IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
November 2023 Vol.:28, Issue:4

A Review on Medical Significance of Benzimidazole Derivatives

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Submitted: 22 October 2023
Accepted: 27 October 2023
Published: 30 November 2023

Keywords: Benzimidazole, antiviral, anti-fungal, CNS depressant, anti-inflammatory

ABSTRACT

Benzimidazole is a heterocyclic aromatic organic compound consist of a fusion of benzene and imidazole. Benzimidazole has a variety of therapeutic uses, including antineoplastic, antifungal, antiparasitic, analgesic, antiviral, and antihistamine agent, as well as in cardiovascular disease, neurology, endocrinology, and ophthalmology.

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INTRODUCTION

Benzimidazole is a type of aromatic organic compound that can be used in pharmaceutical chemistry. It's a combination of benzene and imidazole. It's a bicyclic compound and is now a popular moiety with many pharmacological properties. It's a tautomeric system, meaning it has free imino hydrogen. The most common benzimidazole compound in nature is N-ribosyl-dimethyl benzimidazole, which acts as an axial ligand for cobalt in vitamin B12.[1]

So far, a number of chemical modifications have been made around the backbone (the core) to enhance the various biological activities of benzimidazole. Due to their wide range of biological activities, benzimidazole has been identified as an important heterocycle compound. This review has summarised and reported various activities of benzimidazole (e.g., analgesic, anti-inflammatory, anti-tumor, anthelmintic, anti-cancer, anti-oxidant, antioxidant, anti-protective, anti-fungal and anti-viral).[2]

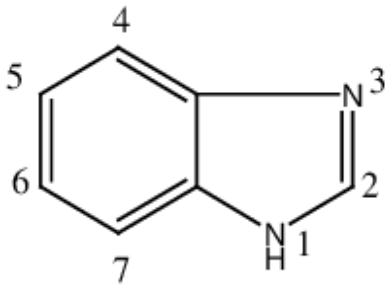


Figure 1: Benzimidazole

So far, a bunch of different chemical changes have been done to the backbone to make it better at different biological functions. Benzimidazole has become a really important compound because it has a lot of different biological activities. This review looked at all the different activities that benzimidazole can do, like analgesia, anti-inflammatory, anti-tumor, and anti-cancer. It also looked at how it can help with anthelmintic, anti-bacterial and antiviral drugs.[3]

SYNTHESIS OF BENZIMIDAZOLE

There are several synthetic methodologies available for the synthesis of benzimidazole. In general, the condensation of O-phenylene Diamine with Carboxylic Acids and their Nitrile, Imidates, and Orthoester Derivatives has been widely used in this reaction. Direct condensation of o-aryl Diamine with aldehydes is not a suitable synthetic pathway for these

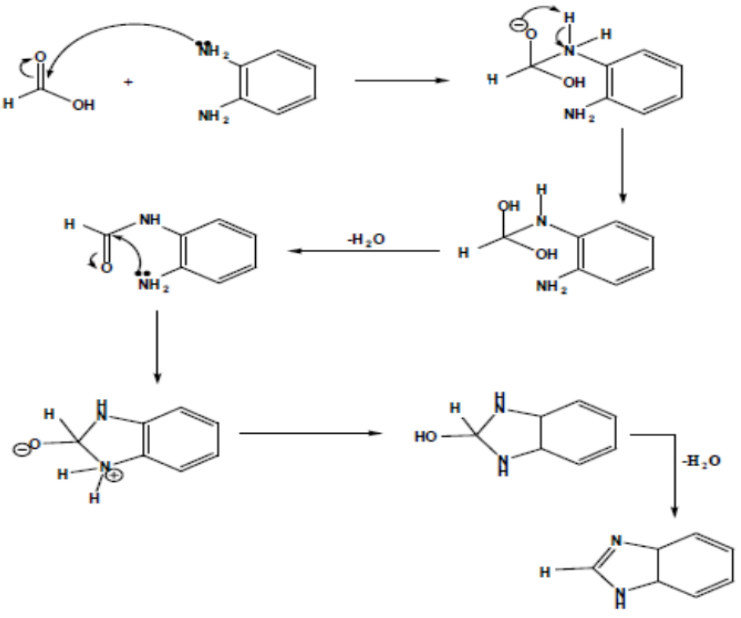
molecules, as it results in a complex combination of 1, 2-disubstituted benzimidazole and bis-dihydrobenzimidazole as side products. However, the use of transition metal catalysts, such as copper (II) acetate and lead tetra-acetate, in these reactions has improved the results. Additionally, rhenium, palladium, and rhodium are used as catalysts. Benzimidazole is commercially available. But the use of transition metal catalysts namely copper (II) acetate and lead tetra-acetate in these reactions afforded better results. Ruthenium, palladium and rhodium catalysts have also been used. Benzimidazole is commercially available. The usual synthesis involves condensation of o-phenylenediamine with formic acid, or the equivalent trimethylorthoformate[4]:

