

A Short Review on Potential Activities of Benzimidazole Derivatives

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ABSTRACT

Benzimidazole derivatives have shown hopeful activity in the treatment of several diseases, for this reason, the synthesis of novel benzimidazole remains a main focus for researchers. This review article summarizes the chemistry of different derivatives of benzimidazole along with their biological activities. The review article also covers the most active benzimidazole derivatives that have shown considerable pharmacological actions.

Keywords: Benzimidazole, Heterocyclic, Substituted benzimidazole, Pharmacological activities, Rivoglitazone, Candesartan.

INTRODUCTION

Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a privileged structure in medicinal chemistry. Nowadays is a moiety of choice which possesses many pharmacological properties. The most prominent benzimidazole compound in nature is *N*-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B₁₂.^[1]

The use of benzimidazole dates many years back for study of structural modifications and their pharmacological actions. Various benzimidazole derivatives were synthesized with the substitution of fluorine, propylene, tetrahydroquinoline which resulted in compounds with increased stability, bioavailability and significant biological activity.^[2-3] In light of the affinity they display towards a variety of enzymes and protein receptors, medicinal chemists would certainly classify them as privileged 'sub-structures' for drug designing. The incorporation of the

nucleus is an important synthetic strategy in studies of drug discovery. In the past few decades, benzimidazole and its derivatives have received much attention due to their chemotherapeutic values.^[4]

Benzimidazole derivatives play very efficient role in the medical field with plenty of useful therapeutic activities like anti-inflammatory^[5], antimicrobial^[6], Diuretic^[7], antiviral^[8], anticancer^[9], Antiprotozoal^[10], Antiulcer^[11], anti-oxidant^[12], Anti-Asthmatic^[13], Anti-Diabetic^[14], Cysticidal^[15], Analgesic^[16], antihypertensive^[17], anthelmintics^[18], anti-HIV^[19], anti-convulsant^[20], and spasmolytic^[21] activity. Benzimidazole and its derivatives have been showing hopeful activity in the treatment of several diseases, for these reasons, they achieved much attention as important pharmacophore and privileged structure in medicinal chemistry.

In order to obtain more effective chemotherapeutic agents, a variety of reports have been presented on the synthesis and

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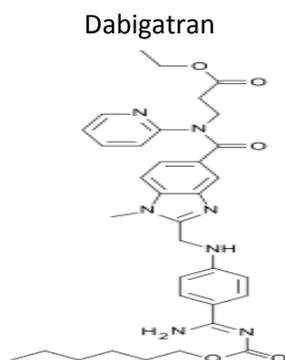
biological evaluation of novel benzimidazole derivatives. The literature survey revealed the importance of the substitutions at 1, 2 and 5 positions of the benzimidazole ring for their pharmacological activities.

This review summarizes to know about the different derivatives of benzimidazole with their pharmacological activities. The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research.

COMPOUNDS HAVING BENZIMIDAZOLE NUCLEUS

AS ORAL ANTICOAGULANTS

Dabigatran is an oral anticoagulant drug that acts as a direct thrombin (factor IIa) inhibitor. It can be used for the prevention of stroke in patients with atrial fibrillation. The drug was developed as an alternative to warfarin, since it does not require maintenance of international normalized ratio or monitoring by frequent blood tests, while offering similar efficacy in preventing ischemic events. Dabigatran can also be used to prevent the formation of blood clots in the veins (deep venous thrombosis) in adults who have had an operation to replace a hip or knee.^[22]

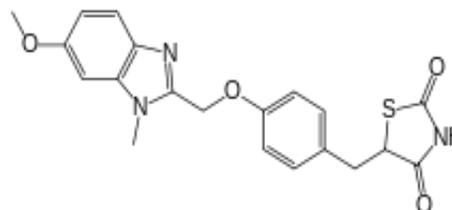


AS ORAL ANTIDIABETIC

Oral hypoglycemic drugs are used only in the treatment of type 2 diabetes which is a disorder involving resistance to secreted insulin. The oral

antidiabetic containing benzimidazole includes Rivoglitazone.^[23]

