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CURRENT TRENDS, MODERN SYNTHETIC APPROACH, SAR AND BIOLOGICAL ACTIVITIES OF BENZIMIDAZOLE DERIVATIVES

Nihar Ranjan Kar [1], Prasanthi Samathoti [2], S. Muralitharan [3], Sruti Ranjan Mishra [4], Aditya Vikram Jain [5], Preeti Yadav [6] and G. Dharmamoorthy [7]*

[1] Assistant Professor, Centurion University of Technology and Management, Gopalpur, Balasore, Odisha, India.
[2] Associate Professor, MB School of Pharmaceutical Sciences, Mohan Babu University, Sree Sainath Nagar, Tirupati, Andhra Pradesh.
[3] Tamilnadu Physical Education and Sports University, Chennai.
[4] Professor Cum Principal, Danteswari College of Pharmacy, Borpadar, Raipur Road, Jagdalpur, Chhattisgarh, C.G.
[5, 6] Associate Professor, Department of Pharmacy, IIMT College of Medical Sciences, IIMT University, Ganga Nagar, Meerut.
[7] Professor, Department of Pharmaceutical Analysis, MB School of Pharmaceutical Sciences, Mohan Babu University, (Erstwhile Sree Vidyaniketan College of Pharmacy), Tirupati.
*Corresponding Author Email: dharmamoorthy111@gmail.com

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Abstract

Background: Benzimidazole is a heterocyclic compound with a benzene ring fused to an imidazole ring. It is commercially available as a white, odorless, and tasteless powder. O-phenylenediamine and formic acid are condensed to form benzimidazole. The most common benzimidazole substance found in nature is N- riosyldimethylbenzimidazole, which functions as an axial ligand for cobalt in vitamin B12. **Aim:** The main objective of the review is to explore Current trends, modern synthetic approach, SAR and Biological activities of benzimidazole derivatives. **Method and material:** All the data were collected from online published article which in indexed in SCOPUS, WOS, and UGC. **Result:** Benzimidazole derivatives are generally well-tolerated, but they can cause side effects such as nausea, vomiting, and diarrhea. They can also interact with other medications, so it is important to talk to your doctor before taking them. **Conclusion:** In order to inform the reader on the chemical and pharmacological properties of these compounds, the goal of this article is to provide them a thorough overview of the substituted benzimidazoles.

Keywords: Benzimidazole, heterocyclic compound, imidazole ring, N- riosyldimethylbenzimidazole

INTRODUCTION

In the disciplines of medical and pharmaceutical chemistry, benzoimidazole is well recognised as a substantial and prominent component of physiologically relevant molecules [1,2,3,4,5]. These heterocycles continue to be essential structural motifs in the thoughtful creation of novel medications due to their wide range of biological effects.

The substance has a variety of pharmacological activities, including antioxidant, antiviral, antibacterial, anticancer, and anti-inflammatory actions [5,6,7,8]. A common class of chemotherapeutic medications continues to be molecules that interact with DNA/RNA in medicinal chemistry [9,10,11,12].

Amidines are essential structural elements of many physiologically active chemicals, such as significant pharmaceutical and biochemical agents. Through interactions with hydrogen bonds and electrostatic fields, these derivatives dramatically increase the stability of the molecule/biological target combination [13,14]. It has been shown in a

number of earlier investigations that adding one or two positively charged amidine moieties to the terminal of heteroaromatic benzimidazole/benzothiazole derivatives significantly improves their biological activity [13,14,15,16,17,18,19].

Furthermore, the heteroaromatic derivative's functionalization was made easier by the presence and arrangement of amidine groups, which pointed it in the direction of interactions with negatively charged molecules like DNA and RNA. For instance, it has been shown that specific benzimidazole and benzothiazole derivatives with an amidine group have strong antitumor effects by binding to single-stranded RNA, the minor groove of adenine-thymine DNA, or the adenine-thymine rich region of cytosine-thymine DNA [20,21].

They can also intercalate into double-stranded RNA and cytosine-thymine DNA. Additionally, research on the antibacterial properties of dicationic compounds with amidine moiety, such as pentamidine, has been going on since the turn of the 20th century.

