REVIEW

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BENZIMIDAZOLE: A REVIEW ON ITS SYNTHESIS, PROPERTIES AND VARIOUS BIOLOGICAL ACTIVITIES

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ABSTRACT

Benzimidazole is a heterocyclic aromatic organic compound that consists of the fusion of benzene and imidazole. These compounds are weak basic and are soluble in dilute acids. Due to their special structural features and electron-rich environment, Benzimidazole containing drugs bind to a variety of therapeutic targets, thereby exhibiting a broad spectrum of bioactivities. Numerous benzimidazole based drugs have been extensively used in the clinic to treat various types of diseases with high therapeutic potential. Benzimidazole derivatives play important role in medical field with so many Pharmacological activities such as antimicrobial, antiviral, antidiabetic, anti-inflammatory, anti-fungal, antiviral, anthelmintic and anticancer activity. Benzimidazole compounds are widely used due to its various properties which includes:- bioavailability, increased stability and large number of biological activities.

KEYWORDS:- Heterocyclic, Anti-viral, Anti-diabetic, Anti-inflammatory.

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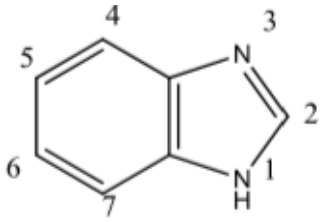
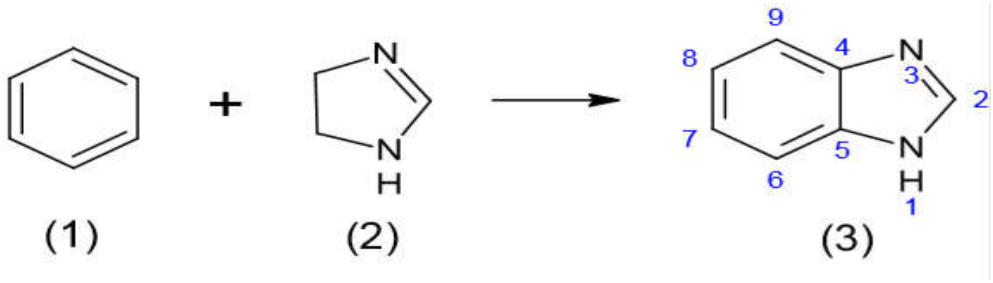
INTRODUCTION

Benzimidazole rings are the most important nitrogen-containing heterocyclic compound, which are widely explored and utilized by the pharmaceutical industry for drug discovery.It is an important pharmacophore and privileged structure in medicinal chemistry.



BENZIMIDAZOLE

Due to their special structural features and electron-rich environment, Benzimidazole containing drugs bind to a variety of therapeutic targets, thereby exhibiting a broad spectrum of bioactivities. Numerous benzimidazole based drugs have been extensively used in the clinic to treat various types of diseases with high therapeutic potential. Benzimidazole derivatives play important role in medical field with so many Pharmacological activities such as antimicrobial, antiviral, antidiabetic, anti-inflammatory, anti-fungal, antiviral, anthelmintic and anticancer activity. Benzimidazole (3) is generally the fusion of benzene (1) and imidazole (2).



Benzimidazoles are remarkably effective compounds, extensive biochemical and pharmacological studies have confirmed that these molecules are effective against various strains of microorganisms. Due to their enormous medicinal value, the research and development of benzimidazole-containing drugs is an increasingly active and attractive topic of medicinal chemistry. The prepared compounds of benzimidazole were subjected to physiochemical studies like melting point determination, TLC and percentage yield. The structures of synthesized compounds were characterized by IR and NMR spectroscopy. The Benzimidazoles are also known as benzoglyoxalines. They have been also named as derivatives of o-phenylenediamine.