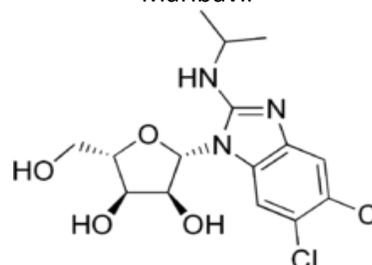
Rivoglitazone



AS ORAL ANTIVIRAL

Antiviral drugs are a class of medication used specifically for treating viral infections such as influenza, herpes virus, viral hepatitis, human cytomegalovirus (HCMV) and human immunodeficiency virus (HIV) etc. The oral antiviral drug containing benzimidazole includes Maribavir which is used for the prevention and treatment of human cytomegalovirus (HCMV) disease in hematopoietic stem cell/bone marrow transplant patients. The oral antiviral containing benzimidazole includes Maribavir.^[24]

Maribavir

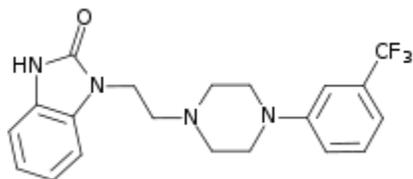


DRUGS IN HSDD

HSDD (hypoactive sexual desire disorder) is the most commonly reported female sexual complaint and characterized by a decrease in sexual desire that causes marked personal distress and/or personal difficulties. The benzimidazole drug used in HSDD is Flibanserin which is a 5-HT_{1A} receptor agonist and 5-HT_{2A} receptor antagonist used as a non-hormonal treatment for pre-menopausal women with HSDD that had initially been investigated as an antidepressant. The drug containing

benzimidazole used in HSDD includes Flibanserin.^[25-26]

Flibanserin

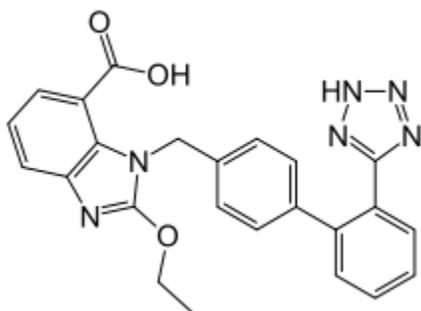


AS ANTI-HYPERTENSIVE

Antihypertensive are a class of drugs that are used to treat hypertension (high blood pressure). Antihypertensive therapy seeks to prevent the complications of high blood pressure, such as stroke and myocardial infarction. The anti-hypertensive containing benzimidazole is Candesartan and Telmisartan.

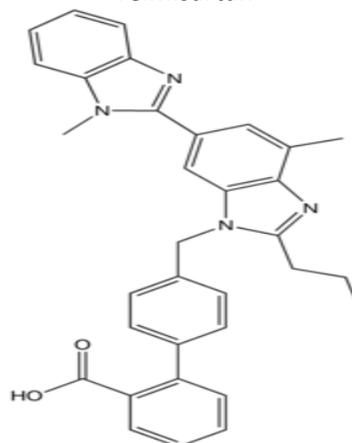
Candesartan is an angiotensin-II receptor antagonist used mainly for the treatment of hypertension. Candesartan is also available in a combination formulation with a low dose thiazide diuretic, invariably hydrochlorothiazide, to achieve an additive antihypertensive effect. Candesartan/hydrochlorothiazide combination preparations are marketed under various trade names.^[27]

Candesartan



Telmisartan is an angiotensin-II receptor antagonist used in the management of hypertension.

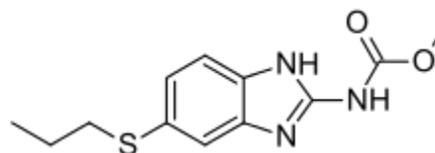
Telmisartan



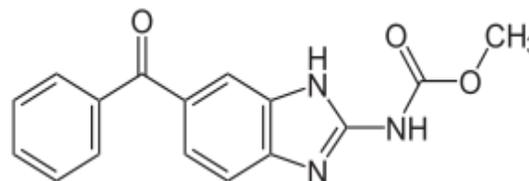
AS ANTHELMINTICS

These are the drugs used for the treatment of a variety of parasitic worm infestations. The drugs containing benzimidazole are albendazole, mebendazole, thiabendazole which are broad spectrum anthelmintics, effective against nematode infestations, including roundworms, tapeworms, whipworm, hookworm and flukes of domestic animals and humans.^[28-29]

