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A review of Benzimidazole derivatives' potential activities

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Abstract
Benzimidazole derivatives are a class of molecules with various biological properties that have received medicinal chemistry attention. This review addresses benzimidazole derivatives' drug discovery and development potential. Anticancer, antibacterial, anti-inflammatory, antiviral, and antiparasitic actions are reviewed. The structure-activity relationship (SAR) and mechanisms of benzimidazole derivatives are also discovered. Benzimidazole derivatives with therapeutic purposes are also emphasised. This review discusses the therapeutic uses of benzimidazole derivatives. It aids researchers, medicinal chemists, and pharmaceutical scientists in developing innovative benzimidazole-based medications. This review can aid in discovering new lead compounds and optimising existing benzimidazole derivatives for enhanced therapeutic efficacy.

Keywords: Benzimidazole, heterocyclic, anticancer, antibacterial, anti-inflammatory

1. Introduction
Heterocyclic compounds possess a cyclic structure with two or more different kinds of atoms in the ring. These types of compounds are very widely distributed in nature and are essential to life, playing a vital role in the metabolism of all living cells, e.g., the pyrimidine and purine bases of the genetic material DNA, the essential amino acids proline and hisitidine,the vitamins and coenzymes, etc. There are a vast number of pharmacologically active heterocyclic compounds, many of which are in regular clinical use [1, 2]. A wide range of synthetic and naturally occurring heterocyclic compounds find their use in medicines and also in pesticides, agrochemicals, polymers, etc. This attracts the attention of scientists, who carry out more and more research leading to novel heterocyclic molecules having useful biological activities Of the wide variety of heterocyclic systems known till date, the nitrogen heterocycles are of great importance, and benzimidazole is one among such important nitrogen heterocyclic species because of its synthetic utility and broad spectrum of pharmacological activity [3, 4]. The benzimidazole nucleus is an important heterocyclic ring since several of its derivatives have pharmacological properties and have been marketed as commercial products. Most significantly, the benzimidazole ring system has been found to be an integral part of Vitamin B_{12} in the form of 5,6-dimethyl-1-(-D-ribofuranosyl) benzimidazole. Many benzimidazole derivatives with different pharmacological properties, such as anthelmintic, antiulcer, cardiotonic, antihypertensive, etc., have already been reported. The literature precedence revealed that the substitutions at 1, 2, and 5 positions of the benzimidazole moiety are crucial for the compounds to exhibit a wide range of pharmacological activities. The zimidazole ring system can theoretically be derived by the fusion of an imidazole ring through its 4-bond to a benzene ring (Figure 2) [1].
The two nitrogen's present in the imidazole ring are different from one another in their nature, and this makes the properties of the ring system diverse in character. The nitrogen-bearing hydrogen atom is sp3 in character and is often referred to as pyrrole nitrogen, while the other is sp2 in character and is also referred to as pyridine nitrogen. The hydrogen atom attached to the nitrogen in benzimidazole exhibits tautomerism, as shown below [1, 4]. This isomerism analogous to that found in imidazoles and amidines. Due to this tautomerism, certain benzimidazole derivatives that appear at first as isomers are in reality the tautomerism. The 4 and 5 positions are equivalent to the 6 and 7 positions because of this

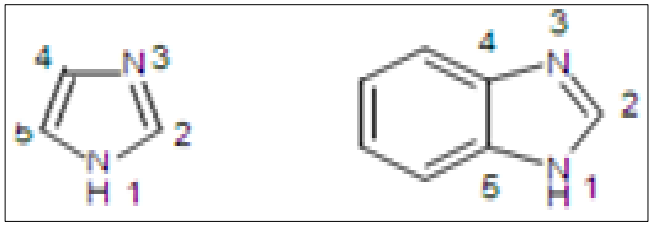


Fig 1 and 2: [Pyrrole and indole ring]

6 and 7 positions because of this tautomerism. For example, 5-methylbenzimidazole is a tautomer of 6-methylbenzimidazole (Figure-1) [1].