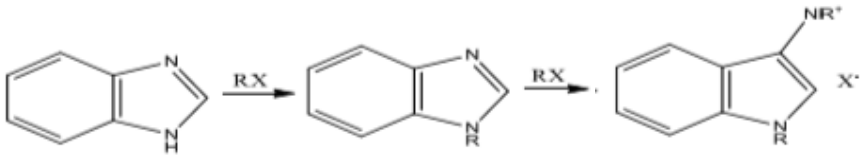
PHYSICAL PROPERTIES OF BENZIMIDAZOLE

- Molecular formula- $C_7H_6N_2$
- Molecular weight- 118.139 g/mol
- Colour- Colourless
- Boiling point- >360˚C
- Melting point- 170.5˚C
- Solubility- Freely soluble in alcohol, sparingly soluble in ether. Soluble in aqueous solutions of acids and strong alkalis.
- Stability- High degree of chemical stability
- PH- Weak base

CHEMICAL PROPERTIES OF BENZIMIDAZOLE

Reactions of the benzimidazole ring: The benzimidazole ring possesses a high degree of stability. Benzimidazole is not affected by concentrated sulphuric acid, hot hydrochloric acid as well as alkalis.

Alkylation: Benzimidazoles, undergoes alkylation with alkyl halides, yielding 1-alkylbenzimidazoles and under more vigorous conditions, 1,3-dialkylbenzimidazolium halides.



Alkylation of benzimidazole: Benzimidazoles also react with acylating, Grignard reagents and metal. The benzimidazole also forms mannich bases by reacting formaldehyde and piperidine.

Hydrogenation and dehydrogenation reactions: Benzimidazole ring was stable to reduction. 2-Phenylbenzimidazole gives only 2-cyclohexylbenzimidazole

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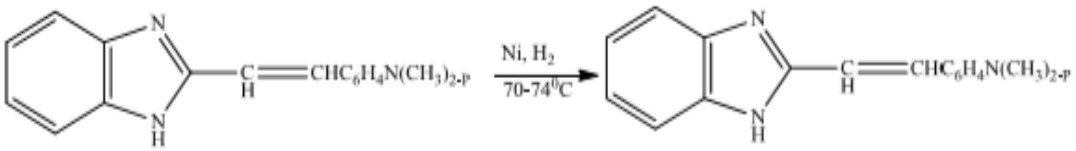


Fig: Hydrogenation of benzimidazole

Cleavage of the imidazole ring: The imidazole ring of benzimidazoles may be cleaved by reacting with acid anhydrides and halide.

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.

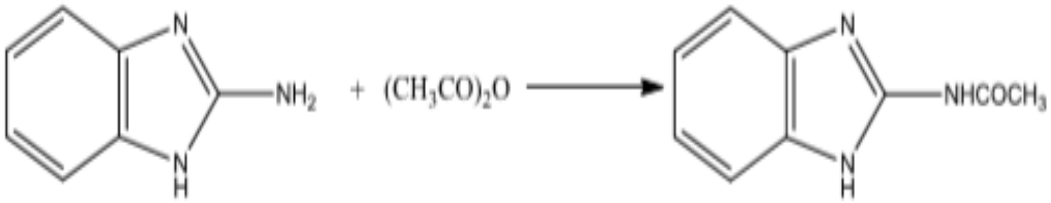


Fig: Reaction of Oxidation of benzimidazole

Because of the stability of the benzimidazoles ring to oxidation it is possible to oxidize substituent group without affecting the ring.

Nitration: Nitration of benzimidazoleappears to take place at the 5 or 6 positions. However, the nitro group may also enter the 4 or 7 positions, especially if the 5 or 6 position is blocked.

Halogenation: Aqueous solution of 2,5 (or 2,6)-dimethylbenzimidazole on treatment with saturated solution of bleaching powder at 0-5℃., 1-chloro-2,5(or 2,6)-dimethylbenzimidazole is obtained.

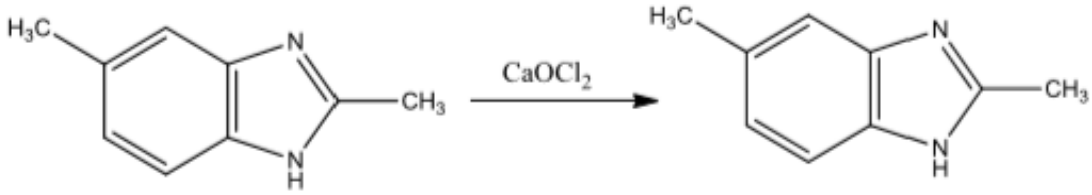


Fig: Halogination of benzimidazole

BIOLOGICAL ACTIONS OF BENZIMIDAZOLE:

Benzimidazole have biochemical and pharmacological properties and confirmed that benzimidazole molecules are effective against various strains of microorganisms. Benzimidazoles are the class of bioactive heterocyclic compounds that exhibit a range of biological activities.