These studies have shown its effectiveness in treating a number of disorders [22,23]. It has been shown that several derivatives with comparable properties display binding affinity to the minor groove of DNA at AT-rich sites [24,25]. many biophysical studies [26] as well as many crystallographic analysis have supported this claim. The chemical characteristics of 2,5-disubstituted furane derivatives, which might include one or two amidine functional groups, have received a lot of attention in study.

Benzimidazole is a heterocyclic compound with a benzene ring fused to an imidazole ring. It is commercially available as a white, odorless, and tasteless powder. O-phenylenediamine and formic acid are condensed to form benzimidazole. The most common benzimidazole substance found in nature is N- riosyldimethylbenzimidazole, which functions as an axial ligand for cobalt in vitamin B12.Benzimidazole and its derivatives have a wide range of pharmacological activities, including antihelminthic, antifungal, antidiabetic, anticancer, and antiviral. They are used in the treatment of a variety of diseases, including parasitic infections, fungal infections, diabetes, cancer, and HIV.

The mechanism of action of benzimidazole derivatives varies depending on the specific compound. However, they generally work by interfering with the metabolism of the target organism. For example, antihelminthic benzimidazole derivatives disrupt the metabolism of parasitic worms, leading to their death. Antifungal benzimidazole derivatives inhibit the growth of fungi by interfering with their cell wall synthesis. Antidiabetic benzimidazole derivatives improve insulin sensitivity and help to lower blood sugar levels.

Benzimidazole derivatives are generally well-tolerated, but they can cause side effects such as nausea, vomiting, and diarrhea. They can also interact with other medications, so it is important to talk to your doctor before taking them. The article you mentioned is a comprehensive review of the chemistry and pharmacological properties of substituted benzimidazoles. It is a valuable resource for anyone interested in learning more about this important class of compounds.

Here are some additional information about the pharmacological properties of benzimidazole derivatives: [27-30]

- **Antihelminthic:** Benzimidazole derivatives are used to treat a variety of parasitic infections, including roundworms, tapeworms, and hookworms. They work by disrupting the metabolism of the parasites, leading to their death.
- **Antifungal:** Benzimidazole derivatives are used to treat a variety of fungal infections, including athlete's foot, jock itch, and ringworm. They work by inhibiting the growth of fungi by interfering with their cell wall synthesis.
- **Antidiabetic:** Benzimidazole derivatives are used to treat type 2 diabetes. They work by improving insulin sensitivity and helping to lower blood sugar levels.
- **Anticancer:** Benzimidazole derivatives are being investigated for the treatment of cancer. They work by interfering with the growth and spread of cancer cells.
- **Antiviral:** Benzimidazole derivatives are being investigated for the treatment of HIV and other viruses. They work by interfering with the replication of the viruses.

Benzimidazole derivatives are a promising class of compounds with a wide range of therapeutic applications. They continue to be an important area of research for the development of new drugs to treat a variety of diseases.

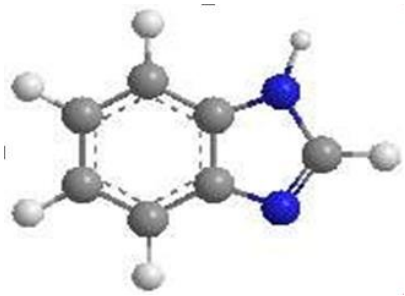

Fig 1: 3D Model of 1H-benzimidazole

In 1944, Woolley proposed that benzimidazole may exhibit comparable characteristics to purines, thereby leading to the first recognition of the therapeutic potential associated with the benzimidazole nucleus. Brink's investigation led to the identification of 5,6-dimethylbenzimidaozle as a breakdown product of vitamin B12, afterwards revealing that various compounds of Brink had properties similar to vitamin B12. The first discoveries prompted extensive research on the nucleus, with the aim of investigating its numerous functions and applications. The benzimidazole molecule exhibits a diverse array of pharmacokinetic and pharmacological attributes in its derivative forms.