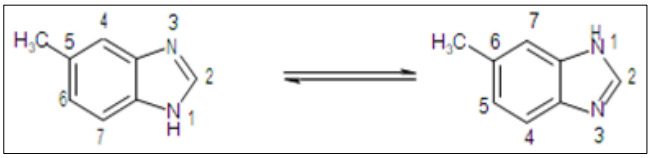


Fig 3 and 4: [5-methylbenzimidazole and 6-methylbenzimidazole]

To prevent any confusion between the two automers, both named structures are written with the other in parentheses, for example, 5 (6)-methylbenzimidazole. When the group attached to the nitrogen at the 1-position is other than hydrogen, such atomerism is prevented and only isomeric forms exist. Thus, 1,5-dimethylbenzimidazole and 1,6-dimethylbenzimidazole exist as separate, isomeric compounds.

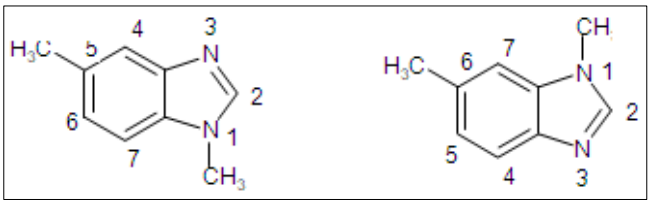


Fig 4 and 5: [,1,5-dimethylbenzimidazole and 1,6-dimethylbenzimidazoleexist]

2. Methods for synthesizing benzimidazoles

Detailed reviews covering the synthesis and chemistry of both imidazole's and benzimidazoles have been published. Generally, benzimidazoles can be synthesized from a variety of starting materials, including a few of the listed ones.

1. *o*-Phenylenediamines
2. *o*-(*N*-acylaminoand*N*–aryolamino)arylaminesand itroarenes
3. *o*-Nitroarylaminesando-dinitroarenes
4. *o*-substituted-*N*-benzylideneanilines
5. Amidines
6. Otherheterocycliccompounds

1. Fromo-Phenylenediamine

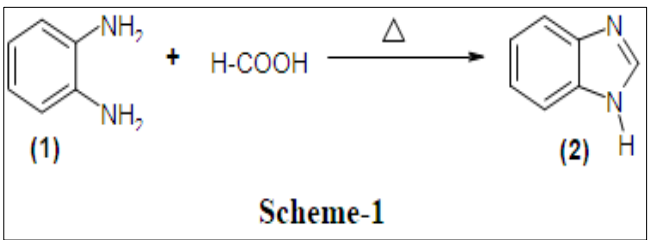


Fig 6 and 7: [o-Phenylenediamine and carboxylic acids]

o-Phenylenediamine (1) interacts with carboxylic acids and their derivatives, amino-ethers, carbonyl compounds, and nitriles to produce benzimidazoles with diverse substituents.

3. By reaction with carboxylic acids and their derivatives

By condensing o-phenylenediamine (1) with carboxylic acids under a range of circumstances, substituted benzimidazoles can be synthesized in high yields. First prepared 2,5(or 2,6)-dimethyl benzimidazole by refluxing 4-methyl-o phenylenediamine in glacial acetic acid. In 1878, the parent benzimidazole (2) was produced by heating (1) with formic acid (Scheme-1) [1]. Since then, a large number of benzimidazoles have been synthesized from and aliphatic acids (1,3). The most satisfactory method for the synthesis of 2-alkylbenzimidazoles (3, R = alkyl) was developed by Phillips, which involves refluxing equimolar quantities of the diamine and the aliphatic carboxylic acid in 4Nhydrochloricacid for 3 to 4 hr (Scheme-2) [1, 2].

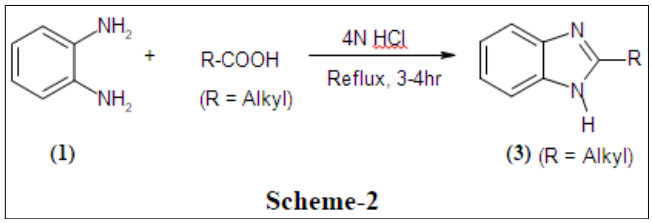


Fig 7 and 8: [o-phenylenediamine and 2-alkylbenzimidazoles]

The concerning mechanistic route for the formation of benzimidazoles by the reaction of 1 with an organic acid has already been studied [2, 9]. Furthermore, the role of hydrochloric acid in the reaction has also been investigated [1, 4] The catalytic action of hydrochloric acid is explained on the basis of activation of the carboxyl group by protonation of oxygen. The intermediate in the reaction is an addition product formed by the attack of a nitrogen's shared electron pair on the carbonyl group of the protonated acid. However, researcher concluded that the monoacyl derivative was the essential intermediate for the formation of the benzimidazolringe. [1, 4].