This ring system is present in numerous antiprotozoal, antihelmintics, anti-HIV, anticonvulsant, antiinflammatory, antihepatic, and antineoplastic, antiulcer, activities. Resistance to number of antimicrobial agents (β-lactam antibiotics, macrolides, quinolones, and vancomycin) among a variety of clinically significant . The drug is resistance among Gram-positive bacteria such as staphylococci, enterococci, and streptococci.

Benzimidazoles also act as anti-inflammatory agents. Inflammation is a local reaction of the vascular and supporting elements of a tissue to injury resulting in the formation of a protein-rich exudates; it is a protective response of the nonspecific immune system that serves to localize, neutralize, or to destroy an injurious agent in preparation for the process of healing.

Inflammation is divided into acute and chronic patterns. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the choice treatment in various inflammatory diseases such as arthritis, rheumatisms. Imidazole and fused imidazole with six-membered rings, occupy central position among those compounds that are used as analgesic and anti-inflammatory agents.

Benzimidazole derivatives are also used as anticancer agents. Cancer is a malignant disease characterized by uncontrolled proliferation of cells which may be rapid or slow, depending on the type of cancer; a number of anticancer drugs are currently in clinical practice.

2-Substituted benzimidazoles act as potential anticancer. For example, bis-benzimidazole derivatives were active compounds in interfering

with DNA topoisomerase I and were also found to be cytotoxic against breast adenocarcinoma.

Many benzimidazole derivatives are widely used for the treatment of parasitic diseases.Benzimidazole derivatives are used as antihelminth preparations in the world veterinary and medical practice, including thiabendazole, oxfendazole, albendazole, fenbendazole, triclabendazole, oxibendazole, cambendazole, parbendazole, nocodazole, flubendazole, etc.

Benzimidazole derivatives play major role in treating HBV infection. Hepatitis B virus (HBV) infection results in both acute and chronic hepatitis. roughly 4 million deaths from the resulting cirrhosis and hepatocellular carcinoma every year.

Some benzimidazole derivatives produce various effects upon the central nervous system, including psychostimulant, neuroleptic, antidepressant, tranquilizer (anxiolytic), anticonvulsant, and hypnotic action.

A large number of patents describe benzimidazole derivatives of use in the textile industry as wetting, emulsifying, foaming, or softening agents or as dispersants for use in dyeing.

A number of aminobenzimidazoles have been used for the preparation of sulfur and azo dyes of use in the textile industry.

Another use has been in the preparation of fluorescent dyes for use in such preparations as inks for marking clothes to be dry-cleaned. Thus, Benzimidazole derivatives have wide range of biological actions & industrial applications.