The benzimidazole nucleus is a bioactive heterocyclic compound that exhibits a diverse range of biological properties. These properties encompass antiparasitic, anticonvulsant, analgesic, antihistaminic, antiulcer, antihypertensive, antiviral, anticancer, antifungal, anti-inflammatory, proton pump inhibitory, and anticoagulant activities. A variety of drugs, such as albendazole, mebendazole, and thiabendazole, have been developed by the process of optimising the substituents around the benzimidazole nucleus. The term "benzimidazole" is often used at positions 3, 5, and 8.

A number of benzimidazole compounds, namely LY 12277172 and LY 127123, have shown notable effectiveness in inhibiting picorna viruses.The user's text is too short to be rewritten in an academic manner. Previous studies have shown the use of certain derivatives of benzimidazoles as pharmacophores in the development of anticonvulsant drugs, provided that appropriate substituents are present. In the last decade, there has been a notable surge in research efforts focused on the synthesis of bioactive molecules derived from benzimidazole. The benzimidazole nucleus is now used in the synthesis of essential intermediates for many chemical processes. [31-35]

Chemistry of Benzimidazoles

The chemistry of benzimidazoles is a vast and complex field. Here is a brief overview of some of the key concepts:

- **Structure:** Benzimidazole is a heterocyclic compound with a benzene ring fused to an imidazole ring. The imidazole ring is a five-membered ring with two nitrogen atoms. The benzene ring is a six-membered ring with alternating single and double bonds.
- **Synthesis:** There are many different ways to synthesize benzimidazoles. One common method is to condense o-phenylenediamine with a carboxylic acid. Another method is to condense a substituted hydrazine with a carbonyl compound.
- **Reactivity:** Benzimidazoles are relatively reactive compounds. They can undergo a variety of reactions, including electrophilic substitution, nucleophilic substitution, and addition reactions.
- **Pharmacological properties:** Benzimidazoles have a wide range of pharmacological properties. They are used in the treatment of a variety of diseases, including parasitic infections, fungal infections, diabetes, cancer, and HIV.

The chemistry of benzimidazoles is a constantly evolving field. New methods of synthesis are being developed, and new pharmacological applications are being discovered. Benzimidazoles are a promising class of compounds with the potential to treat a variety of diseases.

Here are some specific examples of the chemistry of benzimidazoles:

- **Electrophilic substitution:** Benzimidazoles can undergo electrophilic substitution reactions at the nitrogen atoms in the imidazole ring. This can be used to introduce substituents into the ring.
- **Nucleophilic substitution:** Benzimidazoles can also undergo nucleophilic substitution reactions at the nitrogen atoms in the imidazole ring. This can be used to synthesize new compounds with different biological activities.
- **Addition reactions:** Benzimidazoles can undergo addition reactions with alkenes and alkynes. This can be used to synthesize new compounds with different properties.

The chemistry of benzimidazoles is a complex and fascinating field. It is a valuable tool for the synthesis of new compounds with potential therapeutic applications.

The benzimidazoles consist of a phenyl ring that is fused to an imidazole ring, as seen in the structural representation of benzimidazole illustrated in Figure 2. [36-37]

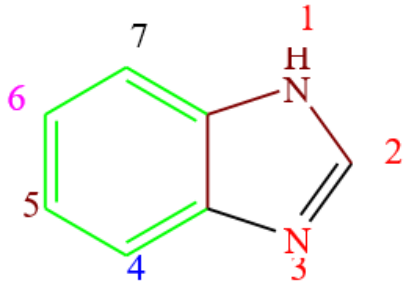

Fig 2: Phenyl ring that is fused to an imidazole ring

The first benzimidazole chemical was successfully synthesised by Hoebrecker in 1872. Included in this accomplishment was the reduction of 2-nitro-4-methylacetanilide, which produced 2,5 (or 2,6)-dimethylbenzimidazole. The substances known as benzimidazoles may also be referred to as benzoglyoxalines or benzimidazoles. Particularly in previous literature, these substances have also been referred to as o-phenylenediamine derivatives. This nomenclature would identify benzimidazole as methenyl-o-phenylenediamine and 2-methylbenzimidazole as ethenyl-o-phenylenediamine. These substances have also been classified as derivatives of the mixture that makes up the ring's imidazole moiety. It should be noted that benzimidazole has also been known by other names, including o-phenyleneformamidine, 2 (3H)-benzimidazolone, and 2 (3H) benzimidazolethione, which are also known as o-phenyleneurea and o-phenylenethiourea, respectively. These names are shown in Figures 3 and 4, respectively.