For aromatic carboxylic acids, however, Phillips' procedure fails to give any respectable yields of 2-arylbenzimidazoles (2,5). Aromatic carboxylic acids were reported to give good yields of 2-arylbenzimidazoles (4, R = Ar) when heated with 1 in a sealed tube at 180–190ºC better procedure for the preparation of 2-arylbenzimidazoles (4) from aromatic carboxylic acid involves the use of polyphosphoric acid (PPA) or polyphosphate ester (PPE) as dehydrating agents. Alternatively, phosphorus pentoxide has also been reported as a dehydrating agent for the preparation of 2-arylbenzimidazoled derivatives (Scheme-3) [4].

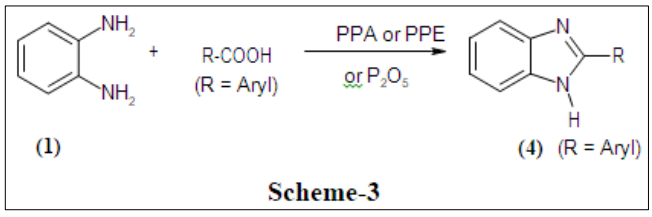


Fig 8 and 9: [o-phenylenediamine(1) and of 2-arylbenzimidazoles(4)]

In recent years, the steps described above have been used to synthesise a range of benzimidazoles with thiazolyl,

thiadiazolyl, and isothiazolyl substituents at 2-positions 36-37. In a similar way, the other benzimidazoles synthesized. Niementowski initially examined the reaction between 4-methyl-o-phenylenediamine dihydrochloride (5) and esters, preparing 5-methyl benzimidazole (6, X = 5(6)-methyl) by condensation of equimolar amounts of (5) and ethyl formate at 225 °C in a sealed tube for 3 hours (Scheme-4) [1, 4].

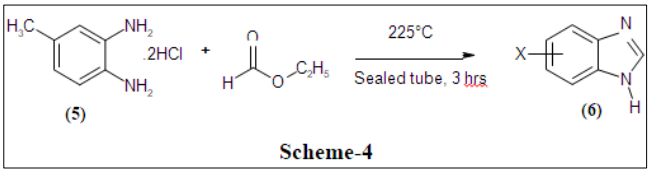


Fig 10 and 11: [4-methyl-o-phenylenediamine dihydrochloride (5) and esters, 5-methyl benzimidazole (6)]

A farther treatment of 1 with acetic anhydride gave 2-methyl benzimidazole (3, R = CH3), whereas a shorter treatment yielded only N, N'-diacetyl-phenylenediamine (Scheme-5). Reinhardt reported that dilute hydrochloric acid enhanced yields of 2-methylbenzimidazole from 1 and 2% acetic anhydride. Similarly, treatment of the free base of 5, i.e., 4-methyl-o-phenylenediamine, with acetyl chloride in refluxing benzene yielded 2,5 (2,6)-dimethyl benzimidazole. In contrast, when the reaction was conducted at the ambient temperature, the corresponding 4-methyl-N, N'-diacetyl-o-phenylenediamine was the sole product [1, 4, 5].

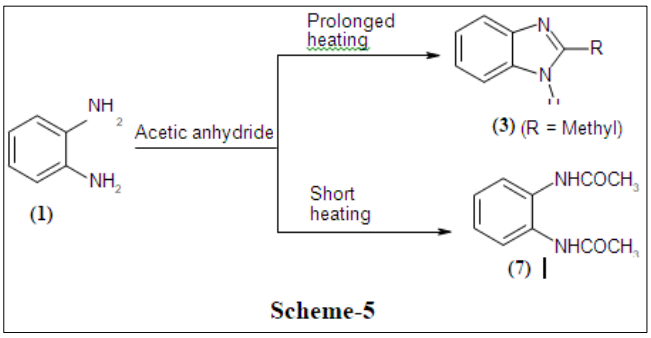


Fig 12, 13 and 14: [o-phenylenediamine(1), 2-methyl benzimidazole (3) and 2,5 -dimethyl benzimidazole(7)]