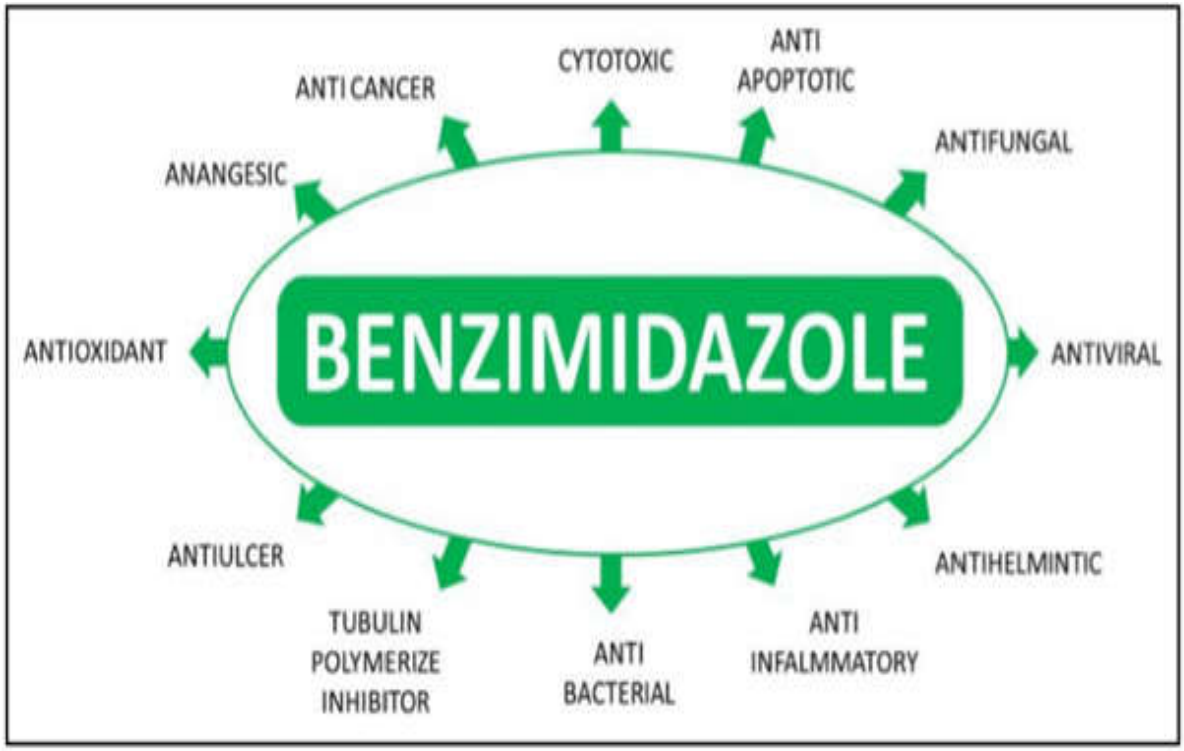
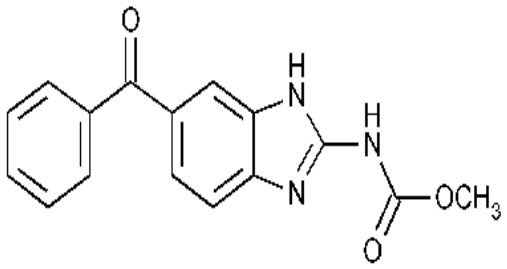


Fig: Various Biological activities

DRUGS HAVING BENZIMIDAZOLE NUCLEUS

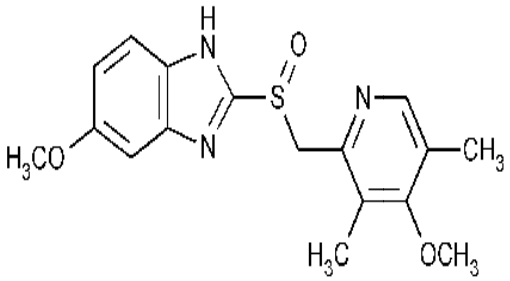
1. **Anthelmintic:**These are the drugs that either kill or expel infesting helminthes. Some drugs containing benzimidazole nucleus are Thibendazole, Mebendazole, and Albendazole etc.



MEBENDAZOLE

2. **Anti-ulcer drugs**

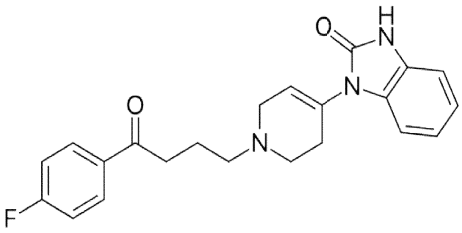
These are the drugs which inhibits both basal and stimulated gastric acid secretion. Some drugs containing benzimidazole nucleus are Pantoprazole, Rabeprazole, Lansoprazole, Omeprazole etc.



OMEPRAZOLE

3. **Anti-psychotic agents**

Some drugs containing benzimidazole nucleus are droperidol, pimozide, and benperidol.

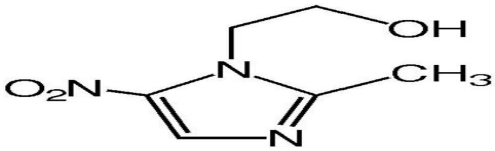


DROPERIDOL

4. **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.