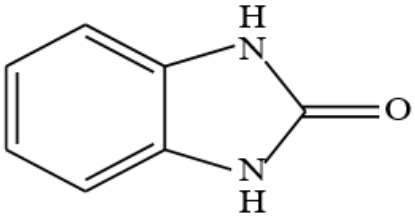

Fig 3: 2 (3H)- benzimidazolone

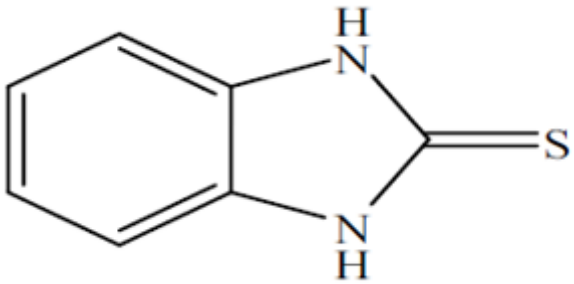

Fig 4: 2 (3H) benzimidazolethione

Multiple Methods For Producing Benzimidazoles:

There are many different methods for producing benzimidazoles. Some of the most common methods include:

1. Condensation of o-phenylenediamine with a carboxylic acid: This is the most common method for producing benzimidazoles. O-phenylenediamine is condensed with a carboxylic acid in the presence of a base, such as sodium hydroxide. The reaction product is a benzimidazole derivative. [38]

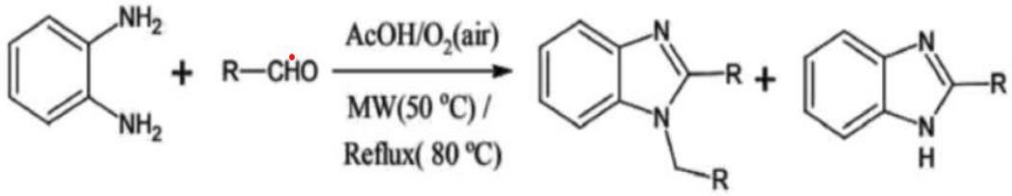

Fig. 5: O-phenylenediamine is condensed with a carboxylic acid

2. Condensation of a substituted hydrazine with a carbonyl compound: This method is similar to the previous method, but a substituted hydrazine is used instead of o-phenylenediamine. The substituted hydrazine is condensed with a carbonyl compound in the presence of a base. The reaction product is a benzimidazole derivative. [39-40]