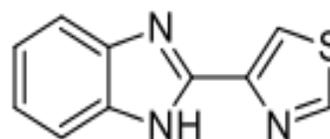
Albendazole



Mebendazole



Tiabendazole or thiabendazole



AS FUNGICIDAL

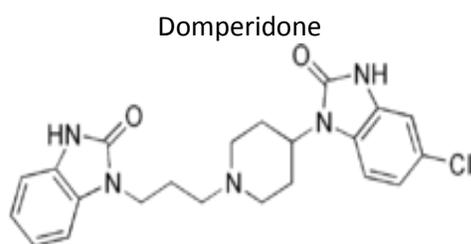
Examples of benzimidazole class fungicides include benomyl, carbendazim, chlorfenazole, cypendazole, debacarb, fuberidazole, furophanate, mecarbinzid, rabenzazole, thiabendazole, thiophanate.

Carbendazim is a systemic fungicide with protective and curative action. It is absorbed through the roots and green tissues. It acts by inhibiting beta-tubulin synthesis, inhibiting development of germ tubes and the growth of mycelia. It is compatible with most of the insecticides. It is used for the control of blast, sheath blight, brown spot, powdery mildew, scab, anthracnose & leaf spot diseases in various crops.^[30]



DRUGS IN GIT

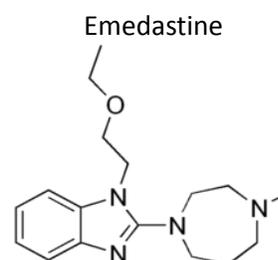
Domperidone is the example of drug containing benzimidazole, is a peripheral, specific dopamine receptor blocker. Domperidone is given in order to relieve nausea and vomiting; to increase the transit of food through the stomach (as a prokinetic agent through increase in gastrointestinal peristalsis); and useful in gastroparesis to increase lactation (breast milk production) by release of prolactin. It is also used in the scientific study of the way dopamine (an important neurotransmitter) acts in the body.^[31]



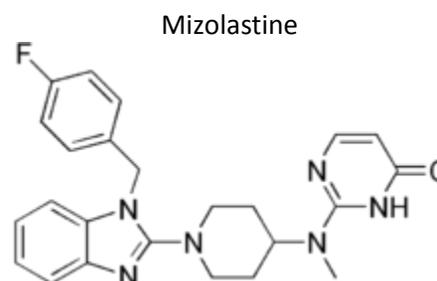
DRUGS IN ALLERGIC CONJUNCTIVITIS

The drugs containing benzimidazole are Emedastine, Mizolastine, Clemizole, and Astemizole.^[32]

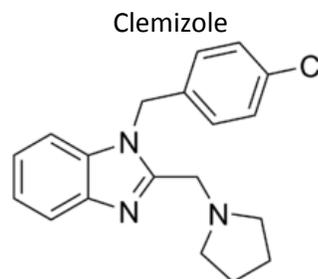
Emedastine is a second generation antihistamine used in eye drops to treat allergic conjunctivitis. It acts as a H₁ receptor antagonist. It works by blocking certain natural substances, histamines that cause allergic symptoms.



Mizolastine is a once daily, non-sedating antihistamine. It blocks H₁ receptors and is commonly fast-acting. It does not prevent the actual release of histamine from mast cells, just prevents it binding to receptors.

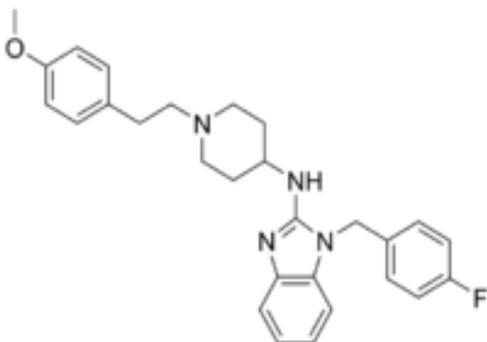


Clemizole: Clemizole is an H₁-antihistamine, i.e. a drug that is used to treat allergic reactions.