Niementowski synthesized 2-substituted 5 (6)-methyl benzimidazoles (8,X=5 (6)-methyl,R =H,CH3orPh) by heating freebase(5) with the corresponding amides (Schme-6)

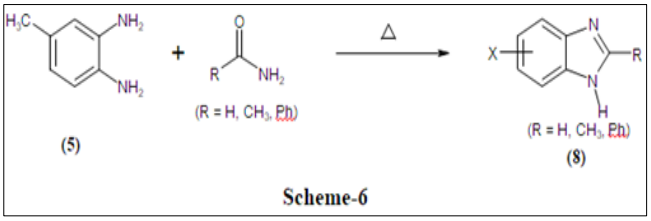


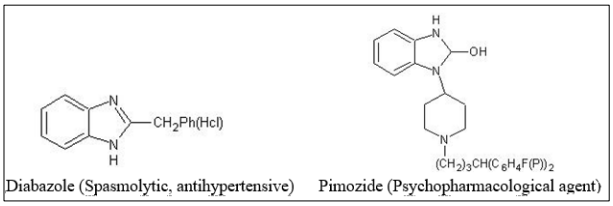
Fig 14 and 15: [Synthesis of 2-substituted benzimidazoles from o-nitroanilines and aryl aldehydes via an in situ nitro reduction]

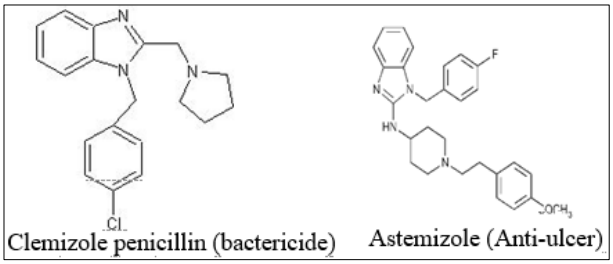
4. Compounds having benzimidazole nucleus

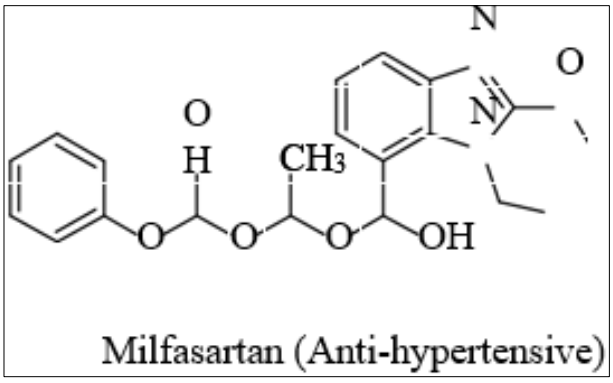
5-Dimethylbenzimidazole's role in vitamin B12 piques experts' curiosity. Plenty of antibacterial, antifungal, anti-helminthic, anti-allergic, anti-neoplastic, local analgesic, antihistaminic, anti-leishmanial, vasodilator, anti-hypertensive, spasmolytic, and anti-ulcer effects were found in benzimidazole derivatives. 2010 [4, 5, 6].

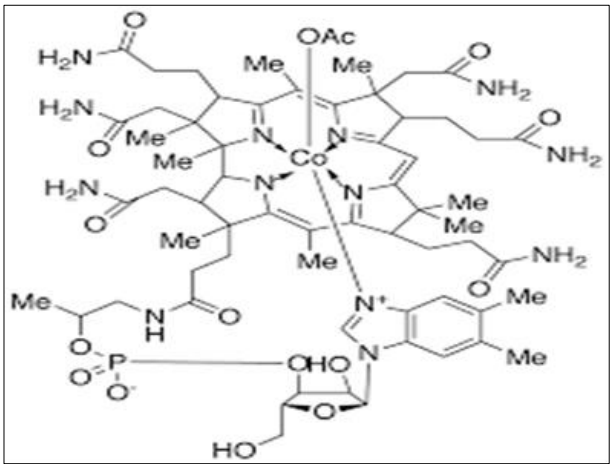
Anti inflammetry. anti-histaminic, antibacterial, anticancer, and cyclooxygenase inhibitory properties have been reported in many 2-substituted benzimidazoles. Some benzamidiazole eosides, such as 5,6-dichlorobenzimidazole-1-D-ribofuranoside (DRB) and its 2-substituted variants, inhibit human cytomegalovirus. 5, 6-dinitrobenzimidazole can also replace 5, 6-dimethylbenzimidazole in coryne's vitamin B12 molecule. Bacteria, diphtheria, and 2-trifluorobenzimidazoles are powerful [4].