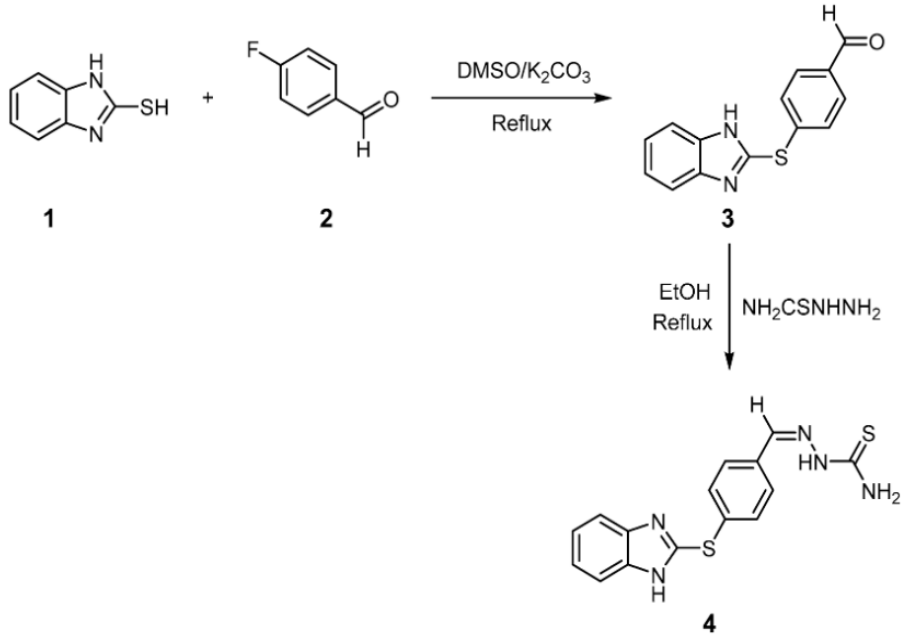

Fig. 6: Preparation of 4-[(1*H*-benzimidazol-2-yl)sulfanyl]benzaldehyde and 2-({4-[(1*H*-benzimidazol-2-yl)sulfanyl]phenyl}methylidene)hydrazine-1-carbothioamide.

3. Reaction of a benzimidazole with a diazonium salt: A benzimidazole can be reacted with a diazonium salt to produce a new benzimidazole derivative. The diazonium salt is generated in situ from a primary aromatic amine. The reaction is carried out in the presence of a base. [39-40]

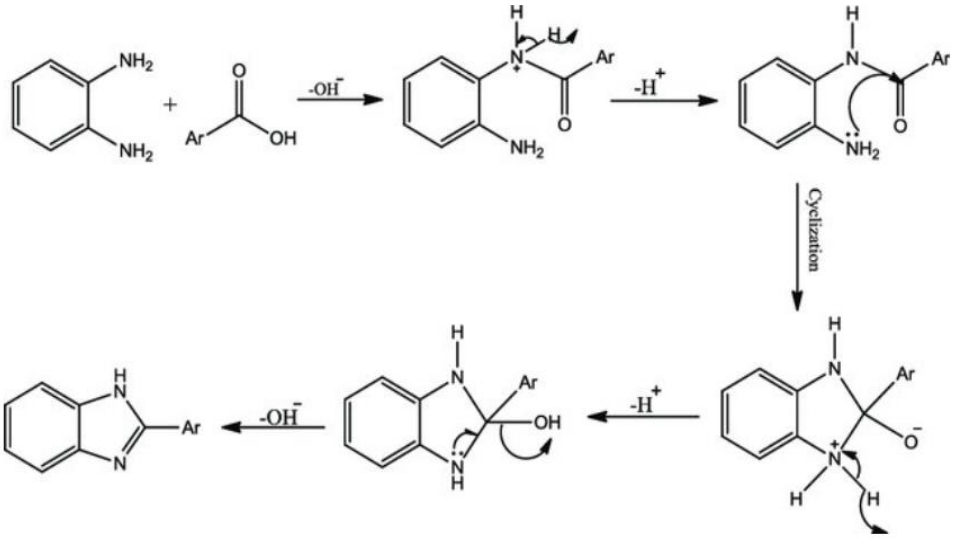

Fig 7: Reaction with a diazonium salt

4. Ring expansion of a succinimide: A succinimide can be ring-expanded to produce a benzimidazole. The ring expansion is catalyzed by a base.

5. Palladium-catalyzed coupling reaction: A benzimidazole can be synthesized by a palladium-catalyzed coupling reaction between an aryl halide and a hydrazine. The reaction is carried out in the presence of a base.

These are just a few of the many methods that can be used to produce benzimidazoles. The choice of method will depend on the specific benzimidazole derivative that is desired. [41-47]

General Procedure for the Synthesis of 2-Substituted Benzimidazoles

Sure, here is a general procedure for the synthesis of 2-substituted benzimidazoles:

1. Prepare the carbonyl compound. The carbonyl compound can be an aldehyde, ketone, carboxylic acid, or acid anhydride. The carbonyl compound should be dry and free of impurities.
2. Prepare the o-phenylenediamine. O-phenylenediamine is a solid, so it should be dissolved in a solvent, such as ethanol or methanol.
3. Combine the carbonyl compound and o-phenylenediamine in a reaction vessel. The reaction vessel should be dry and inert.
4. Add a base to the reaction vessel. The base will help to promote the condensation reaction. A common base is sodium hydroxide.
5. Heat the reaction mixture. The reaction mixture should be heated to a temperature of 100-150 degrees Celsius.
6. Monitor the reaction. The reaction should be monitored to ensure that it is complete.
7. Isolate the product. The product can be isolated by distillation or extraction.