$$C_6H_4 (NH_2)_2 + HC (OCH_3)_3 \rightarrow C_6H_4N (NH) CH + 3 CH_3OH$$

CHEMISTRY OF BENZIMIDAZOLE

Benzimidazole consists of fused aromatic imidazole ring system in which a benzene ring is fused to the 4, 5 positions of an imidazole ring .it is also called as azindole, 1-H-benzimidazole, O-benzimidazolebenzoglyoxaline, 1, 3-diazaindene.it possess both acidic & basic property. The NH group present in benzimidazole is strongly acidic and weakly basic. Benzimidazole have capacity to form salts. Benzimidazole with unsubstituted NH groups exhibit fast prototropic tautomerism which leads to an equilibrium mixture of asymmetrically Substituted compounds[5].

MECHANISM OF RING FORMATION



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 the 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 positions & at chloro, methoxy group at 5, and 6 position shows antiparasitic activity.

5. The introduction of the pyridine group at 2 positions, methyl group at 3 or5, 6 position shows Anti-diabetic activity.

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

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

PHYSICAL PROPERTIES OF BENZIMIDAZOLE

Benzimidazole has a melting point that is reduced by the addition of a substituent in the first position. It is also more soluble in non-polar solvents due to the addition of H_2, N_2, and Cl_2 substituents at different positions in the molecule. It is usually soluble in polar solvent with imide. The addition of a polar group to the molecule increases its solubility in polarized solvents. Due to its weak basic nature, benzimidazole dissolves in dilute acids. It distills at temperatures above 300 °C.[7]

PHARMACOLOGICAL EFFECT OF BENZIMIDAZOLE

Most of the benzimidazole analogs are also known for their clinical use. Some of them are as follows:

1. Benzimidazole Analogues asAnthelmintic agent:

These are the drugs that either kill the helminthes or expel the helminths from the body. Some drugs that contain benzimidazole as the nucleus are thiendazole, mebendazole, albendazole etc.

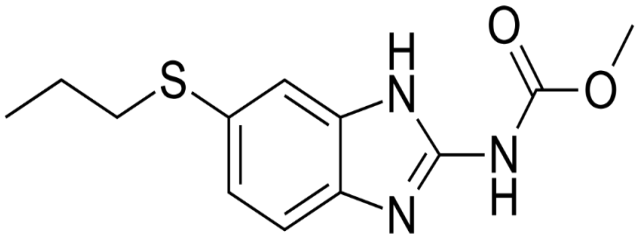


Figure 2: Albendazole

2. Benzimidazole Analogues as Anti-psychotic agents:

Benzimidazole analogs as anti-psychotic drugs In psychosis, the patient's thoughts become illogical, bizarre, and disorganized. The patient has difficulty comprehending the reality of the world around them and their own condition. Benzimidazole-containing drugs (nucleus) Droperidol, Pimozide, Benperidol.