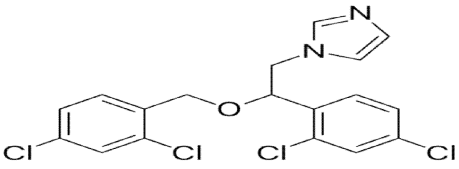


METRONIDAZOLE

5. **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).

Most common antifungal agents containing imidazole nucleus are Clotriamazole, Miconazole and Ketoconazole.



MICONAZOLE

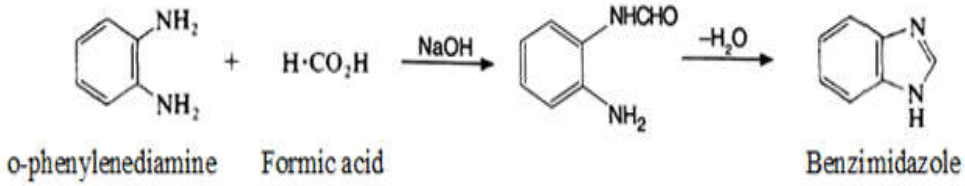
SYNTHERSIS OF BENZIMIDAZOLE

Material and method: - Reaction of o-phenylenediamine (OPDA) with carbonyl compounds, under strong acidic conditions, gives benzimidazole. Formic acid is used as carbonyl compound under reflux condition to produce benzimidazole nucleus. The reaction was monitored by thin layer chromatography.

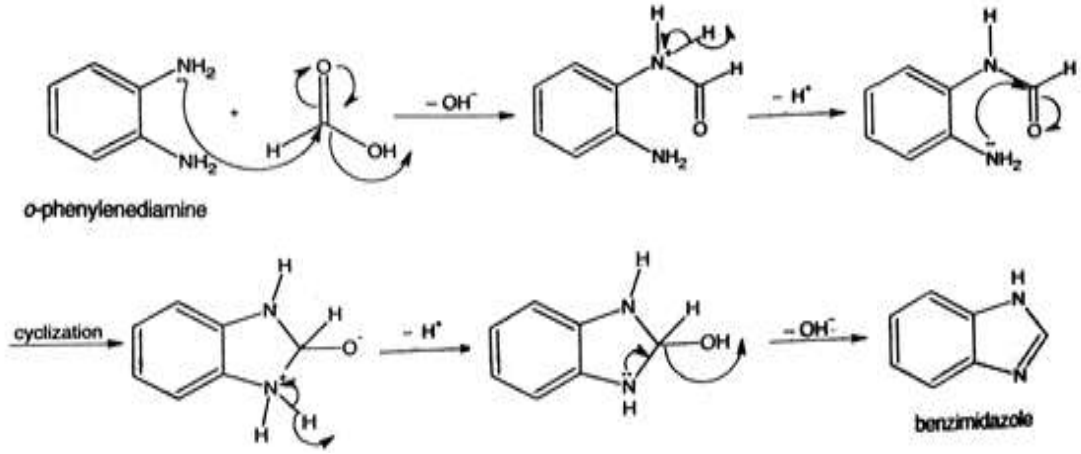
Procedure for the Synthesis of Benzimidazoles

1. A RBF of 250ml was taken and 9gm of o-phenylenediamine was placed in it.
2. Then 5.83g of 90% formic acid was added into o-phenylenediamine.
3. The mixture was heated on water bath at 100˚C for 2 hours.
4. The mixture was then cooled and 10% sodium hydroxide solution was added into it slowly, with constant rotation of flask, until the mixture is just alkaline to litmus.
5. The synthesized benzimidazole was filtered off and washed with ice cold water.

Reaction:



Mechanism:



RECRYSTALLISATION PROCESS

1. The synthesized product was dissolved in 400ml of boiling water.
2. Then, 2g of decolourising carbon was added into it and it was digested for 15 minutes.
3. The product was filtered rapidly through a preheated Buchner funnel and a flask at the pump.
4. The filtrate was cooled to about 10˚C and washed with 25ml of water and dried.
5. The yield of benzimidazole was then calculated.