Here is a specific example of the synthesis of a 2-substituted benzimidazole: [48-57]

- **Starting materials:**
  - o-Phenylenediamine
  - Acetaldehyde
  - Sodium hydroxide
- **Procedure:**
  - Dissolve o-phenylenediamine in ethanol.
  - Add acetaldehyde to the solution.
  - Add sodium hydroxide to the solution.
  - Heat the solution to 100 degrees Celsius.
  - Monitor the reaction until it is complete.
  - Distil the product to isolate it.

The product of this reaction is 2-acetylbenzimidazole.

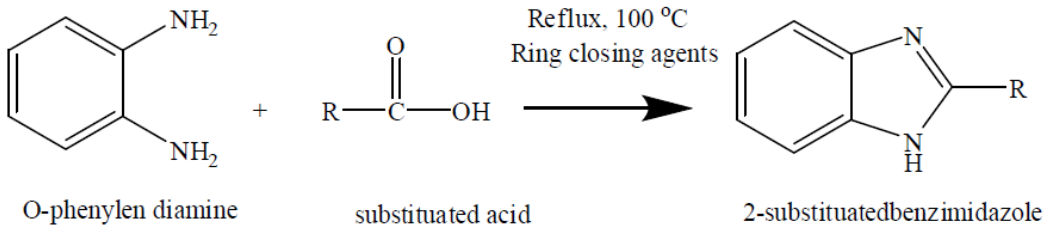

Fig 8: Synthesis of 2-Substituted Benzimidazoles

Biological Importance of Benzimidazole

The "Master Key," also known as the benzimidazole nucleus, is the key core of multiple compounds that act at various sites to create a variety of pharmacological effects. A broad variety of chemical compounds may fit into the seven places of the benzimidazole nucleus, however the majority of physiologically active benzimidazole-based compounds include functional groups at positions 1, 2, and/or 5(or 6). As a result, the compounds contain derivatives of the nucleus that are mono-, di-, or tri-substituted. Antihypertensive, anti-inflammatory, antibacterial, antifungal, anthelmintic, antiviral, antioxidant, antiulcer, anticancer, and pyschoactivity are a few of the main effects. As mentioned in, there are several products that include benzimidazole. [58-69]

Benzimidazole and its derivatives have a wide range of biological activities, including antihelminthic, antifungal, antidiabetic, anticancer, and antiviral. They are used in the treatment of a variety of diseases, including parasitic infections, fungal infections, diabetes, cancer, and HIV.

The biological importance of benzimidazole can be summarized as follows:

- **Antihelminthic:** Benzimidazole derivatives are used to treat a variety of parasitic infections, including roundworms, tapeworms, and hookworms. They work by disrupting the metabolism of the parasites, leading to their death.
- **Antifungal:** Benzimidazole derivatives are used to treat a variety of fungal infections, including athlete's foot, jock itch, and ringworm. They work by inhibiting the growth of fungi by interfering with their cell wall synthesis.
- **Antidiabetic:** Benzimidazole derivatives are used to treat type 2 diabetes. They work by improving insulin sensitivity and helping to lower blood sugar levels.
- **Anticancer:** Benzimidazole derivatives are being investigated for the treatment of cancer. They work by interfering with the growth and spread of cancer cells.
- **Antiviral:** Benzimidazole derivatives are being investigated for the treatment of HIV and other viruses. They work by interfering with the replication of the viruses.

Benzimidazole derivatives are a promising class of compounds with a wide range of therapeutic applications. They continue to be an important area of research for the development of new drugs to treat a variety of diseases.