Benzimidazole derivatives inhibit several viruses, such as HIV, HSV-1, RNA, influenza, and HCMV. Benzimidazole replaced with a sugar residue at C-2 is a powerful glycogen phosphorylase inhibitor and a candidate for diabetic mellitus medication development [1, 6, 7].

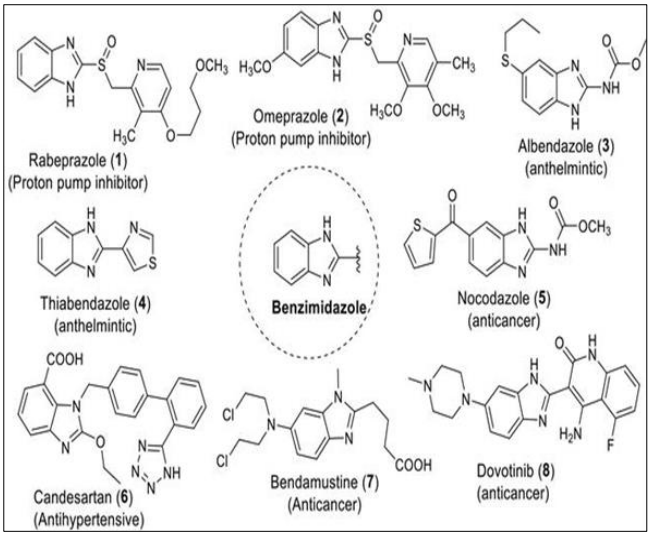








Vitamin -B 12
Compounds containing benzimidazole nucleus [4].

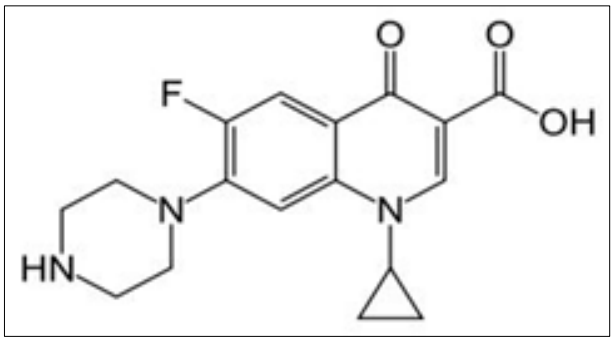


Target-Based Benzimidazole Derivatives

Ref: N. S.,*et al* (2020) [10]

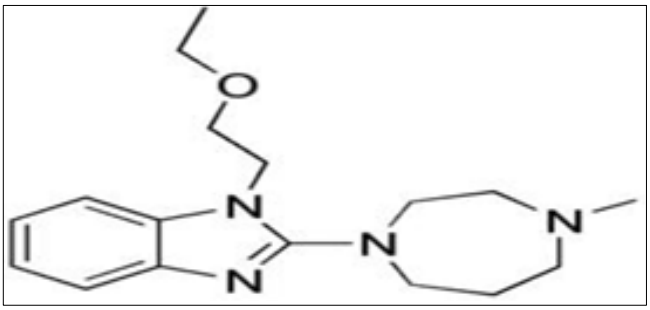
4.1 As a fungicide drugs
Benomyl, carbendazim, and chlorphenazole are all examples of fungicides that belong to the benzimidazole class. Cypendazole, Debacarb, Fubaridazole, Furofanate, Mecarbinizid, Rabenzazole, Thiabendazole, and Thiofanate, Arbendazim are a systemic fungicide that can be used both to prevent and treat fungal infections. The plant takes it up via its roots and its green tissues. It stops the production of beta-tubulin, stops the creation of germ tubes, and stops mycelia growth. It is suitable for use alongside the majority of pesticides. This substance is applied topically to prevent diseases such as blasts, sheath blight, brown spots, powdery mildew, scab, anthracnose, and leaf spot from spreading in various crops [1, 4].

