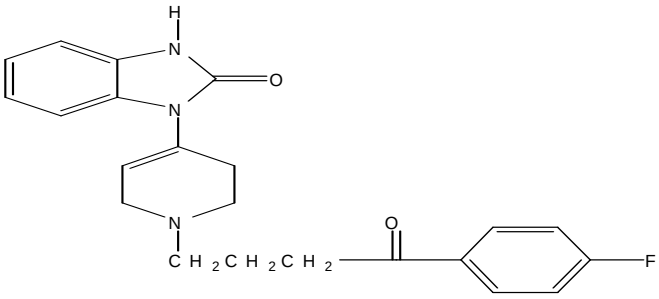


Figure-14: Droperidol

Anthelmintic:

In the present investigation, we reported the synthesis of 2-alkyl and aryl substituted benzimidazole derivatives in the presence of ring closing agents eg: (poly phosphoric acid and other solvents) and the synthesized compounds were screened for their anthelmintic activity.[40]

These are the drugs that either kill or expel infesting helminthes. Some drugs containing benzimidazole nucleus are Thibendazole, Mebendazole, and Albendazole etc.

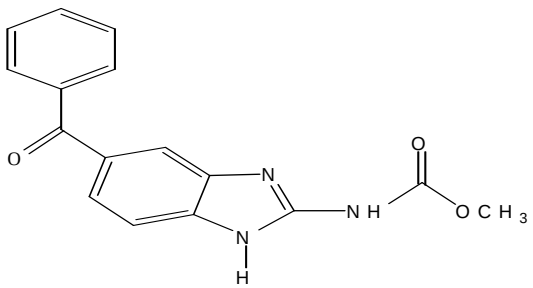


Figure 15: **Mebendazole**

Anti-protozoal agents:

These are the drugs which are used to treat the amoebiasis caused by E.histolytica. They exert cytotoxicity by damaging DNA and result in DNA helix destabilization strand breakage. The antiprotozoal drugs containing imidazole nucleus are metronidazole, benznidazole.

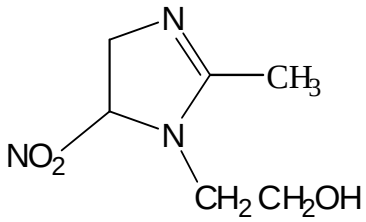
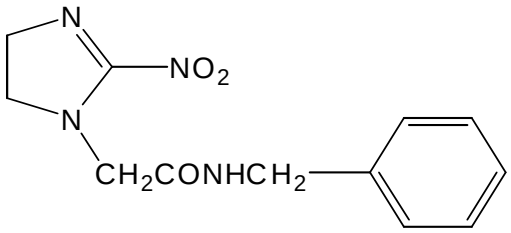


Figure 16: Metronidazole



Benznidazole

Antifungal:

These are the drugs used for superficial and deep fungal infections. Fungal infections are termed mycoses and in divided in to superficial infections (skin, nails, and scalp) and systemic infections (deeper tissues and organs) some conditions are blastomycosis, histoplasmosis, candidiasis, coccibiomycosis etc. superficial fungal infections can be classified in to the *dermatomycoses* and *candidiasis*. Dermatomycosis are infections of the skin, nails, hair and superficial candidiasis, the yeast-like organism infects the mucous membranes of mouth, skin), vagina or skin[14-16].

Anti-cancer:

Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. Cancer cells can spread to other parts of the body through the blood and lymph systems. Cancer is not just one disease but diseases. Cancer is a class of diseases in which a group of cells display uncontrolled growth, invasion, and sometimes metastasis. Most cancers form a tumour but some, like leukaemia, do not.[17, 18] the existing anticancer agents are not sufficient enough to solve this problem. Limited activity, rapid development of resistance and the adverse effects, over rides their usefulness. Benzimidazole nucleus is the key building block for a variety of compounds that play crucial roles in the function of a number of biologically important molecules.[19, 20] Benzimidazole as ‘‘lead’’ molecule, binds with other heterocyclic act by intercalation or block cell growth by inhibit the enzymes directly

responsible for the formation of nucleic acids. This inhibition is believed to prevent DNA transcription, which ultimately leads to cell death, which explains the use of these drugs to treat cancer.[21, 22]