Here are some specific examples of the biological importance of benzimidazole:

- **Albendazole:** Albendazole is an antihelminthic drug that is used to treat a variety of parasitic infections, including roundworms, tapeworms, and hookworms. It is also used to treat giardiasis, an infection caused by a parasite called Giardia lamblia.
- **Mebendazole:** Mebendazole is another antihelminthic drug that is also used to treat giardiasis. It is also used to treat pinworms and whipworms.
- **Thiabendazole:** Thiabendazole is an antifungal drug that is used to treat a variety of fungal infections, including athlete's foot, jock itch, and ringworm. It is also used to treat strongyloidiasis, an infection caused by a parasitic worm called Strongyloides stercoralis.
- **Voriconazole:** Voriconazole is an antifungal drug that is used to treat more serious fungal infections, such as those that affect the lungs or the blood. It is also used to prevent fungal infections in people who are at high risk, such as those who have had an organ transplant.
- **Olaparib:** Olaparib is a PARP inhibitor that is used to treat certain types of cancer, such as ovarian cancer and breast cancer. PARP inhibitors work by blocking a protein that is involved in DNA repair. This can lead to the death of cancer cells.

These are just a few examples of the many ways that benzimidazole and its derivatives are used in medicine. Benzimidazole is a versatile compound with a wide range of potential therapeutic applications. It is an important area of research for the development of new drugs to treat a variety of diseases. [69-70]

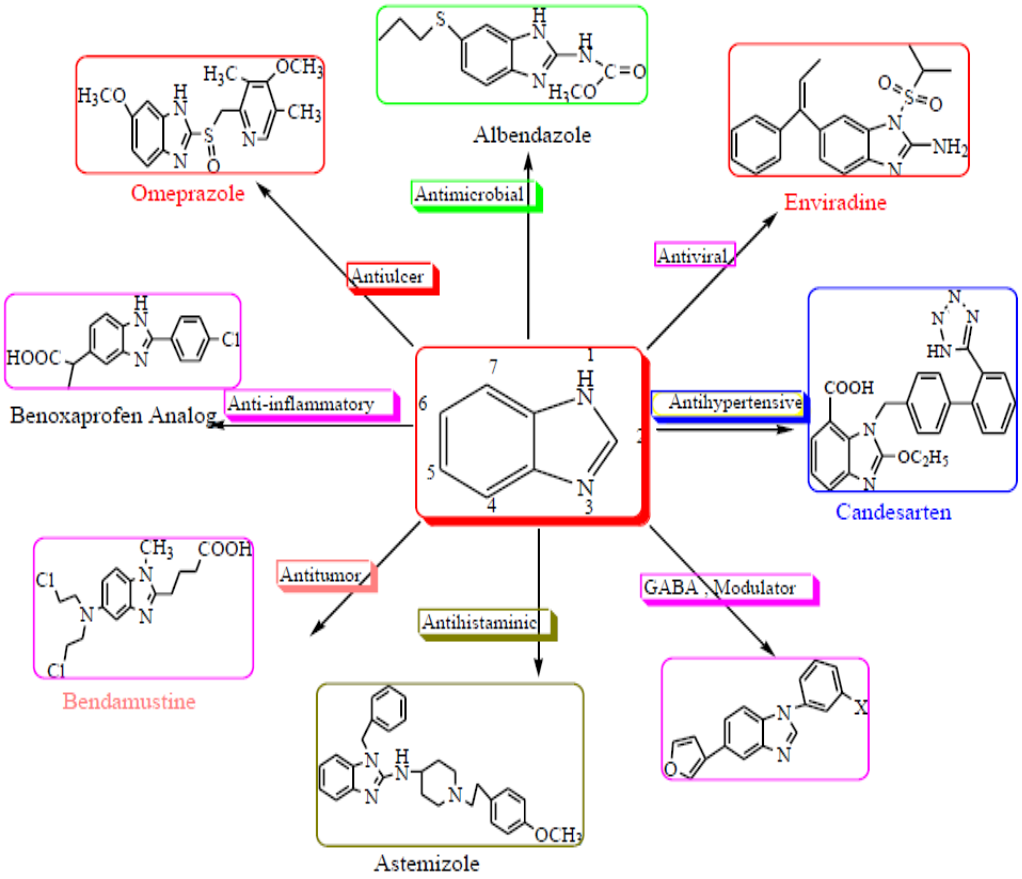

Fig 9: Benzimidazole, a multifunctional nucleus

Structural Activity Relationship of benzimidazole:

The structural activity relationship (SAR) of benzimidazoles refers to the relationship between the structure of a benzimidazole compound and its biological activity. SAR studies have shown that the structure of the benzimidazole ring is essential for its biological activity. The substituents on the benzimidazole ring can also significantly alter its biological activity.