4.2. As antimicrobial drugs
Ciprofloxacin: Ciprofloxacin is an antibiotic that belongs to the class of medicines known as Quinolone. It is used to treat infections caused by certain bacteria. It is most usually used. Treat skin, sinus, bone, and lung infections. Ear, stomach, kidney, prostate, and bladder.



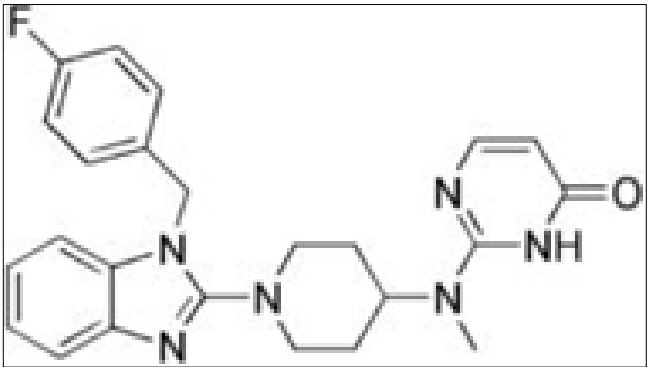
Ciprofloxacin

4.3 As anti allergic conjunctivitis drugs
The drugs containing benzimidazole are Emedastine, Mizolastine, Clemizole, and is a second generation antihistamine used in eye drops to treat allergic conjunctivitis. It acts as a H_1 receptor antagonist. It works by blocking certain natural substances, histamines that cause allergic symptoms.



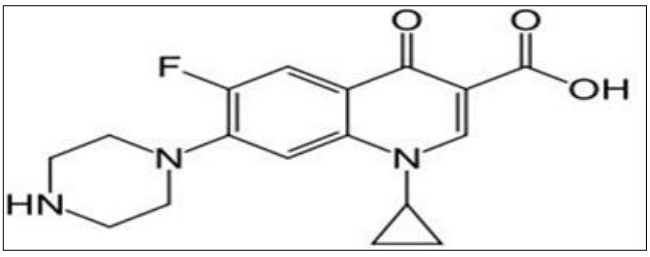
Emedastin

Mizolastine is a once daily, non-sedating antihistamine. It blocks H_1 receptors and is commonly fast-acting. It does not prevent the actual release of histamine from mast cells, just prevents it binding to receptors [4, 11]



Mizolastine

4.4. As an antimicrobial drugs
Ciprofloxacin: Ciprofloxacin is an antibiotic that belongs to the class of drugs known as quinolones. It is used to treat infections caused by by specific bacteria. It is most typically used to treat infections of the skin, sinuses, bone, lungs, ear, abdomen, kidney, prostate, and bladder [11-13]