Astemizole: Astemizole is a long-acting, highly selective H₁-antihistamine with minimal central and anticholinergic effects. Astemizole is used in the treatment of Conjunctivitis, Allergic Rhinitis, and Urticaria.

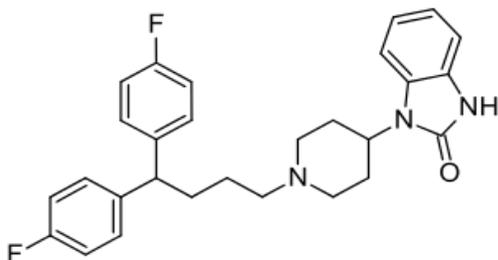
Astemizole



AS ANTIPSYCHOTIC

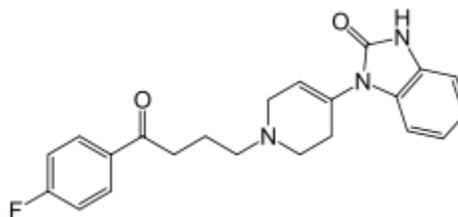
In psychosis, thinking of patient becomes illogical, bizarre and loosely organized. Patient has difficulty in understanding reality and their own conditions. These drugs are used in schizophrenia and chronic psychosis. Some drugs containing benzimidazole nucleus are droperidol, pimozide, and benperidol.^[33-35]

Pimozide



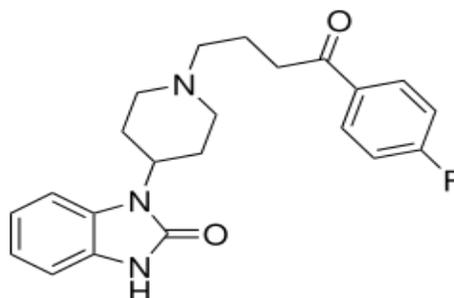
Droperidol: is an antidopaminergic drug used as an antiemetic and antipsychotic. Droperidol is also often used for neuroleptanalgesic anesthesia and sedation in intensive-care treatment.

Droperidol



Benperidol: It is an antipsychotic, which can be used for the treatment of schizophrenia, but it is primarily used to control antisocial hypersexual behaviour, and is sometimes prescribed to sex offenders as a condition of their parole, as an alternative to anti-androgen drugs such as cyproterone.

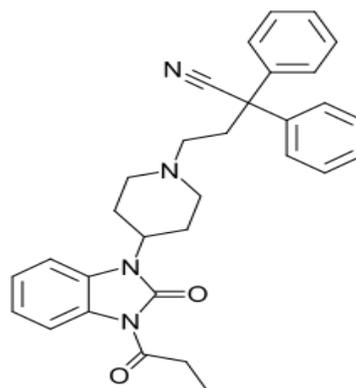
Benperidol



AS ANALGESIC

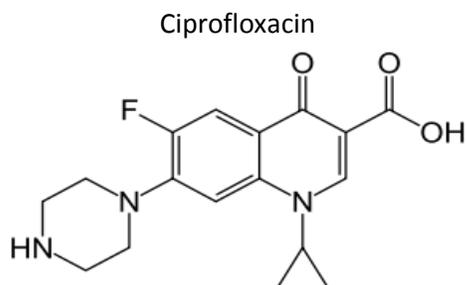
Bezitramide: It is a narcotic analgesic. Bezitramide itself is a prodrug which is readily hydrolyzed in the gastrointestinal tract to its main metabolite, despropionyl-bezitramide.