Here are some of the key findings of SAR studies on benzimidazoles:

- The presence of the imidazole ring is essential for biological activity.
- The substituents on the 2-position of the benzimidazole ring have the greatest impact on biological activity.
- Electron-withdrawing substituents on the 2-position of the benzimidazole ring tend to increase biological activity.
- Electron-donating substituents on the 2-position of the benzimidazole ring tend to decrease biological activity.
- The substituents on the 5-position of the benzimidazole ring also have an impact on biological activity, but to a lesser extent than the substituents on the 2-position.

SAR studies have been used to design new benzimidazole compounds with improved biological activity. For example, SAR studies have been used to design new antifungal benzimidazole compounds that are more effective against drug-resistant fungi.

Here are some examples of how the SAR of benzimidazoles has been used to design new drugs:

- The antihelminthic drug albendazole was designed based on SAR studies. Albendazole has a 2-chlorophenyl substituent, which is an electron-withdrawing group that increases its biological activity.
- The antifungal drug voriconazole was also designed based on SAR studies. Voriconazole has a 5-fluorophenyl substituent, which is an electron-withdrawing group that increases its biological activity.
- The PARP inhibitor olaparib was designed based on SAR studies. Olaparib has a 4-methylpyrimidine substituent, which is an electron-donating group that decreases its toxicity.

SAR studies are a valuable tool for the design of new benzimidazole compounds with improved biological activity. They are an important part of the drug discovery process. [71-72]

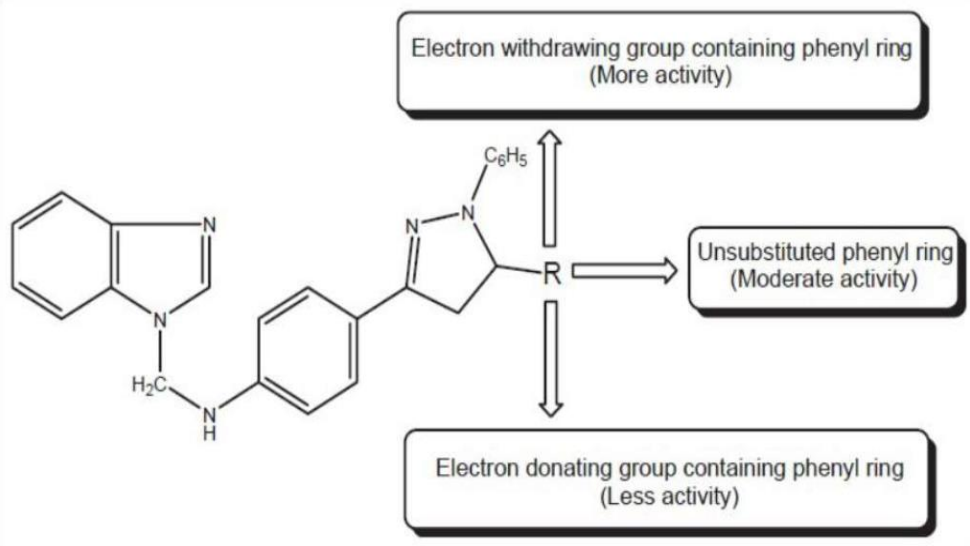

Fig 10: Structural Activity Relationship of benzimidazole

CONCLUSION

Anti-microbial, anti-viral, anti-diabetic, and anti-cancer activity are some of the biological benefits that may be attributed to benzimidazoles, which belong to a possible family of bioactive heterocyclic compounds and demonstrate these characteristics. This exhaustive review describes the chemistry of a number of different derivatives of substituted benzimidazole as well as the antibacterial activity of these compounds.

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