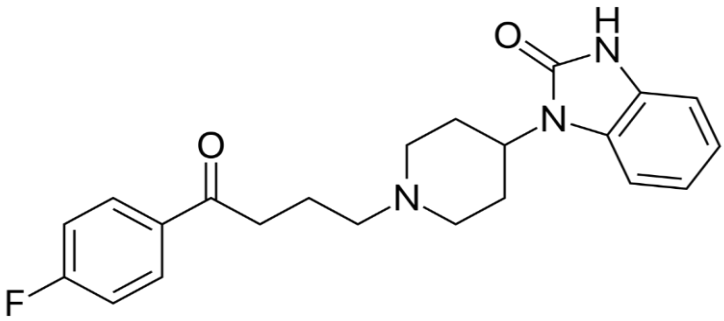


Figure 3: Droperidol

3. Benzimidazole Analogues as Anti - Ulcer Agent :

The sore that develop on the lining of the stomach, oesophagus or small intestine. The causative agent of ulcer is the Helicobacter pylori bacteria. Ulcer occurs when that the gastric acid damages the lining of the digestive tract. Anti- ulcer agent acts by inhibiting or suppression of gastric acid production, protecting of gastrointestinal mucosa from acid injury or neutralization of Acid. Example for that is Pantoprazole.

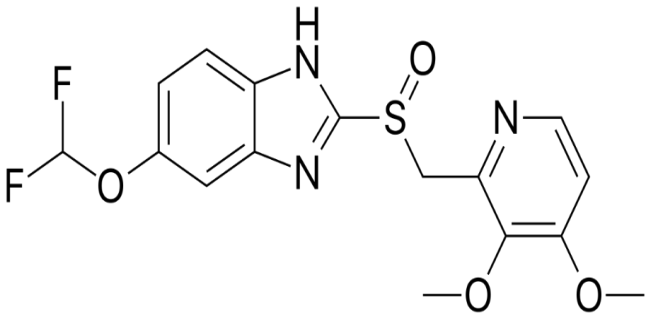


Figure 4: Pantoprazole

4. Benzimidazole Analogues as Anti protozoal agents:

Zymidazole analogues as anti-protozoan agents. These are drugs used to treat E. histolytica, which is an amebic disease. They cause cytotoxicity due to damage to DNA and break down the helix of the strand. Anti-protozoan drugs containing benzimidazole nucleus Metronidazole, Benznidazole, etc.

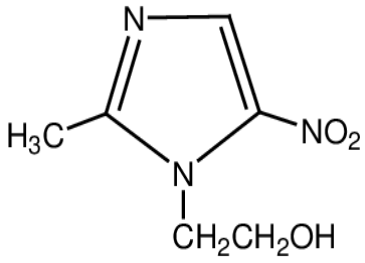


Figure 5: Metronidazole

5. Benzimidazole Analogues as Antifungal agent:

As an antifungal agent, benzimidazole analogs are the drugs used to treat superficial and deep fungal infections. Fungal infections are called mycoses and can be divided into superficial infections (skin, nails, and scalp) and systemic infections (deeper tissues and organs). Some of the conditions that can lead to fungal infections are blastomycosis and histoplasmosis. Other conditions that can cause fungal infections are candidiasis and coccibomycosis. The most common antifungal agents containing imidazole are clotriamazole, miconazole, and ketoconazole.

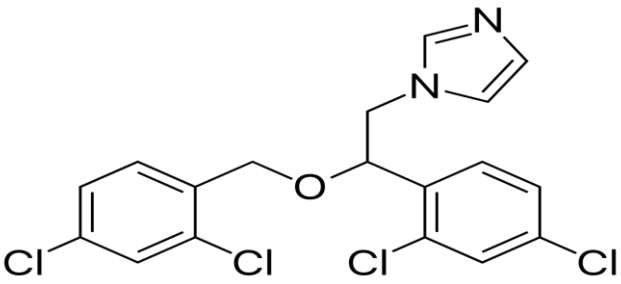


Figure 6: Miconazol

6. Benzimidazole Analogues as Antibacterial and Antifungal Agents:

Most of the benzimidazole derivatives exhibit antibacterial activity. For example, derivatives of pyrimido [1, 6-a] benzimidazole represents a new class of DNA-gyrase inhibitors, which are effective antibacterial agents. Benzimidazole derivatives such as benomyl, carbendazim, fuberidazole and thia-bendazole are developed as fungicides that have high activity against many opportunistic fungi.