Bezitramide

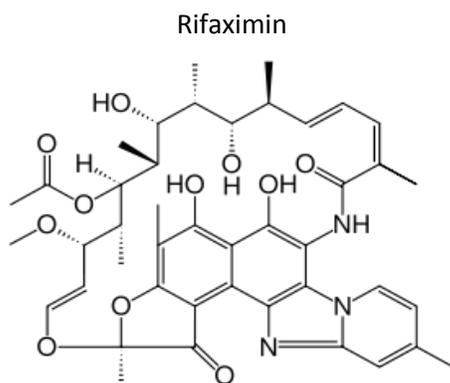


AS ANTIMICROBIAL

Ciprofloxacin: Ciprofloxacin is an antibiotic that belongs to the family of medications known as quinolones. It is used to treat infections caused by certain bacteria. It is most commonly used to treat infections of the skin, sinuses, bone, lung, ear, abdomen, kidney, prostate, and bladder.

**AS ANTI-DIARRHEAL**

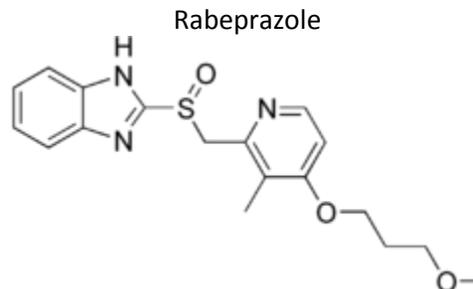
Rifaximin: It is a semisynthetic antibiotic based on rifamycin. It is used in the treatment of traveler's diarrhea and hepatic encephalopathy.^[36]

**AS ANTI-NEOPLASTIC**

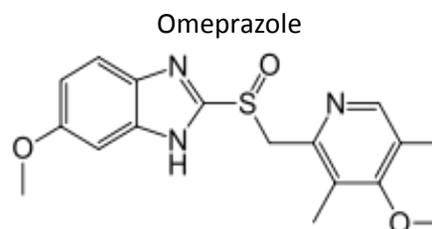
Nocodazole: It is an anti-neoplastic agent which exerts its effect in cells by interfering with the polymerization of microtubules.

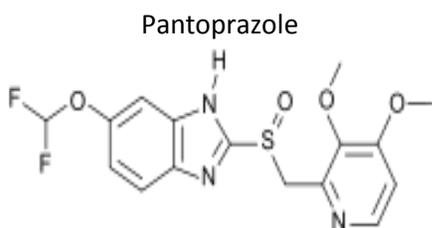
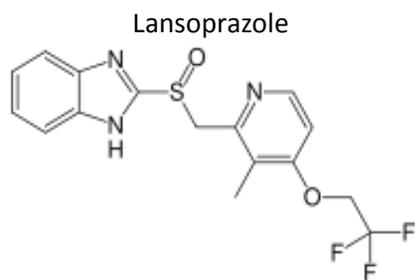
**AS ANTIULCER DRUG**

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 drugs containing benzimidazole nucleus are Rabepazole, Omeprazole, Lansoprazole, Pantoprazole, etc. These drugs belong to class of proton pump inhibitor.^[37-39]



Omeprazole: It is a proton pump inhibitor used in the treatment of dyspepsia, peptic ulcer disease, gastroesophageal reflux disease, laryngopharyngeal reflux, and Zollinger–Ellison syndrome.

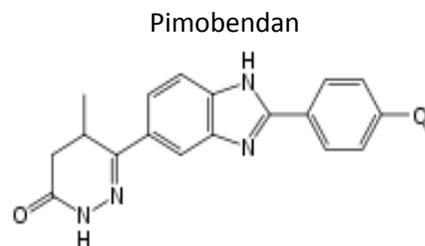




AS CALCIUM SENSITIZER

Pimobendan: It is a calcium sensitizer with positive inotropic and vasodilator effects. It is also a selective inhibitor of phosphodiesterase III (PDE3). Pimobendan is used in the management of heart failure in dogs, most commonly caused by myxomatous mitral valve

disease (also known as endocardiosis), or dilated cardiomyopathy.^[40]



CONCLUSION

Benzimidazoles find several applications in different areas of chemistry. The position and type of substituents on the benzimidazole ring are responsible for a variety of biological activity. It will be interesting to observe that these modifications can be utilized as potent therapeutic agents in future. This comprehensive overview summarizes the chemistry of different derivatives of substituted benzimidazole along with their biological activity.

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