Furtheremore, benzimidazoles showed anticancer activity against DNA topoisomerase I [23, 24] and colon cancer cell lines [25]. The need for anticancer agents that selectively kill or inhibit the growth of neoplastic cells without affecting non-cancerous host tissues is high and persistent. Thus, the aim of the current study was the synthesis of novel benzimidazole derivatives that incorporated different heterocycles of anticancer activity, such as different compounds with the backbone of chalcones and acethydrazides, which have been found to exhibit potent cytotoxic activity against the growth of suspended leukemia [26] and lymphomas [27]. They were also active in a number of solid tumor screens, e.g., HELA uterine carcinoma, PC12, SOS bone osteosarcoma, lung MB9812, lung A549 and Mcf-7 breast growth [28-30] Also, it was of interest to prepare benzimidazole N-glycoside Schiffis bases skeleton as bioisosteric of naturally occurring molecules, hopping to produce anticancer agents of high potency and selectivity.[31]

Anti-microbial:

Despite of the availability of a number of antimicrobial agents the main matter of concern in the treatment of microbial infections is the limited number of efficacious antimicrobial drugs. Many of the currently available drugs are toxic, enable recurrence because they are bacteriostatic/fungistatic and not bactericidal/fungicidal or lead to the development of resistance due in part to the prolonged periods of administration. The impact is more acute in developing countries due to nonavailability of desired medicines (Tomar et al., 2007; Sharma et al., 2009). There is a real perceived need for the discovery of new compounds that are endowed with antibacterial and antifungal activities, possibly acting through mechanism of actions, which are distinct from those of well known classes of antimicrobial agents to which many clinically relevant pathogens are now resistant (Sharma et al., 2009; Tuncbilek et al., 2009; Sharma et al., 2009). Benzimidazoles exhibit significant activity as potential antitumor agents, antimicrobial agents, smooth muscle cell proliferation inhibitors, a treatment for intestinal cystitis, and in diverse area of chemistry (Ansari et al., 2009; Kumar et al. 2008). The outcome of numerous attempts to develop new structural prototype in the search for effective antimicrobials indicates that the benzimidazoles still remain as one of the most versatile class of compounds against microbes (Kumar et al., 2006; Goker et al., 2005). The benzimidazole has been an important pharmacophore and

privileged structure in medicinal chemistry, encompassing a diverse range of microbial activities (Goker et al., 2005). A total of seven benzimidazole derivatives were synthesized in two

Series by introducing different substituents at different positions.[41]

Study on Structural modifications and their Pharmacological actions

The use of Benzimidazole dates many years back[42]. 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.[43, 44] 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 activity[45,46]. 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[47]. 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.[48] hence, there will always be a vital need to discover new chemotherapeutic agents to overcome the emergence of resistance and ideally shorten the duration of therapy. Due to the structural similarity to purine, antibacterial ability of benzimidazoles are explained by their competition with purines resulting in inhibition of the synthesis of bacterial nucleic acids and proteins.[49, 50]

The benzimidazole motif occurs in many approved and investigational drugs. Well-known examples of approved benzimidazole-based drugs include omeprazole (Prilosec, a proton-pump inhibitor), candesertan (anti-hypertensive, an angiotensin II receptor antagonist), mebendazole (treatment of worm infestations) and astemizole (an anti-histamine).[51]

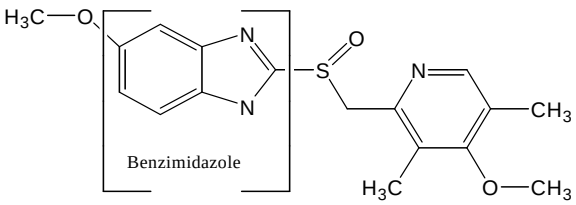


Figure: Omeprazole

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