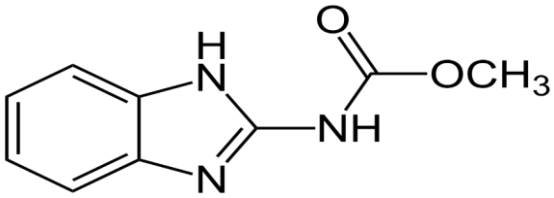


Figure 7: Carbendazim

7. Benzimidazole Analogues as CNS Depressants:

Some benzimidazole derivatives produce various, in type and strength, effects upon the central nervous system, including psycho-stimulant, neuroleptic, antidepressant, tranquilizer (anxiolytic), anticonvulsant, and hypnotic action. example for this is pimozide.

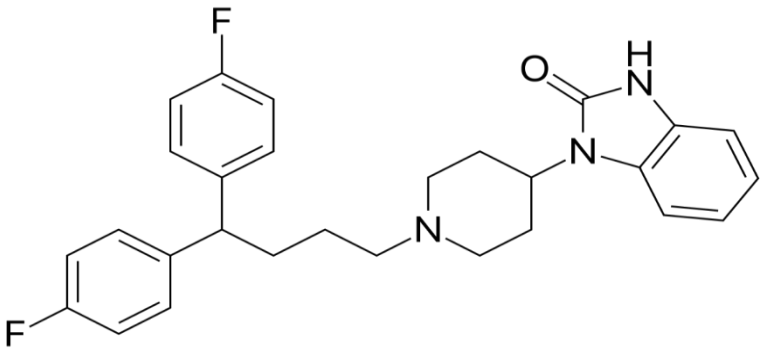


Figure 8: Pimozide

8. **Benzimidazole Analogues as Analgesic, Anti-inflammatory, and Antipyretic Agents:**

In recent years, much effort was devoted to studying the analgesic drug etonitazene, a benzimidazole analog selectively interacting with opiate receptors of the μ-subtype. Etonitazene is a highly potent analgesic drug, has approximately 1000-1500 times more potency than morphine. It has a strong potential similar to that of morphine and has a strong tendency to produce respiratory depression and is therefore not used in humans.

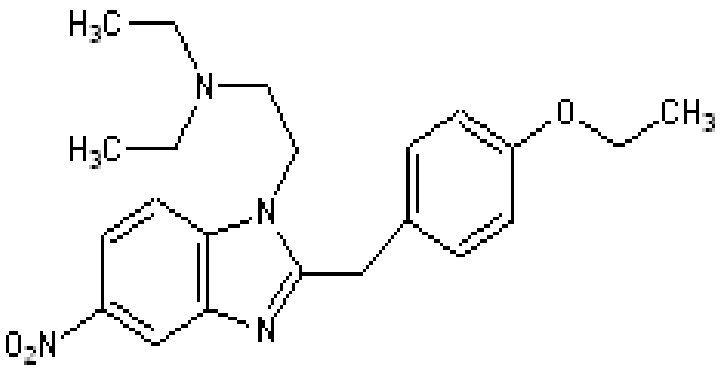


Figure 9:Etonitazene

9. Benzimidazole Analogues as Hypo-glycemic Agents:

The condensed benzimidazole derivative 9-(2-diethyl aminoethyl)-2, 3-dihydroimi-dazo [1, 2-a] benzimidazole dihydrochloride (diabenol) was reported to possess hypoglycemic and antiaggregant properties.