Fig: Reflux Condenser

Fig: Recrystallisation

CALCULATIONS:

Percentage yield of o-phenylenediamine was calculated by using formula:-

% yield = (practical yield/theoretical yield) × 100

Molecular formula of benzimidazole = $C_7H_6N_2$

Molecular weight of o-phenylenediamine= 108g/mol

Molecular weight of benzimidazole= 118g/mol

Theoretical yield:

108g of o-phenylenediamine forms 118g of benzimidazole

Therefore, 9g of o-phenylenediamine will form X g of benzimidazole.

X= (118× 9)/108 = 9.83g

Theoretical yield = 9.83g

Practical yield = 8.67g

%yield= (8.67/9.8)×100= 83%

So, the percentage yield of synthesised Benzimidazole was found to be 83%.

Evaluation of Benzimidazole:-

Evaluation is a systematic determination of a subject's merit, worth and significance, using criteria governed by a set of standards.

- **Loss on drying (LOD):**Loss on drying is a widely used test method to determine the moisture content of a sample, although occasionally it may refer to the loss of any volatile matter from the sample. Loss in drying does not usually refer to molecularly bound water or water of crystallisation. The test determines the amount of volatile matter of any kind (including water) that can be driven off.

Procedure:

1. A crucible was taken and weighed.
2. Then, appropriate amount of sample was weighed in it.
3. The crucible was then placed in hot air oven at 105˚c for 1 hour.
4. Again the weight was taken and then the dry weight was calculated by subtracting crucible weight.

Formula:

% loss on drying= (initial weight- final weight/ initial weight) × 100

= (3g – 2.6g/3g) × 100

= (0.4/3) ×100= 13.3%

- **Melting point:** Melting point is a temperature at which the solid and liquid forms of a pure substance can exist in equilibrium. As heat is applied to a solid, its temperature will increase until the melting point is reached. Determining the melting point of a compound is one way to test if the substance is pure.

Procedure:

1. A capillary tube was filled with crystals and it was then placed in melting point apparatus.
2. The temperature of the apparatus should be high enough to make a rapid determination.

Result: The melting point of synthesised Benzimidazole was found to be 171˚C

- **Thin layer chromatography:**It is a chromatography technique used to separate non- volatile mixtures. It can be performed on a sheet of glass, plastic, or aluminium foil, which is coated with a thin layer of adsorbent material, usually silica gel, aluminium oxide, or cellulose.

Procedure:

1. A plate was prepared using silica gel G slurry and was placed in hot air oven for activation for 30 minutes at 110˚C.
2. Meanwhile, the solvent system was prepared using n-hexane and ethyl acetate in the ration 3:7.
3. As benzimidazole is soluble in alcohol, we dissolved some crystals of benzimidazole in methanol.
4. In another beaker, o-phenylenediamine was dissolved in methanol, which is taken as standard.
5. On TLC plate, one spot of benzimidazole and one spot of o-phenylenediamine was drawn using capillary tube.
6. The plate was placed in beaker and was allowed to run.
7. Then, the Rf value of both the spots was calculated.

Rf (retention factor) is defined as the distance travelled by the compound divided by the distance travelled by the solvent.

Rf= "Distance travelled by solute/Distance travelled by solvent"

Rf value of o-phenylenediamine was found to be= 2cm/2.5cm = 0.8

Rf value of benzimidazole was found to be = 1.8cm/2.5cm = 0.72

RESULT:

S.NO.	TEST PERFORMED	STANDARD	RESULT
1	MELTING POINT	170-173˚C	171˚C
2	TLC	Rf- 0.8	Rf-0.72
3	LOSS ON DRYING		13.3%

Table 1: COMPARISION BETWEEN STANDARD DATA AND EXPERIMENTAL DATA.

CONCLUSION:

The benzimidazole ring is an important pharmacophore in modern drug discovery.The synthesis of benzimidazole derivatives as a source of new antimicrobial agents. The Benzimidazole derivatives are a resource for medicinal research. From the above work it was concluded that benzimidazoles and its derivatives possess pharmacological activity with lower toxicities. Thus, Benzimidazole derivatives have wide diverse of biological activity.

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CONFLICT OF INTEREST REPORTED: NIL ; SOURCE OF FUNDING: NONE REPORTED