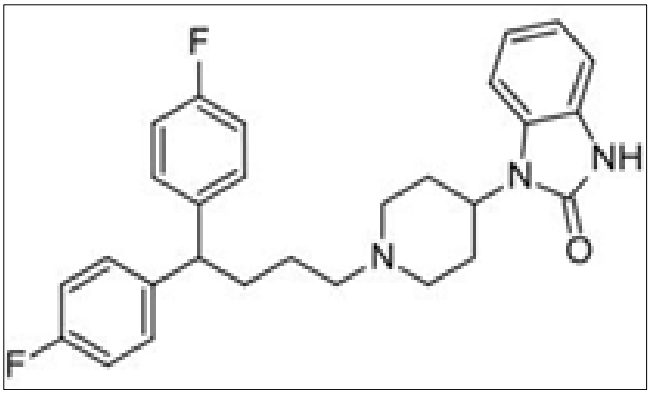


Ciprofloxacin

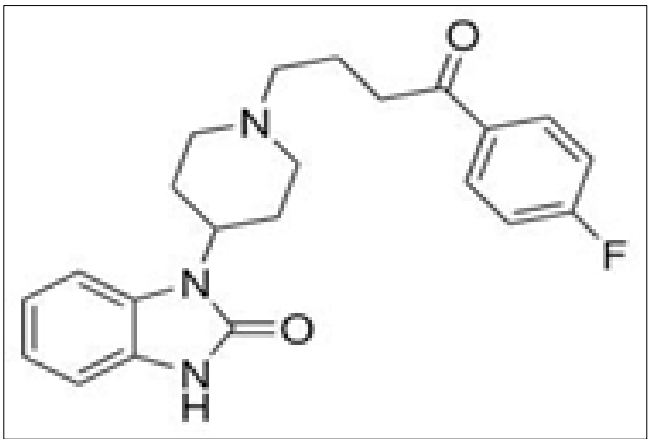
4.5 sAntiulcer drug
These are the drugs used as a short-term treatment in healing and symptomatic relief of duodenal ulcers and erosive or ulcerative gastroesophageal reflux disease (GERD); Gastric ulcer (GU), Peptic ulcer disease (PUD), (Zollinger-Ellison syndrome), Helicobacter pylori eradication to reduce risk of duodenal ulcer recurrence. Some medications containing benzimidazole nucleus are Rabeprazole, Omeprazole, Lansoprazole, Pantoprazole, etc.These medications belong to class of proton pump inhibitor like Rabeprazole, omeprazole [7-11]

4.6. As an antipsychotic drug

In psychosis, the thinking of the patient becomes illogical, weird and loosely arranged. The patient has difficulties in understanding the reality and his situations. These medications are used in schizophrenia and persistent psychosis. Some medications containing the benzimidazole nucleus are droperidol, pimozide, and benperidol [1, 3, 5].



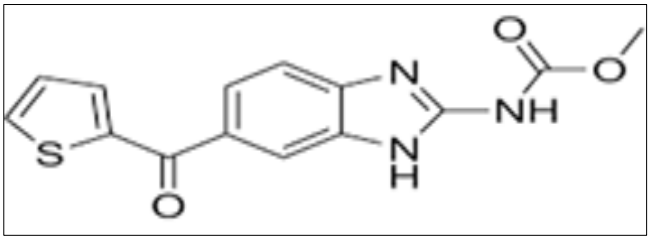
Pimozide



Benperido

4.7 As anti-neoplastic

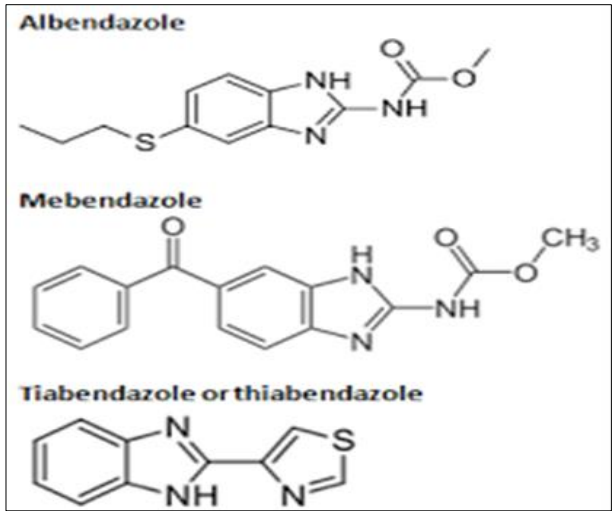
Nocodazole: It is an anti-neoplastic drug which exerts its impact on cells by interfering with the polymerization of microtubules.



Nocodazole

4.8. As a anti helminthic drug

These are the medications that are used to treat parasitic worm infections. Albendazole, mebendazole, and thiabendazole are benzimidazole-containing medications that are effective against nematode infestations such as roundworms, tapeworms, whipworms, hookworms, and flukes in domestic animals and people [1, 4, 8].



5. Conclusion

Bezimidazoles have proven to have a substantial part in drug discovery and development, with much emphasis placed on benzimidazole heterocyclic-based chemical molecules. Therapeutic medicines with the benzimidazole nucleus have applications in producing pharmaceuticals that are currently being studied. Modern concept and distinctive experiments have been studied and will be used at some point to discover numerous newly synthesized medications. In the future, benzimidazoles could be utilized as potent medicinal agents. This article describes the chemistry and biological activities of several substituted benzimidazole derivatives. This article is anticipated to be helpful to any researchers interested in benzimidazole-based heterocyclic medicinal chemistry.

6. Conflict of interests: The authors declare that they have no competing interests:

7. Financial disclosure: All authors declare no financial support.

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