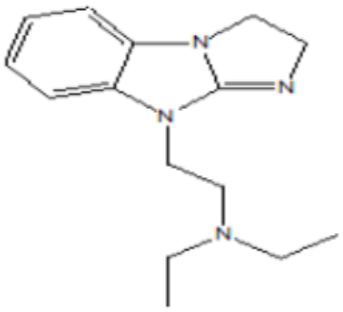


Figure 10:Diabenol

10. Benzimidazoles Analogues as Antiallergic Agents:

The group of effective long-action blockers of the histamine receptors includes astemizole and mizolastine.

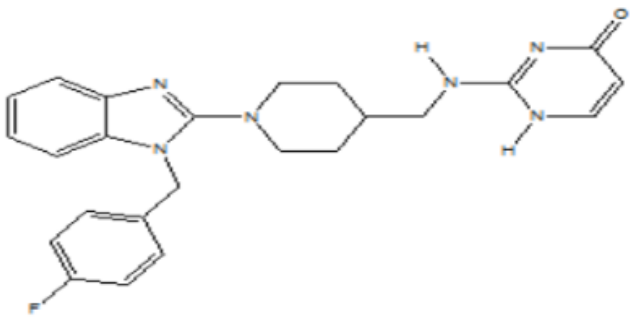


Figure 11: Astemizole

11. Benzimidazole Analogues as Cardio-vascular Agents:

2-benzylbenzimidazole (dibazole) which was capable of decreasing the tone of smooth muscles of the blood vessels and internal organs. This compound is widely used as a spasmolytic and hypotensive remedy. Antihypertensive activity is characteristic of most of benzimidazole derivatives which are capable of blocking calcium channels.

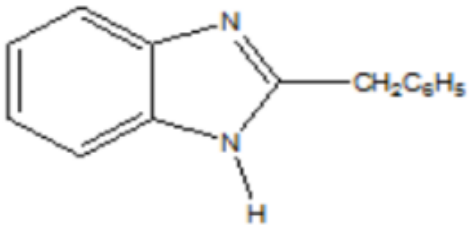


Figure 12: Dibazole

12. Benzimidazole Analogues As Antitumor Agents:

Bendamustine, benzimidazole analog, which is available in the market and used for the treatment of leukemia. It belongs to the family of drugs called alkylating agents. It is also studied for the treatment of sarcoma.[8-19]

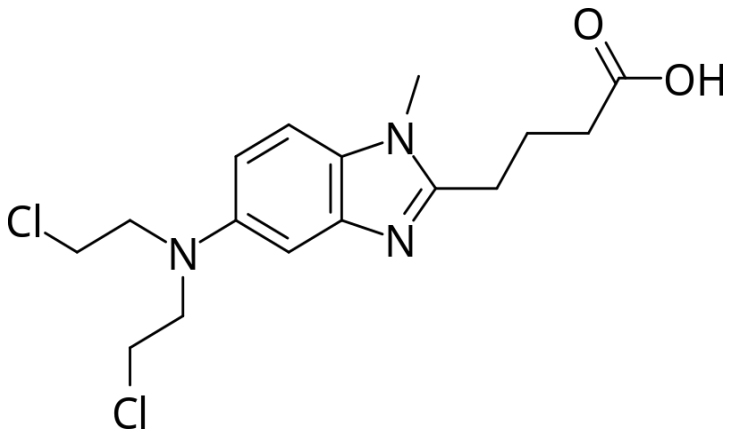


Figure 13: Bendamustine

CONCLUSION

Benzimidazole ring is a very important pharmacophore in drug discovery. Some substituted benzimidazole derivative drugs are more active. The synthesis of Benzimidazole derivatives is a privileged scaffold, with a wide range of therapeutic uses including antitumor, antifungal and anti-parasitic drugs, analgesics, antiviral and antihistamine drugs, cardiovascular disease, neurology and endocrinology drugs.

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